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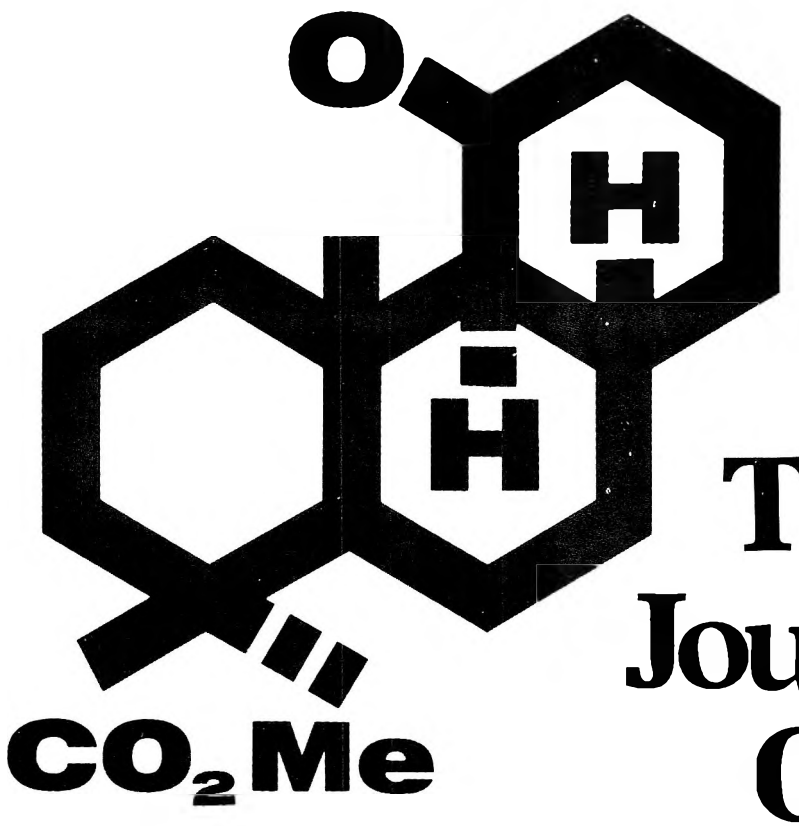

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APRIL 14, 1978

A Systematic Approach to the Classification and Nomenclature of Reaction Mechanisms

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Contribution No. 3708 from the Department of Chemistry, University of California, Los Angeles, California 90024

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A universally applicable method for naming organic and inorganic reaction mechanisms is introduced. It is based on simple valence-bond representations of electron flow, and is thus conceptually and intuitively simple and easily grasped. Through its use, relationships between various types of concerted processes may be readily perceived, and their arrangement into classes naturally follows. Aside from its use as a perceptual or pedagogical tool, it is designed to be incorporated into chemical information systems, where it could potentially serve as the basis for a new literature search method.

More than four decades have passed since the introduction by Ingold[2] of his mechanistic nomenclature scheme and the familiar representational tool which has come to be known as "arrow pushing". His thinking has greatly changed the way we think about organic chemistry; an intuitive grasp of mechanistic principles is now essential to the practicing chemist.

Yet it remains difficult for students to assimilate this intuitive construct mostly because there exists no formalism relating different reactions on a mechanistic level. In an attempt to remedy this while involved in teaching the subject, this author has stressed similarities between concerted reactions with the same overall path of electron flow, hence referred to as *isomorphic* reactions. I found that this approach, which, for example, relates S_N2, Elcb, nucleophilic addition to carbonyl, and nucleophilic addition to a nitrile group, could effectively impart a sense of cohesiveness to the seemingly random collection of reactions and mechanisms which threatens the beginning student of organic chemistry.

It further became apparent that the isomorphicity concept could be extended to serve as the basis for a systematic means of naming, encoding, and classifying reaction mechanisms. With such means available, it would be routinely possible to uncover analogies which would be missed by the usual intuitive approach to mechanism. Information about mechanisms, and hence, reactions, could be concisely incorporated into information storage/retrieval systems such as those of Chemical Abstracts Service. Reactions could then be arranged into easily-searched indices; this would facilitate literature searches and allow new reactions to be placed into perspective with previously known mechanisms. The resulting broad overview of mechanism would lead to unexplored areas of chemistry, in much the same way as Mendeleev's overview of the properties of the elements, formalized as the periodic table, led to the discovery of new elements.

Some recent attempts to systematize organic mechanism should be mentioned. The work of Mathieu et al.,[3] which was recently reworked by Guthrie,[4] is basically a generalization and refinement of Ingold's original work, does not recognize the concept of isomorphic reactions, and can incorporate only simple mechanisms such as dissociation or displacement. Several departures from Ingold's work have been developed. Hendrickson[5] has systematized and enumerated most of the known or hypothetical six-electron pericyclic reactions. He recognizes that these fall into several (five-center, six-center, seven-center) broad isomorphic classes, but his scheme cannot conveniently be expanded to include the remaining wide variety of reaction types. A similar approach has been developed independently by Stevens.[6]

Woodward and Hoffmann's classic treatment of orbital symmetry[7] is similarly restricted to a limited set of reactions; here, the emphasis is on systems in which the molecular orbital makeup of a reaction influences its outcome rather than on developing a view of organic mechanism as a whole.

The only truly universal and systematic scheme that has appeared is that which Ugi and his co-workers developed for the encoding of chemical transformations.[8] In this system, reactants and products are represented in the form of bond/electron (BE) matrices, and a transformation may be represented as an operator (R) matrix, which converts the reactant BE matrix to the product BE matrix by simple addition. It may be algebraically possible to extract concise symbols from R matrices which would represent general reaction types, but as it stands, the system is far too cumbersome to be used either as a teaching aid or in a manual information retrieval system.

In this paper, a prototype notation scheme[9] will be introduced, and its application to a variety of types of organic reaction mechanisms will be described. This scheme is based on simple valence-bond representations of structure and mech-

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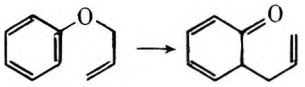
anism, and is easily grasped on an intuitive level. Yet it is capable of representing a mechanism in a manner which reveals on inspection the general and specific classes to which it belongs, its relationship to mechanisms in other classes, and its elements of symmetry.

The Concerted Process and Its Skeleton

Any chemical transformation involving covalent bonds may be written as a linear sequence of one or more irreducibly synchronous or "concerted" electronic processes interspersed with processes of a translational or conformational nature. A concerted process (CP) may be defined as a single event mapping one discrete set of intermediates into another by a net flow of electrons. Although in the strictest sense mechanistic description of a concerted process must include a quantum mechanical description of this electron flow, the word "mechanism" as routinely used by experimental chemists does not include such descriptions and, partly because the scheme would otherwise be too cumbersome, a CP will hence be defined in terms of its initial and final states.

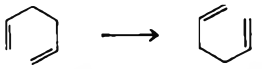
The problem of naming a stepwise reaction mechanism clearly reduces to the problem of finding a unique, systematic, and descriptive name for each of its component CPs. The overall mechanism may then be named simply by concatenation of the CP names into the proper sequence.

Consider now how we might dissect a CP in order to assess the features by which it might be named and classified. As an example let's use the first step of the familiar Claisen rearrangement.



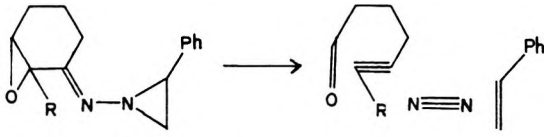
Starting with the standard valence-bond representation, we will follow a process of pruning away characteristics of increasing relevance to the nature of the CP. First we may eliminate substituents,

next we may eliminate heteroatoms,

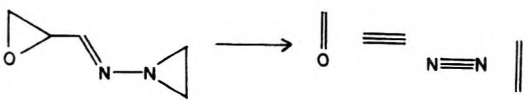


and finally we may eliminate electrons which do not participate in the reaction.

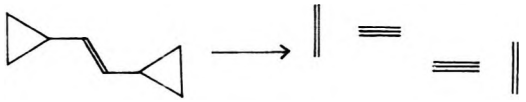
What we are left with is the skeleton of the CP, the dynamic electrons superimposed over a static array of nuclei, which for visual clarity will be represented as open circles.[10] Note the emergence of symmetry during the dissection process. For the purposes of illustration, we may similarly treat a rather complex example, the recently reported Eschenmoser epoxyhydrazone fragmentation.[11]



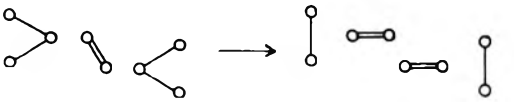
Eliminating substituents,



heteroatoms,



and nonparticipating electrons.



yields a CP skeleton again possessing a beautiful symmetry. Of course, a reaction such as the above fragmentation need not necessarily be concerted; the point in using it was to show how we might look at one particular mechanistic representation of the reaction.

Levels of Mechanistic Information

Looking at this dissection process in reverse, we may now set up a hierarchy of types of information about an individual CP. On the most fundamental level we have the CP skeleton, an array of nuclei whose topological disposition is defined by a superimposed array of dynamic (i.e., participating) electrons (Level 1). Of lesser importance in influencing the nature of the CP is the pattern of static bonding among the atomic centers (Level 2), the identity of the nuclei in the skeleton (Level 3), orbital symmetry factors (Level 4), and the substitution pattern onto the path of electron flow (Level 5). Exerting a still weaker influence are such factors as geometry of the molecules involved, as dictated by conformational preferences (Level 6), and the chemical environment, as well as remote structural features of the molecules which might exert some minor influence (Level 7). These categories might not always fall in this exact order, but the hierarchy remains useful for our purposes of classification. Categories of CPs corresponding to certain levels do already exist; for example, "electrocyclic" and "associative" correspond to Level 1, "extrusion" and "Alder-ene" correspond to Level 2, and "hydroboration" and "acyl transfer" correspond to Level 3. Yet these names clearly are useless in any systematic sense, and many classes in each level remain unnamed and unnoticed.

These levels of information further suggest how we might compile a reaction index for routine manual use. A CP skeleton may be viewed as an archetype, representing a broad class of isomorphic CPs. Within each such broad class there would be divisions at Level 2, each representing a subclass of reactions which are, in a loose sense, isoelectronic; within each such division there would be categories representing different patterns of atomic substitution. From this point on it would probably prove most convenient to list individual CPs as they actually appear, with reference to the overall reaction if the CP is an element in a multistep reaction. An abstractor compiling entries for the index would be expected to exercise common sense in breaking a reaction down into its individual CPs, but this introduces no human element that is not already present in today's abstracting/indexing systems.

To develop such a manual index, we will need a notation scheme which embodies the following characteristics: (a) it must be universally applicable; (b) encoding and decoding must be convenient and easily learned; (c) it must be adaptable to computer use; and (d) it must allow successive incorporation of information, so that, for example, a Level 3 name can be immediately identified as a member of a Level 2 class by reduction to the Level 2 name on inspection, and similarly down to Level 1.

In the next section, a notation scheme at Level 1, i.e., a means of generating a unique name for each CP skeleton (archetype), will be described. Following this will be a dis-

Table I. Two-Center CPs

Notation	CP Skeleton	Example
(10)	O· O ⟷ O·····O	$H^+ + H^- \longrightarrow H_2^{+\cdot}$
(20)	O: O ⟷ O—O	HETEROLYSIS
(11)	O· ·O ⟷ O—O	HOMOLYSIS
(22)	O: :O ⟷ O═O	CARBENE DIMERIZATION
(33)	O⋮ ⋮O ⟷ O≡O	$2\ N \longrightarrow N_2$

cussion of ways in which these names may be modified to incorporate Level 2 and Level 3 information.

Level 1 Notation

If the process of dissection described above is applied to a variety of the most commonly occurring mechanisms, a relatively small number of archetypes are obtained.[12] These archetypes are of two distinct kinds: (a) those in which only bond formation or bond cleavage alone occurs, and (b) those involving simultaneous bond formation and cleavage. We might refer to type (a) archetypes as "primitive" CPs and type (b) archetypes might be called "compound" CPs. As will be explained later, *the primitive CPs may be used as elements from which the compound CPs may be constructed by several kinds of homologation.* The principle behind this homologation is that a primitive CP, taken in the "retro" sense, has a certain number of dynamic electrons available for participation in another CP. Starting with a primitive CP, we may replace one or more atomic centers with retro-CPs, or fragments thereof, having the same number of available dynamic electrons, and thus obtain a compound CP. A retro-CP functioning in this way as an element of a compound CP will hence be referred to as a "sub-CP".

For the purposes of classification, no distinction is made between forward and reverse directions; however, it is always assumed that a sub-CP proceeds in a direction formally opposite that of the compound CP in which it functions as an element.[13]

A. Symbols. 1. Parentheses. The basic form of the notation is that of a pair of parentheses containing a sequence of terms. A term is defined as either a numeral or a closed pair of parentheses. Simple ligation is represented by only two terms; more than two designates the joining of the components into a bonded ring.[14] The order of these terms corresponds to the arrangement of the designated atoms or sub-CPs into the ring; larger numerals are placed to the left.

2. Numerals. An atomic center gaining or losing n electrons in a CP is represented by the numeral n. In general, $(mn) \equiv (nm)$, but it is useful to retain the convention of placing the larger numeral to the left.

3. Equals Sign. An atomic center or sub-CP gaining a different number of electrons than it loses in a CP is undergoing a valence change. This is represented by two terms representing its capacity in each of the two valence states separated by an equals sign. Its use will become clearer when demonstrated with examples (see section D, below).

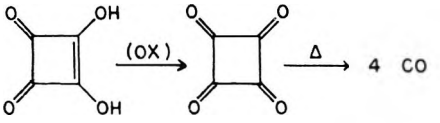
B. Primitive CPs. Some Examples. 1. Two-Center CPs. The symbols introduced above for the representation of CP skeletons (open circle = atomic center, dot = free electron, dotted line = one-electron bond, unbroken line = two-electron bond) will continue to be used in the tables that follow. Table I contains examples of known or possible two-center CPs. These will function not only in the capacity of sub-CPs, but also as models for the assembly of compound CPs from sub-CPs. The notation symbols are self-explanatory.

The list presented is not necessarily complete; other two-center CPs are, at least in principle, possible. The rarity of processes involving odd numbers of dynamic electrons or many dynamic electrons per atomic center is worthy of note.

2. Primitive Cyclic CPs. The simple ligation of more than two atomic centers at one time is assumed for our purposes to proceed in a cyclic fashion, resulting in the interconnection of the centers into a ring. The number of bonds to a given center should equal, or approximate as closely as possible, the number of dynamic electrons on that center at the outset. Table II contains an enumeration of some of the simpler primitive cyclic CPs. Moving from left to right in the table one finds an increase in the number of electrons per center; the CPs are arranged vertically into three major groups, those with two, three, and four centers. Clearly, the two-center CPs constitute special cases of primitive cyclic CPs and are shown in the table as such.

The notation symbols provide useful information on inspection. Note that the *number* of numerals between the parentheses always represents the number of atomic centers and that the *sum* of the numerals always equals the number of electrons in a CP.

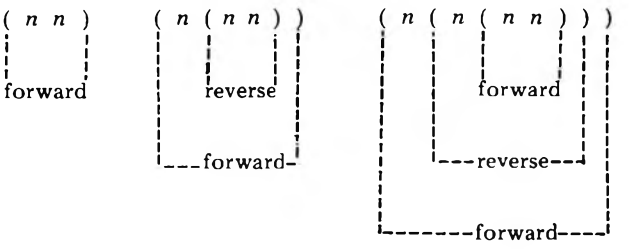
This table is included primarily for illustrative purposes. While the author is aware of no documented examples of cyclic reactions such as those in the table, one might imagine that reactions such as (2222) would occur in the *retro* sense upon pyrolysis of appropriate precursors:



The usefulness of the primitive cyclic CPs will become clear when they are used as prototypes from which the common cyclic CPs can be constructed by homologation, as illustrated in Table III. The sequence (22), (222), and (2222), illustrated by the diagonals in Table II, will serve in this capacity.

C. Compound CPs. Some Examples. These fall into three broad classes: (1) simple cyclic CPs, where one or more atomic centers is replaced by an entire two-center retro-CP; (2) linear CPs, where one or more atomic centers is replaced by only one center of a two-center retro-CP; and (3) complex CPs, where the role of sub-CP is filled by polyatomic CPs.

1. Simple Cyclic CPs. The top row of Table III contains the sequence of primitive cyclic CPs possessing two dynamic electrons per center. A two-electron center participates in a divalent sense in primitive CPs; a (11) CP, taken in the retro sense, exhibits one electron on each center and may function analogously to a two-electron center. The familiar cyclic CPs may be generated by substituting "(11)" for "2" in the notation and O–O for Ö in the graph representation, as illustrated in Table III. Note that the inner parentheses imply a reaction occurring in the reverse sense from that of the overall reaction; if the latter were to function as a sub-CP in a CP of greater complexity, a further reversal would be implied:



Note also that the number of numerals encountered between two complementary parentheses represents the ring size of

Table II. "Primitive" Cyclic CPs

(10)	(20)	(30)	(40)			
	(11)	(21)	(31)	(41)	(42)	
			(22)	(32)	(33)	
(111)	(211)	(311)	(411)	(421)	(431)	(441)
		(221)	(321)	(331)	(332)	(432)
			(222)	(322)	(422)	(333)
(1111)	(2111)	(3111)	(4111)	(4211)	(4311)	(4411)
		(2211)	(3211)	(4121)	(4131)	(4141)
		(2121)	(3121)	(3221)	(4221)	(4321)
			(2221)	(3212)	(4212)	(4312)
				(2222)	(3321)	(4231)
					(3231)	(4222)
					(3222)	(3331)
						(3322)
						(3232)

a cyclic process and that the total number of electrons in a CP may still be obtained as the sum of the numerals.

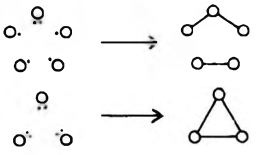
Some examples will clarify the symbols in Table III. In the leftmost column, we have a two-electron series; examples are heterolysis, (20), and attack of Br^+ on a double bond, ((11)0). In the four-electron series in the next column, carbene dimerization, (22), carbene addition to olefins, (2(11)), and 2 + 2 cycloadditions, ((11)(11)), serve as examples; known examples in the six-electron series are the reaction of phosphines with ozone, (22(11)), reaction of butadiene with sulfur dioxide, (2(11)(11)), Diels–Alder and many others, ((11)(11)(11)), and allyl + diene cycloadditions ((11)(11)(11)0). Examples exist of photochemical ((11)(11)(11)(11)) reactions, but the eight-electron series remains for the most part undeveloped. Several ten-electron reactions are known.

Hypothetical CPs may be constructed using other primitive CPs from Table II; for example, one might formulate several series of odd-electron CPs to complete Table III. But for the most part, known chemistry of purely cyclic CPs is limited to the examples given.

It is useful, in understanding the use of the notation, to consider how we might regenerate the graph representation of a CP from the notation symbols. Each term within the outermost pair of parentheses represents an element in a ring; these elements are so arranged (terms representing retro-CPs are represented in their bonded state) to give an initial state, as, for example, in a (2(11)(11)) reaction:

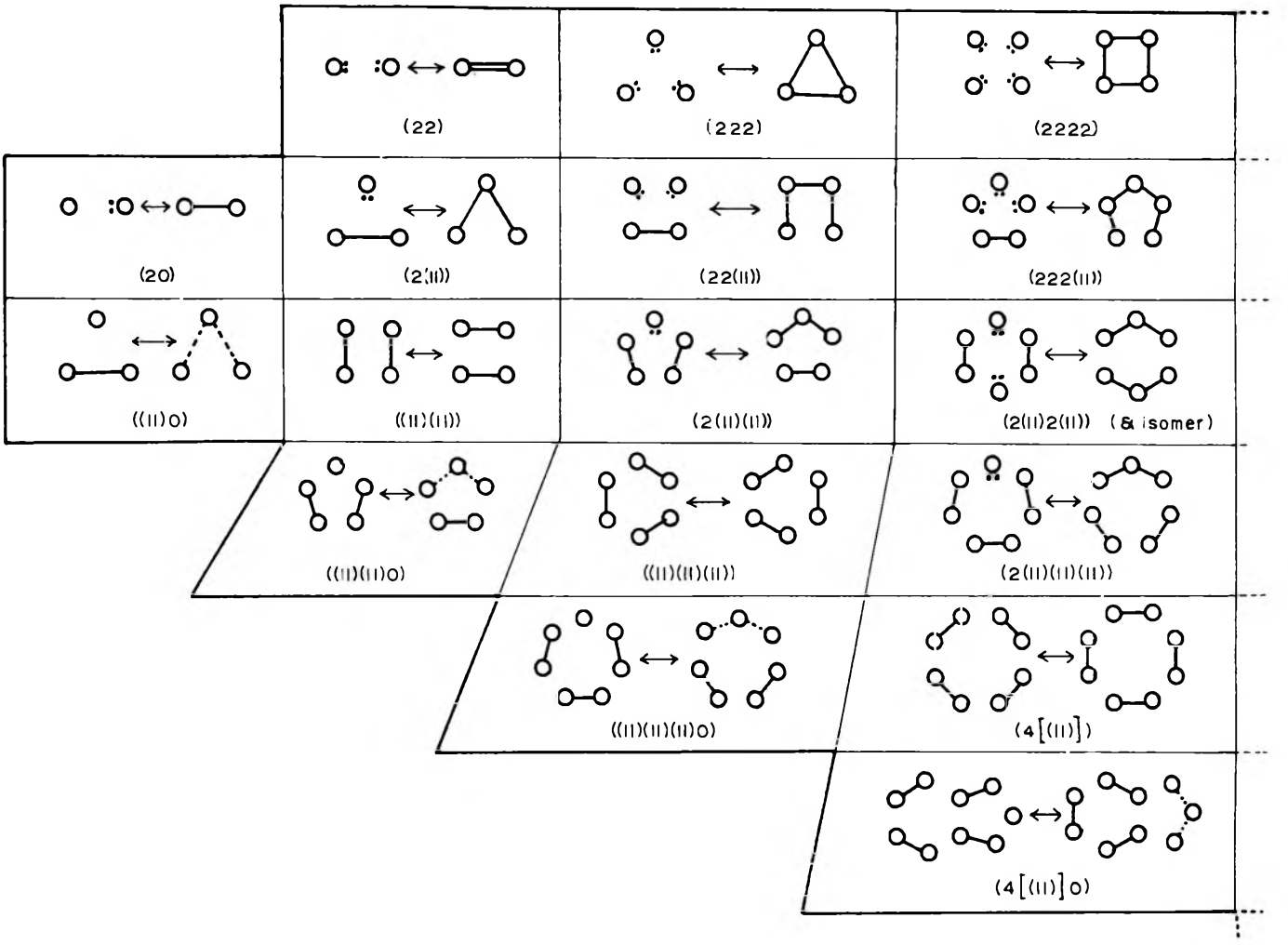
The retro-(11) operations are then performed, affording an entirely nonbonded state (which should not be interpreted as having any physical significance):

Finally, the binding of these elements into a fully bonded ring (except, of course, where prior bonds existed) affords the final state, in an operation analogous to the primitive CP containing the same number of terms (shown below for comparison).

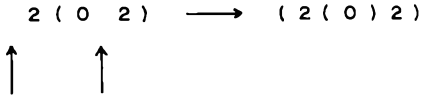


One ambiguity of this system is that cyclic CPs with fewer than one electron per center result in cyclic arrangements with partial bonding. One-electron bonds are shown in the accompanying skeletal symbols; these are not necessarily implied by the notation but are fairly representative of reactions in these classes. It should be mentioned that ((11)(11)(11)0) can equally well represent both allyl + diene and pentadienyl + olefin type cycloadditions; the former is as shown in the table, but the latter could be thought to possess the skeleton which is represented by the same notation.

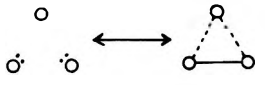
Table III. Simple Cyclic CPs



2. Linear CPs. Another series of well-known reactions may be generated by allowing only one center of a retro-CP (rather than both) to fulfill the function of an individual center of a two-center primitive CP. For example, a retro-(20) exhibits two dynamic electrons on one center and none on the other; each of these centers can combine as an element in another CP proceeding in the forward direction. A (2(0)2) reaction is thus formally defined as a 2 reacting with the 0 of a retro-(02); the notation is generated in a parallel fashion by placing a set of parentheses around the two components involved in the "forward" reaction:

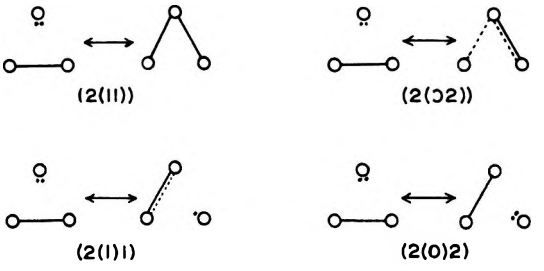


It should be noted that in order to represent a sub-CP a closed set of parentheses must contain two terms; hence, (2(0)2) cannot represent a cycloaddition such as



which, in fact, is properly represented by the notation (220). Two parentheses containing only one term rather represents the transfer of an entity between two others and does not itself represent a term since the parentheses are not a complementary pair. Again, the number of numerals contained within a complementary pair (in this case, two) represents the ring size of the sub-CP.

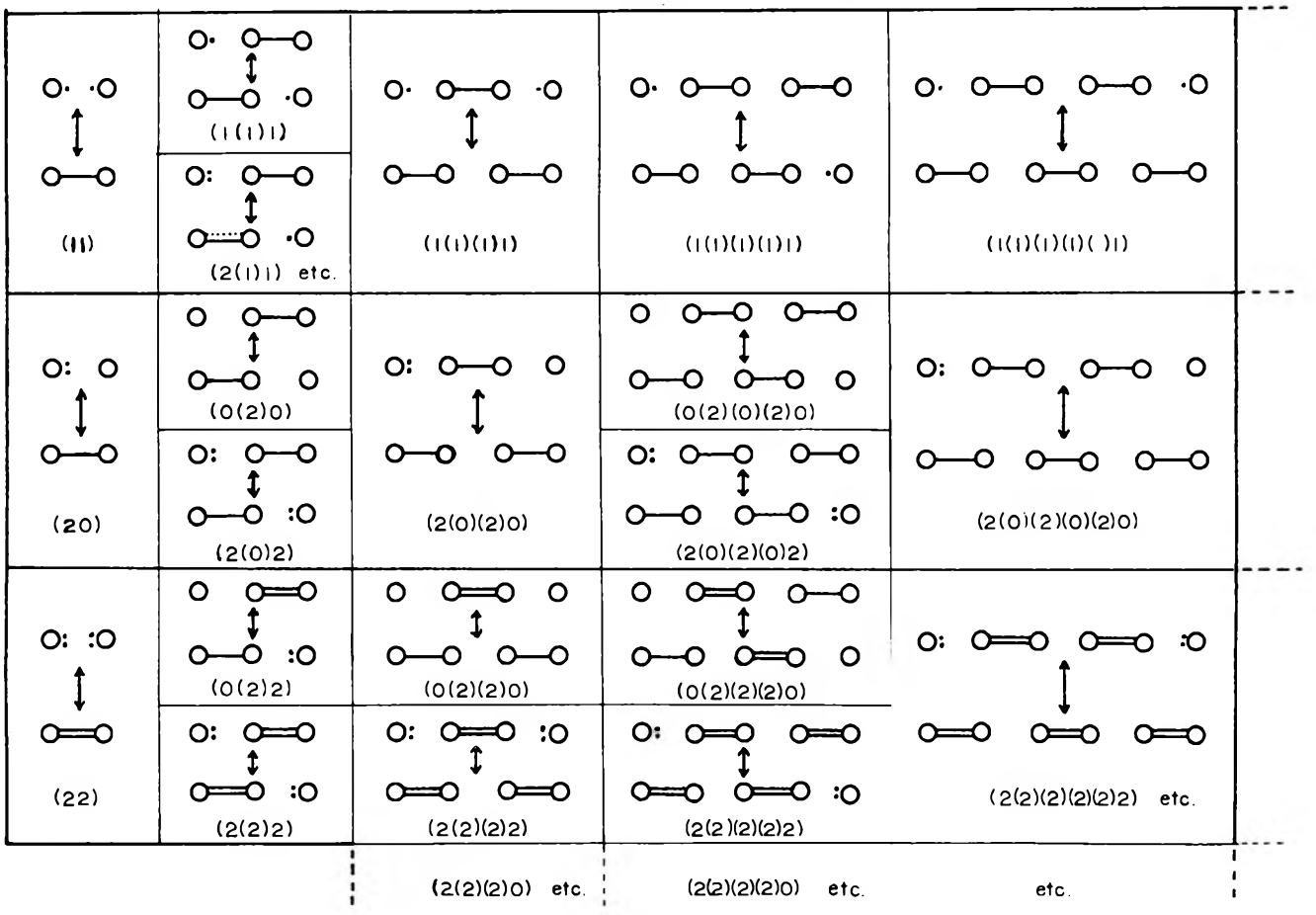
For the purpose of comparing the way linear and cyclic CPs are generated from their component parts, the following examples are useful:



A (2(11)) CP is exemplified by carbene addition to an olefin, (2(0)2) represents reactions such as S_N2, and the other two have no obvious counterparts in chemistry but are included for the purpose of demonstrating the use of the notation.[15]

Table IV enumerates some of the more commonly encountered linear CPs. It can be seen that these fall into several sequences of linear homologues, in which the notation symbols are built up in the manner prescribed above. It is also worth noting that the symmetry of a CP is preserved in the symbols and is thus immediately seen on inspection. Starting with the (11) reaction, a sequence of linear radical reactions is built up: (1(1)1), the radical abstraction, is followed by (1(1)(1)1), exemplified by fragmentation of an azo compound, and so on to cover radical additions to conjugated systems and multibond radical fragmentations. Another series beginning with (2(1)1) is, in principle, possible, although no real examples come to mind. The (20) series is quite fruitful, generating counterparts to a great deal of known ionic chemistry: nucleophilic and

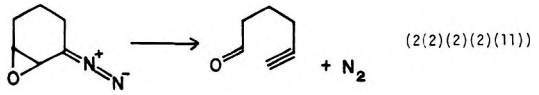
Table IV. Some Representative Linear CPs



electrophilic additions and substitutions correspond to (2(0)2) and (0(2)0), respectively; (2(0)(2)0) would represent protonation of an enamine; further out we have such reactions as protonation of a diene, general acid catalysis of carbonyl addition, ionic fragmentations, S_N2', and so on. The (22) series calls to mind a variety of obscure and intriguing reactions involving carbenes and other amphiphilic atoms, such as carbene–carbene rearrangements and azine pyrolysis. More hypothetical possibilities arise by successive substitution of zero-electron centers; these are perfectly plausible but constitute little, if any, of known chemistry.

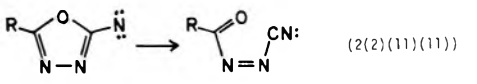
3. Linear-Cyclic, Spirocyclic, and Bicyclic CPs. These are constructed in an analogous fashion to simple linear CPs except that the role of sub-CP is filled by cyclic as well as diatomic CPs. Consider again the familiar (2(11)) CP:

Taken in a retro sense, we have available a divalent center and a (11) sub-CP (also divalent) which may participate as components of a forward CP; some simple combinations which result are shown in Table V. One can generate from a linear-cyclic CP an entire series of homologous CPs in the same fashion as the linear series arise. An example from known chemistry is the fragmentation due to Eschenmoser,

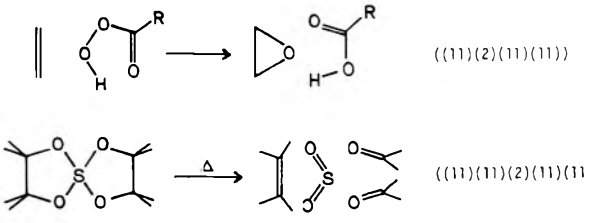


as well as ((11)(2)(2)(2)(2)(11)), which is the corresponding aziridine fragmentation introduced above as a CP skeleton.

Also known are linear cyclics such as



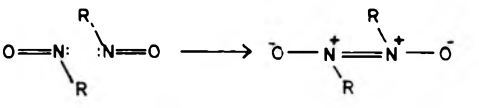
Bicyclic reactions are an essentially unexplored class; a few examples of higher spirocyclic reactions are known, such as



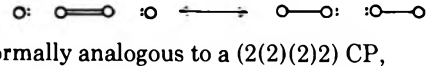
Clearly, a great deal of potentially useful chemistry lies waiting in these categories.

D. Valence Change. An assumption underlying the construction of complex CPs from sub-CPs is that an atomic center which is shared by two sub-CPs functions in the same capacity within each of the sub-CPs.

This is sometimes not the case. For example, consider the dimerization of a nitroso compound

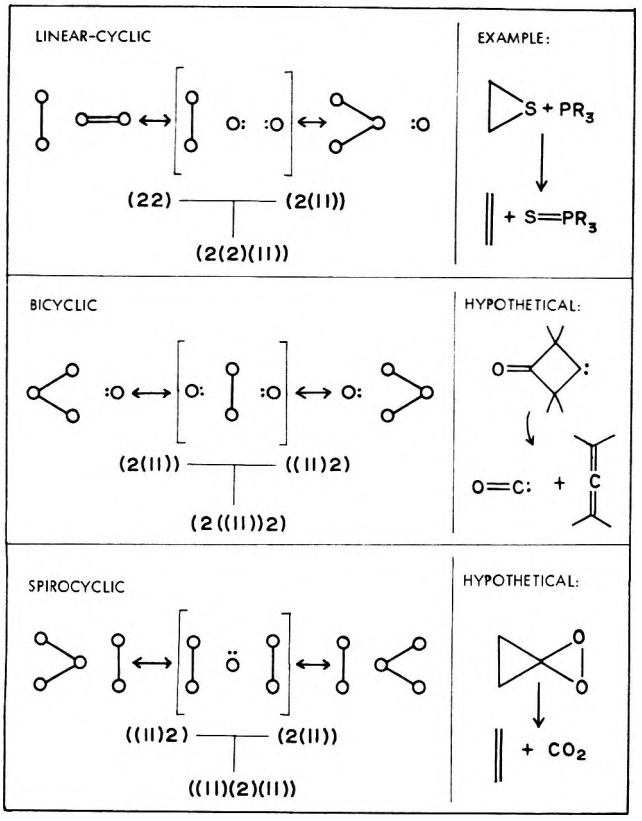


whose skeleton may be written as



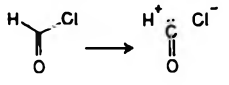
This is formally analogous to a (2(2)(2)2) CP,

Table V. Complex CPs



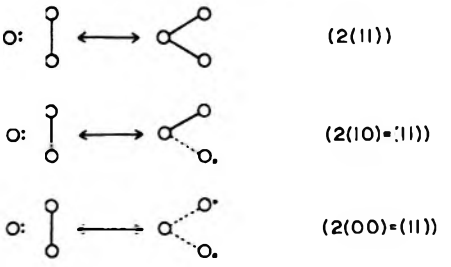
but it differs in that nitrogen functions both as a nucleophile and an electrophile; it participates as a 2 in a (22) and as a 0 in a retro-(20). In a situation such as this, both numerals will appear in the notation, separated by an equals sign, and this combination will fulfill the function of a single numeral. The notation for this reaction is therefore (2(0 = 2)(2 = 0)2). The term "valence change" is appropriate if we consider that in the context of mechanism the word valence would logically refer to the number of dynamic electrons on a given center (the numeral of the notation). A useful interpretation of the equals sign is as a combined right and left parenthesis, so that in evaluating and comparing notations the sub-CPs may be algorithmically extracted. As we read from right to left we have as sub-CPs (2(0), (2)(2), and (0)2); the extraneous parentheses are preserved since these indicate the capacity in which a sub-CP functions. (2(0) indicates a retro-(20) CP in which the "0" center participates further. This unit may also be found in (2(0)2), which is representative of, inter alia, addition of a nucleophile to a carbonyl group. The nitroso group does, in fact, function in this manner in nitroso dimerization. Likewise, (2)(2) represents a retro-(22) in which each center is involved in another CP.

1,1-Eliminations and additions comprise another group of CPs embodying valence change:



Indeed, this is a primitive CP, in that it embodies only bond cleavage in the forward direction. As mentioned previously,[14] these reduce to linear homologations of two-center CPs by interpretation of the equals sign and thus will not be confused with the corresponding primitive cyclic CP [in this case (220)].

The equals sign may be used to indicate valence change in a sub-CP as well as at an individual atomic center. For example, retro-(11) may function at least in principle as a bis-univalent (11), univalent–zerovalent (10), or bis-zerovalent (00) component of a complex CP:

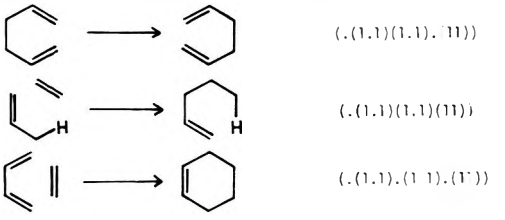


The equals sign is read, as before, as a combined right and left parenthesis. It should be evident that the Level 1 scheme as presented here may be adapted to fit CPs of almost any degree of complexity.[16]

Higher Level Notation

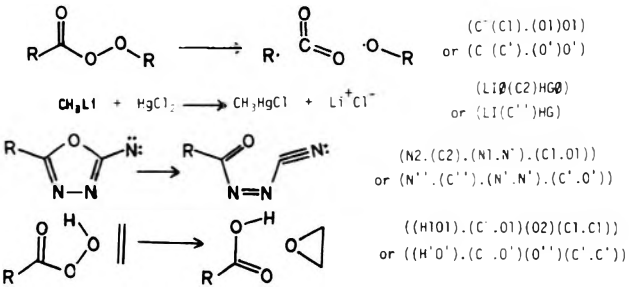
One major advantage of Level 1 notation as introduced above is that it can readily be made to incorporate further information about the CP. A Level 1–2 notation may be generated if we introduce the symbols "." and ":", which are to represent the fixed bonding pattern within the CP, and denote single and double static bonds, respectively. These symbols, when placed between two terms, denote the presence of fixed bonding between the corresponding atomic centers.

Consider, for example, a Cope rearrangement, an Alder-ene reaction, and a Diels–Alder reaction, which are all members of the ((11)(11)(11)) class. They are named as follows:



It is advantageous to assume a convention which places this punctuation as far to the left as possible (colon taking precedence over period); in this way ambiguity is avoided. Since, in the case of a cyclic CP, connection between first and last terms is assumed, a fixed bond connecting the corresponding atomic centers may be indicated by punctuation prior to the first term.

Further refinement, with incorporation of Level 3 information, is possible with the incorporation of symbols representing the elements. For this purpose, we may use either the internationally accepted symbols for the elements, converted to upper case, or otherwise the elemental symbols used by Wiswesser Line-Formula Notation,[17] thus opening the possibility of incorporating even more structural information. These symbols might be incorporated immediately adjacent to the numeral representing the corresponding atomic center. An alternative would be to remove the numerals entirely, modifying elemental symbols with accent marks to correspond to the number of dynamic electrons on the corresponding center. Examples of both are given below:



It will again be advantageous in cases of ambiguity to adopt a convention which places lower atomic numbers to the left. Note that Level 3 information may be incorporated independently of Level 2 information, if this is desired.

The basic format of notation introduced in this paper is amenable to modification which incorporates essentially any desired amount of static structural information. Information about the specific electronic, vibrational, or conformational states of the components of a CP is much more difficult to incorporate, and this can probably be done only by adding a large variety of additional symbols and modifying the syntax. Yet the notation as it stands is capable of being quite specific; at this point it would seem practical to leave the rest to intuition.

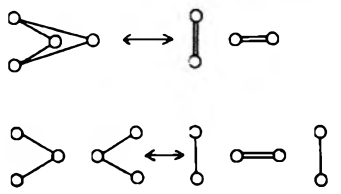
The system as presented here may well contain flaws which give rise to ambiguities or redundancies, causing it to fail under certain circumstances. These can be uncovered only with use; it is, nevertheless, a useful tool in its present imperfect and informal state. It is adaptable to computer use as such, or with very slight modification. It has been pointed out that the scheme as presented here does not lend itself to oral rendition and therefore would be of limited value for teaching purposes. The systematic nomenclature of organic compounds suffers similarly, but we willingly tolerate such difficulties so that we may use it as a tool for searching the literature.

At present, this investigation will concentrate on compiling as broad a list of known CPs as possible. We wish to understand what rules permit a given CP to exist in the physical world; we will attempt to test new possibilities with this goal in mind, hoping that our results will lead us to new reactions of practical significance.

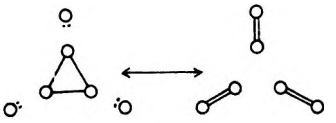
Acknowledgment. The author wishes to thank Professors D. S. Kemp and O. L. Chapman for financial support during the development of this project. The work was also supported in part by a National Institutes of Health Fellowship (No. 1 F32 CA05666-01) from the National Cancer Institute, DHEW.

References and Notes

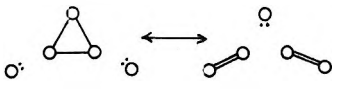
(1) Address correspondence to this author at the Department of Chemistry, Rutgers–The State University, New Brunswick, N.J. 08903.
(2) For a review, see C. K. Ingold, "Structure and Mechanism in Organic Chemistry", 2nd ed, Cornell University Press, Ithaca, N.Y., 1969, Chapters 5–15.
(3) J. Mathieu, A. Allais, and J. Vails, *Angew. Chem.*, **72**, 71 (1960).
(4) R. D. Guthrie, *J. Org. Chem.*, **40**, 402 (1975).
(5) J. B. Hendrickson, *Angew. Chem., Int. Ed. Engl.*, **13**, 47 (1974).
(6) R. V. Stevens, private communication.
(7) R. B. Woodward and R. Hoffmann, *Angew. Chem., Int. Ed. Engl.*, **8**, 781 (1969).
(8) J. Blair, J. Gasteiger, C. Gillespie, and I. Ugi, *Tetrahedron*, **30**, 1845 (1974).
(9) The name NUMEN, for NUmerical MEchanistic Notation, is suggested. Presented here are versions NUMEN-1, NUMEN-12, and NUMEN-123, incorporating successively three different levels of information (see section on this topic).
(10) Graphs of this kind will be used throughout this paper; aside from the open circles as symbols for nuclei, all symbols will retain the same meanings as when used in traditional Lewis structures (dot = nonbonding electron, solid line = bonding pair, broken line = one-electron or fractional bond).
(11) D. Felix, R. Muller, U. Horn, R. Joos, J. Schreiber, and A. Eschenmoser, *Helv. Chim. Acta*, **55**, 1276 (1972).
(12) It is not within the scope of the present paper (nor within the power of the author) to make any statements concerning what kinds of CP archetypes are presently known or unknown; at this point the author is aware of about 30 types, but the list is certainly not complete. Ugi and co-workers[8] claim 38 general *R*-matrix types with a maximum of three bonds broken during the transformation, but this refers to overall transformations rather than strictly to CPs.
(13) It has been suggested that the distinction between forward and reverse directions be retained, the notation thus providing more information about the reaction in question. If this is desired, the notation as it stands may be designated as representing a reaction proceeding from an overall less bonded to a more bonded state, and a minus sign (−) preceding the notation would reverse this meaning.
(14) Noncyclic multicenter primitive CPs will always reduce to linear homologations of two-center CPs; see section D in text.
(15) The representation of the Diels–Alder reaction as ((11)(11)(11)) rather than ((20)(20)(20)) and similar representations of other reactions have been criticized by a referee on the grounds that the former notation implies an unpairing of electrons, which is in contrast with the molecular orbital picture of such reactions in which such pairing is maintained. The author recommends that the ((11)(11)(11)) notation be retained; first, because it correctly does not imply any preferred direction of electron flow around the ring, and second, because the substitution of (20) for (11) in all positions is valid only when no other terms are present, as illustrated by the comparison of (2(11)) and (2(02)).
(16) Two further types of CPs are, except in special cases, not capable of being represented by the notation as it stands. Tricyclic or higher polycyclic CPs are one such type, and situations where a sub-CP shares each of more than two atomic centers with another sub-CP comprise the other. Both situations are highly unlikely, and it seems unnecessary to complicate the notation scheme just to accommodate them. The simplest example of the first type, the cycloreversion of tetrahedrane to two acetylene molecules, may still be represented by noting its similarity to a ((11)(2)(2)(11)) CP:



For the time being, it can be included in the latter class. Likewise, a CP such as



may be included in the (2(2)2(2)2) class:



Of course, any reaction for which it is impossible to write a traditional valence-bond mechanism (such as transition-metal catalyzed hydrocarbon isomerizations) is incapable of being represented within this scheme.
(17) E. G. Smith and P. A. Baker, Ed., "The Wiswesser Line-Formula Chemical Notation (WLN)", 3rd ed, Chemical Information Management, Cherry Hill, N.J., 1975.

On the Problem of Regioselectivity in the Photochemical Ring-Opening Reaction of 3-Phenyl- and 3-Vinyl-Substituted Cyclopropenes to Indenes and 1,3-Cyclopentadienes[1]

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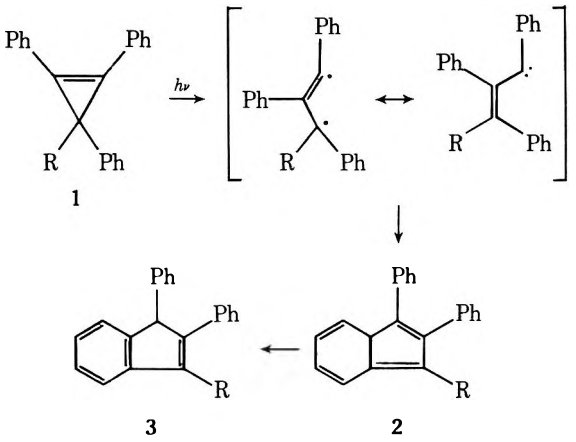
The photochemical rearrangement of several 3-phenyl- and 3-vinyl-substituted cyclopropenes to indenes and 1,3-cyclopentadienes has been studied. The rearrangements were shown to be derived from the π,π^* singlet state since triplet sensitization led to no reaction or else resulted in a 2 + 2 dimerization reaction. When an unsymmetrical cyclopropene such as 1,3-diphenyl-2-methyl-3-benzylcyclopropene (**9**) was used, a mixture of 1-methyl-2-phenyl-3-benzylindene (**10**; 80%) and 1-phenyl-2-methyl-3-benzylindene (**11**; 20%) was obtained. Irradiation of 1,3-diphenyl-2-methyl-3-vinylcyclopropene (**32**) produced a mixture of 3-methyl-1,2-diphenyl- (**27**), 1-methyl-2,3-diphenyl- (**28**), and 2-methyl-1,3-diphenyl-1,3-cyclopentadiene (**33**) as well as 1-methyl-2-phenyl-3-vinylindene (**34**) in good yield. The major products formed correspond to cleavage of the cyclopropene bond attached to the methyl group. Two fundamentally different mechanisms seem plausible. One path involves cyclopropene ring opening to give a 1,3-diradical intermediate which subsequently decays to a vinylcarbene. An alternate path involves π–π^* bridging in the excited singlet state to give a bicyclo[2.1.0]pentane diradical, which then undergoes a subsequent fragmentation. Some support for the carbene mechanism was obtained from the irradiation of 1-phenyl-2,3,3-trimethylcyclopropene (**52**). The distribution of methoxy ethers obtained from the irradiation of this compound in methanol also corresponds to cleavage of the cyclopropene bond attached to the methyl group.

The thermal and photochemical reactions of strained, small ring molecules have been extensively studied.[2] Cyclopropene is one of the simplest of such molecules in terms of chemical composition and at the same time perhaps the most strained of the compounds hitherto known, if strain energy is calculated per carbon atom.[3] Vinylcarbenes have frequently been proposed as intermediates in the thermal and photochemical reactions of cyclopropenes.[4–24] The mechanism for the interconversion of the cyclopropene ring and the corresponding bond-cleaved species continues to be of both theoretical and experimental interest. Extended Hückel calculations carried out on the parent vinylcarbene system suggest a triplet diradical type structure for the ground state of this system.[25–28] Recent ESR experiments by Arnold and coworkers[11] support this conclusion. These workers found that the irradiation of vinyldiazo compounds generates vinylcarbenes as stable triplet species. The temperature dependence of the ESR signal indicates that the triplet is the ground state and that the singlet state is not thermally populated within the temperature range (5–30 K) examined. More recent calculations by Davis, Goddard, and Bergman predict that the thermal ring-opening reaction of cyclopropene first proceeds to a diradical planar intermediate, which subsequently decays to a carbene.[28]

During the last few years the photochemistry of cyclopropene derivatives has attracted considerable interest. The photochemical behavior of this small ring system was shown to be markedly dependent on the multiplicity of the excited state involved.[11] Singlet states react by σ-bond cleavage to give products which can be attributed to vinylcarbenes.[9,10] In contrast, triplet states generated by sensitization techniques give 2 + 2 dimers.[29–32] The cyclopropene singlet is known to have a very inefficient ($<10^{-3}$) intersystem crossing efficiency,[32] which accounts for the absence of 2 + 2 dimers from direct irradiation experiments. One of the more frequently encountered photochemical reactions of 3-aryl-substituted cyclopropenes involves rearrangement to indenes.[7,8] Formally analogous to the vinylcyclopropane–cyclopentene isomerization, this rearrangement can also be effected by acid,[33] transition metals,[34–36] or heat.[5]

The reaction has been proposed to proceed via an isoindene intermediate (2) which subsequently undergoes a thermally allowed [1,5] sigmatropic shift to give the aromatic indene **3**.[5]



While several examples of this transformation have been reported, the photochemistry of unsymmetrically substituted cyclopropenes has remained uninvestigated.[37–39] We have therefore undertaken a careful study of the products and mechanism of the photolysis of several unsymmetrical 3-aryl- and 3-vinyl-substituted cyclopropenes. During the course of our investigation we encountered an unusual substituent effect on the mode of ring opening of these systems. In this paper we report our observations which, when taken together, present a consistent and satisfying mechanistic rationale for the ring-opening reaction.

Results

3-Phenyl-substituted cyclopropenes were prepared by treating variously substituted cyclopropenyl cations with Grignard reagents according to the general procedure of Breslow and co-workers.[40] In all the cases studied, nucleophilic attack by the Grignard reagent on the cyclopropenyl cation afforded the 1,2-diphenyl-substituted cyclopropene (**5**) as the major product. This is consistent with Breslow's previous observations in that nucleophilic attack occurs preferentially on the carbon atom of the cyclopropenyl cation which is best able to localize the positive charge.[40,41] The mixture of isomers could readily be separated by silica gel chromatography.

Irradiation of 3-methyl-1,2,3-triphenylcyclopropene (**7**) in benzene for relatively short periods of time provided 1,2-diphenyl-3-methylindene (**8**) in 75% isolated yield. The

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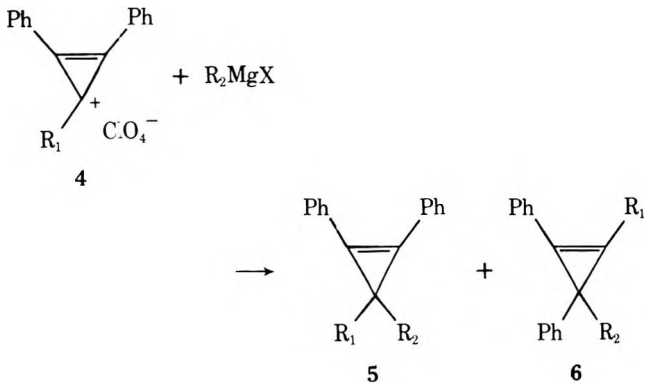
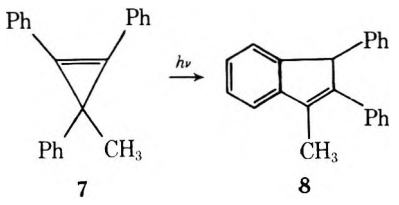
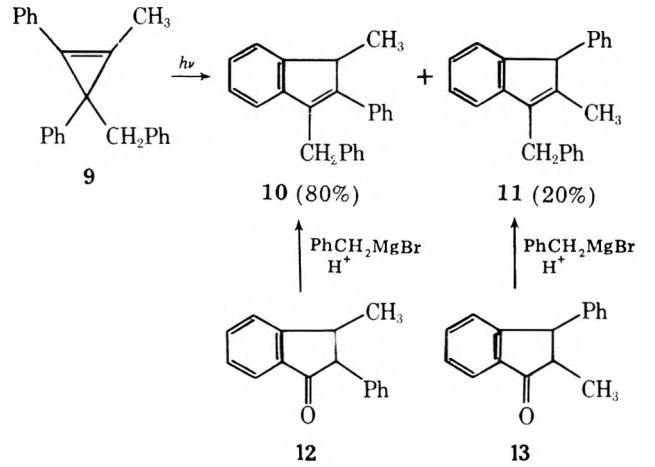


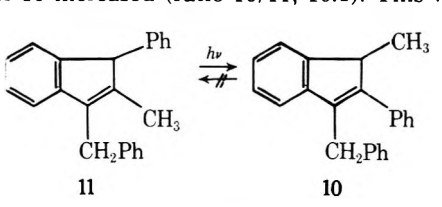
structure of this product was unambigously established by comparison with an authentic sample.



When the irradiation of an unsymmetrical cyclopropene such as 1,3-diphenyl-2-methyl-3-benzylcyclopropene (**9**) was carried out in benzene for 1 h, a 4:1 mixture of 1-methyl-2-phenyl-3-benzylindene (**10**) and 1-phenyl-2-methyl-3-benzylindene (**11**) was obtained. The structures of these indenes

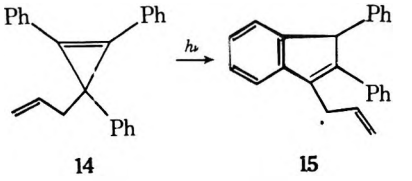


were confirmed by comparison with authentic samples prepared by treating 2-phenyl-3-methyl- (**12**) and 2-methyl-3-phenylindanone (**13**) with benzylmagnesium bromide, followed by dehydration of the resulting alcohols. A study of product distribution vs. the extent of irradiation established that the ratio of **10**/**11** varied as a function of time. At longer exposures, owing to a secondary photoreaction of **11**, the amount of **10** increased (ratio **10**/**11**, 10:1). This was independently demonstrated by the quantitative conversion of **11** to **10** in benzene under comparable photolytic conversions. The observed rearrangement represents an exchange of the indene 1 and 2 carbon atoms and is analogous to the process recently described by Morrison and Palensky[42] for related substituted indenes, except that in their case, the presence of an alkyl group at the 3 position completely quenched the photoreaction. The above rearrangement proceeds exclusively in one direction since the irradiation of indene **10** resulted in recovered starting material, even under lengthy photolytic conditions. It should be noted, however, that when the irradiation of cyclopropene **9** was carried out for short periods of time (10 min, <10% conversion) the ratio of indenes (**10**/**11**) was 4:1. This result clearly indicates that **10** is the predominant primary photoproduct and is not formed from **11** under the kinetic conditions employed. It is also important to note that the thermolysis of cyclopropene **9** gave indene **11** as the exclusive product. Thus, the excited-state and ground-state behavior of this small ring system are quite distinct.

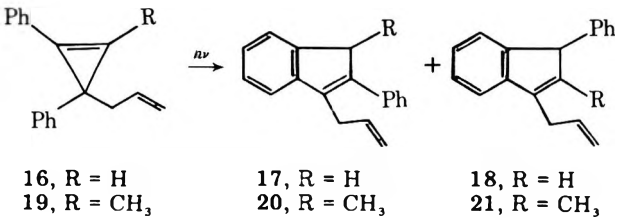


In order to help elucidate the correct mechanism for indene formation, the photochemistry of **9** was carried out in methanol. Under these conditions, no detectable quantities of indenes **10** and **11** were present in the crude photolysate. Unfortunately, all attempts to separate the complex mixture of photoproducts were unsuccessful. Nevertheless, examination of the NMR spectrum of the crude photolysate clearly showed the presence of several methoxy ethers and a number of triphenyl-substituted pentadienes. It should be noted that the indene skeleton is retained on irradiation in methanol and that the relative quantum yields for the disappearance of **9** are the same in methanol and benzene.

Attention was next turned to the photochemical behavior of 2-allyl-1,2,3-triphenylcyclopropene (**14**). We hoped that with this system the initially generated vinylcarbene would undergo internal cycloaddition to give a bicyclo[3.1.0]hex-2-ene. We had previously reported the successful utilization of such a process in proving the intermediacy of a vinylcarbene in the photolysis of 1,2-diphenyl-3-methyl-3-allylcyclopropene.[38] Irradiation of **14** in benzene, however, gave 3-allyl-1,2-diphenylindene (**15**), mp 79–81 °C, as the exclusive photoproduct. It would seem that if a vinylcarbene intermediate is involved in this reaction, the rate of cycloaddition of the intermediate with the neighboring double bond is not rapid enough to afford bicyclohexene in competition with indene formation. Also complicating matters here is the possibility of forming isomeric *cis*- and *trans*-vinylcarbenes.

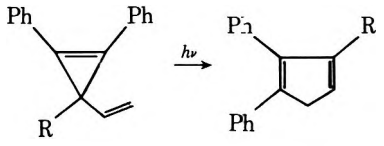


Additional examples of indene formation are provided by the photolysis of 3-allyl-1,3-diphenylcyclopropene (**16**) and 3-allyl-3-methyl-1,3-diphenylcyclopropene (**19**). The structures of the resulting photoproducts were verified by comparison with independently synthesized samples. In both of these cases, the major indene (**17** or **20**) formed (80%) was derived from cleavage of the cyclopropene bond attached to the R substituent. In neither case were we able to detect the presence of a bicyclo[3.1.0]hex-2-ene.



During our studies with the above 2-arylcyclopropenes, it occurred to us that a similar photoreaction should take place with the closely related 3-vinylcyclopropene system. In order

to establish this possibility, a number of 3-vinyl-substituted diarylcyclopropenes were prepared by treating variously substituted cyclopropenyl cations with vinyl Grignard reagents and separating the mixture of isomers formed by column chromatography. Although indenes are generally formed from the irradiation of 3-aryl-substituted cyclopropenes, the photolysis of 1,2,3-triphenyl-3-vinylcyclopropene (**22**) resulted

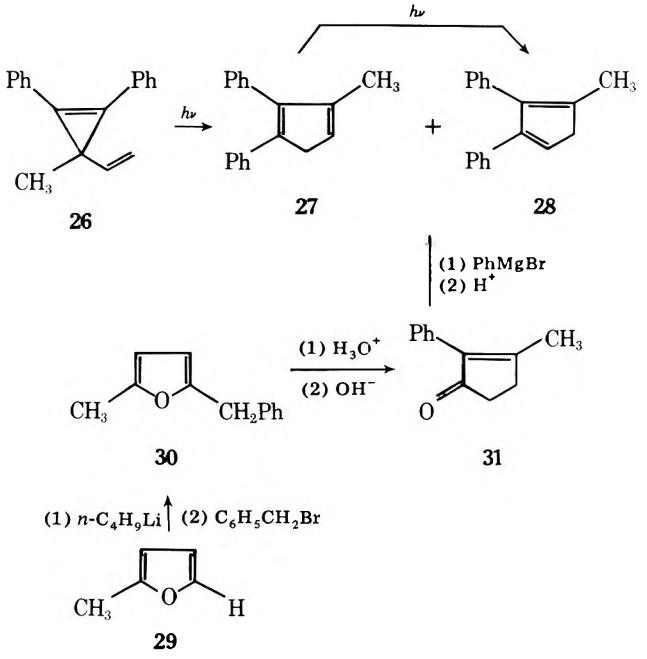


22, R = Ph
24, R = H
26, R = CH_3

23, R = Ph
25, R = H
27, R = CH_3

in the exclusive formation of 1,2,3-triphenyl-1,3-cyclopentadiene (**23**). Similar rearrangements were also found to occur with cyclopropenes **24** and **26**. The photolysis of these systems was sufficiently free of byproducts that the reaction can be considered to be of general synthetic utility for the construction of substituted 1,3-cyclopentadienes. The structures of the 1,3-cyclopentadienes were established by comparison with authentic samples (see Experimental Section).

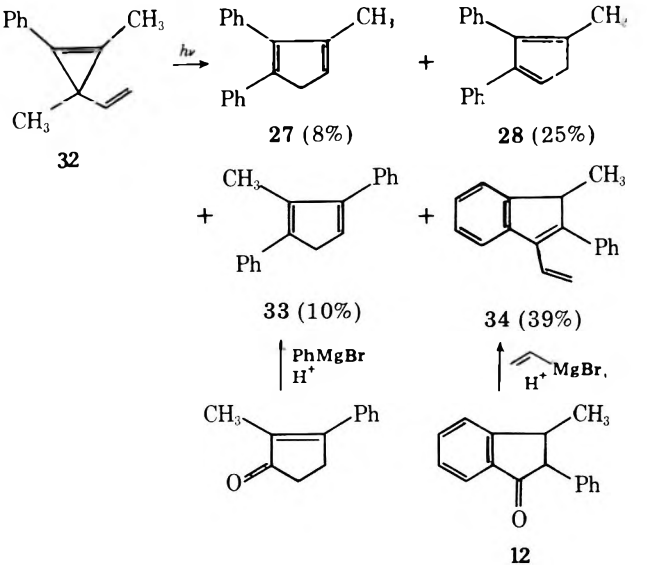
In the studies involving the photochemistry of cyclopropene **26**, considerable difficulty was experienced in isolating a pure sample of cyclopentadiene **27**. In addition to **27** (75%), a sig-



nificant quantity (ca. 25%) of the isomeric 1-methyl-2,3-diphenylcyclopentadiene (**28**) was present in the crude photolysate. The structures of both products were established by comparison with independently synthesized samples. The synthesis of 2-methyl-3-phenylcyclopentenone (**31**) involved the metalation of 2-methylfuran with butyllithium to give 2-lithio-5-methylfuran,[43] which was condensed with benzyl bromide. The resulting 2,5-disubstituted furan (**30**) was hydrolyzed to the corresponding diketone, which was subsequently subjected to a base-induced cyclization to afford cyclopentenone **31**. Treatment of this material with phenyl Grignard reagent followed by an acid-induced dehydration afforded a 1:3 mixture of cyclopentadienes **27** and **28**.

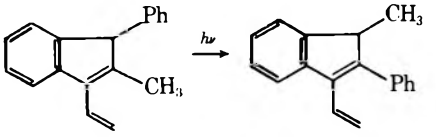
At first glance it would seem as though the formation of **28** is derived by means of a [1,5]sigmatropic hydrogen shift from cyclopentadiene **27**. McLean[44-46] and others[47,48] have shown that equilibration of 1,3-cyclopentadienes can be established through a purely thermal 1,5 migration of a hydrogen atom. This process is so facile that in certain systems it takes place at an appreciable rate even at room temperature.[45] If the above two cyclopentadienes were rapidly equilibrating at room temperature, then the ratio of **27**/**28** should be the same regardless of the method of generation. We note, however, that a different distribution of cyclopentadienes was obtained from the photolysis of **26** than from the acid-catalyzed dehydration of the benzylic alcohol derived from **31**. Furthermore, the ratio of the two cyclopentadienes derived from the photolysis of cyclopropene **26** varied as a function of time. With short exposures, cyclopentadiene **27** accounts for nearly all of the product produced. At longer exposures, owing to a secondary photoreaction of **27**, the amount of **28** increased. Thus, the presence of **28** in the crude photolysate derived from **26** can be attributed to a subsequent photoreaction of **27** rather than to a thermally induced 1,5-hydrogen shift.

We next turned our attention to the photochemistry of the isomeric 2-methyl-1,3-diphenyl-3-vinylcyclopropene (**32**) system in order to assess the regioselectivity of the bond cleavage reaction. Subjection of **32** to conditions similar to that used with **26** gave a mixture of 1-methyl-2,3-diphenyl- (**28**), 1,2-diphenyl-3-methyl- (**27**) and 2-methyl-1,3-diphenyl-



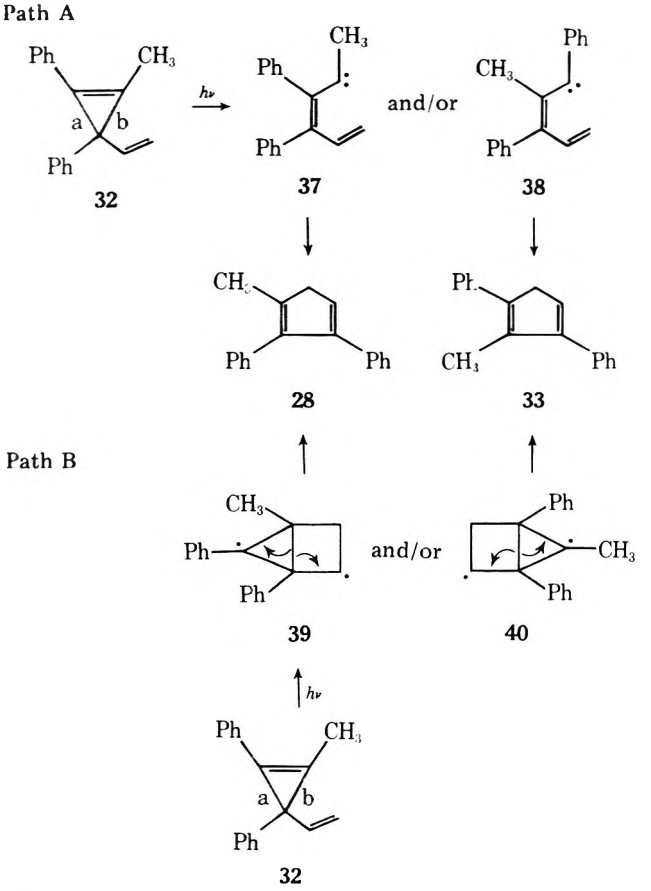
1,3-cyclopentadiene (**33**) as well as 1-methyl-2-phenyl-3-vinylindene (**34**) in good yield. The structures of **33** and **34** were based on their spectroscopic and analytical properties and were further confirmed by comparison with authentic samples.

The small amount (ca. 8%) of **27** present in the crude reaction mixture can be attributed to a thermally induced 1,5-hydrogen shift of the initially produced cyclopentadiene **28**. This contention stems from the fact that the photolysis of an enriched sample of **28** (containing **27** as the contaminant) does not produce additional quantities of **27**. It should also be noted that the isomeric 1-phenyl-2-methyl-3-vinylindene (**36**) was



not present in the crude photolysate. What complicates the problem here is that when an authentic sample of **36** was independently synthesized and subjected to irradiation, it quantitatively rearranged to indene **34**. This reaction is analogous to that previously described with the related ben-

Scheme I



zyl-substituted indene system (i.e., 11 → 12). As a consequence of this, the determination of the regioselectivity of bond cleavage of cyclopropene **32** is made more difficult. Nevertheless, examination of the crude photolysate by NMR spectroscopy at low conversions of **32** showed that no significant quantities of **36** were present. Thus, the major products obtained from **32** correspond to the preferential cleavage of the cyclopropene bond attached to the methyl group (ratio (**27** + **28** + **34**)/**33** 7:1).

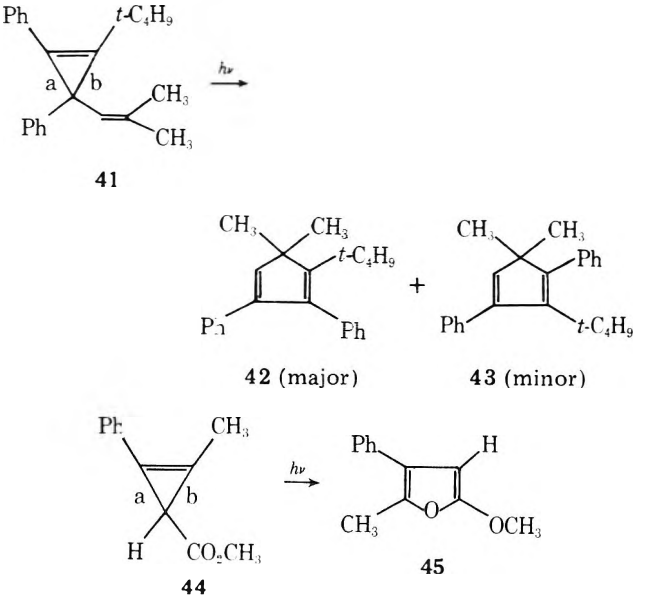
The excited state responsible for the photorearrangement of the 3-aryl- and 3-vinyl-substituted cyclopropenes is a π–π^* singlet since sensitization with thioxanthone led to no reaction with cyclopropenes **7**, **9**, **22**, and **26** and gave a 2 + 2 dimer with **24**. This is consistent with DeBoer's earlier observation that the intersystem crossing efficiencies of aryl-substituted cyclopropenes are close to 0.[32] Thus, it can be concluded that both the 1,3-cyclopentadienes and indenes arise from the singlet excited state of the cyclopropene and that the corresponding triplet does not undergo a ring-opening reaction. Recent experimental results by Pincock and Moutsokapas[49] with an optically active cyclopropene also support the argument that the cyclopropene triplet does not ring open. There seems to be a barrier on the cyclopropene–vinylcarbene triplet surface which does not exist on the singlet surface and which accounts for the difference in photobehavior of the singlet and triplet states.[50]

Quantum yield studies were carried out on a merry-go-round apparatus equipped with a series of 3000-Å lamps. The quantum efficiencies for product formation from cyclopropenes **22**, **24**, and **26** were 0.027, 0.031, and 0.022. Although the reaction efficiency of the rearrangement was quite low, the photolysis was free of byproducts, and the isolated yields of cyclopentadienes were high. The low quantum efficiencies will be discussed below in connection with the reaction mechanism.

Discussion

The mechanism by which these substituted cyclopropenes undergo rearrangement is of considerable interest. Two fundamentally different mechanisms seem possible and are presented in Scheme I. Path A involves cyclopropene ring opening to give a butadienylcarbene followed by electrocyclic ring closure. In the case of the 3-aryl-substituted cyclopropene system, the initially formed isoindene (i.e., **2**) would be expected to undergo a rapid 1,5-hydrogen shift to give an indene derivative (i.e., **3**). The above route bears a strong similarity to mechanisms previously suggested to rationalize the products derived from substituted cyclopropenes on electronic excitation.[4–23,38] The alternate path (B) involves π–π bridging of the excited cyclopropene to give a diradical intermediate which subsequently cleaves to produce either the isoindene or 1,3-cyclopentadiene ring system. The bridging and cleavage steps are related to the first two formal steps of a di-π-methane rearrangement.[51] The two mechanistic possibilities illustrated in Scheme I make use of the unsymmetrical 3-vinyl-substituted cyclopropene ring system **32**. Analogous pathways can also be drawn for indene formation from the irradiation of the 3-aryl-substituted cyclopropenes.

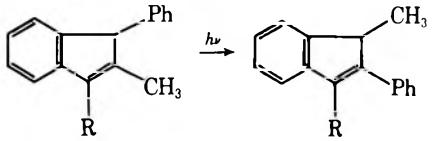
The most dramatic result requiring discussion is the unusual substituent effect on the mode of ring opening of the unsymmetrical diarylcyclopropenes. In all the cases studied, the major product (indene or cyclopentadiene) formed was derived from cleavage of the cyclopropene bond attached to the methyl group (bond b). Similar findings have recently been made by others in related systems. Thus, Zimmerman and Aasen report that cyclopentadiene **42** is the major cyclo-



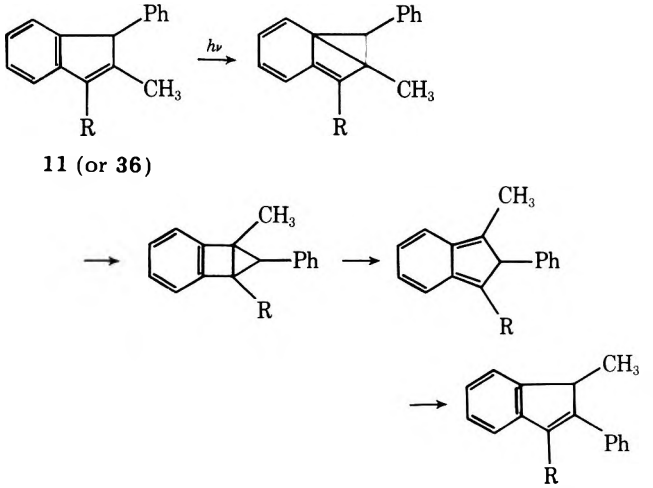
pentadiene produced from the direct irradiation of cyclopropene **41**.[39] Similarly, Pincock and Moutsokapas have shown that methyl 1-methyl-2-phenylcyclopropen-3-carboxylate (**44**) is converted exclusively to 2-methoxy-5-methyl-4-phenylfuran (**45**) on direct irradiation.[49] The formation of this furan occurs by cleavage of the cyclopropene single bond which is methyl- rather than phenyl-substituted.

The molecular forces controlling this regioselectivity require comment. It is well-known that phenyl substituents stabilize free radicals, and thereby lower carbon–carbon bond energies in saturated three-membered rings.[52,53] Were this effect to operate in the cyclopropene system, methylphenylcyclopropene **32** should undergo preferential cleavage of bond a. We note, however, that the major cyclopentadiene (or indene) produced corresponds to cleavage of bond b. In the Results

it has been pointed out that this selectivity is a result of a kinetic preference and not to either interconversion of products or selective destruction of the indene corresponding to bond a cleavage. It should be noted, however, that on extended irradiation, indene **11** (and/or **36**) quantitatively rearranges to the corresponding isomer **10** (and/or **34**). This photorearrangement may be depicted as proceeding via the following steps: (1) an electrocyclic ring closure, (2) a [1,3]sigmatropic shift, (3) ring opening to an isoindene, and (4) a [1,5]sigmatropic hydrogen shift. The above process is analogous to that recently described by Morrison and Palensky for related substituted indenes.[42] Careful monitoring of the arylcyclopropene photolyses for short periods of time (<10% conversion) clearly shows that the ratio of the initially observed indenes is not affected by this subsequent interconversion.



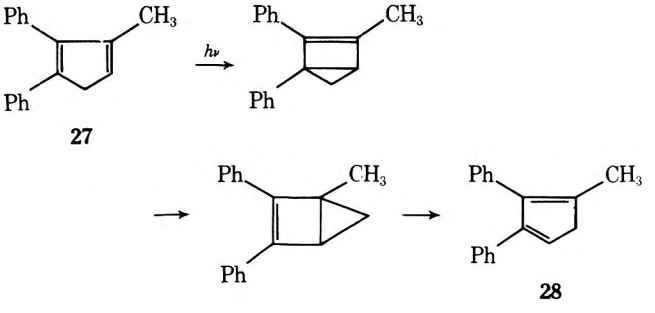
11, R = $CH_2C_6H_5$ **10**, R = $CH_2C_6H_5$
36, R = CH=CH_2 **34**, R = CH=CH_2



11 (or **36**)

10 (or **34**)

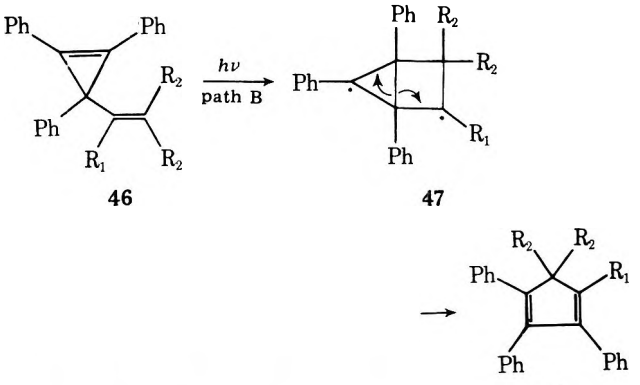
A mechanism similar to that outlined above could also account for the formation of cyclopentadiene **28** from **27**. As was pointed out in the Results, the presence of **28** in the crude photolysate from cyclopropene **26** is due to a secondary photoreaction of the initially generated cyclopentadiene **27** rather than to a thermally induced [1,5]sigmatropic hydrogen shift. This rearrangement may be proceeding by two consecutive 1,3-hydrogen shifts. Alternatively, the rearrangement may be envisioned as occurring by (1) a ring closure, (2) a [1,3]sigmatropic shift, and (3) a subsequent ring-opening reaction. The first and last steps of the above sequence are well-documented reactions.[54–58] In fact, Baldwin and Andrews[59] have recently reported a photochemical carbon skeleton rearrangement of cyclopentadiene which proceeds by a photochemical 1,3-carbon migration of a transient bicyclo[2.1.0]-pent-2-ene valence isomer, thus providing an excellent analogy for this pathway.



27

28

Turning now to the matter of regioselectivity of the cyclopropene ring opening, we note that the predominant scission of bond b can be nicely accommodated by path B (see Scheme I). According to this mechanism π–π bridging would be expected to give the most stable diradical (**39**) and thus lead to the preferential formation of 1-methyl-2,3-diphenyl-1,3-cyclopentadiene (**28**). A similar explanation would also account for the regioselectivity observed for indene formation with cyclopropenes **9**, **16**, and **19**. Zimmerman and Aasen[39] have noted that the quantum yield for the rearrangement of cyclopropene **46b** is twice as large as that for **46a**. This is a reasonable corollary of path B since π–π bridging of **46b** to give a housane diradical (i.e., **47b**) would be expected to be facilitated over **47a** as a result of the phenyl group being located at a center bearing odd electron density. These workers have also found that cyclopropene **46c** reacts with a lower direct irradiation efficiency than **46a**. This also fits the diradical mechanism (path B) since the isopropylidene group must approach the excited cyclopropene π bond, and steric hindrance should make this process more difficult. As was pointed out by other investigators,[60,61] quantum yields are not necessarily directly related to excited-state rate constants. Nevertheless, the above data does suggest that path B is a very reasonable possibility.



46 **47** **48**

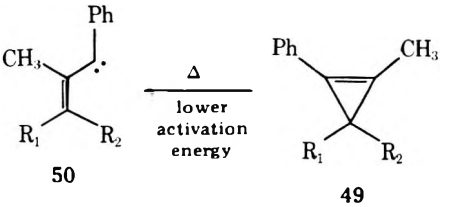
a, $R_1 = R_2 = H$; **b**, R_1 = Ph, R_2 = H; **c**, R_1 = H, $R_2 = CH_3$

According to the carbene mechanism for cyclopentadiene or indene formation (path A, Scheme I), preferential formation of the more stabilized carbene **38** (phenyl-substituted) might be expected. This is not the case. It should be pointed out that theory predicts[28] that it is the 1,3-diradical singlet state which results on thermal opening of the cyclopropene ring. This may also be the case for the electronically excited singlet state. The initially produced 1,3 diradical may then decay to the carbene, which could undergo subsequent reactions characteristic of a singlet vinylcarbene. Thus, one possibility to account for the preferential bond b cleavage (carbene route) is that the initially generated vinyl radical is inductively destabilized by the attached phenyl group. A great deal of evidence can be cited to support the thesis that vinyl-free radicals possess sp^2 hybridization and a low inversion barrier for radical equilibration.[62–65] Conjugation of a radical center in an sp^2-hybridized orbital with an adjacent phenyl group may not be significant as a result of the high degree of strain that would be generated by radical delocalization into the phenyl ring. On the other hand, a vinyl radical containing an attached alkyl group could be stabilized by a favorable nonconjugative interaction, which is of course what is implied in the term "inductive effect".[66]

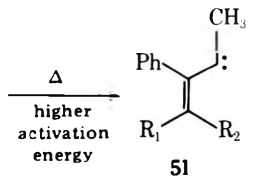
Alkyl-substituted cyclopropenes are known to decompose with activation energies in the range of 30–40 kcal/mol. For example, Bergman and co-workers have studied the thermal racemization of optically active 1,3-diethylcyclopropene.[12] These workers have suggested that ring cleavage and rotation occur simultaneously in this system, leading to a vinylcarbene intermediate. The activation energy for racemization was found to be 32.6 kcal/mol. Although a racemization experiment on an appropriately 1,2-diaryl-substituted cyclopropene was not carried out, Battiste and co-workers have examined the products formed on pyrolysis of a number of tetraaryl-substituted cyclopropenes.[5] These molecules rearrange to indenes by a process much like the one we have been discussing with an activation energy of 40 kcal/mol. This 7-kcal difference in the ring-opening step suggests that phenyl groups can affect the C–C single bond energies in cyclopropenes in a strikingly different manner than that encountered with the related cyclopropane ring system.[52,53]

If the "inductive destabilization" rationale for bond cleavage were correct, one might expect that the thermal ring opening of an unsymmetrical cyclopropene would follow the same general pattern as that encountered photochemically. This was not the case. Thus, thermolysis of cyclopropene **9** afforded indene **11** (bond a cleavage) as the exclusive product. It would appear, therefore, that inductive destabilization of the initially generated vinyl radical by the attached phenyl ring can not account for the regioselectivity of bond cleavage in the excited state since this argument demands similar behavior on thermolysis. Recent MO calculations by Pincock and Boyd[50] suggest a reasonable interpretation of the thermal results. These workers have found that the presence of a vinyl and phenyl group on the cyclopropene double bond opposite the σ bond which is breaking results in a substantial increase (ca. 8 kcal/mol) in the activation barrier for bond cleavage. Their results suggest that cross conjugated carbenes such as **51** are less stable than linearly conjugated systems like **50**. This explanation also accounts for the very high activation energy (40 kcal/mol) observed in the tetraphenylcyclopropene pyrolysis.[5]

An alternate explanation which could account for the observed photochemical regioselectivity (carbene route) involves reversible cyclopropene ring opening followed by rate-limiting cyclopentadiene formation. The fact that vinylcarbene intermediates generated from the decomposition of vinyldiazo



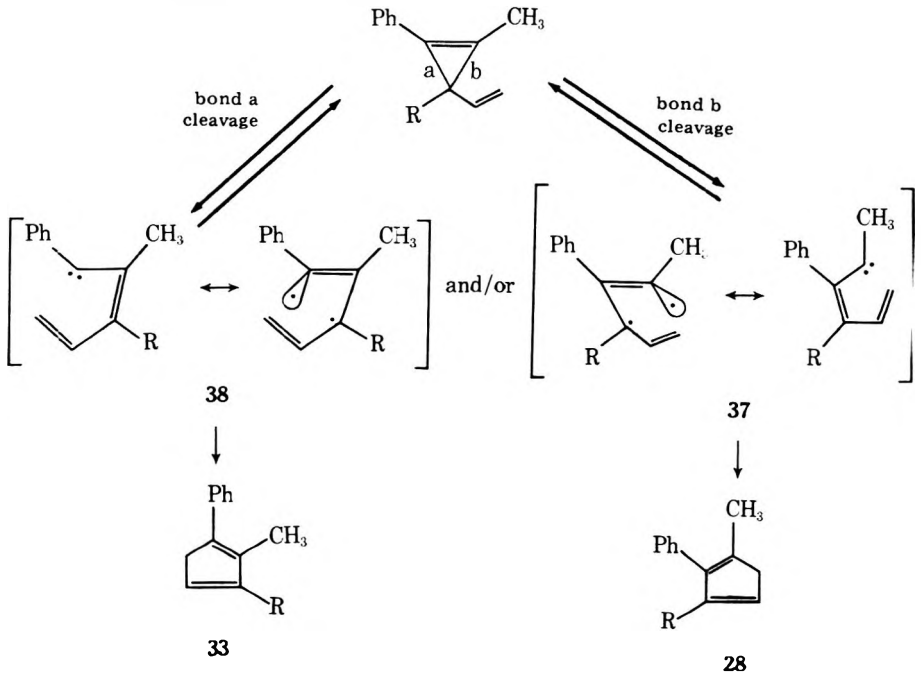
50 49



51

compounds[67,68] give predominantly cyclopropene products provides some support for this suggestion. In fact, the ring closure of vinylcarbenes is the basis of the synthetic procedures used for the preparation of cyclopropenes.[67–77] Bergman and co-workers have also found that the vinylcarbene intermediate generated from the pyrolysis of 1,3-diethylcyclopropene undergoes ring closure nine times faster than it goes on to product.[12] Moreover, recent results with the optically active cyclopropene ester **44** have shown that photochemical racemization occurs 2.5 times as fast as conversion to furan **45**.[49] The low quantum efficiency observed for the singlet states of the 3-aryl- and 3-vinylcyclopropenes (Φ ca. 0.02) can also be attributed to a rapid return of the carbene intermediate to the cyclopropene ring. This reversibility could easily represent the major deactivation pathway for these systems. Thus, the possibility exists that the distribution of cyclopentadienes (or indenes) is a result of the greater reactivity of the methyl-substituted carbene **37** over the phenyl-substituted isomer **38**. Since the quantum yields are so low, it may be possible that the observed regioselectivity is the result of some rate constant other than ring opening. The effects noted only correspond to fractions of kilocalories in pathway energy differences.

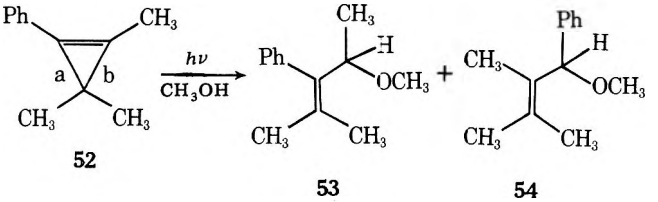
Still another possibility to account for the observed regioselectivity involves the close approach of the excited singlet surface of cyclopropene **49** with the ground-state surfaces of vinylcarbenes **50** and **51**. The preferential cleavage of the cyclopropene bond attached to the methyl group agrees well with the "funnel theory" of excited-state to ground-state conver-



sions as outlined principally by Michl.[78] Close approach of the two surfaces greatly enhances internal conversion and therefore gives a route for excited singlet cyclopropene to open to vinylcarbene and then either return to ground-state cyclopropene or rearrange to the 1,3-cyclopentadiene or indene. Since the carbene derived from bond b cleavage (i.e., **37**) is higher lying than that derived from bond a cleavage (i.e., **38**), it could be more easily funneled into from the excited singlet surface of the cyclopropene.

In order to help distinguish between paths A and B (see Scheme I), the photochemistry of a representative 3-aryl- (**9**) and 3-vinylcyclopropene (**24**) was carried out in methanol. The complete suppression of indene formation with cyclopropene **9** is consistent with the formation of a vinylcarbene intermediate which is trapped by protonation in methanol to give an allyl cation.[79] Subsequent loss of a proton or nucleophilic attack by methanol could, in principle, afford four different methoxy ethers and numerous *cis*- and *trans*-pentadiene isomers. The methanol results with cyclopropene **9**, while not very clean, are highly suggestive of the involvement of a vinylcarbene in the formation of the indene skeleton. The trapping experiment was unsuccessful with the 3-vinylcyclopropene system. The only product isolated here was 1,2-diphenyl-1,3-cyclopentadiene (**25**). Failure to trap a carbene intermediate derived from **24** does not necessarily eliminate this species as a reaction intermediate. The absence of methanol insertion products with this system may be due to the facile intramolecular cyclization path available to the butadienyl carbene. The probability of trapping a vinylcarbene derived from the 3-arylcyclopropene ring would be expected to be greater than that for the 3-vinyl system since the cyclization step with the former would involve a loss of aromaticity and therefore should proceed at a slower rate. Alternatively, the vinyl-substituted cyclopropene system may rearrange to the 1,3-cyclopentadiene via path B, whereas a vinylcarbene intermediate (path A) may operate in indene formation.

Some additional support for the carbene mechanism was obtained from the irradiation of 1-phenyl-2,3,3-trimethylcyclopropene (**52**). The only products obtained from the irradiation of **52** in methanol are methoxy ethers **53** (78%) and



52 53 54

54 (9%). The identity of these compounds was established by comparison with independently synthesized samples (see Experimental Section). It is particularly worthy to note that the distribution of the methoxy ethers obtained corresponds to preferential bond b cleavage (78%) and is closely related to the results encountered with the 3-aryl- and vinyl-substituted cyclopropenes. In all of these cases, the major product is derived from cleavage of the cyclopropene bond attached to the methyl group. Even though cyclopropene **39** does not contain a π bond at the the 3 position, it still prefers to undergo bond b fragmentation. The quantum yield for ether formation is identical ($\Phi = 0.03$) to that for cyclopentadiene ($\Phi = 0.03$) or indene ($\Phi = 0.03$) formation. We conclude therefore that the bulk of the evidence is compatible with the involvement of a vinylcarbene intermediate in the formation of the indene ring system. By analogy, one could argue that the same mechanism also holds with the vinylcyclopropenes, especially since the distribution of products obtained from the irradiation of the unsymmetrical system (i.e., **32**) is similar to that obtained from the photolysis of cyclopropene **52**. It should be pointed out, however, that a fortuitous distribution of products could be occurring here. Since it was not possible to trap a carbene with any of the vinylcyclopropenes, the rearrangement of this system may be proceeding by a different pathway (i.e., path B). Further work is necessary to establish this point.

Experimental Section[80]

Irradiation of 3-Methyl-1,2,3-triphenylcyclopropene (7) in Benzene. A solution containing 100 mg of 3-methyl-1,2,3-triphenylcyclopropene[81] (**7**) in 150 mL of benzene was irradiated for 1 h under an argon atmosphere with a 550-W Hanovia lamp equipped with a Pyrex filter sleeve. Removal of the solvent under reduced pressure left a pale yellow solid which was recrystallized from acetic acid to give 75 mg (75%) of 1,2-diphenyl-3-methylindene (**8**): mp 90–91 °C; IR (KBr) 3.30, 3.34, 6.24, 6.71, 6.82, 6.90, 6.96, 7.28, 9.31, 12.73, 13.18, 13.35, 13.49, 13,85, 14.37 μm; UV (95% ethanol) 295 nm (ϵ 16 700), 230 (15 800); NMR ($CDCl_3$, 100 MHz) τ 7.68 (d, 3 H, J = 2.0 Hz), 5.09 (q, 1 H, J = 2.0 Hz), 2.6–3.10 (m, 14 H); *m/e* 280 (M^+, base), 267.

Anal. Calcd for $C_{22}H_{18}$: C, 93.57; H, 6.43. Found: C, 93.21; H, 6.61.

The structure of this material was further established by comparison with an authentic sample prepared according to the procedure of Koelsch and Johnson.[82]

Preparation of 1,3-Diphenyl-2-methyl-3-benzylcyclopropene (9). To a stirred slurry containing 12 g of 1,2-diphenyl-3-methylcyclopropenyl perchlorate[83] in 250 mL of anhydrous tetrahydrofuran at −78 °C was added 50 mL of a 1.0-M solution of benzylmagnesium chloride in ether. The mixture was stirred at 4 °C for 4 h and at room temperature for 12 h. After quenching the solution with a saturated ammonium chloride solution, the organic layer was washed with water and dried over magnesium sulfate. Removal of the solvent left a yellow oil which was chromatographed over silica gel using a 15% benzene–hexane mixture as the eluent. The first fraction isolated from the column contained 3.05 g of 1,2-diphenyl-3-benzyl-3-methylcyclopropene (27%): mp 58–59 °C; IR (neat) 3.29, 3.43, 5.50, 6.24, 6.69, 6.91, 7.29, 9.32, 13.18, 13.45, 14.24, 14.58 μm; NMR ($CDCl_3$, 100 MHz) τ 8.59 (s, 3 H), 7.06 (s, 2 H), 2.56–3.05 (m, 15 H); UV (95% ethanol) 339 nm (ϵ 18 700), 322 (24 700), 230 (18 900); *m/e* 296 (M^+), 281, 205 (base), 178

Anal. Calcd for $C_{23}H_{20}$: C, 93.20; H, 6.80. Found: C, 92.86; H, 6.94.

The second component isolated from the chromatography column contained 6.58 g of a white crystalline solid, mp 47–48 °C, whose structure was assigned as 1,3-diphenyl-2-methyl-3-benzylcyclopropene (**9**) on the basis of the following data: IR (KBr) 3.32, 5.40, 6.24, 6.73, 6.95, 9.31, 13.20, 14.43 μm; NMR ($CDCl_3$, 100 MHz) τ 7.84 (s, 3 H), 6.66 (d, 1 H, J = 13.0 Hz), 6.58 (d, 1 H, J = 13.0 Hz), 2.7–3.2 (m, 15 H); UV (95% ethanol) 264 nm (ϵ 10 550); *m/e* 296 (M^+), 205 (base), 91.

Anal. Calcd for $C_{23}H_{20}$: C, 93.20; H, 6.80. Found: C, 92.90; H, 7.01.

Irradiation of 1,3-Diphenyl-2-methyl-3-benzylcyclopropene (9). A solution containing 113 mg of **9** in 250 mL of benzene was irradiated with a 450-W Hanovia lamp equipped with a Corex filter sleeve. Removal of the solvent under reduced pressure left a yellow oil which was shown to contain two components in a 4:1 ratio by NMR analysis. Chromatography of the mixture over silica gel resulted in the separation of the two products. The major component (80%) of the reaction mixture was identified as 1-methyl-2-phenyl-3-benzylindene (**10**), mp 74–75 °C, on the basis of its spectroscopic properties: IR (neat) 3.30, 6.24, 6.71, 6.83, 6.89, 12.28, 14.32 μm; NMR ($CDCl_3$, 100 MHz) τ 8.78 (d, 3 H, J = 8.0 Hz), 6.12 (q, 1 H, J = 8.0 Hz), 6.02 (s, 2 H), 2.6–3.1 (m, 15 H); UV (95% ethanol) 296 nm (ϵ 16 800), 229 (15 200); *m/e* 296 (M^+), 205 (base), 204, 190, 177, 164, 91. Anal. Calcd for $C_{23}H_{20}$: C, 93.20; H, 6.80. Found: C, 93.33; H, 6.79.

The structure of this material was unambiguously verified by comparison with an authentic sample. A 1.8-g sample of 2-phenyl-3-methylindanone (**12**)[82] was treated with 12 mL of a 1.0-M solution of benzylmagnesium chloride in ether at 0 °C followed by heating at reflux for 1.5 h. The reaction mixture was hydrolyzed with a saturated ammonium chloride solution, and the ether layer was washed with water and dried over magnesium sulfate. The solvent was removed under reduced pressure, and the crude residue was added to 9 mL of glacial acetic acid, 1 mL of concentrated sulfuric acid, and 0.4 mL of water. The mixture was stirred for 15 min at room temperature and then poured onto ice water and extracted with ether. The ethereal layer was washed with a saturated sodium bicarbonate solution and water, and then dried over magnesium sulfate. The solvent was re-

moved under reduced pressure, and the crude residue was purified by silica gel chromatography using a 5% ether–hexane mixture as the eluent. The major component isolated was identical in every detail with a sample of 1-methyl-2-phenyl-3-benzylindene (**10**) obtained from the irradiation of **9**.

The minor component isolated from the crude photolysate obtained from the irradiation of **9** was identified as 1-phenyl-2-methyl-3-benzylindene (**11**) on the basis of its characteristic data: mp 103–104 °C; IR (KBr) 6.25, 6.72, 8.43, 9.31, 9.72, 10.60, 13.26, 13.80, 14.54 μm; NMR ($CDCl_3$, 100 MHz) τ 8.12 (s, 3 H), 6.12 (s, 2 H), 5.70 (s, 1 H), 2.68–3.2 (m, 14 H); UV (95% ethanol) 265 nm (ε 9400); *m/e* 296 (M^+), 206, 205 (base), 91.

Anal. Calcd for $C_{23}H_{20}$: C, 93.20; H, 6.80. Found: C, 93.34; H, 6.49.

The structure of this material was further verified by comparison with an authentic sample. To a 2.4-g sample of 2-methyl-3-phenylindanone (**13**)[84] dissolved in 100 mL of ether was added 16 mL of a 1.0-M solution of benzylmagnesium chloride in ether. The mixture was stirred for 2 h at 25 °C and then hydrolyzed with a saturated ammonium chloride solution. The ethereal layer was separated, washed with water, and dried over magnesium sulfate. Removal of the solvent left a crude oil which was taken up in 45 mL of glacial acetic acid which contained 5 mL of concentrated sulfuric acid and 2 mL of water. The mixture was stirred at room temperature for 30 min, poured onto ice water, and extracted with ether. The ether layer was washed with a saturated sodium bicarbonate solution and dried over magnesium sulfate. Removal of the solvent left a yellow oil which solidified on standing. Recrystallization of this material from ethanol gave 1.2 g (37%) of 1-phenyl-2-methyl-3-benzylindene (**11**), mp 103–104 °C, which was identical in every detail with the minor component isolated from the photolysis of cyclopropene **9**.

When the irradiation of 1,3-diphenyl-2-methyl-3-benzylcyclopropene (**9**) was carried out for 2.5 h, the only product present in the crude photolysate was 1-methyl-2-phenyl-3-benzylindene (**10**). Further studies showed that 1-phenyl-2-methyl-3-benzylidene (**11**) was quantitatively converted to 1-methyl-2-phenyl-3-benzylindene (**10**) on irradiation. Thus, a 91-mg sample of **11** in 250 mL of benzene was irradiated for 2.5 h. Removal of the solvent under reduced pressure followed by thick-layer chromatography gave a pure sample of 1-methyl-2-phenyl-3-benzylindene (**10**) as the only isolable product.

Preparation of 3-Allyl-1,2,3-triphenylcyclopropene (14). To a stirred slurry containing 0.5 g of triphenylcyclopropenyl bromide[85] in 40 mL of anhydrous tetrahydrofuran at −78 °C was added 5 mL of a 0.67-N allylmagnesium bromide solution in ether. The mixture was stirred for 2 h and then allowed to warm to room temperature. After quenching the solution with a saturated ammonium chloride solution, the organic layer was washed with water and dried over magnesium sulfate. Removal of the solvent left a yellow oil which was chromatographed on a thick-layer plate to give 0.31 g (70%) of 3-allyl-1,2,3-triphenylcyclopropene (**14**) as a crystalline solid: mp 64–65 °C; IR (KBr) 3.49, 3.64, 5.67, 6.26, 6.43, 6.89, 7.02, 9.52, 10.19, 11.09, 13.34, 14.64 μm; UV (95% ethanol) 333 nm (ε 22 000), 316 (26 600), 228 (28 700); NMR ($CDCl_3$, 60 MHz) τ 6.80 (d, 2 H, *J* = 7.5 Hz), 5.05 (d, 1 H, *J* = 17.0 Hz), 4.95 (d, 1 H, *J* = 7.5 Hz), 4.50–3.80 (m, 1 H), 2.20–3.00 (m, 15 H); *m/e* 308 (M^+), 306, 267 (base).

Anal. Calcd for $C_{24}H_{20}$: C, 93.46; H, 6.54. Found: C, 93.16; H, 6.66.

Irradiation of 3-Allyl-1,2,3-triphenylcyclopropene (14) in Benzene. A solution containing 100 mg of **14** in 150 mL of benzene was irradiated for 1 h under an argon atmosphere with a 550-W Hanovia lamp equipped with a Pyrex filter sleeve. Removal of the solvent under reduced pressure left a yellow oil which slowly crystallized on standing to give 83 mg (83%) of 3-allyl-1,2-diphenylindene (**15**): mp 83–85 °C; IR (KBr) 3.28, 3.30, 6.10, 6.24, 6.69, 6.80, 6.89, 9.30, 9.71, 10.05, 10.95, 13.23, 14.30 μm; UV (95% ethanol) 295 nm (ε 19 300), 228 (20 500); NMR ($CDCl_3$, 100 MHz) τ 6.54 (dd, 2 H, *J* = 5.0, 2.0 Hz), 5.09 (t, 1 H, *J* = 2.0 Hz), 4.87 (dd, 1 H, *J* = 8.0, 1.5 Hz), 5.19 (dd, 1 H, *J* = 17.0, 1.5 Hz), 3.6–4.1 (m, 1 H), 2.6–3.1 (m, 18 H); *m/e* 308 (M^+), 268, 267 (base), 265.

The structure of this material was unambiguously verified by comparison with an independently synthesized sample. To a solution containing 2.6 g of 2,3-diphenylindanone[86] in 75 mL of ether and 25 mL of benzene was added 5 mL of a 2.37-M solution of allylmagnesium chloride in tetrahydrofuran. The reaction mixture was stirred for 1 h at 25 °C, and then a saturated ammonium chloride solution was added. The organic layer was separated, washed with water, and dried over magnesium sulfate. Removal of the solvent left 2.9 g of a yellow oil which was added to a mixture containing 17 mL of acetic acid, 2 mL of sulfuric acid, and 1 mL of water. The resulting mixture was stirred for 5 min at 25 °C and then diluted with water and neutralized with sodium bicarbonate. The aqueous mixture was extracted with ether and dried over magnesium sulfate. Removal of the solvent under reduced pressure left 2.5 g of 3-allyl-1,2-diphenylindene (**15**), which was identical in every detail with the material obtained from the irradiation of **14**.

Preparation of 3-Allyl-1,3-diphenylcyclopropene (16). To a stirred suspension containing 6.0 g of 1,2-diphenylcyclopropenyl perchlorate[87] in 200 mL of anhydrous tetarhydrofuran at −78 °C was added 50 mL of a 0.67-M allylmagnesium bromide solution in ether. The mixture was stirred for 4 h at −78 °C and then allowed to warm to room temperature. At the end of this time a saturated ammonium chloride solution was added, and the organic layer was separated, washed with water, and dried over magnesium sulfate. Removal of the solvent left a clear yellow oil which was chromatographed on a silica gel column using hexane as the eluent. The first component isolated contained 1.7 g (41%) of a clear oil whose structure was assigned as 3-allyl-1,2-diphenylcyclopropene on the basis of the following data: IR (neat) 3.29, 3.46, 5.52, 5.99, 6.24, 6.70, 6.92, 9.32, 9.72, 10.92, 13.24, 14.52 μm; UV (95% ethanol) 336 nm (ε 20 800), 318 (27 900), 310 (23 800), 228 (18 900), 225 (18 200); NMR ($CDCl_3$, 100 MHz) τ 7.48–7.88 (m, 3 H), 4.99 (d, 1 H, *J* = 9.0 Hz), 4.92 (c, 1 H, *J* = 18.0 Hz), 3.72–4.20 (m, 1 H), 2.20–2.80 (m, 10 H); *m/e* 232 (M^+), 191, 178 (base), 91.

Anal. Calcd for $C_{18}H_{16}$: C, 93.06; H, 6.94. Found: C, 92.69; H, 7.09.

The second component isolated from the column contained 0.8 g (20%) of a clear oil whose structure was assigned as 3-allyl-1,3-diphenylcyclopropene (**16**) on the basis of its spectral data:[88] IR (neat) 3.48, 3.63, 5.88, 6.28, 6.43, 6.92, 7.12, 9.48, 10.18, 11.08, 13.18, 14.48 μm; UV (95% ethanol) 260 nm (ε 12 400); NMR ($CDCl_3$, 100 MHz) τ 7.09 (d, 2 H, *J* = 5.5 Hz), 4.95–5.20 (m, 2 H), 3.8–4.6 (m, 1 H), 2.4–3.0 (m, 11 H); *m/e* 232 (M^+), 192, 191 (base), 91.

Irradiation of 3-Allyl-1,3-diphenylcyclopropene (16). A solution containing 100 mg of **16** in 150 mL of hexane was irradiated for 10 min under an argon atmosphere with a 550-W Hanovia lamp equipped with a Vycor filter sleeve. Removal of the solvent under reduced pressure left a light yellow oil which contained two components. The major component (80%) could be obtained in pure form by column chromatography and was identified as 2-phenyl-3-allylindene (**17**) on the basis of its spectral properties and by comparison with an independently synthesized sample: IR (neat) 3.20, 3.63, 6.25, 6.39, 6.87, 7.01, 7.11, 7.14, 7.34, 9.84, 10.19, 11.04, 13.29, 13.59, 14.54 μm; UV (95% ethanol) 293 nm (ε 18 700), 227 (11 900); NMR ($CDCl_3$, 100 MHz) τ 6.52 (dt, 2 H, *J* = 6.0, 1.5 Hz), 6.25 (s, 2 H), 4.68–5.02 (m, 2 H), 3.68–4.09 (m, 1 H), 2.40–2.90 (m, 9 H); *m/e* 232 (M^+), 191 (base).

The structure of this material was further verified by comparison with an authentic sample. To a solution containing 4.16 g of 2-phenylindanone in 100 mL of ether was added 40 mL of a 0.67-M allylmagnesium bromide solution in ether. After stirring for 1 h at room temperature, a saturated ammonium chloride solution was added. The organic phase was separated, washed with water, and dried over magnesium sulfate. Removal of the solvent left 4.9 g of 1-allyl-2-phenyl-1-indanol: NMR ($CDCl_3$, 100 MHz) τ 8.39 (s, 1 H), 7.33 (broad t, 2 H, *J* = 6.0 Hz), 6.70 (broad d, 2 H, *J* = 8.0 Hz), 6.36 (broad t, 1 H, *J* = 8.0 Hz), 4.76 (d, 1 H, *J* = 10.0 Hz), 4.72 (d, 1 H, *J* = 18.0 Hz), 3.80–4.25 (m, 1 H), 2.44–2.68 (m, 9 H).

This material was used in the next step without further purification. To 1.1 g of the crude indanol was added 5 mL of a mixture containing 0.5 mL of sulfuric acid, 4.25 mL of glacial acetic acid, and 0.25 mL of water. The solution was stirred for 5 min at 25 °C and then diluted with water. The solution was neutralized with sodium bicarbonate and extracted with ether. The ether extracts were washed with water and dried over magnesium sulfate. Removal of the solvent left 0.94 g (92%) of 3-allyl-2-phenylindene (**17**) as a colorless oil which was identical in every detail with the major component isolated from the photolysis of cyclopropene **16**.

The minor component present in the crude photolysate derived from the photolysis of **16** was assigned the structure of 1-phenyl-3-allylindene (**18**) on the basis of its NMR spectrum ($CDCl_3$, 100 MHz): τ 6.71 (dt, 2 H, *J* = 6.0, 1.5 Hz), 5.45 (broad s, 1 H), 6.64–6.94 (m, 2 H), 3.70–4.15 (m, 1 H), 3.70 (d, 1 H, *J* = 1.5 Hz), 2.40–2.90 (m, 9 H). It was not possible to completely separate this isomer from indene **17** even by extensive chromatography.

Preparation of 1,3-Diphenyl-2-methyl-3-allylcyclopropene (19). To a suspension containing 5 g of 3-methyl-1,2-diphenylcyclopropenyl perchlorate[83] in 500 mL of tetrahydrofuran at −78 °C was added 100 mL of a 0.67-M allylmagnesium bromide solution in ether. The mixture was stirred at −78 °C for 4 h and then allowed to warm

to room temperature. The mixture was quenched with a saturated ammonium chloride solution and extracted with ether. The ethereal layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give a clear oil which was chromatographed on silica using hexane as the eluent. The first component isolated contained 2.3 g (55%) of 3-allyl-3-methyl-1,2-diphenylcyclopropene: bp 70–71 °C (0.01 mm); IR (neat) 3.38, 3.47, 5.52, 6.08, 6.26, 6.70, 6.94, 7.31, 8.64, 9.33, 9.73, 10.95, 13.25, 14.55 μm; UV (95% ethanol) 338 nm (ε 21 400), 320 (28 600), 229 (18 200); NMR ($CDCl_3$, 100 MHz) τ 8.54 (s, 3 H), 7.44 (d, 2 H, J = 7.5 Hz), 5.05 (d, 1 H, J = 9.5 Hz), 5.01 (d, 1 H, J = 17.0 Hz), 3.84–4.32 (m, 1 H), 2.24–2.92 (m, 10 H); m/e 246 (M^+), 231, 206, 205 (base), 77.

Anal. Calcd for $C_{19}H_{18}$: C, 92.63; H, 7.37. Found: C, 92.59; H, 7.35.

The second component isolated from the thick-layer plate contained 1.3 g (31%) of a clear liquid whose structure is assigned as 1,3-diphenyl-2-methyl-3-allylcyclopropene (**19**) on the basis of its spectral data: bp 80–81 °C (0.01 mm); IR (neat) 3.27, 3.44, 5.39, 6.25, 6.69, 6.93, 9.33, 10.02, 10.94, 13.14, 14.40 μm; UV (95% ethanol) 262 nm (ε 16 900); NMR ($CDCl_3$, 100 MHz) τ 7.74 (s. 1 H), 7.10 (d, 2 H, J = 8.0 Hz), 5.10 (d, 1 H, J = 8.0 Hz), 4.99 (d, 1 H, J = 14.0 Hz), 3.96–4.44 (m, 1 H), 2.48–3.16 (m, 10 H); m/e 246 (M^+), 231, 205 (base), 77.

Anal. Calcd for $C_{19}H_{18}$: C, 92.63; H, 7.37. Found: C, 92.55; H, 7.37.

Irradiation of 1,3-Diphenyl-2-methyl-3-allylcyclopropene (19). A solution containing 150 mg of **19** in 200 mL of benzene was irradiated for 50 min with a 550-W Hanovia lamp equipped with a Pyrex filter sleeve. Removal of the solvent followed by thick-layer chromatography gave two products. The major component in the reaction mixture (58%) was a colorless oil whose structure was assigned as 1-methyl-2-phenyl-3-allylindene (**20**) on the basis of its characteristic spectral properties: IR (KBr) 3.30, 3.33, 3.40, 3.45, 6.15, 6.24, 6.82, 6.90, 9.30, 9.70, 10.95, 13.60, 14.70 μm; UV (95% ethanol) 294 nm (ε 11 900), 230 (11 600), 226 (10 800); NMR ($CDCl_3$, 100 MHz) τ 8.80 (d, 3 H, J = 7.0 Hz), 6.62 (d, 2 H, J = 5.0 Hz), 6.14 (q, 1 H, J = 7.0 Hz), 4.95 (d, 1 H, J = 10.0 Hz), 4.90 (d, 1 H, J = 15.0 Hz), 3.72–4.16 (m, 1 H), 2.48–2.98 (m, 9 H); m/e 246 (M^+), 206, 205 (base), 77.

The structure of this material was unambiguously verified by comparison with an authentic sample. To a stirred solution containing 1.0 g of 2-phenyl-3-methylindanone (**12**) in 25 mL of ether was added 7.5 mL of a 0.67-M allylmagnesium bromide solution in ether. The mixture was stirred for 1 h at room temperature and then quenched by a saturated ammonium chloride solution. The aqueous layer was extracted with ether, and the ethereal solution was washed with water and dried over magnesium sulfate. Removal of the solvent left a clear oil which was taken up in a mixture containing 9 mL of acetic acid, 1 mL of concentrated sulfuric acid, and 10 drops of water. The reaction mixture was stirred for 5 min and extracted with ether. The ethereal solution was neutralized with a 5% sodium bicarbonate solution, washed with water, and dried over magnesium sulfate. Removal of the solvent left 0.8 g of a yellow oil which was purified by thick-layer chromatography to give 0.65 g (63%) of 1-methyl-2-phenyl-3-allylindene (20), identical to the major photoproduct obtained from the photolysis of **19**.

The minor component (5%) present in the photolysis mixture derived from **19** was identified as 1-phenyl-2-methyl-3-allylindene (**21**) on the basis of its characteristic spectral data: IR (neat) 3.32, 3.45, 6.12, 6.24, 6.71, 6.90, 9.75, 10.05, 10.90, 12.85, 13.30, 13.65, 14.35 μm; UV (95% ethanol) 263 nm (ε 6900), 220 (17 800); NMR ($CDCl_3$, 100 MHz) τ 8.16 (s, 3 H), 6.68 (d, 2 H, J = 5.5 Hz), 5.72 (s, 1 H), 4.80–5.24 (m, 2 H), 3.82–4.28 (m, 1 H), 2.64–3.10 (m, 9 H); m/e 246 (M^+), 206, 205 (base), 108, 77.

The structure of this material was further verified by comparison with an independently synthesized sample. To a stirred solution containing 1.0 g of 2-methyl-3-phenyl-1-indanone (**13**) in 25 mL of ether was added 7.5 mL of a 0.67-M allylmagnesium bromide solution in ether. The reaction mixture was stirred for 1 h at 25 °C followed by the addition of a saturated ammonium chloride solution. Extraction of the mixture with ether followed by washing with water and drying over magnesium sulfate gave 1.0 g of a pale yellow oil on removal of the solvent. This material was taken up in a mixture containing 9 mL of acetic acid, 1 mL of concentrated sulfuric acid, and 10 drops of water. The solution was stirred for 5 min and extracted with ether. The ethereal layer was washed with a 5% sodium bicarbonate solution followed by water. After drying over magnesium sulfate, the solvent was removed under reduced pressure to give 0.76 g of a yellow oil. This material was purified by thick-layer chromatography to give 0.6 g (65%) of 1-phenyl-2-methyl-3-allylindene (**21**) which was identical to the minor component obtained from the photolysis of **19**.

Preparation of 1,2,3-Triphenyl-3-vinylcyclopropene (22). A 0.7-M solution of vinylmagnesium bromide in 100 mL of tetrahydrofuran was slowly added to a suspension of triphenylcyclopropenyl perchlorate[85] in 250 mL of tetrahydrofuran at −78 °C. The reaction mixture was allowed to warm to room temperature and was stirred for 4 h. After quenching with a saturated ammonium chloride solution, the organic layer was diluted with ether, washed with water, and dried over magnesium sulfate. The solvent was removed under reduced pressure to give a yellow oil which recrystallized from methanol to give 3.0 g (75%) of 1,2,3-triphenyl-3-vinylcyclopropene (**22**) as a crystalline solid: mp 87–88 °C; IR ($CHCl_3$) 3.34, 5.49, 6.17, 6.73, 6.95, 7.14, 9.33, 9.74, 10.05, 10.95 μm; NMR ($CDCl_3$, 60 MHz) τ 4.92 (dd, 1 H, J = 11.0, 1.0 Hz), 4.86 (dd, 1 H, J = 16.0, 1.0 Hz), 3.38 (dd, 1 H, J = 16.0, 11.0 Hz), 2.2–2.9 (m, 15 H); UV (95% ethanol) 330 nm (ε 21 000), 314 (23 600), 227 (29 500); m/e 294 (M^+), 218, 217, 215, 202, 115, 91.

Anal. Calcd for $C_{23}H_{18}$: C, 93.84; H, 6.16. Found: C, 93.99; H, 6.42.

Irradiation of 1,2,3-Triphenyl-3-vinylcyclopropene (22). A solution containing 354 mg of **22** in 400 mL of benzene was irradiated with a 550-W Hanovia lamp equipped with a Pyrex filter sleeve for 5 h. Removal of the solvent followed by thick-layer chromatography gave 250 mg (70%) of a crystalline solid, mp 157–158 °C, whose structure was assigned as 1,2,3-triphenylcyclopentadiene (**23**): IR (KBr) 3.10, 6.25, 6.68, 6.95, 7.28, 8.25, 9.34, 9.73, 10.24, 10.84, 10.95, 11.28, 11.44, 12 95, 13.16, 13.56, 14.41 μm; UV (95% ethanol) 305 nm (ε 11 000), 246 (30 200); NMR ($CDCl_3$, 60 MHz) τ 6.40 (d, 2 H, J = 2.0 Hz), 3.48 (t, 1 H, J = 2.0 Hz), 2.70–3.0 (m, 15 H).

The structure of this material was further confirmed by comparison with an authentic sample prepared according to the procedure of Pauson and Williams.[89]

Preparation of 1,2-Diphenyl-3-vinylcyclopropene (24). A 0.86-M solution of vinylmagnesium bromide in tetrahydrofuran was slowly added to a suspension of 5.0 g of diphenylcyclopropenyl perchlorate[87] in 300 mL of tetrahydrofuran at −78 °C. The reaction mixture was allowed to warm to 25 °C and was stirred at this temperature for 4 h. At the end of this time the solution was quenched with a saturated ammonium chloride solution. The organic layer was diluted with ether, washed with water, and dried over magnesium sulfate. Removal of the solvent left 2.8 g of a yellow oil which was sublimed at 35 °C (0.03 mm) to give 2.4 g (65%) of 1,2-diphenyl-3-vinylcyclopropene (**24**) as a crystalline solid: mp 31–32 °C; IR (neat) 3.34, 3.53, 5.53, 6.22, 6.33, 6.77, 7.02, 7.72, 7.88, 8.62, 9.42, 9.83, 11.23, 13.33, 14.63 μm; NMR ($CDCl_3$, 60 MHz) τ 7.23 (d, 1 H, J = 7.0 Hz), 5.08 (dd. 1 H, J = 10.0, 3.0 Hz), 4.74 (dd, 1 H, J = 17.0, 3.0 Hz), 4.28 (ddd, 1 H, J = 17.0, 10.0, 7.0 Hz), 2.2–2.8 (m, 10 H); UV (95% ethanol) 332 nm (ε 26 300), 315 (32 100) 236 (21 400), 227 (27 700); m/e 218 (M^+), 217, 216. 215, 203, 202, 115, 77.

Anal. Calcd for $C_{17}H_{14}$: C, 93.53; H, 6.47. Found: C, 93.18; H, 6.58.

Irradiation of 1,2-Diphenyl-3-vinylcyclopropene (24). A solution containing 105 mg of **24** in 150 mL of benzene was irradiated with a 550-W Hanovia lamp equipped with a Pyrex filter sleeve for 75 min. Removal of the solvent left a pale yellow oil which contained a single product as judged from NMR analysis. Purification of this product was accomplished by preparative thick-layer chromatography. The only material isolated from the thick-layer plate was a crystalline solid, mp 68–70 °C, whose structure was identified as 1,2-diphenylcyclopentadiene (**25**) (67% isolated yield) on the basis of its characteristic spectral data: IR (KBr) 3.29, 6.24, 6.72, 6.95, 7.35, 8.19, 9.40, 9.73, 10.36 10.79, 11.03, 11.19, 12.83, 13.03, 13.30, 14.28 μm; UV (95% ethanol) 308 nm (ε 9200), 233 (20 000); NMR ($CDCl_3$, 60 MHz) τ 6.55 (t, 1 H, J = 1.5 Hz), 3.58 (td, 1 H, J = 5.0, 1.5 Hz), 3.36 (td, 1 H. J = 5 0, 1.5 Hz), 2.6–3.0 (m, 10 H).

The structure of this material was unambiguously established by comparison with an authentic sample prepared according to the procedure of Rio and Charafi.[90]

Preparation of 1,2-Diphenyl-3-methyl-3-vinyl- (26) and 1-Methyl-2,3-diphenyl-3-vinylcyclopropene (32). To a suspension of 4.0 g of 3-methyl-1,2-diphenylcyclopropenyl perchlorate in 100 mL of tetrahydrofuran at −78 °C was added 100 mL of a 0.67-M vinylmagnesium bromide solution in tetrahydrofuran. The reaction mixture was allowed to warm to 25 °C and was stirred for 4 h at this temperature. The excess Grignard reagent was destroyed by the addition of a saturated ammonium chloride solution. The organic layer was taken up in ether, washed with water, and dried over magnesium sulfate. Removal of the solvent left a yellow oil which was subjected to silica gel chromatography using hexane as the eluent. The first component isolated from the column contained 1.93 g (65%) of 1,2-diphenyl-3-methyl-3-vinylcyclopropene (**26**): mp 34–35 °C; IR (neat)

3.32, 3.48, 5.52, 6.23, 6.30, 6.77, 6.99, 7.36, 9.38, 9.76, 10.07, 11.19, 13.30, 14.63 μm; NMR ($CDCl_3$, 100 MHz) τ 8.44 (s, 3 H), 5.03 (d, 1 H, J = 9.5 Hz), 4.93 (d, 1 H, J = 17.5 Hz), 4.25 (dd, 1 H, J = 17.5, 9.5 Hz), 2.42–2.82 (m, 10 H); UV (95% ethanol) 332 nm (ε 26 100), 315 (31 000), 227 (21 800); m/e 232 (M^-, base), 217, 215.

Anal. Calcd for $C_{18}H_{16}$: C, 93.06; H, 6.94. Found: C, 93.04; H, 7.13.

The second component isolated from the chromatography column contained 0.27 g (9%) of a clear oil which crystallized on standing and whose structure was assigned as 1-methyl-2,3-diphenyl-3-vinylcyclopropene (**32**): mp 38–39 °C; IR (neat) 3.33, 3.47, 5.28, 6.17, 6.26, 6.71, 6.93, 7.12, 9.31, 10.06, 11.02, 13.16, 14.32, 14.49 μm; NMR ($CDCl_3$, 100 MHz) τ 7.70 (s, 3 H), 5.14 (d, 1 H, J = 10.0 Hz), 4.91 (d, 1 H, J = 17.0 Hz), 3.60 (dd, 1 H, J = 17.0, 10.0 Hz), 2.5–2.9 (m, 10 H); UV (95% ethanol) 260 nm (ε 15 900); m/e 232 (M^+, base), 217, 215.

Anal. Calcd for $C_{18}H_{16}$: C, 93.06; H, 6.94. Found: C, 92.68; H, 7.05.

Since the yield of **32** was so low (i.e., 9%), an alternate synthetic procedure was used to prepare larger quantities of this material. To a solution containing 2.0 g of bis(1,2-diphenyl)cyclopropenyl ether[87] in 200 mL of benzene at 25 °C was added 35 mL of a 1.1-M vinylmagnesium bromide solution in tetrahydrofuran. The mixture was stirred at 35 °C for 3.5 h and subsequently quenched with a saturated ammonium chloride solution. The organic layer was extracted with water and dried over magnesium sulfate. Removal of the solvent left a colorless oil whose NMR spectrum showed that it contained mostly 3-vinyl-1,3-diphenylcyclopropene: NMR ($CDCl_3$, 100 MHz) τ 5.02 (dd, 1 H, J = 17.0, 1.5 Hz), 4.96 (dd, 1 H, J = 10.0, 1.5 Hz), 3.54 (dd, 1 H, J = 17.0, 10.0 Hz), 2.2–3.0 (m, 1 H).

The above sample was taken up in 100 mL of tetrahydrofuran and cooled to −78 °C. To this solution was added 30 mL of a 1.7-M methyllithium solution in ether. The mixture was allowed to warm to 25 °C for 30 min and then cooled to −78 °C. To this solution was added 1.1 g of methyl iodide in 50 mL of tetrahydrofuran. After the addition was complete, the solution was stirred at room temperature for 1 h and then quenched with a saturated ammonium chloride solution. The organic layer was dried over magnesium sulfate and concentrated under reduced pressure to give a yellow oil. This material was chromatographed on a silica gel column using hexane as the eluent to give a pure sample (80%) of 1-methyl-3-vinyl-2,3-diphenylcyclopropene (**32**), which was identical to the minor component obtained from the reaction of 1,2-diphenyl-3-methylcyclopropenyl perchlorate with vinylmagnesium bromide.

Irradiation of 1,2-Diphenyl-3-methyl-3-vinylcyclopropene (26). A solution containing 114 mg of **26** in 125 mL of benzene was irradiated with a 450-W Hanovia lamp equipped with a Pyrex filter sleeve for 4 h. Removal of the solvent followed by thick-layer chromatography gave 74 mg (65%) of a colorless oil whose structure was assigned as 1,2-diphenyl-3-methylcyclopentadiene (**27**) on the basis of its spectral data: IR (neat) 3.28, 3.43, 5.67, 6.24, 6.71, 6.95, 7.26, 9.32, 9.68, 10.50, 10.93, 13.18, 14.34 μm; UV (95% ethanol) 298 nm (ε 8400), 220 (14 300); NMR ($CDCl_3$, 100 MHz) τ 8.20 (broad s, 3 H), 6.66 (broad s, 2 H), 3.88 (broad s, 1 H), 2.5–3.0 (m, 10 H); m/e 232 (M^+, base), 217, 215, 154, 105, 91, 77.

Anal. Calcd for $C_{18}H_{16}$: C, 93.06; H, 6.94. Found: C, 92.97; H, 7.07.

Continued irradiation of a sample of cyclopentadiene **27** resulted in its equilibration with 1-methyl-2,3-diphenylcyclopentadiene (**28**). In fact, small quantities of **28** were present in the crude photolysate derived from the irradiation of cyclopropene **26**. All attempts to separate the isomeric 1,3-cyclopentadienes failed. The structure of **28** was assigned on the basis of its NMR spectrum and by an independent synthesis.

A solution containing 8.2 g of 2-methylfuran in 50 mL of tetrahydrofuran was added to a mixture containing 50 mL of a 2.4-M n-butyllithium solution in hexane and 50 mL of tetrahydrofuran at −35 °C. The solution was allowed to warm to −10 °C and was kept at this temperature for 4 h. At the end of this time, 17 g of benzyl bromide in 50 mL of tetrahydrofuran was added, and the mixture was warmed to 25 °C and allowed to stand for 12 h at this temperature. The mixture was poured over water, extracted with ether, and dried. Removal of the solvent left 11.6 g of a yellow oil which was taken up in a mixture containing 20 mL of acetic acid, 10 mL of water, and 1 mL of a 10% sulfuric acid solution. The resulting solution was heated at reflux for 4 h, and then poured onto ice and extracted with ether. The ethereal solution was washed with 5% sodium bicarbonate solution and water, and dried over magnesium sulfate. Removal of the solvent left 10.5 g of a yellow oil which was used in the next step without purification.

A solution containing 5.0 g of the above oil and 2.5 g of potassium hydroxide in 50 mL of methanol was heated at reflux for 5 h. The mixture was poured onto water, extracted with ether, washed with water, and dried over magnesium sulfate. Removal of the solvent followed by distillation of the crude residue at 94 °C (0.01 mm) gave a clear oil which solidified on standing. Recrystallization of this material gave 2.7 g of 2-phenyl-3-methylcyclopentenone (**31**): mp 60–61 °C; IR (KBr) 3.29, 3.44, 5.92, 6.11, 6.25, 6.70, 6.98, 7.27, 8.84, 10.63, 13.09, 14.30 μm; UV (95% ethanol) 248 nm (ε 8300), 221 (14 100); NMR ($CDCl_3$, 100 MHz) τ 7.88 (s, 3 H), 7.31–7.61 (m, 4 H), 2.53–2.91 (m, 5 H); m/e 172 (M^+, base), 129, 115, 77.

Anal. Calcd for $C_{12}H_{12}O$: C, 83.69; H, 7.02. Found: C, 83.65; H, 7.18.

To a solution containing 106 mg of **31** in 50 mL of ether was added 1.5 mL of a 2.0-M phenyllithium solution at 0 °C. After stirring at 0 °C for 1 h, the solution was poured onto water and extracted with ether. The ether layer was washed with water and dried over magnesium sulfate. Removal of the solvent left a clear oil which was dissolved in 5 mL of ethanol containing 0.5 mL of acetic acid. The solution was heated at reflux for 30 min, cooled, and poured onto ice water. The mixture was extracted with ether, washed with a 5% sodium bicarbonate solution and water, and dried over magnesium sulfate. Removal of the solvent left a clear oil whose NMR spectrum indicated it to be a 1:3 mixture of 1,2-diphenyl-3-methyl- (**27**) and 1-methyl-2,3-diphenylcyclopentadiene (**28**). The NMR, IR, and mass spectra of this mixture were identical to that obtained from the photolysis of cyclopropene **26**. The mixture of isomeric cyclopentadienes could not be separated by extensive column chromatography. The NMR spectrum of 1-methyl-2,3-diphenylcyclopentadiene (**28**) was obtained from the crude reaction mixture and showed signals at τ 7.96 (s, 3 H), 6.88 (d, 2 H, J = 2.0 Hz), 3.76 (t, 1 H, J = 2.0 Hz), and 2.5–3.0 (m, 10 H).

Irradiation of 1-Methyl-2,3-diphenyl-3-vinylcyclopropene (32). A solution containing 132 mg of **32** in 125 mL of benzene was irradiated with a 450-W Hanovia lamp equipped with a Pyrex filter sleeve for 2 h. Removal of the solvent under reduced pressure left a pale yellow oil which was shown to contain four major components by NMR analysis. The major fraction (39%) present in the crude photolysate was identified as 1-methyl-2-phenyl-3-vinylindene (**34**) on the basis of its spectral data and by comparison with an independently synthesized sample: IR (neat) 3.25, 3.32, 6.20, 6.66, 6.81, 8.60, 8.85, 9.28, 9.94, 10.90, 13.00, 13.38, 14.29 μm; UV (95% ethanol) 303 nm (ε 16 000), 232 (18 300); NMR ($CDCl_3$, 100 MHz) τ 8.77 (d, 3 H, J = 5.0 Hz), 6.10 (q, 1 H, J = 5.0 Hz), 4.51 (d, 1 H, J = 11.5 Hz), 4.12 (d, 1 H, J = 18.0 Hz), 3.21 (dd, 1 H, J = 18.0, 11.5 Hz), 2.55–2.79 (m, 10 H); m/e 232 (M^+), 217 (base), 215, 208, 205, 193, 178, 130, 115, 91, 77.

Anal. Calcd for $C_{18}H_{16}$: C, 93.06; H, 6.94. Found: C, 92.97; H, 7.27.

The structure of this material was further verified by comparison with an independently synthesized sample prepared by treating 2-phenyl-3-methyl-1-indanone (**12**) with vinylmagnesium bromide followed by an acid-catalyzed dehydration by a procedure similar to that used for the synthesis of the related allyl- and benzylindenes.

The minor component (10%) present in the crude photolysate was identified as 1,3-diphenyl-2-methylcyclopentadiene (**33**) on the basis of its spectral data and by comparison with an independently synthesized sample: mp 130–132 °C; IR (KBr) 3.34, 3.45, 6.28, 6.74, 6.97, 7.26, 8.47, 9.31, 9.74, 10.18, 10.39, 11.26, 12.80, 13.11, 13.55, 14.32 μm; UV (95% ethanol) 288 nm (ε 8300), 237 (14 500); NMR ($CDCl_3$, 100 MHz) τ 7.88 (t, 2 H, J = 1.0 Hz), 6.62 (q, 2 H, J = 1.0 Hz), 3.64 (broad s, 1 H), 2.5–2.9 (m, 10 H); m/e 232 (M^+, base), 217, 215, 154.

Anal. Calcd for $C_{18}H_{16}$: C, 93.06; H, 6.94. Found: C, 92.74; H, 6.77.

The structure of this material was further established by comparison with an independently synthesized sample. A solution containing 11.6 g of 2-phenylfuran[91] in 50 mL of tetrahydrofuran was added to a mixture containing 40 mL of a 2.4-M n-butyllithium solution in hexane and 50 mL of tetrahydrofuran at −30 °C. The solution was stirred for 2 h at −10 °C, and then 9 g of ethyl bromide in 50 mL of tetrahydrofuran was added at −30 °C. The solution was kept at −30 °C for 1 h and was then allowed to warm to room temperature. After stirring for 12 h at 25 °C, the mixture was poured onto water and extracted with ether. The ether layer was dried over magnesium sulfate and concentrated under reduced pressure to give 11.5 g of a yellow oil. An 8.1-g sample of oil was taken up in a mixture containing 30 mL of acetic acid and 15 mL of a 20% sulfuric acid solution. The resulting mixture was heated at reflux for 4 days, poured onto water, extracted with ether, washed with a 5% sodium bicarbonate solution, and dried over magnesium sulfate. Removal of the solvent left a dark oil which was dissolved in 50 mL of methanol which contained 2.5 g of potas-

sium hydroxide. The solution was heated at reflux for 3 h, poured onto water, and extracted with ether. The ether layer was dried over magnesium sulfate and concentrated under reduced pressure to give a yellow oil which was subjected to Florisil column chromatography. Elution of the column with benzene gave a 6.2-g sample of 2-methyl-3-phenylcyclopentenone (**35**): mp 52–53 °C (lit.[92] mp 53–55 °C); IR (KBr) 3.51, 5.88, 6.14, 6.67, 6.90, 7.23, 7.43, 8.11, 9.07, 9.26, 9.41, 11.79, 13.08, 14.37 μm; NMR ($CDCl_3$, 100 MHz) τ 8.06 (t, 3 H, J = 2.0 Hz), 7.36–7.56 (m, 2 H), 6.98–7.19 (m, 2 H), 2.40–2.66 (m, 5 H).

To a solution containing 250 mg of the above cyclopentenone in 25 mL of ether was added 3.0 mL of a 2.0-M phenyllithium solution. After stirring at 0 °C for 1 h, the solution was poured onto water and extracted with ether. The ether layer was washed with water and dried over magnesium sulfate. Removal of the solvent left 230 mg of a clear oil which was dissolved in 5 mL of ethanol containing 0.5 mL of acetic acid. After refluxing for 30 min, the mixture was poured over ice, extracted with ether, washed with a 5% sodium bicarbonate solution, and dried over magnesium sulfate. Removal of the solvent left 190 mg of a crystalline solid, mp 130–132 °C, which was identical to a sample of 1,3-diphenyl-2-methylcyclopentadiene (**33**) isolated from the irradiation of cyclopropene **32**.

The middle band isolated from the thick-layer separation of the crude photolysate derived from cyclopropene **32** contained 40 mg (30%) of a clear oil whose NMR spectrum indicated it to be a 1:3 mixture of 1,2-diphenyl-3-methyl- (**27**) and 1-methyl-2,3-diphenylcyclopentadiene (**28**).

Preparation and Irradiation of 1-Phenyl-2-methyl-3-vinylindene (36). To a stirred solution containing 1.15 g of 2-methyl-3-phenylindanone (**13**) in 25 mL of ether was added 8.5 mL of a 0.67-M vinylmagnesium bromide solution in ether. The reaction mixture was stirred for 1 h at room temperature followed by the addition of a saturated ammonium chloride solution. The solution was extracted with ether, washed with water, and dried over magnesium sulfate. Removal of the solvent left a pale yellow oil which was taken up in 9 mL of acetic acid which contained 1 mL of sulfuric acid and 1 mL of water. After stirring for 15 min at 25 °C, the mixture was poured onto ice and extracted with ether. The ethereal solution was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give a pale yellow oil which crystallized on standing. The structure of this material was assigned as 1-phenyl-2-methyl-3-vinylindene (**36**): mp 70–71 °C; IR (KBr) 3.44, 6.12, 6.26, 6.72, 6.91, 7.26, 8.46, 9.33, 9.72, 10.08, 10.93, 13.15, 13.47, 14.30 μm; UV (95% ethanol) 270 nm (ε 7300); NMR ($CDCl_3$, 100 MHz) τ 8.06 (s, 3 H), 5.66 (s, 1 H). 4.48 (d, 1 H, J = 12.0 Hz), 4.14 (d, 1 H, J = 17.0 Hz), 3.14 (dd, 1 H, J = 17.0, 12.0 Hz), 2.38–3.0 (m, 9 H); m/e 232 (M^+), 217 (base), 215, 202, 115.

Anal. Calcd for $C_{18}H_{16}$: C, 93.06; H, 6.94. Found: C, 93.02; H, 7.22.

A solution containing 50 mg of **36** in 125 mL of benzene was irradiated with a 450 W-Hanovia lamp equipped with a Corex filter sleeve for 1 h. Removal of the solvent left a pale yellow oil which consisted mostly of 1-methyl-2-phenyl-3-vinylindene (**34**) as evidenced by NMR analysis. Thick-layer chromatography of the crude photolysate gave a pure sample of **34**.

Irradiation of 1-Phenyl-2,3,3-trimethylcyclopropene (52) in Methanol. A solution containing 130 mg of 1-phenyl-2,3,3-trimethylcyclopropene[93] (**52**) in 150 mL of methanol was irradiated with a 450-W Hanovia lamp equipped with a Vycor filter sleeve for 1 h. Removal of the solvent under reduced pressure left a crude yellow oil which was shown to contain two major products as judged by NMR analysis. Thick-layer chromatography of the mixture resulted in the separation of these two components. The major product isolated from the thick-layer plate was a colorless oil whose structure was assigned as 2-methoxy-3-phenyl-4-methylpent-3-ene (**53**; 78%) on the basis of its characteristic spectral data: IR (neat) 3.37, 3.46, 6.24, 6.73, 6.96, 7.34, 7.54, 7.76, 8.32, 9.10, 9.26, 9.36, 10.54, 11.90, 13.05, 14.27 μm; NMR ($CDCl_3$, 60 MHz) τ 8.95 (d, 3 H, J = 6.0 Hz), 8.51 (s, 3 H), 8.18 (s, 3 H), 6.71 (s, 3 H), 5.61 (q, 1 H, J = 6.0 Hz), 2.6–3.1 (m, 5 H); m/e 190 (M^+), 175, 159, 144, 143 (base), 142, 141, 129, 115, 91.

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 82.38; H, 9.88.

The structure of this material was further confirmed by comparison with an authentic sample. To a solution containing 0.81 g of 3-phenyl-4-methyl-3-penten-2-ol[94] and 1 mL of methyl iodide in 10 mL of tetrahydrofuran was added 0.24 g of sodium hydride. The mixture was stirred at 25 °C for 24 h, quenched with water, and extracted with ether. The ether layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure. The resulting residue was purified by thick-layer chromatography, and the major component isolated was identical in every detail with a sample of **53** obtained from the photolysis of **52**.

The minor product (9%) obtained from the irradiation of 1-phenyl-2,3,3-trimethylcyclopropene (**52**) was identified as 1-methoxy-1-phenyl-2,3-dimethyl-2-butene (**54**) on the basis of its characteristic spectral data: IR (neat) 3.44, 6.24, 6.70, 6.91, 7.29, 7.49, 7.66, 8.40, 8.68, 8.87. 9.18, 9.69, 10.29, 10.90, 11.23, 12.87, 13.78, 14.38 μm; NMR ($CDCl_3$, 60 MHz) τ 8.59 (broad s, 3 H), 8.36 (broad s, 3 H), 8.18 (broad s, 3 H), 6.87 (s, 3 H), 4.79 (s, 1 H), 2.6–3.0 (m, 5 H); m/e 190 (M^+), 175, 158, 143 (base), 129, 115, 105, 91, 77.

Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.54. Found: C, 82.19; H, 9.91.

The structure of this material was unambiguously confirmed by comparison with an authentic sample. To a solution containing 1.0 g of 2,3-dimethyl-1-phenylbut-2-en-1-one[95] in 75 mL of dioxane and 25 mL of water was added 2.2 g of sodium borohydride. The mixture was stirred at 25 °C for 24 h and was then added to 75 mL of water and extracted with ether. The ether layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give 0.92 g of a pale oil. This material was taken up in 15 mL of tetrahydrofuran which contained 1 mL of methyl iodide. A 0.32-g sample of sodium hydride was added, and the mixture was stirred at room temperature for 24 h. At the end of this time, the solution was quenched with water and extracted with ether. The ethereal layer was washed with water, dried over magnesium sulfate, and concentrated under reduced pressure to give 0.83 g of 1-methoxy-1-phenyl-2,3-dimethyl-2-butene (**54**), which was identical in every detail with the minor component isolated from the irradiation of **52**.

Quantum Yield Determinations. All quantitative measurements were made on a rotating assembly at room temperature using a Rayonet reactor equipped with 3000-Å lamps. Samples were degassed to 5×10^{-3} mm in three freeze–thaw cycles and then sealed. Benzophenone–benzhydrol actinometry was used for quantum yield determinations.[96] Reliably reproducible output rates of 1.73×10^{17} quanta/s were recorded. After the irradiation the degree of reaction was determined by quantitative NMR. The conversions were run to 15% or less. The mass balances in these runs were generally better than 95%.

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Vinylcyclopropene Photochemistry: Photochemistry Applied to Organic Synthesis. Exploratory and Mechanistic Organic Photochemistry[1,2]

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3-Vinylcyclopropenes have been found to rearrange photochemically to afford cyclopentadienes. The reaction is of both synthetic and mechanistic interest. Direct irradiation of 3-vinyl-1,2,3-triphenylcyclopropene led to 1,2,3-triphenylcyclopentadiene, 3-(1-phenylvinyl)-1,2,3-triphenylcyclopropene gave 1,2,3,4-tetraphenylcyclopentadiene, and 3-isobutenyl-1,2,3-triphenylcyclopropene yielded 1,2,3-triphenyl-5,5-dimethylcyclopentadiene and 3-isobutenyl-1,2-diphenylindene in a 2.5:1 ratio, while 3-isobutenyl-1,3-diphenyl-2-*tert*-butylcyclopropene afforded 1-*tert*-butyl-2,3-diphenyl-5,5-dimethylcyclopentadiene, 1,3-diphenyl-2-*tert*-butyl-5,5-dimethylcyclopentadiene, 1,2-diphenyl-3-*tert*-butyl-5,5-dimethylcyclopentadiene, and 3-isobutenyl-1-*tert*-butyl-2-phenylindene in a 3:1:4:3 ratio. Similar photolysis of 1,2,3-triphenyl-3-methylcyclopropene gave 3-methyl-1,2-diphenylindene, while irradiation of 1-methyl-2,3,3-triphenylcyclopropene produced 1-methyl-2,3-diphenylindene. Sensitization of the vinylcyclopropenes led to product only in the case of the isobutenyl-substituted cyclopropenes; the vinyl-bearing molecules were unreactive. Quantum yields were determined for direct and sensitized runs, and where triplet reactivity resulted the sensitized efficiencies were slightly more than tenfold greater than the direct run quantum yields. The results revealed a competing vinyl walk reaction in appropriately substituted reactants. This arises from an incipient di-π-methane rearrangement. A trend of quantum efficiencies was observed in which terminal methyl substitution on the vinyl group inhibits reactivity. Similarly, phenyl substitution at the α carbon of the vinyl group was found to enhance reactivity. Finally, phenyl substitution at carbon 1 of the cyclopropene ring enhanced the reaction efficiency. Regioselectivity was encountered when the cyclopropene π bond was unsymmetrically substituted. Here preference is for new carbon to carbon bond formation at the three-ring π-bond position bearing the alkyl rather than the aryl group. The cyclopentadiene-forming reaction proved to be more efficient than indene formation and dominates where both are a priori possibilities. Carbene and diradical mechanisms are considered.

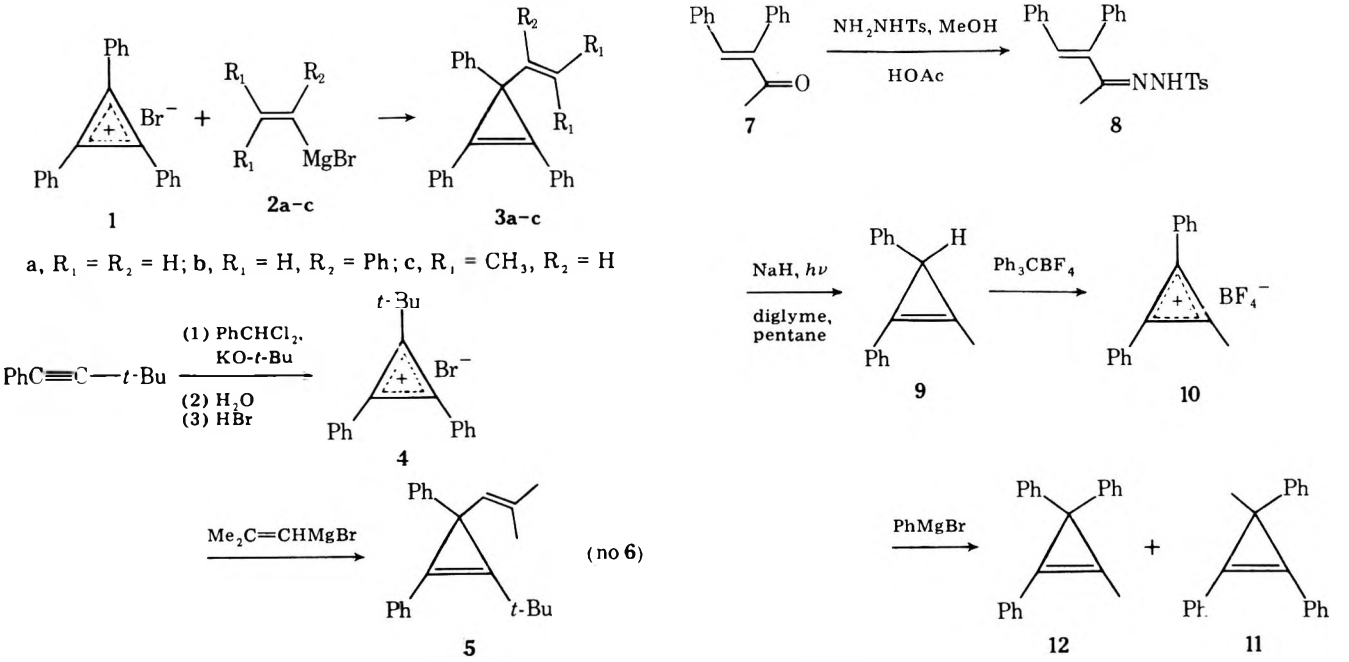
One of the most general of photochemical reactions is the di-π-methane rearrangement.[3] We have been more broadly interested in the photochemistry of molecules containing two π moieties. Our investigations have led us to a study of vinylcyclopropenes. For this study we selected cyclopropenes having some aryl substitution on the three-ring π bond and substitution at the carbon (i.e., C-3) bearing the vinyl group. We were interested in the type of photochemistry observed, in the effect of substitution on the reaction course and reaction efficiency, and in the mechanisms of reactions encountered.

Synthesis of Photochemical Reactants. 3-Vinylcyclopropenes have not been reported previously in the literature.[4] Syntheses are outlined in Chart I, following the known[5,6] reaction of organomagnesium compounds with a cyclopropenium salt. In the preparation of *tert*-butylcyclopropene **5**, no trace of 3-isobutenyl-1,2-diphenyl-3-*tert*-butylcyclopropene (**6**), an a priori product of the reaction, was detectable. Presumably steric hindrance presented a kinetic barrier to formation of this isomer.

Two non-vinyl-substituted cyclopropenes, desired for comparison purposes, 1,2,3-triphenyl-3-methylcyclopropene (**11**)[6] and 1-methyl-2,3,3-triphenylcyclopropene (**12**), also were obtained as outlined in Chart I.[7,8]

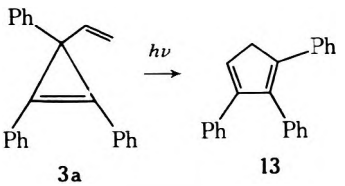
Exploratory Photolyses of the Vinylcyclopropenes and Proof of Product Structures. Irradiation of 3-vinyl-1,2,3-triphenylcyclopropene (**3a**) in *tert*-butyl alcohol using a 450-W medium-pressure lamp and a Pyrex filter for 3.25 h

Chart I. Synthesis of Vinylcyclopropenes



0022-3263/78/1943-1493$01.00/0

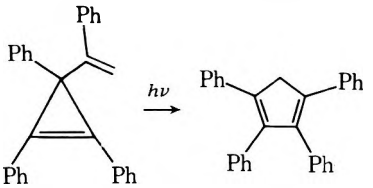
afforded 1,2,3-triphenylcyclopentadiene[9] (13) in 87% yield, identified by the physical data and by independent synthesis. The photoreaction can be depicted as in eq 1a.



(1a)

3a 13

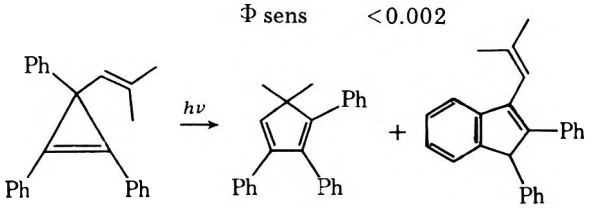
Φ direct 0.027
Φ sens <0.001



(1b)

3b 14

Φ direct 0.049
Φ sens <0.002



(1c)

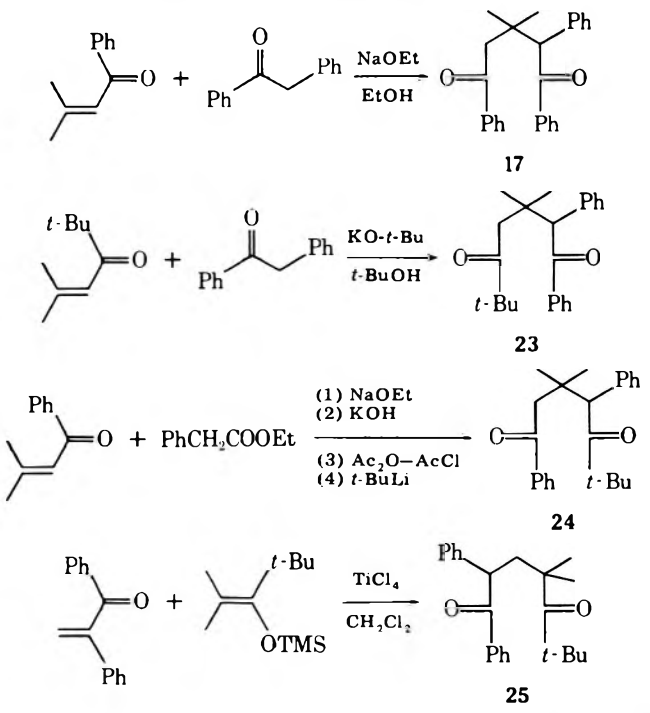
3c 15 16

	15	16
Φ direct	0.010	0.004
Φ sens	0.133	0

Irradiation of the tetraphenylvinylcyclopropene **3b** gave 1,2,3,4-tetraphenylcyclopentadiene (**14**),[10] identified by comparison with an authentic sample. The reaction is shown in eq 1b.

At this juncture it appeared that the reaction involved a formal ring expansion with a [1,3]sigmatropic rearrangement leading from a vinylcyclopropene to a cyclopentadiene. This facilitated structure elucidation in the remaining cases studied.

Chart II. Synthesis of the Diones



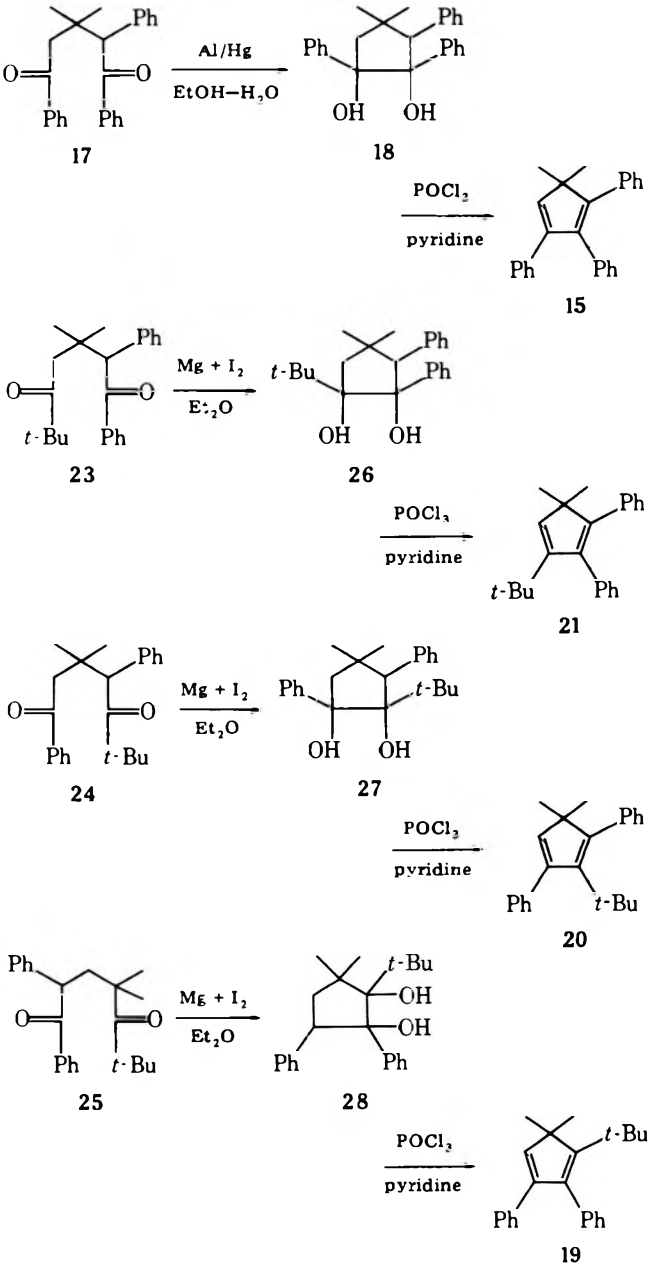
17

23

24

25

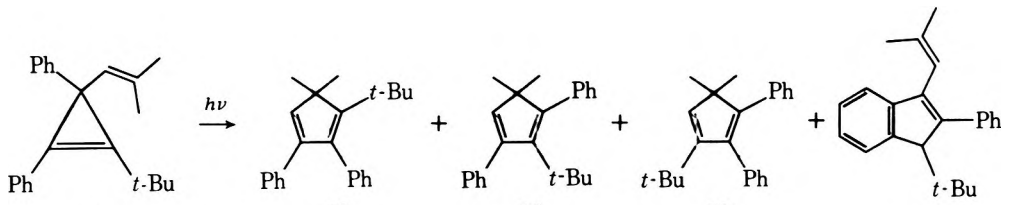
Chart III. Synthesis of the Cyclopentadienes



Thus, irradiation of 3-isobutenyl-1,2,3-triphenylcyclopropene (**3c**) gave a cyclopentadiene as the major product (eq 1c). The above formulation of the reaction suggested this to be 1,2,3-triphenyl-5,5-dimethylcyclopentadiene (**15**), which was established by synthesis (see Charts II and III). Additionally, a minor product (**16**) was isolated; however, spectroscopic data indicated that this was not a cyclopentadiene.

The other cyclopentadienes required for structure proofs also were prepared by the general approach of Wislicenus,[10a] and the syntheses are outlined in Charts II and III.

The minor photoproduct (**16**) was an isomer of the cyclopropene reactant as judged from mass spectral and elemental analytical data. It exhibited two three-hydrogen peaks at τ 8.02 and 8.41, each split slightly. A one-hydrogen peak at τ 3.79 also was present. This pattern proved to be general and characteristic of isobutenyl groups in the compounds studied in this investigation and related studies.[11] In addition, there was a τ 5.02 one-hydrogen peak. The minor splitting indicated it to be a methine not adjacent to other hydrogen-bearing carbons. The ultraviolet spectrum possessed absorption at 239 nm (ϵ 17 900) and 305 (14 300), which immediately suggested



	19	20	21	22
Φ direct	0.003	0.001	0.004	0.003
Φ sens	0.13	0	0.06	0

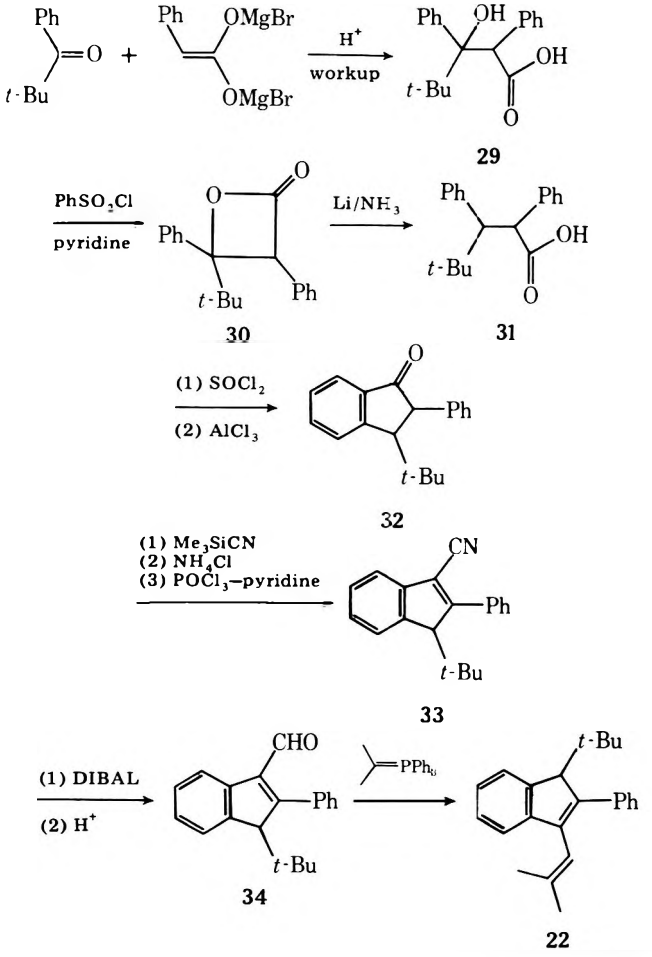
(1d)

a 3-vinyl-3-indene chromophore since this was characteristic of other such indenes studied (vide infra; also note Experimental Section).

This information led to the assignment of the minor photoisomer as 1,2-diphenyl-3-isobutenylindene (**16**). Thus, we may formulate the photochemistry of 3-isobutenyl-1,2,3-triphenylcyclopropene (**3c**) as in eq 1c.

To cast light on the regioselectivity of the photoreaction, 3-isobutenyl-1,3-diphenyl-2-*tert*-butylcyclopropene (**5**) was examined. Direct irradiation of **5** gave a four-component (**19–22**) product mixture which was separated by silica gel chromatography (eq 1d). The first three products (i.e., **19, 20,** and **21**) proved to be isomeric cyclopentadienes. Their structures were deduced from spectral evidence and were confirmed by independent synthesis as outlined in Charts II and III. The first two of these cyclopentadienes were those expected on the basis of a formal ring expansion as noted above; these were 1-*tert*-butyl-2,3-diphenyl-5,5-dimethylcyclopentadiene (**19**) and 2-*tert*-butyl-1,3-diphenyl-5,5-dimethylcyclopentadiene (**20**). The third photoproduct was established as 1,2-diphenyl-3-*tert*-butyl-5,5-dimethylcyclopentadiene (**21**); this isomer clearly did not derive from a simple [1,3]sigmatropic ring expansion. The fourth photoproduct, also isomeric with the cyclopropene reactant (high-resolution mass spectrometry), was shown to be 1-*tert*-butyl-2-phenyl-3-isobutenylindene (**22**) by independent synthesis (Chart IV).

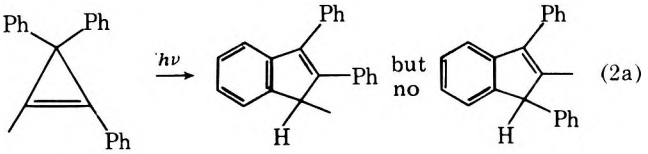
Chart IV. Synthesis of *tert*-Butylindene 22



Comparison Studies Using 3-Arylcyclopropenes. Although the present study is the first dealing with the photochemistry of 3-vinylcyclopropenes, 3-arylcyclopropenes have received some attention. The primary unimolecular photochemistry observed has been indene formation.[12] There has been little mechanistic speculation and no evidence upon which to base a mechanism. However, it has been suggested that the reaction may proceed by fission to give an open biradical of the type $R\dot{C}{=}CR\dot{C}R'_2$.[12a,c,d] Depending on geometry,[13] this may be just a resonance form of one electronic configuration of the corresponding carbene $R\bar{C}CR{=}CR'_2$.

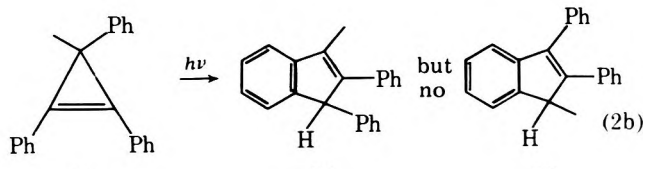
We noted a potential parallel between these 3-phenylcyclopropene systems and the 3-vinylcyclopropenes of our investigation. In particular, the photochemical behavior of 1-methyl-2,3,3-triphenylcyclopropene (**12**) promised to allow a comparison of the reaction regioselectivity with that encountered in the case of *tert*-butyldiphenylisobutenylcyclopropene **5**.

Irradiation of methyltriphenylcyclopropene **12** led to one photoproduct, 1-methyl-2,3-diphenylindene (**35**),[14] an authentic sample of which proved identical to the photoproduct (i.e., **35**). The isomeric indene (**36**) was not detectable (i.e., <5%). Thus, the reaction is regiospecific in forming one of two a priori likely indene products and hence parallels the behavior of the *tert*-butyldiphenylisobutenylcyclopropene **5** (see eq 2a).



(2a)

Another 3-phenylcyclopropene of interest was 3-methyl-1,2,3-triphenylcyclopropene (**11**). Simple extrapolation of the skeletal change observed thus far to this reactant seemed likely to lead to the isomeric indene **37**. This is merely a tautomer of **35** which was formed in the photolysis of the 1-methyl-2,3,3-triphenylcyclopropene (**12**). This photolysis was carried out and did indeed lead to 1,2-diphenyl-3-methylindene (**37**), as noted in eq 2b. The product was known and



(2b)

Table I. Quantum Yields

Reactant	Registry no.	Run[a]	Φ (cyclopentadiene)	Φ (indene)	% conv	Sensitizer
Vinyltriphenylcyclopropene **3a**	62747-62-0	2A	0.028	0	7.0	
		2B	0.027	0	3.9	
		5A	0.001	0	0	Xanthone
Styryltriphenylcyclopropene **3b**	62747-63-1	3A	0.037	0	49	
		3B	0.039	0	34	
		3C	0.047	0	5.5	
		3D	0.049	0	5.1	
		6A	0.016	0	2.1	Xanthone
		6B	0.013	0	2.5	Xanthone
		6C	0.002	0	2.4	4-Dimethylaminobenzophenone
Isobutenyltriphenylcyclopropene (**3c**)	62747-64-2	1A	0.0102	0.004	21.2	
		1B	0.0097	*b*	5.9	
		1C	0.0099	*b*	4.2	
		4A	0.140	0	35.6	4-Dimethylamino-benzophenone
		4B	0.128	0	61.7	
tert-Butylisobutenylcyclopropene **5**	62747-65-3	7A	0.003 (1-*tert*-Bu) 0.001 (2-*tert*-Bu) 0.004 (3-*tert*-Bu)	0.003	20	
		8B	0.13 (1-*tert*-Bu) 0 (2-*tert*-Bu) 0.06 (3-*tert*-Bu)	0	63	Xanthone

[a] Run numbers correspond to the Experimental Section. [b] Not determined.

synthesized by the literature procedure[14] for direct comparison. In this instance none (<5%) of the tautomer **35**, an a priori possibility, was formed.

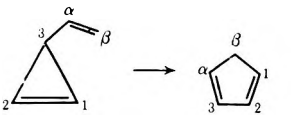
Quantum Yield Determinations and Determination of Multiplicities. We were interested in determining the reaction efficiencies for the various 3-vinylcyclopropene rearrangements in order to correlate these with structure. Also, we were interested in determining efficiencies as a function of direct vs. sensitized conditions with the aim of determining the multiplicity of the excited state undergoing the rearrangement.

All of the quantum yield determinations were carried out with a Wisconsin black box apparatus[15] using solution filters to isolate the wavelength range absorbed by the reactant or sensitizer. An electronic actinometer[16] was employed; this utilized two 1P28 photomultipliers, a multiplexed voltage to frequency converter, and two digital counters. This was calibrated prior to each run and for each wavelength filter used. Low enough conversions were used in each case so that light absorption by products was unimportant; extrapolation to zero time was employed where necessary. Only in the case of 1,3-diphenyl-2-*tert*-butyl-3-isobutenylcyclopropene (**5**) was it not possible to avoid some product light absorption, and up to 20% of the light could have been captured by products, thus diminishing the determined efficiencies by this amount. The reaction efficiency for formation of the unexpected cyclopentadiene **21** is an operational, but not directly theoretically significant number, since this product derives from a two-photon mechanism (vide infra).

The results of the quantum yield determinations are summarized in Table I; note also eq 1a–d. Details of the runs are outlined in the Experimental Section.

Turning now to information bearing on the reaction multiplicity, we note that xanthone (E_T = 71–74 kcal/mol[17a,b]) and *p*-dimethylaminobenzophenone (E_T = 67 kcal/mol[17c]) have energies which should be much higher than any of the triplets of the cyclopropenes studied because of their styrene (E_T = 62 kcal/mol[18]) and *cis*-stilbene (E_t = 57 kcal/mol[19]) chromophores.

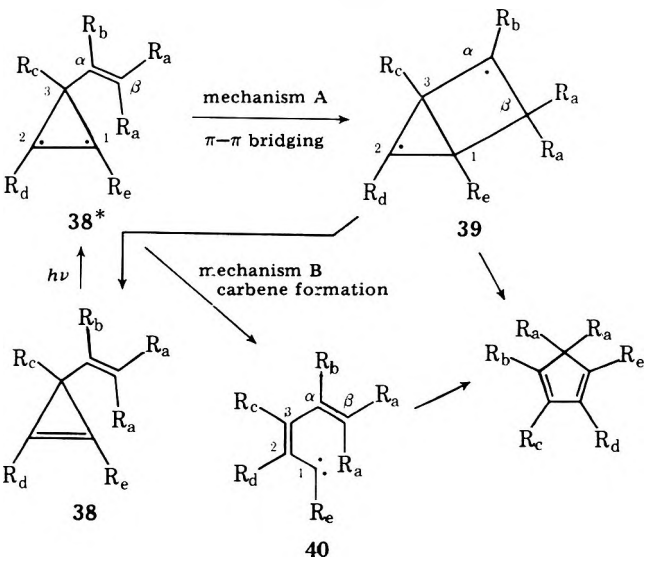
Interpretative Discussion. The first item for discussion is the gross reaction mechanism. Operationally, the skeletal change corresponds to a [1,3]sigmatropic rearrangement in which a three-ring σ bond moves 1,3 and attaches itself to the terminal carbon of the vinyl group (i.e., bond 1–3 breaks and reforms as 1–β, eq 3).



(3)

Two a priori mechanisms seem reasonable. The first of these is termed mechanism A (note Chart V). It begins with π–π bridging in the excited state, with the terminal carbon of the vinyl group bonding to one end of the excited cyclopropene double bond. This leads to housane biradical **39** which may be viewed as a 1,4 diradical in two ways: $\dot{C}_2$–C_1–C_β–$\dot{C}_\alpha$ or $\dot{C}_2$–C_1–C_3–$\dot{C}_\alpha$. Fission of the central bond of such diradicals is common in photochemistry.[20] The first type of fission

Chart V. Possible Mechanisms for the Cyclopropene Rearrangement



merely regenerates the vinylcyclopropene reactant. The second type leads to the observed cyclopentadiene product.

Alternative mechanism B is also shown in Chart V. Here, the excited state undergoes fission of bond 1–3 to give carbene **40,** followed by an electrocyclic closure to give cyclopentadiene product. Indeed, there is evidence for the formation of carbenes and diradical configurations of carbenes from cyclopropenes both thermally[21] and photochemically.[12,22]

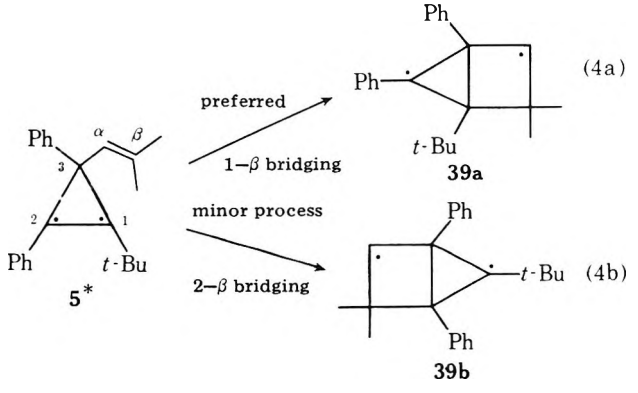
Both mechanisms are skeletally equivalent and lead to the change outlined in Chart V. With regard to the formation of indenes, as encountered in the present study and also as described in the literature,[12] either mechanism will account for the observed products. A diradical variant of the carbene mechanism has already been considered as a possibility in the literature[12a,c,d] (vide supra).

Our evidence accords nicely with the excited-state diradical mechanism A. While mechanism B can not be ruled out, it does not fit the evidence as well.

The first cogent evidence to be considered is the effect of phenyl substitution as group R_b (note Chart V) on the α position of the vinyl group of the 3-vinylcyclopropenes. Reference to eq 1a and 1b (note also Table I) shows that this phenyl substitution enhances the reaction efficiency by nearly a factor of two. This is understood on the basis of mechanism A (note Chart V); here odd-electron density becomes concentrated on the α carbon of housane diradical **39,** where aryl substitution should stabilize. In this argument, we recognize that quantum yields do not invariably parallel excited-state rate constants.[20b] Nevertheless, strongly suggestive evidence is provided.

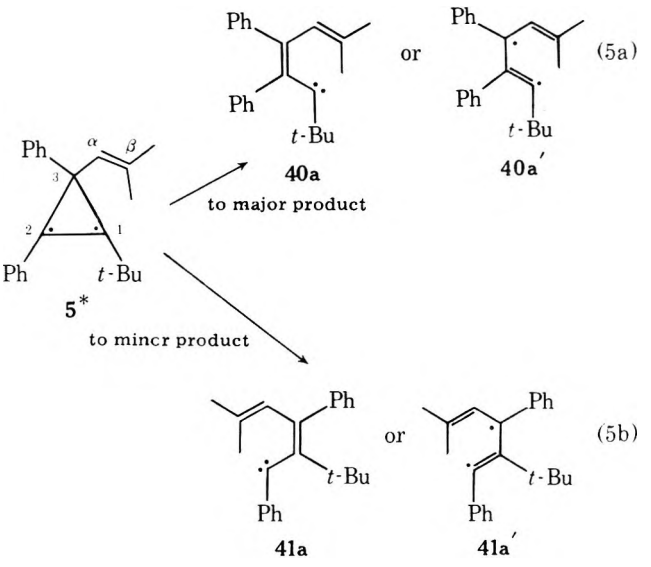
The second point concerns the regioselectivity encountered both in the photorearrangement of *tert*-butyldiphenylisobutenylcyclopropene **5** and in the irradiation of methyltriphenylcyclopropene **12.** Here a consistent pattern is observed.

In the case of the isobutenylcyclopropene **5,** there is a preference for that product arising from bonding between C-1 and the β carbon (note Chart V and eq 1d), although bonding between C-2 and the β carbon was an a priori possibility. This makes sense in terms of mechanism A, where there is a preference for R_d to be phenyl rather than *tert*-butyl as a consequence of the demand for odd-electron delocalization by the phenyl substituent. This can be formulated as shown in eq 4a,b.

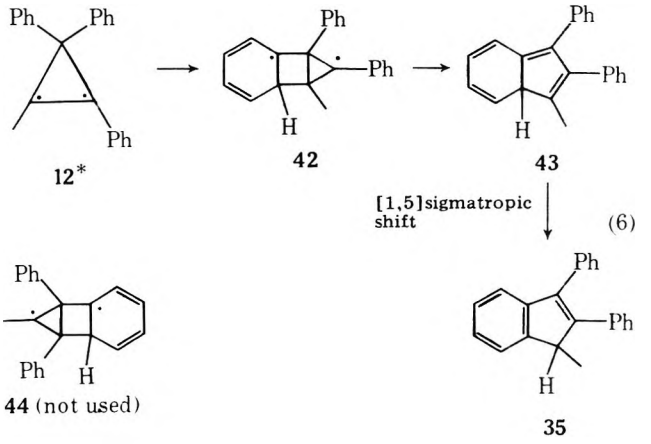


Conversely, mechanism B seems in discord with the reaction regioselectivity since it would require fission of that cyclopropene bond which would afford the less stable *tert*-butyl-substituted carbene (or its diradical configuration **41a'**) rather than the more stable aryl-stabilized carbene **41a** (eq 5a,b).

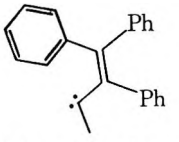
The same logic applies to the preferential formation of one indene (i.e., **35** in eq 2a) in the photolysis of 1-methyl-2,3,3-triphenylcyclopropene (**12**). The diradical mechanism predicts that bridging between the excited cyclopropene double bond



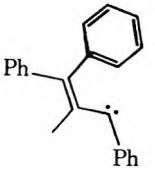
and the ortho position of a phenyl group at C-3 should be preferred since this gives maximum odd-electron delocalization (compare **42** vs. **44,** eq 6).



Again, the carbene mechanism B would require formation of the non-aryl-stabilized carbene **45** in order to account for the regiospecificity.



45 (less stabilized; used in mech B)



46 (more stabilized; not used in mech B)

If there is a weakness in this argument, it derives from our lack of knowledge of the effect of phenyl substitution on the kinetics of opening of the cyclopropenyl σ bond. Thus, for example, on excitation the phenyl group is initially coplanar with the three-ring since it is part of an excited styryl moiety. Hence, it does not overlap initially with the σ bond breaking to form a carbene (or diradical configuration). Still, if more energy were to be gained by overlap with the σ rather than with the π component of the carbene, phenyl rotation should occur.

Another result of interest is the higher reaction efficiency observed in the direct irradiations of the simple vinylcyclopropenes relative to the isobutenyl analogues (note Table I and equations 1a–d). This is logically derived from steric hindrance in the approach of the β carbon of the vinyl group to the electronically excited cyclopropene π bond as pictured in mechanism A. To the extent that there is a trend in carbene reactivity, the present experimental results are the reverse of that which one would expect. Where preferences are shown, it is the more substituted π bond which tends to be more reactive;[23] thus, mechanism B would suggest that the diminished reactivity of the isobutenyl-substituted cyclopropenes is in contrast to expectation.

Additionally, the carbene mechanism could lead to either of two stereoisomers in the case of the reaction of 3-vinylcyclopropenes; for example, note carbenes **40a** and **41a** in eq 5a and 5b. Both carbenes have the divalent carbon pictured cis to the terminal double bond, thus mechanistically allowing electrocyclic closure to the cyclopentadiene product. One might argue that the observed regioselectivity could be accounted for on the basis of a carbene process (i.e., mechanism B) if ring opening of excited state **5*** to give the *tert*-butyl-substituted carbene **40a** afforded the cis isomer required for completion of the reaction while ring opening to give the phenyl-substituted carbene gave the trans stereoisomer of **41a**, which could not cyclize.[24] However, the case of the 3,3-diphenylcyclopropene **12** has no such stereochemical possibilities since carbenes **45** and **46** both have a *cis*-phenyl group; yet, the same regiospecificity was observed.

Another point is that in addition to preferentially obtaining the cyclopentadiene **19**, which would have to be derived from the less stable *tert*-butylcarbene **40a**, the only indene product (**22**) is the one expected from the trans isomer (**40b**) of the same carbene (**40a**). This argues against unfavorable carbene stereochemistry controlling since the stereoisomer of phenylcarbene **41**, which is unfavorable for cyclopentadiene formation, should be favorable for indene generation. Yet, the indene derived from the more stable carbene **41b** (isomer of **41a**) is not observed.

Finally, in connection with the carbene mechanism, one might concern himself that three-ring opening is reversible and that the less stable of the two carbenes preferentially closes to cyclopentadiene while the more stable carbene reverts preferentially to cyclopropene. Indeed, reversion to cyclopropene could be more rapid than five-ring formation for entropy reasons, and formation of cyclopropenes from carbenes is expected. However, the transition state in carbene mechanism B has some residual carbene character, and the transition state derived from the more stable carbene should be favored. This is tantamount to saying that the effect of carbene stabilization by phenyl should be greater on the first step's preequilibrium constant than in slowing five-ring cyclization in the second step by virtue of the more stable carbene being less reactive. The three-ring opening step involves formation of a full carbene center, while the second step only partially dissipates this valence.

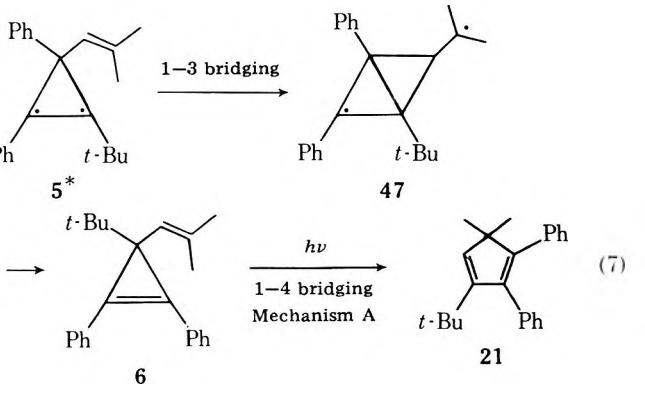
We now turn to the reaction multiplicity. In the nonisobutenyl examples, the evidence points to the excited singlet as the rearranging species. Thus, sensitization of reactants gave no rearrangement.

In the case of the 3-isobutenylcyclopropenes **3c** and **5**, both direct and sensitized irradiations led to reaction. The direct irradiations do indeed represent reactions of the excited singlets rather than mere intersystem crossing to give the triplets with subsequent reaction. This is clear from inspection of eq 1c and 1d, which reveal that the indene products resulting from the direct irradiation are absent in the sensitized runs. Also, the minor cyclopentadiene photoproduct **20** that formed on the direct irradiation of *tert*-butylisobutenylcyclopropene **5** was absent in the sensitized runs. This means that the direct irradiations had product distributions distinctly different from those of the sensitized runs and that the products must derive from an excited state other than the triplet state.

Remarkably, the isobutenyl triplet quantum yields were approximately an order of magnitude greater than the singlet ones. The regioselectivity was enhanced even further in the triplet reaction compared with the singlet process. This marked triplet reactivity though was confined to the isobutenyl-bearing reactants. It is possible that the reactivity difference between the simple vinyl cases and these is derived from steric hindrance of the free rotor energy dissipation,[25] often diminishing the reactivity of triplets having potentially rotating π bonds.

Bearing on the carbene vs. diradical mechanism is Pincock's finding[22d,e] that three-ring opening does not appear to occur in an analogous cyclopropene triplet. Since bimolecular photochemistry intervened, the argument is not entirely conclusive. But the high triplet reactivity of the presently studied vinylcyclopropenes contrasts and thus suggests the lack of carbene involvement in the sensitized examples.

The last aspect requiring discussion is the formation of a product not derived from the mechanisms discussed above. Thus, 1,2-diphenyl-3-*tert*-butyl-5,5-dimethylcyclopentadiene (**21**) was isolated in both the direct and sensitized reactions of *tert*-butylisobutenylcyclopropene **5**. This is a product which would be expected from an isomeric cyclopropene reactant, namely, 1,2-diphenyl-3-*tert*-butyl-3-isobutenylcyclopropene (**6**). Such a cyclopropene can be seen as arising from an incipient di-π-methane rearrangement to give diradical **47** (note eq 7), which then can revert to reactant or proceed onward to



(7)

the isomeric cyclopropene **6**.[26] This cyclopropene then should proceed onward to give the observed anomalous cyclopentadiene product **21**. NMR monitoring of the reaction did not reveal the cyclopropene intermediate (i.e., **47**), and thus it appears to be consumed as rapidly as it is formed; with a *cis*-stilbenyl chromophore, enhanced absorbtion by **6** is indeed expected.

In summary, the rearrangement of vinylcyclopropenes reveals itself, independent of which mechanism eventually proves to be correct, to be a potentially useful synthetic approach to substituted cyclopentadienes. The reaction promises to be especially general and thus adds to the repertoire of organic photochemical processes. Further efforts on the reaction mechanism and the limits of the reaction are continuing in our laboratories.

Experimental Section[27]

1,2,3-Triphenyl-3-methylcyclopropene. The cyclopropene was prepared by the method of Breslow and Dowd.[6]

1,2-Diphenyl-3-methyl- and 2,3-Diphenyl-1-methylindene. The indenes were prepared by the method of Koelsch and Johnson.[14]

***trans*-3,4-Diphenylbut-3-en-2-one Tosylhydrazone.** A solution

of 29.1 g (131 mmol) of *trans*-3,4-diphenylbut-3-en-2-one[28] and 24.4 g (131 mmol) of *p*-toluenesulfonylhydrazine in 500 mL of anhydrous methanol containing 2 mL of glacial acetic acid was refluxed for 3 h. After cooling, the tosylhydrazone was filtered and washed with methanol. Drying in vacuo gave 44.9 g (88%) of the tosylhydrazone: mp 142–144.5 °C; NMR ($CDCl_3$) τ 8.03 (s, 3 H, CH_3), 7.53 (s, 3 H, CH_3), 2.20–3.33 (m, 16 H, aromatic and vinyl), 1.75 (broad s, 1 H, NH); IR ($CHCl_3$) 2.79, 3.03, 3.11, 3.25, 3.31, 3.42, 3.48, 6.26, 6.70, 6.94, 7.24, 7.50, 7.67, 7.78, 7.90, 8.47, 8.63, 9.20, 9.49, 9.86, 11.03, 11.24, 12.00, 12.38, 14.53 μm.

1,3-Diphenyl-2-methylcyclopropene. The following procedure is based on the general method of Dürr.[7] A degassed suspension of 19.5 g (50.0 mmol) of 3,4-diphenylbut-3-en-2-one tosylhydrazone and 3.00 g (125 mmol) of oil-free sodium hydride in 3 L of 9:1 (v/v) pentane–diglyme was irradiated, with vigorous stirring, through a 2-mm Pyrex filter with a 450-W medium-pressure mercury lamp until TLC analysis indicated complete consumption of the starting material. The suspension was filtered, and the filtrate was thoroughly washed with water. The pentane solution was dried and concentrated in vacuo to give 7.20 g of a light yellow oil. The oil was taken up in ca. 10 mL of pentane and stored in a freezer overnight. The solid impurities were removed by filtration, and the filtrate was concentrated in vacuo. This was repeated to give 6.10 g (59%) of NMR-pure cyclopropene. Attempts to chromatograph the cyclopropene led to extensive decomposition: NMR (CCl_4) τ 7.68 (s, 3 H, CH_3), 7.20 (s, 1 H, CH), 2.54–3.35 (m, 10 H, aromatic); IR (CCl_4) 3.26, 3.29, 3.42, 5.43, 6.26, 6.73, 6.94, 7.42, 8.35, 9.08, 9.35, 9.78, 11.05, 14.53 μm. MS Calcd for $C_{16}H_{14}$: *m/e* 206.10955. Found: *m/e* 206.10986.

1,2-Diphenyl-3-methylcyclopropenium Fluoroborate. The general method of Breslow[8] was used. To a solution of 9.24 g (28.0 mmol) of trityl fluoroborate in 50 mL of dry acetonitrile was added a solution of 6.10 g (29.6 mmol) of 1,3-diphenyl-2-methylcyclopropene in 75 mL of anhydrous ether. After stirring for 30 min the solution was diluted with 800 mL of cold anhydrous ether. The precipitate was filtered and dried to give 3.65 g (45%) of the fluoroborate salt: NMR (CD_3CN) τ 6.79 (s, 3 H, CH_3), 1.48–2.36 (m, 10 H, aromatic); IR (KBr) 3.16, 3.28, 3.35, 3.42, 6.30, 6.71, 7.08, 7.48, 7.67, 7.73, 7.85, 8.54, 9.60, 13.05, 14.67 μm.

The fluoroborate was also prepared from 1,2-diphenyl-3-methylcyclopropene.[29]

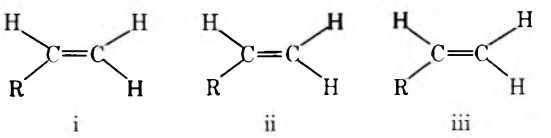
1-Methyl-2,3,3-triphenylcyclopropene. Method A. To a stirred suspension of 4.89 g (16.8 mmol) of 1,2-diphenyl-3-methylcyclopropenium fluoroborate in 200 mL of anhydrous ether was added 20 mL of 1 M phenylmagnesium bromide in ether. After 1 h the mixture was poured into water and extracted with ether. The ether extract was dried and concentrated in vacuo to give a 2:1 mixture of 1,2,3-triphenyl-3-methylcyclopropene and 1-methyl-2,3,3-triphenylcyclopropene. The cyclopropenes were separated by column chromatography on silica gel.

Method B. A mixture of 45.0 g (388 mmol) of diphenyldiazomethane and 10.0 g (51.6 mmol) of 1-phenylpropyne was stirred at room temperature until the purple color disappeared. The excess 1-phenylpropyne was removed in vacuo. Ether was added and the benzophenone azine was removed by filtration. The azine was washed with ether, and the combined filtrates were concentrated in vacuo. From the residue 437 mg (3.3%) of 1-methyl-2,3,3-triphenylcyclopropene, mp 94–95.5 °C, was obtained after chromatography on a 2.5 × 7.5 cm silica gel column and recrystallization from ethanol: NMR (CCl_4) τ 7.60 (s, 3 H, CH_3), 2.33–3.17 (m, 15 H, aromatic); IR ($CHCl_3$) 3.25, 3.27, 3.32, 3.44, 3.52, 5.40, 6.23, 6.72, 6.94, 7.12, 8.70, 8.95, 9.36, 9.77, 10.03, 10.20, 10.97, 11.29, 14.51 μm; UV (EtOH) λ_{max} 261 nm (ϵ 15 900). MS Calcd for $C_{22}H_{18}$: *m/e* 282.14085. Found: *m/e* 282.14034.

1,2,3-Triphenyl-3-isobutenylcyclopropene. To a stirred ether suspension (200 mL) of 6.94 g (20.0 mmol) of triphenylcyclopropenium bromide[30] was added 50.0 mmol of isobutenylmagnesium bromide[31] in 50 mL of tetrahydrofuran. The suspension was stirred for 30 min before quenching with water. The aqueous phase was extracted with ether, and the extract was washed with water, dried, filtered, and concentrated in vacuo. The residue, a yellow oil which crystallized on standing, was purified by percolating through a 2.5 × 15 cm column of silica gel, eluting with 2.5 L of hexane. The colorless solid product was recrystallized from ethanol to give 4.06 g (63%) of the pure cyclopropene: mp 133–135 °C; NMR (CCl_4) τ 8.42 (broad s, 3 H, CH_3), 8.23 (broad s, 3 H, CH_3), 4.33 (broad s, 1 H, vinyl), 2.29–3.07 (m, 15 H, aromatic); IR (CCl_4) 3.24, 3.26, 3.31, 3.37, 3.43, 5.52, 6.24, 6.72, 6.93, 7.28, 7.70, 8.05, 8.55, 8.68, 10.78, 11.01, 11.41, 14.01, 14.35, 14.55 μm; UV (EtOH) λ_{max} 331 nm (ϵ 20 500), 313 (25 500), 228 (26 600).

Anal. Calcd for $C_{25}H_{22}$: C, 93.12; H, 6.88. Found: C, 93.09; H, 6.98.

1,2,3-Triphenyl-3-vinylcyclopropene. To a stirred ether (200 mL) suspension of 6.94 g (20.0 mmol) of triphenylcyclopropenium bromide[30] was added 40.0 mmol of vinylmagnesium bromide[31] in 50 mL of tetrahydrofuran. The reaction mixture was stirred at room temperature for 30 min before quenching with water. The aqueous solution was extracted with ether, and the extract was washed with water, dried, and concentrated in vacuo. The product was percolated through a 2.5 × 90 cm column of silica gel. Elution with 4 L of hexane and recrystallization from ethanol gave 3.54 g (60.2%) of a pure colorless solid: mp 88.5–90.0 °C; NMR (CCl_4) τ 4.90 (d, 1 H, see i below), 4.96 (d, 1 H, see ii below), 3.45 (dd, 1 H, see iii below), 2.00–3.04 (m,



15 H, aromatic); IR (CCl_4) 3.22, 3.26, 3.29, 3.43, 3.46, 5.50, 6.18, 6.25, 6.37, 6.72, 6.92, 7.13, 7.25, 7.55, 7.67, 7.78, 8.12, 8.55, 8.67, 9.13, 9.35, 9.78, 10.11, 10.38, 10.79, 11.06, 13.93, 14.60, 15.00 μm; UV (EtOH) λ_{max} 328 nm (ϵ 20 500), 313 (22 700), 227 (20 500).

Anal. Calcd for $C_{23}H_{18}$: C, 93.84; H, 6.16. Found: C, 93.93; H, 5.97.

1,2,3-Triphenylcyclopentadiene. A sample of 1,2,5-triphenyl-1,5-pentanedione was prepared according to the procedure of Allen and Barker.[32] To a solution of 5.00 g (15.5 mmol) of the dione in 120 mL of 2:1 ethanol–water (v/v) was added a large excess of freshly prepared aluminum amalgam, prepared from 1.44 g of aluminum foil and 2% aqueous mercuric chloride followed by rinsing. The mixture was refluxed for 3 h, cooled, and filtered. The solid materials were washed with ether and the combined filtrates concentrated in vacuo. From the colorless oil 1.00 g of the desired diol, mp 132.5–133.5 °C (lit. 132.5–133.5 °C), was obtained by trituration from methanol. The residue obtained from concentration of the filtrate was chromatographed on a 2.5 × 90 cm silica gel column (Matheson, Coleman and Bell; grade 62, 60–200 mesh, slurry packed in 5% ether–hexane). The elution was with 500-mL fractions; fractions 5–7 contained 1.98 g of the desired diol, making the total yield 2.98 g (59.6%). Dehydration of the diol as described by Pauson[9] gave the cyclopentadiene: NMR (CCl_4) τ 6.47 (d, 2 H, J = 1.5 Hz, CH_2), 3.60 (t, 1 H, J = 1.5 Hz, vinyl), 2.70–3.21 (m, 15 H, aromatic); IR (CS_2) 3.23, 3.25, 3.28, 3.47, 5.16, 5.38, 5.58, 6.25, 7.31, 7.42, 7.74, 8.05, 8.24, 8.50, 9.35, 9.44, 9.75, 10.24, 10.87, 11.02, 11.33, 11.48, 14.45 μm; UV (EtOH) λ_{max} 239 nm (ϵ 24 200), 310 (8080). MS Calcd for $C_{23}H_{18}$: *m/e* 294.14085. Found: *m/e* 294.14061.

1,2,3-Triphenyl-3-(1-phenylvinyl)cyclopropene. To a stirred ether (200 mL) suspension of 5.10 g (15.0 mmol) of triphenylcyclopropenium bromide[30] was added 20.0 mmol of 1-phenylethenylmagnesium bromide[31] in 30 mL of tetrahydrofuran. The reaction mixture, after stirring for 45 min, was hydrolyzed by pouring it into water. The aqueous solution was extracted with ether, and the extract was washed with water, dried, and concentrated in vacuo. The resulting yellow oil, which crystallized on standing, was recrystallized from ethanol to give 2.55 g (48%) of the pure cyclopropene: mp 121.5–122.5 °C; NMR (CCl_4) τ 4.63 (s, 2 H, vinyl), 2.00–3.10 (m, 20 H, aromatic); IR (CCl_4) 3.24, 3.26, 3.31, 3.48, 5.52, 6.24, 6.37, 6.71, 6.92, 7.15, 7.24, 7.78, 8.15, 8.55, 8.68, 9.33, 9.84, 10.44, 10.72, 11.12, 14.35, 14.55, 14.95 μm; UV (EtOH) λ_{max} 332 nm (ϵ 17 700), 318 (20 800), 228 (28 100).

Anal. Calcd for $C_{29}H_{22}$: C, 94.01; H, 5.99. Found: C, 93.87; H, 5.98.

1,2-Diphenyl-3-*tert*-butylcyclopropenium Bromide. The following is patterned after the general procedure of Breslow.[30] To a mixture of 7.14 g (50.0 mmol) of *tert*-butylphenylacetylene and 13.46 g (120 mmol) of potassium *tert*-butoxide in 250 mL of dry benzene was added 9.66 g (60.0 mmol) of benzal chloride. The stirred mixture was refluxed under nitrogen for 1.5 h. After cooling the mixture was poured into water and extracted with ether. The ether extract was washed with water, and the ether–benzene solution was dried over anhydrous magnesium sulfate. The cyclopropenium salt was precipitated by bubbling dry hydrogen bromide through the solution. The product was filtered off and dried in vacuo to give 6.20 g (38%) of the bromide: NMR (Me_2SO-d_6) τ 8.33 (s, 9 H, *t*-Bu), 1.33–2.27 (m, 10 H, aromatic); IR (KBr) 3.25, 3.36, 6.27, 6.67, 6.76, 6.92, 7.29, 7.58, 8.24, 11.76, 12.72, 12.90, 14.66 μm.

1,3-Diphenyl-2-*tert*-butyl-3-isobutenylcyclopropene. To a stirred ether (200 mL) suspension of 1,2-diphenyl-3-*tert*-butylcyclopropenium bromide was added 50.0 mmol of isobutenylmagnesium bromide in 50 mL of tetrahydrofuran. The reaction mixture was

stirred at room temperature for 2 h, poured into water, and extracted with ether. The combined ether extract was washed with water and saturated aqueous sodium chloride. The dried ether solution was concentrated in vacuo to give a light yellow oil. The oil was percolated through a 2.5 × 20 cm column of silica gel. Elution with 3 L of hexane gave a colorless oil which was triturated from methanol at −78 °C and recrystallized from methanol to give 2.80 g (46.3%) of the pure cyclopropene: mp 61–63 °C; NMR (CCl_4) τ 8.72 (s, 9 H, *t*-Bu), 8.48 (broad s, 3 H, CH_3), 8.24 (broad s, 3 H, CH_3), 4.56 (broad s, 1 H, vinyl), 2.56–3.10 (m, 10 H, aromatic); IR (CCl_4) 3.23, 3.26, 3.29, 3.33, 3.37, 3.41, 3.43, 3.48, 5.45, 6.27, 6.72, 6.79, 6.93, 7.19, 7.27, 7.35, 7.84, 8.38, 8.53, 8.71, 9.33, 9.42, 9.74, 10.38, 11.01, 11.85, 13.94, 14.33, 14.50, 15.10, 15.70 μm; UV (EtOH) λ_{max} 263 nm (ϵ 19 900), 204 (43 000).

Anal. Calcd for $C_{23}H_{26}$: C, 91.33; H, 8.67. Found: C, 91.33; H, 8.69.

3,3-Dimethyl-1,2,5-triphenyl-1,5-pentanedione. To 8.00 g (50.0 mmol) of 3,3-dimethylacrylophenone[33] and 9.60 g (49.0 mmol) of deoxybenzoin in 150 mL of anhydrous methanol was added 50 mL of a solution of sodium methoxide in anhydrous methanol (prepared by dissolving 1.20 g of sodium in 50 mL of anhydrous methanol). The solution was refluxed for 3 h. The cooled reaction mixture was acidified with glacial acetic acid. The methanol was removed in vacuo, and the residue was taken up in ether–water. The aqueous solution was extracted with ether. The combined extract was washed with water and saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate. The ether was concentrated in vacuo, leaving an oil which was chromatographed on a 2.5 × 200 cm silica gel column (Matheson, Coleman and Bell; grade 62, 60–200 mesh, slurry packed in hexane): fractions 1–6, 3 L of hexane, 2.32 g of unidentified material; 7–9, 1.75 L of 0.5% ether–hexane, 3.32 g of 3,3-dimethylacrylophenone; 10–22, 1.9 L of 0.5% ether–hexane, 3.84 g of deoxybenzoin; 23–29, 1.75 L of 1% ether–hexane, 2.13 g of deoxybenzoin; 30–40, 2.75 L of 2.5–7.5% ether–hexane, 3.02 g (17.3%) of the desired diketone as a colorless oil. The dione was sufficiently pure enough for further transformations. A portion of the dione was rechromatographed and molecularly distilled to give a material with an unchanged NMR spectrum: NMR (CCl_4) τ 8.80 (s, 3 H, CH_3), 8.75 (s, 3 H, CH_3), 6.52–7.40 (AB q, 2 H, J = 16 Hz, CH_2), 4.67 (s, 1 H, CH), 1.97–3.03 (m, 15 H, aromatic); IR (NaCl) 3.23, 3.26, 3.30, 3.37, 3.42, 3.48, 5.97, 6.25, 6.32, 6.70, 6.90, 7.12, 7.20, 7.34, 7.70, 8.03, 8.22, 8.50, 8.63, 9.30, 9.68, 9.93, 10.00, 10.35, 10.78, 11.10, 11.80, 12.75, 13.10, 13.31, 13.52, 14.30, 14.53, 15.18 μm.

Anal. Calcd for $C_{25}H_{24}O_2$: C, 84.24; H, 6.79. Found: C, 84.14; H, 6.83.

4,4-Dimethyl-1,2,3-triphenyl-1,2-cyclopentanediol. To a solution of 921 mg (2.59 mmol) of 3,3-dimethyl-1,2,5-triphenyl-1,5-pentanedione in 30 mL of 2:1 (v/v) ethanol–water was added a tenfold excess of aluminum amalgam prepared from 240 mg of aluminum foil by dipping in 2% aqueous mercuric chloride followed by rinsing with ethanol and ether. The mixture was refluxed for 4.5 h, cooled, and filtered. The solid material was washed with ether, and the filtrate was concentrated in vacuo to give 778 mg (83.6%) of a mixture of diastereomeric diols. The major stereoisomer was separated by fractional recrystallization from hexane, giving 368 mg (39.5%), and the minor isomer was isolated in a less pure state. For further transformation either isomer or a mixture of the isomers was successfully used. Major isomer: mp 186.5–188 °C; NMR ($CDCl_3$) τ 8.85 (s, 3 H, CH_3), 8.60 (s, 3 H, CH_3), 6.90–8.05 (AB q, 2 H, J = 14 Hz, CH_2), 5.73 (s, 1 H, CH), 8.17 (broad s, 1 H, OH), 7.90 (broad s, 1 H, OH), 2.30–3.05 (m, 15 H, aromatic); IR ($CHCl_3$) 2.86, 2.89, 3.22, 3.26, 3.32, 3.37, 3.47, 6.26, 6.73, 6.94, 7.35, 7.60, 7.85, 8.78, 9.08, 9.28, 9.47, 9.70, 10.08, 14.40 μm.

Minor isomer: mp 129–135 °C; NMR (CCl_4) τ 8.73 (s, 3 H, CH_3), 8.67 (s, 3 H, CH_3), 7.03–7.73 (AB q, 2 H, J = 15 Hz, CH_2), 6.47 (s, 1 H, CH), 6.80 (broad s, 1 H, OH), 6.07 (broad s, 1 H, OH), 2.40–3.20 (m, 15 H, aromatic).

Anal. Calcd for $C_{25}H_{26}O_2$: C, 83.76; H, 7.31. Found: C, 83.64; H, 7.36.

5,5-Dimethyl-1,2,3-triphenylcyclopentadiene. A mixture of the above diols was prepared from 712 mg (2.00 mmol) of 1,2,5-triphenyl-3,3-dimethyl-1,5-pentanedione as described above. The diols (531 mg, 1.48 mmol) were dissolved in 12 mL of dry pyridine containing 0.80 mL (8.73 mmol) of phosphorous oxychloride and refluxed for 23 h. After cooling, the solution was partitioned between ether and water. The aqueous solution was extracted with ether, and the combined extract was washed with saturated aqueous ammonium chloride, water, and saturated aqueous sodium chloride. The ether solution was dried and concentrated in vacuo. The crude product was chromatographed on a 20 × 20 cm × 2 mm silica gel plate (E. Merck AG Darmstadt; GF-254). After three developments with hexane, the fastest moving band was collected and the residue recrystallized from ethanol to give 411 mg (84%) of the cyclopentadiene as a colorless solid: mp 137.5–138.5 °C; NMR (CCl_4) τ 8.67 (s, 6 H, CH_3's), 3.67 (s, 1 H, vinyl), 2.20–3.33 (m, 15 H, aromatic); IR (CCl_4) 3.27, 3.30, 3.37, 3.42, 3.48, 6.30, 6.72, 6.81, 6.92, 7.41, 8.32, 8.61, 9.32, 9.77, 11.09, 12.15, 12.64, 12.91, 13.10, 13.50, 13.95, 14.32 μm; UV (EtOH) λ_{max} 300 nm (ϵ 3200), 242 (32 900).

Anal. Calcd for $C_{25}H_{22}$: C, 93.12; H, 6.88. Found: C, 93.08; H, 6.93.

Ethyl 3,3-Dimethyl-2,5-diphenyl-5-oxopentanoate. A solution of sodium ethoxide in ethanol was prepared by dissolving 1.95 g of sodium in 40 mL of absolute ethanol. To the solution was added 12.3 g (75.0 mmol) of ethyl phenylacetate and 14.0 g (87.5 mmol) of 3,3-dimethylacrylophenone. The solution was stirred at room temperature for 26 h and poured into dilute aqueous acetic acid. The aqueous solution was extracted with ether, and the combined ether extract was washed with saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride. The ether solution was dried over anhydrous magnesium sulfate and concentrated in vacuo. The yellow oil was subjected to chromatography on a 2.5 × 140 cm silica gel column (Matheson, Coleman and Bell; grade 62, 60–200 mesh, slurry packed in hexane): fractions 1–4, 3 L of 0.5% ether–hexane, nil; 5–9, 2.5 L of 1% ether–hexane, 9.22 g of a mixture of ethyl phenylacetate and an unidentified product; 10–17, 4 L of 1% ether–hexane, 9.56 g (39.5%) of the desired keto ester as a yellow oil. The spectral properties were as follows: NMR ($CDCl_3$) τ 8.87 (t, 3 H, J = 7 Hz, $-OCH_2CH_3$), 8.67 (s, 3 H, CH_3), 8.63 (s, 3 H, CH_3), 6.53–7.42 (AB q, 2 H, J = 16 Hz, CH_2), 4.07 (d of q, 2 H, J = 1.5, 7.0 Hz, $-OCH_2CH_3$), 5.97 (s, 1 H, CH), 1.92–2.80 (m, 10 H, aromatic); IR ($CHCl_3$) 3.18–3.50 broad, 5.80, 5.95, 6.25, 6.32, 6.70, 6.82, 6.91, 7.30, 7.39, 7.53, 7.69, 7.87, 7.97, 8.05, 8.20, 8.51, 8.58, 8.70, 8.91, 8.97, 9.15, 9.26, 9.62, 9.71, 9.96, 10.10, 10.36, 10.85, 12.42, 14.56 μm. MS Calcd for $C_{21}H_{24}O_3$: *m/e* 324.17254. Found: *m/e* 324.17192.

3,3-Dimethyl-2,5-diphenyl-5-oxopentanoic Acid. To a solution of 29.0 g (518 mmol) of potassium hydroxide in 200 mL of 95% ethanol was added 17.2 g (53.1 mmol) of ethyl 3,3-dimethyl-2,5-diphenyl-5-oxopentanoate. The solution was refluxed for 45 min. After cooling, water was added and the mixture was extracted with ether. The ether extract was discarded. The aqueous solution was acidified with glacial acetic acid, and the mixture was extracted with ether. The ether extract was washed with saturated sodium bicarbonate, water, and saturated sodium chloride. The dried solution was concentrated in vacuo to give 11.2 g (75%) of the crude acid. Recrystallization from ether–pentane gave the pure acid, mp 111–113 °C, in slightly diminished yield: NMR ($CDCl_3$) τ 8.84 (s, 3 H, CH_3), 8.76 (s, 3 H, CH_3), 6.62–7.26 (AB q, 2 H, J = 15 Hz, CH_2), 5.88 (s, 1 H, CH), 1.90–2.81 (m, 10 H, aromatic), 0.52 (broad s, 1 H, COOH); IR ($CHCl_3$) 2.70–4.10, 5.08, 5.29, 5.83–5.97, 6.25, 6.32, 6.70, 6.90, 7.07, 7.22, 7.35, 7.55, 7.70, 8.13, 8.30, 8.48, 8.60, 9.00, 9.27, 9.68, 9.90, 11.08, 14.55, 15.05 μm.

Anal. Calcd for $C_{19}H_{20}O_3$: C, 77.00; H, 6.80. Found: C, 77.14; H, 6.50.

4,4-Dimethyl-3,5-diphenyl-3,4-dihydro-2-pyrone. A mixture of 1.50 g (5.06 mmol) of 3,3-dimethyl-2,5-diphenyl-5-oxopentanoic acid, 25 mL of acetic anhydride, and 10 mL of acetyl chloride was refluxed for 46 h. After removal of the solvent in vacuo, the residue was taken up in ether and washed with aqueous sodium carbonate, water, and saturated aqueous sodium chloride. The ether solution was dried and concentrated in vacuo to give the crude enol lactone in almost quantitative yield. Recrystallization from ether–pentane gave the pure product (1.13 g, 80.1%) as a colorless solid: mp 96.5–98 °C; NMR ($CDCl_3$) τ 9.00 (s, 3 H, CH_3), 8.88 (s, 3 H, CH_3), 6.32 (s, 1 H, CH), 4.30 (s, 1 H, vinyl), 2.21–3.00 (m, 10 H, aromatic); IR ($CHCl_3$) 3.26, 3.32, 3.35, 3.40, 5.67, 6.00, 6.24, 6.69, 6.91, 7.19, 7.30, 7.40, 7.58, 7.65, 7.84, 8.24, 8.47, 8.60, 8.82, 8.93, 9.30, 9.57, 9.75, 10.68, 10.81, 11.17, 11.49, 11.81, 14.71 μm.

Anal. Calcd for $C_{19}H_{18}O_2$: C, 81.98; H, 6.52. Found: C, 82.02; H, 6.53.

2,2,5,5-Tetramethyl-4,7-diphenyl-3,7-heptanedione. To 1.20 g (4.31 mmol) of 4,4-dimethyl-3,5-diphenyl-3,4-dihydro-2-pyrone in 15 mL of anhydrous ether under nitrogen was added 8.0 mL of 1.1 M *tert*-butyllithium in pentane. After 10 min the reaction mixture was poured into saturated aqueous ammonium chloride. The aqueous solution was extracted with ether, and the combined ether extract was washed with water and saturated aqueous sodium chloride. The solvent was removed in vacuo to yield an oil which was chromatographed on a 2.5 × 90 cm silica gel column (Matheson, Coleman and Bell; grade 62, 60–200 mesh, slurry packed in hexane): fractions 1–9, 4.5 L of hexane, 129 mg of unidentified material; 10–14, 1.25 L of 1% ether–hexane, 141 mg of unidentified material; 15–18, 1 L of 1% ether–hexane, 742 mg of the desired dione; 20–23, 1 L of 1% ether–hexane, 125 mg of starting enol lactone. The crude yield of dione was 55.1%

based on unrecovered enol lactone. The dione, a colorless oil, was triturated from hexane at −78 °C. Recrystallization from hexane gave the pure dione as white needles: mp 76–78 °C; NMR ($CDCl_3$) τ 8.97 (s, 9 H, *t*-Bu), 8.86 (s, 3 H, CH_3), 8.84 (s, 3 H, CH_3), 6.59–7.37 (AB q, 2 H, J = 16 Hz, CH_2), 5.23 (s, 1 H, CH), 1.90–2.72 (m, 10 H, aromatic); IR ($CHCl_3$) 3.22, 3.26, 3.31, 3.35, 3.42, 3.47, 5.92, 6.23, 6.32, 6.69, 6.75, 6.88, 7.19, 7.32, 8.14, 8.28, 8.47, 9.35, 9.90, 10.25, 10.83, 11.12, 11.47, 14.33, 14.50 μm.

Anal. Calcd for $C_{23}H_{28}O_2$: C, 82.10; H, 8.39. Found: C, 82.08; H, 8.28.

4,4-Dimethyl-1,3-diphenyl-2-*tert*-butyl-1,2-cyclopentanediol. A solution of magnesium and iodine in 50 mL of ether was prepared by adding 6.75 g (26.6 mmol) of iodine in small portions to a suspension of 1.31 g (53.9 mg-atom) of magnesium powder in refluxing ether. To this solution under nitrogen was added an ether solution containing 3.07 g (9.14 mmol) of 2,2,5,5-tetramethyl-4,7-diphenyl-3,7-heptanedione. The mixture was refluxed overnight, cooled, and poured into saturated ammonium chloride. The aqueous solution was extracted with ether, and the combined ether extract was washed with water and saturated aqueous sodium chloride. The solution was dried over anhydrous magnesium sulfate, and the solvent was removed in vacuo to give the crude product as a yellow oil which was chromatographed on a 2.5 × 90 cm silica gel column (Matheson, Coleman and Bell; grade 62, 60–200 mesh, slurry packed in 2% ether–hexane): fraction 1, 5 L of 2% ether–hexane, 0.420 g of unidentified material; 2–5, 1 L of 2% ether–hexane, 0.850 g of starting diketone; 6–16, 2.5 L of 2% ether–hexane, 1.24 g of diol; 17 and 18, 0.5 L of 50% ether–hexane, 0.600 g of unidentified material. The yield based on unrecovered starting material was 68%. The pure diol was obtained in slightly diminished yield by recrystallization from ether–hexane: mp 113.5–115.5 °C; NMR ($CDCl_3$) τ 9.48 (s, 9 H, *t*-Bu), 8.88 (s, 3 H, CH_3), 8.84 (s, 3 H, CH_3), 7.34–7.96 (AB q, 2 H, J = 14 Hz, CH_2), 6.72 (s, 1 H, OH), 6.54 (s, 1 H, CH), 6.48 (s, 1 H, OH), 2.24–2.80 (m, 10 H, aromatic); IR ($CHCl_3$) 2.76, 2.83, 3.31, 3.46, 3.48, 6.24, 6.70, 6.79, 6.92, 7.15, 7.22, 7.32, 7.83, 8.00–8.50, 9.04, 9.50–9.70, 9.90, 10.15, 10.75, 14.30 μm.

Anal. Calcd for $C_{23}H_{30}O_2$: C, 81.61; H, 8.93. Found: C, 81.83; H, 8.92.

5,5-Dimethyl-1,3-diphenyl-2-*tert*-butylcyclopentadiene. A solution of 86 mg (0.25 mmol) of 4,4-dimethyl-1,3-diphenyl-2-*tert*-butyl-1,2-cyclopentanediol and 0.140 mL (1.53 mmol) of phosphorous oxychloride in 2 mL of dry pyridine under nitrogen was refluxed for 17 h. The solution was cooled and partitioned between ether and water. The ether was washed with saturated ammonium chloride, water, and saturated sodium chloride. The solution was dried over anhydrous magnesium sulfate and concentrated in vacuo to give 70 mg (93%) of the cyclopentadiene. The crude product was recrystallized from ethanol to yield 61 mg (81%) of the pure cyclopentadiene: mp 148.5–151.5 °C; NMR ($CDCl_3$) τ 9.08 (s, 9 H, *t*-Bu), 8.92 (s, 6 H, CH_3's), 3.92 (s, 1 H, vinyl), 2.60–3.01 (m, 10 H, aromatic); IR (CCl_4) 3.24, 3.26, 3.29, 3.31, 3.35, 3.41, 3.44, 3.48, 6.24, 6.75, 6.83, 6.95, 7.20, 7.35, 7.38, 7.75, 7.95, 9.18, 9.37, 9.74, 13.70, 14.28 μm; UV (EtOH) λ_{max} 235 nm (ϵ 6800).

Anal. Calcd for $C_{23}H_{26}$: C, 91.33; H, 8.67. Found: C, 91.06; H, 8.90.

2,2,4,4-Tetramethyl-6,7-diphenyl-3,7-heptanedione. Following the general procedure of Mukaiyama,[34] a solution of 4.00 g (20.2 mmol) of 1,1-dimethyl-2-*tert*-butyl-2-trimethylsilyloxyethylene[35] in 25 mL of methylene chloride was added to a stirred solution of 4.20 g (20.2 mmol) of 2-phenylacrylophenone and 4.00 g (20.5 mmol) of titanium tetrachloride at −78 °C and under nitrogen. Stirring at −78 °C was continued for 30 min. The solution was poured into dilute aqueous sodium carbonate, and the aqueous phase was extracted with methylene chloride. The combined extract was dried over anhydrous magnesium sulfate. The solvent was removed in vacuo to give an oil which was chromatographed on a 2.5 × 90 cm silica gel column (Matheson, Coleman and Bell; grade 62, 60–200 mesh, slurry packed in hexane): fractions 1–9, 2.25 L of 0.5% ether–hexane, 2.96 g of unidentified material; 10–14, 1.25 L of 0.5% ether–hexane, 0.500 g of impure dione. The dione (fractions 10–14) was sufficiently pure enough for further transformation. A portion of the dione was recrystallized from hexane to give a colorless solid: mp 66–68 °C; NMR ($CDCl_3$) τ 8.77 (s, 12 H, t-Bu and CH_3), 8.74 (s, 3 H, CH_3), 8.02 (dd, 1 H, J = 3, 14 Hz, CH_2), 7.14 (dd, 1 H, J = 8, 14 Hz, CH_2), 5.42 (dd, 1 H, J = 3, 8 Hz, CH), 1.96–2.92 (m, 10 H, aromatic); IR ($CHCl_3$) 3.23, 3.30, 3.38, 3.47, 5.94, 6.25, 6.33, 6.70, 6.77, 6.90, 7.20, 7.42, 7.85, 8.13, 8.27, 8.51, 9.30, 9.62, 9.75, 10.00, 10.28, 10.67, 14.40 μm.

Anal. Calcd for $C_{23}H_{28}O_2$: C, 82.10; H, 8.39. Found: C, 82.11; H, 8.36.

1,2-Diphenyl-3-*tert*-butyl-4,4-dimethyl-2,3-cyclopentanediol. To a stirred ether (20 mL) suspension under nitrogen of 300 mg (12.5 mg-atom) of magnesium powder was added 1.52 g (6.00 mmol) of iodine in small portions. When the iodine color had disappeared, an ether solution containing 336 mg (1.00 mmol) of 2,2,4,4-tetramethyl-6,7-diphenyl-3,7-heptanedione was added. The reaction mixture was stirred at reflux for 9 h. The mixture was hydrolyzed by the addition of saturated aqueous ammonium chloride. The aqueous solution was extracted with ether, and the combined ether extract was washed with saturated aqueous sodium chloride. The ether solution was dried over anhydrous magnesium sulfate, filtered, and concentrated in vacuo. The crude diol was purified by chromatography on a 20 × 20 cm × 2 mm silica gel plate (E. Merck AG Darmstadt; GF-254). The diol band was collected after elution with 5% ether–hexane. The solid was recrystallized from ether–hexane to give 261 mg (77.2%) of pure diol: mp 128.5–131.5 °C; NMR ($CDCl_3$) τ 9.20 (s, 9 H, *t*-Bu), 8.62 (s, 3 H, CH_3), 8.48 (s, 3 H, CH_3), 7.83 (broad s, 1 H, OH), 7.15 (AB of ABX, 2 H, CH_2), 5.84 (X of ABX, 1 H, CH), 5.60 (s, 1 H, OH), 2.01–3.25 (m, 10 H, aromatic); IR ($CHCl_3$) 2.82, 2.87, 3.24, 3.27, 3.33, 3.37, 3.41, 6.23, 6.33, 6.69, 6.88, 6.92, 7.15, 7.23, 7.29, 7.39, 7.81, 8.55, 9.41, 9.70, 9.76, 9.95, 10.15, 10.69, 10.87, 11.30, 11.51, 14.22 μm.

Anal. Calcd for $C_{23}H_{30}O_2$: C, 81.61; H, 8.93. Found: C, 81.68; H, 8.96.

1-*tert*-Butyl-2,3-diphenyl-5,5-dimethylcyclopentadiene. To a solution of 88 mg (0.26 mmol) of 1,2-diphenyl-3-*tert*-butyl-4,4-dimethyl-2,3-cyclopentanediol in 2 mL of dry pyridine was added 1.07 g (1.68 mmol) of phosphorous oxychloride. The solution was refluxed for 18 h. After cooling, the reaction mixture was poured into aqueous ammonium chloride. The aqueous solution was extracted with ether, and the combined ether extract was washed with aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride. The dried solution was concentrated in vacuo and the residue chromatographed on a 20 × 20 cm × 2 mm silica gel plate (E. Merck AG Darmstadt; GF-254). After two developments with hexane, the plate was divided into two bands. The first band (largest R_f) contained 25 mg (32.6%) of the desired cyclopentadiene. The second band contained 54 mg (61.3%) of unreacted starting material. Recrystallization from methanol gave the diene as a colorless solid: mp 73–75.5 °C; NMR (CCl_4) τ 8.84 (s, 9 H, *t*-Bu), 8.54 (s, 6 H, CH_3's), 4.06 (s, 1 H, vinyl), 2.60–3.32 (m, 10 H, aromatic); IR ($CHCl_3$) 3.26, 3.32, 3.37, 3.41, 3.43, 3.45, 3.48, 6.25, 6.77, 6.94, 7.10, 7.19, 7.25, 7.34, 7.50, 7.53, 8.15, 8.33, 9.71, 10.47, 10.79, 13.97, 14.99 μm; UV λ_{max} 282 nm (ϵ 5200). MS Calcd for $C_{23}H_{26}$: *m/e* 302.20345. Found: *m/e* 302.20379.

1,2-Diphenyl-3,3,6,6-tetramethyl-1,5-heptanedione. To 10 mL of freshly distilled *tert*-butyl alcohol containing 1.40 g (12.5 mmol) of potassium *tert*-butoxide was added 3.92 g (20.0 mmol) of deoxybenzoin and 2.80 g (20.0 mmol) of 2,2,5-trimethylhex-4-en-3-one.[36] The stoppered flask was shaken vigorously to dissolve the solid materials. The solution was stirred under nitrogen at room temperature for 96 h. The reaction mixture was neutralized and partitioned between ether and water. The combined ether extract was washed with saturated aqueous sodium bicarbonate and water. The solution was dried and concentrated in vacuo to give an oil which was chromatographed on a 2.5 × 90 cm silica gel column (Matheson, Coleman and Bell; grade 62, 60–200 mesh, slurry packed in hexane): fractions 1–3, 1 L of hexane, 243 mg of unidentified material; 4–7, 0.8 L of 0.5% ether–hexane, 2.68 g (40%) of pure dione; 8–11, 0.8 L of 1% ether–hexane, 1.88 g of a mixture of dione and deoxybenzoin. The dione was recrystallized from hexane to give 2.47 g (36.8%) of a colorless solid: mp 90.5–93 °C; NMR ($CDCl_3$) τ 8.93 (s, 9 H, *t*-Bu), 8.86 (s, 3 H, CH_3), 8.84 (s, 3 H, CH_3), 6.25–6.98 (AB q, 2 H, J = 18 Hz, CH_2), 4.48 (s, 1 H, CH), 1.93–2.90 (m, 10 H, aromatic); IR ($CHCl_3$) 3.24, 3.26, 3.29, 3.36, 3.40, 3.45, 5.10, 5.18, 5.51, 5.88, 5.96, 6.25, 6.32, 6.69, 6.75, 6.77, 6.87, 6.90, 7.15, 7.20, 7.29, 7.38, 7.60, 7.65, 7.92, 8.08, 8.33, 8.45, 8.59, 8.89, 9.33, 9.63, 9.71, 9.85, 9.95, 10.44, 10.71, 10.80, 11.01, 11.64, 11.79, 14.16 μm.

Anal. Calcd for $C_{23}H_{28}O_2$: C, 82.10; H, 8.39. Found: C, 82.10; H, 8.40.

1-*tert*-Butyl-2,3-diphenyl-4,4-dimethyl-1,2-cyclopentanediol. An ether (5 mL) solution of 500 mg (1.49 mmol) of 1,2-diphenyl-3,3,6,6-tetramethyl-1,5-heptanedione was added to an ether solution of the magnesium–iodine reagent (a tenfold excess) prepared as described above. The solution was refluxed for 16 h. After cooling, the reaction mixture was poured into saturated aqueous ammonium chloride. The aqueous solution was extracted with ether, and the combined extract was washed with saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride. The dried solution was concentrated in vacuo, and the residue was chromatographed on a 20 × 20 cm × 2 mm silica gel plate (E. Merck AG Darmstadt; GF-254). The diol band was collected eluting with 5% ether–hexane and recrystallized from ethanol to give 411 mg (82%) of the pure diol: mp 163–164 °C; NMR ($CDCl_3$) τ 9.29 (s, 9 H, *t*-Bu),

8.85 (broad s, 6 H, CH_3), 7.47–8.19 (AB q, 2 H, J = 14 Hz, CH_2), 7.00 (broad s, 1 H, OH), 6.35 (s, 1 H, CH), 6.05 (broad s, 1 H, OH), 2.32–3.16 (m, 10 H, aromatic); IR ($CHCl_3$) 2.71–3.18, 3.23, 3.25, 3.32, 3.47, 6.24, 6.32, 6.69, 6.74, 6.81, 6.91, 7.16, 7.22, 7.29, 7.56, 7.73, 8.03, 8.45, 8.88, 8.98, 9.23, 9.42, 9.55, 9.71, 9.97, 10.20, 10.47, 10.98, 11.20, 11.29, 11.90, 14.16 μm.

Anal. Calcd for $C_{23}H_{30}O_2$: C, 81.61; H, 8.93. Found: C, 81.39; H, 8.83.

1,2-Diphenyl-3-*tert*-butyl-5,5-dimethylcyclopentadiene. A solution of 390 mg (1.15 mmol) of 1-*tert*-butyl-2,3-diphenyl-4,4-dimethyl-1,2-cyclopentanediol and 1.80 mL (19.5 mmol) of phosphorous oxychloride in 10 mL of dry pyridine was refluxed for 18 h. After cooling, the reaction mixture was poured into saturated aqueous ammonium chloride, and the aqueous phase was extracted with ether. The combined extract was washed with saturated aqueous sodium bicarbonate, water, and saturated aqueous sodium chloride. The ether solution was dried and concentrated in vacuo. The residue was chromatographed on a 20 × 20 cm × 2 mm silica gel plate (E. Merck AG Darmstadt; GF-254). The fastest moving band was collected and recrystallized from ethanol to give 276 mg (73.9%) of the cyclopentadiene: mp 119–122.5 °C; NMR ($CDCl_3$) τ 8.93 (s, 9 H, *t*-Bu), 8.80 (s, 6 H, CH_3's), 3.97 (s, 1 H, vinyl), 2.44–3.08 (m, 10 H, aromatic); IR (CCl_4) 3.23, 3.25, 3.29, 3.36, 3.40, 3.43, 3.48, 6.25, 6.69, 6.73, 6.76, 6.83, 6.93, 7.18, 7.33, 7.37, 7.49, 7.79, 8.08, 8.31, 8.53, 9.06, 9.30, 9.71, 10.42, 10.68, 10.94, 13.76, 14.12, 14.20 μm; UV (EtOH) λ_{max} 271 nm (ε 7400).

Anal. Calcd for $C_{23}H_{26}$: C, 91.33; H, 8.67. Found: C, 91.05; H, 8.67.

2,3-Diphenyl-4,4-dimethyl-3-hydroxypentanoic Acid. Under Ivanov conditions,[37] an ether (150 mL) solution of 375 mmol of isopropylmagnesium bromide was added dropwise with stirring under nitrogen to a solution of 20.4 g (150 mmol) of phenylacetic acid in 150 mL of anhydrous ether. The solution was stirred at room temperature overnight. To this was added a solution of 22.1 g (136 mmol) of pivalophenone in 150 mL of anhydrous ether over 75 min. The mixture was stirred at reflux for 4 h and then for 18 h at room temperature. The reaction mixture was hydrolyzed by the addition of 250 mL of 5% hydrochloric acid followed by the addition of 200 mL of water. The aqueous solution was extracted with ether, and the extract was washed with water and saturated sodium chloride. The ether solution was dried over anhydrous magnesium sulfate and concentrated in vacuo. The crude product was recrystallized from ether–hexane to give 33.3 g (82%) of the hydroxy acid as a 4:1 mixture of diastereomers. The diastereomers were partially separated by fractional recrystallization from ether–hexane: NMR major isomer ($CDCl_3$) τ 9.32 (s, 9 H, *t*-Bu), 5.40 (s, 1 H, CH), 2.21–3.20 (m, 12 H, aromatic, OH, and COOH); NMR minor isomer ($CDCl_3$) τ 9.04 (s, 9 H, t-Bu), 5.41 (s, 1 H, CH), 2.21–3.20 (m, 12 H, aromatic, OH, and COOH); IR mixture ($CHCl_3$) 2.70–3.13, 3.23, 3.26, 3.34, 3.37, 3.42, 3.47, 5.83, 6.25, 6.69, 6.74, 6.87, 7.16, 7.31, 7.55, 7.78, 7.89, 8.39, 8.52, 8.81, 9.24, 9.33, 9.64, 9.82, 9.97, 10.45, 10.89, 11.20, 14.06, 14.22 μm.

Anal. Calcd for $C_{19}H_{22}O_3$: C, 76.47; H, 7.44. Found: C, 76.27; H, 7.39.

3,4-Diphenyl-4-*tert*-butyloxetan-2-one. The general procedure of Adam[38] was used. A solution of 11.9 g (40.0 mmol) of 2,3-diphenyl-4,4-dimethyl-3-hydroxypentanoic acid (the mixture of diastereomers) and 10 mL (78.5 mmol) of benzenesulfonyl chloride in 200 mL of dry pyridine was stirred for 4 h at room temperature under nitrogen. The reaction mixture was poured into 400 mL of cold 5% hydrochloric acid and extracted with ether. The combined extract was washed with cold 5% hydrochloric acid, water, and saturated aqueous sodium chloride. The solution was dried over anhydrous magnesium sulfate and concentrated in vacuo to give 9.54 g (84.8%) of a mixture of diastereomeric lactones. The mixture of diastereomers was used in subsequent transformations. The major isomer was separated by fractional recrystallization from ether–hexane: mp 107–110 °C; NMR ($CDCl_3$) τ 9.12 (s, 9 H, *t*-Bu), 4.81 (s, 1 H, CH), 2.21–3.02 (m, 10 H, aromatic); IR ($CHCl_3$) 3.23, 3.25, 3.32, 3.34, 3.43, 3.47, 5.46, 6.23, 6.68, 6.83, 6.86, 6.90, 7.15, 7.30, 7.91, 8.22, 8.51, 8.64, 8.70, 9.40, 9.66, 9.74, 9.90, 9.95, 10.18, 10.42, 10.53, 10.91, 11.33, 11.60, 11.76, 13.79, 14.18, 14.93, 16.10 μm.

Anal. Calcd for $C_{19}H_{20}O_2$: C, 81.38; H, 7.20. Found: C, 81.35; H, 7.26.

2,3-Diphenyl-4,4-dimethylpentanoic Acid. To a solution of 360 mg (51.0 mg-atom) of lithium in 150 mL of dry liquid ammonia under nitrogen was added 5.20 g (17.9 mmol) of 3,4-diphenyl-4-*tert*-butyloxetan-2-one (a mixture of diastereomers) in 25 mL of anhydrous ether.[39] After stirring for 1.5 h at reflux, the reaction was quenched by the addition of 3.50 g (65.4 mmol) of solid ammonium chloride. The ammonia was evaporated, and the residue was partitioned between ether and water. The aqueous phase was extracted with ether, and the ether extract was washed with water and saturated aqueous sodium chloride. The dried ether solution was concentrated in vacuo, and the residue was recrystallized from hexane. The product (4.68 g, 90%) was a 1:1 mixture of diastereomers. In subsequent reactions the mixture or either isomer was used successfully. The isomers were separated by fractional recrystallization from hexane. Isomer with mp 184–185 °C: NMR ($CDCl_3$) τ 9.00 (s, 9 H, *t*-Bu), 6.40 (d, 1 H, J = 11 Hz, CH α to carboxyl), 5.89 (d, 1 H, J = 11 Hz, CH β to carboxyl), 2.72–3.24 (m, 10 H, aromatic), 2.02 (broad s, 1 H, COOH); IR ($CHCl_3$) 2.68–3.18, 3.23, 3.25, 3.29, 3.31, 3.34, 3.37, 3.42, 3.46, 5.83, 6.25, 6.33, 6.69, 6.74, 6.87, 7.16, 7.30, 7.55, 7.78, 7.90, 8.38, 8.51, 8.81, 9.01, 9.23, 9.32, 9.64, 9.83, 9.96, 10.44, 10.87, 11.17, 11.49, 11.90, 12.35, 14.06, 14.22 μm.

Isomer with mp 200–202 °C: NMR ($CDCl_3$) τ 9.38 (s, 9 H, *t*-Bu), 6.81 (d, 1 H, J = 11 Hz, CH α to carboxyl), 5.88 (d, 1 H, J = 11 Hz, CH β to carboxyl), 2.36–3.12 (m, 10 H, aromatic), 1.60 (broad s, 1 H, COOH).

Anal. (mp 184–185 °C isomer) Calcd for $C_{19}H_{22}O_2$: C, 80.81; H, 7.86. Found: C, 80.56; H, 7.72.

2-Phenyl-3-*tert*-butyl-1-indanone. A solution of 6.10 g (21.6 mmol) of the mixture of 2,3-diphenyl-4,4-dimethylpentanoic acid isomers and 2 mL of thionyl chloride in 150 mL of dry benzene was refluxed for 1 h. After cooling, 2.93 g (22.0 mmol) of anhydrous aluminum chloride was added in small portions. The resulting solution was refluxed for 1 h. The solution was cooled and poured into cold 5% hydrochloric acid. The aqueous phase was extracted with ether, and the extract was washed with water and saturated aqueous sodium chloride. The ether–benzene solution was dried over anhydrous magnesium sulfate and concentrated in vacuo to give an oil which crystallized on standing. Recrystallization from hexane gave the pure indanone (3.80 g, 66.7%) as a colorless solid: mp 115–117.5 °C; NMR ($CDCl_3$) τ 9.00 (s, 9 H, *t*-Bu), 6.68 (d, 1 H, J = 1.5 Hz, CH), 6.21 (d, 1 H, J = 1.5 Hz, CH), 2.08–3.00 (m, 9 H, aromatic); IR ($CHCl_3$) 3.24, 3.26, 3.30, 3.33, 3.38, 3.40, 3.44, 3.49, 5.88, 6.25, 6.33, 6.71, 6.78, 6.82, 6.85, 6.90, 7.18, 7.32, 7.46, 7.55, 7.62, 7.75, 7.86, 8.16–8.26, 8.54, 8.71, 9.10, 9.18, 9.32, 9.66, 9.86, 10.10, 10.47, 10.70, 11.04, 11.31, 11.60, 11.75, 14.39 μm.

Anal. Calcd for $C_{19}H_{20}O$: C, 86.31; H, 7.63. Found: C, 86.36; H, 7.60.

1-*tert*-Butyl-2-phenyl-3-cyanoindene. Following the general procedure of Evans,[40] a mixture of 2.30 g (8.39 mmol) of 2-phenyl-3-*tert*-butyl-1-indanone, 3 mg of anhydrous zinc iodide, and 3 mL of trimethylsilyl cyanide under nitrogen was stirred at room temperature overnight. The reaction mixture was diluted with ether and washed with water. The ether solution was dried and concentrated in vacuo to give an oil which was analyzed (NMR) as a 1:1 mixture of the desired cyanohydrin trimethylsilyl ethers.

Without further purification, the product was dissolved in 25 mL of 3:1 (v/v) methanol–water containing 300 mg (5.56 mmol) of ammonium chloride. The solution was stirred at room temperature for 4 h before diluting with water and extracting with ether. The combined ether extract was washed with water and dried over anhydrous magnesium sulfate. The solution was filtered and concentrated in vacuo to give the cyanohydrins as a light yellow oil.

The crude cyanohydrins were dissolved in 12 mL of dry pyridine containing 2.34 g (15.2 mmol) of phosphorous oxychloride. The solution was refluxed for 1 h. Upon cooling to room temperature, the solution was poured into cold 5% aqueous hydrochloric acid. The aqueous phase was extracted with ether, and the extract was washed with water and saturated aqueous sodium chloride. The solution was dried and concentrated in vacuo to give 1.92 g of the crude cyanoindene. The crude product was percolated through a 2.5 × 25 cm silica gel column eluting with hexane. Recrystallization of the product from pentane gave 1.34 g (56.5%, based on starting indanone) of pure colorless solid: mp 72–75 °C; NMR ($CDCl_3$) τ 9.18 (s, 9 H, *t*-Bu), 6.04 (s, 1 H, CH), 2.41–3.03 (m, 9 H, *t*-Bu); IR ($CHCl_3$) 3.26, 3.34, 3.35, 3.36, 3.38, 3.40, 4.48, 6.76, 6.83, 6.92, 7.15, 7.30, 7.55, 7.87, 8.68, 8.78, 9.05, 9.22, 9.61, 9.71, 10.15, 10.64, 10.99, 11.49, 11.88, 12.66–13.79, 14.33 μm.

Anal. Calcd for $C_{20}H_{19}N$: C, 87.86; H, 7.01. Found: C, 87.99; H, 7.14.

1-*tert*-Butyl-2-phenyl-3-formylindene. The general procedure of Marshall[41] was employed. To a solution of 590 mg (2.16 mmol) of 1-*tert*-butyl-2-phenyl-3-cyanoindene in 50 mL of dry hexane under nitrogen at −60 °C was added 1.8 mL of a 1.40 M hexane solution of diisobutylaluminum hydride. After stirring for 15 min, the solution was allowed to warm to room temperature and stirring was continued for 2 h. The reaction was quenched by adding 15 mL of saturated aqueous ammonium chloride followed by 10 mL of 5% aqueous hy-

drochloric acid. The two-phase mixture was stirred for 15 min. The aqueous phase was extracted with ether, and the ether–hexane solution was washed with water and saturated aqueous sodium chloride. The dried solution was concentrated in vacuo. The residue was dissolved in 10 mL of 1:1 (v/v) ether–methanol and treated with 10 mL of 5% aqueous hydrochloric acid. After stirring for 2 h, the solution was diluted with water and extracted with ether. The ether solution was dried and concentrated in vacuo to give a red oil. The aldehyde was triturated at −78 °C from hexane. Attempts to chromatograph the product led to complete decomposition of the aldehyde. Recrystallization from hexane–ether gave 310 mg (52.3%) of aldehyde, mp 104–106 °C, sufficiently pure enough for further transformation: NMR ($CDCl_3$) τ 9.29 (s, 9 H, *t*-Bu), 6.16 (s, 1 H, CH), 2.36–3.12 (m, 9 H, aromatic), 0.19 (s, 1 H, CHO); IR ($CHCl_3$) 3.28, 3.29, 3.37, 3.40, 3.42, 3.46, 3.51, 3.52, 6.00, 6.27, 6.43, 6.73 6.79, 6.88, 6.97, 7.20, 7.35, 7.58, 7.75, 7.87, 9.01, 9.17, 9.30, 9.37, 9.77, 10.05, 10.24, 10.63, 11.07, 11.63, 12.66–13.99 μm. MS Calcd for $C_{20}H_{20}O$: *m/e* 276.15141. Found: *m/e* 276.15156.

1-*tert*-Butyl-2-phenyl-3-isobutenylindene. To a stirred suspension of 720 mg (1.74 mmol) of isopropyltriphenylphosphonium iodide in 5 mL of dry tetrahydrofuran at 0 °C under nitrogen was added 1.2 mL of 1.45 M *n*-butyllithium in hexane. The solution was stirred for 45 min at 0 °C. The above aldehyde (311 mg, 1.08 mmol) in 8 mL of dry tetrahydrofuran was added dropwise with stirring to the Wittig reagent. After stirring for 1 h, the reaction mixture was poured into ether–water. The dried ether solution was filtered through Celite and concentrated in vacuo. The residue was chromatographed on a 20 × 20 cm × 2 mm silica gel plate (E. Merck AG Darmstadt; GF-254). After elution with hexane, the fastest moving band was collected to give 151 mg (46.3%) of the indene as a colorless oil: NMR ($CDCl_3$) τ 9.16 (s, 9 H, *t*-Bu), 8.46 (s, 3 H, CH_3), 8.14 (s, 3 H, CH_3), 6.20 (broad s, 1 H, CH), 4.20 (broad s, 1 H, vinyl), 2.41–3.02 (m, 9 H, aromatic); IR (KBr) 3.26, 3.30, 3.34, 3.37, 3.41, 3.45, 3.48, 6.25, 6.70, 6.76, 6.83, 6.93, 7.18, 7.27, 7.34, 7.92, 8.21, 8.37, 8.63, 8.30, 9.72, 10.75, 11.35, 11.82, 12.08, 12.42, 13.07, 13.33, 13.70, 14.31 μm; UV (EtOH) λ_{max} 236 nm (ϵ 19 100), 299 (14 600). MS Calcd for $C_{23}H_{26}$: *m/e* 302.20345. Found: *m/e* 302.20379.

Exploratory Photolysis of 1,2,3-Triphenyl-3-methylcyclopropene. A solution of 483 mg (1.71 mmol) of 1,2,3-triphenyl-3-methylcyclopropene in 500 mL of *tert*-butyl alcohol was purged with vanadous purified nitrogen for 2 h prior to and during the photolysis. The solution was irradiated through a 2-mm Pyrex filter with a Hanovia 450-W medium-pressure mercury lamp in a quartz immersion well. Removal of the solvent in vacuo left 452 mg (93.6%) of a yellow oil which crystallized on standing. The crude photolysate was a 15:1 mixture of 1,2-diphenyl-3-methylindene and starting cyclopropene. The pure indene, mp 91–93 °C (lit. mp 91 °C), was isolated by recrystallization from ethanol. The spectral data were previously unreported: NMR (CCl_4) τ 7.80 (broad s, 3 H, CH_3), 5.32 (broad s, 1 H, CH), 2.53–3.33 (m, 14 H, aromatic); UV (EtOH) λ_{max} 294 nm (ϵ 17 400).

Exploratory Photolysis of 1-Methyl-2,3,3-triphenylcyclopropene. A solution of 173 mg (0.613 mmol) of 1-methyl-2,3,3-triphenylcyclopropene in 250 mL of *tert*-butyl alcohol, distilled from calcium hydride, was purged with purified nitrogen[42] for 1 h prior to and during the photolysis. The solution was irradiated for 2 h through a 2-mm Corex filter with a Hanovia 450-W medium-pressure mercury lamp in a quartz immersion well. Removal of the solvent in vacuo left a yellow oil which was analyzed (NMR) as a 70:30 mixture of 1-methyl-2,3-diphenylindene and starting cyclopropene. Attempts to increase the conversion led to secondary photolysis of the indene. The indene was isolated by column chromatography on silica gel. Recrystallization from ethanol gave the pure indene, mp 105–106 °C (lit. mp 105–106 °C). The isomeric unreported spectral data were as follows: NMR (CCl_4) τ 8.70 (d, 3 H, J = 8 Hz, CH_3), 5.98 (q, 1 H, J = 8 Hz, CH), 2.43–2.90 (m, 14 H, aromatic); UV (EtOH) λ_{max} 303 nm (ϵ 13 300), 234 (17 300).

Exploratory Photolysis of 1,2,3-Triphenyl-3-isobutenylcyclopropene. A solution of 450 mg (1.40 mmol) of 1,2,3-triphenyl-3-isobutenylcyclopropene in 500 mL of anhydrous methanol was purged with purified nitrogen[42] for 1 h prior to and during the photolysis. The solution was irradiated for 4 h through a 2-mm Pyrex filter with a Hanovia 450-W medium-pressure mercury lamp in a quartz immersion well. The solvent was removed in vacuo to give a 2.5:1 mixture of two photoproducts (100% conversion) as a light yellow oil. The product ratio was independent of the percent conversion. The oil was dissolved in 5 mL of hot methanol and allowed to stand for 2 h. The solid material was filtered off to give 268 mg (60%) of NMR-pure 1,2,3-triphenyl-5,5-dimethylcyclopentadiene. The filtrate was concentrated in vacuo, and the residue was chromatographed on a 20 × 20 cm × 2 mm silica gel plate (E. Merck AG Darmstadt; GF-254). After one development with hexane, the fastest moving band was collected. The material was triturated at −78 °C (MeOH) to give, after recrystallization from methanol, 106 mg (26%) of 1,2-diphenyl-3-isobutenylindene. The second band contained nonhydrocarbon material (<5%), presumably methanol incorporation products. This "impurity" was not formed when the photolysis was performed in benzene or *tert*-butyl alcohol. The cyclopentadiene was identical with a sample prepared by an independent method. The structure of the indene rests on its spectral, physical, and microanalytical data: mp 102–104 °C; NMR ($CDCl_3$) τ 8.41 (s, 3 H, CH_3), 8.02 (s, 3 H, CH_3), 5.02 (broad s, 1 H, CH), 3.79 (broad s, 1 H, vinyl), 2.44–3.41 (m, 14 H, aromatic); IR ($CHCl_3$) 3.27, 3.33, 3.37, 3.41, 3.43, 3.50, 5.14, 5.33, 5.55, 5.71, 6.26, 6.70, 6.89, 7.26, 7.45, 8.42, 8.70, 9.32, 9.74, 9.85, 9.98, 10.66, 10.98, 11.49, 11.71, 12.08, 14.47 μm; UV (EtOH) λ_{max} 305 nm (ϵ 14 300). MS Calcd for $C_{25}H_{22}$: *m/e* 322.17215. Found: *m/e* 322.17218.

Anal. Calcd for $C_{25}H_{22}$: C, 93.12; H, 6.88. Found: C, 92.86; H, 6.90.

Exploratory Photolysis of 1,2,3-Triphenyl-3-vinylcyclopropene. A solution of 500 mg (1.70 mmol) of 1,2,3-triphenyl-3-vinylcyclopropene in 500 mL of *tert*-butyl alcohol was purged with purified nitrogen[42] for 1 h and then irradiated with continued purging for 3.25 h through a 2-mm Pyrex filter with a Hanovia 450-W medium-pressure mercury lamp in a quartz immersion well. The solvent was removed in vacuo to give a light yellow oil which crystallized on standing. The recrystallized (ethanol) product (436 mg, 87%) was identical in all respects with an authentic sample of 1,2,3-triphenylcyclopentadiene prepared by the method of Pauson. In runs of varying percent conversion there was no evidence for any indene formation.

Exploratory Photolysis of 3-(1-Phenylvinyl)-1,2,3-triphenylcyclopropene. A solution of 313 mg (0.846 mmol) of 3-(1-phenylvinyl)-1,2,3-triphenylcyclopropene in 200 mL of *tert*-butyl alcohol was purged with purified nitrogen[42] for 1 h prior to and during the photolysis. The solution was irradiated for 35 min through a 2-mm Pyrex filter with a Hanovia 450-W medium-pressure mercury lamp in a quartz immersion well. Removal of the solvent in vacuo left a light yellow oil. The oil was a mixture (3:1) of starting cyclopropene and 1,2,3,4-tetraphenylcyclopentadiene. The oil was taken up in 2 mL of anhydrous ether and allowed to stand overnight. The crystals were filtered to give 62 mg (21%) of pure 1,2,3,4-tetraphenylcyclopentadiene, mp 177–179 °C. This material was identical in all respects with an authentic sample; the mixture melting point was undepressed. The filtrate was concentrated in vacuo, and the residue was recrystallized from ethanol to give 226 mg (70%) of starting cyclopropene. Occasionally the filtrate contained some cyclopentadiene, and in this case the residue was redissolved in ether and the cyclopentadiene was allowed to crystallize out. Filtration removed the cyclopentadiene. The starting material could then be recovered as described above. Again there was no indene product observed.

Exploratory Photolysis of 3-Isobutenyl-1,3-diphenyl-2-*tert*-butylcyclopropene. A solution of 1.40 g (4.63 mmol) of 3-isobutenyl-1,3-diphenyl-2-*tert*-butylcyclopropene in 700 mL of *tert*-butyl alcohol, distilled from calcium hydride, was purged with purified nitrogen[42] for 1 h prior to and during the irradiation. The solution was irradiated for 7.5 h through a 2-mm Corex filter with a Hanovia 450-W medium-pressure mercury lamp in a quartz immersion well. The solvent was removed in vacuo, and the yellow oil was chromatographed on a 2.5 × 140 cm silica gel column (Matheson, Coleman and Bell; grade 62, 60–200 mesh, slurry packed in hexane). Elution with 1 L of hexane gave nil, and 50-mL aliquots were used for fractions 2–38: fractions 2–15, 87 mg of 1,3-diphenyl-2-*tert*-butyl-5,5-dimethylcyclopentadiene; 16–21, 246 mg of a mixture of 1,3-diphenyl-2-*tert*-butyl-3-isobutenylcyclopropene and 1-*tert*-butyl-2-phenyl-3-isobutenylindene; 22–30, 399 mg of a mixture of 1,3-diphenyl-2-*tert*-butyl-3-isobutenylcyclopropene, 1-*tert*-butyl-2,3-diphenyl-5,5-dimethylcyclopentadiene, and 1-*tert*-butyl-2-phenyl-3-isobutenylindene; 31–36, 125 mg of a mixture of 1-*tert*-butyl-2,3-diphenyl-5,5-dimethylcyclopentadiene and 1,2-diphenyl-3-*tert*-butyl-5,5-dimethylcyclopentadiene; 37 and 38, 63 mg of 1,3-diphenyl-3-*tert*-butyl-5,5-dimethylcyclopentadiene.

Fractions 16–28 were combined, and 391 mg of the mixture was chromatographed on a 2.5 × 90 cm silica gel column packed as described above. Elution with hexane in 50-mL fractions gave the following results: fractions 1–5, nil; 6–8, 70 mg of 1-*tert*-butyl-2-phenyl-3-isobutenylindene; 9–12, 126 mg of a mixture of 1-*tert*-butyl-2-phenyl-3-isobutenylindene, 1,2-diphenyl-3-*tert*-butyl-5,5-dimethylcyclopentadiene, and 1,3-diphenyl-2-*tert*-butyl-3-isobutenylcyclopropene; and 13–18, 87 mg of 1,2-diphenyl-3-*tert*-butyl-5,5-dimethylcyclopentadiene. 1-*tert*-Butyl-2,3-diphenyl-5,5-dimethylcyclopentadiene could not be obtained completely free from

the other products. These compounds were identical with samples prepared by independent syntheses.

Photolysis Equipment and Quantum Yield Determinations. Quantum yield irradiations were performed on the black box apparatus previously described.[15] Light output was monitored by ferrioxalate actinometry,[43] and the light absorbed in the reaction cell was determined by the splitting ratio technique.[15]

For the direct irradiations the solution filters employed were as follows: filter A, (a) 2 M nickel sulfate in 5% sulfuric acid, (b) 0.80 M cobalt sulfate in 5% sulfuric acid, and (c) 0.10 M copper sulfate in 5% sulfuric acid (combination (2.5 cm thickness for each of three cells) gave a 38% transmission maximum at 314 nm and was opaque above 353 nm and below 283 nm); filter B, (a) 2 M nickel sulfate in 10% sulfuric acid, (b) 2 M cobalt sulfate in 10% sulfuric acid, and (c) 0.0002 M bismuth trichloride in 10% hydrochloric acid (combination gave an 18% transmission maximum at 280 nm and was opaque above 305 nm and below 255 nm); filter C, (a) 0.19 M nickel sulfate in 10% sulfuric acid, (b) 1 M cobalt sulfate in 10% sulfuric acid, and (c) 0.01 M sodium metavanadate in 0.10 M aqueous sodium hydroxide (combination gave a 16% transmission maximum at 356 nm and was opaque above 388 nm and below 328 nm); filter D, (a) 1 M cobalt sulfate in 5% sulfuric acid, (b) 1 M copper sulfate in 5% sulfuric acid, and (c) 0.10 M sodium metavanadate in 0.10 M aqueous sodium hydroxide (combination gave a maximum transmission of 29% at 370 nm and was opaque above 430 nm and below 345 nm). All filter solutions were stable during the irradiations.

The quantum yields for product formation were determined by high-pressure liquid chromatography (LC) and, where noted, NMR spectroscopy. The columns used for the LC analysis were as follows: column A, a 4 ft × ⅛ in column packed with high-speed, Woelm alumina (particle size 18–30 μm); column B, a 15-¾ × ⅛ in column packed with high-speed, Woelm alumina (particle size, 18–30 μm). For calibration (column A) of the high-pressure liquid chromatographic system with respect to 1,2,3-triphenyl-3-isobutenylcyclopropene and 1,2,3-triphenyl-5,5-dimethylcyclopentadiene, the internal standard employed was 3-(1-phenylvinyl)-1,2,3-triphenylcyclopropene. For calibration of column B with respect to 3-(1-phenylvinyl)-1,2,3-triphenylcyclopropene, 1,2,3-triphenyl-3-vinylcyclopropene, 1,2,3,4-tetraphenylcyclopentadiene, and 1,2,3-triphenylcyclopentadiene, the internal standard used was 1,1-bis(*p*-methoxyphenyl)-2-methyl-1-propene.

The retention times[44] for column A were the following: 1,2,3-triphenyl-5,5-dimethylcyclopentadiene, 7.5 min; 1,2,3-triphenyl-3-isobutenylcyclopropene, 11 min; 3-(1-phenylvinyl)-1,2,3-triphenylcyclopropene, 28 min. The retention times for column B were as follows: 3-(1-phenylvinyl)-1,2,3-triphenylcyclopropene, 3.1 min; 1,2,3,4-tetraphenylcyclopentadiene, 7.5 min; 3-vinyl-1,2,3-triphenylcyclopropene, 1.9 min; 1,2,3-triphenylcyclopentadiene, 5 min; 1,1-bis(*p*-methoxyphenyl)-2-methyl-1-propene, 28.8 min.

Summary of the Quantum Yield Results for the Direct Irradiation of 1,2,3-Triphenyl-3-isobutenylcyclopropene. For each of the runs filter A was used, and 750 mL of purified benzene was used as solvent. The results are listed as follows: starting cyclopropene, mass (mmol), light absorbed, 1,2,3-triphenyl-5,5-dimethylcyclopentadiene (mmol), quantum yield, and percent conversion.

Run 1A: Starting cyclopropene, 145 mg (0.451 mmol), 9.40 mEinstein, 1,2,3-triphenyl-5,5-dimethylcyclopentadiene (0.096 mmol), Φ = 0.0102, 21.2%. Note: analysis by NMR spectroscopy confirmed the above quantum yield; additionally the quantum yield for the formation of 1,2-diphenyl-3-isobutenylindene was estimated to be 0.004.

Run 1B: Starting cyclopropene, 139 mg (0.431 mmol), 2.63 mEinstein, 1,2,3-triphenyl-5,5-dimethylcyclopentadiene (0.026 mmol), Φ = 0.0097, 5.9%.

Run 1C: Starting cyclopropene, 156 mg (0.485 mmol), 2.02 mEinstein, 1,2,3-triphenyl-5,5-dimethylcyclopentadiene (0.020 mmol), Φ = 0.0099, 4.2%.

Summary of the Quantum Yield Results for the Direct Irradiation of 3-Vinyl-1,2,3-triphenylcyclopropene. For each of the runs filter A was used, and 750 mL of purified benzene was used as solvent. The data are listed as follows: starting cyclopropene, mass (mmol), light absorbed, 1,2,3-triphenylcyclopentadiene (mmol), quantum yield, and percent conversion.

Run 2A: Starting cyclopropene, 178 mg (0.604 mmol), 1.54 mEinstein, 1,2,3-triphenylcyclopentadiene (0.042 mmol), Φ = 0.028, 7%.

Run 2B: Starting cyclopropene, 206 mg (0.702 mmol), 1.01 mEinstein, 1,2,3-triphenylcyclopentadiene (0.027 mmol), Φ = 0.027, 3.9%.

Summary of the Quantum Yield Results for the Direct Irradiation of 3-(1-Phenylvinyl)-1,2,3-triphenylcyclopropene. For each of the runs filter A was used, and 750 mL of purified benzene was used as solvent. The data are listed as follows: starting cyclopropene, mass (mmol), light absorbed, 1,2,3,4-tetraphenylcyclopentadiene (mmol), quantum yield, and percent conversion.

Run 3A: Starting cyclopropene, 171 mg (0.462 mmol), 6.22 mEinstein, 1,2,3,4-tetraphenylcyclopentadiene (0.227 mmol), Φ = 0.0365, 49%.

Run 3B: Starting cyclopropene, 151 mg (0.409 mmol), 3.47 mEinstein, 1,2,3,4-tetraphenylcyclopentadiene (0.138 mmol), Φ = 0.0395, 34%.

Run 3C: Starting cyclopropene, 316 mg (0.853 mmol), 1.02 mEinstein, 1,2,3,4-tetraphenylcyclopentadiene (0.048 mmol), Φ = 0.0469, 5.5%.

Run 3D: Starting cyclopropene, 351 mg (0.948 mmol), 1.01 mEinstein, 1,2,3,4-tetraphenylcyclopentadiene (0.049 mmol), Φ = 0.049, 5.1%.

Summary of the Quantum Yield Results for the Sensitized Irradiation of 3-Isobutenyl-1,2,3-triphenylcyclopropene. For run 4A filter C was used, and for run 4B filter D was used. Each run used 750 mL of purified benzene as solvent. The sensitizer used was 4-dimethylaminobenzophenone (enough to absorb 98% of the light). Note: xanthone also was an efficient sensitizer. Run 4A was analyzed by LC and NMR spectroscopy. Run 4B was analyzed by NMR spectroscopy. The data are listed as follows: starting cyclopropene, mass (mmol), light absorbed, 1,2,3-triphenyl-5,5-dimethylcyclopentadiene (mmol), quantum yield, percent conversion, and sensitizer mass.

Run 4A: Starting cyclopropene, 156 mg (0.486 mmol), 1.23 mEinstein, 1,2,3-triphenyl-5,5-dimethylcyclopentadiene (0.173 mmol), Φ = 0.140 (by NMR, Φ = 0.133), 35.6%, 1.99 g.

Run 4B: Starting cyclopropene, 149 mg (0.462 mmol), 2.22 mEinstein, 1,2,3-triphenyl-5,5-dimethylcyclopentadiene (0.285 mmol), Φ = 0.128 (by NMR), 61.7%, 1.59 g.

Note: the 3-isobutenyl-1,2-diphenylindene observed in the direct irradiation was not observed in either run. Chromatography (run 4A) on a 20 × 20 cm × 2 mm silica gel plate after three developments with hexane gave a quantitative mass balance of hydrocarbon material. NMR spectroscopy confirmed the photoproduct to be 1,2,3-triphenyl-5,5-dimethylcyclopentadiene; the absence of the indene was also confirmed.

Summary of the Quantum Yield Results for the Sensitized Irradiation of 3-Vinyl-1,2,3-triphenylcyclopropene. For the sensitized run filter C was used, and 750 mL of purified benzene was used as solvent. Enough xanthone was used to absorb 95% of the light. The data are listed as follows: starting cyclopropene, mass (mmol), light absorbed, 1,2,3-triphenylcyclopentadiene (mmol), quantum yield, percent conversion, and sensitizer mass.

Run 5A: Starting cyclopropene, 178 mg (0.607 mmol), 0.933 mEinstein, 1,2,3-triphenylcyclopentadiene (no significant product formation), Φ < 0.001, ~0%, 2.12 g.

Summary of the Quantum Yield Results for the Sensitized Irradiation of 3-(1-Phenylvinyl)-1,2,3-triphenylcyclopropene. For runs 6A and 6B filter C was used, and xanthone was used as a sensitizer (the xanthone absorbed 70–80% of the incident light). For run 6C filter D was used, and 4-dimethylaminobenzophenone, which absorbed 95% of the incident light, was used as a sensitizer. All runs employed 750 mL of purified benzene as solvent. The data are listed as follows: starting cyclopropene, mass (mmol), light absorbed, 1,2,3,4-tetraphenylcyclopentadiene (mmol), quantum yield, percent conversion, and sensitizer mass.

Run 6A: Starting cyclopropene, 298 mg (0.805 mmol), 1.02 mEinstein, 1,2,3,4-tetraphenylcyclopentadiene (0.017 mmol), Φ = 0.016, 2.1%, 2.07 g of xanthone.

Run 6B: Starting cyclopropene, 223 mg (0.602 mmol), 1.11 mEinstein, 1,2,3,4-tetraphenylcyclopentadiene (0.015 mmol), Φ = 0.013, 2.5%, 2.06 g of xanthone.

Run 6C: Starting cyclopropene, 169 mg (0.457 mmol), 5.01 mEinstein, 1,2,3,4-tetraphenylcyclopentadiene (0.011 mmol), Φ = 0.002, 2.4%, 1.51 g of 4-dimethylaminobenzophenone. Analysis was by NMR spectroscopy.

Summary of the Quantum Yield Results for the Direct Irradiation of 3-Isobutenyl-1,3-diphenyl-2-*tert*-butylcyclopropene. For run 7A filter B was used, and 750 mL of *tert*-butyl alcohol, distilled from calcium hydride, was used as solvent. The analysis was by NMR integration. The results are listed as follows: starting cyclopropene, mass (mmol), light absorbed, 1-*tert*-butyl-2,3-diphenyl-5,5-dimethylcyclopentadiene (mmol), quantum yield, 2-*tert*-butyl-1,3-diphenyl-5,5-dimethylcyclopentadiene (mmol), quantum yield, 3-*tert*-butyl-1,2-diphenyl-5,5-dimethylcyclopentadiene (mmol), quantum yield, 1-*tert*-butyl-2-phenyl-3-isobutenylindene (mmol), quantum yield, and percent conversion.

Run 7A: Starting cyclopropene, 188 mg (0.623 mmol), 14.2 mEin-

stein, 1-*tert*-butyl-2,3-diphenyl-5,5-dimethylcyclopentadiene (0.043 mmol), $\Phi = 0.003$, 2-*tert*-butyl-1,3-diphenyl-5,5-dimethylcyclopentadiene (0.014 mmol), $\Phi = 0.001$, 3-*tert*-butyl-1,2-diphenyl-5,5-dimethylcyclopentadiene (0.056 mmol), $\Phi = 0.004$, 3-isobutenyl-1-*tert*-butyl-2-phenylindene (0.042 mmol), $\Phi = 0.003$, 20%. The percent conversion was obtained by taking the ratio of the integration of vinyl protons of the products to the integration of the vinyl protons of starting material. The integration of the aliphatic region roughly confirmed this.

Summary of the Quantum Yield Results for the Sensitized Irradiation of 3-Isobutenyl-1,3-diphenyl-2-*tert*-butylcyclopropene. For run 8A filter D was used, and for run 8B filter C was used. Each run employed 750 mL of *tert*-butyl alcohol, distilled from calcium hydride, as solvent. The analysis was by NMR integration. The results are listed as follows: starting cyclopropene, mass (mmol), light absorbed, 1-*tert*-butyl-2,3-diphenyl-5,5-dimethylcyclopentadiene (mmol), quantum yield, 3-*tert*-butyl-1,2-diphenyl-5,5-dimethylcyclopentadiene (mmol), quantum yield, percent conversion, and sensitizer mass.

Run 8A: Starting cyclopropane, 233 mg (0.772 mmol), 2.20 mEinstein, 1-*tert*-butyl-2,3-diphenyl-5,5-dimethylcyclopentadiene (0.0097 mmol), $\Phi = 0.004$, 3-*tert*-butyl-1,2-diphenyl-5,5-dimethylcyclopentadiene (0.029 mmol), $\Phi = 0.013$, 5%, 719 mg of 4-dimethylaminobenzophenone.

Run 8B: Starting cyclopropene, 225 mg (0.745 mmol), 2.45 mEinstein, 1-*tert*-butyl-2,3-diphenyl-5,5-dimethylcyclopentadiene (0.15 mmol), $\Phi = 0.13$, 3-*tert*-butyl-1,2-diphenyl-5,5-dimethylcyclopentadiene (0.32 mmol), $\Phi = 0.06$, 63%, 424 mg of xanthone.

In both runs 8A and 8B, 2-*tert*-butyl-1,3-diphenyl-5,5-dimethylcyclopentadiene and 3-isobutenyl-1-*tert*-butyl-2-phenylindene were *not* detected.

Photolysis of 3-*tert*-Butyl-1,2-diphenyl-5,5-dimethylcyclopentadiene. The photolysis was performed on the Wisconsin black box apparatus previously described. Filter B was used, and 750 mL of *tert*-butyl alcohol, distilled from calcium hydride, was used as solvent. The light output was monitored by ferrioxalate actinometry.

A solution containing 256 mg (0.848 mmol) of the cyclopentadiene absorbed 3.30 mEinstein of light. Upon concentration of the solution, no isomeric cyclopentadiene was detectable by NMR spectroscopy. It is estimated that 1% conversion ($\Phi = 0.003$) could have been detected.

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Registry No.—**1**, 12190-18-0; **4**, 65102-01-4; **7**, 38661-88-0; **8**, 56005-69-7; **9**, 65102-39-8; **10**, 65102-02-5; **11**, 58310-19-3; **12**, 62747-66-4; **13**, 4982-35-8; **14**, 15570-45-3; **15**, 62747-67-5; **16**, 62747-68-6; **17**, 65102-40-1; **18**, 65102-41-2; **19**, 62747-69-7; **20**, 62747-70-0; **21**, 62747-71-1; **22**, 62747-72-2; **23**, 65102-18-3; **24**, 65102-42-3; **25**, 65102-23-0; **26**, 65102-24-1; **27**, 65102-25-2; **28**, 65102-26-3; **29** (isomer I), 65102-27-4; **29** (isomer II), 65102-28-5; *cis*-**30**, 65102-29-6; *trans*-**30**, 65102-30-9; **31** (isomer I), 65102-31-0; **31** (isomer II), 65102-32-1; **32**, 65102-33-2; **32** (cyanohydrin TMS ether deriv), 65102-34-3; **32** (cyanohydrin deriv), 65102-35-4; **33**, 65102-36-5; **34**, 65102-37-6; **35**, 51310-25-9; **37**, 62747-73-3; *p*-toluenesulfonylhydrazine, 1576-35-8; trityl fluoroborate, 341-02-6; phenyl bromide, 108-86-1; diphenyldiazomethane, 17421-82-8; 1-phenylpropyne, 673-32-5; isobutenyl bromide, 3017-69-4; vinyl bromide, 593-60-2; 1,2,5-triphenyl-1,5-pentanedione, 58337-98-7; 1,2,3-triphenyl-1,2-cyclopentanediol, 65102-38-7; 1-phenylethenyl bromide, 98-81-7; *tert*-butylphenylacetylene, 4250-82-2; benzal chloride, 98-87-3; 3,3-dimethylacrylophenone, 5650-07-7; deoxybenzoin, 451-40-1; ethyl 3,3-dimethyl-2,5-diphenyl-5-oxopentanoate, 65102-14-9; ethyl phenylacetate, 101-97-3; 3,3-dimethyl-2,5-diphenyl-5-oxopentanoic acid, 65102-15-0; 4,4-dimethyl-3,5-diphenyl-3,4-dihydro-2-pyrone, 65102-16-1; 1,1-dimethyl-2-*tert*-butyl-2-trimethylsilyloxyethylene, 65102-17-2; 2-phenylacrylophenone, 4452-11-3; 2,2,5-trimethylhex-4-en-3-one, 14705-30-7; isopropyl bromide, 75-26-3; phenylacetic acid, 103-82-2; pivalophenone, 938-16-9; trimethylsilyl cyanide, 7677-24-9; isopropyltriphenylphosphonium, bromide, 1530-33-2.

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Photodecomposition of Diethyl Mercurybis(diazoacetate) in Several Heterocyclic Systems[1a]

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The products from the photolysis of diethyl mercurybis(diazoacetate) (1) in the solvent–reactant systems of tetrahydrofuran, tetrahydrothiophene, and pyrrolidine were studied for the determination of the relative importance of the various competing photodecomposition modes. Regioselective insertion reactions into carbon–hydrogen bonds α to the heteroatom were observed, whereas carbon–heteroatom insertion reactions were not observed. Analysis of the organic products, mercury, and nitrogen indicated that carboethoxycarbyne (:$\dot{C}CO_2Et$(A)) could account for 10–30% of the yields of α carbon–hydrogen insertion products. Mercury-containing products from the photodecomposition of 1 in pyrrolidine solution gave evidence for major participation of a mercury carbene (B) intermediate. The evidence also showed that other reaction paths were of little importance.

Monovalent carbon atoms, carbynes, represent an intriguing and little studied class of chemical intermediates. Diethyl mercurybis(diazoacetate) (1),[2] Buchner's compound, has been studied by Strausz et al. and was observed to furnish carboethoxymethyne (A) in low but usable yield under proper photolytic conditions.[3]

$Hg(N_2CCO_2C_2H_5)_2$ $:\dot{C}CO_2C_2H_5$

1 A

We previously reported that photolysis of 1 in chlorocarbon solvents gave products that could arise from association between A and the chlorine atoms; however, the reactions were very complex.[4]

We initiated the study reported here with the objective of finding less complicated reactions that would permit better definition of the photodecomposition paths followed by 1 and allow a better description of the chemistry of the intermediates involved. The heterocyclic solvent–reaction systems of tetrahydrofuran (THF), tetrahydrothiophene (THT), and pyrrolidine were chosen for study because their geometries are well defined and the heteroatom electronic effects are predictable.[5] Thus, meaningful rationalization of the photodecomposition routes and intermediates involved could be obtained from the study of their reaction products.

Results

Photolysis of 1 in THF and THT. Photolysis of 1 in THF gave N_2, Hg, and ethyl α-(tetrahydrofuranyl)acetate (2). Compound 2 was formed in good yield but was not isolated in a good state of purity. Direct hydrolysis of the reaction mixture containing 2 furnished α-(2-tetrahydrofuranyl)acetic acid in 41% yield. Comparison of the acid with a sample prepared unambiguously (see the Experimental Section) served to establish the correct α insertion structure. Products from insertion into either the β carbon–hydrogen bond or the carbon–oxygen bond were not observed.[6]

Photodecomposition of 1 in THT solution gave ethyl α-(2-tetrahydrothienyl)acetate (3) in 54% yield. This product

2 (>41%) 3 (54%)

from α-carbon–hydrogen insertion was identified through its spectral characteristics which were similar to those of 2 and through conversion of the crude reaction product to the corresponding acid in 30% yield. The structure of the acid was confirmed by spectral analysis. The THT system, similar to the THF system, did not yield products resulting from insertion into either the β-carbon–hydrogen bonds or the carbon–sulfur bond.[6]

Olefinic products were observed in small amounts by NMR spectroscopy, but their structures were not determined. Product analysis was performed after nitrogen evolution had ceased even though mercury formation was not complete at that time (Table I).

Photolysis of 1 in Pyrrolidine. Three products were isolated from the photolysis of 1 in pyrrolidine. The major product, 4, was isolated in 48% yield. The structure of 4 was determined from spectral properties and from sodium borohydride reduction[7] to ethyl α-(*N*-pyrrolidino)acetate (5). A

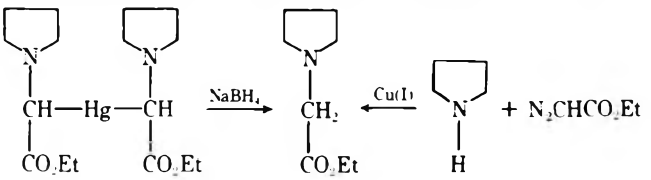

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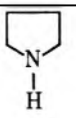
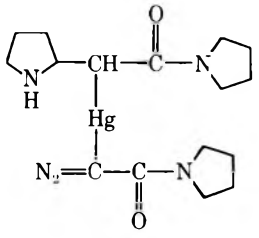
Table I. Mercury and Nitrogen Yields

			
(1) Maximum N_2 Yield, %	90	70	100
(2) Time, min	80	100	60
(3) Hg yield at max N_2 yield, %	20	27	33
(4) Maximum Hg yield, %	70	70	90
(5) Time, min	180	240	170
(6) $2Hg/N_2$ at time = 0	0.19	0.31	0.29
(7) Primary Hg yield, %	9–18	10–21	15–29

sample of **5**, prepared unambiguously from the copper(I)-catalyzed decomposition of ethyl diazoacetate in pyrrolidine,[8] was identical with the product obtained from reduction.

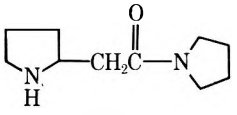
Another mercury-containing product (**6**) was isolated in 19% yield. Compound **6** was sensitive to the light and deposited mercury on standing. Structure **6** should be considered ten-



6 (19%)

tative, but spectroscopic evidence shows that **6** is a diazomercury compound.

Compound **7**, formed from insertion into the α-carbon–hydrogen bond, was isolated in 20% yield. Spectral data were used to determine the structure of **7**. Olefinic products were not observed in the pyrrolidine photolysis reaction.



7 (20%)

Control experiments in THF and pyrrolidine solutions containing ethyl diazoacetate showed that the products observed from **1** were not formed in a route in which **1** was first converted to ethyl diazoacetate followed by photolysis since the control runs were significantly different in the number and types of products obtained. Additionally, dark reaction control experiments with **1** gave no evidence for any significant reactions occurring in the absence of light. Attempts to determine quantum yields were unsuccessful because of the heterogenicity induced from the mercury precipitation.

Mercury and Nitrogen Yields. Mercury and nitrogen yields were accurately determined for all solvent–reactant systems. A plot of the $2Hg/N_2$ ratio (eq 1, Discussion) vs. photolysis time was made and the ratio at $t = 0$ is reported in Table I. The plot could extrapolate to a value of unity if only primary processes occur; a smaller value indicates the fraction of primary process operative.[3] Secondary photolysis processes of mercury-containing intermediates are responsible for the value being less than unity. The extrapolated $2Hg/N_2$ values show a primary Hg yield of 9–21% in THF and THT and a yield of 15–29% in pyrrolidine. The mercury yield equals the carbyne yield in the processes shown by eq 1 and 2 below.

Discussion

The major photodecomposition paths considered for **1** are:[3]

$$\underset{1}{Hg(N_2CCO_2C_2H_5)_2} \xrightarrow{h\nu} Hg + 2N_2 + \underset{A}{:\dot{C}CO_2C_2H_5} \quad (1)$$

$$1 \rightarrow Hg + N_2 + \underset{A}{:\dot{C}CO_2C_2H_5} + N_2\dot{C}CO_2C_2H_5 \quad (2)$$

$$1 \rightarrow N_2 + \underset{B}{C_2H_5O_2C\dot{C}-HgC(N_2)CO_2C_2H_5} \quad (3)$$

$$1 \rightarrow Hg + \underset{C}{2N_2\dot{C}CO_2C_2H_5} \quad (4)$$

$$1 \rightarrow Hg + N_2 + \underset{D}{2C_2H_5OCOCN} \quad (5)$$

Only processes 1 and 2 simultaneously yield N_2, Hg, and A. Analysis of the $2Hg/N_2$ ratio for process 1 as a function of time and extrapolation to time equals zero gave the results shown in Table I. The mercury yield obtained from the $2Hg/N_2$ extrapolation for process 1 equals the carbyne (A) yield; the carbyne yield is one-half the mercury yield if process 2 is used. Thus the carbyne (A) yield in THF and THT solutions is 9–21% and 15–29% in pyrrolidine solution. Prolonged photolysis, after N_2 evolution had ceased, resulted in higher mercury yields indicating that processes other than 1 and 2 are also operative.

The photodecomposition paths followed in both THF and THT solutions appear similar since reaction times and product yields are nearly the same. However, in pyrrolidine solution the photodecomposition paths may be influenced by the solvent since reaction times are shorter, product yields are higher, and mercury-containing materials are observed.

All reactions show an extremely high degree of selectivity for insertion into the α-carbon–hydrogen bond. This could indicate that the intermediate involved in the insertion is associated to a high extent with the heteroatom, or that the heteroatom polarizes the α-carbon–hydrogen bond sufficiently to account for the selectivity.[5,6] If the former case holds, it is unusual that insertion into the carbon–heteroatom is not observed since this is observed in many carbenic reactions.[6]

The mercury-containing compounds, **4** and **6**, observed in the pyrrolidine system give good evidence that process 3 is operative. In fact, process 3 is the major process in this reaction as 67% of the total material balance is found in **4** and **6**. Thus, B is a major intermediate in the reaction.

Process 4 is considered unlikely because reaction energetics favor $C{=}N_2$ bond breakage over C–Hg bond cleavage,[3] and no evidence for the presence of ethyl diazoacetate, formed from C, was obtained. Process 5 is probably inoperative since complete nitrogen evolution was observed and the presence of D could not be confirmed even though reaction conditions would have permitted detection of D.

An estimate of the amount of carbyne participation in the pyrrolidine system can be made as follows. During the nitrogen evolution period, mercury is obtained in 33% yield; after nitrogen evolution stops, mercury is accounted for to the extent of 62% yield in isolated mercury-containing products. These mercury-containing products give a 0.5% yield of mercury per minute on prolonged photolysis. Therefore, the yield of products possible during the nitrogen evolution period from mercury-containing products is 9.9%. The yield of non-mercury products above 9.9% may be attributed to carbyne participation. In the case of α-insertion product **7**, isolated in 20% yield, 11% can come from carbyne and 9.9% can occur from mercury-containing products.

Application of this approach to the THF system gives a 10% yield contribution from carbyne A; in the THT system, a 30% contribution from the carbyne is possible. However, the estimates are weakened for these systems because mercury-containing products were not isolated.

The estimation of carbyne participation depends largely on the use of mercury and nitrogen yields based on hypothetical photodecomposition paths and also relies on the exclusion or determination of other possible reaction intermediates. Beneficial information can be obtained from this approach, but future work will require a more direct carbyne analysis method.

Conclusions

Photodecomposition of 1 in the systems studied suggests that the solvent may influence the reaction course to some extent. However, the major photodecomposition intermediate is the diazomercury carbene (B) while carboethoxycarbyne (A) may account for approximately 10–20% of the reaction.[9] These intermediates show a high degree of selectivity for insertion into the α-carbon–hydrogen bonds.[10] Furthermore, carbon–heteroatom insertion is completely absent, a sharp contrast with the chemistry of carboalkoxycarbenes.[11]

Experimental Section[12]

General Photolysis Procedure. Freshly prepared 1 (0.400 g, 0.937 mmol) was dissolved in 4.0 mL of the solvent system and placed in an 8 in. × 0.5 in. Vycor tube equipped with a rubber septum and gas release needle. The degassed solution was irradiated with a Havovia 450-W medium pressure, mercury-arc vapor lamp equipped with a Vycor filter and water-cooled (20 °C) jacket. The photolysis was carried to 80–90% completion as monitored from the amount of nitrogen evolved. The mercury precipitate was filtered and the filtrate was worked up as specified.

Tetrahydrofuran Solution. Mercury (0.047 g, 25%) was filtered, and the filtrate containing 2 was hydrolyzed to the acid with aqueous sodium hydroxide solution. The acidified solution was extracted thoroughly with ether, dried, and concentrated to give 0.104 g (41%) of α-(α-tetrahydrofurfuryl)acetic acid as a yellow semisolid which was identified by comparison with an authentic sample prepared as described below.

α-(2-Tetrahydrofuryl)acetic Acid. In a 500-mL three-necked flask equipped with a mechanical stirrer, dropping funnel, and thermometer were placed 50 g (0.50 mol) of reagent grade 2-tetrahydrofurfuryl alcohol (Aldrich) and 46 g (0.59 mol) of pyridine.

Freshly distilled thionyl chloride, 63 g (0.53 mol), was added dropwise to the rapidly stirred mixture which was maintained at a temperature below 60 °C with an ice bath. After complete addition, the mixture was stirred for an additional 4 h. The mixture was thoroughly extracted with ether. The ether extracts were dried and concentrated to give crude 2-tetrahydrofurfuryl chloride.

In a 500-mL, three-necked flask equipped with a stirrer, dropping funnel, and condenser were placed 5.8 g (0.12 mol) of sodium cyanide, 5 mL of water, and 15 mL of *N,N*-dimethylformamide. The crude 2-tetrahydrofurfuryl chloride (14.1 g, 0.12 mol) was added to the cyanide solution. The mixture was stirred at reflux for 16 h. Distillation of the mixture up to 160 °C removed most of the solvents. The remaining solution of 2-tetrahydrofurfuryl cyanide was hydrolyzed with sodium hydroxide solution. The basic solution was extracted with ether and acidified. The acidic mixture was extracted with ether, dried, and concentrated to give α-(2-tetrahydrofuryl)acetic acid as a yellow semisolid, identical with the acid obtained from the hydrolyzed photolysis solution: IR (neat) 3632–2341 (COOH), 1732 (C=O), 1300–1130 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.30 (s, 4 H, CH_2), 2.50 (d, 2 H, J = 7 Hz, CH_2), 3.38–3.98 (t, 2 H, J = 7 Hz, CH_2), 3.96–4.55 (m, 1 H, J = 7 Hz, CH); MS *m/e* 130 (33, P), 113 (19, P − OH), 85 (10, P − COOH). Anal. Calcd for $C_6H_{10}O_3$: C, 55.38; H, 7.69. Found: C, 55.12; H, 7.70.

Ethyl α-(2-tetrahydrofuryl)acetate (2) was prepared by heating a mixture of the acid, absolute ethanol, and hydrogen chloride at reflux for 2 h. The oily product had identical spectral properties with that of a crude sample obtained from chromatography of the photolysis mixture: IR (neat) 2922 (CH), 1732 cm^{-1} (C=O); NMR ($CDCl_3$) δ 1.00–1.50 (m, 7 H, ring protons and CH_3), 2.50 (d, 2 H, J = 7 Hz, CH_2), 3.34–3.90 (t, 2 H, J = 7 Hz, CH_2), 3.90–4.54 (m, 3 H, CH_2, CH); MS *m/e* 158 (5, P), 113 (25, P − OC_2H_5), 85 (3, P − $CO_2C_2H_5$), 71 (44, P − CH_2, $CO_2C_2H_5$).

Tetrahydrothiophene Solution. After nitrogen evolution, the mercury (0.056 g, 30%) was removed, and the filtrate was hydrolyzed to the acid by the procedure used for THF. The α-(2-tetrahydrothienyl)acetic acid weighed 0.105 g (35%). Sublimation at 100–120 °C (0.5 mm) furnished white needles: mp 32–33 °C; IR (KBr) 3582–2432 (COOH), 1710 (C=C), 1150–1300 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.25 (s, 4 H, CH_2), 2.51 (d, 2 H, CH_2), 3.32–4.0 (m, 2 H, CH_2), 4.0–4.6 (m, 1 H, CH); MS *m/e* 146 (17, P), 101 (8, P − COOH), 86 (51, P − CH_2, COOH). Anal. Calcd for $C_6H_{10}SO_2$: C, 49.32; H, 6.85; S, 21.92. Found: C, 49.28; H, 6.79; S, 21.88.

Ethyl α-(2-Tetrahydrothienyl)acetate (3). Chromatography of the combined filtrates from four reactions on a 10 in. by 0.75 in. column of alumina ($CHCl_3/CH_2Cl_2$, 1:1) gave 3 in the first 25-mL eluent as a yellow oil, 0.191 g (53.9%). Resolve-Al*[13] (Aldrich) was added to 3 in $CDCl_3$. The obscured methylene doublet at δ 1.57 was clearly shifted downfield to δ 3.27: NMR ($CDCl_3$) δ 1.10–1.36 (m, 7 H, CH_2 CH_3, and ring protons), 3.27 (d, 2 H, J = 7 Hz, CH_2), 4.0–4.6 (m, 5 H, CH_2CH_3, and ring protons); IR (neat) 2952 cm^{-1} (CH), 1732 (C=O), 680 (CS); MS *m/e* 174 (6, P), 146 (14, P − C_2H_5), 101 (10, P − $CO_2C_2H_5$), 86 (54, P − CH_2, $CO_2C_2H_5$).

Pyrrolidine Solution. The photoysis mixture was filtered (Hg, 0.065 g, 35%) and the concentrated filtrate was chromatographed on a 4.5 in. by 0.75 in. alumina column with $CHCl_3$, CH_2Cl_2, and CH_3OH as successive solvents. The first three 25-mL fractions from chloroform elution contained three components which were separated on an alumina column (8 in. by 0.25 in.; $CHCl_3$) and collected in 10-mL fractions.

Component I was identified as ethyl α-mercurybis[α-(N-pyrrolidino)acetate] (4) as a tan semisolid: 0.23 g (48%); IR (neat) 3200–2780 (CH), 1732 (C=O), 1300–1150 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.15–1.50 (t, 6 H, J = 7 Hz, CH_3), 1.60–2.00 (m, 8 H, CH_2), 2.50–3.00 (m, 8 H, CH_2), 3.45 (s, 2 H, CH), 3.90–4.50 (g, 4 H, J = 7 Hz, OCH_2); MS *m/e* 157 (4, P − Hg, $C_8H_{14}NO_2$, $CO_2C_2H_5$), 70 (100, P − Hg, $C_8H_{14}NO_2$, CH_2, $CO_2C_2H_5$). Anal. Calcd for $C_{16}H_{28}N_2O_4Hg$: C, 27.84; H, 4.18; N, 6.50. Found: C, 27.80; H, 4.28; N, 6.72.

Component II was identified as *N,N*-tetramethylene-α-pyrrolidinoacetamide (7), a yellow semisolid: 0.068 g (20%); IR (neat) 3600–3100 (NH), 1632 (C=O), 1250 (CN), 909 cm^{-1} (NH); NMR ($CDCl_3$) δ 1.25 (s, 4 H, CH_2), 1.60–2.30 (m, 7 H, ring protons) 2.40 (d, 2 H, J = 8 Hz, 2-CH_2), 3.35–3.80 (m, 4 H, ring protons), 7.20–7.70 (m, 1 H, NH); MS *m/e* 182 (37, P) 112 (19, P − C_4H_8N), 84 (47, P − C_4H_8N, CO), 70 (100, P − C_4H_8N, CO, C_4H_8N). Anal. Calcd for $C_{10}H_{18}N_2O$: C, 65.93; H, 9.89; N, 15.38. Found: C, 66.06, H, 9.96; N, 15.15.

Component III was tentatively assigned structure 6 on the basis of spectral analysis: unstable yellow oil, 0.092 g (19%); IR (neat) 3600–2500 (NH), 1684 (C=O), 2184 (C=N_2), 1250 (CN), 909 cm^{-1} (NH); NMR ($CDCl_3$) δ 1.20–1.34 (m, 4 H, CH_2), 1.70–2.40 (m, 10 H, ring protons), 2.80 (d, 1 H, J = 7 Hz, HgCH), 3.20–3.95 (m, 9 H, ring protons).

Ethyl α-(N-Pyrrolidino)acetate (5). Ethyl diazoacetate (7.98 g, 0.07 mol) was added dropwise to a stirred mixture at 5–10 °C of pyrrolidine (14.91 g 0.21 mol) and cuprous cyanide (1.57 g, 0.017 mol). After complete addition, the mixture was stirred for 5 h at 5–10 °C. The brown mixture was filtered and extracted thoroughly with chloroform. The concentrated chloroform mixture was distilled at 110–150 °C (0.1 mm) to give 5 as a yellow oil in 77% yield. Anal. Calcd for $C_8H_{15}NO_2$: C, 61.15; H, 9.55; N, 8.92. Found: C, 60.96; H, 9.32; N, 8.99.

Reaction of 4 (0.06 g) with excess sodium borohydride in chloroform produced mercury and 5 which had identical spectral properties with those of an authentic sample: IR (neat) 2930–2882 (CH), 1730 (C=O), 1300–1140 cm^{-1} (CO); NMR ($CDCl_3$) δ 1.05–1.35 (t, 3 H, J = 7 Hz, CH_3), 1.60–2.00 (m, 4 H ring protons, 2.40–2.80 (m, 4 H, ring protons), 3.30 (s, 2 H, CH_2), 3.95–4.30 (q, 2 H, J = 7 Hz, CH_2); MS *m/e* 157 (26, P), 128 (5, P − C_2H_5), 84 (12, P − $CO_2C_2H_5$), 70 (7, P − $CO_2C_2H_5$, CH_2).

Mercury and Nitrogen Yields. Solutions containing 0.40 g (0.937 mmol) of 1 in the appropriate solvent were placed in Vycor tubes and subjected to photolysis. At various time intervals (5–15 min), the nitrogen evolution was determined from water displacement. The sample was removed from photolysis and the mercury precipitate weight was recorded. At least eight data points were used for the t = 0 extrapolations reported in Table I. An error of 10–15% was calculated for these experiments. Fluctuations in lamp intensity and the presence of the mercury precipitate are thought to be responsible for this error.

Registry No.—1, 20363-85-3; 2, 2434-02-8; 3, 65102-19-4; 4, 65102-20-7; 5, 22041-19-6; 6, 65102-21-8; 7, 1078-64-4; α-(α-tetrahydrofurfuryl)acetic acid, 2434-00-6; 2-tetrahydrofurfuryl alcohol, 97-99-4; 2-tetrahydrofurfuryl chloride, 3003-84-7; 2-tetrahydrofurfurylcyanide, 33414-62-9; α-(2-tetrahydrothienyl)acetic acid, 65102-22-9; ethyldiazoacetate, 623-73-4; pyrrolidine, 123-75-1.

References and Notes

(1) (a) This research was supported by the Office of Graduate Research, Southern Illinois University at Edwardsville. (b) Taken in part from the M.S. Thesis of Tai-Teh Wu, Southern Illinois University at Edwardsville, 1976.
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(3) O. P. Strausz, G. J. A. Kennepohl, F. X. Garneau, T. DoMinh, B. Kim, S. Valenty, and P. S. Skell, *J. Am. Chem. Soc.*, **96**, 5723 (1974), and references cited therein.
(4) T. B. Patrick and G. H. Kovitch, *J. Org. Chem.*, **40**, 1527 (1975).
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(8) T. Saegusa, Y. Ito, S. Kobayaski, K. Hirota, and T. Shimizu, *Tetrahedron Lett.*, 6131 (1966).
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(10) Mercury-containing carbenes do not undergo carbon–hydrogen insertion into ordinary hydrocarbons: P. S. Skell and S. J. Valenty, *J. Am. Chem. Soc.*, **95** 5042 (1973).
(11) A. P. Marchand and N. M. Brockway, *Chem. Rev.*, **74**, 431 (1974).
(12) All temperature readings are uncorrected. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and were within ±0.3% of the theoretical values. A Varian T-60 spectrometer was used for ^{1}H NMR analyses with tetramethylsilane as the internal reference. A Varian MAT-111 spectrometer was used for mass spectral analyses at 80 eV. A Perkin-Elmer Model 337 spectrometer calibrated with polystyrene was used for infrared analyses.
(13) See, R. E. Sievers, Ed., "Nuclear Magnetic Resonance Shift Reagents", Acacemic Press, New York, N.Y., 1973, for a review.

Carbon-13 Chemical Shift Response to Substituent Effects in Arylmethyl and Arylhydroxy Carbenium Ions. Evidence for Substituent Interaction in Disubstituted Ions Depending upon the Carbenium-like Character at the Trigonal Carbon

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The interrelations between the ^{13}C NMR shielding effects of para substituents and electronic structure have been investigated in diphenylmethyl and diphenylhydroxy carbenium ions **1** and **2**. The prime dependence of the ^{13}C shieldings upon π charge delocalization effects is established. It is shown that a general description of the chemical shifts, valid on all sites, requires using both π-electron density and π-bond order terms, as illustrated by the correlation obtained at ca. 120 ppm. While for the substituted ring carbons the SCS remain nearly the same as for neutral monosubstituted benzenes, the substituent shifts at C_α are increased by 2.7 in ions **1** as compared to **2**, thus showing that electronic effects at this position are strongly dependent on the withdrawing power of the carbenium center (as confirmed by the unusually small effects of acceptor substituents). Nonadditivity of the C_α SCS in some 4,4′-disubstituted ions demonstrates the existence of important interactions between substituent electron effects. These interactions can be accounted for with the concept of a concerted π-inductive-mesomeric effect: the electron transfer from a substituent to the carbenium center depends upon the demand of this center and therefore upon all the other groups present. The susceptibility of the substrate to these interactions is estimated by a I_{XY} term (expressed with a $\sigma_X{}^+\sigma_Y{}^+$ product) and related to the carbenium character. Long range effects at the unsubstituted ring result from a π-inductive effect without π-electron transfer from the substituent. The C_α bridge acts only as a relay whose efficiency is directly related to the magnitude of its positive charge.

A great deal of attention has been focused over the last years on carbenium ions as they are key intermediates in many organic reactions. In this field, NMR spectroscopy, especially ^{13}C NMR, appears to be one of the most suitable techniques for a charge-delocalization investigation in cations,[1] although Brown[2a] and Kramer[2b] have pointed out that some problems may occur in relating ^{13}C shifts and carbenium ion stabilities. Much of the literature is devoted to the study of substituent effects on the chemical shifts of aryl carbenium ions for which the unusual stabilities have been ascribed to delocalization of positive charge throughout the π-electron system of the aromatic rings. Substituent chemical shifts[3] (SCS) have been chosen as a probe of the ability of groups to disperse the positive charge and have been compared to substituent parameters (generally Brown or Taft constants) deduced from solvolytic reactions in which the transition state is postulated to approximate the character of these ions.[4–6]

The relationships between shieldings and semiempirical MO have been extensively investigated by Olah et al.[7] The fact that, for carbons remote from the carbenium center, the π charge densities are as good as total charge densities in correlating the observed shifts is a definite proof that the dominant influences on screenings are π-system resonance and polarization interactions; moreover, the slope of their regression line[7a] is very close to the usual proportionality constant of 160 ppm/electron density obtained in a large variety of aromatic systems.[1,8] Farnum's point of view[1a] is slightly different, since he uses the total charge density with the questionable assumption of no charge dispersion to the hydrogens. Ray, Kurland, and Colter[5] have also shown that carbon chemical shifts in trityl cations are well correlated with CNDO/2 charges, whereas the crude HMO electron densities poorly reflect the trends. However, a great dispersion of quaternary ipso and α carbons can usually be observed, while an impossibility to describe all the shifts by a general expression using only electron density, whatever the carbons, is also evident.[2] This situation has prompted us to reexamine the possible contribution of other terms—like π-bond orders—to the carbon shielding in aryl carbenium ions. The important question of the additivity of substituent effects in ions is also open to challenge. If saturation of their electronic influences is now a fairly well-documented experimental phenomenon,[6,9–14] its interrelation with the extent of a positive charge at the relevant nuclei is not yet elucidated. Con-

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Table I. Carbon-13 Chemical Shifts in Diphenylmethyl Carbenium Ions[a]

X	Y	Registry no.	C_α	C_β	C_1	C_2	C_3	C_4	$C_{1'}$	$C_{2'}$	$C_{3'}$	$C_{4'}$	Other carbons
H	H	16805-85-9	173.8	−23.3	86.8	87.1	77.2	92.70					
Och_3	H	60665-78-3	153.5	−26.2	80.1	92.6	65.31	125.5	85.9	81.1	76.1	84.9	OCH_3: 5.2
CH_3	H	41912-34-9	168.3	−24.2	84.9	88.2	79.0	111.5	86.7	85.2	76.9	90.1	CH_3: −30.0
F	H	56519-30-3	170.0	−23.5	83.3	91.5	65.75	121.1	86.6	86.1	77.1	91.8	
Cl	H	41912-38-3	170.9	−23.5	84.9	86.7	78.1	102.9	86.3	87.8	77.5	92.9	
CF_3	H	60665-79-4	178.0	−23.2	89.3	85.0	72.7	87.7	88.3	87.4	77.7	96.9	CF_3: 69.3
NO_2	H	60665-80-7	177.5	−22.8	93.5	87.3	70.6	100.3	88.1	91.6	77.9	97.7	
OCH_3	OCH_3	25856-80-0	148.0	−27.4	79.2	88.2	63.4	119.5					OCH_3: 3.8
CH_3	OCH_3	60665-82-9	152.8	−26.6	83.5	82.6	77.2	100.6	79.7	91.3, 95.8	64.4, 65.3	123.2	OCH_3: 4.5 CH_3: −31.6
CF_3	OCH_3	64999-88-8	149.4	−26.1	88.3	79.2	72.3	82.3	80.3	91.3, 95.9	63.9, 66.2	127.8	OCH_3: 6.0 CF_3: 69
NO_2	OCH_3	60065-83-0	146.5	−26.1	91.4	79.0	70.9	96.5	80.5	92.0	67.9	129.6	OCH_3: 6.7
CH_3	CH_3	41912-36-1	164.7	−25.1	84.5	86.5	78.3	107.4					
F	F	39769-49-8	166.4	−23.8	83.2	90.5	65.7	120.5					
Cl	Cl	41912-40-7	167.5	−23.9	84.6	87.1	78.1	102.2					
Br	Br	64999-89-9	167.9	−23.8	85.0	86.5	81.3	93.2					
CF_3	CF_3	60665-81-8	184.8	−21.7	89.5	88.0	73.8	91.6					CF_3: 69.2

[a] Positive downfield values in ppm from internal CH_2Cl_2.

versely, the extent of the dependence of the electronic power of a given substituent with the electron deficiency at the carbenium center is not yet clear. In a ^1H NMR work on diarylmethyl carbenium ions[6] we have anticipated such a dependence of substituent–substituent interactions upon the electron demand by the deficient system, an early recognized fact for successive methyl substitution at a carbenium center.[15,16]

In view of these problems, a comparison of charge delocalization in a number of systems with distinct demands for electron stabilization is needed. Substituted diphenylmethyl and diphenylhydroxy carbenium ions have been chosen, as these two families have closely similar geometry and electronic structure, but the methyl and hydroxy groups clearly generate distinct electron demand at the carbenium center. The data are discussed with respect to INDO charge densities and compared with literature results on like ions. In an attempt to clarify the origin of nonadditivity, we also wished to analyze substituent–substituent interactions in these two disubstituted families with particular emphasis on their dependence upon the electron demand by the carbenium center. An electronic effect transmission from the substituted ring to the other via the positive trigonal carbon will also be examined.

Experimental Section

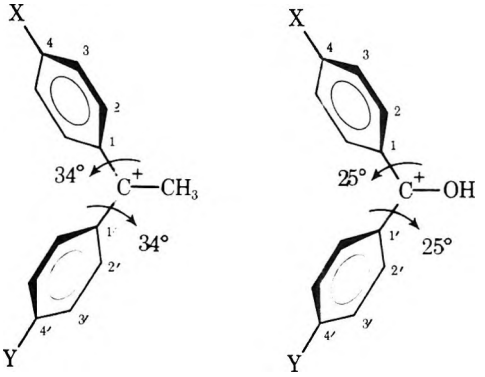
Preparation of Ions. All the carbenium ion samples were formed directly in a 10-mm o.d. Wilmad NMR tube at ca. 0.5 mol/L in three distinct media depending upon the studied ions. Most of the diphenylmethyl carbenium ions **1**—except when attracting groups substitute the aromatic ring—were formed from a 2-mL CD_2Cl_2 solution of the olefin precursor by slowly adding about 0.2–0.3 mL of FSO_3H at −50 °C (method a). As we observed that diphenylmethyl carbenium ions with attracting substituents (NO_2,CF_3) are not stable in CD_2Cl_2 solutions, they were generated by dissolving the proper olefin into FSO_3H at −50 °C (method b). Owing to the greater basicity of the carbonyl group, the more stable diphenylhydroxy carbenium ions **2** were prepared by protonation of substituted benzophenones in 98% H_2SO_4 at room temperature (method c), except for the mono- and dinitro-substituted ions which were obtained by method b. Complete protonation of benzophenone was checked by a study of its cation generated by both methods b and c.

Carbon-13 Nuclear Magnetic Resonance Spectra. The carbon-13 NMR spectra were recorded at 25.03 MHz on a JEOL PS-100 spectrometer equipped with a PFT-100 Fourier transform system, JEC-100 computer, ^2D field frequency lock, and noise-modulated proton-decoupling system. The observed free-induction decay after a 30° pulse width of 9 μs was sampled in 8192 data points with a spectrum width of 6250 Hz and a repetition time of 2 s (digital resolution 1.53 Hz). Either a deuteron signal from internal CD_2Cl_2 (method a or c) or an external 4-mm o.d. CD_2Cl_2 tube held concentrically inside the standard 10-mm tube (method b) was employed for the locking signal, depending on the three distinct media used in the preparation of ions. All spectra were run in the complete noise-decoupling mode.

In methods a and c, chemical shifts were measured from 0.2 mL of internal CH_2Cl_2 dissolved in the solution; in method b, they were obtained from external CH_2Cl_2 contained inside the 4-mm o.d. CD_2Cl_2 tube and were corrected for the bulk magnetic susceptibility using the experimentally determined conversion factor $\delta_{\text{internal } CH_2Cl_2/\text{external } CH_2Cl_2} = -0.80$ ppm. Spectra of diphenylmethyl carbenium ions **1** were recorded at −30 °C, whereas the more stable protonated benzophenones were studied at room temperature. No significant temperature dependence of the chemical shifts was observed in this range. Minor solvent effects are also apparent from an examination of some spectra obtained by each method a, b, or c, and from a comparison of our results on unsubstituted cations with Olah's data.[17]

Results

The ^{13}C chemical shifts of substituted diphenylmethyl carbenium **1** and of substituted diphenylhydroxy carbenium ions **2** are respectively listed in Tables I and II. Specific peak



1 **2**

1a, 2a, Y = H; X = OCH_3, CH_3, F, Cl, H, CF_3, NO_2
1b, 2b, Y = X = OCH_3, CH_3, F, Cl, H, CF_3, NO_2
1c, 2c, Y = OCH_3; X = OCH_3, CH_3, H, CF_3, NO_2

assignments were made primarily by analogy with SCS on substituted benzenes[18] and protonated benzaldehydes and acetophenones.[17b] Typically, ortho and meta carbons can be distinguished from other resonances by a consideration of the relative peak intensities involved in the nuclear Overhauser

Table II. Carbon-13 Chemical Shifts in Diphenylhydroxy Carbenium Ions[a]

X	Y	Registry no.	C_α	C_1	$C_{2(6)}$	$C_{3(5)}$	C_4	$C_{1'}$	$C_{2'(6')}$	$C_{3'(5')}$	$C_{4'}$	Other carbons
H	H	16805-82-6	154.3	75.7	82.5	76.7	88.1					
OCH_3	H	10472-80-7	147.0	67.9	87.6	63.3	118.8	76.3	80.0	76.3	85.3	OCH_3: 3.6
CH_3	H	64999-75-3	152.1	72.9	83.4	77.8	103.7	75.9	81.1	76.4	87.1	CH_3: −31.4
F	H	64999-76-4	152.2	72.1	86.6	64.7	117.8	75.6	81.7	76.6	87.7	
Cl	H	64999-77-5	153.0	74.0	83.8	77.3	96.5	75.6	82.0	76.8	88.2	
Br	H	64999-78-6	153.4	74.5	83.4	80.5	86.3	75.7	82.1	76.9	88.4	
CF_3	H	64999-79-7	154.9	79.2	81.6	73.2	86.2	75.5	83.2	77.0	89.7	
NO_2	H	64999-80-0	154.6	82.1	81.8	71.1	98.5	75.7	83.4	77.2	90.5	
OCH_3	OCH_3	10487-81-7	143.5	68.7	85.1	62.7	115.8					OCH_3: 3.3
CH_3	OCH_3	10487-82-8	146.2	75.3	81.0	77.4	100.0	68.2	86.7	63.0	117.6	OCH_3: 3.5; CH_3: −31.8
CF_3	OCH_3	64999-81-1	145.5	79.2	79.2	72.9	84.1	67.5	88.2	63.9	120.6	OCH_3: 3.8
NO_2	OCH_3	64999-82-2	143.7	82.6	79.7	71.2	97.4	65.5	88.6	64.2	121.6	OCH_3: 4.1
CH_3	NO_2	64999-83-3	151.3	72.7	84.5	78.5	107.6	82.2	81.2	71.2	98.3	CH_3: −30.8
NO_2	NO_2	64999-84-4	157.4	81.2	84.0	71.7	100.0					
F	F	64999-85-5	150.3	72.1	85.9	64.7	117.5					
Cl	Cl	39787-21-8	151.7	74.1	83.4	77.5	96.6					
CH_3	Cl	64999-86-6	150.7	72.8	82.9	77.8	103.9	74.2	82.9	77.1	95.0	CH_3: −31.3
CH_3	CH_3	64999-87-7	150.5	73.1	82.5	77.6	102.1					CH_3: −31.5

[a] Positive downfield values in ppm from internal CH_2Cl_2.

enhancement. In some cases, assignments were also aided by running off-resonance decoupled spectra, which allowed differentiation of carbons bearing hydrogens.

Ortho and meta carbon nonequivalence,[7,17,19] as well as syn–anti isomerism in protonated benzophenone,[20] was generally not observed here because at the experimental temperature C^+–C_{ipso} and C^+–OH rotations are still fast in view of the NMR time scale. Among all the ions, the only two exceptions to this nonequivalence occur in ions **1c**, where X = CF_3 and NO_2; this is because of an increased electron demand by the carbenium center, which in turn reduces the free rotation about the C^+–C_{ipso} bond of the anisyl ring.[7a]

All valence electron MO calculations were performed using the INDO method with the standard parametrization of Pople et al.[21] INDO approximation was preferred over CNDO/2, since it is known to give results as good as with ab initio STO-3G approach in cations.[22] Unless otherwise stated, standard bond lengths and angles as recommended in ref 21a, page 111, were used; this is a current trend in electronic structural studies of ions for which reliable experimental geometries are not available.[7,16] Moreover, we think that this choice has the merit of providing a consistent basis for comparison of charge delocalization in substituted families **1** and **2**.

Owing to their structural analogy, diphenylmethyl and diphenylhydroxy ions can be predicted to have extremely similar conformations, i.e., symmetrical propeller conformations with two equally twisted aryl rings in respect to the nodal plane of the carbenium center.[6,10a] The geometry of ions **1** which has been determined in an earlier ^1H NMR work was retained without further modifications.[6] But a less stringent sterical hinderance between ortho positions in benzophenones has been postulated,[23] so that a twist angle of only 25° was assumed for the aryl rings and 1.47 Å was chosen for the bond length C_1–C_α to allow for an increase in conjugation between the phenyls and the positive carbon. Since only minor conformational changes occur with substituent changes, the geometry of ions **1** and **2** was held constant and independent from the electronic power of substituents.[6,10a] The value of 1.27 Å obtained by Ros[24] in a nonempirical calculation of protonated acetaldehyde was used. This distance just lies between the standard values of 1.36 (C–O bond) and 1.22 Å (C=O bond). Syn–anti positions of the hydrogen bonded to the oxygen were considered in our calculations on ions **2**, but only the average values of the results were used and reported in Table V (supplementary material).

Discussion

(1) Expression of Carbon Chemical Shifts in Aryl Carbenium Ions. There is now considerable evidence that carbon screenings are dominated by charge-polarization effects,[1,7,8,16,25] so carbon shifts can be expected to constitute a quite sensitive probe for understanding charge distribution and substituent effects in aryl carbenium ions. This point will be first studied by a comparison of the carbon shifts in Tables I and II with π-electron parameters derived from INDO–MO calculations.[26] Rather than examining the correlation trends for certain types of carbons, leading to distinct correlations of variable slopes without physical justification of these variations, a general fit was sought for all carbons: systematic deviations would then be attributed to specific influences or properties of the relevant positions. This approach also allows charge-distribution effects to be separated from other factors.

From the carbon shifts (Tables I, II) and π charge densities (Tables IV and V, supplementary material) a rough correlation is observed for all the positions of ions **1a**, **2a** (except where X = OCH_3) and **1b**, **2b** (eq 1).

$$\delta = -(173 \pm 6)q_\pi + 256 \quad (r = 0.943;\ \mathrm{SD} = 9.8). \qquad (1)$$

Ions **1a**, **2a** (where X = OCH_3) and **1c**, **2c** have been excluded, since we previously showed the failure of the INDO method to correctly describe the charge delocalization induced by a methoxy group in some methoxyaryl-substituted ions.[28]

The major deviations are observed for α and substituted carbons (C_1 and C_4), a not unusual comportment given the important structural change they undergo (hybridization, substitution, neighboring effects).[1b,7,16] A great improvement is obtained by inclusion of the bond order term according to the Karplus–Pople evaluation of the dominant paramagnetic terms in carbon screening.[29] Using π charge densities and the sum of the π-bond orders with adjacent carbons, since nonnearest-neighbor terms contribute very little (<2%) and can be omitted,[29-30] in a linear least-squares analysis, eq 2 is obtained

$$\delta = -(207 \pm 4)q_\pi + (72 \pm 4)p_\pi + 187 \quad (r = 0.984;\ \mathrm{SD} = 5.3) \qquad (2)$$

Equation 2 leads to a much better agreement with the observed shifts, particularly for the nonhydrogenated ipso carbons (which have a largely different bond order than those of the tertiary ortho, meta, or para carbons) and appears very satisfactory in view of the covered scale (i.e., 122 ppm for 122 points). Such an agreement is further proof of the generality of the relationships between carbon-13 shifts, π-electron density, and π-bond order.[30] It also establishes that carbon-13 SCS in diphenylmethyl or diphenylhydroxy carbenium ions can definitively be used as a probe of charge delocalization induced by substituents onto distinct carbons.

(2) SCS in Diphenylmethyl and Diphenylhydroxy Carbenium Ions. Although the greatest SCS are observed at the cationic center, other valuable information can be obtained by examination of ring carbons. It is thus interesting to examine SCS with great emphasis on each type of carbon. Due to the strong interactions between the two substituents in para, para'-disubstituted ions, and in an attempt to clarify the causes and origins of such interactions, the discussion will unfold as follow: (i) the substituted aromatic ring of monosubstituted ions **1a** and **2a**, (ii) the α-carbon of mono- and disubstituted ions **1** and **2**, and (iii) the unsubstituted aromatic ring of monosubstituted ions **1a** and **2a**.

(i) Substituted Aromatic Ring of Ions 1a and 2a. In these ions, SCS are very small at C_2 but greater at C_1 and C_3 (as expected from the crude scheme of resonance) and greater at the C_4-substituted carbon.

The agreement between the shifts calculated by eq 2 and the experimental results is quite good for the C_1 para carbons, but nonnegligible deviations (~5 ppm) are observed for the C_4-substituted carbons and, to a lesser extent, for C_3 ortho carbons. Indeed, this fact is not surprising and was also noticed in correlations between carbon-13 shifts and π (or total) electron densities in substituted benzenes[18,30c] and aryl carbenium ions.[1,5,7] The better agreement for C_1 para carbons has been rightly attributed to the predominance of electronic effects over secondary effects in their shieldings, whereas this is not as true at the C_4 and C_3 positions for which neighboring and magnetic anisotropy effects are important. INDO calculations reveal that π-bond orders of other positions are nearly insensitive to the substituent in contrast to C_4 carbons for which large variations of the $X-C_4$ π-bond order term are observed. As a result, the neglect of the π-bond order contribution in the usual simplified δ vs. q_π (or q_t) correlations on the substituted benzenes[7,18] can partially explain the shift of the two regression lines of the substituted and para carbons; small deviations of ortho and meta points from the line of the para carbons also certainly originate[7,18] from such a neglect. Inclusion of the π-bond order allows the most general comparison between distinct families of substituted derivatives, e.g., benzenes or other neutral aromatic compounds and aryl carbenium ions. A good linear relationship with a slope near 1 is obtained when all the SCS of the substituted aromatic ring of ions **1a** are correlated with those of ions **2a**. A similar relationship has also been observed with the analogue carbons of substituted protonated benzaldehydes and acetophenones[31] and even, to some extent, with the substituted benzenes[1c,18] from which substituent parameters are often defined by workers. The only apparent deviations are for the C_4-substituted carbons. This means that, except for the C_4 positions, the various groups para to the substituent X [i.e., $-C^+(CH_3)C_6H_5$, $C^+(OH)C_6H_5$, C^+HOH, $C^+(CH_3)OH$] do not significantly perturb the SCS on the substituted aromatic ring with respect to the substituted benzenes and are independent of the specific electron demand by the relevant group.

However, these conclusions break down in the case of the C_4 points for which nonconstancy of the SCS is clear [e.g., 7.6 ppm for ion **1a** ($X = NO_2$) and 10.4 ppm in **2a** ($X = NO_2$)], while a shift of 20 ppm is observed from the nitrobenzene; other substituents give smaller variations. The nonconstancy in the SCS of the C_4 points was attributed either to a modulation of the σ-electron density at C_4 by the π-polarization of the group para to X[32] or to local variation in the excitation energy.[33] Nevertheless, the fact that the C_1 points of ions **1a** and **2a** are well correlated seems contradictory to the first explanation but rather in agreement with the hypothesis of a local variation in the excitation energy. Indeed, the SCS at the C_1 carbons in ions **1a** and **2a** are well described by a Taft dual-substituent parameter analysis[34] [eq 3 and 4 respectively], using the σ_R° resonance parameters instead of the σ_R^+ set:

$$\delta_{C_1} = 86.8 + 5.5\sigma_I + 18.6\sigma_R^\circ \quad (r = 0.992;\ SD = 0.7) \quad (3)$$

for ions **1a** and

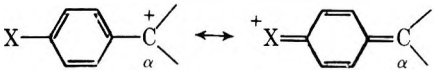
$$\delta_{C_1} = 75.4 + 6.7\sigma_I + 20.0\sigma_R^\circ \quad (r = 0.994;\ SD = 0.6) \quad (4)$$

for ions **2a**.

Despite the strong electron demand by the carbenium center which can be expected to increase electron transfer from the substituent by resonance, the effects at the C_1 carbons do not increase, since the σ_R° set works better than the σ_R^+ set. Furthermore, the susceptibilities to inductive and resonance effects are nearly identical with those reported for substituted benzenes, i.e., 5.7 and 21.2, respectively.

(ii) Substituent Effects at C_α. Examination of the SCS induced at C_α in both series of 4-substituted ion **1a** and **2a** shows that the electron-releasing groups generate major upfield shifts, as they can attenuate the electron deficiency at C_α (20.3 and 7.4 ppm, respectively, for the 4-OCH_3 ions **1a** and **2a**). In contrast, the variations remain small with electron-withdrawing groups (for NO_2: 4.2 and 0.4 ppm). These results are strikingly different from the substituent effects observed in parent neutral molecules;[31] as shown by various examples[35] for such carbons in the α position with respect to a phenyl ring in conjugated systems, the SCS remain small and inverted in accordance with Pople's prediction of as alternation of charges,[21a] while the essential part of the influences is developed at C_β.

The exaltation of effects for releasing groups is consistent with an important transmission of substituent influences by conjugative π-resonance interaction between donor X groups



and the carbenium center, since this "through conjugation" increases in importance because of the greater electron demand at C_α.

More puzzling are the small influences of acceptor groups, particularly in view of the fact that these groups are quite effective at C_1. This is illustrated in Figure 1 where C_α has been plotted vs. C_1 for ions **1** and **2**; thus, while the chemical shifts are proportional for releasing substituents, discrepancies are evident for the attracting NO_2 and CF_3 groups. This minor importance of withdrawing groups on the C_α shifts can be interpreted by the decrease of mesomeric interactions between, for instance, the 4-NO_2-substituted phenyl ring and C_α. This decrease little affects the electron density at this position inasmuch as it can be balanced by a further release from the other fragments bonded to C_α, i.e., the second phenyl ring or the OH group. In accordance with this scheme, it may be observed that the substituent shifts of the CF_3 or NO_2 groups are quite small for protonated benzophenones, where the carbonyl oxygen can conjugate the C_α empty orbital, whereas for enium ions (where hyperconjugative donation from Me is limited), these groups are more efficient. However, such an analysis would indicate more important C_α shifts in styryl or cumyl cations where no group can accommodate the

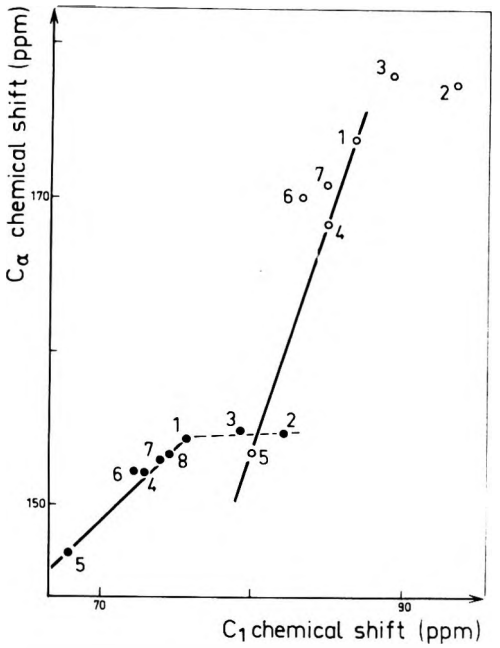


Figure 1. Plot of C_α chemical shifts vs. C_1 chemical shifts: (○) diphenylmethyl carbenium ions, (●) diphenylhydroxy carbenium ions. See ref 52 for the meaning of the numbers.

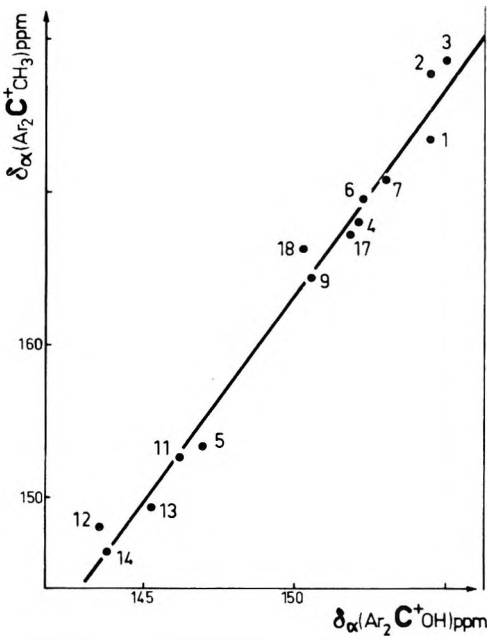


Figure 2. Plot of ^{13}C chemical shifts at C_α in diphenylmethyl carbenium ions **1** vs. ^{13}C chemical shifts at C_α in diphenylhydroxy carbenium ions **2**. See ref 52 for the meaning of the numbers.

positive charge. The available data (4-CF_3-cumyl cation[4c]) suggest a slightly greater shift than expected from a comparison with diphenylmethyl carbenium ions or protonated acetophenones, in accordance with our point of view. INDO calculations on substituted styryl ions also indicate a slightly increased effect for a NO_2 group on the C_α π-electron density with respect to that estimated for ions **1**. This unusual response pattern to substituent effects is clearly exemplified when one attempts to correlate the C_α shifts with the Brown σ^+ constants of the X groups,[36] which have led to some success in the interpretation of the α-carbon shifts of styryl,[4a] cumyl,[4a] or trityl[5] cations. Our results show, however, that, although this is valid for donor groups, any attempt to correlate all the data (including halogens or acceptors) has failed.[37]

Another important point is that the observed trends are very similar in the two families, as illustrated in Figure 2 by the good linear correlation obtained for 14 points, including disubstituted ions, by plotting δC_α in ions **1** vs. the corresponding values in ions **2**[38] (eq 5).

$$\delta_{C_{\alpha(1)}} = (2.7 \pm 0.1)\delta_{C_{\alpha(2)}} - 250 \; (r = 0.993; \text{SD} = 1.33) \quad (5)$$

The slope, which is much greater than 1, indicates that the sensitivity to substituent perturbations is greater for diphenylmethyl carbenium ions. This is consistent with a more developed carbenium character in **1**, where the positive charge can only be partly delocalized on the phenyl rings, whereas in protonated benzophenones the carbonyl oxygen can accomodate some fraction of this charge; i.e., the greater the electron demand at C_α, the greater the π interactions between this position and the releasing groups through the phenyl ring, and therefore the greater the sensitivity of C_α to substituent effects.

Turning now to eq 2, it appears that the INDO method gives a fairly good estimation of the shifts, although the deviations are larger than for the other positions. Such a general representation (although of prime interest to confirm that the δ are a good experimental probe of electron distribution) is not the best suited one for an accurate investigation of substituent shifts on a given position where the immediate environment of the carbon remains constant. So, for a discussion restricted to the C_α position, for the series of ions **1** or **2**, a simplified δ

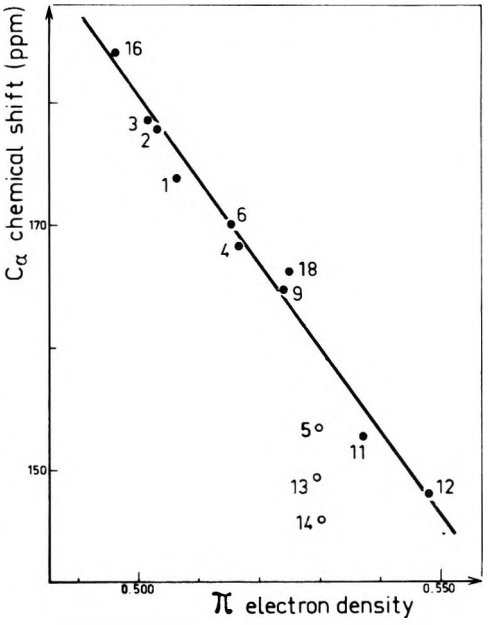


Figure 3. Plot of δ vs. INDO π-electron density for C_α in substituted diphenylmethyl carbenium ions (δ ppm downfield from internal CH_2Cl_2). Points noted (○) are excluded from the correlation; cf. text. See ref 52 for the meaning of the numbers.

vs. q_π plot is very convenient (insofar as the variations of the p_π and q_π terms are proportional). As seen in Figures 3 and 4, good correlations are also obtained (eq 6 and 7) for all disubstituted ions except ions **1b** and **2b**, where X = CF_3, and **1c** and **2c**, where X = H, CF_3 and NO_2:
for ions **1**:

$$\delta_{C_\alpha} = -(677 \pm 38)q_\pi + 519 \; (r = 0.987; \text{SD} = 1.8) \quad (6)$$

and for ions **2**:

$$\delta_{C_\alpha} = -(528 \pm 18)q_\pi + 481 \; (r = 0.995, \text{SD} = 0.12) \quad (7)$$

Nevertheless, the slopes are far higher than the commonly accepted value (~170 ppm/electron), suggesting that the INDO method underestimates substituent-induced charge

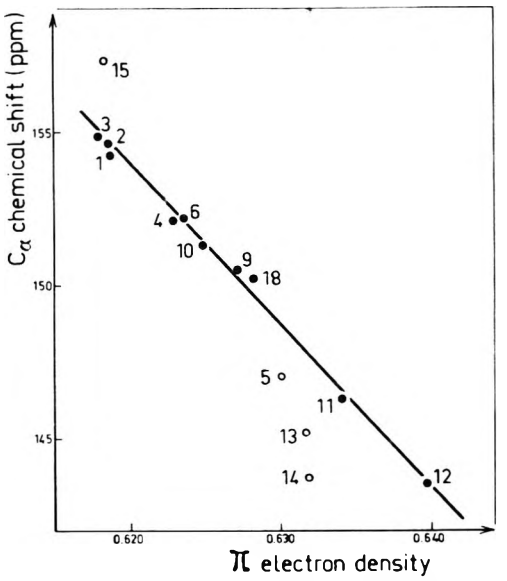


Figure 4. Plot of δ vs. INDO π-electron density for C_α in substituted diphenylhydroxy carbenium ions **2**. The symbols are the same as in Figure 5. See ref 52 for the meaning of the numbers.

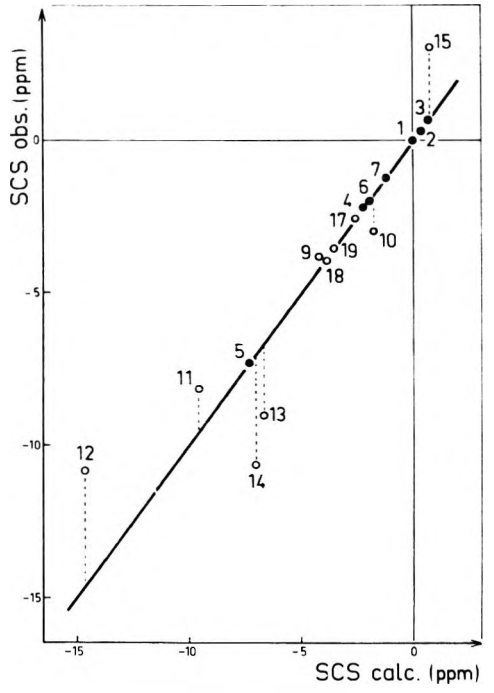


Figure 5. Deviations to additivity of substituent shifts in ions **1**: plot of observed SCS for disubstituted ions **1b** and **1c** (○) vs. calculated values assuming additivity of the SCS observed in monosubstituted ions **1a** (negative SCS correspond to upfield shifts). To provide a scaling of the deviations observed when interactions appear, SCS observed in monosubstituted ions have also been plotted (●): by definition they lie on the theoretical line of unit slope. See ref 52 for the meaning of the numbers.

variations at C_α, whereas it correctly reflects the perturbations induced on C_1 (the neglect of the p_π term, whose variations counteract those of q_π is certainly quite insufficient to account for these discrepancies). These shortcomings suggest that the method does not equally scale the perturbations at the various carbons. Streitwieser[27a] has already pointed out that CNDO calculations bear similar limitations when comparing electron-density changes in polycyclic aromatic ions and in substituted benzyl cations. Larsen and Bouis[39] have also noted an unusually high slope in correlating ^{13}C NMR shifts of benzoyl cations with CNDO charges and have questioned the

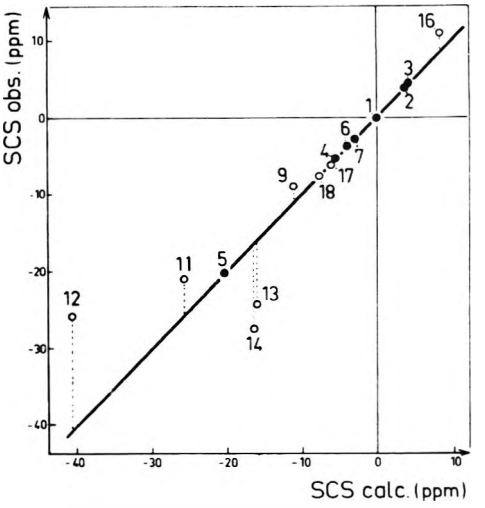


Figure 6. Deviations to additivity of substituent shifts in ions **2**. The symbols are the same as in Figure 7. See ref 52 for the meaning of the numbers.

validity of the CNDO method to accurately express substituent effects in charged species. An alternate explanation would be that the proportionality constant between δ and q_π may be different for C_α and the phenyl carbons; indeed, the possibility of local distortions to the excitation energy has been proposed by Karplus and Pople.[29b] The deviations appearing for ions bearing OCH_3 substituents are very important to the understanding of substituent interactions and will be the topic of a subsequent discussion after an examination of SCS in disubstituted ions.

Substituent–Substituent Interactions in Some Disubstituted Compounds. The SCS observed at C_α for 4,4′-disubstituted ions can be approached by referring to the corresponding shifts in monosubstituted derivatives. This is illustrated in Figures 5 and 6 where we have plotted the δ measured vs. the δ calculated by assuming an additivity of the shifts derived from monosubstituted ions. When this hypothesis of additivity works, the points do fall on lines of unit slopes obtained from the unsubstituted ions **1a** and **2a**. This is indeed observed for groups F, Cl, and CH_3, i.e., groups with weak electronic effects. However major discrepancies are noticed when a strongly conjugating group (like OCH_3) is present: deviations are downfield when the other group is also an electron donor but upfield with a second attractor group (as in 4-OCH_3,4′-NO_2 ions) thereby corresponding to shifts larger than expected, a so-called "exaltation effect". In the same way, downfield deviations are also observed with the electron-withdrawing substituents, i.e., CF_3 and NO_2.

Among the most striking features of these plots, it can be noticed that the 4-OCH_3,4′-NO_2 and the 4-OCH_3,4′-OCH_3 ions roughly correspond to the same δC_α value (143.5 and 143.7 for ions **1c**; 148.0 and 146.5 for **2c**), an evidently surprising fact meaning that NO_2 and OCH_3 would both induce a shielding variation of comparable magnitude on C_α. It can be also seen, going from the monosubstituted ion **1a** to its 4-OCH_3 and 4,4′-dimethoxy derivatives, that the second OCH_3 group exerts on C_α a shift of −5.5 ppm, whereas the first methoxy substitution corresponds to a shift as large as −20.3 ppm. These results extend and substantiate our earlier conclusions[6] derived from the ^1H NMR study of ions **1** where nonadditivity of the β-proton diamagnetic shifts was observed between the diphenylmethyl carbenium ions and its mono and dimethoxy derivatives. This result is in clear contrast with the additive behavior of the shifts in the parent neutral 1,1-diphenylethylenes.[40]

Inasmuch as variations of geometry remain small, whatever

the para substituents,[6] the origin of these deviations must be understood in terms of electronic effects. The remark that deviations to additivity appear larger in methyl carbenium ions 1 than in hydroxy carbenium ions 2, where the electron demand at C_α is reduced, as well as the fact that there is additivity in neutral parents suggest that the extent of electron deficiency at the α-carbenium center is a determining factor in these effects. All of these results lead to the concept that π-electron transfer by a substituent to a carbenium empty orbital is not an intrinsic characteristic of the group but, on the contrary, that it depends on the electron demand of the positive center and therefore on the electronic power of all the other substituents already present. These mutual perturbations in the influences of substituent groups can be accounted for by the Mulliken and Godfrey concepts of π-inductive mesomeric-concerted action.[41,42]

The electron-releasing power of a group such as OCH_3 may be divided into two parts: a mesomeric charge-transfer donation bringing π electrons from the substituent to the conjugated system and a π-inductive effect I_π which redistributes the electrons in the conjugated system without any neat transfer from the substituent. According to the Mulliken and Godfrey points of view, the electron transfer depends upon the I_π effects of all the other substituents; it decreases, for instance, when the I_π effects of the other groups increase.

The existence of such substituent–substituent interactions based on the concept of a concerted π-inductive mesomeric action has been previously demonstrated by the works of Taft et al.[13] or Freedman et al.[10,43] Taft and McKeever[13c] have shown that the donor effects of 4-OCH_3 and $N(CH_3)_2$ on the stabilization energy of trityl anions are nearly the same, while in successive NO_2 substitutions a saturation of electronic influences appears. Conversely, for the stabilization energies of substituted trityl cations, a similar saturation occurs with donor groups.[13b] Saturation is also evident in the ^{19}F NMR spectra of 4-F trityl cations bearing two OCH_3 or $N(CH_3)_2$ groups.[13b] Moreover, Freedman et al.[43] have shown that in para'-substituted *p*-dimethylaminotrityl cations the rotational barrier about the N–aryl bond is substituent dependent and is related to π delocalization: the π bond order and the extent of the electron transfer from $\overline{N}$ to the ring are weakened if the releasing power of the others groups is greater.

The existence of these two π effects is largely illustrated by our results. For example, regarding the 4-OCH_3,4'-OCH_3 ions **1b** and **2b**, it can be ascertained that the strong I_π effect of each methoxy opposes an appreciable electron migration from the other OCH_3. This is felt to be an overall reduction of the electron transfer attributed to each methoxy group as compared to the transfer taking place in the monosubstituted 4-OCH_3 ions **1a** and **2a**. Such a saturation of donor influences does not occur in the disubstituted ions bearing F, Cl, or CH_3 substituents: the π interactions of these groups with the carbenium center act mainly via an I_π effect for which additivity undoubtedly occurs. Conversely, an electron-withdrawing group such as CF_3 or NO_2 exerts an I_π effect which, if a strong releasing substituent is present, leads to an increased electron migration from this last group to the C_α empty orbital: thus, a 31-ppm upfield shift appears from ion **1a** (X, NO_2) to **1c** (X = NO_2) as compared to the 20.3-ppm upfield SCS of ion **1a** (X = OCH_3).

The same type of arguments can be invoked to explain the sequence of the shifts in the 4-NO_2,4'-NO_2 ion and in the 4-NO_2 and the unsubstituted ion **2**. The small mesomeric effect of the NO_2 group in the monosubstituted ion results from an increase in the electron migration from the unsubstituted ring to the α-carbon, as evidenced by large SCS on this ring (see Tables I and II); in contrast, the greater variations between the di- and mononitro ions **2** correspond to an increased effect in the disubstituted ion, since the attracting influence of the NO_2 group cannot now be counterbalanced by any other donating mesomeric effect at the C_α; then, the overall effect of the two NO_2 groups in ions **2b** appears as more than twice the effect of one NO_2 group in ion **2a**.

Table III. Interaction Term I_{XY} (ppm)

Ions	OCH_3, OCH_3	OCH_3, CH_3	OCH_3, CF_3	OCH_3, NO_2	CH_3, NO_2	CH_3, CH_3	NO_2, NO_2	CF_3, CF_3
1	14.8	4.8	−8.3	−10.7		3.9		2.6
2	3.8	1.4	−2.3	−3.6	1.1	0.6	2.5	

Another confirmation of the proposed interpretation is based on the observation of the magnetic nonequivalence of the 2',6' and 3',5' positions in the spectra of ions **1c** where X = NO_2 and CF_3, whereas only time-averaged spectra are recorded at the same temperature for ions **1c** where X = H and OCH_3. As already evidenced by other authors in similar aryl carbenium ions,[7a,10,19,43] the height of the rotational barrier of the C_α–C_1 bond in ions **1c** or **2c** is substituent-dependent: the greater the attracting effect of the X group, the greater the electron donation by electron transfer from the OCH_3 group to the C_α and thus the greater the π-bond order and rotational barrier of the C_α–C_1 bond. However, as already pointed out, the π charge at the α-carbon of ions **1** is clearly greater than in the analogue ions **2** because of the mesomeric electron donation by the oxygen in the latter. Therefore, π-electron demand from the aryl rings for stabilization is smaller in ions **2** and leads to a smaller rotational barrier for the C_α–C_1 bond in ions **2** than in ions **1**; the time-averaged magnetic equivalence for the two ortho and meta anisyl ring carbons in the range −50 to +25 °C substantiates this interpretation.

Definite proof for this dependence of π-electron transfer from a methoxy group upon the electronic structure of ions can be gained by examination of the chemical shifts of the OCH_3 carbons in ions **1c** and **2c**. With respect to the parent monosubstituted 4'-OCH_3 ions, the downfield shifts observed in the disubstituted 4-NO_2,4'-OCH_3 ions (1.5 ppm for **1c** while 0.5 ppm for **2c**) as well as in the disubstituted 4-CF_3,4'-OCH_3 ions (0.8 ppm for **1c** while 0.2 ppm for **2c**) also suggest an increased π-electron transfer from the methoxy when the more attracting groups are present. In contrast, Tables I and II show a reverse trend in the case of disubstituted 4-CH_3,4'-OCH_3 and 4-OCH_3,4'-OCH_3 ions **1c** and **2c**, i.e., an upfield shift of the methoxy group.[44] Moreover, INDO π-electron densities on the oxygen atom (Tables IV and V, supplementary material) parallel the methoxy carbon shifts in ions **1c** and **2c**, and a rough correlation between these two quantities can be obtained ($m = -308 \pm 46$; $i = 576 \pm 85$; $r = 0.922$; $s = 0.5$).

A quantitative description of these substituent–substituent interactions has been carried out by considering the interaction terms I_{XY}. These terms, listed in Table III, are defined in the 4,4'-disubstituted ions as the deviations to a strict additivity of the SCS corresponding to the monosubstitution:

$$I_{XY} = (\delta_{X,Y} - \delta_{H,H}) - [(\delta_{X,H} - \delta_{H,H}) + (\delta_{Y,H} - \delta_{H,H})]$$

where $\delta_{X,Y}$ is the C_α chemical shift in the 4-X,4'-Y ion.

From the above discussion it results that I_{XY} would depend on the charge-transfer effect of the substituent and on its I_π effect which both modulate the transfer from other groups. Before making an accurate separation of these contributions, the success of the models that we have previously proposed to traduce substituent–substituent interactions in the bromination rate constants of polysubstituted benzenes[12b] and in the protonation equilibrium constants of polysubstituted benzophenones[12c] leads us to use an σ^+ representation as an exploratory tool. With a symmetrical model, chosen so as not to introduce an artificial dis-

tinction between the substituents, we obtained for the interaction term:[45]
ions **1**:

$$I_{XY} = 20.4\sigma_X^+\sigma_Y^+ + 0.9 \ (r = 0.989; \text{SD} = 1.3) \qquad (8)$$

ions **2**:

$$I_{XY} = 5.8\sigma_X^+\sigma_Y^+ + 0.1 \ (r = 0.996; \text{SD} = 0.2) \qquad (9)$$

Although the use of σ^+ constants is certainly an oversimplification, these correlations appear to give a quite satisfactory evaluation of substituent–substituent interactions on the ^{13}C chemical shifts. Since the coefficient of the $\sigma_X^+\sigma_Y^+$ term depends only on the structure of the substrate, no matter what the substituents,[46] it may be considered as an estimation of the sensitivity to these interactions and would thereby permit discussing the variations of the sensitivity in connection with the electronic structure of the ions. From the first results obtained here, it is suggested that (for systems of similar geometry) this sensitivity increases with the interactions of the substituted phenyl rings with the carbenium center, i.e., with the electron demand on this position.

As anticipated in our earlier work,[6] Figures 5 and 6 clearly indicate that the INDO method fails in describing the strong π-electron releasing effect of the OCH_3 in the ions **1c** where X = H, CF_3 and NO_2, while it is adequate for ions **1c** and **2c** where X = OCH_3; the CNDO/S approximation[28] is not more successful. On these grounds, we have invoked[6] some inadequacies in the standard parametrization of resonance integrals or atom valence-state ionization potentials. However, we have seen before that π-electron densities at the substituted ring carbons are always well pictured by INDO calculations, a fact which apparently seems contradictory to this assertion. Actually, π-electron density at the substituted ring carbons is mainly developed by π-inductive and polarization effects without important electron transfer from the substituent, whereas the charge at the positive α-carbon is favored by a possible electron migration from the substituent into the empty $2p_z$ orbital; in this last event, it is clear that the adequacy of the C_1–C_α bond is crucial to a good picture of the charge transfer to the aromatic ring. The similar trends in SCS of anisole and ions **1a** and **2a** where X = OCH_3 (see above) give further evidence of the predominance of π-inductive and polarization effects at the anisyl ring carbons, whatever the electron demand by the α-carbon may be. The higher rotational barrier of the C_1–C_α bond in ions **1c** where X = NO_2 and CF_3 suggests that this π-electron migration is governed by the magnitude of the C_1–C_α π-resonance integral as well as by the magnitude of the C_4–OCH_3 π-resonance integral.

(iii) Long Range Substituent Effects. The existence of a transmission of the X substituent electronic effects to the second aromatic ring has been previously investigated by ^{19}F NMR in 4-F,4′-substituted protonated benzophenones[47] and other closely related neutral molecules or ions.[47,48] We very recently pointed out[49] that ^{13}C is a very powerful technique for following the propagation of these influences along the carbon framework.

Tables I and II show that the $C_{1'}$ and $C_{3'}$ positions undergo very small variations, ~2 ppm, while $C_{2'}$ and $C_{4'}$ signals move up to 13.4 ppm in ions **1a** from X = OCH_3 to X = NO_2. These results are easily explained by the existence of π-conjugation between the $C_{2'}$, $C_{4'}$, and C_α positions but are in contrast with the trends observed in the parent hydrocarbons; for example, in the substituted 1,1-diphenylethylenes there is no transmission of the substituent π-electronic effects to the other aromatic ring, particularly at the $C_{2'}$ or $C_{4'}$ positions. The simplified π molecular orbital theory has demonstrated that this results from an absence of electronic interactions between the two distinct sets of carbons (namely starred or unstarred) in an even-alternant hydrocarbon like 1,1-diphenylethylene.[50] In line with this formalism, we can notice that unsubstituted ions **1** and **2** belong to the class of the odd-alternant hydrocarbons[50] for which our data, as well as literature results,[48] show the reverse situation, i.e., that electronic perturbations at the C_4 position strongly affect C_α, $C_{2'}$, and $C_{4'}$ carbons of the same set. It is clear that the C_α bridge acts as a transmitter for such electronic interactions from one ring to the other, probably through the nonbonding orbital centered at the C_α carbon, since the transmission is greater when the energy of this orbital is greater.[51]

In addition, from an extensive comparison of substituent effects across bridged ring systems, Phillips et al.[48] have concluded that, for most of the bridges, there is no π-electron transfer from one ring to the other, since the bridge acts as a relay rather than a transmitter. For the protonated benzophenones, however, they recognize that the situation is not as obvious and question the various contributions of π-inductive and π-electron transfer at the $C_{1'}$ carbon; indeed, due to the absence of direct conjugation between the C_4 and $C_{4'}$ carbons, they are inclined to think that the second effect is absent. Our results allow us to make more precise conclusions.

From our data in Tables I and II, rather good correlations between SCS at the $C_{4'}$ and C_1 carbons can be obtained for each series of ions **1a** and **2a** (eq 10 and 11)

$$\delta_{C_{4'}} = 0.91\delta_{C_1} + 13.6 \ (r = 0.922; \text{SD} = 1.8) \qquad (10)$$

for ions **1a** and

$$\delta_{C_{4'}} = 0.35\delta_{C_1} + 61.7 \ (r = 0.972; \text{SD} = 0.4) \qquad (11)$$

for ions **2a.**

Since π-electron densities at the C_1 carbons are mainly developed by the π-inductive effect, eq 10 and 11 mean that this is also true at the very remote $C_{4'}$ positions. It is then ascertained that C_α acts only as a relay without electron transfer from the substituent to the unsubstituted ring; hence, π electron density at the C_α carbon is the only one developed by π-electron migration from the substituents in ions **1** and **2,** but π-electrons at the C_α carbon in turn polarize the second aromatic ring by a π-inductive effect. Moreover, we have shown above that the magnitude of the π-inductive effect at C_1 is independent of the π-electron demand by C_α, since it is nearly the same in ions **1a** and **2a;** thus, the ratio of the slopes of eq 10 and 11 indicates that the π-polarization at the unsubstituted aromatic ring is greater, by a factor of 2.6, in ions **1a** than in ions **2a.** It is extremely noteworthy that this value is nearly identical with the ratio of the C_α susceptibilities in ions **1a** and **2a,** namely, 2.7 (eq 5). These observations clearly confirm that the C_α bridge acts as a relay for the electronic interactions and that the greater the positive charge at C_α the greater will be the relay efficiency; in other words, the magnitude of the π-inductive effect at the unsubstituted ring is directly related to the π-electron deficiency at the C_α position (q = 0.5063 in diphenylmethyl carbenium and q = 0.6188 in protonated benzophenone), i.e., to the energy of the empty orbital of the π-carbon. This conclusion is in full agreement with the results obtained for various bridges by Phillips and co-workers[48] and with the theoretical predictions of Murell.[51]

Conclusion

^{13}C NMR has been used to investigate the electronic structure of diphenylmethyl and diphenylhydroxy carbenium ions. The ability of the chemical shifts in a range of ~120 ppm as a probe of electronic distribution is demonstrated by general correlations with π-electron density and π-bond order for para, para′-substituted ions **1** and **2.** The importance of the

π-bond order term is borne out when comparing shifts of sites differing in their environment or their substitution degree.

The distinct SCS on the C_α carbenium center are interpreted on the basis of the electron demand at this position, whereas on the substituted ring the shifts remain near the values observed in neutral monosubstituted benzenes, regardless of the electron demand. Nonadditivity of the SCS points out substituent–substituent interactions and substantiate the concept that the π-electron donation from a releasing group (such as OCH_3) is strongly dependent on the electron deficiency at the carbenium center, in accordance with the notions of concerted π-inductive mesomeric action.

Long-range substituent effects from one phenyl ring to the other are observed and interpreted by means of a relay influence of C_α whose electron density does not directly contribute to the observed shifts.

Finally, our results show that ^{13}C chemical shifts are an extremely good means for studying the structure of carbocations inasmuch as specific electronic effects at each carbon are singled out; thus, some insight concerning the nature of transmission of substituent perturbations in the ion framework becomes possible.

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Supplementary Material Available. INDO total and π-electron densities and π-bond orders for diphenylmethyl carbenium ions 1 (Table IV) and diphenylhydroxy carbenium 2 (Table V) (2 pages). Ordering information is given on any current masthead page.

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(37) For example: ions **1a**, $\delta_{C_\alpha} = 14.2\sigma^+ + 169.6$ (r = 0.916; SD = 3.6); ions **2a**, $\delta_{C_\alpha} = 4.5\sigma^+ + 152.4$ (r = 0.876; SD = 1.4).

(38) The fact that the regression line also fits well the disubstituted ions is not in conflict with the existence of substituent–substituent interactions of different magnitudes in ions **1** and **2**. This results from a greater sensitivity to substituent effects and hence from greater interactions in ions **1** than in **2**.

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(45) (a) For ions bearing two acceptor groups, i.e., 4-NO_2,4′-NO_2 and 4-CF_3,4′-CF_3, the estimation of I_{XY} is less satisfactory, although reproduced; thus, these two points have been excluded from eq 8 and 9. (b) As the C_α chemical shifts cannot be expressed by σ^+ constants in monosubstituted ions, a more simple formulation of $\delta_{C_\alpha}(X,Y)$ with $\sigma_X^+\sigma_Y^+$ cannot be attained in contrast with the parent models of ref 12b and 12c.

(46) In a study of the stabilization energies of trityl cations, Freedman (ref 10a, p 1553) defined a saturation ratio "SR" which is the ratio of the substituent effect observed in disubstituted compounds vs. the value calculated assuming additivity of the perturbations observed in monosubstitution; he pointed out that SR is dependent on the nature of the group and is roughly correlated to its σ^+. Our I_{XY} term is more useful for unsymmetrical disubstitution and leads via the $\sigma_X^+\sigma_Y^+$ representation to a measure of the

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1-Phenylallyl Cations and Their Rearrangement to Indanyl Cations in Superacidic Media[1a]

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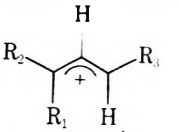
The 2-phenyl-2-penten-4-yl cation (**4**) has been prepared in magic acid solution at −120 °C from 2-phenyl-3-penten-2-ol. Upon raising the temperature, a cyclic ion **12** was observed at −80 °C, which finally rearranged to the indanyl cation **14** at −70 °C. Methyl and deuterium substitution of the phenyl ring allowed identification of the structure of the intermediate ions and determination of the mechanism of the cyclization process.

A large number of stable alkyl-substituted allyl cations have been prepared and investigated[2] in superacidic media, but very few phenylallyl cations[3] are known as stable species at low temperature. At first glance this seems to be surprising since phenyl groups in most other carbocations have been shown to exhibit a greater stabilizing ability than alkyl groups.[4] However, in contrast to alkylated allyl cations, phenylallyl cations can easily undergo intramolecular cyclization to the corresponding indanyl cations, which explains the difficulty in obtaining them as stable species.[3a,b]

While ions **1**, **2**, and **3** were reported to be observable from −50 to −70 °C in FSO_3H–SO_2 or SO_2ClF, **4** could not be detected under these conditions since it rearranged to **14** (Scheme I). A deprotonation–reprotonation sequence was suggested to cause this rearrangement.[3b] Since deprotonation should be less favored in more acidic media, phenylallyl cations are expected to be more stable in FSO_3H–SbF_5–SO_2ClF than in FSO_3H–SO_2. Therefore, we attempted to prepare **4** in magic acid solution and to study its rearrangement under these conditions.

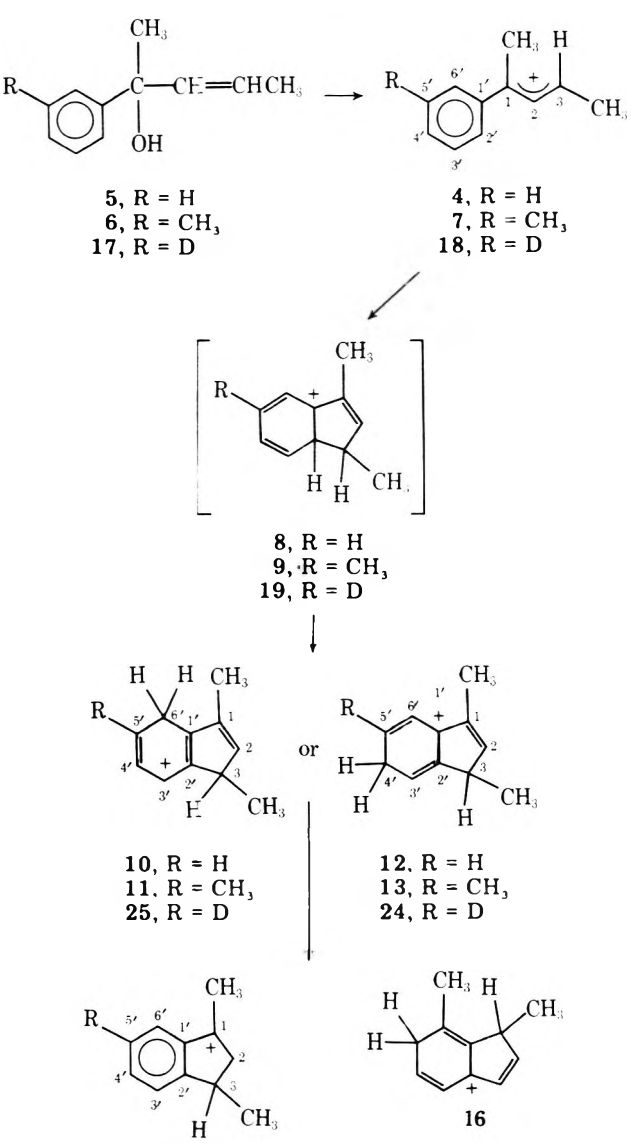


1, $R_1 = CH_3$; $R_2 = R_3 = Ph$
2, $R_1 = R_2 = R_3 = Ph$
3, $R_1 = H$; $R_2 = Ph$; $R_3 = CH_3$
4, $R_1 = R_3 = CH_3$; $R_2 = Ph$

Results and Discussion

When a precooled solution of 2-phenyl-3-penten-2-ol (**5**) in SO_2ClF was slowly added with good stirring to an excess of FSO_3H–SbF_5 in SO_2ClF at −120 °C, the 2-phenylpentenyl cation **4** was obtained. It is stable below −90 °C but starts to rearrange at this temperature (Scheme I). Ion **4** was characterized by its ^1H NMR and ^{13}C NMR spectra (Tables I and II). Conversion of **4** into another ion was observed at −80 °C. This species, however, could not be obtained with complete purity since contamination resulting from rearrangement to the known indanyl cation **14** began to occur at −70 °C. Both

Scheme I



5, R = H
6, R = CH_3
17, R = D

4, R = H
7, R = CH_3
18, R = D

8, R = H
9, R = CH_3
19, R = D

10, R = H
11, R = CH_3
25, R = D

or

12, R = H
13, R = CH_3
24, R = D

14, R = H
15, R = CH_3

16

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Table I. ^{1}H NMR Chemical Shifts (δ) and Multiplicities of Phenylallyl Cations and Their Rearrangement Products

Registry no.	Compd	H(2)	H(3)	H(3′)	H(4′)	H(5′)	H(6′)	Methyl substituents
64999-96-8	4	Aromatic and olefinic protons absorb in a multiplet at 8.3–9.3						C(1)–CH_3 3.6, C(3)–CH_3 3.0 (d)
65027-47-6	12	8.6	4.3	8.6	4.7	8.9	8.2 (d)	C(1)–CH_3 2.7, C(3)–CH_3 1.9 (d)
65036-43-3	13	8.3	4.2	8.3	4.6	–	8.0 (s)	C(1)–CH_3 2.6, C(3)–CH_3 1.7 (d), C(5′)–CH_3 3.0
64999-59-3	14	4.1	3.7	8.1	8.6	8.0	8.6	C(1)–CH_3 3.5, C(3)–CH_3 1.7 (d)
64999-58-2	15	4.2	3.8	8.0	8.4	–	8.3 (s)	C(1)–CH_3 3.7, C(3)–CH_3 1.8 (d), C(5′)–CH_3 2.6

Table II. ^{13}C NMR Chemical Shifts (ppm Downfield of Me_4Si) and Multiplicities of Phenylallyl Cations and Their Rearrangement Products

	C(1)	C(2)	C(3)	C(1′)	C(2′)	C(3′)	C(4′)	C(5′)	C(6′)	Methyl substituents
4	213.7 (s)	136.3 (d)	190.8 (d)	137.8 (s)	135.6 (d)[a]	131.0 (d)	147.3 (d)	131.0 (d)	131.6 (d)[a]	C(1)–CH_3 25.7,[a] C(3)–CH_3 21.6[a]
12	152.9 (s)[a]	181.1 (d)[a]	46.0 (d)	187.4 (s)	146.4 (s)[a]	158.1 (d)[a]	42.5 (t)	171.5 (d)[a]	126.4 (d)	C(1)–CH_3 12.4,[a] C(3)–CH_3 11.1[a]
13	150.7 (s)[a]	175.5 (d)[a]	45.1 (d)	186.4 (s)	145.1 (s)[a]	154.3 (d)[a]	45.6 (t)	191.8 (s)	125.2 (d)	C(1)–CH_3 13.1,[a] C(3)–CH_3 11.2,[a] C(5′)–CH_3 25.4
14	251.8 (s)	56.5 (t)	41.9 (d)	143.9 (s)	184.4 (s)	132.0 (d)[a]	153.9 (d)	128.1 (d)[a]	134.7 (d)[a]	C(1)–CH_3 24.4, C(3)–CH_3 16.9

[a] Relative assignment is uncertain.

isomerizations were irreversible, as demonstrated by recooling the samples to −120 °C. The benzenium ion **8**, which might result from the electrocyclic ring closure of **4**, was eliminated as the intermediate observed at −80 °C on the basis of the ^{13}C NMR spectrum. This spectrum shows three vinylic singlets and four vinylic doublets, while the spectrum of **8** is expected to display two singlets and five doublets in the same region. Therefore, **10** and/or **12** are suggested as possible observable intermediates in the rearrangement sequence **4** → **14**.

In order to differentiate between these two arenium ions, 2-(*m*-tolyl)-3-penten-2-ol (**6**) was treated with FSO_3H–SbF_5. Even at −120 °C **7** could only be observed as a minor component in the spectrum of the cyclic intermediate. Rearrangement to the indanyl cation **15** occurred at −60 °C. As expected for both **11** and **13**, the ^{13}C NMR spectrum of the intermediate ion showed four olefinic singlets and three olefinic doublets.

Based on the ^{1}H NMR spectrum, the identification of **13** was possible. Since H(6′) of **13** is the only proton attached to an even numbered carbon in the heptatrienyl backbone, it should be the most shielded olefinic proton. For the same reason, H(4′) should be the most shielded vinylic hydrogen in **11**. Figure 1b clearly shows that the olefinic resonance at highest field is a singlet, in accord with H(6′) of **13**. On the contrary, H(4′) of **11** should display a doublet.

Analogously, the high-field absorption of Figure 1a can be assigned to H(6′) of **12**, a doublet split by H(5′), whereas H(4′) of **10** should show a triplet. As observed previously with other benzenium ions,[5] the methylene group of both **12** and **13** absorbed as a broad singlet. Only trace amounts of **16** could be detected together with **12**, indicating that in the allyl cation **7** C(3) attacks selectively at the C(2′) position to yield the corresponding arenium ion **9**.

Mechanism. As depicted in Scheme I, the electrocyclic ring closure of **4** and **7** to **8** and **9** is proposed to be the initial step. Further rearrangements by a series of two 1,2-hydride shifts yield **12** and **13**, respectively. A deprotonation–reprotonation sequence cannot be accountable for the formation of **12** and **13** since this would imply protonation of indenes on the aromatic ring. This hypothesis, however, is in contrast to the observation that indanyl cations do not show deuterium incorporation in their six-membered rings when they are prepared from phenylallyl alcohols and FSO_3D.[3] The observation that **7** cyclizes faster than **4** can be explained by the fact that

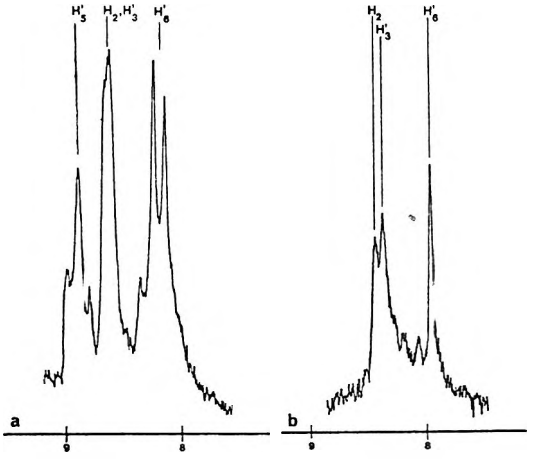


Figure 1. ^{1}H NMR spectra (olefinic protons) of (a) ion **12** and (b) ion **13** at 100 MHz.

the additional methyl group (R) stabilizes the allyl cation **7**, where R is attached to an uncharged carbon atom. The formation of **12** and **13** furthermore demonstrates that the 1,2-hydride shifts are kinetically preferred over a 1,8-hydride shift, which would yield **14** and **15** directly from **8** and **9**.

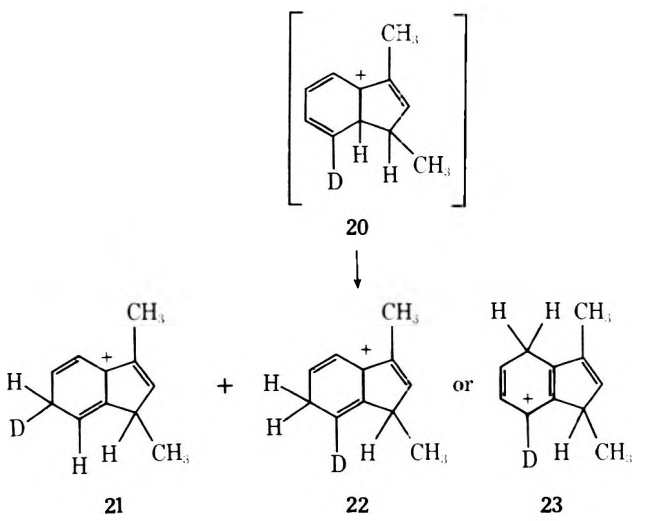
12 may be regarded as a benzenium ion with a vinyl substituent in the para position, whereas **10** is a benzenium ion with an *o*-vinyl group. It is well-known that alkylbenzenes yield *p*-alkylbenzenium ions when dissolved in strong acids.[5] Therefore, we suggest that **12** can be observed as an intermediate because it is the thermodynamically most stable arenium ion.

Finally, the formation of **14** can proceed either via a series of intramolecular hydride shifts or via a deprotonation–reprotonation mechanism.

In order to prove the suggested reaction mechanism, we prepared, the meta-deuterated alcohol **17** and studied its ionization and further cyclization (Scheme II). Since secondary kinetic isotope effects are generally small, we expected **18** to yield equal amounts of **19** and **20**. At −80 °C these products then rearranged to the benzenium ions **24** and **21** + **22**, respectively. As expected for a mixture of these ions, the most shielded olefinic absorptions were a doublet (H(6′) of **21** and **22**) and a singlet (H(6′) of **24**) centered at δ 8.2. Since both

Scheme II

17 → 18 → 19 → 24 or 25



of the alternative structures, **23** and **25**, should show doublets at δ 8.2, the identity of the intermediates could be confirmed by this experiment.

However, the singlet (**24**) was of lower intensity than the doublet (**21** + **22**), indicating a loss of deuterium from the 5′ position. Since a deprotonation–reprotonation mechanism was already excluded above, we suggest that in the cyclic intermediates (e.g., **24**) slow 1,2-hydride migrations are taking place, yielding small equilibrium concentrations of isomeric benzenium ions. In this equilibration process deuterium can be washed out of the 5′ position to yield the observed spectrum.

The formation of **14** has already been observed by Pittman and Miller[3b] when **5** was treated with FSO_3H at −70 °C. Neither **4** nor **12** have been observed under these conditions. Therefore, we treated **5** with FSO_3H–SO_2ClF at −120 °C. In contrast to our observations in magic acid, the indanyl cation **14** was not formed, even at −120 °C. Therefore, it is proposed that when magic acid is substituted for an acid of lower acidity another mechanism becomes operative. In such media an alternative route is deprotonation to a transient indene and a subsequent reprotonation, as proposed by Pittman and Miller.[3b]

Experimental Section

Materials. Magic acid was prepared from triply distilled FSO_3H and doubly distilled SbF_5; a 1:1 molar ratio was used in all experiments. 2-Phenyl-3-penten-2-ol (**5**) was commercially available (Chemical Samples Co.).

2-(*m*-Tolyl)-3-penten-2-ol (6) was prepared from *m*-methylacetophenone (Aldrich Chemical Co.) and 1-propenylmagnesium bromide (obtained from 1-bromo-1-propene, Chemical Samples Co.) in THF: bp 104 °C (4 mm); ^1H NMR (CCl_4) δ 1.5 (d, 3 H, J = 4 Hz, CH_3), 1.6 (s, 3 H, CH_3), 5.5 (m, 2 H, olefinic CH), 7.1 (m, 4 H, phenyl CH).

2-(*m*-Deuteriophenyl)-3-penten-2-ol (17). *m*-Bromoacetophenone (Eastman) was converted into its ethylene ketal by refluxing and stirring with ethylene glycol and a small amount of *p*-toluenesulfonic acid in petroleum ether (bp 35–55 °C) for 36 h: ^1H NMR (CCl_4) δ 1.9 (s, 3 H, CH_3), 4.1 (m, 4 H, CH_2), 7.7 (m, CH).

The ethylene ketal was treated with magnesium turnings in THF, and the Grignard compound was then hydrolyzed with D_2O–D_2SO_4 at room temperature to give *m*-deuterioacetophenone. Deuterium incorporation was ascertained by the observed 4:3 phenyl CH/CH_3 proton ratio, the substantial simplification of the ring proton absorption in the ^1H NMR spectrum, and the ^2H NMR spectrum (absorption at δ 7.6).

17 was prepared by reacting *m*-deuterioacetophenone with 1-propenylmagnesium bromide in THF: bp 54–55 °C (0.1 mm); ^2H NMR (acetone) δ 7.6 (relative to internal acetone-d_6).

Preparation of Ions. A dilute solution of the corresponding alcohol in SO_2ClF at −120 °C was added dropwise with good stirring to an approximately 1:2 (by volume) solution of FSO_3H–SbF_5 in SO_2ClF at −120 °C. The preparation of **4** and **18** required extremely slow addition to avoid further rearrangement due to local heating. Intermediate ions **12**, **21**, **22**, and **24** (observed at −90 °C) were prepared by warming up the former solutions by a careful increase of the probe temperature in the ^1H NMR or ^{13}C NMR spectrometers, and they were stable up to −80 °C. Ion **13** was observed in the original solution even at −120 °C and was stable up to −70 °C. The spectra of indanyl cations **14** and **15** were recorded at −60 °C.

Proton Magnetic Resonance Spectra. ^1H NMR spectra were obtained on a Varian Associates Model A56/60A or HA-100 spectrometer equipped with a variable-temperature probe. External Me_4Si (capillary) was used as a reference for the carbenium ions and internal Me_4Si for their precursors.

Carbon-13 Magnetic Resonance Spectra. The spectrometer used was a Varian Associates Model XL-100 equipped with a broad band decoupler and variable-temperature probe. Chemical shifts were measured from external (capillary) Me_4Si.

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Registry No.—**5**, 4743-67-3; **6**, 64999-97-9; **17**, 64999-98-0; *m*-deuterioacetophenone, 64999-99-1; *m*-methylacetophenone, 585-74-0; 1-bromo-1-propene, 590-14-7.

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Solvent and Structure Effects on the Rates of Bromine Addition to Acetylene Derivatives. Analogies and Differences in Electrophilic Additions to Double and Triple Bonds

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The rates of bromine addition to phenylacetylene, 1-hexyne, and 3-hexyne were measured in acetic, formic, and trifluoroacetic acids and in methanol–water mixtures and compared to those for the corresponding ethylenic derivatives. From the analysis of solvent effects it is concluded that nucleophilic assistance by the solvent is important in many solvents in the case of hexynes and that typical reactivity ratios k^o/k^a for nucleophilically unassisted brominations are of the order of 10^3 for the pair styrene/phenylacetylene and 10^8 for 1-hexene/1-hexyne. Structural effects on the rate of bromination in methanol for substituted phenylacetylene and diphenylacetylenes indicate a highly asymmetrically charged transition state. The possible reasons for the different k^o/k^a ratios in halogen additions relative to those observed in acid-catalyzed hydrations are discussed.

Following the wave of interest in the chemistry of vinyl cations, several recent studies[1-10,13,14] have appeared concerning the mechanism of electrophilic additions to acetylene derivatives.

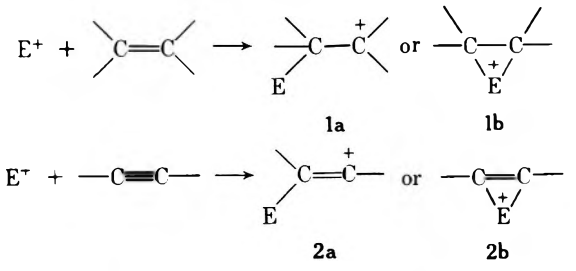
Kinetic and stereochemical evidence has been presented which points to very close mechanistic analogies between electrophilic additions to double and triple bonds. In both cases, the slow step of the reaction is indicated[1] as the formation of cations 1 or 2 (Scheme I) either in the "open" (**a**) or in the "bridged" (**b**) geometry, depending on the bridging ability of E.

The analogies are particularly evident[4] in the case of acid-catalyzed hydration (E = H). The reaction for both ethylene and acetylene derivatives is dominated by a slow proton transfer from the solvent to the substrate and is characterized by very similar mechanistic parameters,[5] such as the general acid catalysis, solvent isotope effects, and substituent effects.

The addition of halogens, in particular bromine, which has been more widely investigated, is a more complicated case where analogies but also differences between alkenes and alkynes have been observed.[6-11] Here the comparison is made difficult by a variety of factors such as the very high reactivity of alkenes in most solvents and the very large solvent effect.

One of the most debated questions[1,4,7,10,13,14] in the field of electrophilic additions to unsaturated systems concerns the relative reactivities of olefins and acetylenes, k^o/k^a, observed in the limiting cases of bromination[6-10] (values ranging from 10^3 to 10^7) and of acid-catalyzed hydration[4,5] (values close to unity) for typical cognate pairs such as styrene/phenylacetylene and *n*-alkenes/*n*-alkynes. Different hypotheses have been presented[1a,1c,7,10] to explain the different relative reactivities. However, in our opinion, some of the rate data for bromination reported in the literature and taken as a basis for discussions needed to be revised, particularly those obtained by competition techniques.[7,10] Moreover, a more systematic analysis of solvent and substituent effects on the bromination of alkynes was important to obtain the mechanistic information required by a correct comparison of kinetic data with that of the corresponding olefins.

Scheme I



We have therefore investigated the bromination of phenylacetylene,[12] 1-hexyne, and 3-hexyne in a variety of hydroxylic solvents and of that substituted phenylacetylenes and diphenylacetylenes in methanol. The results herein are compared to those available in the literature relative to the corresponding olefinic systems, and an attempt is made to offer a rationale for the widely different reactivity ratios observed for bromination and acid-catalyzed hydrations.

Results

The rates of bromination of phenylacetylene, 3-hexyne, and 1-hexyne in various solvents have been measured by conventional spectroscopic techniques or by a stopped-flow method under pseudo-first-order conditions (except in CF_3CO_2H).

The bromine concentration was kept low enough ($<3 \times 10^{-4}$ M) to apply[6] the proper kinetic law which includes[9,15,16] the effect of added bromine ion (eq 1). k_ψ is the second-order observed rate constant and K the equilibrium constant for the tribromide ion formation ($Br_2 + Br^- \rightleftharpoons Br_3^-$). The k_2 values were either directly measured, $(k_2)_{dir}$ (in the absence of Br^-), or evaluated, $(k_2)_{ext}$, as the intercept of the plot of the function $k_\psi(1 + K[Br^-])$ vs. $[Br^-]$. Where the k_2 constants could be obtained in either way, satisfactorily similar values (see Table I) were obtained.

$$k_\psi = (k_2 + k_{Br^-}[Br^-])/(1 + K[Br^-]) \cdots \quad (1)$$

The solvents of choice were those listed in Table I. The rate of bromination of phenylacetylene in CF_3CO_2H is unaccessible due to the instability of the substrate in the solvent; it is also unstable in HCO_2H, and the rate constant reported in Table I is a very approximate value. The k_2 values are in Table I, and the individual second-order-rate constants, k_ψ, measured in the presence of KBr (and used to calculate, through eq 1 and published[17] K constants, the $(k_2)_{ext}$ values of Table I) are in Table II (see paragraph at end of paper regarding supplementary material).

The rates in Table I are compared to those available in the literature for the corresponding olefins, i.e., styrene, *cis*-3-hexene, and 1-pentene. The exact analogue of 1-hexyne, namely, 1-hexene, is virtually just as reactive[18] as 1-pentene, but much more data are available[19,20] for the latter than for the former. Table III shows the k^o/k^a ratios thus evaluated; they are obviously to be taken as approximate values from

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Table I. Second-Order Rate Constants, k_2 (M^{-1} s^{-1}),[a] for the Bromination of Phenylacetylene,[f] 3-Hexyne,[f] and 1-Hexyne[f] at 25 °C

	Phenylacetylene		3-Hexyne		1-Hexyne	
Solvents	$(k_2)_{dir}$	$(k_2)_{ext}$	$(k_2)_{dir}$	$(k_2)_{ext}$	$(k_2)_{dir}$	$(k_2)_{ext}$
CH_3CO_2H[b]	4.3×10^{-3}		5.8×10^{-3}		1.74×10^{-4}	
HCO_2H	$\approx 1 \times 10^{-3}$		1.85×10		2.1×10^{-1}	
CF_3CO_2H			5.3		1.5×10^{-2}	
MeOH	3.8×10^{-1}	9.0×10^{-1}	6.8×10^{-1}[c]	7.5×10^{-1}	0.93×10^{-1}	1.1×10^{-1}
80% MeOH[d]	3.3×10	2.6×10	8.3	7.0	3.9×10^{-1}	4.1×10^{-1}
50% MeOH[d]	1.5×10^{3}		1.25×10^{2}		1.8	
H_2O		3.1×10^{4}[e]		1.1×10^{3}[e]		1.45×10[e]

[a] $(k_2)_{dir}$ when directly measured in the absence of bromide ions; $(k_2)_{ext}$ when obtained as the intercept of the plot of the function $k_\psi(1 + K[Br^-])$ vs. $[Br^-]$ (see eq 1) from data obtained in the presence of KBr (see Table II). The following K values from ref 14 were used: 16 (H_2O), 108 (80% MeOH), and 177 (MeOH). [b] Data from ref 6. [c] A value of 6.2×10^{-1} M^{-1} s^{-1} has been reported (ref 8). [d] Used v/v. [e] In the presence of 1% methanol (v/v). [f] Registry no.: phenylacetylene, 536-74-3; 3-hexyne, 928-49-4; 1-hexyne, 693-02-7.

Table III. Relative Reactivities, k^o/k^a,[a] for the Bromination in Various Solvents at 25 °C

Solvents	$\frac{k(\text{styrene})}{k(\text{phenylacetylene})}$	$\frac{k(\text{3-}cis\text{-hexene})}{k(\text{3-hexyne})}$	$\frac{k(\text{1-pentene})}{k(\text{1-hexene})}$
CH_3CO_2H	2.6×10^{3}[b]	3.7×10^{5}[b]	6.5×10^{4}[c,d]
HCO_2H			4.9×10^{6}[c]
CF_3CO_2H			4.6×10^{7}[e]
MeOH	1.3×10^{3}[d]	7.8×10^{4}[f]	4.1×10^{3}[c,d]
80% MeOH			3.5×10^{4}[c]
50% MeOH	1.5×10^{3}[d]		5.0×10^{5}[c,d]
H_2O	0.36×10^{3}[d,g]		1.7×10^{6}[c,d]

[a] The ratio between published k_2(olefin) (from the proper reference) and $(k_2)_{dir}$ when available, or $(k_2)_{ext}$ of Table I for the corresponding acetylene derivatives. [b] From ref 7. [c] From ref 19. [d] From ref 11. [e] From ref 20. [f] From ref 8 and 9. [g] Probably underestimated (see ref 21).

experimental data obtained from different laboratories and different techniques.

The rates of bromination for six-substituted phenylacetylenes and nine-substituted 1,2-diphenylacetylenes were measured in methanol at 25 °C, and the k_2 values were all (but in one case) obtained directly, in the absence of Br^-. The data are collected in Table IV.

Discussion

A comparative analysis of the kinetic results on the bromination of acetylene and ethylene derivatives is made easier by a preliminary distinction between aryl- and alkyl-substituted terms. The bromination of arylacetylenes presents the same general features of that of arylethylenes. As judged from data for the pair styrene/phenylacetylene, the reactivity ratio, $k^o/k^a \simeq 10^3$, is not sensitive to solvent changes from acetic acid to water[21] and is not much affected by the presence of substituents in the phenyl ring. On the other hand, solvent changes have a large effect upon the relative rates of alkyl-substituted derivatives. The k^o/k^a values for the pair 1-pentene/1-hexyne increase from 10^3 to as much a 5×10^7 due to solvent effects within the range of hydroxylic media investigated.

There is, however, one common feature which we would like to reassess in spite of recent reports[7,10] on the equalizing effects of solvent or structure;[22] electrophilic addition of bromine to alkenes occurs faster than that to alkynes. This is at odds as already pointed out with the behavior of double and triple bonds toward protonation; in this case the reactivity ratio is close to unity for both aryl and alkyl derivatives.

Before attempting to offer a rationale for the lower reactivity of alkynes than alkenes toward bromine addition, let us analyze in some detail the results herein reported. The generally accepted mechanism for the bimolecular bromination of alkynes may be described as in Scheme II. It is analogous to that suggested[16] for alkenes, including the π complex **3**, which following Dubois and other authors[8,10,19,23,24] is a

Scheme II

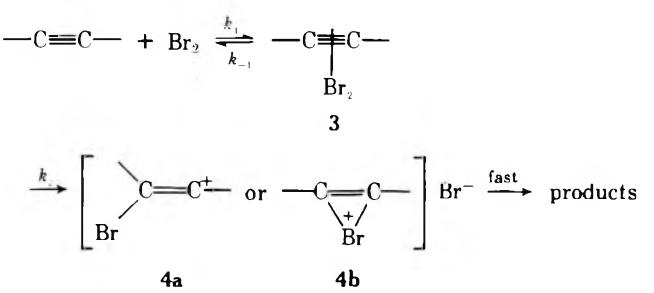


Table IV. Second-Order Rate Constants, k_2 (M^{-1} s^{-1}), for the Bromination of Substituted Phenylacetylenes and Diphenylacetylenes in Methanol at 25 °C

X—C_6H_4—C≡CH			X—C_6H_4—C≡C—C_6H_4—X′			
X	Registry no.	k_2	X	X′	Registry no.	k_2
4-Me	766-97-2	3.85×10	4-MeO	H	7380-78-1	2.05×10
4-Ph	29079-00-3	2.3×10	4-Me	4-Me	2789-88-0	5.25×10^{-1}
H		0.95	4-Me	H	3287-02-3	1.95×10^{-1}
4-Br	766-96-1	2.1×10^{-1}	4-Me	3-Me	65016-20-8	1.4×10^{-1}
3-Cl	766-83-6	1.5×10^{-2}	4-Me	3-Cl	65016-21-9	4.2×10^{-2}
4-NO_2	937-31-5	4.6×10^{-4}[a]	H	H	501-65-5	4.9×10^{-3}
			H	4-Cl	5172-02-1	2.5×10^{-3}
			H	3-Cl	51624-34-1	1.1×10^{-3}
			3-Cl	3-Cl	5216-30-8	4.4×10^{-5}

[a] $(k_2)_{ext}$ from data obtained in the presence of KBr and the application of eq 1.

Table V. Minimum[a] Estimates of Nucleophilic Assistance, k_s/k_c, for the Bromination of 3-Hexyne and 1-Hexyne

	CF_3CO_2H	HCO_2H	CH_3CO_2H	MeOH	MeOH (80%)	MeOH (50%)	H_2O
3-Hexyne	1	2	65	225	70	18	6
1-Hexyne	1	9	700	11 250	1314	90	25

[a] See ref 27 b.

significant kinetic precursor of the reaction transition state.

Solvent Effects. The slow step of the reaction is indicated as the formation of ionic species **4a** or **4b** and Br^- is in the form of ion pairs or free ions, depending on the solvent. Such an indication is confirmed here by the very large increase in the rate observed on going from less polar solvents to water, as expected for reactions proceeding via a rate-limiting ionization process.

The solvent effect is therefore to be discussed in terms of solvation energies of the two ions: cation **4** (**a** or **b**) and bromide ion. Small anions like Br^- are strongly solvated;[25] carbon cations, particularly those with delocalized charge, have low solvation energies. We have recently shown[4] that vinyl cations resulting from the protonation of aryl- and alkylacetylene derivatives in moderately concentrated sulfuric acid solutions have rather modest solvation requirements which are quite similar to those of their saturated counterparts, i.e., the carbonium ions generated by protonation of aryl- and alkylethylene derivatives. Thus, in this case, since solvation is not important for cations but only for the anion, this being common to all brominations, one should expect very similar solvent effects for cognate pairs of alkenes and alkynes. As anticipated, this is true for aryl derivatives, but not for alkyl derivatives.

Dubois and his co-workers[11,19,20] have extensively investigated the solvent effects on alkene bromination and have concluded that the process resembles a purely S_N1 process in each case, from 1-pentene, to styrene, and to 1,2-diphenylethylene, and that solvation is essentially electrophilic in character. A plot of log k vs. Y, the Winstein and Grunwald[26] parameter, is reasonably linear, although "dispersion"[27a] is observed; i.e., different slopes are obtained in methanol–water mixtures and carboxylic acids (see Figure 1). The deviations are not serious in view also of the uncertainty on the Y values and of the expected leaving group effect on Y.

The k^o/k^a for styrene and phenylacetylene is virtually unaffected by solvent changes, and therefore the solvent effect for the latter compound describes also an S_N1-like, electrophilically assisted process.

A plot of log k vs. Y for 1-hexyne and 3-hexyne is shown in Figure 1. The type and magnitude of the deviations from linearity are clearly diagnostic of solvent nucleophilic assistance. To evaluate the importance of the solvent nucleophilic assistance there are several criteria very recently discussed.[27b] The Grunwald–Winstein equation based on the Y and N parameters would allow calculation of m and l, electrophilic and nucleophilic susceptibility parameters. Unfortunately, there are serious discrepancies concerning the Y value for trifluoroacetic acid (1.84;[28] but following other estimates it is >4.2 in the t-BuCl scale[29] and 4.57 in the 2-adamantyl tosylate scale[27b]) and several uncertainties on other Y and N values for the solvents used.

We will rather follow the approach suggested by Schleyer et al.[27b] and evaluate the relative importance of the solvent nucleophilically assisted process, k_s, and the solvent electrophilically assisted process, k_c, through eq 2. This is based on the following assumptions and evidence: (a) the bromination of 1-pentene is not accelerated by nucleophilic assistance in any solvent, and (b) the alkynes do not benefit of any nucleophilic assistance in CF_3CO_2H. The treatment is clearly independent of any solvent parameters. Table V shows the k_s/k_c ratios obtained for the two alkynes. These ratios clearly indicate that the bromination of 3-hexyne in methanol and methanol–water mixtures is mainly nucleophilically assisted and that the same reaction for 1-hexyne, less reactive than for 3-hexyne (see below), is essentially nucleophilically assisted in all solvents but the two strongest acids. The values for 1-hexyne are comparable to those computed[27b] for the solvolysis of *sec*-alkyl tosylates, and in all solvents except CF_3CO_2H and HCO_2H the reaction should be classified toward the S_N2 end of the S_N spectrum (according to Schleyer et al.[27]). Therefore, following this analysis, the solvent effect on k^o/k^a for alkyl derivatives can be accounted for. The ratio is close to 10^8 and may be lowered to 10^3 when a good nucleophilic solvent like methanol is used.

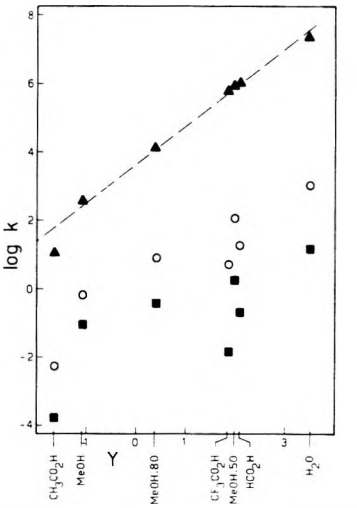


Figure 1. Plot of log k vs. Y for the bromination of 1-pentene (▲), 3-hexyne (○), and 1-hexyne (■). The Y values are taken from ref 24b.

$$k_s/k_c = [k(\text{alkyne})/k(\text{1-pentene})]_{\text{any solvent}} / [k(\text{alkyne})/k(\text{1-pentene})]_{CF_3CO_2H} \cdots \quad (2)$$

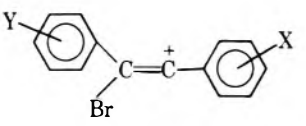
Such a conclusion accords with the results of Dubois et al.[9] on the effect of bromide ion on on the bromination of alkenes and alkynes: the effect is much larger for the latter, particularly in methanol. Following the authors interpretation of the salt effect, alkyne bromination is much more nucleophilically assisted by bromide ions than that of alkenes.

Substituent Effects. The rate constants for the bromination in methanol of the substituted phenylacetylene derivatives reported in Table IV are well (r = 0.993) correlated by the Hammett equation, using σ^+; no deviation is noticeable in spite of the 10^5 factor in rates between the two extremes. The ρ^+ value of −4.6 clearly indicates that a large fraction of positive charge is developed at the α-carbon in the transition state.

The ρ^+ value in methanol is slightly smaller than that (−5.2) reported by Pincock and Yates[6] for the same system in acetic acid. The same trend was observed for substituted styrenes: ρ^+ is −4.3 in methanol[30] and −4.7 in acetic acid.[31] The small difference in ρ^+ observed on going from acetic acid to methanol is one more argument against nucleophilic assistance by the solvent in the bromination of aryl derivatives. The larger (by ca. 10%) ρ^+ values obtained in the case of phenylacetylenes than in that of styrenes is a commonly observed fact, and the reasons for the trend have been detailed elsewhere.[1b-d,4]

The effect of substituents on the bromination in methanol of diphenylacetylene derivatives can be simply explained in

terms of a reaction leading to a vinyl cation (5) like transition state, where the positive charge is developed essentially into



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the carbon atom next to the better substituted phenyl ring $[(-\sigma^+_x) > (-\sigma^+_y)]$. The type of analysis of rate data described by Dubois and Ruasse[32] for the bromination of substituted 1,2-diphenylethylenes allows evaluation of ρ^+_x values of −4.6 (Y = H) and −4.2 (Y = *m*-Cl) for substituents in the better substituted ring and ρ_y values of −1.7 (X = *p*-Me) and −1.6 (X = H) for substituents in the other ring. The above values, although approximate, are comparable to the corresponding ones calculated[32] for the *trans*-1,2-diphenylethylenes in methanol at 25 °C: $\rho^+_x = -5.0$ (Y = H) and −4.95 (Y = *m*-Cl); $\rho_y = -1.9$ (X = *p*-Me) and −1.5 (X = H). They are also similar to those observed[33] for the solvolysis of β-bromovinyl arenesulfonates (Y—C_6H_4(Br)C=C(O_3SAr)C_6H_4-X) in acetic acid at 25 °C: $\rho^+_x = -4.9$ and $\rho_y = -1.1$.

The basic conclusion from the above analysis is that the transition-state picture in terms of charge distribution is a highly asymmetrical one, much more resembling an open cation like **5** than any bridged species.

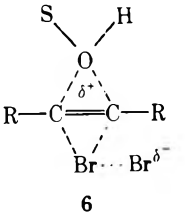
The effect of substituents on 1,2-*n*-alkyl-substituted ethylenes in methanol,[18] being defined by the Taft equation, log $k/k_0 = -3.2\Sigma\sigma^*$, does not reveal any duality such as that observed for 1,2-diarylethylenes and strongly suggests a bridged transition-state structure. Substituent effects for a number of 1,2-dialkylacetylenes have been reported by Kornprobst and Dubois;[8] however, the structural changes are not so important as to significantly vary the rate constants and offer information on the transition-state geometry. Some of the data of Table I are more informative in this respect when the effect of nucleophilic assistance due to the solvent is taken into account. The k_2(3-hexyne)/k_2(1-hexyne) ratios in the least nucleophilic solvents (350 in CF_3CO_2H and 90 in HCO_2H) are indicative of the effects upon electrophilic bromination due to β-*n*-alkyl substituents. They are of the same order of magnitude as those observed for the corresponding alkenes (k_2(*cis*-3-hexene)/k_2(1-hexene or 1-pentene) = 67 in CH_3CO_2H[7] and 130 in MeOH[8,11]) but sharply different from those reported for β-alkyl substitutions in the series of both 1-arylethylenes (k_2(*trans*-β-methylstyrene)/k_2(styrene) = 1.1 in CH_3CO_2H[34] and 2.5 in MeOH[35]) and 1-arylacetylenes (k_2(1-phenylpropyne)/k_2(phenylacetylene) = 0.5 in CH_3CO_2H[7]). These results, when also compared to those reported for the addition of arenesulfenyl chloride to alkynes,[3c] indicate a bridged symmetrically charged transition state for simple alkynes as well as for alkenes.

The Nature of the Transition State. The present results and the results of other authors would lead to the following partial conclusions. (1) The rate-limiting step in electrophilic bromination of olefins and acetylenes is the formation of ionic species more or less highly paired. The nucleophilically assisted pathway is limited to the case of alkylacetylene derivatives in good nucleophilic media or in the presence of even low concentrations of Br^-.

(2) The bromination of 1-aryl derivatives in both series proceeds via a very asymmetrically charged transition-state structure. On the other hand, Yates and McDonald[36] found that ground-state steric constraints in the case of *cis*-1,2-diphenylethylene are preserved or increased in the transition state of the reaction. From these conflicting indications, the emerging transition-state picture is that of a species with a large fraction of positive charge on the α-carbon but frozen in a spatial layout similar to that of a bridged (or of π complex) structure.

In our opinion, stereochemical results are of little help in defining the transition state since in following mechanistic Scheme I they are related to the subsequent fast product-determining step of the reaction. Moreover, available stereochemical studies have been carried out under conditions which are too far removed from those under which rate data were obtained. Still they would indicate an essentially open β-bromo-substituted cationic intermediate in both series.

(3) Based on both structural (see above) and stereochemical evidence, there is general agreement concerning the bridged geometry of the transition state of alkylethylene derivatives. The same conclusions can be reached for alkylacetylenes on the basis of the structural effects discussed above. However, in many hydroxylic media, the bromination proceeds via a nucleophilically assisted path and structures **6** or **7** could de-



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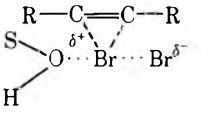

7

scribe the transition state. Reports[7] that bromine addition to 1-hexyne in acetic acid leads to *trans*-dibromo adducts and not to solvent-incorporated products would favor structure **7** were it not for the quite different conditions used for product analyses ($[Br_2] = 4.15$ M) and kinetic measurements ($[Br_2] < 3 \times 10^{-4}$ M).

(4) Theoretical studies on $C_2H_2F^+$ [37a] and $C_2H_2Cl^+$ [37b] and on the corresponding saturated ions[38] $C_2H_4F^+$ and $C_2H_4Cl^+$ reveal significant differences. In the case of adducts to acetylene, only the open ions are thermodynamically stable while the bridged structures are in energy maxima. The difference in energy between bridged and open geometries depends on the nature of the halogen (30 kcal mol^{-1} for F, 10 kcal mol^{-1} for Cl). On the contrary, in the case of the adducts to ethylene, both open and bridged species are in energy minima and only the relative level changes with the halogen. When this is Cl, the bridged structure is more stable than the open one. These computations parallel the results obtained by Olah and Bollinger[39] from ^1H NMR studies.

Calculations on the corresponding brominated cations have not been carried out, but we do not expect dramatic deviations from the trend observed on going from fluorinated to chlorinated ions. Although counterions and solvent have not been included in these models and spectroscopic evidence was obtained in conditions far removed from those of additions, there are clear indications of a large difference in energy between halogen-bridged ions from alkenes and the analogous ones from alkynes. It is noteworthy that theoretical studies carried out on protonated acetylene, $C_2H_3^+$, and ethylene, $C_2H_5^+$, indicate[40] that the relative energies of open and bridged structures are rather similar for the two ions. Ab initio computations within the SCF-HF limits indicate the open structure as the more stable species, but when configuration interactions (CI) are included the bridged structure results in lower energy.

The Relative Reactivities of Olefins and Acetylenes. Let us now face the problem of the different reactivity ratios in the limiting case of protonation and electrophilic bromination. The k^o/k^a values for styrene/phenylacetylene are 0.6 for hydration and 10^3 for bromination; for the pair 1-pentene/1-hexyne they are 10 for hydration and 10^8 for bromination.

For reasons detailed in previous papers,[1b,1c,4] we prefer to take as "normal" the ratios obtained in the hydration reactions. This implies the assumption that the lower stability of vinyl cations than that of their saturated analogues is almost entirely compensated by the lower strength of the triple bond than that of the double bond being broken in the addition of a proton. As mentioned above, in this case the open or bridged character of the transition state is apparently immaterial since the balance between the two geometries is rather similar in the two series.

To explain the high ratios observed in bromination reactions let us start from the alkyl derivatives. In this case, the transition state and the intermediate are bridged structures. From what theoretical studies clearly indicate a β-chloroethyl (and, by extension, a β-bromoethyl) cation gains in stability by bridging, whereas a β-chlorovinyl (and, perhaps, a β-bromovinyl) cation does not. Therefore, if it is true that there is an even balance between initial and transition-state energies in the case of protonation where neither one of the two systems gains by bridging, this balance must break down in the addition of halogens and strongly favor the ethylene derivatives.

Such an explanation cannot be simply applied to the case of aryl derivatives. However, the available results can be reconciled with the proposed rationale when the following points are considered. (a) The k^o/k^a ratio is much lower (by a factor of ca. 10^5) for aryl derivatives than for alkyl derivatives. (b) Thermochemical data indicate that the transition state for 1,2-diphenylethylene is partially bridged. Such bridging could be energetically more beneficial in the case of ethylene derivatives than in those of acetylene.

Other factors are perhaps to be taken into account to explain the k^o/k^a ratio for 1-aryl derivatives. The balance, fortuitously, even in the case of protonation, may change in the case of formation of destabilized cations such as the β-bromo cations involved in the bromination.[41] As mentioned above, substituent effects are larger in the case of reactions leading to vinyl cations than in those leading to the saturated ones. Scattered data from solvolysis studies[33,42] would, however, indicate that such effects can not account for a 10^3 factor, but, perhaps, for a factor of 10 in the k^0/k^a ratio.

A more intriguing problem is that of the π-complex transient species. Since the rate of bromine consumption, following Scheme II, may be expressed[19] as $v = K_\pi k_2[Br_2][substrate]$, where $K_\pi = k_1/k_{-1}$, the relative stability of the π complexes from alkene and alkynes may be quite important in explaining the k^c/k^a ratios observed. Such an argument has been brought forward by Olah and Hockswender[10] which argued that it would require more energy for π-complex formation from an alkyne due to the reduced total electron availability. Unfortunately, although evidence of π-complex formation from hexynes and iodine has been reported,[43] data on the stability of π complexes from alkynes are not available.

Experimental Section

Materials. Bromine and potassium bromide were of high analytical reagent grade and used without purification. The salt was dried (24 h at 140 °C) before use. The water used was twice distilled from alkaline $KMnO_4$ solutions. Commercial absolute methanol was treated with bromine (a few drops per liter) and, after standing overnight, fractionally distilled over potassium carbonate and redistilled. Formic acid (>99%) was refluxed for 5 h over phtalic anhydride and then fractionally distilled. Reagent grade trifluoroacetic acid was purified by fractional distillation. Phenylacetylene, 1-hexyne, 3-hexyne, and diphenylacetylene were commercial products which were further purified by standard procedures.

Substituted phenylacetylenes were prepared from the corresponding acetophenones by literature methods and purified by standard procedures: *p*-methylphenylacetylene, bp 79–81 °C (30 mm) [lit.[44] bp 79–82 °C (31–33 mm)]; *p*-biphenylacetylene, mp 88 °C (lit.[45] mp 86–87 °C); *p*-bromophenylacetylene, mp 65 °C (lit.[46] mp 63.5 °C); *m*-chlorophenylacetylene, bp 70–72 °C (15 mm) [lit.[47] bp 71 °C (15 mm)]; *p*-nitrophenylacetylene, mp 151–152 °C (lit.[48] mp 149 °C). These were checked by spectroscopic or chromatographic methods, as well as by elemental analysis.

Substituted diphenylacetylenes were obtained by described procedures; the new compounds were obtained from the corresponding 1,2-diphenylethylenes via bromination and dehydrohalogenation: di-*m*-chlorophenylacetylene, mp 81–82 °C (lit.[49] mp 81.5 °C); (*m*-chlorophenyl)phenylacetylene, bp 150 °C (3.5 mm) [lit.[50] bp 53 °C (3–5 mm)]; (*p*-chlorophenyl)phenylacetylene, mp 127–128 °C (lit.[51] mp 128 °C); (*p*-methylphenyl)phenylacetylene, mp 79–80 °C (lit.[52] mp 78–79 °C); di-*p*-methylphenylacetylene, mp 136–137 °C (lit.[53] mp 136 °C); (*p*-methoxyphenyl)phenylacetylene, mp 92–93 °C (lit.[54] mp 89–90 °C); **(*m*-chlorophenyl)-*p*-methylphenylacetylene,** mp 82 °C. Anal. Calcd for $C_{14}H_{11}Cl$: C, 79.45; H, 4.89; Cl, 15.65. Found: C, 79.59; H, 5.10; Cl, 15.45; **(*m*-methylphenyl)-*p*-methylphenylacetylene,** mp 73 °C. Anal. Calcd for $C_{16}H_{14}$: C, 93.16; H, 6.84. Found: C, 93.01; H, 6.62. These compounds were also checked by spectroscopic or chromatographic methods. All solid compounds were crystallized from absolute methanol containing small amounts (2–3% relative to the acetylene derivative) of bromine.

Kinetics. The bromination rates were measured on a Gilford 2400 or a Durrum D-110 stopped-flow spectrophotometer by following the disappearance (a) of bromine in the wavelength region of 450–480 nm for kinetic runs in the absence of KBr and (b) of the tribromide ion in the region around 270 nm for kinetic runs carried out in the presence of KBr. Bromine solutions were freshly prepared and protected from light. The measurements in water were made for solutions containing 3×10^{-3} M H_2SO_4 to prevent bromine hydrolysis and in 1% methanol (v/v) to ensure the solubility of alkynes ($1–5 \times 10^{-4}$ M). The alkyne concentrations in the kinetic solutions were $1–5 \times 10^{-2}$ M in methanol and formic acid and $1–10 \times 10^{-3}$ M in water–methanol mixtures; the ratios $[alkyne]/[Br_2]_0$ were in the range 20–100 to ensure pseudo-first-order conditions. Only for trifluoroacetic acid solutions were the rate constants obtained under true second-order conditions, and bromine concentrations were determined spectrophotometrically using published[55] extinction coefficients.

In the case of some diphenylacetylene derivatives, in methanol the kinetic solutions had to be pretreated as described[56] with a little bromine (1–2%) before achieving good reproducible results. Quite erratic results, for unexplained reasons, were obtained in the case of *p*-nitrophenylacetylene solutions in the absence of added potassium bromide.

Supplementary Material Available: Kinetic data for the bromination of phenylacetylene, 3-hexyne, and 1-hexyne in MeOH, 80% MeOH, and H_2O in the presence of KBr (Table II, 2 pages). Ordering information is given on any current masthead page.

References and Notes

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Synthesis of Alkenes from Carbonyl Compounds and Carbanions α to Silicon. 6. Synthesis of Terminal Allenes and Allyl Chlorides[1,2]

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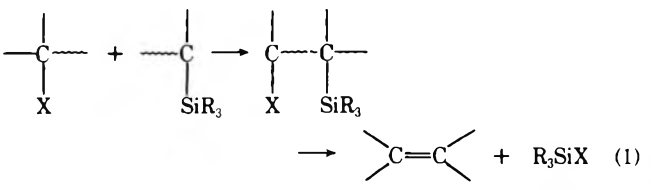
Aldehydes and ketones can be converted into terminal allenes or allylic chlorides by reactions with α-silylvinyl carbanions **2** followed by subsequent transformations. The mechanisms and the stereoselectivity of these reactions are discussed.

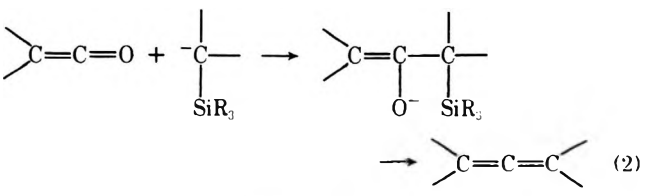
Reactions which lead to the synthesis of alkenes are of great importance to organic chemistry. Numerous named reactions (Hofmann, Saytzeff, Cope, Wittig) have been developed for this purpose. Recently, an alkene synthesis, based on the propensity of β-functionalized organosilicon compounds to undergo elimination, has been introduced.[3-5] The generality of the reaction can be expressed by eq 1 in that any



(1)

union of two fragments which brings together the β relationship of the silyl group and a good leaving group can be considered as an alkene synthesis.[5] A useful version of eq 1 involves the condensation of carbonyl compounds with carbanions α to silicon.[3-5] The reaction bears obvious similarity to the Wittig reaction[6] and its many modifications.

In the course of developing the synthetic utility of the silicon-based alkene synthesis, we became interested in extending the reaction to the preparation of allenes.[1] A priori, two approaches exist. One is to employ ketene as the starting material (eq 2), and the other is to react a carbonyl compound with a vinyl carbanion α to silicon (eq 3). We have chosen to explore the second approach (eq 3) not only because of the ready



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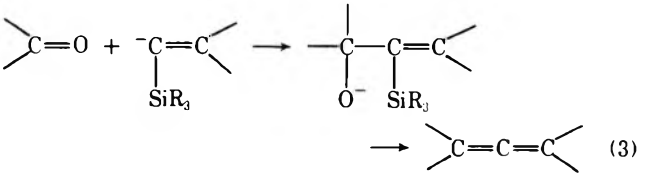

(3)

availability of the carbonyl compounds in general, but also because of the recognition that the vinylsilane moiety is a latent functionality which can be manipulated subsequently.[7]

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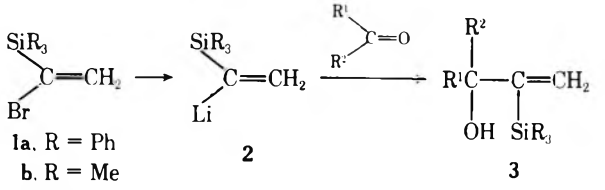
Results and Discussion

Synthesis of Terminal Allenes. Vinyl carbanions α to silicon could readily be generated from α-bromovinylsilanes either by a metal–halogen exchange reaction[8-10] or by reaction with magnesium.[9,11,12] We have used either α-bromovinyltriphenylsilane[8,9] (**1a**) or α-bromovinyltrimethylsilane (**1b**)[10,11] as the precursor. Reaction of **1a** with *n*-butyllithium at −24 °C, or **1b** with *tert*-butyllithium at −78 °C, gave the vinyl carbanions **2** in good yield. The vinyl carbanions reacted with a wide variety of carbonyl compounds to give the β-hydroxyvinylsilanes **3** in isolated yields ranging from 65 to

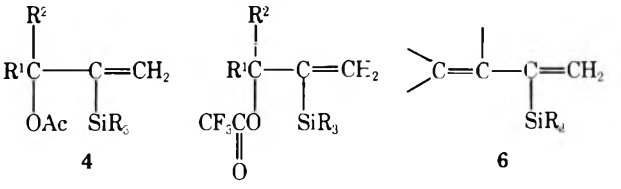


1a, R = Ph
b, R = Me

2 **3**

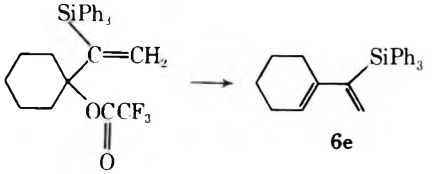
80%.[10,12] As expected, the trimethylsilyl compounds of **3** are more volatile and could be purified by distillation, whereas the triphenylsilyl compounds could be purified by crystallization if necessary. We found that it is easier to work with the trimethylsilyl series because the purity of each compound can be ascertained easily from the ^{1}H NMR spectrum by virtue of the sharp singlet due to the trimethylsilyl protons as well as by GC because of its volatility.

In view of the propensity of β-functionalized organosilicon compounds to undergo elimination, it was thought that these β-hydroxyvinylsilanes **3** should lead to allenes with little difficulty; surprisingly, this was not the case. For example, **3a** (R = R^1 = Ph; R^2 = H), when treated with dilute acid or sodium hydride, was recovered unchanged. The acetate derivative **4a** or the trifluoroacetate **5a** prepared from **3a** with the acid anhydride and pyridine were both resistant to elimination either on heating to 200 °C or dilute acid treatment. The trifluoroacetate **5a** did, however, hydrolyze quite readily, giving back the starting alcohol **3a**. The trifluoroacetates, in cases where they were derived from aliphatic ketones, underwent elimi-



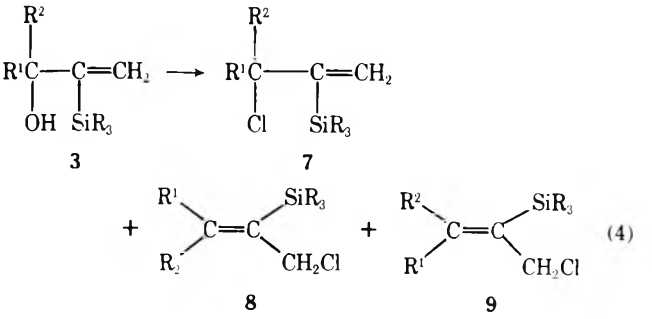
4 **5** **6**

nation of trifluoroacetic acid on warming to give a silyl diene (e.g., **5e** → **6e**). Treatment of the β-hydroxyvinylsilanes **3** with



5e **6e**

thionyl chloride afforded a mixture of chlorides **7**–**9** (eq 4). The relative proportions of each chloride depend on the structure of **3**, the solvent of reaction, as well as the temperature. Discussion on the rearrangement process will be deferred to the later part of the paper. It should be pointed out, however, that the conversion of **3** to **7** was found to be applicable only to **3** derived from aldehydes (i.e., R^2 = H) or aryl ketones (R^1 = R^2 = Ar). For β-hydroxyvinylsilanes **3** derived from aliphatic ketones, the products of thionyl chloride treatment were the dienes of structure **6**. The chlorides (**7**–**8**) did not give allene



3 **7** **8** **9** (4)

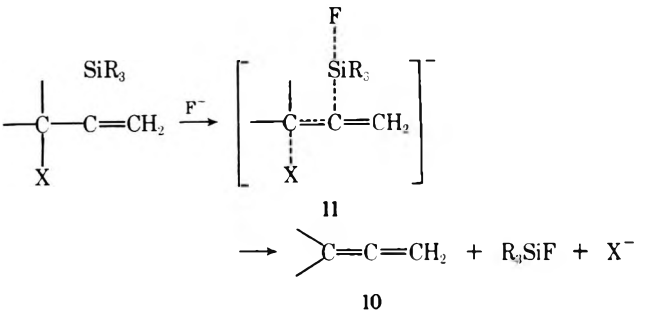
on heating to 175 °C or on treatment with alcoholic silver nitrate. The resistance to elimination must in part be due to the difficulty of cleaving the carbon–silicon bond in the vinyl system with nucleophiles. Indeed, nucleophilic cleavage of the silicon–vinyl carbon bond is rare in general.[13] Several reports have appeared in the literature to indicate that fluoride ion may be a particularly effective nucleophile for such cleavage. It has been known that fluoride ion can cleave the silicon–alkynyl carbon bond.[14] More pertinent was the report by Cunico and Dexheimer[15] which showed that fluoride can effect the β elimination of β-chlorovinyltrimethylsilane to give acetylene (eq 5).

$$CHCl=CHSiMe_3 + F^- \rightarrow HC\equiv CH + Me_3SiF + Cl^- \quad (5)$$

We thus attempted the β elimination of the vinylsilyl system (**7**–**9**) with fluoride ion and the results were most satisfying. When compound **7a** was dissolved in either Me_2SO or CH_3CN with some anhydrous fluoride salt at room temperature, it was transformed quantitatively to phenylallene (**10a**). The order of efficacy of the fluoride salts appears to be tetraalkylammonium fluoride (R_4NF, R = CH_3 or C_2H_5 or *n*-C_4H_9) > cesium fluoride > potassium fluoride. This may simply be a reflection of the order of solubilities of the salts in organic solvent. Other halides are not effective in promoting the elimination. Treatment of **7a** with tetraethylammonium chloride, bromide, or iodide under identical or more forcing conditions gave no allene and the starting materials were recovered quantiatively.

The nature of the substituents on the silyl group have some effect on the rate of elimination. Under identical conditions, the triphenylsilyl compound **7a** underwent elimination five times faster than the corresponding trimethylsilyl compound **7g**. The rate of formation of allene is also dependent upon the nature of the leaving group. The trifluoroacetate **5a** eliminated to give phenylallene cleanly, albeit slightly slower than the chloride **7a**. The acetate **4a**, on the other hand, did not eliminate at room temperature in Me_2SO in the presence of fluoride ion. Only on heating to 150 °C did elimination occur to give phenylallene.

A possible mechanism which is compatible with all these observations can involve a rate-determining step where formation of the silicon–fluoride bond is concerted with the breakage of the silicon–carbon bond as well as the departure of the leaving group (**11**).[16,17] The difference in reactivity between the triphenylsilyl and the trimethylsilyl groups can



11 **10**

be explained by the argument that methyl is electron donating and the trimethylsilyl group is thus less susceptible to attack by the fluoride ion.

A number of allenes have been prepared by this method from the starting carbonyl compounds (Table III). The convenience of the procedure is enhanced by carrying out the preparation without purification of the intermediate chlorides **7–9**. In cases where the chlorides could not be prepared, the trifluoroacetates **5** could be used as the precursors to allenes. The yields of the allenes obtained were nearly the same whether the triphenylsilyl compounds or the trimethylsilyl compounds were used. It was, however, easier to use the trimethylsilyl compounds because in the final purification of allenes the other product of the reaction, trimethylfluorosilane, was volatile and could be removed with ease.

We have so far applied this method to the preparation of 1,2-alkadienes. With the availability of α-silylalkenyl carbanions,[18,19] there is no apparent reason why the reaction could not be applied to nonterminal allenes.

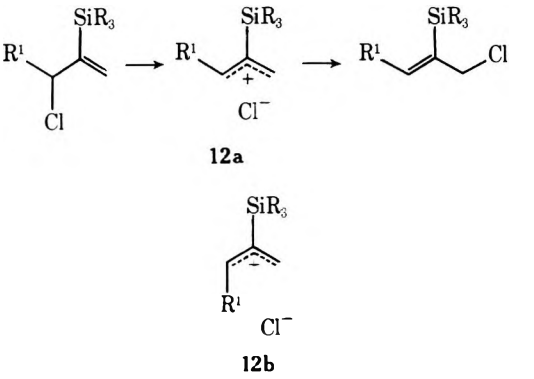
The advantages of the present method appear to be: (1) the starting carbonyl compounds are in general readily available; (2) a double bond elsewhere in the molecule is not affected (e.g., **9d** and **9f**); and (3) more importantly, because of the mild conditions in the allene generation step, the allenes produced were free of contamination by the isomeric acetylenes. Most other methods for synthesizing allenes result in acetylenic impurities in the produot due to isomerization of the allenes under strongly basic conditions often employed.[20,21] No such problem exists by utilizing the silicon method, since strong base is not employed in the final step.

Conversion of R^1CHO into $R^1CH{=}CHCH_2Cl$. The reactions of the β-hydroxyvinylsilanes **3** with thionyl chloride to give a mixture of allylic chlorides **7–9** (eq 4) deserve closer scrutiny. The formation of the three isomeric chlorides was of course not unexpected in view of the familiar allylic rearrangement.[22,23] What is interesting is the subtle variation of the relative proportions of the chlorides **7–9** with solvent and structural parameters in this reaction. We have investigated in some detail the chlorination reactions of **3** derived from aldehydes and trimethylvinyl carbanion (i.e., **3**, R^2 = H; R = CH_3). In general, the rearranged chlorides (**8** and **9**), being more substituted, are more stable than the nonrearranged chloride (**7**), which has a terminal double bond. The rearranged chlorides (**8** and **9**) were indeed formed to the greater extent, often to the exclusion of **7**, if the chlorination were carried out in a polar solvent (e.g., ether) or if the products were allowed to be equilibrated thermally (by heating to 140 °C for 2–3 h). In specific cases, however, with the use of a nonpolar solvent (e.g., CCl_4) at room temperature it was possible to obtain pure **7**. For example, treatment of the compound **3a** with thionyl chloride in carbon tetrachloride gave chloride **7a** in quantitative yield. However, when this chloride was dissolved in dimethyl sulfoxide or heated, an allylic rearrangement occurred giving **8a** exclusively.

These observations are consistent with an ionic mechanism for the allylic rearrangement. In a medium of higher solvating power, formation of what was probably an intimate ion pair **12a** took place. Internal return of the chloride ion would give **8** regioselectively. In addition to being regioselective, the rearrangement is often highly stereoselective, giving predominantly the *Z* isomer **8** with the *E* isomer **9** present in most cases in <10%. The stereoselectivity may be due to the preference of the intermediate carbenium ion for the transoid configuration (**12a**)[24] rather than the cisoid configuration (**12b**).

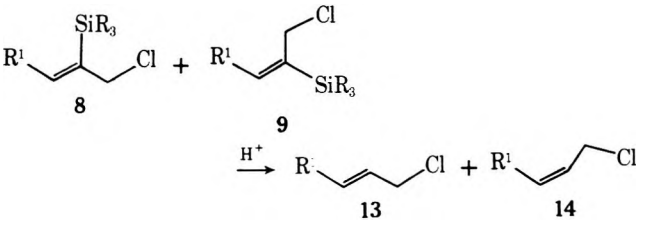
The assignment of *Z* stereochemistry to the major isomer in the mixture **8** and **9** rests on ^1H NMR evidence[25] as well as on chemical transformation. The replacement of the trimethylsilyl group in vinylsilanes by a proton under electrophilic conditions has been firmly established to proceed with retention of stereochemistry.[26,27] Thus, the mixture chlorides **8** and **9**, on reaction with gaseous HCl in chloroform, was converted in good yield to the olefins **13** and **14**. The major isomer **13** was assigned to be *E* on the basis of the coupling constant (15–19 Hz) of the olefinic protons in the 220-MHz spectrum. The assignment was also supported by their infrared spectra where the prominent band at ~960 cm^{-1} was observed. The presence of the minor *Z* isomer (**14**) was also evident from the 220-MHz ^1H NMR spectra and the relative ratio of the *E*/*Z* isomers could be deduced (Table IV). The protodesilylation reactions not only establish the stereochemistry of the chloride, but also constitute a viable method of transforming stereoselective R^1CHO into (*E*)-$R^1CH{=}CHCH_2Cl$ (**3** → **8** → **13**).[1b]

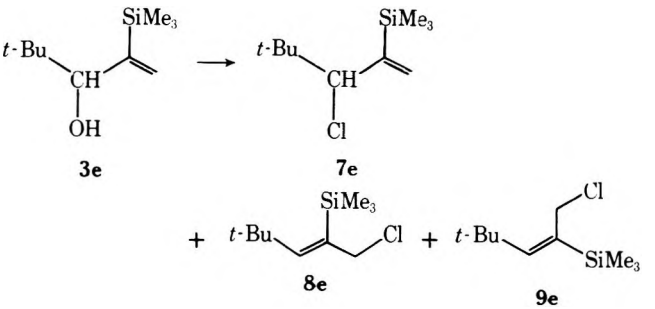
The stereoselectivity of the conversion of R^1CHO to $R^1CH{=}CHCH_2Cl$ depends obviously on the relative proportion of **8** and **9** during the thionyl chloride reaction. It would seem that the structure of R should play a role in determining the extent of stereoselectivity. For R being aryl and most aliphatic groups, the isomer **8** predominates. However, if R^1 is sufficiently bulky, one would expect steric interaction between R^1 and the trimethylsilyl group to be sufficient to render **8** to be the less favored isomer. Such is the case when R^1 is the *tert*-butyl group. When β-hydroxyvinylsilane **3l** was treated with thionyl chloride in ether, chlorination did occur; however, the three isomers **7l**, **8l**, and **9l** were obtained in a ratio of 1:4:3, respectively, according to ^1H NMR and VPC analysis. Furthermore, when the reaction mixture was heated neat to 150 °C for a period of 3 h the ratio of isomers changed to **7l**/**8l**/**9l** = 3:0:2. No further change of isomeric ratio was observed on prolonged heating. It is clear that the steric interaction of the trimethylsilyl group with the *tert*-butyl group modifies somewhat the relative stabilities of the isomers.



12a

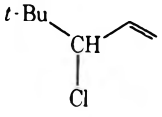
12b



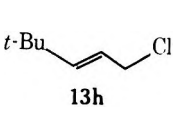


Treatment of the original mixture of isomers (i.e., **7l/8l/9l** = 1:4:3) with HI afforded a mixture of olefins **15h**, **13h**, and **14h** in a ratio identical with that of the starting vinylsilanes. Treatment of this same isomeric mixture of vinylsilanes with trifluoroacetic acid gave, however, only **13h** and **14h** with little **15h**. The terminal vinylsilane **7l** is apparently more resistant to electrophilic substitution than the nonterminal ones. On further standing in TFA, compound **7l** did disappear, but not to the corresponding olefin **15h**. Instead, it appeared to rearrange slowly to **8l–9l** and then underwent protodesilylation to give **13h** and **14h** only.

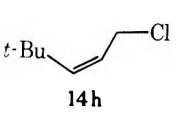
An interesting possibility thus presented itself by these results. It would seem that it is possible to produce the *Z* isomer **14h** stereoselectively under these conditions even though it is thermodynamically less stable. Indeed, on treating the heated vinylsilane mixture (i.e., **7l/8l/9l** = 3:0:2) with TFA, the olefin obtained was predominantly **14h** (85% Z). The overall result is therefore the stereoselective conversion of pivaldehyde into the sterically less favored *Z* olefin **14h**.[28]



15h



13h



14h

Summary

Methods have been found which permit the conversion of carbonyl compounds into terminal allenes. The stereoselective transformations of aldehydes into $RCH{=}CHCH_2Cl$ has also been described. The relative stability of β-functionalized vinylsilanes (**3**, **4**, **7**, **8**, and **9**) to elimination, together with the observation that fluoride ion can promote such elimination easily, have some interesting consequences. For example, it is possible to modify the vinylsilyl group of **7** into an epoxysilyl group by epoxidation of the double bond, and subsequently promote the β elimination of halosilane by fluoride ion, thus generating reactive allene oxides.[29] Another feature of the present work is the recognition that the silyl group can serve as a device for stereochemical control in the synthesis of alkenes (e.g., $RCH{=}CHCH_2Cl$). The silyl group can subsequently be displaced by proton or other electrophiles, thus paving the way for the stereoselective synthesis of di-, tri-, and tetrasubstituted alkenes.[30]

Experimental Section

Common chemicals were obtained from commercial sources and were purified as necessary. Melting points were obtained on a Gallenkamp melting point apparatus and are uncorrected. Infrared spectra were recorded on Perkin-Elmer Model 257 or Unicam SP1000 grating infrared spectrometers. Spectra were calibrated with the 1601-cm^{-1} band of polystyrene film. Nuclear magnetic resonance spectra (^1H NMR) were recorded on Varian Associates T-60 or HR-220 spectrometers as indicated. Mass spectra were recorded either by direct insertion on an E A1-MS-902 mass spectrometer or by GC–MS with an LKB-9000 spectrometer at 70 eV. Microanalyses were performed by Scandinavian Microanalytical Laboratories, Herlev, Denmark. Gas chromatographic (GC) analyses were performed on an F&M Model 5751-A research chromatograph. Two 6 ft × 1/8 in. stainless steel columns were used: 10% SE-30 Ultraphase on Chromosorb W A/W-DMCS, or 10% Apiezon-L on Chromosorb W A/W-DMCS. Preparative thin-layer and column chromatography were done on silica gel.

α-Bromovinyltriphenylsilane (1a). The title compound was prepared according to the literature procedure.[8] It had mp 132–134 °C (lit.[8] mp 128–129 °C).

α-Bromovinyltrimethylsilane (1b). To a solution of 0.5 mol of trichlorovinylsilane in 500 mL of CCl_4 irradiated with a daylight lamp was added dropwise a solution of 0.5 mol of Br_2 in 100 mL of CCl_4 over a period of 1–2 h. Occasional cooling was necessary as the reaction was highly exothermic. After the addition, the mixture was stirred for 1 h, and the solvent was then removed. To the solvent-free mixture was added slowly 0.65 mol of quinoline, and the reaction mixture was distilled at reduced pressure to give α-bromovinyltrichlorosilane in 82% yield [bp 70–71 °C (53 mm); lit.[29] bp 145.4 °C (749 mm)].

To a solution of CH_3MgI in 1.5 L of anhydrous ether (prepared from 1.5 mol of CH_3I and 37 g of Mg in 1.5 L of anhydrous ether) was added dropwise a solution of 0.4 mol of α-bromotrichlorovinylsilane in 500 mL of anhydrous ether over a period of 2 h. After the addition, the reaction mixture was heated under reflux for another 5 h. The reaction mixture was hydrolyzed with water, and then dried with anhydrous $MgSO_4$. Removal of the solvent from the reaction mixture, followed by fractional distillation at reduced pressure, gave the desired α-bromovinyltrimethylsilane in 70% yield [bp 56.7 °C (67 mm); lit.[11] bp 26–27 °C (15 mm)].

1-Substituted-2-trisubstituted-silyl-2-propen-1-ols (3). The title alcohols were prepared from the reaction of α-silylvinyl carbanions[8] with appropriate carbonyl compounds. The following is a general procedure for the preparation of the triphenylsilyl compounds (**3a–f**).

To a solution of 0.025 mol of α-bromovinyltriphenylsilane in 60 mL of anhydrous ether at −24 °C (dry ice–CCl_4 bath) under a N_2 atmosphere was added slowly, by means of a syringe, a solution of 0.025 mol of *n*-butyllithium. The resulting mixture was kept stirred at the same temperature for 1.5 h. A solution of 0.025 mol of carbonyl compound in 10 mL of dried ether was added. The reaction mixture was stirred at −24 °C for 5 h, then stirring was continued overnight at room temperature. The reaction mixture was poured into 50 mL of 10% HCl and the organic phase was extracted, dried, and evaporated to give the desired alcohol (Table I).

Following is a general procedure for the preparation of the trimethylsilyl compounds (**3g–l**).

To a solution of 0.05 mol of α-bromovinyltrimethylsilane in 150 mL of anhydrous ether at −78 °C under a N_2 atmosphere was added slowly by means of a syringe a solution of 0.052 mol of *tert*-butyllithium in pentane.[10] The resulting mixture was kept well stirred at the same temperature for 2 h. A solution of 0.05 mol of carbonyl compound in 10 mL of anhydrous ether was added. The reaction mixture was stirred at −78 °C for another hour and was then allowed to warm up to room temperature by itself. After hydrolysis (50 mL of water) and drying with anhydrous $MgSO_4$, the reaction mixture was reduced in volume in vacuo and fractionally distilled at low pressure to give the desired alcohol (Table I).

Reaction of 1-Substituted-2-silyl-2-propen-1-ols (3) with Acetic Anhydride/Pyridine. To a solution of 50 mmol of the alcohol **3** in 10 mL of pyridine at room temperature was added dropwise 5.0 g of acetic anhydride (10% excess). The reaction was exothermic. The mixture was heated under reflux for 2 h, cooled, and poured into 20 mL of water. The reaction mixture was extracted with 2 × 20 mL of ether. The ether solution was dried over anhydrous $MgSO_4$ and evaporated in vacuo to give the corresponding acetates **4** in quantitative yields.

The following acetates have been prepared. They all have proper spectroscopic and/or analytical data consistent with structures: 3-acetoxy-3-phenyl-2-triphenylsilyl-1-propene (**4a**), mp 90–91 °C (hexane); 3-acetoxy-3-cyclohexyl-2-trimethylsilyl-1-propene (**4j**), bp 76–78 °C (0.1 mm); 3-acetoxy-4-methyl-2-trimethylsilyl-1-pentene (**4k**), bp 54–56 °C (0.75 mm); 3-acetoxy-2-trimethylsilyl-1-tridecene (**4c**), bp 104–106 °C (0.1 mm); 3-acetoxy-3,3-diphenyl-2-triphenylsilyl-1-propene (**4b**), mp 164–167 °C (EtOH).

Reaction of 1-Substituted-2-silyl-2-propen-1-ols (3) with Trifluoroacetic Anhydride/Pyridine. To a solution of 50 mmol of the alcohol **3** in 10 mL of pyridine at 0 °C was added dropwise 12 g of trifluoroacetic anhydride (10% excess). The reaction mixture was stirred at room temperature for 2 h, poured into 20 mL of water, and extracted with 2 × 20 mL of ether. The organic solution was dried over anhydrous $MgSO_4$ and evaporated in vacuo to give the corresponding acetates **5** in quantitative yield. No further purification of these compounds was undertaken.

1-Trifluoroacetoxy-1-phenyl-2-triphenylsilyl-2-propene (5a): IR (CCl_4) 1780 cm^{-1}; ^1H NMR (CCl_4) δ 5.95 (m, 1 H), 6.35 (m, 1 H), 6.55 (m, 1 H), 7.2–7.8 (m, 20 H).

1-(α-Trifluoroacetoxycyclohexyl)-1-triphenylsilylethylene (5e): IR (CCl_4) 1785 cm^{-1}; ^1H NMR (CCl_4) 0.9–2.5 (m, 11 H), 5.85 (AB, 2 H), 7.2–7.8 (m, 15 H). When this trifluoroacetate was dissolved in Me_2SO, heated on a steam bath to aid dissolving, a precipitate formed. The mixture was poured into water and extracted with ether. The ether solution was dried over $MgSO_4$ and evaporated in vacuo. Recrystallization of the residue from EtOH gave a solid, mp 89–93 °C, assigned to be **1-cyclohexenyl-1-triphenylsilylethylene (6e):** IR (KBr) 2920, 1435, 1115, 700 cm^{-1}; ^1H NMR ($CDCl_3$) δ 1–2.5 (m, 6 H), 5.4 (d, J = 2.5 Hz, 1 H), 5.76 (m, 1 H), 6.08 (d, J = 2.5 Hz, 1 H), 7.2–7.8 (m, 15 H).

Table I. Physical Data and Yields of 3

	R	R^1	R^2	Registry no.	Mp or bp, °C (mmHg)	Yield, %	^{1}H NMR, δ	Analyses
3a	Ph	Ph	H	52629-60-4	84–85	75	1.8 (s, 1 H), 5.5 (t, 1 H), 5.8 (t, 1 H), 6.2 (t, 1 H), 7.2–7.8 (m, 20 H)	C,H
3b	Ph	Ph	Ph	52629-61-5	108.5–109.5	80	2.6 (s, 1 H), 5.7 (d, 1 H), 5.9 (d, 1 H), 7.2–7.8 (m, 25 H)	C,H
3c	Ph	n-$C_{10}H_{21}$	H	52629-62-6	*a*	75	0.9–1.6 (m, 22 H), 4.2 (m, 1 H), 5.5 (m, 1 H), 6.2 (m, 1 H), 7.2–7.5 (m, 15 H)	*b*
3d	Ph	C_6H_5CH=CH–	H	65071-60-5	*a*	80	5.0 (m, 1 H), 5.7–6.5 (m, 4 H), 7.2–7.8 (m, 20 H)	*b*
3e	Ph	c-C_5H_{10}		65071-61-6	*a*	75	0.9–2.4 (m, 11 H), 5.5 (d, 1 H), 6.00 (d, 1 H), 7.2–7.8 (m, 15 H)	*c*
3f	Ph	CH_3	$(CH_3)_2C$=C-H$(CH_2)_2$–	65071-62-7	*a*	75	0.9–2.5 (m, 14 H), 5.0 (b, 1 H), 5.6 (d, 1 H), 7.2–7.8 (m, 15 H)	*c*
3g	Me	Ph	H	5166-96-7	82–84 (0.9)	80	0.15 (s, 9 H), 3.7 (s, 1 H), 5.5 (m, 1 H), 6.0 (AB, 2 H), 7.6 (s, 5 H)	*c*
3h	Me	Ph	Ph	51666-98-9	*a*	80	0.2 (s, 9 H), 3.0 (s, 1 H), 5.5 (AB, 2 H), 7.4 (s, 1 H)	*c*
3i	Me	n-$C_{10}H_{21}$	H	58672-92-7	118–119 (0.03)	75	0.1 (s, 9 H), 0.7–1.7 (m, 21 H), 1.9 (s, 1 H), 4.15 (t, 1 H), 5.5 (AB, 2 H)	C,H
3j	Me	c-C_6H_{11}	H	58649-14-2	64–66 (0.025)	75	0.2 (s, 9 H), 0.8–2.15 (m, 12 H), 3.85 d, 1 H), 5.45 (AB, 2 H)	*c*
3k	Me	i-Pr	H	58649-15-3	82–84 (16)	76	0.1 (s, 9 H), 0.9 (d, 6 H), 1.5–2.0 (m, 2 H), 3.85 (d, 1 H), 5.55 (AB, 2 H)	*c*
3l	Me	t-Bu	H	61628-61-3	69–71 (5)	79	0.15 (s, 9 H), 0.9 (s, 9 H), 1.85 (b, 1 H) 3.90 (s, 1 H), 5.6 (AB, 2 H)	C,H

[a] Purified by column chromatography. Purity ascertained by TLC or GC. [b] Exact mass of the molecular ion to within ±10 ppm. [c] Molecular weight established by low-resolution mass spectrum.

Table II. Physical Data of Isomeric Chlorides 7–9

Registry no.	R	R^1	R^2		Mp or bp, °C (mmHg)	^{1}H NMR, δ	Analyses
52629-67-1	Ph	Ph	H	**7a**	148–149	5.85 (AB, 2 H), 6.7 (t, 1 H), 7.5 (s, 5 H), 7.1–7.8 (m, 15 H)	C,H
65071-63-8	Ph	Ph	H	**8a**	148–149	4.25 (s, 2 H), 6.6 (s, 1 H), 7.0–7.8 (m, 20 H)	C,H
52629-69-3	Ph	Ph	Ph	**8b**	147–148	4.2 (s, 2 H), 6.6–7.8 (m, 25 H)	*b*
65085-85-0	Ph	n-$C_{10}H_{21}$	H	**8c**	*a*	0.9–2.1 (m, 21 H), 4.15 (s, 2 H), 6.85 (t, 1 H), 7.2–7.8 (m, 15 H)	*b*
65071-64-9	Ph	PhCH=CH–	H	**8d**	*a*	4.19 (s, 2 H), 6.4–7.8 (m, 23 H)	*b*
55287-91-7	Me	Ph	H	**7g**	*c*	0.1 (s, 9 H), 5.65 (m, 2 H), 6.1 (m, 1 H), 7.2 (s, 5 H)	*b*
58844-31-8				**8g**	89–90 (1.5)	0.2 (s, 9 H), 4.2 (s, 2 H), 6.8 (s, 1 H), 7.0–7.4 (m, 5 H)	C,H
58649-16-4	Me	n-$C_{10}H_{21}$	H	**8i**	90–100 (0.05)	0.22 (s, 9 H), 0.7–2.3 (m, 21 H), 3.9 (s, 2 H), 6.28 (t, 1 H)	C,H
58649-17-5	Me	c-C_6H_{11}	H	**8j** + **9j** (~90:10)	66–67 (0.35)	**8j**: 0.22 (s, 9 H), 0.7–2.3 (m, 11 H), 4.0 (s, 2 H), 6.08 (d, 1 H)	C,H
64645-72-3						**9j**: 0.14 (s), 0.7–2.3 (m), 4.05 (s), 5.78 (d)	
58649-18-6	Me	i-Pr	H	**8k** + **9k** (~85:15)	73–75 (12)	**8k**: 0.22 (s, 9 H), 1.05 (d, 6 H), 2.6 (m, 1 H), 4.05 (s, 2 H), 6.08 (d, 1 H)	C,H
64645-71-2						**9k**: 0.14 (s), 1.05 (d), 2.6 (m), 4.1 (s), 5.78 (d)	
61628-64-6	Me	t-Bu	H	**7l** + **8l** + **9l**[d]	90–97 (14)	**7l**: 0.16 (s, 9 H), 1.0 (s, 9 H), 4.25 (b, 1 H), 5.5 (d, 1 H), 5.8 (bd, 1 H)	
61628-62-4						**8l**: 0.30 (s, 9 H), 1.15 (s, 9 H), 4.05 (s, 2 H), 6.35 (s, 1 H)	C,H
61628-63-5						**9l**: 0.15 (s, 9 H), 1.2 (s, 9 H), 4.2 (s, 2 H), 5.75 (s, 1 H)	

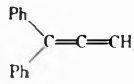
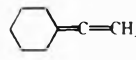
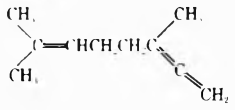
[a] Not crystalline. [b] Molecular weight determined by low-resolution mass spectrum. [c] Rearranged to **8g** on distillation. [d] Proportions varied; see text.

3-Trifluoroacetoxy-3,7-dimethyl-2-triphenylsilyl-1,6-octadiene (5f): IR (CCl_4) 1760 cm^{-1}; ^{1}H NMR (CCl_4) δ 1.2–2.3 (m, 13 H), 4.8 (m, 1 H), 5.9 (AB, 2 H), 7.2–7.8 (m, 15).

Reaction of 1-Substituted-2-silyl-2-propen-1-ols (3) with Thionyl Chloride. To a solution of 50 mmol of alcohol **3** in 40 mL of CCl_4 (or Et_2O) at room temperature was added dropwise a solution of 7.1 g of $SOCl_2$ (20% excess) in 20 mL of CCl_4 (or Et_2O). The reaction was exothermic and an ice bath was used occasionally to cool down the reaction mixture to below room temperature. The reaction mixture was generally kept well stirred for 2 h before workup. The solvent was evaporated under vacuo to give a residue which was purified by either recrystallization or distillation (Table II).

Fluoride Ion Promoted Formation of Terminal Allenes. General Procedure. To a solution of 0.02 mol of β-functionalized silane (**5**, **7**, **8**, or **9**) in 15–20 mL of solvent (Me_2SO or CH_3CN) was added 0.025 mol of inorganic fluoride (tetraalkylammonium, potassium or cesium fluoride). The reaction mixture was stirred for 2–10 h, poured into 20 mL of water, washed with 2 × 10 mL of water, dried

Table III. Preparation of 1,2-Alkadienes (9)

	1,2-Alkadiene	Registry no.	Method[a]	Isolated yield,[b] %	Bp, °C (mmHg)	IR, cm^{-1}	^1H NMR, δ
9a	$PhCH=C=CH_2$	2327-99-3	A B	59 60	83–85 (2.4)	*c*	*c*
9b		14251-57-1	A B	45[d] 50	100 (0.025)	*e*	*e*
9c	$n\text{-}C_{10}H_{21}CH=C=CH_2$	52629-63-7	A B	44 48	63–64 (0.1)	1960	0.75–2.25 (m, 21 H), 4.6 (m, 2 H), 5.05 (m, 1 H)
9d	$PhCH=CH\text{-}CH=C=CH_2$	65071-53-6	A	35	70–75 (0.075)	1960	4.9 (d, 2 H), 5.65–6.8 (ABC, 3 H), 7.1–7.6 (m, 5 H)
9e		5664-20-0	C	20	*f*	1955	1.1–2.3 (m, 10 H), 4.4 (m, 2 H)
9f		65071-54-7	C	20	*f*	1955	1.5 (s, 3 H), 1.6 (s, 3 H), 1.5–2.3 (m, 7 H), 4.4 (m, 2 H), 4.95 (m, 1 H)

[a] Method A, triphenylsilyl adduct and via chlorination; method B, trimethylsilyl adduct and via chlorination; method C, triphenylsilyl adduct and via trifluoroacetylation. [b] Isolated yield based on starting carbonyl compound. [c] Compared with authentic sample synthesized according to J. Hayami, N. Oko, and A. Kaji, *Tetrahedron Lett.*, 1385 (1968). [d] Purified by thin layer chromatography. [e] Compared with authentic sample prepared according to ref 21. [f] Purified by bulb-to-bulb distillation.

Table IV. Preparation of 13 and 14 by the Protodesilylation of Vinylsilanes 8 and 9

R^1	Bp, °C (mmHg)	Yield[a]	*J* of olefinic protons of major isomer, Hz[b]	*E*/*Z*[b]	Analysis
C_6H_5	*c*	90[d]	*c*	*c*	*c*
$n\text{-}C_{10}H_{21}$	76–77 (0.06)	74 (66)	15	85/15	*e*
$c\text{-}C_6H_{11}$	53 (1.3)	65 (62)	18.8	85/15	*e*
i-Pr	58–60 (89)	75 (45)[f]	15.3	90/10	*e*

[a] Yield determined by VPC with isolated yield in parentheses. [b] Determined from 220 MHz proton NMR spectrum. [c] Compound compared with authentic sample. [d] ^1H NMR showed that cinnamyl chloride was the sole compound in the product. [e] Analyzed by exact mass to within ±10 ppm of calculated mass of the molecular ion. [f] Lower isolated yield due to loss in distillation because of the low boiling point of the compound.

over anhydrous $MgSO_4$, and evaporated in vacuo. The product was subsequently purified by distillation under reduced pressure.

Synthesis of 1,2-Alkadienes from Carbonyl Compounds without Purification of Intermediate Steps. The carbonyl compounds were reacted with α-silylvinyl carbanions to give the alcohols **3** as previously described. The alcohols were used without purification for $SOCl_2$ reaction or trifluoroacetylation using procedures as described. Again, the products were not purified. Elimination with fluoride ion was carried out (vide supra). A typical procedure is outlined below.

Synthesis of 1,2-Tridecadiene. To a solution of 8.8 g (0.024 mol) of α-bromovinyltriphenylsilane in 60 mL of anhydrous ether at −24 °C, an equimolar amount of *n*-butyllithium was added slowly and stirred for 1–1.5 h. An equimolar amount of undecanal in 10 mL of ether was added slowly and the reaction mixture was stirred at −24 °C for 1 h. The stirring was continued at room temperature overnight. The reaction mixture was poured into 50 mL of 10% HCl and the organic phase was extracted and washed with 1 × 50 mL of water, dried over anhydrous $MgSO_4$, and evaporated in vacuo to give the crude product **3c**. The crude alcohol was dissolved in 25 mL of CCl_4 and a 25% excess of thionyl chloride was added. The reaction was stirred for 2 h and then evaporated in vacuo to give the crude chloride **8c**. The crude chloride was dissolved in Me_2SO (25 mL/g of Et_4NF) and Et_4NF was added (10% excess). The mixture was stirred for 2 h at room temperature. The reaction mixture was portioned between 25 mL of ether and 25 mL of water. The ether phase was dried over $MgSO_4$ and evaporated in vacuo to give crude product. The crude product was treated with 10 mL of hexane and cooled. Filtration gave triphenylsilanol; distillation of the filtrate gave 1,2-tridecadiene, bp 63–64 °C (0.1 mmHg), in 44% yield. Similar procedures were followed for the other allenes (Table III). For the trimethylsilyl adducts the hexane precipitation step was omitted.

Reaction of 1-Substituted-3-chloro-2-trimethylsilyl-1-propene (8 and 9) with Gaseous Hydrogen Chloride. Dried gaseous HCl was bubbled into a solution of **8** and **9** (1 g) in 10 mL of chloroform for ~5 min. The mixture was stirred at room temperature for 2–5 days. The reaction mixture was followed by GC analysis, which revealed the formation of the desilylated products **13** and **14**. The products were purified by distillation at reduced pressure (Table IV).

Reaction of 1-Chloro-4,4-dimethyl-2-trimethylsilyl-2-pentenes (8h and 9h) and 3-Chloro-4,4-dimethyl-2-trimethylsilyl-1-pentene (7h) with Trifluoroacetic Acid. To a solution of 0.2 g of a mixture of **7h**, **8h**, and **9h** in 5 mL of $CHCl_3$ was added 0.2 g of trifluoroacetic acid and the solution was stirred at room temperature for 2 days. The reaction mixture was poured into 10 mL of water, washed with 10 mL of 10% $NaHCO_3$, dried over anhydrous $MgSO_4$, and evaporated under vacuo to give the allylic chlorides **13h** and **14h**. The allylic chlorides **13h** and **14h** had spectroscopic properties identical with those reported in the literature.[28]

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Registry No.—**1a**, 18676-45-4; **1b**, 13683-41-5; **4a**, 52629-65-9; **4b**, 65071-55-8; **4c**, 65071-56-9; **4j**, 62527-81-5; **4k**, 62527-82-6; **5a**, 52629-66-0; **5e**, 65071-57-0; **5f**, 65071-58-1; **6e**, 65085-86-1; **13** (R^1 = $C_{10}H_{21}$), 58649-19-7; **13** (R^1 = $c\text{-}C_6H_{11}$), 58649-21-1; **13** (R^1 = *i*-Pr), 58649-23-3; **14** (R^1 = $C_{10}H_{21}$), 58649-20-0; **14** (R^1 = $c\text{-}C_6H_{11}$), 58649-22-2; **14** (R^1 = *i*-Pr), 58649-24-4; $R^1R^2C{=}O$ (R^1 = Ph; R^2 = H), 100-52-7; $R^1R^2C{=}O$ (R^1,R^2 = Ph), 119-61-9; $R^1R^2C{=}O$ (R^1 = $C_{10}H_{21}$;

R_2 = H), 112-44-7; $R^1R^2C{=}O$ (R^1 = PhCH=CH; R_2 = H), 14371-10-9; $R^1R^2C{=}O$ (R^1,R^2 = c-C_5H_{10}), 108-94-1; $R^1R^2C{=}O$ (R^1 = CH_3; R^2 = $Me_2C{=}CH(CH_2)_2$), 110-93-0; $R^1R^2C{=}O$ (R^1 = c-C_6H_{11}; R^2 = H), 2043-61-0; $R^1R^2C{=}O$ (R^1 = *i*-Pr; R^2 = H), 78-84-2; $R^1R^2C{=}O$ (R^1 = *t*-Bu; R^2 = H), 630-19-3; trichlorovinylsilane, 75-94-5; α-bromovinyltrichlorosilane, 18038-34-1; acetic anhydride, 108-24-7; trifluoroacetic anhydride, 407-25-0; $SOCl_2$, 7719-09-7.

References and Notes

(1) Preliminary accounts of this work have been disclosed: (a) T. H. Chan and W. Mychajlowskij, *Tetrahedron Lett.*, 171 (1974); (b) T. H. Chan, W. Mychajlowskij, B. S. Ong, and D. N. Harpp, *J. Organomet. Chem.*, C-1 (1976).
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Oxidation of Hydrocarbons. 8. Use of Dimethyl Polyethylene Glycol as a Phase Transfer Agent for the Oxidation of Alkenes by Potassium Permanganate[1a]

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Dimethyl polyethylene glycol solubilizes potassium permanganate in benzene or methylene chloride and can thus be used as a phase transfer agent for permanganate oxidations. If benzene is used as the solvent, dimethyl polyethylene glycol will not efficiently extract potassium permanganate from an aqueous solution, but it will solubilize the solid reagent. When methylene chloride is used as the solvent, potassium permanganate may be transferred from either an aqueous solution or from the solid phase. The products obtained from the oxidation of terminal alkenes were found to be the corresponding carboxylic acids with one less carbon, while nonterminal alkenes gave diones, diols, and ketols as well as carboxylic acids. The distribution of products may be controlled through selection of the appropriate conditions. A comparison has been made with the use of a quaternary ammonium ion, a crown ether, and acyclic polyethers as phase transfer agents for the oxidation of alkenes by permanganate.

Historically the use of permanganate ion as an oxidant for hydrocarbons has been limited because of its low solubility in most nonpolar solvents.[1b] However, the observation that potassium permanganate could be extracted from water into benzene by use of phase transfer agents substantially increased the potential usefulness of this reagent. The first phase transfer agent used was tricaprylmethylammonium chloride.[2] Since that time other ammonium[3–5] and arsonium[6] salts have been used with varying degrees of success. In 1967 Pedersen[7] reported that crown ethers could also be used to solubilize potassium permanganate in benzene, and Sam and Simmons[8] later observed that excellent yields could be obtained from the oxidation of organic compounds in these solutions. This method, although highly efficient, has not been widely applied, probably because of the rather high cost of crown ethers.

The work described in this report was originally designed to compare, under identical conditions, the usefulness of crown ethers and quaternary ammonium salts as phase transfer agents for permanganate oxidations. However, during the course of the study we were informed of work from Lehmkuhl's laboratory which indicated that dimethyl polyethylene glycols could also be used as phase transfer agents for potassium permanganate.[9] Consequently the scope of the study was enlarged to evaluate the usefulness of dimethyl polyethylene glycol in relationship to a typical quaternary ammonium ion phase transfer agent (Adogen 464) and a typical crown ether (dicyclohexano-18-crown-6) for the oxidation of alkenes.

The linear phase transfer agents (which Lehmkuhl called "Schleifenathers",[10] but which are also known as "glymes"[11]) consisted of a mixture of dimethyl polyethylene glycols with dimethyl octaethylene glycol as the principal component.[12] Previous work had shown that polyethers formed complexes with various cations,[13] and Lehmkuhl et al. have used them effectively as phase transfer agents for nucleophilic substitution reactions.[14]

In more recent studies (where these and other complexing

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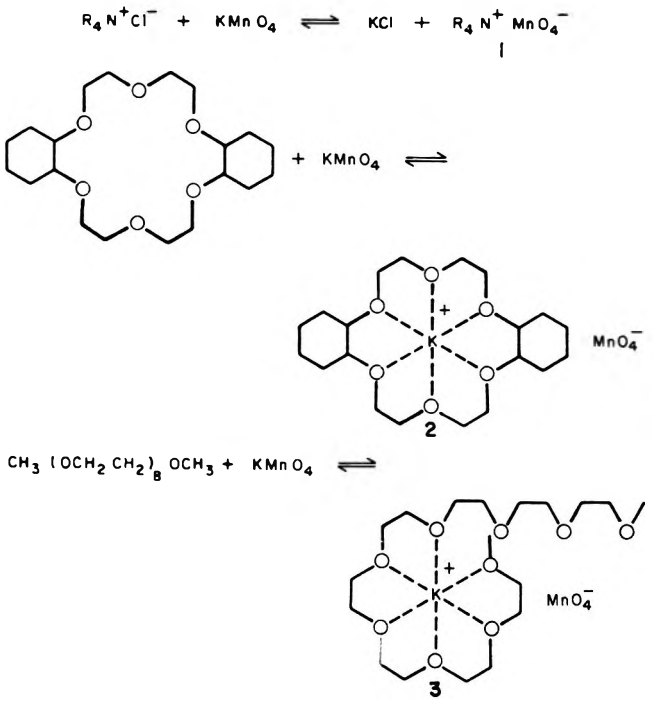


Figure 1.

agents have been referred to as "hosts"), Cram and his coworkers have compared the complexing abilities of crown ethers and the corresponding noncyclic compounds.[15] In general, they found that preorganization into a crown increases the amount of complex present, but nonconverging systems are also induced to form ordered arrangements of binding sites in the presence of cations. This leads to the formation of complexes, albeit with somewhat lower binding energies.

Results and Discussions

The phase transfer equilibria involved in the reactions under consideration may be visualized as in Figure 1. Of the products depicted only **2** has been isolated and characterized.[8] It is possible that **3** has a greater complexity than indicated. For example, models show that it is possible for the oxygens to arrange themselves about the central ion in a nonplanar fashion. Furthermore, Bush and Truter[16] have shown that a crown ether containing ten oxygens wraps itself around the potassium ion in a pattern similar to the seam of a baseball.

Initial experiments indicated quite clearly, however, that this acyclic polyether could not be used to extract aqueous potassium permanganate into a nonpolar solvent such as benzene. Instead of bringing the permanganate ion into solution in the nonaqueous phase, it appears that the polyether moved into the aqueous phase and slowly reduced the oxidant. To overcome this problem we have used a modification of the procedure described by Sam and Simmons[7] wherein solid potassium permanganate is brought into solution directly without first dissolving it in water. When dimethyl polyethylene glycol is added to an organic solvent along with pulverized potassium permanganate, a transfer from the solid to the liquid phase takes place, and any alkene present is oxidized. This provides for a very simple procedure that gives products in good yields and high purity.

It is apparent that the oxygens in **3** would be more exposed than those in **2**, and this may explain why **3** cannot be used to transfer permanganate from an aqueous phase into benzene. The available oxygens would be hydrophilic, and thus the complex would be more soluble in the aqueous solution.

The fact that the dimethyl polyethylene glycol complex is more soluble in water than in benzene can be used to advantage during the purification of products. If the benzene solution is extracted with water, all but traces of the phase transfer agent are removed, making it easier to distill or crystallize the product. In fact, a reasonably pure product is often obtained simply by flash evaporation of the solvent, whereas use of quaternary ammonium salts or crown ethers always gives initial products contaminated by the phase transfer agent.

Table I. Oxidation of 1-Decene[a]

Solvent system	Phase transfer agent	Products (%)
Benzene plus 10% acetic acid	Polyether[b]	Nonanoic acid (80)
Benzene plus 10% acetic acid	Crown ether[c]	Nonanoic acid (80), octanoic acid (5)
Benzene plus 10% acetic acid	Adogen 464	Nonanoic acid (90), octanoic acid (4)
Benzene/ water plus 8% acetic acid	Adogen 464	Nonanoic acid (90), octanoic acid (5)
Benzene/ water	Polyether[b]	Nonanoic acid (10), 1-decene (90)
Methylene chloride/ water plus 8% acetic acid	Polyether[b]	Nonanoic acid (95)

[a] The reactions were conducted at room temperature using 4 mol of potassium permanganate per mole of alkene. [b] Dimethyl polyethylene glycol. [c] Dicyclohexano-18-crown-6.

However, if a more polar organic solvent such as methylene chloride is used along with dimethyl polyethylene glycol, potassium permanganate may be extracted from an aqueous solution. Although use of this medium gives an initial product contaminated by the phase transfer agent, it is a superior solvent in almost every other way. It is more volatile (and thus more easily removed), less expensive, and more resistant to oxidative degradations. Foglia et al.[5] also found that methylene chloride was a better solvent than benzene when used in conjunction with aqueous permanganate and a phase transfer agent.

The products obtained from the oxidation of three different alkenes have been compared in Tables I–III. It can be seen that the yields obtained by the use of dimethyl polyethylene glycol compare well with those produced using other phase transfer catalysts. In fact, the highest yield of nonanoic acid was obtained from the oxidation of 1-decene in methylene chloride using dimethyl polyethylene glycol in conjunction with aqueous permanganate (Table I). The same procedure also gave the highest yield of 5,6-decanedione from the oxidation of *trans*-5-decene (Table II) and a very good yield of dodecanedioic acid from the oxidative cleavage of cyclododecene (Table III). On the other hand, we were not able to obtain any diol from the oxidation of *trans*-5-decene using dimethyl polyethylene glycol in conjunction with alkaline aqueous permanganate (Table II), whereas the other phase transfer agents gave diols in about 20% yields. Other alkenes have been reported to give diols in yields of 50–80% when this procedure was used with quaternary ammonium salts or crown ethers.[3,5]

The formation of diones during the oxidation of nonterminal alkenes (Tables II and III) is of interest because they have not previously been reported as products from aqueous permanganate oxidations.[1b] The only report of the production of diones in substantial quantities was made by Sharpless et al.[17] in 1971. They found that diones were formed when nonterminal alkenes were oxidized by potassium permanganate in acetic anhydride solutions. We have also noted the forma-

Table II. Oxidation of *trans*-5-Decene[a]

Solvent system	Phase transfer agent	Products (%)
Benzene plus 15% acetic acid	Polyether[b]	Valeric acid (69), 5,6-decanedione (28)
Benzene plus 15% acetic acid	Adogen 464	Valeric acid (59), 5,6-decanedione (20)
Benzene plus 15% acetic acid	Crown ether[c]	Valeric acid (44), 5,6-decanedione (36)
Methylene chloride/ water plus 8% acetic acid	Polyether[b]	Valeric acid (45), 5,6-decanedione (53)
Methylene chloride/ aqueous sodium hydroxide	Polyether[b]	Valeric acid (43), 5,6-decanedione (7), 5-hydroxy-6-decanone (11), 5-decene (20)
Methylene chloride/ aqueous sodium hydroxide	Crown ether[c]	Valeric acid (3), 5,6-decanedione (2), 5-hydroxy-6-decanone (30), 5,6-decanediol (19), 5-decene (10)
Methylene chloride/ aqueous sodium hydroxide	Adogen 464	Valeric acid (26), 5-hydroxy-6-decanone (11), 5,6-decanediol (20), 5-decene (14)

[a] The reactions were conducted at room temperature using 3 mol of oxidant per mole of alkene. [b] Dimethyl polyethylene glycol. [c] Dicyclohexano-18-crown-6.

tion of diones where acetone is used as a solvent[18] and have therefore come to the conclusion that their formation is promoted by the use of nonaqueous solvents. In the presence of water a reaction intermediate, such as a ketol, is apparently intercepted and converted into one of the products more commonly found in aqueous permanganate oxidations.

Mechanistic studies of the oxidation of alkenes in aqueous solutions have indicated that ketols are formed by the reaction sequence depicted in Scheme I.[1b,19] In the absence of water the hydrolysis of **5** would be prevented, and it could quite conceivably undergo further reaction with oxidant to give the dione as suggested in Scheme II. The oxidation of **5** has been depicted as a hydrogen atom abstraction process in analogy with the oxidation of alcohols,[1b] although a hydride transfer would also result in dione formation.

It has been noted by Krapcho et al.[20] that the addition of

Scheme I

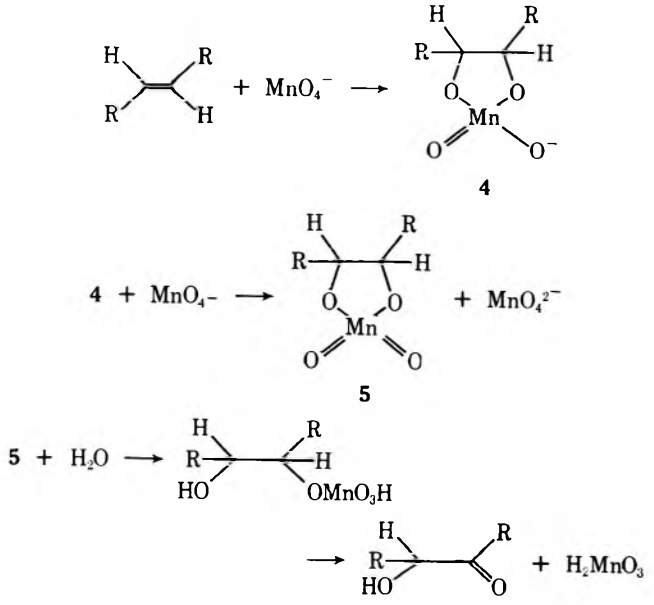
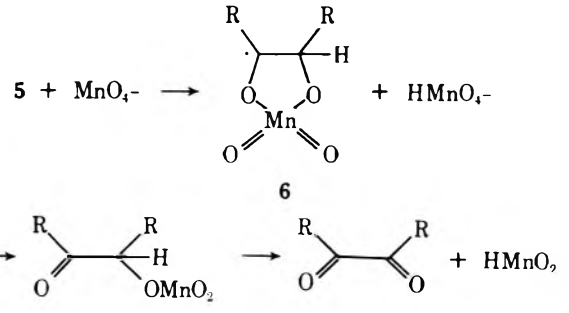


Table III. Oxidation of Cyclododecene

Solvent system	Oxidant ratio[a]	Phase transfer agent	Products (%)
Benzene plus 17% acetic acid	3.3	Polyether[c]	1,2-Cyclododecanedione (16), dodecanedioic acid (59), cyclododecene (23)
Benzene plus 17% acetic acid	3.3	Crown ether[d]	1,2-Cyclododecanedione (22), dodecanedioic acid (56), cyclododecene (12)
Benzene plus 17% acetic acid	3.3	Adogen 464	1,2-Cyclododecanedione (8), dodecanedioic acid (58), cyclododecene (9)
Methylene chloride plus 17% acetic acid	3.3	Polyether	1,2-Cyclododecanedione (8), dodecanedioic acid (77), cyclododecene (1)
Methylene chloride plus 17% acetic acid	3.3	Crown ether	1,2-Cyclododecanedione (7), dodecanedioic acid (83), cyclododecene (3)
Methylene chloride plus 17% acetic acid	3.3	Adogen 464	1,2-Cyclododecanedione (7), dodecanedioic acid (83), cyclododecene (2)
Methylene chloride plus 17% acetic acid	2.2	Adogen 464	1,2-Cyclododecanedione (18), dodecanedioic acid (63), 2-hydroxycyclododecanone (6), cyclododecene (6)
Methylene chloride plus 17% acetic acid	1.6	Adogen 464	1,2-Cyclododecanedione (14), dodecanedioic acid (40), 2-hydroxycyclododecanone (6), cyclododecene (23)
Methylene chloride plus 7% acid	2.2	Adogen 464	1,2-Cyclododecanedione (19), dodecanedioic acid (27), 2-hydroxycyclododecane (7), cyclododecene (23)
Methylene chloride/ water plus 10% acetic acid	2.2	Adogen 464	1,2-Cyclododecanedione (69), dodecanedioic acid (13), 2-hydroxycyclododecane (3), cyclododecene (9)
Methylene chloride/ water plus 10% acetic acid	2.2	Polyether[c]	1,2-Cyclododecanedione (16), dodecanedioic acid (82)
Methylene chloride/ aqueous NaOH	1.0	Benzyltriethylammonium chloride	1,2-Cyclododecanediol (50)[b]

[a] Number of moles of potassium permanganate per mole of alkene. [b] Reference 3. [c] Dimethyl polyethylene glycol. [d] Dicyclohexano-18-crown-6.

Scheme II



acetic acid prevents formation of overoxidation products when terminal alkenes are cleaved by permanganate ion. For example, they have reported that the oxidation of 1-octene by permanganate ion in a two-phase water/pentane system containing a phase transfer catalyst gives about 10% hexanoic acid in addition to the major product, heptanoic acid. Addition of a few milliliters of acetic acid decreased the amount of hexanoic acid formed and increased the yield of heptanoic acid.

The reduction of permanganate produces hydroxide ions which, in the absence of acetic acid, probably promote the overoxidation reaction in some way. The production of hydroxide ion when powdered potassium permanganate is used in a nonaqueous system also interferes with the progress of the reaction because the reduction product becomes a sticky gelatinous mass of manganese(IV) hydroxide that is difficult to filter and which may occlude considerable quantities of permanganate ion as it precipitates. This often brings the reaction to a premature termination with a great deal of unreacted starting material remaining. We have found that the addition of sufficient acetic acid to neutralize the hydroxide ions formed alleviates this problem and thus promotes a more complete reaction.

The use of solid potassium permanganate results in the formation of a brown precipitate consisting mainly of manganese dioxide. However, it can easily be demonstrated that this precipitate is also an oxidant; addition of concentrated hydrochloric acid releases copious quantities of chlorine, and unreacted alkene is converted to the corresponding vicinal dichloride. At least part of this residual oxidant is likely manganate ion (MnO_4^{2-}) which, because it is a dianion, cannot be easily solubilized by phase transfer agents. Because of this it is often preferable to use aqueous permanganate as the source of oxidant. The precipitated manganate ion then dissolves in the water and disproportionates to permanganate and manganese dioxide.[1b]

Experimental Section

Materials. Dimethyl polyethylene glycol was obtained as a mixture consisting of 1.5% dimethyl tetraethylene glycol, 9.0% dimethyl pentaethylene glycol, 12.5% dimethyl hexaethylene glycol, 15.9% dimethyl heptaethylene glycol, 16.4% dimethyl octaethylene glycol, 14.5% dimethyl nonaethylene glycol, 10.3% dimethyl decaethylene glycol, 5.8% dimethyl undecaethylene glycol, 2.8% dimethyl dodecaethylene glycol, 1.2% dimethyl tridecaethylene glycol, and 0.6% dimethyl tetradecaethylene glycol.[12] **Adogen 464,** a methyltrialkyl(C_8–C_{10})ammonium chloride, was obtained from Ashland Chemicals. **Dicyclohexano-18-crown-6** was obtained from the Aldrich Chemical Co. **Cyclododecene** was purified by a bromination–debromination procedure[21] as follows. Commercially available cyclododecene (180 g, 1.08 mol) was dissolved in 200 mL of methylene chloride and placed in a 500-mL, three-necked, round-bottomed flask. The solution was stirred magnetically and bromine (170 g, 1.06 mol) was added dropwise until the color of the solution remained orange. The solution was warmed and stirred for a further 30 min, the solvent was removed by rotary evaporation, and the residue was distilled under vacuum [170 °C (1.5 mm)] to give 280 g (0.86 mol) of 1,2-dibromocyclododecane. The dibromide was dissolved in ether (150 mL) and acetic acid (15 mL) and stirred vigorously while two 10-g portions of zinc dust were added. At this point the solution began to boil and an ice bath was raised into place during the addition of the remaining zinc (40 g). Water (50 mL) was added when the temperature of the solution began to drop, and the two layers were separated. The organic layer was washed with 2 × 100 mL of 10% HCl to remove zinc oxide and bromine and then by 2 × 100 mL of water. The solution was dried over anhydrous magnesium sulfate, concentrated on a flash evaporator, and distilled under vacuum [86–88 °C (4.5 mm)] to give 102 g (0.61 mol, 57%) of cyclododecane. Analysis of the product by GLC indicated it to be 60% trans and 40% cis. **1-Decene** and ***trans*-5-decene** were obtained commercially (Aldrich) and used without further purification.

General Oxidation Procedures. A. Alkene (0.054 mol) was dissolved in 130 mL of solvent (methylene chloride or benzene) and 25 mL of acetic acid in a 500-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer. About 3 g of phase transfer agent (Adogen 464, dicyclohexano-18-crown-6, or dimethyl polyethylene glycol) dissolved in 20 mL of solvent was added, followed by powdered potassium permanganate (0.177 mol) in small portions during a period of 2 h. An ice bath was used to maintain the temperature below 30 °C. The mixture was then stirred vigorously overnight, cooled, and treated with 100 mL of water and 5 g of sodium bisulfite to reduce any excess oxidant. After 20 min the solution was acidified (concentrated HCl) and the manganese dioxide was reduced by addition, in small portions, of the required amount of sodium bisulfite. Any solid carboxylic acids which precipitated were collected by filtration, and the nonaqueous layer was separated. The aqueous layer was saturated with sodium chloride and extracted with 2 × 50 mL of ether. The combined organic layers were extracted with 2 × 100 mL of 5% of sodium hydroxide solution to remove any additional carboxylic acids, dried over anhydrous magnesium sulfate, and concentrated by rotary evaporation. The resulting yellow oil could then be analyzed directly by GLC (when benzene and dimethyl polyethylene glycol had been used as solvent and phase transfer agent) or distilled under vacuum and then analyzed.

The precipitated carboxylic acids were dissolved in a 5% sodium hydroxide solution and combined with the basic solutions from previous extractions. The solution was filtered to remove any residual manganese dioxide, acidified with concentrated hydrochloric acid, and extracted with 2 × 250 mL of ether. This solution was dried over magnesium sulfate and evaporated to give purified carboxylic acids. The yields obtained under various conditions are given in Tables I–III.

B. Alkene (0.054 mol) was dissolved in a mixture of methylene chloride (130 mL), acetic acid (25 mL), and water (100 mL) in a 500-mL, three-necked, round-bottomed flask equipped with a mechanical stirrer. About 3.5 g of phase transfer agent (Adogen 464 or dimethyl polyethylene glycol) dissolved in 20 mL of methylene chloride was added. The mixture was cooled in an ice bath and powdered potassium permanganate (0.177 mol) was added in small portions over a 1-h period. The mixture was stirred vigorously for another 6 h, cooled, and treated with 5 g of sodium bisulfite to reduce any excess oxidant. After 20 min the solution was acidified (concentrated HCl) and the manganese dioxide reduced by addition, in small portions, of the required amount of sodium bisulfite. The products were then isolated as described above.

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Registry No.—1-Decene, 872-05-9; *trans*-5-decene, 7433-56-9; cyclododecene, 1501-82-2; dimethyl polyethylene glycol, 24991-55-7; potassium permanganate, 7722-64-7.

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Equilibration Studies: Amide–Imidate and Thioamide–Thioimidate Functions

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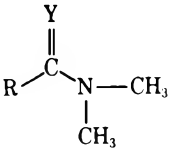
Heats of methylation and vaporization have been determined for the following isomer pairs: *N,N*-dimethylbenzamide (**1**)–*N*-methyl-*O*-methylbenzimidate (**2**); *N,N*-dimethylacetamide (**3**)–*N*-methyl-*O*-methylacetimidate (**4**); and *N,N*-dimethylthiobenzamide (**5**)–*N*-methyl-*S*-methylthiobenzimidate (**6**). These enthalpies are used to calculate liquid- and gas-phase enthalpy differences for the isomer pairs: [$\Delta H°_l$, $\Delta H°_g$ (kcal/mol)] -17.8 ± 1.8, -16.6 ± 3.2, **1**–**2**; -17.0 ± 1.5, -16.3 ± 2.5, **3**–**4**; -4.5 ± 0.7, -2.7 ± 2.4, **5**–**6**. These values are used, in conjunction with earlier studies, to suggest that the gas-phase enthalpy difference between an unstrained dialkylamide and the corresponding dialkylimidate will be 15 ± 3 kcal/mol, and the enthalpy difference between a dialkylthioamide and the corresponding dialkylthioimidate will be 2 ± 3 kcal/mol in favor of the amides. The enthalpy difference between an unstrained amide and its corresponding imidic acid isomer is estimated as 8 ± 3 kcal/mol in the vapor.

Gas-phase energy differences provide readily available fundamental data about chemical binding energies. This information can be useful in establishing relative chemical bond strengths and in testing energy predictions of current theory. Corresponding condensed-phase energy differences are important in understanding the effects of association and/or environment on molecular energies and in providing information about the prospective driving forces for chemical reactions.[1-4]

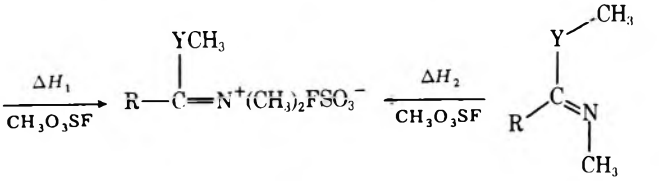
Our continuing studies of energy differences between alkylmeric and protomeric isomers have been most extensive for amide–imidic acid derivatives. We now report that the gas- and liquid-phase enthalpy differences between the *N,N*-dimethylamide–*N*-methyl-*O*-methylimidate and *N,N*-dimethylthioamide–*N*-methyl-*O*-methylthioimidate functions are unaffected by alkyl or aromatic substitution. This relative insensitivity to intramolecular environment, in conjunction with earlier data, suggests that parent systems provide useful guides to energy differences of alkylmeric isomers. This data also may be used to provide an estimate of the energy difference between parent amide–imidic acid systems.

Results

Heats of methylation and heats of vaporization were determined for the isomer pairs *N,N*-dimethylbenzamide (**1**)–*N*-methyl-*O*-methylbenzimidate (**2**), *N,N*-dimethylacetamide (**3**)–*N*-methyl-*O*-methylacetimidate (**4**), and *N,N*-dimethylthiobenzamide (**5**)–*N*-methyl-*S*-methylthiobenzimidate (**6**) (Table I). The differences in the heats of methylation give the differences in liquid-phase enthalpies for the isomer pairs ($\Delta H°_l$, Table II).[5] Inclusion of the differences in the heats of vaporization in a standard thermodynamic cycle gives the differences in the gas-phase enthalpies ($\Delta H°_g$, Table II). In these cases, the differences in the heats of vaporization of each isomer and the resulting correction for the differential molecular environment in the condensed and vapor phases are not large. Apparently the intermolecular forces in these liquids, unlike those in previous cases, are comparable for each isomer of the pair.[2,6]



1, R = C_6H_5; Y = O
3, R = CH_3; Y = O
5, R = C_6H_5; Y = S



$\Delta H°_l = \Delta H_1 - \Delta H_2$

2, R = C_6H_5; Y = O
4, R = CH_3; Y = O
6, R = C_6H_5; Y = S

Table I. Enthalpies of Methylation and/or Vaporization for Methyltropic Isomers 1–6 (kcal/mol)

Compd	$\Delta H°_{meth}$ [a]	$\Delta H°_{vap}$ [b]
1	16.6 ± 1.2	14.8 ± 0.7
2	34.4 ± 0.6	13.6 ± 0.7 [d]
3	16.1 ± 0.7	10.9 ± 0.5 [a]
4	33.1 ± 0.8	10.2 ± 0.5
5	26.1 ± 0.2	17.6 ± 0.9
		6.0 ± 0.2 [c]
6	36.6 ± 0.3	15.8 ± 0.8

[a] The estimated error is 5% (see ref 1 for discussion) for 3 runs in each case. [b] The error is the standard deviation. [c] The heat of fusion. [d] In kcal/mL.

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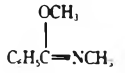
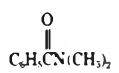
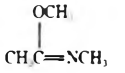
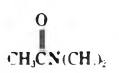
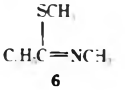
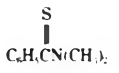
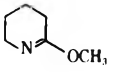
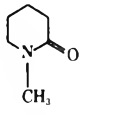
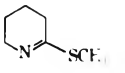
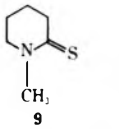
Table II. Enthalpy Differences for the Isomer Pairs (kcal/mol)

Registry no.	Isomer pair[a]	Registry no.	$\Delta H°_l$	$\Delta H°_g$[b]
1775-61-7	 2  1	611-74-5	−17.8 ± 1.8	−16.6 ± 3.2
3619-34-9	 4  3	127-19-5	−17.0 ± 1.5	−16.3 ± 2.5
40780-82-3	 6  5	15482-60-7	−4.5 ± 0.7	−2.7 ± 2.4
5693-62-9	 8  7	931-20-4	−17.4 ± 0.5[c]	−14.1 ± 2.0[c]
19766-29-1	 10  9	13070-07-0	−4.6 ± 2.2[d]	−2.1 ± 3.2[d]

[a] The amides and thioamides **1**, **3**, **5**, **7**, and **9** are of lower enthalpy. [b] With the addition of 1.5 kcal/mol due to possible differences in kinetic and zero point energies, this value can be considered $\Delta E°_{\text{chem binding}}$. [c] Reference 6. [d] Reference 2.

Table III. Combustion Analyses

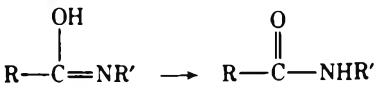
Compound	Registry no.	% C		% H		% N		% S	
		Calcd	Obsd	Calcd	Obsd	Calcd	Obsd	Calcd	Obsd
N,N-Dimethyl-*O*-methylbenzimidatium fluorosulfonate	60045-86-5	45.62	45.48	5.36	5.45	5.32	5.13	12.18	12.24
N,N-Dimethyl-*O*-methylacetimidatium fluorosulfonate	63985-90-0	29.84	29.74	6.01	5.86	6.96	6.97	15.94	16.00
N,N-Dimethyl-*S*-methylthiobenzimidatium fluorosulfonate	60011-05-4	42.98	42.69	4.96	4.96	5.01	5.01	22.96	22.77

The imidates **2** and **4** show a single NMR resonance for the *N*-methyl protons and are assigned the *E* configuration as shown.[7] The thioimidate **6** shows two *N*-methyl resonances, consistent with the 45:55 *E/Z* ratio previously assigned.[8]

Discussion

The gas-phase enthalpy differences of 16.6 ± 3.2 for the acyclic aromatic amide–imidate isomer pair **1–2** and of 16.3 ± 2.5 for the acyclic alkyl amide–imidate isomer pair **3–4** are quite close to the value of 14.1 ± 2.0 for the cyclic alkyl amide–imidate isomer pair *N*-methylvalerolactam–*O*-methylvalerolactim (**7–8**), as shown in Table II. This comparison suggests that the enthalpy difference for unstrained dialkylamide–dialkylimidate pairs is relatively independent of the nature of the group bonded to carbon. A value of 15 ± 3 kcal/mol seems a reasonable estimate for this gas-phase energy difference.[9] The large energy difference in favor of the amide, which persists or is amplified in the liquid phase, provides a rationale for the driving force of a number of synthetically useful conversions.[2,10] The independence of the energy difference towards the intramolecular environment suggests that measurements of enthalpy differences of alkyltropic functional groups will serve as a useful guide for general enthalpy differences in a number of systems.[11,12]

Previous comparisons of the gas-phase enthalpy differences of 1-methyl-2-pyridone–2-methoxypyridine and 2-pyridone–2-hydroxypyridine[1] show that the net conversion of NCH_3, OCH_3 to NH, OH σ bonds provides approximately 7.4 kcal/mol in favor of the OH isomer. Accordingly, it can be estimated that benzamide, *N*-alkylbenzamides, acetamide, and *N*-alkylacetamides will be 9 kcal/mol more stable enthalpically in the gas phase than the corresponding imidic acids. If these enthalpy estimates are generally applicable, a general gas-phase energy difference in favor of an unstrained amide over its imidic acid may be estimated as 8 ± 3 kcal/mol.



$\Delta H°_g = -8 \pm 3$ kcal/mol

A value of 26 kcal/mol has been calculated for the energy difference between formamide and its isomeric imidic acid.[13]

A comparison of the gas-phase enthalpy difference for **5–6** of 2.7 ± 2.4 kcal/mol with the previously determined value of 2.1 ± 3.2 kcal/mol for 1-methyl-2-thiopiperidone–2-methylthio-3,4,5,6-tetrahydropyridine (**9–10**) is given in Table II. It seems reasonable that this enthalpy difference will also be relatively insensitive to intramolecular environment and that a general enthalpy difference of 2 ± 3 kcal/mol may be assigned between unstrained dialkylthioamides–dialkylthioimidates. The previously noted destabilization of a thiocarbonyl isomer relative to the corresponding oxygen system clearly persists in this case.[2]

Experimental Section

Melting points and boiling points are uncorrected. Elemental analyses were performed by Mr. J. Nemeth and associates.

The reactants **1**, **2**, **3**, **4**, **5**, and **6** were analytically pure materials which had physical properties, infrared spectra, and nuclear magnetic resonance spectra consistent with the assigned structures.[14] All materials are liquids except **5**. *Methyl fluorosulfonate is reported to be very toxic and should be handled with appropriate caution;*[15] it (Aldrich) was distilled and stored in a dry argon atmosphere at −15 °C.

***N,N*-Dimethyl-*O*-methylbenzimidatium fluorosulfate** was prepared from separate reactions of **1** and **2** with excess methyl fluorosulfonate in ethylene dichloride. Removal of the solvent and excess methylating agent in vacuo gave quantitative yields: mp 95–98 °C; NMR (acetonitrile-d_3) δ 7.70 (ArH), 3.90 (OCH_3), 3.42, 3.13 [$N(CH_3)_2$]; IR (Nujol) 1610, 1600, 1510 cm^{-1};[16] combustion analysis, Table III.

***N,N*-Dimethyl-*O*-methylacetimidatium fluorosulfonate** was prepared by a procedure similar to that used above from **3** and from **4**: mp 117–120 °C; NMR (acetonitrile-d_3) δ 4.00 (OCH_3), 3.18, 3.07 [$N(CH_3)_2$], 2.35 (CCH_3); IR (Nujol) 1680 cm^{-1};[16] combustion analysis, Table III.

***N,N*-Dimethyl-*S*-methylthiobenzimidatium fluorosulfonate** was prepared by a procedure similar to that used above from **5** and from **6**: mp 103–106 °C; NMR (Me_2SO-d_6) δ 7.33 (ArH), 3.55, 3.20 [$N(CH_3)_2$], 2.17 (SCH_3); IR (Nujol) 1616, 1269, 1068, 774 cm^{-1};[16] combustion analysis, Table III.

Heats of methylation and vaporization for 1–6 and the heat of fusion of 5 were determined by the techniques previously described.[2] The only detectable products from the calorimetric runs were the fluorosulfonate salts. The salts were isolated and shown to be virtually identical with authentic material by IR and NMR criteria.

Acknowledgment. We are grateful to the National Science Foundation for support of this work.

Registry No.—Methyl fluorosulfonate, 421-20-5.

References and Notes

(1) P. Beak, *Acc. Chem. Res.*, **10**, 186 (1977), and references cited therein.
(2) P. Beak, D. S. Mueller, and J. Lee, *J. Am. Chem. Soc.*, **96**, 3867 (1974).
(3) P. Beak, F. S. Fry, J. Lee, and F. Steele, *J. Am. Chem. Soc.*, **98**, 171 (1976).
(4) P. Beak, J. Covington, and S. G. Smith, *J. Am. Chem. Soc.*, **98**, 8284 (1976).
(5) The conversion of values for the solid **5** to the liquid requires the determination of the heat of fusion (Experimental Section).
(6) P. Beak, J. Bonham, and J. T. Lee, *J. Am. Chem. Soc.*, **90**, 1569 (1968).
(7) C. O. Meese, W. Walter, and M. Berger, *J. Am. Chem. Soc.*, **96**, 2259 (1974). For a case in which both isomers are detected, see A. C. Satterthwait and W. P. Jencks, *J. Am. Chem. Soc.*, **96**, 7045 (1974).
(8) W. Walter and C. O. Meese, *Chem. Ber.*, **109**, 922 (1976).
(9) Justification for the assumption that differences in kinetic energies of the isomers will lead to enthalpy differences which are negligible with respect to the enthalpy differences is given in ref 2 and 6.
(10) For examples, see L. E. Overman and L. A. Clizbe, *J. Am. Chem. Soc.*, **98**, 2353 (1976); L. E. Overman, *ibid.*, **98**, 2901 (1976); R. G. Glushkov and V. B. Granik, *Adv. Heterocycl. Chem.*, **12**, 185 (1970); and ref 2, footnotes 35 and 36.
(11) For another example, note that the enthalpy differences of a 2- and 4-pyrone system and a 2- and 4-pyridone system are 9.7 ± 2.3 kcal/mol: P. Beak, T. S. Woods, and D. S. Mueller, *Tetrahedron*, **28**, 5507 (1972), and ref 2.
(12) It is possible to perturb the amide–imidate enthalpy difference by intramolecular effects. For example, as earlier noted,[6] the enthalpy difference is reduced by 6 kcal/mol when the functions are part of an aromatic ring, a result which allows a thermodynamic estimate of the relative aromaticity of the pyridine and pyridone rings. For discussion, see A. K. Burnham, J. Lee, T. G. Schmalz, P. Beak, and W. H. Flygare, *J. Am. Chem. Soc.*, **99**, 1836 (1977).
(13) L. Radom, W. J. Hehre, and J. A. Pople, *J. Am. Chem. Soc.*, **93**, 289 (1971).
(14) (a) *N*-Methyl-*O*-methylbenzimidate: H. Paul, A. Weise, and R. Settmer, *Chem. Ber.*, **98**, 1450 (1965). (b) *N*-Methyl-*O*-methylacetimidate: H. Bredereck, F. Effenberger, and E. Henseleit, *Chem. Ber.*, **98**, 2754 (1965). (c) *N*-Methyl-*S*-methylthiobenzimidate: B. Böttcher and F. Bauer, *Justus Liebigs Ann. Chem.*, **568**, 218 (1950).
(15) D. M. W. Van den Ham and D. Van der Meer, *Chem. Eng. News*, **54**, 5 (1976).
(16) Satisfactory analytical data were obtained.

Modified Cephalosporins: Synthesis of Benzo[3,4]cephams[1]

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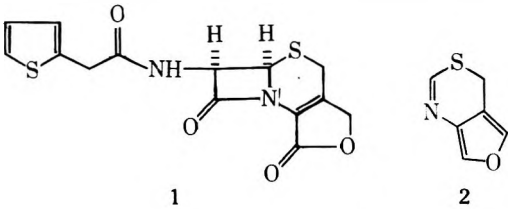
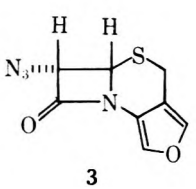
A synthetic route to a benzo[3,4]cepham system is described. The key step of the synthesis involved treatment of the novel 7-*tert*-butoxycarbonyl-4*H*-benzo-3,1-thiazine (**4**) with azidoacetyl chloride and triethylamine to furnish the *trans*-β-lactam **13a**. Conversion of **13a** to the cephalosporin analogue **17** followed established synthetic methodology.

A novel totally synthetic route to (±)-desacetylcephalothin lactone (**1**) was recently reported from our laboratories, the key step being the reaction of azidoacetyl chloride/triethylamine with the novel 4*H*-furo[3,4-*d*]-1,3-thiazine (**2**) to give the furo[3,4]cephams **3**.[3] This paper describes the synthesis of benzo[3,4]cephams via the new thiazine **4**.



1

2



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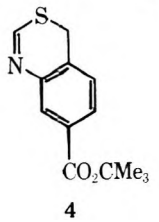
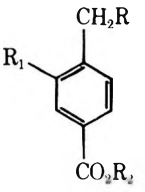


4

Reaction of 4-bromomethylbenzoic acid (**5**) with nitric acid gave the 3-nitro compound **6**, which was converted into the *tert*-butyl ester **7**. Silver perchlorate promoted hydrolysis of



5, R = Br; $R_1 = R_2 = H$
6, R = Br; $R_1 = NO_2$; $R_2 = H$
7, R = Br; $R_1 = NO_2$; R_2 = *tert*-butyl
8, R = OH; $R_1 = NO_2$; R_2 = *tert*-butyl
9, R = OH; $R_1 = NH_2$; R_2 = *tert*-butyl
10, R = OH; R_1 = NHCHO; R_2 = *tert*-butyl
11, R = OCHO; R_1 = NHCHO; R_2 = *tert*-butyl
12, R = Cl; R_1 = NHCHO; R_2 = *tert*-butyl

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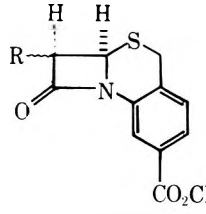
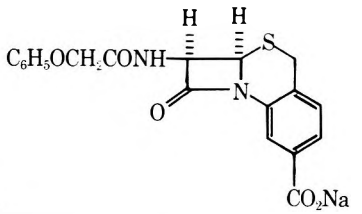
7 furnished the alcohol **8**, which was hydrogenated (5% Pt/C) to amine **9**. Attempts to prepare the *N*-formylcarbinol **10** by selective N-formylation failed. However, **9** was readily transformed into a mixture of **10** and *O,N*-diformate **11** by reaction with formic acetic anhydride in pyridine. Treatment with ammonia caused selective hydrolysis of the *O*-formate group to give **10** in 56% yield from **8**.

The next stage of the synthesis required the transformation of the *N*-formylcarbinol **10** into a thioformate derivative bearing chlorine on the benzylic carbon since previous experience indicated that this compound would cyclize directly to thiazine **4**.[3] Accordingly, **10** was transformed into the benzylic chloride **12** by reaction with triphenylphosphine/carbon tetrachloride[4] and this substance in turn treated with P_4S_{10}. The resulting product, formulated as thiazine **4** rather than the thioformate, was unstable in the solid state and polymerized ($t_{1/2} \sim 15$ min) to a material insoluble in organic solvents. However, solutions of **4** could be kept for several days without deterioration. Its NMR spectrum showed a 2-H singlet at 3.93 ppm for the methylene protons and a 1-H singlet at 7.45 ppm for the vinyl proton on the thiazine ring, as well as the expected resonances for the *tert*-butyl and three aromatic protons.

Because of the instability of the benzothiazine **4** it was necessary to treat solutions of **4**, obtained directly from the P_4S_{10} reaction, with azidoacetyl chloride/triethylamine in order to form the β-lactam system.[5] This afforded the expected *trans*-β-lactam **13a** in 60% yield from **12**. The trans





a, *trans*-6,7-H; b = *cis*-6,7-H

17

13a, R = N_3
14a,b, R = NH_2
15a,b, R = *p*-$NO_2C_6H_4CH{=}N$
16a,b, R = $C_6H_5OCH_2CONH$

stereochemistry in **13a** follows from the 2.2-Hz coupling constant for the 6 and 7 protons, which is in agreement with literature values reported for analogous systems.[6]

The conversion of the 7α-azido-*trans*-cepham **13a** into the 7β-amino cis series was accomplished as follows. Azide **13a** was reduced with aqueous $(NH_4)_2S$[3] to the amine **14a**, which was converted into the Schiff's base **15a** with *p*-nitrobenzaldehyde. Equilibration of **15a** with diisopropylethylamine produced a 1:5 mixture of the *cis*- and *trans*-*p*-nitrobenzylidene derivatives **15b** and **15a**, respectively.[7] Fractional crystallization provided in ~75% yield the starting trans isomer **15a** and the cis isomer **15b** (~10% yield) admixed with ca. 10% of **15a**.

Hydrolysis of the *p*-nitrobenzylidene group of **15b** gave the *cis*-amine **14b**, which was treated directly with phenoxyacetyl chloride to give **16b**. The cis arrangement of the β-lactam protons in **16b** (and also in **14b** and **15b**) was confirmed by the expected 4.5-Hz coupling constant for the 6- and 7-H signals.[6] For preparative purposes it proved to be most convenient to reequilibrate the recovered trans Schiff's base **15a** several times and then to process the combined fractions enriched in the cis isomer as before. This provided a 1:3 mixture of the *cis*- and *trans*-7-phenoxyacetamido esters **16b** and **16a**, respectively, which was then separated chromatographically.

Transformation of the *cis*-*tert*-butyl ester **16b** into the amorphous sodium salt **17** was accomplished following established methodology. Salt **17** showed no antibacterial activity in vitro at a concentration of 100 μg/mL against a variety of gram-positive and -negative organisms.

Experimental Section

Melting points are uncorrected. Infrared spectra were measured as KBr disks on a Perkin-Elmer 237B spectrometer. NMR spectra were obtained with Varian A-60 and HA-100 instruments using ca. 5% w/v solutions in $CDCl_3$. Chemical shifts are given in ppm from Me_4Si. Elemental analyses were performed by the Analytical Department at Syntex Research.

3-Nitro-4-bromomethylbenzoic Acid (6). 4-Bromomethylbenzoic acid (**5**; 2 g, 9.3 mmol) was added slowly with stirring to fuming nitric acid (10 mL) at −10 to −20 °C. After 0.5 h the reaction mixture was poured into ice water, and the crystalline product was collected and dried to yield 1.8 g (74%) of **6**, mp 93–94 °C (from $CHCl_3$/hexane).

Anal. Calcd for $C_8H_6BrNO_4$: C, 36.95; H, 2.33; N, 5.39; Br, 30.73. Found: C, 37.00; H, 2.29; N, 5.18; Br, 30.57.

***tert*-Butyl 3-Nitro-4-bromomethylbenzoate (7).** A solution of the acid **6** (2 g, 8.7 mmol), glyme (3 mL), isobutylene (ca. 15 g), and concentrated H_2SO_4 (0.2 mL) was heated in an autoclave at 50 °C for 18 h. After cooling with dry ice the reaction mixture was diluted with CH_2Cl_2 (100 mL), and the resulting solution was washed with 10% Na_2CO_3 (4 × 15 mL) and H_2O (to neutral), dried (Na_2SO_4), and evaporated to give **7** (2.1 g, 72%), mp 64 °C (from Et_2O/hexane).

Anal. Calcd for $C_{12}H_{14}NO_4Br$: C, 45.59; H, 4.46; N, 20.24; Br, 25.28. Found: C, 45.21; H, 4.38; N, 20.14; Br, 24.89.

***tert*-Butyl 3-Nitro-4-hydroxymethylbenzoate (8).** A solution of the ester **7** (0.32 g, 1 mmol) in acetone (5 mL) was stirred for 48 h at 20 °C with a solution of $AgClO_4$ (0.4 g, 1.9 mmol) dissolved in water (2.5 mL). The reaction mixture was filtered, and the bulk of the acetone was evaporated under reduced pressure. Ether (100 mL) was added, and the resulting solution was washed with H_2O (3 × 25 mL) and brine (1 × 25 mL), dried (Na_2SO_4), and evaporated. The residue was dissolved in EtOAc and filtered through a column of SiO_2 (5 g) to yield after evaporation of the solvent the hydroxymethyl derivative **8** (0.2 g, 77%): mp 73–74 °C (Et_2O/hexane); NMR 1.6 (s, *tert*-butyl H's), 5.08 (s, CH_2OH), 7.90 (d, J = 8 Hz, 5-H), 8.28 (dd, J = 2, 8 Hz, 6-H), 8.68 ppm (d, J = 2 Hz, 2-H).

Anal. Calcd for $C_{12}H_{15}NO_5$: C, 56.91; H, 5.97; N, 5.53. Found: C, 57.16; H, 6.03; N, 5.14.

***tert*-Butyl 3-Formamido-4-hydroxymethylbenzoate (10).** A solution of the nitro compound **8** (1.27 g, 5 mmol) in EtOH (25 mL) was hydrogenated over 5% Pd/C (0.05 g) until the uptake of hydrogen ceased (ca. 4 h). The catalyst was removed by filtration, and the alcohol was evaporated under reduced pressure to afford the crude amine **9** as an oil, which was dissolved in pyridine (8 mL) and treated with a solution of formic acetic anhydride (2 mL) in pyridine (4 mL). After keeping it at 0 °C for 18 h, the reaction mixture was evaporated to dryness, dissolved in MeOH (40 mL), and treated with several drops of MeOH saturated with NH_3. After TLC examination revealed that hydrolysis of the diformate was complete (ca. 5 h), the MeOH was evaporated and the residue was dissolved in EtOAc and filtered through a short column of SiO_2 (15 g). After evaporation of the combined eluates the residue was crystallized from Et_2O/petroleum ether to yield **10** (0.7 g, 56% from **8**), mp 128–129 °C.

Anal. Calcd for $C_{13}H_{17}NO_4$: C, 62.14; H, 6.82; N, 5.57. Found: C, 62.26; H, 6.74; N, 5.44.

***tert*-Butyl 3-Formamido-4-chloromethylbenzoate (12).** A solution of alcohol **10** (2.5 g, 10 mmol) in dry DMF (40 mL) was treated with $(C_6H_5)_3P$ (3.95 g, 15 mmol) and CCl_4 (2.15 g, 14 mmol) and then heated to 50 °C for 0.5 h. The solvent was evaporated under reduced pressure, and the residue was dissolved in CH_2Cl_2 and adsorbed on a column of SiO_2 (70 g). Elution with CH_2Cl_2 and mixtures of CH_2Cl_2/EtOAc (9:1 and 4:1) gave **12** mixed with $(C_6H_5)_3PO$. Rechromatography on SiO_2 (80 g) and slow elution with CH_2Cl_2 gave a series of fractions which were combined and crystallized from Et_2O/hexane to furnish **12** (1.55 g, 58%), mp 89–90 °C.

Anal. Calcd for $C_{13}H_{16}NO_3Cl$: C, 57.88; H, 5.98; N, 5.19; Cl, 13.16. Found: C, 57.50; H, 5.81; N, 5.22; Cl, 12.93.

7-*tert*-Butoxycarbonyl-4*H*-benzo-3,1-thiazine (4). A solution of **12** (1.08 g, 4 mmol) in dry THF (100 mL) was stirred with P_4S_{10} (1.6 g, 7.5 mmol) at 45 °C for 0.5 h. The reaction mixture was cooled and stirred briefly with 10% aqueous NaOH (50 mL). The organic phase was separated, diluted with CH_2Cl_2 (100 mL), washed with saturated NaCl (2 × 50 mL), and dried (Na_2SO_4). Since **4** polymerized rapidly in the solid state, the foregoing CH_2Cl_2 solution was evaporated to a volume of 60 mL by distillation under reduced pressure and used

immediately in the next reaction: NMR 1.58 (s, *tert*-butyl H's), 3.93 (s, CH_2S), 7.1 (d, J = 8.5 Hz, 5-H), 7.88 (dd, J = 2, = 8.5 Hz, 6-H), 7.95 (d, J = 2 Hz, 8-H), 8.45 ppm (s, 2-H).

(±)-7α-Azido-3c-*tert*-butoxycarbonylbenzo[3,4]cepham (13a). The foregoing solution of 4 was treated sequentially with Et_3N (1.73 g, 17.3 mmol) and a solution of azidoacetyl chloride (1.5 g, 12 mmol) in CH_2Cl_2 (30 mL) in five portions over a 1-h period in a N_2 atmosphere. After 1 h the reaction mixture was washed with saturated NaCl (2 × 40 mL), dried (Na_2SO_4), and evaporated. The crude product was dissolved in CH_2Cl_2 and filtered through SiO_2 (25 g) to yield **13a** (0.8 g, 60% from **12**): mp 113–114 °C (Et_2O/hexane); IR 2130, 1775, 1710 cm^{-1}; NMR 1.61 (s, *tert*-butyl H's), 3.88, 4.13 (AB q, J = 17 Hz, CH_2S), 4.78 (d, J = 2.2 Hz, 7-H), 4.94 (d, J = 2.2 Hz, 6-H), 7.25 (d, J = 8 Hz, 3a-H), 7.76 (dd, J = 2, 8 Hz, 3b-H), 8.32 ppm (d, J = 2 Hz, 3d-H).

Anal. Calcd for $C_{15}H_{16}N_4O_3S$: C, 54.20; H, 4.85; N, 16.86; S, 9.65. Found: C, 54.45; H, 4.87; N, 16.70; S, 9.27.

(±)-7α-Amino-3c-*tert*-butoxycarbonylbenzo[3,4]cepham (14a) and 7α-Phenoxyacetamide Derivative 16a. A solution of lactam **13a** (0.33 g, 1 mmol) in MeOH (15 mL) was stirred with 22% aqueous $(NH_4)_2S$ (1 mL, ~3 mmol) at 20 °C for 20 min. The reaction mixture was concentrated to ca. 7 mL under reduced pressure, diluted with CH_2Cl_2 (50 mL), washed with saturated NaCl (2 × 25 mL), dried (Na_2SO_4), and evaporated to yield the amine **14a** (0.13 g) as an oil: NMR 1.61 (s, *tert*-butyl H's), 3.71, 4.08 (AB q, J = 16.5 Hz, CH_2S), 4.36 (d, J = 2 Hz, 6-H), 4.80 (d, J = 2 Hz, 7-H), 7.18 (d, J = 8 Hz, 3a-H), 7.63 (dd, J = 2, 8 Hz, 3b-H), 8.25 ppm (d, J = 2 Hz, 3d-H).

The treatment of amine **14a** (0.1 g, 0.33 mmol) in CH_2Cl_2 (4 mL) containing Et_3N (2 drops) with phenoxyacetyl chloride (0.06 g, 0.36 mmol) for 18 h followed by addition of H_2O and isolation with CH_2Cl_2 gave **16a**: mp 173–174 °C (EtOAc/hexane); IR 3450, 2980, 1775, 1715, 1435 cm^{-1}; NMR 1.62 (s, *tert*-butyl H's), 3.77, 4.10 (AB q, J = 17 Hz, CH_2S), 4.56 (s, CH_2O), 5.14 (d, J = 2 Hz, 6-H), 5.38 (dd, J = 2, 8 Hz, 7-H), 6.94 (d, J = 8 Hz, 3a-H), 7.63 (dd, J = 2, 8 Hz, 3b-H), 8.34 ppm (d, J = 2 Hz, 3d-H).

Anal. Calcd for $C_{23}H_{24}N_2O_5S$: C, 62.71; H, 5.49; N, 6.36; S, 7.28. Found: C, 62.90; H, 5.78; N, 6.20; S, 6.85.

***p*-Nitrobenzylidene Schiff's Base 15a of (±)-7α-Amino-3c-*tert*-butoxycarbonylbenzo[3,4]cepham (14a).** A solution of the crude amine **14a** (0.3 g, 1 mmol) in benzene (50 mL) containing *p*-nitrobenzaldehyde (0.16 g, 1.05 mmol) was stirred with anhydrous $MgSO_4$ (1.2 g) for 18 h. The salt was filtered off and washed with benzene, and the combined filtrates were evaporated to dryness. The residue was twice crystallized from EtOH to yield **15a**: mp 187–193 °C dec; IR 3450, 3000, 1770, 1710, 1380, 1110 cm^{-1}; NMR, 1.61 (s, *tert*-butyl H's), 3.86, 4.14 (AB q, J = 17 Hz, CH_2S), 5.03 (dd, J = 2, 2 Hz, 7-H), 5.24 (d, J = 2 Hz, 6-H), 7.26 (d, J = 8 Hz, 3a-H), 7.70 (dd, J = 2, 8 Hz, 3b-H), 7.97, 8.27 (AA'BB' pattern, p-$NO_2C_6H_4$), 8.32 (d, J = 2H, 3d-H), 8.65 ppm (broad, CH=N). This substance failed to give a satisfactory elemental analysis.

Equilibration of the Schiff's Base 15a. A solution of the Schiff's base **15a** (0.66 g, 1.5 mmol) in THF (35 mL) was cooled to 0 °C and treated with *i*-Pr_2NEt (1 mL) in a N_2 atmosphere. After 1 h the reaction mixture was diluted with benzene (200 mL), washed with H_2O (2 × 100 mL), 0.1 N HCl (2 × 100 mL), H_2O (2 × 100 mL), pH 8 phosphate/citrate buffer (2 × 100 mL), and saturated NaCl (2 × 100 mL), dried ($MgSO_4$), and evaporated to give a 1:4 mixture of **15b** and **15a**, respectively, as an oil. Recrystallization of this product from EtOH gave the starting **15a** (0.49 g) and a second crop (0.065 g) consisting of a 9:1 mixture of **15b** and **15a**, respectively.

(±)-7β-Phenoxyacetamido-3c-*tert*-butoxycarbonylbenzo[3,4]cepham 16b. A solution of the second crop of material (0.065 g, 0.15 mmol) from the preceding experiment in $CHCl_3$ (0.5 mL) was added with stirring to a solution of dinitrophenylhydrazone (DNPH; 0.035 g, 0.175 mmol) and p-TsOH·H_2O (0.035 g, 0.175 mmol) in EtOH (3 mL). After 45 min the reaction mixture was filtered and the collected precipitate washed with EtOH (2 × 5 mL). The filtrate was evaporated to dryness under reduced pressure, and the resulting residue was dissolved in Et_2O (50 mL) and washed with pH 8 phosphate/citrate buffer (20 mL). The Et_2O layer was dried over $MgSO_4$ and evaporated to yield the crude amine **14b** (0.05 g, 0.16 mmol), which was dissolved in CH_2Cl_2 (3 mL) containing 1 drop of Et_3N and treated with phenoxyacetyl chloride (0.03 g, 0.18 mmol). After 18 h the reaction mixture was worked up by addition of H_2O and isolation with CH_2Cl_2 to afford **16b** (0.065 g): mp 228–229 °C (EtOAc/hexane); IR 3290, 3250, 3100, 1780, 1705, 1675, 1555, 1430 cm^{-1}; NMR 1.62 (s, *tert*-butyl H's), 3.80, 4.10 (AB q, J = 17 Hz, CH_2S), 4.57 (s, CH_2O), 5.28 (d, J = 4.5 Hz, 6-H), 5.92 (dd, J = 4.5, 9 Hz, 7-H), 6.92 (d, J = 8 Hz, 3a-H), 7.69 (dd, J = 2, 8 Hz, 3b-H), 7–7.4 (m, C_6H_5O), 8.15 ppm (d, J = 2 Hz, 3d-H).

Anal. Calcd for $C_{23}H_{24}N_2O_5S$: C, 62.71; H, 5.49; N, 6.36; S, 7.28. Found: C, 63.02; H, 5.40; N, 6.19; S, 7.35.

Sodium (±)-7β-Phenoxyacetamidobenzo[3,4]cepham-3c-carboxylate (17). The *cis-tert*-butyl ester **16b** (0.022 g, 50 μmol) was dissolved in cold trifluoroacetic acid (TFA; 0.6 mL), and this solution was kept at 0 °C for 5 min. The solvent was removed under reduced pressure, the residue was dissolved in THF (2 mL), and a solution of $NaHCO_3$ (0.005 g, 60 μmol) in H_2O (0.5 mL) was added. The resulting solution was evaporated to dryness under reduced pressure to afford the sodium salt **17** (~0.026 g) as an amorphous solid: IR ($CHCl_3$) 3300, 3000, 1777, 1695, 1675, 1535, 1440, 1210 cm^{-1}; NMR (Me_2SO-d_6) 3.97, 4.18 (AB q, J = 16 Hz, CH_2S), 4.62 (s, CH_2O), 5.33 (d, J = 4.5 Hz, 6-H), 5.72 (d, J = 4.5 Hz, 7-H), 6.96–7.40 (m, C_6H_5O and 3b-H), 7.62 (dd, J = 2, 8 Hz, 3a-H), 8.05 ppm (d, J = 2 Hz, 3d-H).

(±)-7β-Phenoxyacetamido-3c-*tert*-butoxycarbonylbenzo[3,4]cepham (16b) by Multiple Reequilibration of Recovered Schiff's Base 15a. A solution of the Schiff's base **15a** (0.49 g, 1.1 mmol) in THF (26 mL) was cooled to 0 °C and treated with *i*-Pr_2NEt (0.74 mL) in a N_2 atmosphere. After 1 h the reaction mixture was processed as described previously, the crude product crystallizing from EtOH to give **15a** (0.33 g) and second (0.04 g), third (0.05 g), and mother liquor (0.04 g) fractions consisting of mixtures of **15a** and **15b**. The recovered **15a** was reequilibrated and fractionated by crystallization four more times, and the second, third, and mother liquor fractions were combined to yield 0.42 g of a 2–3:1 mixture of **15a** and **15b**, respectively. This mixture was hydrolyzed as before with DNPH and *p*-TsOH followed by acylation with phenoxyacetyl chloride to produce roughly a 1:3 mixture of **16b** and **16a**, respectively. Crystallization from EtOAc/hexane furnished **16b** (0.035 g), mp 228–229 °C, a second crop consisting of a 1:3 mixture of **16a** and **16b**, respectively, and a third crop of **16a** (ca. 90% pure by TLC). The second crop of material was separated by chromatography over SiO_2 (20 g) eluting with hexane/EtOAc (75:35) to yield, after combination of the appropriate fractions, pure samples of **16a** (0.12 g), mp 167–168 °C (EtOAc/hexane), and **16b** (0.045 g), mp 228–229 °C (EtOAc/hexane), identical in all respects with samples obtained as described in earlier experiments.

Registry No.—**4**, 65276-89-3; **5**, 6232-88-8; **6**, 55715-03-2; **7**, 65276-90-6; **8**, 65276-91-7; **9**, 65276-92-8; **10**, 65276-93-9; **12**, 65276-94-0; **13a**, 65276-95-1; **14a**, 65276-96-2; **14b**, 65276-97-3; **15a**, 65276-98-4; **15b**, 65276-99-5; **16a**, 65277-00-1; **16b**, 65277-01-2; **17**, 65277-02-3; isobutylene, 115-11-7; formic acetic anhydride, 2258-42-6; P_4S_{10}, 12066-62-5; azidoacetyl chloride, 30426-58-5; phenoxyacetyl chloride, 701-99-5; *p*-nitrobenzaldehyde, 555-16-8.

References and Notes

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Substituted γ-Lactones. 28.[1] 3-(Phenylmethylene)-2,4(3*H*,5*H*)-furandiones

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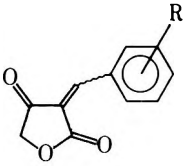
2,4(3*H*,5*H*)-Furandione (β-tetronic acid, **1**) undergoes a base-catalyzed aldol condensation with aromatic aldehydes to afford the 1:1 condensation products 3-(arylmethylene)-2,4(3*H*,5*H*)-furandiones **2**. The 1:1 condensation products **2** are also obtained when the reaction is acid catalyzed, and this constitutes a more convenient synthesis of **2**. The furandiones **2** are formed as a mixture of two geometric isomers, whose structures have been tentatively assigned on the basis of ^{1}H NMR data. Preliminary investigations dealing with condensations of **1** with aliphatic aldehydes reveal that, under all conditions employed, the products contain 2 equiv of **1** and 1 equiv of the aldehyde. Also explored are the cycloaddition reactions of **2** with triethyl phosphite, which lead to the novel furo[3,4-*d*]-1,2-oxaphospholene ring system.

The lignans constitute a group of naturally occurring substances which are currently attracting much attention because several members of this group have shown significant activity against several tumor systems in mice.[3] As a result, the development of convenient syntheses of lignans and lignan-type structures on which we published some time ago[4] again became of interest to us.

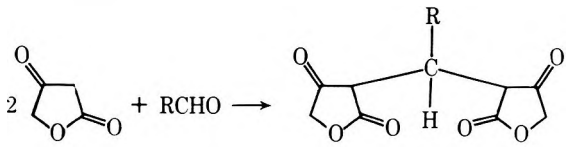
The molecule, 2,4(3*H*,5*H*)-furandione (**1**), commonly known as β-tetronic acid,[5] represents a potentially valuable building block for the preparation of these compounds. Since **1** possesses the necessary functionalities at the 3 and 4 position, it should be easily transformed into 3,4-unsymmetrically disubstituted furanones. As a logical first step toward the synthesis of lignan precursors, the preparation of 3-(phenylmethylene)-2,4(3*H*,5*H*)-furandiones, **2**, by an aldol type condensation of **1** with substituted aromatic aldehydes was explored. The resulting **2** compounds could be converted into



2

the desired lignans and lignan-type compounds via a second aldol-type condensation.

Several obstacles appeared to shed doubt on the development of a lignan synthesis based on **1** as a viable synthon. First, according to earlier reports, it is claimed that **1** does not undergo an aldol condensation reaction with aldehydes in a 1:1 ratio but rather they react in a 2:1 ratio to give compounds of general structure **3**.[6] Since there appeared to be no theoretical reason why the 1:1 aldol condensation product should not form, we decided to reinvestigate aldol condensations of **1** and substituted aromatic aldehydes.



1 **3**

A second obstacle in the development of a lignan synthesis based on **1** as a starting material is the lack of a reliable method for its preparation. While there exists considerable literature[7] concerned with the synthesis of **1**, the procedures which are reported and the yields which are quoted could not be repeated either by us[8] or by others.[9,10] Such attempts resulted either in complete irreproducibility or gave much lower yields than indicated in the published accounts.[7] Consequently, it was necessary to develop a reliable synthesis for **1** in order to achieve a viable lignan synthesis.

The present paper describes the results of our efforts in affecting (1) a reliable synthesis of **1** and (2) the aldol condensation of **1** with substituted aromatic aldehydes to afford the α-(phenylene)-2,4(3*H*,5*H*)-furandiones **2**. We also report on the reaction between **2** and triethyl phosphite to yield the novel furo[3,4-*d*]-1,2-oxaphospholene ring system.

Results and Discussion

Synthesis of 2,4(3*H*,5*H*)-Furandione (β-Tetronic Acid, 1). Experiments in our laboratories have indicated that with certain modifications the method of Kumler[11] offered the best preparation for **1**. The synthesis starts with the bromination of ethyl acetoacetate, followed by pyrolysis of the crude dibromination product to yield 3-bromo-2,4(3*H*,5*H*)-furandione. These steps can be done on a fairly large scale. The next step involves a catalytic debromination with PtO_2. With this catalyst, only anhydrotetronic acid was obtained.[2b,8] While it is known that platinum and its compounds are rather poor dehydrohalogenation catalysts, palladium is usually the better catalyst for this reaction.[12] Use of palladium on carbon (5–10%), under approximately 40 lbs of hydrogen pressure, results in good yields (80%) of **1**. This method is now being continuously used in our laboratories and represents a reliable method to obtain **1** in a convenient manner.

Acid-Catalyzed Aldol Condensations of 1 with Aromatic Aldehydes. Since it is known that the protons in the 3 position of **1** are fairly acidic (pK_a = 3.76),[11] the acid-catalyzed aldol condensation of **1** with aromatic aldehydes, affording the 1:1 condensation products, should be possible. It was found that the reaction of **1** with 3 equiv of a substituted aromatic aldehyde, in the absence of solvent and introducing hydrogen chloride gas, results in the formation of the desired 1:1 condensation product. In the case of solid aldehydes, the reaction was performed in a melt of the aldehyde to which **1** and the HCl was added. The mixture would solidify after a few minutes. For workup the solid was broken up and then washed with a suitable solvent to remove the excess aldehyde. The resulting type **2** compounds were easily purified by recrystallization. These acid-catalyzed condensations proceed equally well with both electron-donating and electron-withdrawing groups on the aromatic ring of the aldehydes. The 3-(arylmethylene)-2,4(3*H*,5*H*)-furandiones, **2**, are highly colored substances and they are easily characterized by their spectral data (IR, NMR, and UV). The results of the acid-catalyzed aldol condensations of **1** and substituted aromatic aldehydes are summarized in Table I.

Acid-Catalyzed Aldol Condensations of 1 with Aliphatic Aldehydes. Preliminary experiments with aliphatic

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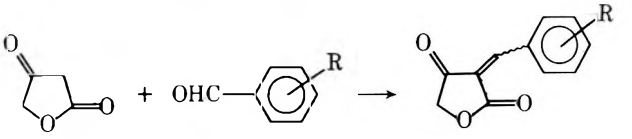
Table I. 3-(Phenylmethylene)-2,4(3*H*,5*H*)-furandiones



Compd	R	Formula	Mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	% yield
2a	2-Chloro	$C_{11}H_7ClO_3$	117–118	59.34	59.20	3.17	3.32	43
2b	4-Chloro	$C_{11}H_7ClO_3$	110–111	59.34	59.15	3.17	3.22	40
2c	2-Nitro	$C_{11}H_7NO_5$	159–160	56.63	56.57	3.03	3.31[b]	25
2d	H	$C_{11}H_8O_3$	154.5–155.5	70.21	70.71	4.25	4.29	30
2e	2-Hydroxy	$C_{11}H_8O_4$	Dec >178	64.70	64.75	3.95	4.21	15
2f	3,4-Methylenedioxy	$C_{12}H_8O_5$	198.5–200	62.07	62.34	3.47	3.31	55
2g	*a*	$C_{13}H_{10}O_3$	204–205	72.89	72.96	4.71	4.86	41
2h	3,4-Dimethoxy	$C_{13}H_{12}O_5$	197–198	62.90	62.61	4.82	4.68	45
2i	4-Dimethylamino	$C_{13}H_{13}NO_3$	223–225	67.52	67.76	5.67	5.87[c]	42
2j	3,4,5-Trimethoxy	$C_{14}H_{14}O_6$	187	60.43	60.56	5.07	5.21	50

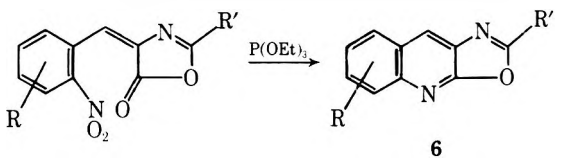
[a] Cinnamaldehyde was used as the reacting aldehyde. [b] Anal. Calcd: N, 6.01. Found: N, 5.91. [c] Anal. Calcd: N, 6.06. Found: N, 6.26.

aldehydes and 1 indicate that, under acid conditions, the aldol condensation does not occur, permitting the self-condensation of the reacting aldehyde exemplified by the formation of the 1,3,5-trioxane when pivalaldehyde is the reacting species. Under basic conditions aliphatic aldehydes react with 1 to form only the bis-condensation product of type **3**. Consequently, a more detailed investigation is presently underway to determine the parameters needed for 1:1 aldol condensation between 1 and aliphatic aldehydes.

^{1}H NMR Spectra of 1 and 2a–j. The ^{1}H NMR spectrum of 1 exhibits peaks in three areas; the peak due to the enolic OH group is extremely broad and not visible. Only the appearance of a HOD peak after exchange of a solution of 1 with D_2O reveals the presence of an enol form. The proton at the vinyl position of the enol form gives rise to a peak at δ 5 and the peak due to the methylene group appears at δ 4.75. The areas covered by the peaks are in a ratio of 1:2, thus indicating the compound to exist completely in the enolic form.

All type 2 compounds show two characteristic singlets between δ 4.7 and 4.85 which are not exchangeable with D_2O. This implies that type 2 compounds are not involved in a keto–enol equilibrium. A likely explanation for these two peaks, attributed to the methylene protons, is to assume that all type 2 compounds occur as two geometric isomers, A (*E* isomer) and B (*Z* isomer). The differences in the chemical shift of their respective methylene protons are thought to be caused by a long-range shielding effect due to the phenyl ring. Examination of Dreiding models points out that, in both isomers, the phenyl ring and the furanone ring are essentially coplanar. Furthermore, the models reveal that in isomer A the phenyl group is closer to the methylene protons than in isomer B. Using isoshielding lines according to Johnson and Bovey[13] the difference in the chemical shifts for these two protons in structures A and B was calculated to be 0.11 ppm, which is in accord with the observed value of 0.1 ppm. Integration of these two methylene peaks attributed to the *Z* and *E* isomers of **2** (specifically shown in the case of **2b**) permits us to estimate the ratio of A and B to be 2:3.

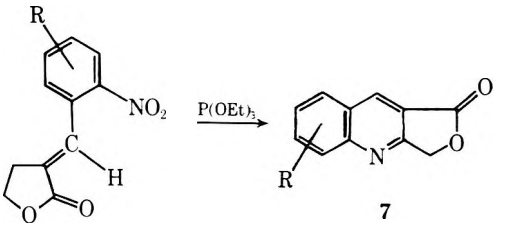
Reactions of 2 with Triethyl Phosphite. It has been shown that 2-nitrobenzylidene azlactones are cyclized under the influence of triethyl phosphite to oxazoloquinolines.[14a]



6

Similarly, α-(2-nitrobenzylidene)-γ-butyrolactones undergo a cyclization where the geometry of the double bond is maintained, and nitrene insertion, followed by oxidative dehydration, occurs to afford a furo[3,4-*b*]quinolin-1(3*H*)-one[8,14b,15] such as **7**.

It was anticipated that, in the case of **2b**, treatment of it with triethyl phosphite might also afford the quinoline derivative **7**.



7

When an isomeric mixture of **2b** was treated with triethyl phosphite, the anticipated reductive cyclization did not take place, but rather a white precipitate was formed instantly. It was shown by elemental analysis and spectroscopic data to have structure **8**. The reaction is general and the isolation of the crystalline oxaphospholenes, **8**, is straightforward since they are insoluble in ether, whereas the starting materials are soluble. Table II summarizes the results.

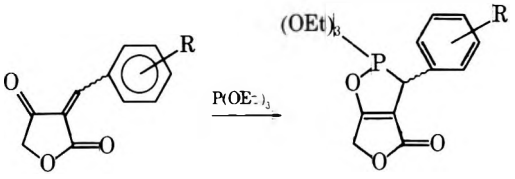
The result of these reactions is reminiscent of the chelatropic cycloaddition of trimethyl phosphites to α,β-unsaturated ketones as reported by Ramirez.[16]

These novel furo[3,4-*d*]-1,2-oxaphosphol-4(6*H*)-ones were characterized by their spectroscopic (IR and NMR) properties. In the ^{1}H NMR, the protons at the 6 position of these furanones **8** exhibit a doublet (J = 4 Hz) which is attributed to long-range three-bond ^{31}P–^{1}H coupling. The pattern for the benzylic proton coupled to phosphorus overlaps the quartet of doublets of the ethyl (CH_2) protons. However, integration of the different regions of the NMR spectrum is in agreement with the proposed structure. The lactone carbonyl group can be easily recognized in the IR spectrum by the peak in the range between 1730 and 1760 cm^{-1}.

Experimental Section

Melting points were determined with a Fischer-Johns melting point apparatus and are uncorrected. Infrared spectra were recorded using a Beckman IR-18A infrared spectrophotometer. Nuclear magnetic resonance spectra were recorded on Varian T-60 spectrometer with tetramethylsilane as internal standard. Mass spectra were obtained on a Perkin-Elmer RMU-7 instrument. Microanalysis were performed by either Chemalytics, Inc., of Tempe, Ariz., or Integral Microanalytical Laboratories, Inc., of Raleigh, N.C.

Table II. 2,2,2-Triethoxy-2,5-dihydro-3-(substituted phenyl)furo[3,4-*d*]-1,2-oxaphosphol-4(6*H*)-ones



2 8

Compd	Registry no.	R	Formula	Mp, °C	C, % Calcd	C, % Found	H, % Calcd	H, % Found	% yield
8a	65276-42-8	4-Chloro	$C_{17}H_{22}ClO_6P$	108–108.5	52.52	52.44	5.70	5.53[a]	40.5
8b	65276-43-9	2-Nitro	$C_{17}H_{22}NO_8P$	138–139	51.13	51.32	5.55	5.65[b]	69
8c	65276-44-0	4-Nitro	$C_{17}H_{22}NO_8P$	123–124	51.13	50.76	5.55	5.34[c]	71
8d	65276-45-1	3,4-Methylenedioxy	$C_{18}H_{23}O_8P$	123	54.27	54.05	5.82	5.75[d]	69
8e	65276-46-2	3,4-Dimethoxy	$C_{19}H_{27}O_8P$	128–129	55.07	54.73	6.57	6.53[e]	68
8f	65276-47-3	3,4,5-Trimethoxy	$C_{20}H_{29}O_9P$	130–132	54.05	53.89	6.58	6.29[f]	22

[a] Anal. Calcd: Cl, 9.12. Found: Cl, 9.61. [b] Anal. Calcd: N, 3.51. Found: N, 3.24. [c] Anal. Calcd: N, 3.51. Found N, 3.19. [d] Anal. Calcd: P, 7.78. Found P, 7.78. [e] Anal. Calcd: P, 7.47. Found P, 7.32. [f] Anal. Calcd: P, 6.97. Found: P, 7.03.

α-Bromotetronic Acid. This compound was prepared by pyrolysis of ethyl α,γ-dibromoacetoacetate according to the procedure of Kumler.[11] The resulting solids were triturated with several portions of benzene to remove colored impurities and dried at room temperature. The slightly tan product was used without further purification: mp 183 °C dec (lit.[11] 183 °C dec). Protected from moisture and light the product could be stored for several months.

Tetronic Acid (1). To 250 mL of methanol was added 34.2 g (0.108 mol) of barium hydroxide octahydrate and 39.0 g (0.217 mol) of α-bromotetronic acid. Only a small residue remained after vigorous stirring. The solution was stirred a few minutes with 0.5 g of decolorizing carbon at room temperature and filtered through kieselguhr. (A large stock solution of barium α-bromotetronate was often made, using proportionally larger quantities, from which aliquots were taken for hydrogenolysis. The remaining solutions was refrigerated and used within a few days.) The solution (ca. 280 mL) was added to a nitrogen-flushed Parr bottle to which had been added an additional 34.2 g of $Ba(OH)_2 \cdot 8H_2O$ followed by 1 g of 5% palladium on carbon. The bottle was flushed with hydrogen, charged to 40 psi, and shaken until additional hydrogen uptake was negligible (ca. 5 h); the theoretical pressure drop was 17.3 psi. If less than 90% of the theoretical hydrogen uptake was observed, additional palladium on carbon was added. The nearly colorless solution was filtered through kieselguhr and the methanol was evaporated at reduced pressure. The resulting aqueous slurry was diluted with water to 200 mL and adjusted carefully to pH 0.5 using concentrated hydrochloric acid (ca. 17 mL) while monitoring with a narrow range pH paper (Fisher, short range No. 1). The solution was extracted with ether, and the ether layer was dried over anhydrous sodium sulfate and concentrated to a small volume. Crystals formed on cooling which were washed with cold ether. A second crop was similarly obtained from the mother liquor and ether washings. Drying was accomplished in a vacuum dessicator over calcium sulfate (Drierite). The yield after ten 100-mL hand extractions was 14 g (65%), mp (slight sinter at 135 °C) 142–144 °C (lit.[6a] sinters at 135, 141 °C). Twenty-four-hour extraction in a liquid–liquid extractor gave 80% yields. The tetronic acid was generally used without further purification; ethyl acetate can be used for additional recrystallization if necessary. The product was stored in a freezer for several months with no apparent deterioration: NMR (Me_2SO-d_6) δ 4.65 (s, 2 H), 4.97 (s, 1 H) [lit.[9] 4.67 (s, 2 H), 4.97 (s, 1 H)].

General Procedure for Preparation of α-(Phenylmethylene)-2,4(3*H*,5*H*)-furandiones. To a 3 equiv excess of the appropriate aldehyde was added 1 equiv of tetronic acid and 1.1 equiv of concentrated hydrochloric acid. The mixture was stirred vigorously until solidification occurred. The solid was then broken up and washed with either hexane or ether (depending on the solubility of the aldehyde in the solvent). The crude condensation product was then recrystallized from abolute ethanol or ethyl acetate. Analogously, the following compounds were prepared.

2a: IR (KBr) 1765, 1710, and 1615 cm^{-1}; NMR (Me_2SO-d_6) δ 4.7 and 4.8 (2 s, 2 H), 7.65 (m, 3 H), 8.15 (d, 1 H), 8.63 (m, 1 H); mass spectra M^+ 222 (20), M + 2 224 (8).

2b: IR (KBr) 1760, 1710 cm^{-1}; NMR (Me_2SO-d_6) δ 4.72 and 4.85 (2 s, 2 H), 7.17 (d, 2 H, J = 8 Hz), 7.5 (s, 1 H), 8.2 (d, 2 H, J = 8 Hz); mass spectra M^+ 222 (42.6), M + 1 223 (6.7), M + 2 224 (16.7).

2c: IR (KBr) 1760, 1720 cm^{-1}; NMR ($CDCl_3$) δ 4.67 and 4.8 (2 s, 2 H), 7.8 and 8.33 (m, 5 H); mass spectra M^+ 233.

2d: IR (KBr) 1760, 1700 cm^{-1}; UV (EtOH) 336, 253 nm (sh); UV (EtOH + HCl) 336, 231 nm; NMR ($CDCl_3$) 4.65 and 4.78 (2 s, 2 H), 7.62 (m, 3 H), 8.05 (s, 1 H), 8.45 (M= 2 H); mass spectra M^+ 188 (63.34), M + 1 189 (8.41).

2e: IR (KBr) 3310, 1740, 1690 cm^{-1}; NMR (Me_2SO-d_6) δ 4.67 and 4.78 (2 s, 2 H), 6.47 (s, 1 H, exchangeable with D_2O), 6.8–7 (m, 3 H), 8.35 (d, 1 H, J = 2.5 Hz), 10.78 (dd, 1 H, J = 8, 2.5 Hz); mass spectra M^+ 204.

2f: IR (KBr) 1740, 1685, cm^{-1}; UV (EtOH) 402, 282 (sh), 252 nm; NMR (Me_2SO-d_6) δ 4.67 and 4.78 (2 s, 2 H), 6.20 (s, 2 H), 7.13 (d, 1 H, J = 8 Hz), 7.83 (t, 1 H, $J \sim 1.4$ Hz), 8.03 (s, 1 H, J = 8, 1.4 Hz), 8.42 (t, 1 H, $J \sim 1.4$ Hz); mass spectra M^+ 232.

2g: IR (KBr) 1750, 1685 cm^{-1}; NMR (Me_2SO-d_6) δ 4.6 and 4.65 (2 s, 2 H), 7.2–8.2 (m, 8 H); mass spectra M^+· 214 (100), M + 1 215 (14.7).

2h: IR (KBr) 1770, 1705 cm^{-1}; NMR (Me_2SO-d_6) δ 3.90 and 3.97 (2 s, 6 H), 4.7 and 4.8 (2 s, 2 H), 7.1 (d, 1 H, J = 8 Hz), 7.57 (s, 1 H), 8.15 (d, 1 H, J = 8 Hz), 8.77 (s, 1 H); mass spectra M^+ 248 (100), M + 1 249 (13.4).

2i: IR 1725, 1670 cm^{-1}; NMR (Me_2SO-d_6) δ 3.20 (s, 6 H), 4.7 and 4.8 (2 s, 2 H), 7.13 (d, 2 H, J = 9 Hz), 7.85 (s, 1 H), 7.92 (d, 2 H, J = 9 Hz); mass spectra M^+ 231.

2j: IR (KBr) 1780, 1695 cm^{-1}; NMR (Me_2SO-d_6) δ 3.81 and 3.83 (2 s, 9 H), 4.65 and 4.76 (2 s, 2 H), 7.83 (s, 1 H), 8.06 (s, 2 H); mass spectra M^+· 278 (100), M + 1 279 (15.8).

General Procedure for Reactions of 3-(Phenylmethylene)-2,4(3*H*,5*H*)-furandiones with Triethyl Phosphite to Give 2,2,2-Triethoxy-2,5-dihydro-3-(substituted phenyl)furo[3,4-*d*]-1,2-oxaphosphol-4(6*H*)-ones. To a fivefold excess of triethyl phosphite was added the furandione. The mixture was stirred vigorously at room temperature. Formation of a white crystalline product occurred within 5 min in most cases. The product was filtered and washed with ether to yield analytically pure 2,2,2-triethoxy-2,3-dihydro-3-(substituted phenyl)furo[3,4-*d*]-1,2-oxaphosphol-4(6*H*)-one (8). Analogously, the following compounds were prepared.

8a: IR (KBr) 1740 cm^{-1}; NMR ($CDCl_3$) δ 1–1.65 (m, 9 H), 3.8–4.6 (m, 7 H), 4.7–4.8 (d, 2 H, $J_{^{31}P-^1H}$ = 4 Hz), 7.2–7.7 (m, 4 H); mass spectra M^+ 388 (25.75), M + 1 389 (5.37).

8b: IR (KBr) 1765 cm^{-1}; NMR ($CDCl_3$) δ 1.28 (m, 9 H), 4.08 (m, 7 H), 4.75 (d, 2 H, $J_{^{31}P-^1H}$ = 3 Hz), 5.23 (d, 1 H, J = 27 Hz), 7.2–8.2 (m, 4 H); mass spectra M^+ 399.

8c: IR (KBr) 1760 cm^{-1}; NMR ($CDCl_3$) δ 1–1.7 (m, 9 H), 3.9–4.8 (pentet and singlet, 7 H), 4.9 (d, 2 H, $J_{^{31}P-^1H}$ = 4 Hz), 7.8–8.2 (AB q, 4 H, J = 8, 4 Hz); mass spectra M^+ 399, M + 1 400.

8d: IR (KBr) 1740 cm^{-1}; NMR ($CDCl_3$) δ 1.33 (m, 9 H), 4.13 (m, 7 H), 4.75 (d, 2 H, $J_{^{31}P-^1H}$ = 4 Hz), 5.92 (s, 2 H), 6.55–7.25 (m, 3 H); mass spectra M^+ 398.

8e: IR (KBr) 1750 cm^{-1}; NMR ($CDCl_3$) δ 1.1–1.7 (m, 9 H), 3.8–4.6 (m, 13 H), 4.8 (d, 2 H, $J_{^{31}P-^1H}$ = 4 Hz), 6.9–7.5 (m, 3 H); mass spectra M^+ 414 (36.6), M + 1 415 (7.4).

8f: IR (KBr) 1730 cm^{-1}; NMR ($CDCl_3$) δ 1.1–1.7 (m, 9 H), 3.8–4.6 (m, 16 H), 4.8 (d, 2 H, $J_{^{31}P-^1H}$ = 4 Hz), 6.90 (d, 2 H, $J \cong 1$ Hz); mass spectra M^+ 444 (44.4), M + 1 445 (11.1).

Base-Catalyzed Reaction of 1 with 3,4-Dimethoxybenzaldehyde. To 0.5 g of 1 and 4.15 g of 3,4-dimethoxybenzaldehyde in 250 mL of absolute ethanol was added 10 drops of pyridine. The solution was refluxed for 12 h and cooled, and the solvent was removed in

vacuo. The residue was washed with ether and crystallized from 2-propanol. The product was identical with the acid-catalyzed product **2b**: yield 60%.

3,3'-(1,1'-Octanediylidene)bis[4-hydroxy-2(5*H*)-furanone]. Following the same procedure for base catalysis, 1-octanal was reacted with tetronic acid. The white product was recrystallized at 0 °C from (1:150) ethyl acetate–cyclohexane: mp 198 °C; NMR ($CDCl_3$) δ 0.5–2.2 (m, 15 H), 3.96 (t, 1 H, J = 8 Hz), 4.72 (s, 4 H), 10.66 (s, 2 H, exchangeable with D_2O). Anal. Calcd for $C_{16}H_{22}O_6$: C, 61.92; H, 7.15. Found: C, 61.71; H, 7.09.

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Registry No.—**1**, 4971-56-6; (*E*)-**2a**, 65276-56-4; (*Z*)-**2a**, 65276-57-5; (*E*)-**2b**, 65276-58-6; (*Z*)-**2b**, 65276-59-7; (*E*)-**2c**, 65276-60-0; (*Z*)-**2c**, 65276-61-1; (*E*)-**2d**, 65276-62-2; (*Z*)-**2d**, 65276-48-4; (*E*)-**2e**, 65276-49-5; (*Z*)-**2e**, 65276-50-8; (*E*)-**2f**, 65276-51-9; (*Z*)-**2f**, 65276-52-0; (*E*)-**2g**, 65276-53-1; (*Z*)-**2g**, 65276-54-2; (*E*)-**2h**, 65276-55-3; (*Z*)-**2h**, 65276-37-1; (*E*)-**2i**, 65276-38-2; (*Z*)-**2i**, 65276-39-3; (*E*)-**2j**, 65276-40-6; (*Z*)-**2j**, 65276-41-7; α-bromotetronic acid, 1192-50-3; o-chlorobenzaldehyde, 89-98-5; *p*-chlorobenzaldehyde, 104-88-1; o-nitrobenzaldehyde, 552-89-6; benzaldehyde, 100-52-7; o-hydroxybenzaldehyde, 90-02-8; 3,4-methylenedioxybenzaldehyde, 120-57-0; cinnamaldehyde, 104-55-2; 3,4-dimethoxybenzaldehyde, 120-14-9; 4-dimethylaminobenzaldehyde, 100-10-7; 3,4,5-trimethoxybenzaldehyde, 86-81-7; triethyl phosphate, 122-52-1; 1-octanal, 124-13-0; 3,3'-(1,1'-octanediylidene)bis[4-hydroxy-2(5*H*)-furanone], 65276-34-8.

References and Notes

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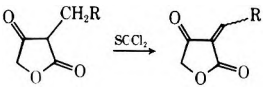
(10) Certain compounds of type **2** were recently obtained by a sequence which does not proceed via **1**. Substituted 3-benzyl-β-tetronic acids were dehydrated by thionyl chloride to give type **2** compounds. However, since the yields of this reaction were less than acceptable for a good synthetic procedure and the choice of substituents is severely limited, this pathway does not represent a generally applicable alternative pathway for the preparation of the desired furandiones **2**. See ref 6b.



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Macrocyclic Ureas as Masked Isocyanates

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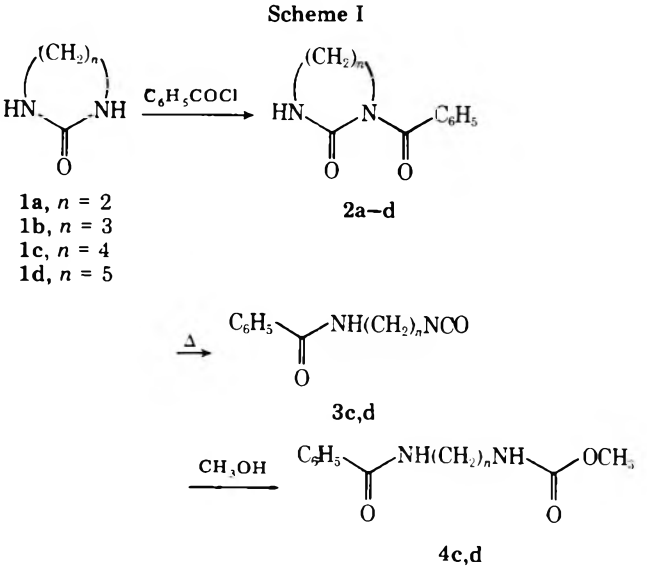
Macrocyclic *N*-aroylureas, synthesized by aroylation of macrocyclic ureas with mono- and dicarboxylic acid chlorides, undergo a facile thermal ring-opening reaction to give *N*-aroylamidoalkylene isocyanates **3**. Treatment of the crude isocyanates with methanol yields the corresponding methyl carbamates **4**.

The blocking of isocyanate groups has been attempted previously in order to formulate stable one-component polyurethane systems.[1] Heating of the blocked isocyanates generate the free isocyanates with release of the blocking agent. The ideal blocking agent should become part of the polymer backbone after release, thereby eliminating the need for well-ventilated working areas. This paper deals with the design of blocked isocyanates in which the blocking agents are incorporated into the polyurethane backbone.

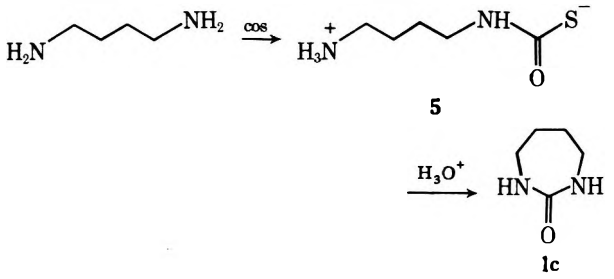
The key to the design of functional blocking agents was our observation that certain 1,3-disubstituted ureas undergo facile thermal dissociation to produce isocyanate and an amine derivative.[2] If the urea group is part of a cyclic system, both fragments could conceivably be incorporated into a growing polymer chain. In order to test this hypothesis, the *N*-benzoylureas **2** were synthesized as model compounds. While the five- and six-membered ring ureas **2a** and **2b** (n = 2 and 3) did not appreciably dissociate upon heating in an inert high-boiling solvent, the seven- and eight-membered ring ureas **2c** and **2d** undergo ring opening on refluxing in o-dichloroben-

Scheme I



zene to give the corresponding novel benzoylamidoalkyl isocyanates **3**, as evidenced by infrared spectroscopy (NCO at 2270 cm^{-1}) and conversion into methyl ω-benzoylamidoalkyl carbamates **4c** and **4d** on heating with excess methanol (Scheme I). Heating of **1c** and **1d** with excess methanol in benzene did not yield the corresponding carbamates **4c** or **4d**.

The required seven- and eight-membered ring macrocyclic ureas were synthesized by novel procedures. Reaction of tetramethylenediamine with carbonyl sulfide gives rise to the formation of the inner salt **5**, which was treated without isolation with concentrated hydrochloric acid to give perhydro-1,3-diazepin-2-one (**1c**).

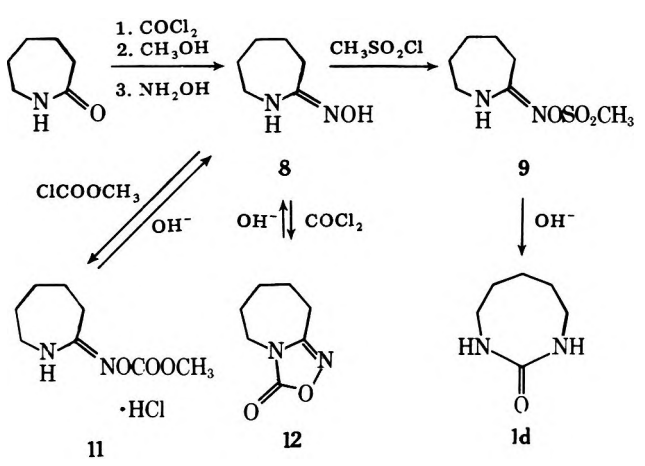


The synthesis of the eight-membered ring urea, perhydro-1,3-diazocin-2-one (**1d**), starting with caprolactam required several steps (see Scheme II) but gave satisfactory yields in all of them. Thus, low-temperature phosgenation of caprolactam produces 3,4,5,6-tetrahydro-7-chloro-2*H*-azepine[3] which on treatment with methanol gives 3,4,5,6-tetrahydro-7-methoxy-2*H*-azepine (**7**) in 65–70% yield. The lactam ether **7** converts with hydroxylamine to the amide oxime **8** which is easily converted to the mesylate **9**. Lossen rearrangement of **9** in base gives the desired cyclic urea **10** in nearly quantitative yield. The last step was found to be superior to all other known procedures for the preparation of pentamethyleneurea from **8**,[4] the tosylate of **8**,[5] or other precursors.[6]

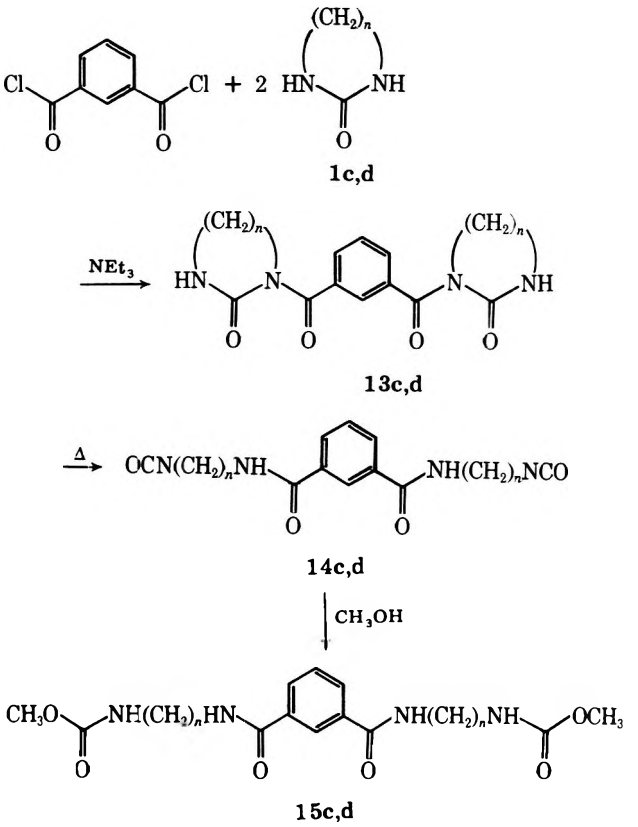
Attempts to prepare the urea **1d** from other O-acylated derivatives of **8** via Lossen degradation failed: Methyl chloroformate and phosgene treatment of **8** lead to **11** and **12**, respectively, but both compounds were hydrolyzed back to the amide oxime **8** on treatment with dilute aqueous base.

As a model for a polymer system, isophthaloyl chloride was reacted with 2 equiv of **1c** or **1d** to give the bisurea derivatives **13c** and **13d**. Heating of **13** in *o*-dichlorobenzene produces the diisocyanates **14c** and **14d**, as evidenced by infrared spectroscopy and trapping with methanol to give the biscarbamates **15c** and **15d**. Heating of **13c** or **13d** in methanol did not produce **15**, indicating that this difunctional monomer is stable in alcohol (Scheme III).

Scheme II



Scheme III



The formation of polyurethanes from **13** and suitable polyols will be the subject of a forthcoming paper.

Experimental Section[7]

Perhydro-1,3-diazepin-2-one (Tetramethyleneurea) (1c). To 88 g (1 mol) of tetramethylenediamine in a mixture of 250 mL of ethanol and 250 mL of water, 62.5 g (1.04 mol) of carbonyl sulfide gas was added with stirring over a period of 80 min. The temperature rose from 32 to 45 °C during the addition and the salt formed in the reaction precipitated after the addition was completed. The reaction mixture was heated to 60 °C and 8 mL of concentrated HCl was added dropwise over a period of 3 min. The reaction mixture was then heated at 73–83 °C for 3 h, during which time hydrogen sulfide evolved and the precipitated salts went into solution. The solution was cooled and extracted with hot chloroform using a liquid–liquid continuous extractor. Evaporation of the chloroform yielded 77.1 g of the crude urea, mp 157–164 °C. Sublimation at 150–190 °C (0.1 mm) afforded 67 g (59%) of **1c**, mp 166–170 °C (lit.[4] mp 172 °C).

1-Benzoylperhydro-1,3-diazepin-2-one (1-Benzoyltetramethyleneurea) (2c). To a mixture of 5.7 g (0.05 mol) of tetramethyleneurea **1c** and 7.6 g (0.075 mol) of triethylamine in 200 mL of ethylene dichloride, 7 g (0.05 mol) of benzoyl chloride was added dropwise over a period of 10 min at 82–85 °C with stirring. The reaction mixture was refluxed for 90 min. Cooling to room temperature and filtration yielded 11.3 g of a mixture of amine hydrochloride salts and benzoyltetramethyleneurea. Trituration of the 11.3 g in 100 mL of water and filtration afforded 5.85 g of benzoyltetramethyleneurea, mp 207–208 °C. Ethylene dichloride was removed from the first filtrate by evaporation, and the 7.25-g residue obtained was triturated in water. Filtration afforded an additional 2.7 g of product, mp 182–192 °C. The total yield was 8.55 g (78%).

Anal. Calcd for $C_{12}H_{14}N_2O_2$: C, 66.03; H, 6.46; N, 12.83. Found: C, 65.98; H, 6.29; N, 13.02.

Methyl 4-Benzoylamidobutylcarbamate (4c). A solution of 0.5 g (0.0023 mol) of *N*-benzoyltetramethyleneurea (**2c**) in 20 mL of *o*-dichlorobenzene was refluxed for 2 h and, after cooling to 65 °C, 1.0 g of methanol was added. Short heating converted all of the generated isocyanate into the carbamate as evidenced by infrared spectroscopy. On cooling, 0.35 g (61%) of methyl 4-benzoylamidobutylcarbamate (**4c**), mp 126–127 °C, was obtained.

Anal. Calcd for $C_{13}H_{18}N_2O_3$: C, 62.38; H, 7.24; N, 11.19. Found: C, 62.18; H, 6.97; N, 10.91.

3,4,5,6-Tetrahydro-7-methoxy-2*H*-azepine (7) was obtained

in 65–70% yield on treating a suspension of the hydrochloride of 3,4,5,6-tetrahydro-7-chloro-2*H*-azepine[3] in carbon tetrachloride with excess methanol. Removal of solvent and excess methanol in vacuo leaves a thick oil, which is treated with a saturated Na_2CO_3 solution. Extraction of the aqueous phase with methylene chloride and vacuum distillation of the liquid residue, left after evaporating the solvent, gave **7**, bp 60–61 °C (20 mm) (lit.[8] bp 65–67 °C at 24 mm).

Hexahydro-2*H*-azepin-2-one oxime (ε-Caprolactam Oxime) (8) was prepared in nearly quantitative yield by following a literature procedure and reacting equivalent amounts of **7** and hydroxylamine hydrochloride in refluxing methanol in the presence of excess $NaHCO_3$ as hydrogen chloride scavanger; mp 169–170 °C (lit.[4] mp 166 °C).

Hexahydro-2*H*-azepin-2-one (*O*-Methylsulfonyl)oxime (9). To an ice-cooled suspension of 5.20 g (0.04 mol) of oxime **8** in 30 mL of pyridine was added dropwise 4.5 g (0.04 mol) of methanesulfonyl chloride. A light-tan solution was formed from which colorless crystals of pyridinium chloride precipitated toward the end of the addition. After additional cooling for 2 h, most of the solvent was removed in vacuo, and the remaining oily residue was triturated with 20–30 mL of water, causing separation of colorless crystals. Filtration and ice-water washings left 7.6 g (90%) of **9**, mp 89–90 °C.

Anal. Calcd for $C_7H_{14}N_2O_3S$: C, 40.77; H, 6.84; N, 13.59. Found: C, 40.92; H, 7.04; N, 13.70.

Perhydro-1,3-diazocin-2-one (1d). A suspension of 7.6 g (0.037 mol) of mesylate **9** in a sodium hydroxide solution (2.5 g of NaOH in 50 mL of water) was stirred at room temperature for 2 h. The starting material dissolves slowly, and toward the end of the reaction colorless crystals of the urea started to precipitate. The newly formed suspension was transferred to a liquid–liquid extractor and extracted with refluxing chloroform for 2 h. The dried extract was evaporated to dryness, leaving colorless crystals of **1d**: 4.5 g (95%); mp 240–245 °C; identical in IR comparison with an authentic sample.[4]

Hexahydro-2*H*-azepin-2-one (*O*-Methoxycarbonyl)oxime Hydrochloride (11). Heating a suspension of 2.6 g (0.02 mol) of oxime **8** in 20 mL of chloroform with 4.0 g of methyl chloroformate for 4 h converted the starting material into a voluminous precipitate. Filtration and washing with chloroform leaves 3.30 g (75%) of **11**, mp 158–160 °C, with loss of hydrogen chloride.

Anal. Calcd for $C_8H_{15}ClN_2O_3$:[9] C, 43.15; H, 6.79; N, 12.58. Found: C, 42.38; H, 6.88; N, 12.29.

Treatment of **11** with NaOH–H_2O as described for the conversion of **9** into **10** resulted in the recovery of amide oxime **8**, as evidenced by IR comparison with authentic material.

3a,4,5,6,7,8-Hexahydro-3*H*-2,1,3a-oxidazolo[3,4-*a*]azepin-3-one (12). Solid amide oxime **8** (12.8 g, 0.1 mol) was added in small portions to a cold solution of 30 g (0.3 mol) of phosgene in 100 mL of benzene. The obtained suspension was heated to reflux for 3 h, during which time the starting material dissolved. Cooling of the obtained solution and concentrating in vacuo gave an amber oil, which solidifed on standing. Treatment with water and filtration afforded 11.8 g (76%) of **12**, mp (from H_2O) 40–41 °C; colorless needles; IR (KBr) 1765 cm^{-1} C=O).

Anal. Calcd for $C_7H_{10}N_2O_2$: C, 54.53; H, 6.54; N, 18.17. Found: C, 54.46; H, 6.38; N, 18.11; mol wt 146 (vapor pressure osmometric in $CHCl_3$).

Treatment of **12** with concentrated (50%) or diluted sodium hydroxide solution yielded only amide oxime **8** and no urea **10**.

1-Benzoylperhydro-1,3-diazocin-2-one (*N*-Benzoylpentamethyleneurea) (2d). To 2.56 g (0.02 mol) of pentamethyleneurea and 3.03 g (0.03 mol) of triethylamine in 100 mL of ethylene dichloride at reflux, 2.81 g (0.02 mol) of benzoyl chloride was added dropwise with stirring. Cooling and filtration afforded 1.85 g of triethylamine hydrochloride. The solvent was removed from the filtrate by evaporation, affording a 7.1-g residue. The residue was triturated with 200 mL of ethyl acetate and filtered, yielding 0.8 g of a mixture of amine hydrochloride and pentamethyleneurea. Evaporation of the filtrate yielded 4.3 g (92%) of *N*-benzoylpentamethyleneurea, mp 150–152 °C.

Anal. Calcd for $C_{13}H_{16}N_2O_2$: C, 67.22; H, 6.96, N, 12.06. Found: C, 67.45; H, 7.02, N, 12.21.

Methyl 5-Benzoylamidopentylcarbamate (4d). A solution of 0.5 g (0.0021 mol) of *N*-benzoylpentamethyleneurea (**2d**) in 20 mL of o-dichlorobenzene was refluxed for 4 h. After cooling to 85 °C, a total of 1.0 g of methanol was added and the solution was refluxed for another hour. Evaporation of the solvent and excess methanol and trituration of the residue with water yielded 0.3 g (52%) of **4d**, mp 75–78 °C.

Anal. Calcd for $C_{14}H_{20}N_2O_3$: C, 63.61; H, 7.62; N, 10.59. Found: C, 63.58; H, 7.52; N, 10.53.

1,1′-Isophthaloylbis(perhydro-1,3-diazepin-2-one) (13c). To 22.8 g (0.2 mol) of tetramethyleneurea (**1c**) in 400 mL of ethylene dichloride, 20.3 g (0.1 mol) of isophthaloyl chloride in 150 mL of ethylene dichloride was added dropwise with stirring over a period of 33 min. The temperature rose from 21 to 26 °C and a precipitate formed during the addition. The reaction mixture was stirred at room temperature for 1 h after which 22.2 g (0.22 mol) of triethylamine in 30 mL of ethylene dichloride was added dropwise with stirring over a period of 35 min. The temperature rose from 24 to 34 °C during the addition. The reaction mixture was heated to 51 °C and then cooled to below 10 °C. Filtration yielded 46.45 g of a mixture of triethylamine hydrochloride and product. Washing in water and filtration afforded 22.8 g (64%) of **13c**, mp 238–240 °C. An additional 1.3 g (3.6%) of **13c** was recovered from the ethylene dichloride filtrate.

Anal. Calcd for $C_{18}H_{22}N_4O_4$: C, 60.32; H, 6.19; N, 15.63. Found: C, 60.29; H, 6.21; N, 15.53.

Bis[(4-Methoxycarbamoyl)butyl]isophthalamide (15c). A solution of 2.5 g (7.0 mmol) of **13c** in 50 mL of *o*-dichlorobenzene was refluxed for 4.5 h. The solution was cooled to room temperature and 4 mL of methanol was added. Heating at 80–85 °C converted all the generated isocyanate into the carbamate, as evidenced by infrared spectroscopy. The product precipitated on cooling and was separated from the solvent by filtration. Trituration with chloroform and filtration yielded 1.2 g (42%) of **15c**, mp 179–180 °C (water).

Anal. Calcd for $C_{20}H_{30}N_4O_6$: C, 56.86; H, 7.16; N, 13.26. Found: C, 56.80; H, 7.40; N, 13.15.

1,1′-Isophthaloylbis(perhydro-1,3-diazocin-2-one) (13d). To a suspension of 25.6 g (0.2 mol) of pentamethyleneurea (**1d**) in 200 mL of 1,2-dichloroethane is added dropwise with stirring a solution of 20.3 g (0.1 mol) of isophthaloyl chloride in 100 mL 1,2-dichloroethane. The starting material is slowly dissolved, but a new precipitate is formed at the same time. The resulting thick mixture is kept for 18 h at room temperature after which 20.0 g (0.2 mol) of triethylamine is added gradually and the temperature is raised to ca. 70 °C. Most of the precipitate dissolves within 2–3 h, leaving only triethylamine hydrochloride undissolved. Filtration of the hot solution affords 18.40 g of triethylamine hydrochloride, and evaporation of the filtrate yields a colorless residue which after stirring with 200 mL of water for 30 min, filtration, and water washing leaves 31.40 g (81%) of **13d**, mp 183–184 °C; further purification by recrystallization from isopropyl alcohol.

Anal. Calcd for $C_{20}H_{26}N_4O_4$: C, 62.16; H, 6.78; N, 14.50. Found: C, 62.10, H, 6.93; N, 14.42.

Bis[(5-methoxycarbamoyl)pentyl]isophthalamide (15d). A solution of 1.0 g (1.03 mmol) of crude **13d** in 5 mL of *o*-dichlorobenzene was refluxed for 1.5 h. After cooling to room temperature, 10 mL of methanol was added and the reaction mixture was heated at 80–90 °C for 1 h. Complete conversion of the generated isocyanate to the carbamate was evidenced by infrared spectroscopy (disappearance of NCO). Solvent and excess methanol were removed by vacuum distillation; the oily residue was taken up in methanol. Diluting with water caused slow precipitation of colorless crystals which were filtered off after standing for 24 h: 0.6 g (52%) of **15d**, mp 144–145 °C (2-propanol–water).

Anal. Calcd for $C_{22}H_{34}N_4O_6$: C, 58.65; H, 7.61; N, 12.43. Found: C, 58.51; H, 7.75; N, 12.38.

Registry No.—**1**, 19055-93-7; **1d**, 5700-13-0; **2c**, 65252-81-5; **2d**, 54236-70-3; **4c**, 65252-82-6; **4d**, 65252-83-7; **8**, 19214-08-5; **9**, 65252-84-8; **11**, 65252-85-9; **12**, 65252-86-0; **13c**, 65252-87-1; **13d**, 65252-88-2; **15c**, 65252-89-3; 15d, 65252-90-6; benzoyl chloride, 98-88-4; isophthaloyl chloride, 99-63-8.

References and Notes

(1) For examples, see E. Müller, *Methoden Org. Chem. (Houben-Weyl), 4th Ed.*, **14(2)**, 61 (1963).
(2) H. Ulrich and A. A. R. Sayigh, *Angew. Chem., Int. Ed. Engl.*, **5**, 704, 724 (1966).
(3) Stamicarbon N. V., Belgian Patent 609 822 (1962); *Chem. Abstr.* **57**, 16505 (1962); British Patent 1 007 413 (1965); *Chem. Abstr.* **64**, 18158 (1966).
(4) H. Behringer and H. Meier, *Annalen*, **607**, 67 (1957).
(5) A. Le Berre, C. Renault, and P. Giraudeau, *Bull. Soc. Chim. Fr.*, 2345 (1971).
(6) S. Ozaki, T. Mukaiyama, and K. Uno, *J. Am. Chem. Soc.*, **79**, 4358 (1957).
(7) Melting points are uncorrected; analyses were by Galbraith Laboratories, Knoxville, Tenn.; IR spectra were determined with a Perkin-Elmer 267 and a Beckman Acculab 4 spectrophotometer.
(8) R. E. Benson and T. L. Cairns, *J. Am. Chem. Soc.*, **70**, 2115 (1948).
(9) No satisfactory C value was obtained from several analyses; this might be due to contamination by HCl or partial decomposition of **11**.

2',3',5'-Tri-O-benzoyl[4-^{13}C]uridine. An Efficient, Regiospecific Synthesis of the Pyrimidine Ring[1]

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A synthesis of 2',3',5'-tri-O-benzoyl[4-^{13}C]uridine is described in which sodium [1-^{13}C]acetate is converted to the protected nucleoside in ten steps with an overall yield of 81%. The route is general and permits the regiospecific introduction of carbon or nitrogen into one or more positions in the pyrimidine ring.

Uracil and uridine are commonly used intermediates in chemical and biological syntheses. Although short, moderate-yield routes to these compounds are available,[3-8] there are no general high-yield, regiospecific approaches suitable for introducing isotopic labels into the pyrimidine ring. For example, the traditional one-step synthesis of uracil by the acid-catalyzed condensation of malic acid and urea gives an acceptable yield of ~60%,[5] but only permits C(2) to be conveniently labeled regiospecifically from commercially available, isotopically enriched material.[9] Longer, regiospecific routes such as the procedure developed by Shaw and coworkers[10] for building the pyrimidine ring onto the nitrogen atom of the amino sugar[11] or the stepwise construction of uracil from acetic acid suffer from several steps with unacceptably low yields. After surveying the literature, we decided that the pyrimidine ring could best be constructed via a condensation of potassium cyanate and β-alanine,[12] especially if the yields for the reduction of cyanoacetic acid (**3**) to β-alanine (**4**)[3,13,14] and conversion of dihydrouracil (**5**) to uracil (**8**)[3,7,15] could be improved, since each of the ring atoms in the base can be introduced unambigously. This has been accomplished, and we now report a ten-step synthesis of uridine tribenzoate from acetic acid which permits the atoms in the pyrimidine ring to be labeled selectively and proceeds in an overall yield of 81%.

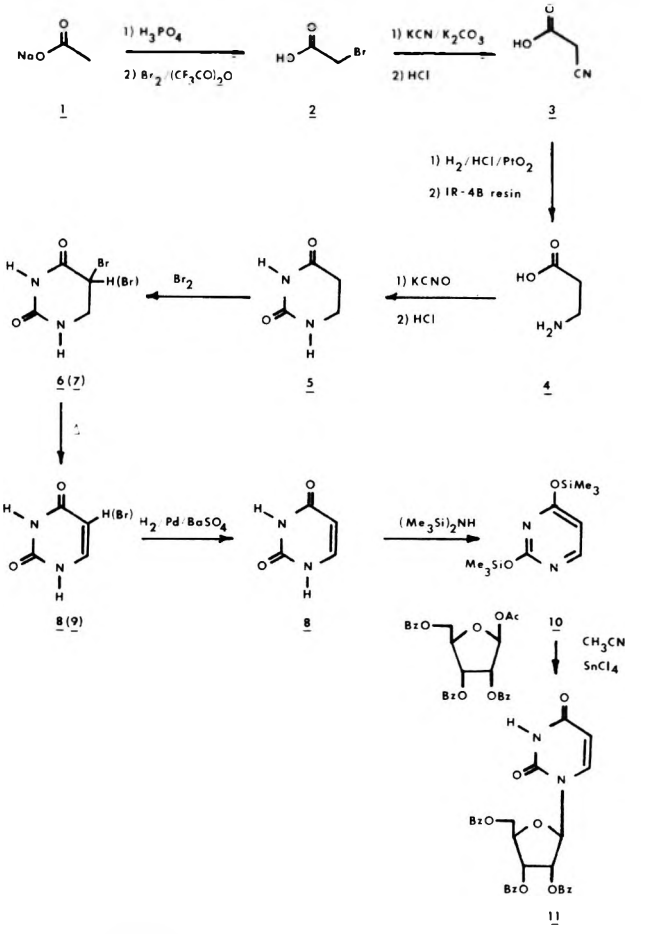
Results and Discussion

Synthesis. In selecting a synthetic route to 2',3',5'-tri-O-benzoyl[4-^{13}C]uridine, we decided to use the sequence of reactions shown in Scheme I because of its versatility for labeling the carbons and nitrogens in the pyrimidine ring regiospecifically. C(4) and C(5) in the uracil moiety are derived from C(1) and C(2) in acetic acid, C(6) and N(1) from potassium cyanide, and C(2) and N(3) from potassium cyanate. The three building blocks are simple compounds and are available commercially with ^{13}C and ^{15}N in any position.

Sodium [1-^{13}C]acetate was selected as the starting material because the free acid is more expensive than its sodium salt. Although generation of acetic acid by treatment of sodium acetate with phosphoric acid[16] gave material containing a small amount of water, the "wet" acetic acid could be used in the bromination step to give [1-^{13}C]bromoacetic acid (**2**) in an overall yield of 95%. In contrast to the recent report by Climie and Evans,[17] we found that the bromination proceeded smoothly in trifluoroacetic anhydride with a catalytic amount of phosphorus tribromide. The conversion of **2** to cyanoacetic acid (**3**) was quantitative.

Several procedures have been used to reduce cyanoacetic acid (**3**) to β-alanine (**4**), including reductions with Raney nickel[7,13,14,18] and palladium,[3] but the yields were unacceptable for our purposes. Previous workers[3,18] used large ratios of catalyst to cyanoacetic acid in the reduction; however, in our hands **3** was not completely consumed in the presence of palladium after 7 days at 50 psi, even when additional "catalyst" was added periodically. Alternatively we found that the nitrile was cleanly reduced to the desired amino acid in 16 h at 50 psi with Adam's catalyst. By carrying out the reduction in the presence of hydrochloric acid, it was possible to suppress the side reactions which are common during reduction of cyanides to primary amines[19] and to obtain a quantitative yield of β-alanine. Conversion of β-alanine to dihydrouracil proceeded smoothly, according to the procedure developed by Lengfield and Stieglitz.[12]

Scheme I. Synthesis of 2',3',5'-Tri-O-benzoyl[4-^{13}C]uridine



The bromination–dehydrobromination sequence reported by Gabriel[15] appeared to be a logical procedure for introducing the C(4)–C(5) double bond. However, we found that it was impossible to carry out the bromination of dihydrouracil (**5**) under conditions where **5** was completely consumed without formation of at least 10% of the dibromo derivative **7**.[20] This problem was solved by deliberately overbrominating **5** and carrying out the thermal elimination of hydrogen bromide on **6** and **7**. The resulting mixture of **8** and **9** was then treated with hydrogen in the presence of palladium on barium sulfate.[21] Under these conditions, 5-bromouracil (**9**) was smoothly converted to uracil (**8**), which was resistant to hydrogenation. In this way, dehydrogenation of dihydrouracil was carried out

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Table I

Compd[f]	Assignment	Chemical shifts, ppm[c] δ ^{1}H	Chemical shifts, ppm[c] δ ^{13}C	Coupling constants, Hz[d] J_{HH}	$^2J_{^{13}CCH}$	$^3J_{^{13}CCCH}$	$^1J_{^{13}CC}$
[1-^{13}C]Bromoacetic acid[a] (2)	$-CH_2-$	3.90 (d)	27.83 (d)		4.6		62.4
	$-^{13}CO_2H$		168.06				
[1-^{13}C]Cyanoacetic acid[a] (3)	$-CH_2$	3.80 (d)	24.50 (d)		8.0		57.6
	$-^{13}CO_2H$		165.26				
[1-^{13}C]-3-Aminopropionic acid[a] (4)	$-^{13}CO_2H$		175.85				
	C(2)	2.60 (d of t)	32.94 (d)	6.5	5.1	6.3	50.5
	C(3)	3.21 (d of t)	35.93				
[4-^{13}C]-5,6-Dihydrouracil[a] (5)	N(1)	7.40 (br s)		2.6 ($J_{1,6}$)			
	C(2)		173.22				
	N(3)	9.83 (br s)					
	^{13}C(4)		170.87				
	C(5)	2.43 (d of t)	30.38 (d)	6.7	6.3	6.6	48.0
	C(6)	3.21 (d of t)	35.32	($J_{5,6}$)			
[4-^{13}C]Uracil[a] (8)	N(1), N(3)	10.90 (br s)					
	C(2)		151.43				
	^{13}C(4)		164.25				
	C(5)	5.46 (d of d)	100.15 (d)	7.6	1.9	10.6	65.1
	C(6)	7.33 (d of d)	142.09				
2′,3′,5′-Tri-*O*-benzoyl[4-^{13}C]-uridine[b,e] (11)	C(2)		150.07				
	N(3)	9.13					
	^{13}C(4)		162.49				
	C(5)	5.57 (d of d)	103.39 (d)	8.1	1.0	10.8	65.9
	C(6)	7.73 (d of d)	139.60				

[a] Me_2SO-d_6. [b] $CDCl_3$. [c] Shifts relative to Me_4Si, letters in brackets refer to coupling patterns observed. [d] Coupling values are estimated to be accurate within 0.2 Hz. [e] The rest of the ^{1}H and ^{13}C NMR spectra for the sugar moiety are as follows: ^{1}H NMR 4.70 (3, m, C(5′) and C(4′) protons), 5.73 (2, m, C(2′) and C(3′) protons, $J_{1'2'}$ = 5.3 Hz), 6.20 (1, d, C(1′), $J_{1'2'}$ = 5.3 Hz), 7.20–7.53 (9, m, *m*- and *p*-benzoate protons), 7.77–8.07 (6, m, *o*-benzoate protons), 9.07 (1, br s, N(3) proton); ^{13}C NMR 63.73 (C(5′)), 73.77 (C(2′)), 80.64 and 88.33 (C(4′) and C(1′)), 128.60 and 129.91 (ortho and meta carbons of benzoates at C(2′) and C(3′)), 128.86 and 129.71 (ortho and meta carbons of benzoate at C(5′)), 133.74 (*p*-benzoate carbons), 165.36 (carbonyl of benzoates at C(2′) and C(3′)), 166.06 (carbonyl of benzoate at C(5′)). [f] Registry no.: **2**, 57858-24-9; **3**, 65138-33-2; **4**, 65138-34-3; **5**, 65138-35-4; **8**, 61101-07-3; **11**, 65102-76-3.

in an excellent overall yield. Since we were interested in obtaining the nucleoside, we found it advantageous to convert dihydrouracil (**5**) to the trimethylsilyl derivative[22] of uracil (**10**) without purification at intermediate stages. **10** can be easily purified by distillation and used directly in the stannic chloride fusion[23,24] with 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside.[25] We also found that it was more efficient to purify uracil via hydrolysis of the bistrimethylsilyl derivative (**10**) than by the usual crystallization or chromatography procedures. When conversion of **10** to **11** was carried out in acetonitrile, the reaction with the sugar was highly selective for the N(1) position of the pyrimidine.[23] Pure 2′,3′,5′-tri-*O*-benzoyl[4-^{13}C]uridine was obtained by medium-pressure chromatography on silica gel.

NMR Spectra. Chemical shifts (^{1}H and ^{13}C) and coupling constants for all of the labeled compounds that we prepared are listed in Table I. Assignments were based on coupling patterns, nuclear Overhauser enhancements, and comparisons with other compounds.[26,27,28]

Two- and three-bond ^{13}C–^{1}H coupling constants were obtained from ^{1}H spectra and confirmed by an analysis of the corresponding proton-coupled ^{13}C spectra.[29] Few values for the type of compounds listed in Table I are reported in the literature because of experimental problems involved in obtaining the data from ^{13}C in natural abundance. However, the coupling constants measured in this study are in agreement with trends reported by others.

Two-bond ^{13}C–^{1}H couplings between an sp^2-hybridized carbon, in particular a carbonyl carbon, and a proton attached to an sp^3-hybridized carbon usually lie between 4.0 and 8.0 Hz.[30] This range encompasses the values found for compounds **2–5**. Two-bond ^{13}C–^{1}H couplings where both carbons are sp^2 hybrids are noticably smaller (1.0–4.0 Hz),[27,32,33] as is seen for uracil (**8**) and 2′,3′,5′-tri-*O*-benzoyluridine (**10**).

Generally three-bond ^{13}C–^{1}H coupling constants, where the carbon atom is in a carbonyl group, are comparable to or greater than the corresponding two-bond couplings.[30,31] However, values for three-bond couplings can vary considerably depending on hybridization, conformation, and the electronegativity of attached substituents.[32,34] Coupling constants reported in the literature range from 0.7 to 16 Hz, with the maximum values found for conformations where the C(2)–C(3) and C(1)–H dihedral angle is 180°. Larger couplings are found between a carbonyl carbon and a β-hydrogen on an sp^2-hydribized carbon where the dihedral angle is ~180° and range from 7 to 16 Hz.[27,32] In comparison, we found $^3J_{^{13}C-^1H}$'s of 10.6 and 10.8 for **8** and **10**, respectively. If the β carbon is sp^3 hybridized, the three-bond coupling is usually much smaller because of changes in electronegativity and conformation.[34] Thus, values of $^3J_{^{13}C-^1H}$ for **4** and **5** are significantly smaller when compared to those for **8** and **10**. Also, it is interesting to note that $^3J_{^{13}C-^1H}$ for **4** and **5** are almost identical. Since one would expect the heterocycle and the amino acid to adopt similar conformations, the fact that β-alanine is zwitterionic implies that the charged carboxylate and ammonium moieties have little effect on $^3J_{^{13}C-^1H}$.

The carbon–carbon one-bond couplings shown in Table I fall within the range reported for $^1J_{^{13}C-^{13}C}$ in compounds where one of the carbons is in a carbonyl group.[28] We did not see any $^2J_{^{13}C-^{13}C}$ couplings and conclude that their magnitudes were all less than ~1 Hz.

Conclusion

Since 2′,3′,5′-tri-*O*-benzoyluridine (**11**) is a precursor for the synthesis of a large number of biologically important pyrimidine nucleosides such as 4-thiouridine,[35,36] 2-thiouridine,[37] 2,4-dithiouridine,[36] cytidine,[35,38] and 2-thiocytidine,[38] this approach serves as a convenient, high-yield, regiospecific

entry into these compounds. We are presently using this approach to synthesize [1-^{15}N]- and [3-^{15}N]uracil.

Experimental Section

General. Boiling and melting points are uncorrected. ^{1}H NMR spectra were recorded on a Varian Associates Model EM-390 spectrometer. ^{13}C NMR spectra were recorded on a Varian Associates Model XL-100-15 spectrometer. The chemical shifts given are δ values in parts per million downfield relative to Me_4Si. Unless otherwise indicated, the purity of the reactions was determined by spectral comparison (NMR) with an unlabeled authentic sample, and isotopic purity was checked at each stage by careful integration of the expanded portion of the ^{1}H spectrum where $^2J_{^{13}C-^1H}$ couplings were observed. Isotopic enrichment (90 ± 1%) was also confirmed by mass spectral analysis. Sodium [1-^{13}C]acetate (90% isotopic enrichment) was obtained from Koch Isotopes. The ^{1}H NMR and ^{13}C NMR spectra are recorded in Table I.

The yields reported for these optimized procedures were duplicated at least five times with unlabeled material before committing labeled material to the sequence, and yields of the individual steps were reproducible to within 1%. In addition, two batches of labeled material were brought through the sequence with the same overall yield.

[1-^{13}C]Acetic Acid (12). A 50-mL recovery flask, fitted with a magnetic stirring bar, was charged with 25.95 g (0.183 mol) of phosphorus pentoxide and capped with a rubber septum. Air (20 cm^3) was removed via a syringe to create a partial vacuum, and 10.0 g (0.555 mol) of water was slowly added via a syringe to the cooled flask (ice bath) at a rate such that no appreciable buildup in pressure was observed. After addition was complete, the flask was heated (oil bath) at 70 °C until all the phosphorus pentoxide had dissolved (approximately 2 h). The contents of the flask were allowed to cool and 7.50 g (90.4 mmol) of fused anhydrous sodium [1-^{13}C]acetate was added to the flask. After the flask was fitted with a short-path distillation apparatus, the oil bath was heated to 210 °C and the [1-^{13}C]acetic acid (bp 103–105 °C) was collected in a tared receiver. The reaction flask was flamed *gently* with a bunsen burner to drive over the last of the acetic acid (this drives over a small amount of water which can be carried over into the bromination step), giving 6.2 g (theoretical 5.5 g) of distillate. Therefore, assuming quantitative collection of acetic acid (confirmed by NMR analysis of the remaining phosphoric acid residue), the distillate contained 0.7 g (39 mmol) of water. This "wet" acetic acid was used directly in the bromination reaction.

[1-^{13}C]Bromoacetic Acid (2). (A) From "Wet" [1-^{13}C]Acetic Acid. Trifluoroacetic anhydride (44.90 g, 0.214 mol) was carefully added to the cooled (ice bath) [1-^{13}C]acetic acid from the previous experiment. (*Caution.* The reaction is very exothermic due to hydrolysis of some of the trifluoroacetic anhydride by the water in the acetic acid and due also to the formation of the mixed anhydride. Since this anhydride is low boiling, care must be taken to prevent any loss. It is recommended that the trifluoroacetic anhydride be slowly added to the magnetically stirred acetic acid by way of a dropping funnel, protected with a dry ice condenser and drying tube.) After addition of trifluoroacetic anhydride was complete, 0.40 g (1.5 mmol) of phosphorus tribromide was added to the reaction mixture and the dropping funnel was charged with 14.43 g (90.2 mmol) of bromine. The reaction flask was then heated with an oil bath (maintained at 60 °C). When trifluoroacetic anhydride started to reflux, bromine was slowly added to the reaction flask at a rate such that a pale bromine color is just maintained in the flask. After addition was complete and the bromine color had been completely discharged (6–7 h),[39] 3.39 g (0.188 mol) of water was carefully added to the cooled reaction mixture (*caution:* vigorous reaction). This amount of water represents the theoretical amount[40] required to hydrolyze all of the anhydrides and phosphorus tribromide left at the end of the reaction. Trifluoroacetic acid (along with hydrogen bromide) was removed by distillation and the remaining colorless liquid solidified on standing to afford [1-^{13}C]bromoacetic acid (mp 46–48 °C). The distillate, after evaporation at room temperature under a slow stream of nitrogen, afforded a small amount of [1-^{13}C]bromoacetic acid which had azeotroped with solvent.[41] The total yield of [1-^{13}C]bromoacetic acid was 11.81 g (85.7 mmol, 95%).

(B) From Anhydrous Acetic Acid.[42] Trifluoroacetic anhydride (25 g, 0.119 mol) was carefully added to 2.40 g (40 mmol) of acetic acid and the mixture was allowed to cool to room temperature. To the magnetically stirred solution 6.40 g (40 mmol) of bromine was slowly added, and stirring was continued at room temperature for 22 h, by which time all the bromine color had been dissipated. The mixture was cooled, hydrolyzed with 2.25 g (0.125 mol) of water, and worked up as before, giving 5.56 g (40 mmol, 100%) of bromoacetic acid.

[1-^{13}C]Cyanoacetic Acid (3). A stirred solution of 2.78 g (20 mmol) of [1-^{13}C]bromoacetic acid in water (6 mL) was carefully neutralized with 1.49 g (11 mmol) of anhydrous potassium carbonate, followed by slow addition of 1.40 g (21.5 mmol) of potassium cyanide in water (5 mL). The mixture was allowed to stir at ambient temperature (22 °C) for 15 min and heated at 60 °C (oil bath) for 25 min. The solution was cooled to 10 °C and acidified by the addition of 3.63 mL of an 18.5% aqueous solution (21.8 mmol) of hydrochloric acid.

The product was extracted with diethyl ether in a continuous extractor for 72 h, the ether extract was dried over anhydrous sodium sulfate, and solvent was removed to afford 1.71 g (20 mmol, 100%) of [1-^{13}C]cyanoacetic acid. NMR analysis indicated that no [1-^{13}C]-bromoacetic acid remained.

[1-^{13}C]-β-Alanine Hydrochloride, [1-^{13}C]-3-Aminopropionic Acid Hydrochloride (13). To a solution of 1.70 g (20 mmol) of [1-^{13}C]cyanoacetic acid in water (25 mL) was added 6 mL of concentrated hydrochloric acid. The mixture was hydrogenated at 50 psi over platinum oxide (0.25 g) and the theoretical uptake of hydrogen was realized after 16 h.

The catalyst was filtered off and washed with water (4 × 15 mL). The filtrate and washings were combined and water was removed at reduced pressure giving 3.0 g of a pale yellow solid. (The theoretical yield was 2.47 g; thus, not all the water had been removed.)

[1-^{13}C]-β-Alanine, [1-^{13}C]-3-Aminopropionic Acid (4). The hygroscopic [1-^{13}C]-β-alanine hydrochloride from the reduction was dissolved in deionized water (40 mL) and applied to 25 mL of IR-4B resin [previously washed successively with 1% aqueous hydrochloric acid (250 mL), 1% aqueous sodium hydroxide, and finally deionized water (500 mL)]. The free amino acid was eluted from the column with deionized water (250 mL). Removal of water under reduced pressure gave 1.78 g (100%) of a pale yellow solid.

[4-^{13}C]-5,6-Dihydrouracil, [4-^{13}C]-5,6-Dihydro-2,4-dihydroxypyrimidine (5). To a solution of 1.78 g (20 mmol) of [1-^{13}C]-β-alanine in water (20 mL) was added 1.64 g (20 mmol) of potassium cyanate dissolved in 20 mL of water. The solution was *slowly* evaporated to dryness by heating in an oil bath (100 °C) under a stream of nitrogen. A syrupy residue, consisting of the potassium salt of [1-^{13}C]-β-ureidopropionic acid, solidified on standing. This potassium salt was acidified with 40 mL of 18% hydrochloric acid (6 N), the solution was evaporated to dryness, and the residue was heated at 170 °C for 30 min. The solid residue was thoroughly washed with 5-mL portions of water until all of the potassium chloride had been removed (negative silver nitrate test), and the residue was dried over phosphorus pentoxide to afford 1.85 g of [4-^{13}C]-5,6-dihydrouracil. The water washings were continuously extracted with ether for 72 h to afford a further 0.42 g (100%) of crude [4-^{13}C]-5,6-dihydrouracil.

(Bis-O-trimethylsilyl)[4-^{13}C]uracil, 2,4-Bis(trimethylsiloxy)[4-^{13}C]pyrimidine (10). A magnetically stirred suspension of 1.14 g (10 mmol) of [4-^{13}C]-5,6-dihydrouracil in 15 mL of glacial acetic acid was heated in an oil bath (maintained at 105 °C) until all the solid had dissolved. The flask was fitted with a dropping funnel and protected with an efficient dry-ice condenser. The dropping funnel was charged with 2.40 g (15 mmol) of bromine dissolved in 10 mL of glacial acetic acid and the solution was added slowly to the solution of dihydrouracil at 105 °C at such a rate to just maintain the bromine color. After all of the bromine color had been dissipated (3–4 h), the solvent was removed on a rotary evaporator under reduced pressure to afford a white solid. ^{1}H NMR analysis confirmed the absence of any starting dihydrouracil and showed the solid to contain 5-bromodihydrouracil and 5,5-dibromodihydrouracil in approximately equal proportions. The solid mixture was heated at 210 °C (oil bath, preheated) for 25 min under a stream of nitrogen to assist in the removal of the hydrogen bromide generated during the elimination, giving a mixture of [4-^{13}C]uracil and [4-^{13}C]-5-bromouracil. The mixture was dissolved by gentle heating in 100 mL of 50% aqueous ethanol and the resulting solution was hydrogenated over 1.0 g of 5% palladium on barium sulfate for 5 h (theoretical uptake was complete after 2 h). The solution was heated to boiling and the catalyst was removed by filtration and washed with hot water (4 × 15 mL). The combined filtrate and washings were evaporated to dryness under reduced pressure to afford crude [4-^{13}C]uracil (1.10 g, 99%) as a pale yellow solid. The [4-^{13}C]uracil was silylated by heating a stirred suspension in hexamethyldisilazane (8 mL) at reflux under a dry nitrogen atmosphere for 16 h. The solution was concentrated at reduced pressure [90 °C (50 mm)] before the vacuum was lowered to 7 mm to remove the remaining solvent. The residue was distilled to afford 2.40 g (94% from dihydrouracil) of 2,4-bis(trimethylsiloxy)[4-^{13}C]pyrimidine [bp 125 °C (5 mm) (lit.[22] 135 °C (7 mm))] as a colorless liquid (extremely moisture sensitive, collected and stored under dry nitrogen).

2',3',5'-Tri-*O*-benzoyl[4-^{13}C]uridine, 1-(2,3,5-Tri-*O*-benzoyl-β-D-ribofuranosyl)-2,4-dihydroxy[4-^{13}C]pyrimidine (11). To a solution at 10 °C containing 4.68 g (9.3 mmol) of 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside[25] and 2.0 g (8.6 mmol) of bis(*O*-trimethylsilyl)[4-^{13}C]uracil (10) in 100 mL of dry acetonitrile under a dry nitrogen atmosphere was added 1.6 g (6.1 mmol) of freshly distilled (from P_2O_5) stannic chloride in 50 mL of dry acetonitrile. The resulting solution was stirred at room temperature (22 °C) for 16 h and the solvent was removed at 22 °C under reduced pressure. The residue was dissolved in 300 mL of 1,2-dichloroethane and shaken with 250 mL of a saturated sodium bicarbonate solution. The resulting emulsion was allowed to settle and as much of the clear organic layer as possible was removed. A further 100 mL of 1,2-dichloroethane was added to the emulsion and the process was repeated. After the fifth extraction, the remaining bicarbonate layer was filtered through Whatman No. 1 filter paper to break up the emulsion and the resulting clear bicarbonate layer was extracted twice more with 50 mL of organic solvent. The combined organic extract was dried (sodium sulfate and magnesium sulfate) and the solvent was removed to afford 4.81 g of a light, creamy white crystalline solid. Medium-pressure chromatography on silica gel (ICN, 0.032–0.063 mm or 230–400 mesh) using methylene chloride–2% methanol as the eluant afforded 4.30 g (7.74 mmol, 90%) of 2',3',5'-tri-*O*-benzoyl[4-^{13}C]uridine as a white crystalline solid: mp 142–143 °C (lit.[35] 142–143 °C).

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Registry No.—**10**, 65102-77-4; **12**, 1563-79-7; **13**, 65138-36-5; trifluoroacetic acid anhydride, 407-25-0; 1-*O*-acetyl-2,3,5-tri-*O*-benzoyl-β-D-ribofuranoside, 6974-32-9.

References and Notes

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(40) Allowance must be made for the water (39 mmol) initially in the [1-^{13}C]-acetic acid. The amount of water used allows for a 5% excess over the theoretical.
(41) The amount of material which azeotroped over is effected by the amount of water present in the mixture. Hence, the amount of water added for the hydrolysis was carefully calculated to minimize the water left after hydrolysis.
(42) It is necessary to use anhydrous acetic acid to obtain the reported yield. We have not used this procedure with [1-^{13}C]acetic acid because of the high cost of the labeled material.

Steroid Total Synthesis. 11.[1,2] (+)-Estr-4-ene-3,17-dione from a Chiral Lactone

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Optically pure (+)-estr-4-ene-3,17-dione and (−)-estra-4,9-diene-3,17-dione have been synthesized from the prochiral 5,9-diketoheptanoic acid via the lactone **11**. The selective microbiological reduction of **10** produced optically pure **11**, which was converted to the masked Mannich base **16** and subsequently condensed with 2-methylcyclopentane-1,3-dione to give predominantly the trans diene **17**. This key intermediate was then transformed into (+)-estr-4-ene-3,17-dione via **24** and also to (−)-estra-4,9-diene-3,17-dione by the cyclization of the polyketone **20**.

An asymmetric synthesis of (+)-estr-4-ene-3,17-dione (**27**) is described starting from the chiral lactone **11** (Scheme I) obtained by the selective microbiological reduction of 5,9-diketoheptanoic acid. Condensation of the amine **16**,

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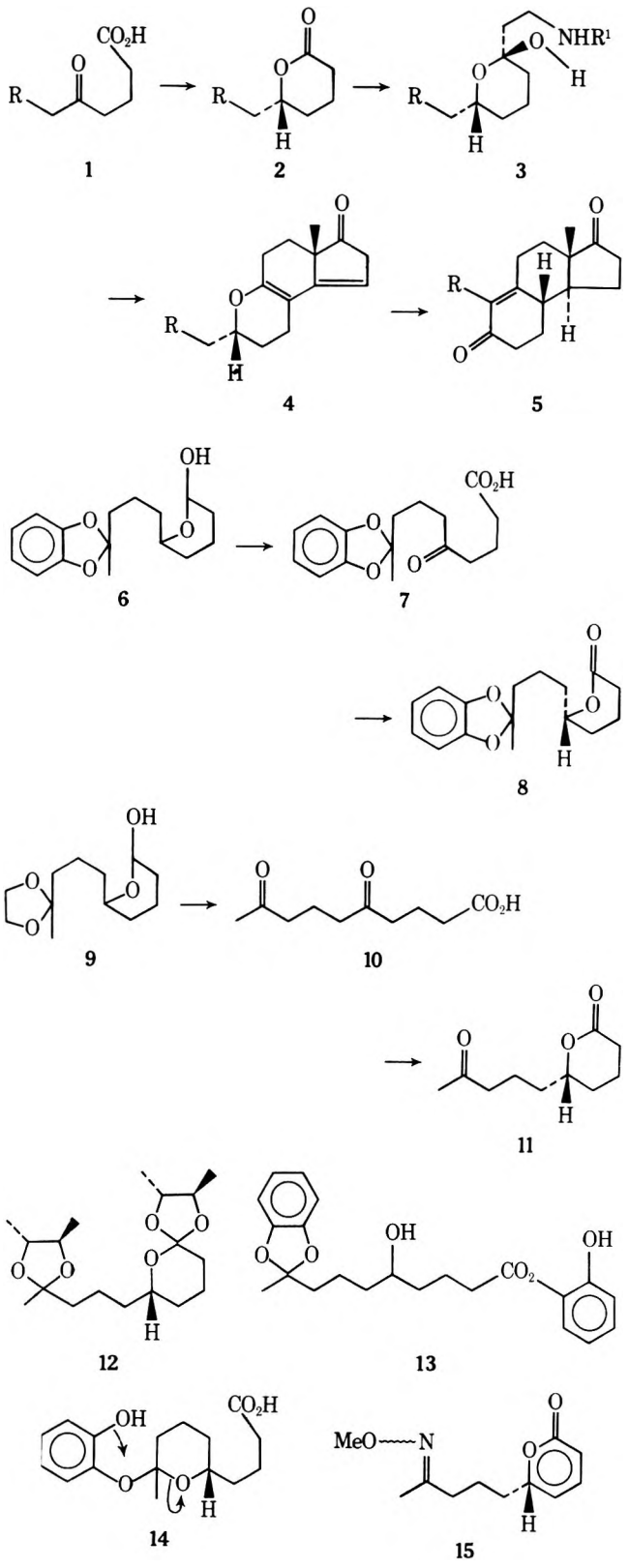
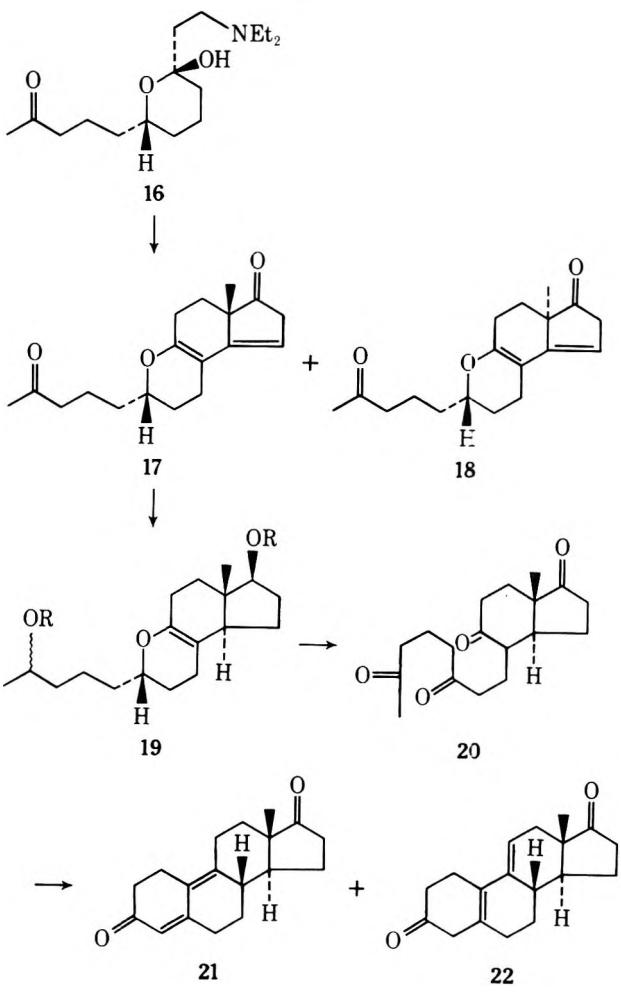
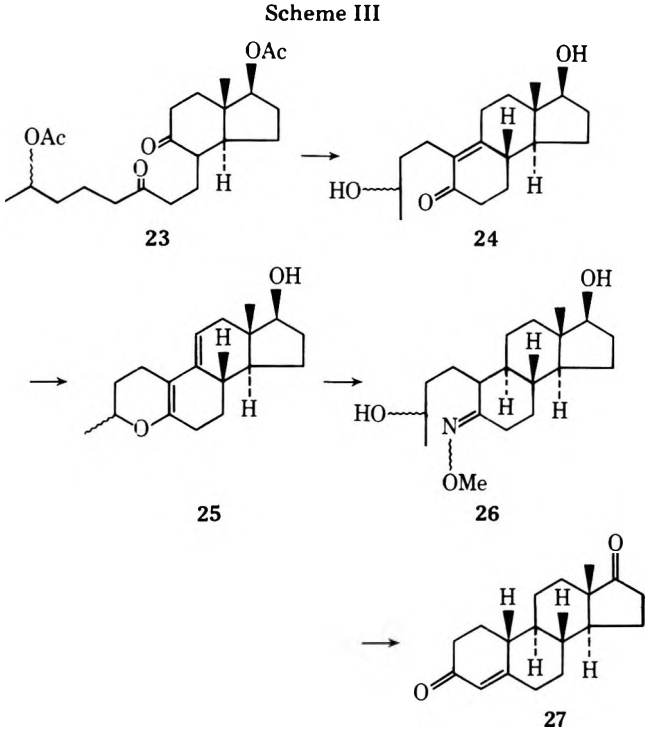
Scheme I



Scheme II



Scheme III



(Scheme II), derived from this lactone, with 2-methylcyclopentane-1,3-dione gave predominantly the 13β trans diene **17**, indicative of a highly diastereoselective process. Suitable manipulations of this key substrate **17** then generated the target compounds **21**, **22**, and **27** (Scheme III).

Previous publications[3,4] from our laboratories have described routes to optically pure 19-nor steroids (e.g., **27**) which involve a classical resolution of masked Mannich bases, of the type **3**, to introduce the controlling chiral carbon (*pro*-C_5). These bases on condensation with 2-methylcyclopentane-1,3-dione then lead to the versatile dienes **4**, with high asymmetric induction, giving mainly the 13β arrangement.

This paper describes a related route based on some of our earlier work[5] in which asymmetry was introduced early in the synthesis via optically active lactones which are generated by the microbiological reduction of δ-keto acids.

Results and Discussion

The microbiological reduction of δ-keto acids to the corresponding hydroxy acids[6] of high optical purity is a simple and efficient method and has proved useful in our total synthesis of retro-steroids.[5] Extension of this reduction to keto acids with suitably functionalized side chains had not been described previously and seemed to us to offer an excellent entry into natural 19-nor steroids.

Our previous success with catechol as a ketone-protecting group[7] made the keto acid **7** our first choice for reduction. This material is readily available from the hemiacetal **6**[8] by simple oxidation with chromic acid,[9] or by direct addition of the Grignard reagent, derived from the catechol ketal of 1-chloro-4-pentanone, to glutaric anhydride.

While the microbiological reduction of **7** to the lactone **8** was observed, the conversions were low due to the toxic effects of the substrate or the generated hydroxy acid on the microorganism. With the diketo acid **10**,[10] however, a selective reduction and excellent conversion to the lactone **11** was observed. On the basis of molecular rotation comparison with **2** (R = methyl and *n*-butyl), the new lactone was also of high optical purity. To confirm the optical purity of our material we made use of a new method for determining the enantiomeric purity of chiral δ-lactones[11] which involves the formation of an ortho ester derivative with (−)-(2*R*,3*R*)-butanediol and subsequent analysis by GC. Exposure of the keto lactone **11** to the butanediol generated the expected ketal ortho ester **12** which showed only one peak on GC analysis, whereas with the racemic keto lactone the ketal ortho ester mixture of diastereomers showed two cleanly resolved peaks.

As we had already shown in a model study with racemic material that the keto lactone **11** could be converted to the ketalized material **8** via the adduct **13** by simple pyrolysis, we anticipated no problems for the optically active substrate. However, this failed to be the case, and when the lactone **11** was ketalized as before, examination of the protected lactone **8** showed that extensive racemization had occurred. This could be the result of an intermediate such as **14** being formed in which the pyran oxygen is derived from the carbonyl group, leading to inversion at C_5. Subsequent closing of the ketal results in the formation of the enantiomeric alcohol, and if such a process occurs at the same time as normal ketalization, then the overall effect is racemization.

The protection of the ketopentyl side chain, however, is possible by the formation of the oxime ether **15**. These oxime ethers are easily formed, are stable to acidic and basic environments, and have proved moderately useful to us[12] and others.[13]

Exposure of the keto lactone **11** to methoxylamine produces the protected product **15**, without apparent racemization, as a mixture of syn and anti isomers. This mixture was not separated but used directly and treated with vinylmagnesium chloride[5] to furnish a vinyl ketone. This was trapped with diethylamine to yield a Mannich base, which on mild acid treatment gave **16**. This acid treatment, which was designed to separate neutral impurities formed in this reaction, yielded an added bonus in removing the oxime ether protecting group. These mild conditions for ketone regeneration must be a result of internal assistance by the hydroxyl group, as in general more vigorous hydrolysis conditions have to be employed.[12]

With the pure material **16** in hand, the key condensation with 2-methylcyclopentane-1,3-dione in a mixture of toluene and acetic acid at reflux yielded the two dienes **17** and **18** in approximately a 3:1 ratio from which the required (trans) 13β isomer was readily obtained by direct crystallization. Reduction of both carbonyl groups with lithium aluminum hydride formed the diol which on stereoselective hydrogenation gave **19** (R = H), which was processed in two ways.

One sequence of reactions involved the hydration and subsequent oxidation of **19** (R = H) to the tetraketone **20**, which we then hoped to cyclize to the 19-nor steroid **21**. There is some precedent in the literature[14] that such a cyclization could be possible; however, when the reaction conditions described by these authors were applied to **20**, complex mixtures resulted which contained little of the desired material. In contrast, when heated at reflux in toluene with piperidinium acetate,[15] **20** gave a mixture of the two ketones **21** and **22** in approximately 70% yield. Exposure of isomer **22** to *p*-toluenesulfonic acid in toluene at reflux resulted in a 60% yield of the conjugated isomer **21**. The physical data for compound **21** compare well with the reports in the literature;[16] however, **22** could not be compared with previously synthesized material as no data are given,[17] and the structure rests solely on our ^1H NMR, IR, and UV spectra (see Experimental Section). Whether ring A forms first in the cyclization of **20** and this then reacts further to give the above mixture of ketones is not known.

The other set of transformations carried out on substrate **19** (R = H) involved protection of the diol as a diacetate (**19**, R = Ac), followed by hydration of the enol ether and subsequent oxidation to the diketone **23**. Exposure of this material to dilute methanolic base then brought about cyclization and hydrolysis to yield the tricyclic compound **24**, which on acid treatment afforded the mixture of diastereomers **25**. Conversion of this material to optically pure (+)-estr-4-ene-3,17-dione (**27**) then followed the course previously described by us.[12] Selective hydrogenation of **25** followed by treatment with methoxylamine generated the diol **26**, which on oxidation and cyclization gave **27**, identical in all respects with material synthesized previously by us[3] and others.[18]

In summary, the work described herein offers an efficient route to optically pure 19-nor steroids in relatively few steps starting with the easily prepared lactone **11**. There are no separation problems, and the overall yields to the key intermediates **17**, **20**, and the mixture of **21** and **22** from the lactone **11** are 45, 34, and 27%, respectively.

Experimental Section[19]

8-(2-Methyl-1,3-benzodioxol-2-yl)-5-oxooctanoic Acid (7). The crude hemiacetal[8] **6** (29 g) dissolved in acetone (380 mL) was cooled to −10 °C, treated over a period of 30 min with a fresh solution of Jones chromic acid mixture,[9] and then stirred overnight at room temperature. aqueous sodium bisulfite solution (50 mL, 20%) was added, and the products were extracted into ether to yield the crude keto acid. This material was partitioned between ether and aqueous sodium hydroxide solution (5%), and the aqueous phase was then acidified (6 N H_2SO_4) and extracted with ether. Removal of the solvents followed by distillation (oil-jacketed flask) yielded the pure material (16.7 g): bp 185–195 °C (0.1 mm); ^1H NMR ($CDCl_3$) δ 9.7 (s, 1, CO_2H), 6.8 (s, 4, C_6H_4), 2.5 (m, 6, CH_2CO), 1.9 (m, 6, CH_2), 1.6 (s, 3, CH_3); mass spectrum *m/e* 292 (M^+). Anal. Calcd for $C_{16}H_{20}O_5$: C, 65.74; H, 6.9. Found: C, 65.63; H, 7.1.

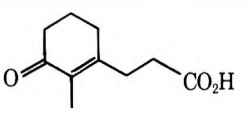
5,9-Diketodecanoic Acid (10). The hemiacetal[8] **9** (30 g; crude material containing 5–8% toluene) was dissolved in acetone (150 mL), treated with aqueous sulfuric acid (0.5 N, 75 mL), and left at room temperature for 2 h. Brine (1 L) was added, and the crude keto hemiacetal was extracted into dichloromethane (21.9 g). This material was dissolved in acetone (110 mL), cooled to 5 °C, and treated over 20 min with Jones chromic acid mixture (88.5 mL), followed by stirring at room temperature for 18 h and then quenching with aqueous sodium bisulfite solution (20%, 50 mL). Extraction with more acetone (4 × 200 mL) yielded the crude diketo acid on removal of the solvents. This material was then dissolved in dichloromethane, washed with brine, and dried. Crystallization of the solid residue (22.1 g) from isopropyl ether gave pure **10** (13.6 g): mp 78–80 °C; ^1H NMR ($CDCl_3$) δ 10.9 (s, 1, CO_2H). 2.5 (m, 8, CH_2CO), 2.17 (s. 3, $COCH_3$), 2.0 (m, 4, CH_2). Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.06. Found: C, 60.15; H, 7.96.

(*S*)-Tetrahydro-6-[3-(2-methyl-1,3-benzodioxol-2-yl)propyl]-2*H*-pyran-2-one (8). The culture of *Margarinomyces bubaki* 459 M was grown aerobically as previously described,[6] dosed with the keto acid **7** (12 g, ~0.5 g/L) in ethanol, and then agitated anaerobically for

24 h. The total mixture was extracted to yield a crude extract (8.6 g) which was distilled (Kugelrohr) to give one major fraction (2.9 g), bp 165–195 °C (0.1 mm). This product was dissolved in ether and extracted with aqueous sodium carbonate solution (10%) to yield a neutral fraction (1.1 g) which was chromatographed on silica (50 g). Elution with a benzene–ethyl acetate mixture (9:1) yielded the lactone (485 mg), which was distilled to give pure material (446 mg): bp ~200 °C (0.02 mm); $[\alpha]^{20}_D$ −36.8° (*c* 1, dioxane). The ^1H NMR and IR spectra were identical with those of racemic material.[8]

(*S*)-Tetrahydro-6-(4-oxopentyl)-2*H*-pyran-2-one (11). The broth was prepared as before, the diketo acid was fed (1 g/L, 30 g), and the mixture was stirred anaerobically for 24 h. The pH of the medium was adjusted to 2, and the products were extracted into dichloromethane. Removal of the solvents and distillation of the residue (28.5 g) through a 4 in vacuum-jacketed Vigreaux column yielded one major fraction (17.4 g): bp 130–132 °C (0.1 mm); $[\alpha]^{20}_D$ −45.5° (c 0.091, dioxane); IR (film) 1725 and 1710 (keto lactone) cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.4 (m, 1, CHO), 2.5 (m, 4, CH_2CO), 2.0 (s, 3, $COCH_3$), 1.7 (m, 8, CH_2). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.02; H, 8.94.

A simple assay for the progress of the fermentation was based on the reaction of **10** with aqueous base when the cyclohexenone A was



A

formed. This material had bp 130–140 °C (0.02 mm) (Kugel-Rohr); UV max (95% ethanol) 242 nm (ε 12 800). Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.87; H, 7.54.

Thus aliquots from the broth were brought to pH 12 with aqueous sodium hydroxide solution, filtered, and assayed by UV spectroscopy.

Enantiomeric Purity Determination of 11. A solution of the keto lactone **11** (1.8 g), (−)-(2*R*,3*R*)-butanediol (3 g), and *p*-toluenesulfonic acid (100 mg) in benzene (50 mL) was heated at reflux in conjunction with a Dean and Stark water trap for 4 h. After this time the total reaction mixture was absorbed onto an alumina column (Woelm neutral, grade III, 100 g) and developed with a mixture of ether and hexane (1:9). Fractions 10–55 (10 mL each) were collected and concentrated to yield the pure ketal ortho ester (2.23 g). Anal. Calcd for $C_{18}H_{32}O_5$: C, 65.82; H, 9.82. Found: C, 65.83; H, 9.81.

The racemic keto lactone (1.8 g) was treated as above to yield the pure mixture of diastereomers (2.66 g) after chromatography. GC analysis of these samples was performed with an HP5710A gas chromatograph on a 1 m × 4 mm glass column containing 5% OV-210 supported on GCQ 100–120 mesh. It is of interest that the ortho esters of both **11** and **2** (R = CH_3)[11] in the 5*S* series have the higher retention times as in the case of **12**.

(*R,S*)-Tetrahydro-6-(4-oxopentyl)-2*H*-pyran-2-one. (*RS*)-Tetrahydro-6-[3-(2-methyl-1,3-ethylenedioxol-2-yl)propyl]-2*H*-pyran-2-one (52.4 g)[8] was dissolved in acetone (150 mL), treated with aqueous sulfuric acid (2 N, 45 mL), and left at room temperature for 16 h. Brine was added and the keto lactone was isolated with benzene. Distillation gave the pure material (26 g), bp 134 °C (0.05 mm). Anal. Calcd for $C_{10}H_{16}O_3$: C, 65.19; H, 8.75. Found: C, 65.35; H, 8.59.

(*R,S*)-Tetrahydro-6-[3-(2-methyl-1,3-benzodioxol-2-yl)propyl]-2*H*-pyran-2-one. The keto lactone (15 g) in benzene (300 mL) was treated with catechol (20 g) and *p*-toluenesulfonic acid (0.6 g) and heated at reflux in conjunction with a Soxhlet extractor containing calcium hydride in the thimble. After 18 h the mixture was cooled and chromatographed directly on silica gel (650 g). Elution with 5, 10, and 15% ethyl acetate–benzene mixtures yielded the ketal ester **8** (28 g) as an oil: ^1H NMR ($CDCl_3$) δ 6.8 (m, 8, $(C_6H_4)_2$), 6.1 (s, 1, OH), 4.5 (m, 1, CHO), 1.6 (s, 3, CH_3); IR (film) 3300 (phenolic and aliphatic OH), 1700 (ester C=O), 1480, 1275, 740 (catechol ketal) cm^{-1}. Short-path destructive distillation yielded catechol (12.11 g) and the lactone (12.2 g), bp 157–162 °C (0.2 mm). This material was identical in all respects with a sample prepared from **6** by oxidation.[8] Anal. Calcd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.3. Found: C, 69.84; H, 7.34.

When the above sequence was applied to the optically active keto lactone **11** (7.8 g; $[\alpha]^{20}_D$ −46°), the chemically pure ketal **8** (5.5 g), bp 170 °C (0.5 mm), was obtained. This was identical in all respects with the racemic material and had a specific rotation of $[\alpha]^{20}_D$ −7° (*c* 0.5, dioxane), indicating extensive racemization.

***syn,anti*-(*S*)-Tetrahydro-6-(4-methoxyiminopentyl)-2*H*-pyran-2-one (15).** An ice cold solution of lactone **11** (39.1 g) in pyridine (240 mL) was treated with a cold solution (10 °C) of methoxylamine hydrochloride (35.6 g) in pyridine (200 mL) and stirred 30 min more at 10 °C. The mixture was then cooled to 0 °C, treated with triethylamine (61 mL), stirred 15 min more, and filtered free of solids. The residue was washed with benzene, and the combined filtrates (benzene and pyridine) were concentrated to yield the oxime ether **15** (44.4 g) as a pale yellow oil.

A sample distilled for analysis had bp 110–120 °C (0.05 mm); $[\alpha]^{25}_D$ −44.6° (*c* 1.0817, $CHCl_3$); ^1H NMR ($CDCl_3$) δ 4.3 (m, 1, OCH), 3.88 and 3.86 (two s, total of 3, OCH_3), 1.92 and 1.89 (two s, total of 3, N=$CHCH_3$). Anal. Calcd for $C_{11}H_{19}O_3N$: C, 61.94; H, 8.98; N, 6.57. Found: C, 62.18; H, 8.83; N, 6.52.

(2*S*,6*S*)-2-Diethylaminoethyl-6-(4-oxopentyl)-tetrahydropyran-2-ol (16). A solution of the crude oxime ether **15** (44.4 g) in tetrahydrofuran (THF, 850 mL) was cooled to −60 °C and treated over 10 min with a solution of vinylmagnesium chloride (2.2 M, 159 mL), the temperature being held between −50 and −55 °C. After complete addition, stirring was continued at −60 °C for 20 min followed by cooling to −70 °C. Methanol (24 mL) was carefully added, and the reaction mixture was then poured onto a mixture of saturated aqueous ammonium chloride solution (250 mL), ether (500 mL), and ice (100 g). The aqueous phase was reextracted several times with ether, and the combined ether extracts were washed with brine, dried over sodium sulfate, treated with diethylamine, and left at room temperature for 1 h. Removal of the solvents gave the crude Mannich base (62.5 g), which can be purified by acid extraction. To remove the oxime ether protecting group the base was dissolved in acetone (850 mL), treated with aqueous sulfuric acid (2 N, 610 mL) at 0 °C, and then left at room temperature for 24 h.

Most of the acetone was then removed at 30 °C and 20 mm pressure, and the residue was extracted with ether to yield the neutral material (7 g) which was discarded. The aqueous phase was cooled to 0 °C, treated with a sodium hydroxide solution (10 N, 155 mL), and extracted with ether. Removal of the solvents gave the base **16** (45.5 g) as an oil. A sample chromatographed on alumina furnished the analytical sample: IR ($CHCl_3$) 3100 (bonded OH), 1725 (C=O) cm^{-1}. Anal. Calcd for $C_{16}H_{31}NO_3$: C, 67.33; H, 10.94; N, 4.91. Found: C, 67.38; H, 10.66; N, 4.88.

[2*S*-(2α,7aβ)]-2,3,4,7a,8,9-Hexahydro-7a-methyl-2-(4-oxopentyl)-6*H*-cyclopenta[*f*]-1-benzopyran-7-one (17). A mixture of 2-methylcyclopentane-1,3-dione (22 g), toluene (700 mL), and acetic acid (250 mL) was heated to 110 °C, treated over 10 min with a solution of the base **16** (45 g) in more toluene (200 mL), and then stirred 30 min more at this temperature. The temperature was then raised (bath to 130 °C), water was separated with a Dean–Stark trap for 1 h, and the mixture was cooled to room temperature. The cooled mixture was washed with water and saturated sodium bicarbonate solution and dried over sodium sulfate. Removal of the solvents yielded the mixture of dienes **17** and **18** (44 g) as a solid. Crystallization from aqueous methanol gave pure trans material **17** (27.6 g): mp 74–76 °C; $[\alpha]^{25}_D$ −162° (*c* 1.21, $CHCl_3$); UV max (95% ethanol) 252 nm (ε 18 750); IR ($CHCl_3$) 1740 (cyclopentanone), 1712 (C=O), 1642 (dienol ether) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.45 (t, *J* = 2 Hz, C_9–H), 3.77 (m, 1, C_3–H), 2.15 (s, 3, CH_3CO), 1.13 (s, 3, C_{7a}–CH_3). Anal. Calcd for $C_{18}H_{24}O_3$: C, 74.96; H, 8.39. Found: C, 74.76; H, 8.38.

(3*S*,6a*S*,7*S*)-3-[4(*R*,S)-Hydroxypentyl]-6a-methyl-1,2,3,5,6,6a,7,8,9,9a-decahydrocyclopenta[*f*][1]benzopyran-7-ol (19, R = H). The diene **17** (8.24 g) in tetrahydrofuran (170 mL) was added to a slurry of lithium aluminum hydride (4.35 g) in more tetrahydrofuran (430 mL) at 0–5 °C. The mixture was stirred for 30 min at room temperature and then treated carefully with a saturated aqueous solution of sodium sulfate. The solids were filtered off and washed with more tetrahydrofuran, and the solvents were then removed to yield the diol (8.9 g). A sample crystallized from an ether–isopropyl ether mixture had mp 95–102 °C; $[\alpha]^{25}_D$ −180° (*c* 1.0142, $CHCl_3$). Anal. Calcd for $C_{18}H_{30}O_3$: C, 73.94; H, 9.66. Found: C, 73.66; H, 9.56.

The crude material (8.8 g) was dissolved in tetrahydrofuran (270 mL) and hydrogenated at room temperature and pressure over a palladium catalyst (1.2 g of AK4).[20] After 35 h the hydrogen uptake stopped (710 mL) and the solids were filtered off and washed with more solvent. The combined solvents were concentrated to give **19** (9.0 g) as an oil.

[2(*R,S*),6a*S*,7*S*]-2,3,4,6,6a,7,8,9,9a,10,11-Dodecahydro-2,6a-dimethylcyclopenta[5,6]naphtho[2,1-*b*]pyran-7-ol (25). The crude diol **19** (R = H) (9 g) was dissolved in a mixture of pyridine (80 mL) and acetic anhydride (40 mL) and then left for 18 h at room temperature. Removal of the solvents and extraction into benzene yielded the crude diacetate after washing with sodium bicarbonate solution and concentrating to dryness.

This product (**19**, R = Ac; 10 g) in acetone (170 mL) was exposed to dilute aqueous sulfuric acid (1 N, 50 mL), left to stand for 2.5 h, and

then cooled to 5 °C. To this mixture was added a fresh solution of Jones chromic acid mixture (14.2 mL), followed by stirring at room temperature for 2.5 h.

After cooling to 10 °C, sodium bisulfite was added to destroy the excess of oxidant, followed by a 10% aqueous sodium carbonate solution to pH 6–7. The majority of the acetone was then removed in vacuo at 35 °C, and the residue was extracted with benzene to yield the crude diketo diacetate **23** (9.45 g) as an oil.

This product was dissolved in methanol (87 mL) containing potassium hydroxide (2.6 g) and heated at reflux for 1.5 h. Water was then added, and the products were isolated with chloroform, yielding the tricyclic material **24** (7 g) as an oil.

A solution of this material (7 g) in benzene (140 mL) containing *p*-toluenesulfonic acid (200 mg) was heated at reflux for 2 h, cooled, washed with sodium bicarbonate solution and water, dried over sodium sulfate, and then taken to dryness to yield crude **25** (5.6 g) as an oil. Chromatography on silica gel (280 g) and elution with hexane–ether mixtures (2:1 and 1:1) afforded pure **25** (3.66 g) as a crystalline product: mp 60–71 °C; $[\alpha]^{25}_D$ +141.3° (*c* 1.42, $CHCl_3$); UV max (95% ethanol) 248 nm (ϵ 16 000); ^1H NMR ($CDCl_3$) δ 5.26 (m, 1, C_9–H), 1.27 and 1.25 (two d, total of 3, J = 6 Hz, C_2–CH_3), 0.85 (s, 3, C_{6a}–CH_3). Anal. Calcd for $C_{18}H_{26}O_2$: C, 78.76; H, 9.5. Found: C, 78.58; H, 9.95.

(+)-Estr-4-ene-3,17-dione (27). The mixture of diastereomer **25** (3.75 g) dissolved in toluene (40 mL) containing triethylamine (0.37 mL) was hydrogenated in the presence of a palladium catalyst (0.550 g of AK4)[20] at room temperature and pressure until the uptake of hydrogen stopped (2 h, 350 mL uptake). The catalyst was filtered off, and the crude hydrogenation product (3.9 g) was dissolved in pyridine (75 mL) containing water (0.4 mL) and methoxylamine hydrochloride (2 g) and left at ambient temperature for 24 h. Dilution with dichloromethane and washing with brine yielded the crude oxime ether **26** (4.5 g), which was chromatographed on silica gel (110 g) to yield chemically pure material (3.97 g) on elution with hexane–ether (1:4) and ether–methanol (19:1) solvent mixtures.

A solution of this material (1.21 g) in dimethylformamide (6 mL) was added over 10 min to a mixture of chromium trioxide (2.4 g) in more dimethylformamide (8 mL) containing sulfuric acid (0.75 mL)[12] at 0 °C and then stirred 2.5 h at room temperature. The mixture was cooled to 0 °C, treated with aqueous sodium hydroxide solution (10 N, 2.82 mL), and extracted with benzene.

The extract was washed with aqueous sodium bisulfite solution, dried, and concentrated to yield the crude diketone (1.18 g), which was dissolved in methanol (30 mL) containing hydrochloric acid (4 N, 9 mL) and heated in reflux for 2.5 h. After cooling to 0 °C, the mixture was made basic (10 N NaOH, 4.7 mL) and stirred for 2 h at room temperature.

Extraction with benzene followed by chromatography on silica gel yielded pure **27** (354 mg): mp 168–171 °C; $[\alpha]^{25}_D$ +139.2° (*c* 1.0, $CHCl_3$); UV max (95% ethanol) 240 nm (ϵ 17 350).

(−)-Estra-4,9-diene-3,17-dione (21) and (+)-Estra-5(10),-9(11)-diene-3,17-dione (22). The crude reduction product **19** (R = H) (10.1 g, ~80–90% purity) dissolved in acetone at room temperature was treated with aqueous sulfuric acid (1 N, 25 mL), stirred for 2 h, and then cooled to 0 °C. To this mixture was added a fresh solution of Jones chromic acid mixture (37.5 mL) over 15 min followed by stirring at room temperature for 2 h. An aqueous solution of sodium bisulfite (1%, 300 mL) was added, and the tetraketone was extracted with benzene. Chromatography of the crude product on silica gel (420 g) yielded pure **20** (7.7 g) on elution with ether–benzene mixtures (2:1 and 4:1) and ether alone: IR ($CHCl_3$) 1740 (cyclopentanone), 1715 (cyclohexanone and dioxooctyl) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.13 (s, 3, $COCH_3$), 1.17 (s, 3, C_{7a}–CH_3). Anal. Calcd for $C_{18}H_{26}O_4$: C, 70.56; H, 8.55. Found: C, 70.38; H, 8.52.

A solution of **20** (1 g) in toluene (25 mL) was heated at reflux for 16 h with piperidinium acetate (200 mg) and then taken to dryness. The residue was dissolved in dichloromethane, washed with acid (1 N, H_2SO_4), and then chromatographed on silica gel (89 g) to yield pure **22** (319 mg) and pure **21** (323 mg), as judged by TLC.

Crystallization of the first fraction from an ether–hexane mixture gave analytically pure **22**: mp 107–108 °C; $[\alpha]^{25}_D$ +335° (*c* 1.0185, CH_3OH); UV max (95% ethanol) 250 nm (ϵ 20 000); IR ($CHCl_3$) 1730 (cyclopentanone and β,γ-unsaturated cyclohexenone) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.61 (t, J = 3 Hz, C_{11}–H), 0.87 (s, 3, C_{13}–CH_3). Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 79.99; H, 8.25.

The later fraction on crystallization from an ethyl acetate–hexane mixture yielded analytically pure **21**: mp 143–144 °C; $[\alpha]^{25}_D$ −191.4° (*c* 0.4858, CH_3h); UV max (95% ethanol) 301 nm (ϵ 20 600); IR ($CHCl_3$) 1740 (cyclopentanone), 1660, 1610 (cyclohexenone) cm^{-1}; ^1H NMR ($CDCl_3$) δ 5.7 (s, 1, C_4–H), 1.02 (s, 3, C_{13}–CH_3). Anal. Calcd for $C_{18}H_{22}O_2$: C, 79.96; H, 8.20. Found: C, 80.00; H, 7.95.

To isomerize **22** to **21** the pure diene **22** (500 mg) was dissolved in toluene (15 mL) containing *p*-toluenesulfonic acid (50 mg) and heated at reflux for 45 min. After this time the solution was washed successively with an aqueous sodium bicarbonate solution and brine and dried over anhydrous sodium sulfate. Chromatography of the crude product (510 mg) on silica gel (50 g) yielded chromatographically pure **21** (311 mg), mp 139–142 °C. Crystallization from a mixture of ethyl acetate–hexane yielded pure material: mp 142–143 °C; $[\alpha]^{25}_D$ −191 ° (*c* 0.556, CH_3OH).

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Registry No.—**6**, 30693-66-4; **7**, 65121-17-7; (*S*)-**8**, 65166-11-2; (±)-**8**, 30655-84-6; **9**, 23027-03-4; **10**, 34862-10-7; (*S*)-**11**, 36288-49-0; (±)-**11**, 30658-25-4; **12**, 65121-18-8; **15**, 35919-90-5; **16**, 35811-68-8; **17**, 36668-14-1; **18**, 65206-88-4; **19** (R = H) isomer I, 65166-12-3; **19** (R = H) isomer II, 65166-13-4; **19** (R = Ac) isomer I, 65166-14-5; **19** (R = Ac) isomer II, 65166-15-6; **20**, 65166-16-7; (−)-**21**, 5173-46-6; (+)-**22**, 2503-06-2; **23** isomer I, 65149-41-9; **23** isomer II, 65121-03-1; **24** isomer I, 65121-04-2; **24** isomer II, 65121-05-3; **25** isomer I, 65166-09-8; **25** isomer II, 65166-10-1; **26** isomer I, 65121-06-4; **26** isomer II, 65121-07-5; (+)-**27**, 734-32-7; 2-methyl-3-oxo-1-cyclohexenepropionic acid, 65121-08-6; (−)-(2*R*,3*R*)-butanediol, 24347-58-8; (*R*,*S*)-tetrahydro-6-[3-(2-methyl-1,2-ethylenedioxol-2-yl)propyl]-2*H*-pyran-2-one, 30655-83-5; catechol, 120-8-9; vinyl chloride, 75-01-4; 2-methylcyclopentane-1,3-dione, 765-69-5.

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silica gel (0.2–0.5 mm), and thin-layer chromatograms (TLC) were run on Brinkmann silica gel G plates with a UV indicator and developed in an ethyl acetate–benzene mixture (1:1). Spots were made visible by UV light, iodine vapor, or spraying with a 50% aqueous *p*-toluenesulfonic acid solution and heating at 120 °C. Varian HA-100 and A-60 spectrometers were employed to record proton magnetic resonance spectra (^{1}H NMR), and the chemical shifts are relative to tetramethylsilane as an internal standard. Infrared (IR) spectra were recorded on a Beckman IR-9 spectrometer, and ultraviolet (UV) spectra were recorded on a Cary Model 14M spectrophotometer.

(20) AK4 is a 5% palladium on carbon catalyst prepared at F. Hoffmann-La Roche & Co., AG, Basle, Switz.

Formamidinesulfinic Acid Reduction of Dihydrocodeinone Derivatives

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Treatment of dihydrocodeinone (**1f**) with formamidinesulfinic acid afforded mixtures of dihydrothebainone (**3a**) and dihydroisothebainol (**4a**) under both homogeneous and heterogeneous conditions. Similar treatment of 14-hydroxydihydrocodeinone (**1g**) and 3-*O*-methylnatrexone (**1h**) gave predominantly the desired 6β-alcohols (**2g** and **2h**) under heterogeneous conditions. Under homogeneous conditions, **1g** and **1h** yielded mixtures of the 6β-alcohols and the dihydrothebainone derivatives **3b** and **3c**. Deuterium oxide studies established that ketone enolization was involved in the formamidinesulfinic acid reductions.

The reduction of dihydromorphinones **1a–e** to the corresponding 6β-alcohols **2a–e** using formamidinesulfinic acid was first reported by Chatterjie and co-workers.[1,2] Since the stereoselectivity of the new procedure was opposite to that of hydride reductions, its preparative potential was obvious.

In contrast, formamidinesulfinic acid reductions of dihydrocodeinone derivatives were less straightforward. Chatterjie and co-workers[2] reported the reduction of dihydrocodeinone (**1f**) to dihydroisocodeine (**2f**) in 63% yield. Due to the limited solubility of **1f** in the reaction medium,[3] ethanol was added as a cosolvent (homogeneous conditions)[4] in this experiment. However, our attempts to duplicate this reaction yielded dihydrothebainone (**3a**) as the major product.[5] In addition, Cone[6] reported the reduction of 14-hydroxydihydrocodeinone (**1g**) to 6β-alcohol **2g** with formamidinesulfinic acid in the absence of ethanol (heterogeneous conditions).[7]

As we had a need for the dihydroisocodeine compounds, we investigated the formamidinesulfinic acid reduction of dihydrocodeinones **1f–h** under various reaction conditions. During the course of our investigation, we discovered that use of deuterium oxide in the reaction mixture led to the polydeuterated 6β-alcohols.

Results and Discussion

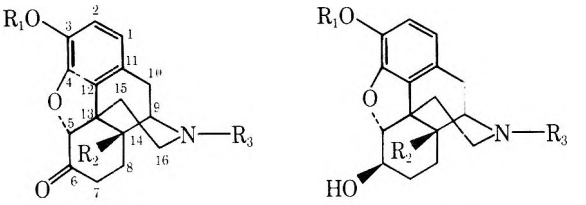
Compounds **1f–h** were treated with formamidinesulfinic acid under both homogeneous[4] and heterogeneous[6b] conditions. In addition, dihydrocodeinone (**1f**) was subjected to four additional experiments in attempts to prepare dihydroisocodeine (**2f**) directly. The results are summarized in Table I.

A comparison of the homogeneous and heterogeneous reactions showed that use of the organic cosolvent facilitated opening of the 4,5α-ether bridge. Moreover, the additional experiments on **1f** further demonstrated that bridge opening did not involve ethoxide formation (condition D) or the reaction temperature (condition E). The subsequent reduction of dihydrothebainone (**3a**) to dihydroisothebainol (**4a**)[8] could be forced to completion by use of a longer reaction time and excess reagent (condition F).

In the case of the dihydromorphinones, the 14-hydroxyl group was evidently nonessential for ketone reduction.[2,9] However, the results with the dihydrocodeinones indicated that the 14-hydroxyl group was necessary to obtain ketone reduction rather than 4,5α-ether bridge opening. For example, some 14-hydroxydihydroisocodeine (**2g**) and 3-*O*-methyl-6β-naltrexol (**2h**) were isolated even under the homogeneous conditions, while no dihydroisocodeine (**2f**) was ever obtained from **1f**. Further study is needed to elucidate the effect of the 14-hydroxyl group.

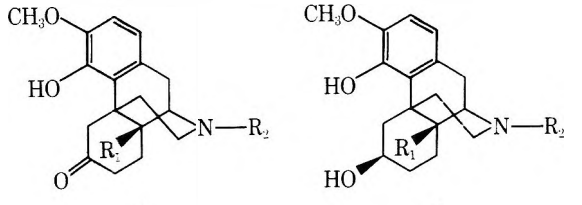
Dihydrocodeinone (**1f**) was also subjected to the heterogeneous reaction conditions with three further variations: (1) omission of the formamidinesulfinic acid, (2) use of sulfur dioxide in place of formamidinesulfinic acid, and (3) use of hydrochloric acid in place of sodium hydroxide. In each case the starting material was recovered unchanged in 98–100% yield. Attempts to reduce naltrexone (**1a**)[1] using variations (1) or (2) above also gave no reduction. These data indicated that both the formamidinesulfinic acid and the sodium hydroxide were necessary for reaction to occur.

Chart I



1 2

a, R_1 = H; R_2 = OH; R_3 = CH_2-c-C_3H_5
b, R_1 = H; R_2 = OH; R_3 = $CH_2CH{=}CH_2$
c, R_1 = H; R_2 = OH; R_3 = CH_2-c-C_4H_7
d, R_1 = H; R_2 = OH; R_3 = CH_3
e, R_1 = R_2 = H; R_3 = CH_3
f, R_1 = R_3 = CH_3; R_2 = H
g, R_1 = R_3 = CH_3; R_2 = OH
h, R_1 = CH_3; R_2 = OH; R_3 = CH_2-c-C_3H_5



3 4

a, R_1 = H; R_2 = CH_3
b, R_1 = OH; R_2 = CH_3
c, R_1 = OH; R_2 = CH_2-c-C_3H_5

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Table I. Formamidinesulfinic Acid Reduction of Dihydrocodeinone Derivatives

Ketone	Registry no.	Conditions[a]	Products (yield)[b]
1f	125-29-1	A	**3a** (69%) and **4a** (10%)
		B	**3a** (33%) and **4a** (36.5%)[c]
		C	**3a** (77.5%)
		D	**3a** (89%)
		E	Mixture of **1f** and **3a** (100%)[d]
		F	**4a** (54%)
1g	76-42-6	A	**2g** (32%) and **3b** (25%)[e]
		B	**2g** (101%)[f]
1h	16617-07-5	A	**2h** (44%) and **3c** (44%)
		B	**2h** (81.5%) and **3c** (16.5%)[g]

[a] Conditions: A, homogeneous (see text); B, heterogeneous (see text); C, same as B except that reaction was run at room temperature; D, same as A except that *p*-dioxane was used in place of ethanol; E, same as A except that reaction was run overnight at room temperature; F, same as A except for increased reaction time and use of excess reagent. [b] Except where indicated, yields are for chromatographed or crystallized samples. [c] One run under these conditions yielded exclusively **4a** (30%). [d] The experiment was stopped when **3a** was observed as the only product being formed. [e] One run under these conditions also yielded **4b** (15.5%). Compound **4b** was not observed in other runs. [f] The product was contaminated with a trace of **3b**. [g] The product was contaminated with **2h**. Compound **3c** was not purified.

It has been suggested that enolization of the ketone is necessary for the formamidinesulfinic acid reduction to occur.[10] Consequently, we repeated the heterogeneous reaction on dihydrocodeinone (**1f**) using deuterium oxide as the solvent, and we obtained dihydrothebainone-5,7,7-d_3 (**3a**) and dihydroisothebainol-5,5,6α,7,7-d_5 (**4a**). In like manner, 6β-naltrexol-5β,6α,7,7-d_4 (**2a**) was prepared from naltrexone (**1a**) and dihydroisomorphine-5β,6α,7,7-d_4 (**2e**) from dihydromorphinone-5β,7-d_2 (**1e**). The deuterated compounds were analyzed by mass spectrometry and NMR (^{1}H and ^{13}C).

The deuterium results established that enolization of the 6-keto compounds occurred under the reaction conditions[11] and that the 6α proton probably came from the solvent. Thus, in the present case, the ease with which enolization takes place may account for the ease with which the observed reactions take place. Moreover, the observed stereoselectivity of the reduction may be due to the fact that it is the enol being reduced. In addition, since back-exchange cannot occur once the reduction has taken place, the use of deuterium oxide in formamidinesulfinic acid reductions provides a convenient procedure for preparing the polydeuterated 6β-alcohols. Such compounds are potentially useful in metabolism studies.

The synthesis of compounds **2g** and **2h** demonstrated that 14-hydroxydihydrocodeinones could be reduced directly to the corresponding 6β-alcohols under the appropriate reaction conditions. Moreover, since compound **2f** could be readily obtained by methylation of dihydroisomorphine (**2e**), the reduction procedure was also applicable to the synthesis of dihydroisocodeine derivatives lacking a 14-hydroxyl group. For both **2g** and **2f** the new procedure was preferable to the previously reported synthesis.[12,13]

Our observations further demonstrate that formamidinesulfinic acid is a potentially valuable reagent in organic synthesis. It is also clear that its reactions are influenced by a number of variables. Further investigations are necessary to elucidate the full nature and magnitude of those variables.

Experimental Section

Infrared (IR) spectra were recorded on a Perkin-Elmer 467 spectrophotometer. Proton magnetic resonance (^{1}H-NMR) spectra were obtained on a Varian HA-100 spectrometer. All chemical shifts are reported in δ values relative to a tetramethylsilane standard. Carbon magnetic resonance (^{13}C-NMR) spectra were determined at 25.03 MHz on a JEOL JNM-PS-100 FT NMR spectrometer interfaced with a Nicolet 1085 20K computer system. Mass spectra were run on an AEI MS-902 mass spectrometer. Analyses were performed by Integral Microanalytical Laboratories, Inc., Raleigh, N.C.

Formamidinesulfinic Acid Reductions Using Homogeneous Conditions.[4] A. General Procedure. A solution of NaOH (0.95 g, 0.024 mol) and formamidinesulfinic acid (0.60 g, 0.0056 mol) in H_2O (60 mL) was added to a solution of the ketone (0.50 g, 0.0017 to 0.0014 mol) in EtOH (120 mL). The resultant mixture was stirred under nitrogen at 80–85 °C for 1 h. It was then cooled to room temperature and the EtOH was removed in vacuo. If a solid precipitated at this point, it was collected and washed with H_2O. The aqueous solution (or filtrate) was then acidified with concentrated HCl and rebasified with concentrated NH_4OH. The aqueous phase was next extracted with $CHCl_3$ (3×), and the combined $CHCl_3$ extracts were dried (Na_2SO_4) and evaporated. If necessary, product mixtures were subsequently chromatographed on silica gel plates (1 mm) to obtain the pure compounds.

B. Dihydrocodeinone (1f). Chromatography afforded 0.35 g (69%) of dihydrothebainone (**3a**) and 0.05 g (10%) of dihydroisothebainol (**4a**). Compound **3a** was obtained as a white foam: IR (CH_2Cl_2) 1715 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.38 (s, 3 H), 3.78 (s, 3 H), 4.25 (d, 1 H, one 5-H, J = 14 Hz), 6.60 ppm (ABq, 2 H). Except for the aromatic carbon signals, the ^{13}C-NMR spectrum of **3a** was similar to that reported for the corresponding 4-desoxy compound.[14] Crystallization of the foam from acetone/hexane (1:1) yielded clear, off-white needles, mp 148–150 °C (lit.[15] 144–146 °C; lit.[16] 138–148 °C). Anal. Calcd for $C_{18}H_{23}NO_3 \cdot H_2O$: C, 67.68; H, 7.89; N, 4.38. Found: C, 67.45; H, 7.64; N, 4.18.

During a repeat of this experiment using 0.20 g of dihydroisocodeine (**2f**), the mixture was heated for 23.5 h with more reducing agent (one-half original amount) being added after 18.5 h. After cooling, the reaction mixture was stirred overnight at room temperature. Subsequent work-up and chromatography afforded 0.11 g (54%) of **4a** as an off-white foam: IR (CH_2Cl_2) no carbonyl; ^{1}H-NMR ($CDCl_3$) δ 2.34 (s, 3 H), 3.3–3.9 (m, 3 H, two 5-H and 6α-**H**), 3.79 (s, 3 H), 6.62 ppm (ABq, 2 H). The ^{13}C-NMR spectrum of **4a** was also similar to that reported for the corresponding 4-desoxy compound.[14] In particular the resonances at δ 25.66 (C-8), 35.41 (C-7), 45.46 (C-5), and 67.79 ppm (C-6) were helpful in determining the stereochemistry of the alcohol. Crystallization of the foam was unsuccessful. Anal. Calcd for $C_{18}H_{25}NO_3$: 303.1834. Found: 303.1831.

C. 14-Hydroxydihydrocodeinone (1g). The reaction yielded 0.16 g (32%) of 14-hydroxydihydroisocodeine (**2g**) and 0.13 g (25%) of 14-hydroxydihydrothebainone (**3b**). Compound **2g** was identical to the product from the heterogeneous reduction. Compound **3b** was obtained as a tan foam: IR ($CHCl_3$) 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 2.36 (s, 3 H), 3.80 (s, 3 H), 3.95 (d, 1 H, one 5-H, J = 14 Hz), 6.62 ppm (ABq, 2 H). Except for the effects of the 14-hydroxyl group,[17] the ^{13}C-NMR spectrum of **3b** was identical to that of **3a**. Crystallization of the foam was unsuccessful. Anal. Calcd for $C_{18}H_{23}NO_4$: 317.1627. Found: 317.1630.

From a repeat reaction was isolated 0.08 g (15.5%) of 14-hydroxydihydroisothebainol (**4b**) as an off-white foam. Compound **4b** was identified by its IR and NMR (^{1}H and ^{13}C) spectra.

D. 3-*O*-Methylnaltrexone (1h).[18] From the reduction of **1h** was obtained 0.22 g (44%) of 3-*O*-methyl-6β-naltrexol (**2h**) as a white solid which precipitated after the removal of EtOH. The white solid was identical to material prepared using the heterogeneous conditions. Subsequent work-up of the filtrate provided 0.22 g (44%) of *N*-cyclopropylmethyl-14-hydroxy-*N*-nordihydrothebainone (**3c**) as a viscous oil: IR ($CHCl_3$) 1710 cm^{-1}; ^{1}H-NMR ($CDCl_3$) δ 3.80 (s, 3 H), 3.93 (d, 1 H, one 5-H, J = 14 Hz), 6.60 (ABq, 2 H). Except for the effects of the *N*-cyclopropylmethyl group,[17] the ^{13}C-NMR spectrum of **3c** was identical to that of **3b**. Anal. Calcd for $C_{21}H_{27}NO_4$: 357.1940. Found: 357.1943.

Formamidinesulfinic Acid Reductions Using Heterogeneous Conditions.[6b] A. General Procedure. The ketone (0.50 g, 0.0017 to 0.0014 mol) was suspended in H_2O (50 mL), and 0.32 M NaOH (0.64 g in 50 mL) was added until the suspension was basic. Formamidinesulfinic acid (0.73 g, 0.0068 mol) was dissolved in the remaining NaOH solution and subsequently added to the suspension of ketone. The resultant mixture was stirred under nitrogen at 50–55 °C until the starting material had been consumed (17 to 30 h). The mixture was then cooled to room temperature and was worked up in the same manner as the aqueous phases obtained from the homogeneous reactions.

B. Dihydrocodeinone (1f). Chromatography of the product mixture afforded 0.165 g (33%) of **3a** and 0.185 g (36.5%) of **4a**. A reaction time of 90 h was required to obtain exclusively **4a**.

C. 14-Hydroxydihydrocodeinone (1g). The reduction afforded 0.51 g (101%) of **2g** as a white foam. The IR and ^{1}H-NMR spectra of the product were identical to those of a reference sample supplied by Dr. Cone. Careful TLC analysis showed that the crude product was contaminated with a trace amount of **3b**. Crystallization of the foam from acetone/water (1:1) gave white needles, mp 167–168 °C (lit.[19] 166–167 °C).

D. 3-*O*-Methylnaltrexone (1h). When the reaction mixture was cooled, **2h** (0.41 g, 81.5%) precipitated as a white solid: mp 172–173 °C; IR ($CHCl_3$) no carbonyl; ^{1}H-NMR ($CDCl_3$) δ 3.46–3.72 (m, 1 H, 6α-**H**), 3.84 (s, 3 H), 4.47 (d, 1 H, 5β-**H**, J = 6 Hz), 6.63 ppm (ABq, 2 H). The ^{13}C-NMR of **2h** was very similar to that of 6β-naltrexol (**2a**).[17] Anal. Calcd for $C_{21}H_{27}NO_4$: C, 70.56; H, 7.61; N, 3.92. Found: C, 70.43; H, 7.84; N, 3.75.

Extraction of the filtrate afforded 0.08 g (16.5%) of a yellow foam. TLC analysis showed a major (**3c**) and a minor (**2h**) component. On repeat runs of this reaction the precipitated product was sometimes contaminated with **3c**.

Deuterium Experiments. A. Dihydrocodeinone (1f). Repetition of the heterogeneous reaction on a one-fifth scale using D_2O as the solvent afforded 58 mg of deuterated **3a** (mass spectrum: d_0, 9.6%; d_1, 26.5%; d_2, 36.3%; d_3, 21.4%; d_4, 6.2%) and 9 mg of deuterated **4a** (mass spectrum: d_0, 0.4%; d_1, 1.4%; d_2, 2.3%; d_3, 14.3%; d_4, 37.8%; d_5, 36.7%; d_6, 7.1%). In the ^{13}C-NMR spectrum of the major product the C-5 resonance was partially collapsed while the C-7 resonance was totally collapsed. Moreover, the C-6 resonance was extremely weak due to the removal of the nearby protons needed for efficient ^{13}C–^{1}H dipolar relaxation.[20] The lower deuterium content of **3a** was due in part to back-exchange during work-up and chromatography.

B. Naltrexone (1a). Reduction[1] of naltrexone (136 mg) using D_2O as the solvent afforded 128 mg of deuterated 6β-naltrexol (**2a**) (mass spectrum: d_1, 3.0%; d_2, 20.3%; d_3, 43.4%; d_4, 32.0%; d_5, 1.3%). In the ^{13}C-NMR spectrum of the product the C-5 resonance was partially collapsed while the C-6 and C-7 resonances were totally collapsed.

C. Dihydromorphinone (1e). The starting material (285 mg) was subjected to an exchange reaction using D_2O and potassium *tert*-butoxide to get 273.5 mg of deuterated **1e** (mass spectrum: d_0, 7.3%; d_1, 41.4%; d_2, 37.9%; d_3, 13.4%). A 200-mg sample of this material was subsequently reduced[2] using D_2O as the solvent. This reaction afforded 45 mg of deuterated dihydroisomorphine (**2e**) (mass spectrum: d_2, 6.3%; d_3, 34.2%; d_4, 56.4%; d_5, 3.1%). The C-5, C-6, and C-7 resonances were completely collapsed in the ^{13}C-NMR spectrum of the product.

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Registry No.—**2f,** 795-38-0; **2g,** 61949-73-3; **2h,** 65150-66-5; **3a,** 847-86-9; **3b,** 6199-38-8; **3c,** 65150,67-6; **4a,** 2447-32-7; formamidinesulfinic acid, 1758-73-2.

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(6) (a) E. J. Cone, *J. Chromatogr.*, **129**, 355 (1976); (b) E. J. Cone, personal communication.
(7) This reaction was carried out at 50–55 °C. Use of a higher reaction temperature led to a complex mixture.[6b]
(8) We have used "iso" to distinguish **4a** from the corresponding 6α isomer.
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Reactions of Magnesium Hydrides. 1. Reduction of Organic Functional Compounds by Magnesium Hydride and 2,6-Diisopropylphenoxymagnesium Hydride

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The reducing properties of magnesium hydride and tetrahydrofuran-soluble 2,6-diisopropylphenoxymagnesium hydride toward some representative organic functional compounds such as benzaldehyde, 4-*tert*-butylcyclohexanone, 1-iodo-, 1-bromo-, and 1-chlorodecanes, iodobenzene, nitrobenzene, ethyl benzoate, benzoyl chloride, 2,2,6,6-tetramethyl-*trans*-4-hepten-3-one, octene, and phenylacetylene have been studied. For the first time it has been shown that MgH_2 (if prepared in an active form) and HMgOR compounds are very effective reducing agents in the reduction of certain organic functional groups. The fact that these hydrides reduce some functional groups at a much faster rate than others indicates their usefulness in functional group selectivity.

Introduction

Simple and complex metal hydrides of boron and aluminum have been known for over two decades for their reducing properties toward organic functional compounds.[1] Some of these hydrides have been found to be extremely reactive but have poor selectivity. For example, $LiAlH_4$ is a very powerful reducing reagent, capable of reducing most functional groups, but is of little value for selective reductions. On the other hand,

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Table I. Reactions of Magnesium Hydride (I)[a] and 2,6-Diisopropylphenoxymagnesium Hydride (II)[b] with Some Representative Functional Groups

Hydride reagent[c]	Organic substrate[c]	Registry no.	Reaction condition[f]	Product(s) (yield(s),[e] %)
I	1-Iododecane	2050-77-3	−40 °C, 1 h	*n*-Decane (10)
			0 °C, 1 h	*n*-Decane (40)
			RT, 24 h	*n*-Decane (100)
II	1-Iododecane		−40 °C, 1 h	*n*-Decane (5)
			0 °C, 1 h	*n*-Decane (20)
			RT, 24 h	*n*-Decane (100)
I	1-Bromodecane	112-29-8	RT, 24 h	*n*-Decane (5)
II	1-Bromodecane		RT, 24 h	*n*-Decane (5)
I	1-Chlorodecane	1002-69-3	RT, 24 h	*n*-Decane (0)
II	1-Chlorodecane		RT, 24 h	*n*-Decane (0)
I	Iodobenzene	591-50-4	RT, 24 h	Benzene (0)
II	Iodobenzene		RT, 24 h	Benzene (0)
I	Benzaldehyde	100-52-7	−40 °C, 1 h	Benzyl alcohol (100)
II	Benzaldehyde		−40 °C, 1 h	Benzyl alcohol (100)
I	Ethyl benzoate	93-89-0	−40 °C, 1 h	Benzyl alcohol (25)
			0 °C, 1 h	Benzyl alcohol (32)
			RT, 24 h	Benzyl alcohol (79)
II	Ethyl benzoate		−40 °C, 1 h	Benzyl alcohol (8)
			0 °C, 1 h	Benzyl alcohol (26)
			RT, 24 h	Benzyl alcohol (82)
I	Benzoyl chloride	98-88-4	−40 °C, 1 h	Benzyl alcohol (20)
			0 °C, 1 h	Benzyl alcohol (45)
			RT, 24 h	Benzyl alcohol (85)
II	Benzoyl chloride		−40 °C, 1 h	Benzyl alcohol (16)
			0 °C, 1 h	Benzyl alcohol (40)
			RT, 24 h	Benzyl alcohol (85)
I	2,2,6,6-Tetramethyl-*trans*-4-hepten-3-one	20859-13-6	RT, 24 h	1,4 Product (4), 1,2 Product (92)
II	2,2,6,6-Tetramethyl-*trans*-4-hepten-3-one		RT, 24 h	1,4 Product (7), 1,2 Product (80)
I	4-*tert*-Butylcyclohexanone[d]	98-53-3	RT, 1 h	4-*tert*-Butylcyclohexanol (100) (cis/trans alcohol = 24:76)
II	4-*tert*-Butylcyclohexanone[d]		RT, 1 h	4-*tert*-Butylcyclohexanol (100) (cis/trans alcohol = 83:17)
I	Benzonitrile	100-47-0	−40 °C, 1 h	Benzonitrile (50), Benzaldehyde (10), Benzyl alcohol (0)
			0 °C, 1 h	Benzonitrile (35), Benzaldehyde (15), Benzyl alcohol (5)
			RT, 24 h	Benzonitrile (0), Benzaldehyde (3), Benzyl alcohol (32)
II	Benzonitrile		−40 °C, 1 h	Benzonitrile (60), Benzaldehyde (7), Benzyl alcohol (0)
			0 °C, 1 h	Benzonitrile (40), Benzaldehyde (32), Benzyl alcohol (2)
			RT, 24 h	Benzonitrile (0), Benzaldehyde (8), Benzyl alcohol (0)
I	Nitrobenzene	98-95-3	RT, 24 h	Nitrobenzene (25)
II	Nitrobenzene		RT, 24 h	Nitrobenzene (20)
I	1-Octene	111-66-0	RT, 24 h	No reaction
I	Phenylacetylene	536-74-3	RT, 24 h	No reaction

[a] Registry no: 7693-27-8. [b] Registry no.: 65276-36-0. [c] Molar ratio of hydride reagent to substrate is 1:1 for MgH_2, 2:1 for II. [d] Molar ratio of hydride reagent to ketone is 4:1. [e] Yields were determined by GLC using suitable internal standard. [f] RT = room temperature.

sodium borohydride, which is a milder reducing agent, is much more useful as a selective reducing agent for compounds containing two or more reducible functional groups. However, because of certain deficiencies suffered by many complex metal hydrides (such as cost, difficulty of preparation, ease of oxidation, etc.), there has been considerable interest in finding new hydrides which can function as ideal reducing agents. In this connection, we have prepared a large number of complex metal hydrides, most of which suffer the same drawbacks as many of the earlier hydrides prepared by other workers.

It does seem rather surprising that although many boron and aluminum hydrides have been prepared and evaluated as selective reducing agents, we can find no mention in the literature of MgH_2 or any of its derivatives (e.g., HMgCl, HMgOR, $HMgNR_2$, and HMgR) undergoing evaluation as reducing agents except for a casual comment that MgH_2 is a very poor reducing agent toward organic functional compounds. Magnesium hydride has been neglected by organic chemists perhaps because of its insoluble nature in all solvents in which it does not react, a fact which might lead one to think that for this reason it would not be a good reducing agent. Recently, we have been able to prepare a very reactive form of magnesium hydride and have demonstrated its ready reactivity with MgX_2, MgR_2, $Mg(OR)_2$, and $Mg(NR_2)_2$ compounds to produce THF-soluble hydridomagnesium halides,[2] alkyl and aryl magnesium hydrides,[3] and alkoxy- and dialkylamino magnesium hydrides.[4] In this report we present the reactions of magnesium hydride and a THF-soluble HMgOR compound (2,6-diisopropylphenoxymagnesium hydride) with several organic functional compounds indicating the heretofore unreported utility of these compounds as selective reducing agents toward organic substrates.

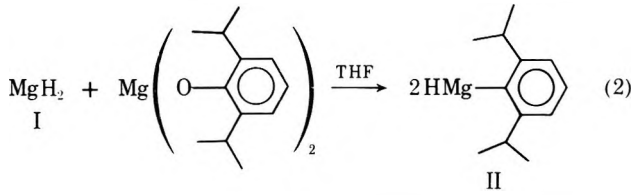
Results and Discussion

A THF slurry of an active form of MgH_2 was prepared by the reaction of diethyl- or diphenylmagnesium with $LiAlH_4$ in diethyl ether followed by separation of the insoluble MgH_2

from the ether soluble $LiAlR_2H_2$ compound and the addition of THF to the ether wet MgH_2 (eq 1).

$$LiAlH_4 + R_2Mg \xrightarrow{Et_2O} MgH_2\downarrow + LiAlH_2R_2 \quad (1)$$

Reaction of this magnesium hydride with bis(2,6-diisopropylphenoxy)magnesium in THF yielded 2,6-diisopropylphenoxymagnesium hydride which is soluble and stable in THF at room temperature (eq 2). Although MgH_2 is known to be



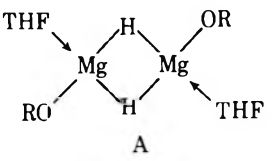
II (2)

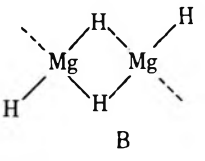
polymeric, we have found this new hydride (II) to be dimeric in refluxing THF.

Magnesium hydride and 2,6-diisopropylphenoxymagnesium hydride were allowed to react with some representative organic functional compounds. The results are reported in Table I. Both magnesium hydride and 2,6-diisopropylphenoxymagnesium hydride reduce 1-iododecane to *n*-decane in quantitative yield after a 24-h reaction period at room temperature. On the other hand, 1-bromodecane, 1-chlorodecane, and iodobenzene were found to be relatively inert to these hydrides. These results indicate better selectivity for C–I reduction to C–H in the presence of other halides since most of the other known hydride reagents that reduce alkyl iodides also reduce bromides and chlorides under the same conditions. For example, $LiAlH_4$, reduced 1-iododecane, 1-bromodecane, and 1-chlorodecane under similar conditions (24 h, room temperature) to give *n*-decane in yields of 100, 100, and 68%, respectively.

Benzaldehyde, ethyl benzoate, and benzoyl chloride were reduced to produce benzyl alcohol in 80–100% yield. In these reactions, magnesium hydride appears to have a slightly higher reactivity than the alkoxylmagnesium hydride although MgH_2 is insoluble in THF, whereas the HMgOR compound is soluble. 2,6-Diisopropylphenoxymagnesium hydride as well as MgH_2 reduce benzaldehyde to benzyl alcohol in 100% yield at −40 °C within 1 h. Under the same conditions, ethyl benzoate and benzoyl chloride are reduced to benzyl alcohol in only 8% and 16% yield, respectively. However, under more forcing conditions (0 °C for 1 h or room temperature for 24 h) it appears that both compounds are reduced at approximately the same rate although at a rate much slower than benzaldehyde. Thus it would appear that aldehydes can be reduced selectively in the presence of Cl, Br, C(=O)Cl and C(=O)OR groups as well as C=C, C≡C, CN, and NO_2 (to be discussed later).

Magnesium hydride and 2,6-diisopropylphenoxymagnesium hydride also react with the enone, 2,2,6,6-tetramethyl-*trans*-4-hepten-3-one, to give predominantly 1,2-reduction (92–80%). Interestingly, 4-*tert*-butylcyclohexanone was reduced rapidly and quantitatively to 4-*tert*-butylcyclohexanol. The ratio of cis to trans alcohol was substantially different in both cases, e.g., 24:76 ratio for magnesium hydride and 83:17 for 2,6-diisopropylphenoxymagnesium hydride, indicating that the HMgOR compound is not reacting as MgH_2 as a result of disproportionation (eq 3). Formation of the cis alcohol in higher yield in the case of reagent II can be explained on steric grounds. The HMgOR compound is dimeric in THF, probably associated via double hydrogen bridge bonds (A), which provides for considerable steric hindrance by the bulky 2,6-diisopropylphenoxy groups. Although MgH_2, which is insoluble in THF, is also believed to be highly associated (linear polymer, B), the hydridic hydrogens are much





more accessible for reaction than the same hydrogens in II which are flanked by such bulky alkoxy groups.

$$2HMgOR \rightleftharpoons MgH_2 + Mg(OR)_2 \quad (3)$$

The high degree of association of 2,6-diisopropylphenoxymagnesium hydride causes this reagent to be much more selective than $LiAlH_4$ which reduces 4-*tert*-butylcyclohexanone to produce only 10% cis alcohol (equatorial attack of hydride) compared to 83% for the HMgOR compound. This high degree of selectivity warrants a more detailed study of the reaction of HMgOR compounds with various cyclohexanones in order to determine the selectivity for a wide range of hindered ketones.

As for the reactions of benzonitrile and nitobenzene, the expected reduction products were not isolated. Instead unidentified products were formed presumably as a result of free-radical polymerization. 1-Octene and phenylacetylene were found to be unreactive toward MgH_2 and 2,6-diisopropylphenoxymagnesium hydride, which is actually an advantageous result in terms of functional group selectivity. We have found that these hydrides add to olefins and alkynes in the presence of certain transition metal catalysts. We will report in more detail on these results later.

Experimental Section

Reactions were performed under nitrogen at the bench using Schlenk tube techniques.

Analytical. Active hydrogen analyses were carried out by hydrolyzing samples with hydrochloric acid on a standard vacuum line and collecting the gas with a Teopler pump.[5] Magnesium was analyzed by EDTA titration at pH 10 using Eriochrome Black T as indicator. GLPC was performed on an F & M Model 720 or 700 gas chromatograph using a 5% Carbowax 20M column.

Materials. Tetrahydrofuran (Fisher Certified Reagent Grade) was distilled under nitrogen over $NaAlH_4$ prior to use. All organic substrates and authentic samples of products were purchased from Eastman Organic Chemicals and used without further purification.

Diethyl- and diphenylmagnesium were prepared by the reaction of the corresponding organomercury compound with magnesium metal by a previously reported procedure.[6]

Preparation of MgH_2 Slurry in THF. To a well-stirred solution of diethylmagnesium (20.0 mmol) in diethyl ether (50 mL) was added dropwise a diethyl ether solution of $LiAlH_4$ (40 mL of 0.5 M solution, 20.0 mmol) at room temperature. An immediate precipitation of white insoluble solid took place. This reaction mixture was stirred further at room temperature for 1 h and was centrifuged. The supernatant solution was removed by syringe and the solid was washed for 3–4 times with fresh diethyl ether. Finally, the ether was removed by syringe and freshly distilled THF was added to the white solid to make a slurry. It was analyzed and stored in the refrigerator at about 0 °C. Anal. Calcd for MgH_2: Mg:H = 1.00:2.00. Found: 1.00:2.00.

Preparation of 2,6-Diisopropylphenoxymagnesium Hydride in THF by the Reaction of MgH_2 with Bis(2,6-diisopropylphenoxy)magnesium in 1:1 Ratio. Bis(2,6-diisopropylphenoxy)magnesium (10.0 mmol) was prepared by the reaction of 10.0 mmol of dimethylmagnesium in diethyl ether (15 mL) with 2,6-diisopropylphenol (3.6 g, 20.0 mmol) in 25 mL of THF. This reaction mixture was refluxed overnight, diethyl ether was removed under vacuum, and fresh THF was added. The THF solution of bis(2,6-diisopropylphenoxymagnesium (10.0 mmol) was added to a well-stirred solution of magnesium hydride (10.0 mmol) in THF (40 mL) at room temperature. The reaction mixture was further stirred for 2 h to give a clear solution. It was analyzed for magnesium, hydrogen, and alkoxy group. Anal. Calcd for HMgOR: MG:H:OR = 1.00:1.00:1.00. Found; 1.00: 0.97:1.04. 2,6-Diisopropylphenol was analyzed by GLPC analysis of the hydrolyzed sample.

General Reactions of Organic Substrates. A 10-mL Erlenmeyer flask with a Teflon-coated magnetic stirring bar was dried in an oven

and allowed to cool under nitrogen flush, then sealed with a rubber septum. The magnesium hydride slurry or 2,6-diisopropylphenoxymagnesium hydride was syringed into the flask. The low reaction temperature was controlled by a dry ice–acetone or ice–water bath, and then the calculated amount of organic substrate (with internal standard) was added to the stirred reagent. After the designated reaction time, the aliquot of the reaction was taken by syringe and quenched with H_2O. A 10-ft column of 5% Carbowax 20M on Chromosorb W was used to separate benzaldehyde, ethyl benzoate, benzonitrile, nitrobenzene, benzoyl chloride, 2,2,6,6-tetramethyl-*trans*-4-hepten-3-one, phenylacetylene, and their products. A 6-ft 10% Apiezon L 60-805 column was used to separate 1-iododecane, 1-bromodecane, 1-chlorodecane, iodobenzene, 1-octene, and their products. Suitable hydrocarbons were used as internal standards.

Acknowledgement. We are indebted to the Office of Naval Research (Contract No. N00014-67-A-0419-005AD) and the National Science Foundation (Grant No. MPS 7504127) for support of this work.

Registry No.—Diethylmagnesium, 557-18-6; $LiAlH_4$, 16853-85-3; bis(2,6-diisopropylphenoxy)magnesium, 65276-35-9; dimethylmagnesium, 2999-74-8; 2,6-diisopropylphenol, 2078-54-8.

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Reactions of Magnesium Hydrides. 2.[1] Stereoselective Reduction of Cyclic and Bicyclic Ketones by Hydridomagnesium Alkoxides

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The stereochemistry of reduction of 4-*tert*-butylcyclohexanone, 2-methylcyclohexanone, 3,3,5-trimethylcyclohexanone, and camphor with a series of alkoxymagnesium hydrides (ROMgH) has been determined. The hydrides employed in this study are MgH_2, CH_3OMgH, *i*-PrOMgH, *t*-BuOMgH, Ph_3COMgH, PhOMgH, 2,6-$Me_2C_6H_3OMgH$, 2,6-*i*-$Pr_2C_6H_3OMgH$, and 2,6-*t*-$Bu_2C_6H_3OMgH$. The yields are excellent and equatorial or endo attack is observed with unusual selectivity compared to most other hydride reagents.

Introduction

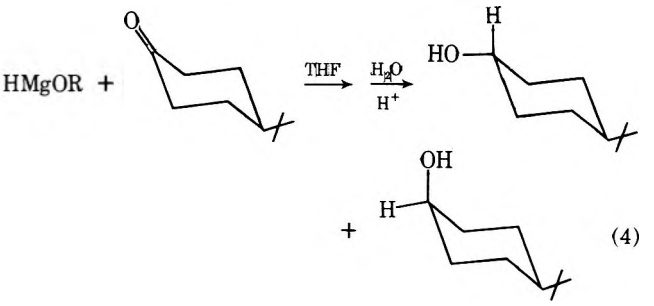
In recent years, the stereoselective reduction of cyclic ketones using hydrides of aluminum and boron has been an area of great interest.[2,3] "Steric approach control" has been considered one of the most important factors responsible for the stereochemical results in these kinds of reactions. For example, $LiAlH(OCH_3)_3$ results in a substantial increase in equatorial attack in the reduction of 4-*tert*-butylcyclohexanone compared to $LiAlH_4$.[3] Recently, lithium trialkylborohydrides have been reported as very selective reducing agents toward cyclic and bicylic ketones[4] presumably because of the increased steric requirement of these hydrides compared to other less sterically hindered metal hydrides. Unfortunately, magnesium hydride has been given little attention as a reducing agent because of its reportedly low reactivity and because of its low solubility in all solvents in which it does not react. However, we have recently found that the reactivity of MgH_2 depends on its method of preparation.[5] For example, MgH_2 prepared by the reaction of dialkylmagnesium compounds with $LiAlH_4$[6] or $MgBr_2$ with NaH[7] (eq 1 and 2) is much more reactive than MgH_2 prepared by other methods.

$$R_2Mg + LiAlH_4 \xrightarrow{Et_2O} MgH_2\downarrow + LiAlR_2H_2 \quad (1)$$

$$NaH + MgBr_2 \xrightarrow{THF} MgH_2 + NaBr \quad (2)$$

This form of MgH_2 reduced 4-*tert*-butylcyclohexanone to 4-*tert*-butylcyclohexanol in quantitative yield within 1 h at room temperature whereas the most reactive MgH_2 prepared previously by other methods performed the same reduction in 33% yield in 24 h. Furthermore, THF soluble hydridomagnesium alkoxides have recently been prepared for the first time in our laboratory and have exhibited a high degree of reactivity toward representative organic functional groups.[1] Because of the obvious advantages of economics and convenience in the preparation of MgH_2 and HMgOR compounds compared to complex metal hydrides of boron and aluminum, we decided to study the stereoselectivity of MgH_2 and HMgOR compounds toward cyclic and bicyclic ketones in some detail (eq 3 and 4).

$$MgH_2 + Mg(OR) \xrightarrow{THF} 2HMgOR \quad (3)$$



(4)

Results and Discussion

The MgH_2 used in these studies was prepared by the reaction of $(C_2H_5)_2Mg$ with $LiAlH_4$ in diethyl ether (eq 1). A slurry of the MgH_2 (prepared by this method) in THF was prepared by removing the supernatant solution containing the ether soluble $LiAl(C_2H_5)_2H_2$ by means of a syringe and then adding freshly distilled THF to the resulting insoluble ether-wet solid (MgH_2). Magnesium hydride prepared in this way was allowed to react with magnesium alkoxides in equal molar ratio in THF in order to prepare the desired alkoxymagnesium hydrides (eq 3, Table I).

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Table I. Preparation of Alkoxymagnesium Hydrides

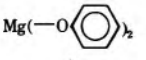
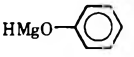
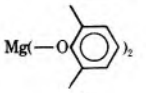
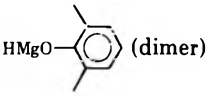
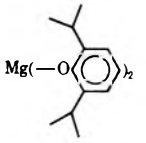
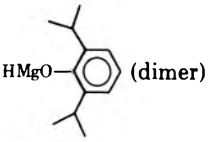
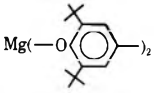
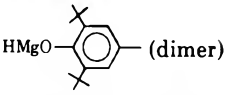
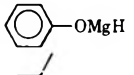
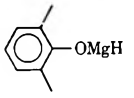
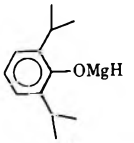
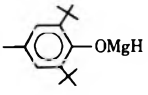
Reactants, mmol		Registry	Reaction	Solubility	Analysis (ratio)	
MgH_2	$Mg(OR)_2$	no.	time, h	in THF	Mg:H:ROH	Product
5.5	$Mg(OCH_3)_2$ (5.5)	109-88-6	40	Insoluble solid	1.00:0.94:-	$HMgOCH_3$
5.4	$Mg(OPr^i)_2$ (5.35)	15571-48-9	24	Insoluble solid	1.00:0.95:-	$HMgOPr^i$
5.1	$Mg(OBu^t)_2$ (5.0)	32149-57-8	24	Insoluble, gelatinous precipitate	1.00:0.95:1.05	$HMgOBu^t$
5.0		7721-07-5	48	Sparingly soluble crystallized from THF	1.00:0.96:1.03	
4.5		65277-19-2	2	Highly soluble	1.00:0.98:1.03	 (dimer)
4.0		65277-20-5	3	Highly soluble	1.00:0.97:1.02	 (dimer)
4.2		65277-21-6	2	Highly soluble	1.00:0.98:1.03	 (dimer)
4.5	$Mg(-OCPh_3)_2$	65277-22-7	2	Highly soluble	1.00:0.97:1.04	$HMg(O-CPh_3)$ (dimer)
	MgH_2		—	Insoluble	1.00:2.02:-	High associated

Table II. Reactions of 4-*tert*-Butylcyclohexanone with Alkoxymagnesium Hydrides at Room Temperature in THF Solvent

					Relative yield, %		
Expt	Hydrides	Registry no.	Molar ratio reagent:ketone	Reaction time, h	Axial-OH	Equatorial-OH	Yield, %
1	MgH_2	7693-27-8	4:1	24	24	76	100
2	MgH_2		2:1	1	53	47	100
				24	53	47	100
3	MgH_2		1:1	1	56	44	90
				24	57	43	92
4	MgH_2		1:2	1	61	39	75
				5	62	38	77
				24	45	55	77
5	CH_3OMgH	32149-52-3	4:1	24	76	24	100
6	*i*-PrOMgH	32149-53-4	2:1	24	9	91	45
			4:1	24	15	85	55
7	*t*-BuOMgH	32149-54-5	4:1	24	69	31	90
8	Ph_3COMgH	65277-23-8	4:1	24	71	29	100
9		32149-55-6	4:1	24	76	24	100
10		65277-24-9	4:1	24	68	32	100
			1:1	24	60	40	92
			0.5:1	24	12.5	87.5	55
11		65276-36-0	4:1	24	83	17	100
12		65277-25-0	4:1	24	82	18	100
			1:1	24	80	20	100
			0.5:1	24	56	44	55

Some time ago during early attempts to prepare alkoxymagnesium hydrides,[8] we reported that these compounds probably dissociate to MgH_2 and $Mg(OR)_2$ since all attempts to prepare HMgOR compounds resulted only in the isolation of physical mixtures of MgH_2 and $Mg(OR)_2$. Unfortunately, previous studies had been carried out in diethyl ether. However, more recently, we have been able to prepare alkoxymagnesium hydrides by the reaction of MgH_2 and $Mg(OR)_2$ in THF[5] and have characterized these compounds by IR, NMR, and x-ray powder diffraction studies. The magnesium alkoxides used in this study (eq 3) for the preparation of the hydridomagnesium alkoxides were prepared by the reaction of 2 molar equiv of the appropriate alcohol with $(CH_3)_2Mg$ in ether/THF solvent under refluxing conditions.

Table III. Reactions of 3,3,5-Trimethylcyclohexanone with Alkoxymagnesium Hydrides at Room Temperature in the THF Solvent and 4:1 Molar Ratio of Reagent/Ketone

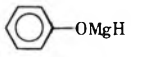
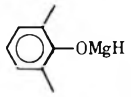
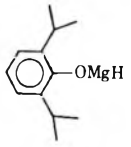
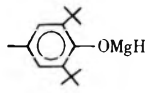
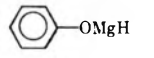
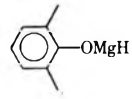
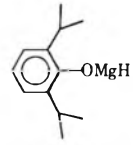
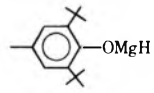
Expt	Hydride	Relative yield, % Axial-OH	Equatorial-OH	Yield, %
13	MgH_2	85	15	92
14	CH_3OMgH	99	1	70
15	*i*-PrOMgH	65	35	40
16	*t*-BuOMgH	99	1	65
17	Ph_3COMgH	99	1	98
18		<99.5	<0.5	100
19		94	6	52
20		99.5	0.5	100
21		>99.5	<0.5	100

Table IV. Reactions of 2-Methylcyclohexanone with Alkoxymagnesium Hydrides at Room Temperature in THF Solvent and 4:1 Molar Ratio of Reagent/Ketone

Expt	Hydride	Relative yield, % Axial-OH	Equatorial-OH	Yield, %
22	MgH_2	35	65	100
23	CH_3OMgH	98	2	97
24	*i*-PrOMgH	68	32	30
25	*t*-BuOMgH	98	2	96
26	Ph_3COMgH	73	27	100
27		99	1	100
28		90	20	100
29		99	1	100
30		99	1	100

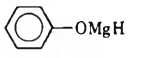
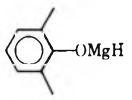
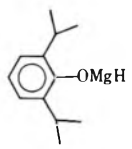
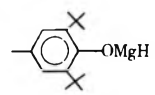
The completion of the reaction was determined by the absence of any gas (methane) during hydrolysis of the product. Interestingly, the alkoxymagnesium hydrides could also be prepared by the addition of equal molar amounts of alcohol to a well-stirred slurry of MgH_2 at −78 °C followed by warming the reaction mixture to room temperature.[9]

$$(CH_3)_2Mg + 2ROH \rightarrow Mg(OR)_2 + 2CH_4 \quad (5)$$

$$ROH + MgH_2 \xrightarrow{THF} HMgOR + H_2 \quad (6)$$

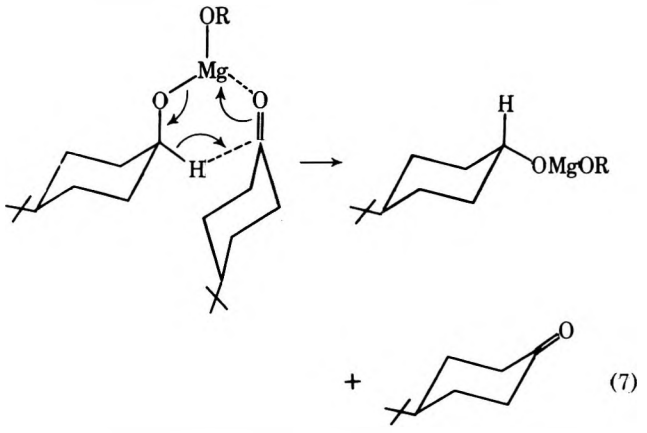
By the reaction of MgH_2 with $Mg(OR)_2$ several HMgOR compounds (where R = Me-, *i*-Pr-, *t*-Bu-, Ph_3C-, Ph, 2,6-dimethylphenyl, and 2,6-di-*tert*-butyl-4-methylphenyl) were prepared (Table I) and allowed to react with four representative ketones, 4-*tert*-butylcyclohexanone, 3,3,5-trimethylcyclohexanone, 2-methylcyclohexanone, and camphor in THF at room temperature. The results are summarized in Tables II–V. Lithium aluminum hydride is considered to be the least sterically hindered hydride that reduces 4-*tert*-butylcyclohexanone (I), 3,3,5-trimethylcyclohexanone (II), 2-methylcyclohexanone (III), and camphor (IV) (10, 80, 24, and 9% equatorial or exo attack, respectively). In comparison, MgH_2 reduced ketones I, II, III, and IV in 24, 85, 35, and 8% equatorial or exo attack, respectively, indicating that MgH_2 has a larger steric requirement than $LiAlH_4$. The larger steric requirement is probably due to the highly polymeric nature of MgH_2. An additional important observation is that MgH_2 exhibits a highly different stereoselectivity toward 4-*tert*-butylcyclohexanone depending on the hydride:ketone ratio. For example, more equatorial attack, 24 → 61%, was observed when the MgH_2:ketone ratio was changed from 4:1 to 1:2. Obviously, the intermediate alkoxymagnesium hydride formed during the reaction in 1:2 ratio is a bulkier reducing species than MgH_2 itself. It would appear then that the stereoselectivity expected in the reactions of cyclic ketones with ROMgH compounds should depend on the steric requirement of the alkoxy group and the aggregation in solution of the resulting hydride reagent. According to the steric bulkiness of the alkoxy group, the degree of stereoselectivity should follow in the order: Ph_3COMgH > *t*-BuOMgH > *i*-PrOMgH > MeOMgH. However, because of the degree of molecular association of the ROMgH compound in solution, we have found the stereoselectivity to be in the reverse order: CH_3OMgH > *t*-BuOMgH > Ph_3COMgH > *i*-PrOMgH. For example, in the reduction of 4-*tert*-butylcyclohexanone 76, 69, 71, and 15% equatorial attack, respectively, was observed. In a similar way 3,3,5-trimethylcyclohexanone showed 99, 99, 99, and 65% equatorial attack, respectively, 2-methylcyclohexanone showed 98, 98, 73, and 68% equatorial attack, respectively, and camphor showed 95, 92, 95, and 92% endo attack, respectively. A similar demonstration of the importance of the association of the reagent in solution is given by the fact that phenoxymagnesium hydride is more selective than 2,6-dimethylphenoxymagnesium hydride because of the higher degree of association of the phenoxy compound in solution. We have found the stereoselectivity of aromatic ROMgH compounds

Table V. Reactions of Camphor with Alkoxymagnesium Hydrides at Room Temperature in THF Solvent and 4:1 Molar Ratio of Reagent/Ketone

Expt	Hydride	Relative yield, % *endo*-OH	*exo*-OH	Yield, %
31	MgH_2	8	92	100
32	CH_3CMgH	5	95	40
33	*i*-PrOMgH	8	92	15
34	*t*-BuOMgH	8	92	20
35	Ph_3COMgH	5	95	100
36		1	99	100
37		1	99	100
38		2	98	100
39		2	98	100

to be in the order: 2,6-*t*-$Bu_2C_6H_3OMgH$ > 2,6-*i*-$Pr_2C_6H_3OMgH$ > C_6H_5OMgH > 2,6-$Me_2C_6H_3OMgH$ for 4-*tert*-butylcyclohexanone (82, 83, 76, and 67% equatorial attack), for 3,3,5-trimethylcyclohexanone (99.5, 99.5, 99.5, and 94% equatorial attack), for 2-methylcyclohexanone (99, 99, 99, and 80% equatorial attack) and for camphor 98, 98, 99, and 99% endo attack, respectively).

Reactions of MgH_2 and 2,6-di-*tert*-butyl-4-methylphenoxymagnesium hydride with excess 4-*tert*-butylcyclohexanone shows that an equilibrium exists between the alkoxymagnesium intermediate and excess ketone according to eq 7, thus providing a pathway of converting kinetic to thermodynamic product.



(7)

In conclusion, active MgH_2 and alkoxymagnesium hydrides have been shown to reduce cyclic and bicyclic ketones to the corresponding alcohols in excellent yield under mild conditions in a reasonable period of time. The stereoselectivity of the reagents is excellent and is controlled by the steric requirement of the alkoxy group and the degree of molecular association of the hydride in solution.

Experimental Section

Apparatus. Reactions were performed under nitrogen at the bench using Schlenk tube techniques.[10] GLPC analyses were performed on an F&M Model 720 gas chromatograph.

Analyses. Gas analyses were carried out by hydrolyzing samples with hydrochloric acid on a standard vacuum line equipped with a Toepler pump. Magnesium was determined by EDTA titration. Alcohol analysis was carried out by GLC.

Materials. Methanol was distilled after treating with magnesium metal. Isopropyl alcohol was distilled over $Al(OPr^i)_3$ and *tert*-butyl alcohol was fractionally crystallized under nitrogen. 2,6-Dimethyl- and 2,6-diisopropylphenol were distilled prior to use. Triphenylmethanol and 2,6-di-*tert*-butylcresol were used without further purification.

Diethyl ether and THF were distilled over $LiAlH_4$ and $NaAlH_4$, respectively. Diethylmagnesium was prepared by the reaction of diethylmercury with magnesium metal at 60–80 °C and a standard solution in diethyl ether was calibrated by magnesium analysis. Lithium aluminum hydride solution in diethyl ether was prepared by the standard method and standardized by aluminum analysis.

Preparation of MgH_2 Slurry in THF. The slurry was prepared according to the procedure described in the previous paper in this series.

Preparation of Alkoxymagnesium Hydrides. A known amount of magnesium alkoxide in THF was made by the reaction of $(CH_3)_2Mg$ in diethyl ether/THF, with 2 molar equiv of the appropriate alcohol followed by reflux of the reaction mixture overnight. The diethyl ether was removed under vacuum and fresh THF was added. This magnesium alkoxide was allowed to react with MgH_2 slurry in THF at room temperature and analyzed (Table I).

Reaction of 2,6-Diisopropylphenol with MgH_2 in THF in 1:1 Molar Ratio. To a well-stirred slurry of MgH_2 (4.0 mmol) in THF (30 mL) at −78 °C was added dropwise a THF (10 mL) solution of 2,6-diisopropylphenol (4.0 mmol). This reaction mixture was allowed to warm to room temperature and stirred for 1 h to give a clear solution. Anal. Calcd for HMgOR: Mg:H: 2,6-*i*-$Pr_2C_6H_3OH$ = 1.00:1.00:1.00. Found, 1.00:0.97:1.04.

General Reaction of Ketones. A 10-mL Erlenmeyer flask with a Teflon-coated magnetic stirring bar was dried in an oven and allowed to cool under nitrogen. The flask was then sealed with a rubber septum, connected by means of a needle to a nitrogen-filled manifold equipped with a mineral oil-filled bubbler. The ketone solutions with internal standard (tetradecane for 4-*tert*-butylcyclohexanone and camphor, hexadecane for 3,3,5-trimethylcyclohexanone, and dodecane for 2-methylcyclohexanone) was syringed into the flask and the known concentration of hydride reagent (solution or slurry) was added to the flask at room temperature. After the designated reaction time, the reaction was quenched with H_2O slowly and dried over $MgSO_4$. A 10-ft 5% Carbowax 20M on Chromosorb W column (150 °C column temperature) was used to separate the products of 4-*tert*-butylcyclohexanone, 3,3,5-trimethylcyclohexanone, and camphor. A 15-ft 10% diglycerol on Chromosorb W column (80 °C) was used to separate the products of 2-methylcyclohexanone. The order of elution for each ketone is the same: the ketone first, the axial or exo alcohol second, and equatorial or endo alcohol last.

Acknowledgment. We are indebted to the National Science Foundation (Grant No. MPS 7504127) and the Office of Naval Research (Grant No. N00014-67-A-0419-005AD) for support of this work.

Registry No.—2,6-Diisopropylphenol, 2078-54-8; 4-*tert*-butylcyclohexanone, 98-53-3; 3,3,5-trimethylcyclohexanone, 873-94-9; 2-methylcyclohexanone, 583-60-8; camphor, 76-22-2.

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Reactions of Magnesium Hydrides. 3. Stereoselective Reduction of Cyclic and Bicyclic Ketones by Dialkylaminomagnesium Hydrides[1]

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Reactions of tetrahydrofuran-soluble dialkylaminomagnesium hydrides, R_2NMgH (where R_2N = *n*-Pr_2N, *i*-Pr_2N, Me(*i*-Pr)N, *s*-Bu_2N, c-$C_6H_{11}N$, 2,6-Me_2-c-C_5H_9N, and Me_3Si(*t*-Bu)N), with cyclic and bicyclic ketones such as 2-methylcyclohexanone, 4-*tert*-butylcyclohexanone, 3,3,5-trimethylcyclohexanone, and camphor have been studied. These new hydride reagents exhibit unusual stereoselectivity in the reduction of these compounds. The selectivity of the hydride reagent has been shown to depend on the steric requirement of the dialkylamino group as well as on the solution aggregation of the hydride reagent.

Introduction

In recent years, the use of metal hydrides as stereoselective reducing agents in organic chemistry has received considerable attention.[2,3] Although numerous reports have appeared in the literature concerning the reduction of cyclohexanones by hydrides of boron and aluminum, nothing is known about reductions with magnesium hydride presumably because of its reported lack of reactivity and also because of its insolubility in all solvents studied.[4] Recently, we reported the first examples of soluble magnesium hydride compounds of empirical formula HMgX (where X = Cl and Br,[5] alkyl and aryl,[6] and alkoxy and aryloxy[7]). In spite of their solubility in THF and their potent reactivity toward cyclic and bicyclic ketones, HMgCl, HMgBr, and HMgR compounds (where R = alkyl and aryl) do not exhibit any unusual selectivity as reducing agents. Interestingly, in an earlier report[8] we showed that MgH_2 (which is insoluble in THF) prepared by the reaction of $(C_2H_5)_2Mg$ with $LiAlH_4$ reduces organic functional groups rapidly in THF solvent. More recently, we have shown that insoluble MgH_2 reacts with $Mg(OR)_2$ compounds to form HMgOR compounds which are soluble in THF and which exhibit considerable stereoselectivity toward cyclic and bicyclic ketones.[9] We have reasoned that if HMgOR compounds are such good stereoselective reducing agents by virtue of their bulky alkoxy group, then similar bulkiness in other groups such as NR_2 groups should produce the same effect.

We would now like to report, for the first time, the reactions of THF soluble dialkylaminomagnesium hydrides with cyclic and bicyclic ketones, showing their unusual stereoselective behavior as reducing agents.

Results and Discussion

Dialkylaminomagnesium hydrides[10] R_2NMgH (where R_2N = *n*-Pr_2N, *i*-Pr_2N, *i*-Pr(Me)N, Ph_2N, c-$C_5H_{11}N$, 2,6-Me_2-c-C_5H_9N, and Me_3Si(*t*-Bu)N) used in these studies were prepared conveniently and quantitatively by the reaction of bis(dialkylamino)magnesium compounds, $(R_2N)_2Mg$, with an active form of MgH_2 in equimolar ratio in THF at room temperature (eq 1). Although MgH_2 is insoluble in THF, a clear solution results when the bis(dialkylamino)magnesium compound is allowed to react with the MgH_2 slurry. The bis(dialkylamino)magnesium compounds in turn were prepared by the reaction of the corresponding dialkylamine with dimethylmagnesium (eq 2). The active form of MgH_2 used in these studies was prepared by the reaction of $LiAlH_4$ with $(C_2H_5)_2Mg$ in diethyl ether at room temperature (eq 3).

$$(R_2N)_2Mg + MgH_2 \xrightarrow{THF} 2HMgNR_2 \quad (1)$$

$$2R_2NH + Me_2Mg \rightarrow (R_2N)_2Mg + 2MeH\uparrow \quad (2)$$

$$Et_2Mg + LiAlH_4 \xrightarrow{Et_2O} MgH_2 + LiAlH_2Et_2 \quad (3)$$

Dialkylaminomagnesium hydrides were also prepared by the reaction of MgH_2 with an equimolar amount of the appropriate amine in THF as exemplified by the preparation of diisopropylaminomagnesium hydride (eq 4). This reation was slower than the redistribution reaction (eq 1); however, it did produce a satisfactory product.

$$i\text{-}Pr_2NH + MgH_2 \xrightarrow{THF} HMgN\text{-}i\text{-}Pr_2 + H_2 \quad (4)$$

The R_2NMgH compounds prepared by the methods just described were allowed to react with four representative ketones, i.e., 4-*tert*-butylcyclohexanone (I), 3,3,5-trimethylcyclohexanone (II), 2-methylcyclohexanone (III), and camphor (IV). The results of these reactions are summarized in Tables II–IV.

$LiAlH_4$ is considered to be the least sterically hindered hydride that reduces cyclic and bicyclic ketones. For example, $LiAlH_4$ produces 10, 80, 24, and 9% equatorial or exo attack, respectively, in ketones I, II, III, and IV. On the other hand, MgH_2 reduced ketones I, II, III, and IV in 23, 85, 35, and 8% equatorial or exo attack, respectively. The increased attack from the least hindered side of the ketone by MgH_2 can be explained by the increased steric requirement of MgH_2 due to its polymeric nature. Each dialkylaminomagnesium hydride reduced the cyclic and bicyclic ketones studied to give significantly more equatorial (or exo) attack than MgH_2 itself. Presumably $HMgNR_2$ compounds are sterically bulkier than MgH_2. The stereoselectivity depends on the combination of the steric bulk of the dialkylamino group plus the aggregation of the hydride reagent although the results are complicated by the fact that it is at least possible that some of these reductions by $HMgNR_2$ compounds take place through a small equilibrium amount of MgH_2 formed by disproportionation.

$$HMgNR_2 \rightarrow MgH_2 + Mg(NR_2)_2$$

The most selective reagent among those studied is trimethylsilyl-*tert*-butylaminomagnesium hydride, which reduced ketones I, II, III, and IV to give the less thermally stable alcohol produced in 73, 99, 98, and 95% yields, respectively. However, the least selective hydrides appear to be 2,6-dimethylpiperidinomagnesium hydride and isopropylmethylaminomagnesium hydride. The latter compound is less stereoselective than the other hydrides presumably because the R_2N group is less bulky. On the other hand, it is hard to explain the lack of selectivity of the 2,6-dimethylpiperidinomagnesium hydride unless a considerable amount of the reduction takes place through MgH_2. This suggestion is not unreasonable since 2,6-dimethylpiperidinomagnesium hy-

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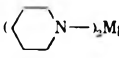
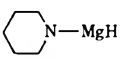
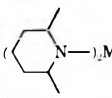
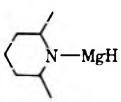
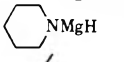
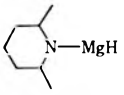
Table I. Preparation of Dialkylaminomagnesium Hydrides in THF[a]

Reactants, mmol MgH_2	Reactants, mmol $Mg(NR_2)_2$	Registry no.	Reaction time, h	Analysis (ratio) Mg:H	Product	Solubility in THF
6.0	$[(n\text{-Pr})_2N]_2Mg$ (6.00)	23293-22-3	1	1.00:0.97	$n\text{-Pr}_2NMgH$	Very soluble
5.85	$[(i\text{-Pr})_2N]_2Mg$ (5.90)	23293-23-4	1	1.00:0.96	$i\text{-Pr}_2NMgH$	Very soluble
5.90	$[i\text{-Pr(Me)N}]_2Mg$ (5.90)	65277-26-1	3	1.00:0.96	$i\text{-Pr(Me)NMgH}$	Sparingly soluble, crystallized from THF
6.00	$[(sec\text{-Bu})_2N]_2Mg$ (5.95)	65277-27-2	2	1.00:0.97	$sec\text{-Bu}_2NMgH$	Moderately soluble, could be crystallized from THF
5.75	$(Ph_2N)_2Mg$ (5.70)	65277-28-3	1	1.00:0.97	Ph_2NMgH	Soluble, could be crystallized from THF
6.00	 (5.96)	65277-29-4	3	1.00:0.95		Moderately soluble, crystallized from THF
5.50	 (5.50)	65277-30-7	2	1.00:0.96		Moderately soluble, crystallized from THF
6.05	$(t\text{-Bu(SiMe}_3)N)_2Mg$	65277-31-8	1.5	1.00:0.97	$t\text{-Bu(SiMe}_3)NMgH$	Very soluble

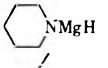
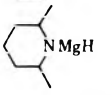
[a] All reactions were carried out at room temperature in THF (50–60 mL).

Table II. Reactions of 4-*tert*-Butycyclohexanone with Aminomagnesium Hydrides in THF[a]

Expt	Hydride	Registry no.	Relative yield, % Axial-OH	Relative yield, % Equatorial-OH	Yield, %
1	MgH_2	7693-27-8	24	76	100
2	$n\text{-Pr}_2NMgH$	65277-32-9	60	40	65
3	$(i\text{-Pr})(Me)NMgH$	65392-10-1	38	62	50
4	$i\text{-Pr}_2NMgH$	33036-48-5	57	43	60
5	$sec\text{-Bu}_2NMgH$	65277-33-0	59	41	55
6		65277-34-1	63	37	39
7		65277-35-2	45	55	70
8	$t\text{-Bu(SiMe}_3)NMgH$	65277-36-3	73	27	75

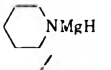
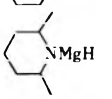
[a] All reactions were carried out in 4:1 molar ratio (hydride/ketone) for 24 h at room temperature.

Table III. Reactions of 3,3,5-Trimethylcyclohexanone with Aminomagnesium Hydrides in THF[a]

Expt	Hydride	Relative yield, % Axial-OH	Relative yield, % Equatorial-OH	Yield, %
9	MgH_2	85	15	92
10	$n\text{-Pr}_2NMgH$	98	2	46
11	$(i\text{-Pr})(Me)$-NMgH	95	5	29
12	$i\text{-Pr}_2NMgH$	95	1	75
13	$sec\text{-Bu}_2NMgH$	99.5	0.5	70
14		98	2	35
15		94	6	52
16	$t\text{-Bu(SiMe}_3)$-NMgH	99	1	82

[a] All reactions were carried out in 4:1 molar ratio (hydride/ketone) for 24 h at room temperature.

Table IV. Reactions of 2-Methylcyclohexanone with Aminomagnesium Hydrides in THF[a]

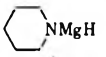
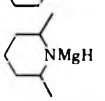
Expt	Hydride	Relative yield, % Axial-OH	Relative yield, % Equatorial-OH	Yield, %
17	MgH_2	35	65	100
18	$n\text{-Pr}_2NMgH$	90	10	28
19	$(i\text{-Pr})(Me)$-NMgH	80	20	40
20	$i\text{-Pr}_2NMgH$	98.5	1.5	85
21	$sec\text{-Bu}_2NMgH$	98	2	62
22		92	8	40
23		82	18	58
24	$t\text{-Bu(SiMe}_3)$-NMgH	98	2	95

[a] All reactions were carried out in 4:1 molar ratio (hydride/ketone) for 24 h at room temperature.

dride, because of its large steric requirement, would be expected to react very slowly with the ketones studied compared to the other hydrides thereby giving a small equilibrium amount of MgH_2 sufficient time to react. The fact that 2,6-dimethylpiperidinomagnesium hydride reduces all ketones in significantly higher yield than the less sterically hindered piperidinomagnesium hydride indicates either (1) that indeed MgH_2 is a major reacting species since it produces the highest yield in all cases or (2) the hydride of greatest steric requirement would be expected to function as the weakest base in terms of producing enolization product.

Indeed we have found that the modest yields of reduction

Table V. Reactions of Camphor with Aminomagnesium Hydrides in THF[a]

Expt	Hydride	Relative yield, % Endo-OH	Exo-OH	Yield, %
25	MgH_2	8	92	100
26	n-Pr_2NMgH	13	87	92
27	(i-Pr)(Me)MgH	10	90	15
28	i-Pr_2NMgH	7	93	45
29	sec-Bu_2NMgH	6	94	55
30		12	88	10
31		7	93	42
32	t-Bu($SiMe_3$)-NMgH	5	95	100

[a] All reactions were carried out in 4:1 molar ratio (hydride/ketone) for 24 h at room temperature.

product are due to enolization of the ketones studied by the R_2NMgH compounds. Although MgH_2 gives quantitative yields in the reduction of ketones in nearly every case studied, its stereoselectivity toward cyclic and bicyclic ketones does not compare with that of the new R_2NMgH compounds, particularly $Me_3Si(t\text{-Bu})NMgH$.

Experimental Section

Apparatus. Reactions were performed under nitrogen at the bench using Schlenk tube techniques. GLPC analyses were performed on an F&M Model 720 gas chromatograph.

Analyses. Gas analyses were carried out by hydrolyzing samples with hydrochloric acid on a standard vacuum line equipped with a Toepler pump. Magnesium was determined by EDTA titration at pH 10 using Eriochrome Black T as an indicator.

Materials. Di-n-propylamine (Eastman), isopropylmethylamine (Eastman), di-sec-butylamine (Pfaltz I. Bauer), piperidine (Fisher), and 2,6-dimethylpiperidine (Aldrich) were dried over molecular sieve 4A and distilled prior to use.

Diethyl ether and THF were distilled over $LiAlH_4$ and $NaAlH_4$, respectively. Diethylmagnesium was prepared by the reaction of diethylmercury with excess magnesium metal at 60–80 °C and a solution in diethyl ether was standardized by magnesium analysis.[9] $LiAlH_4$ solution in diethyl ether was prepared by stirring $LiAlH_4$ in ether (1 M) for 24 h followed by filtration and standardization of the resulting clear solution by aluminum analysis.

Preparation of Trimethylsilyl($tert$-butyl)amine. To a magnetically stirred mixture of $tert$-butylamine (7.3 g, 100 mmol) and triethylamine (10.1 g, 100 mmol) in n-hexane (150 mL) was added dropwise, 10.9 g (100 mmol) of Me_3SiCl. The reaction mixture was stirred for ~2 h and the insoluble white solid (Et_3NHCl) was removed by filtration. The filtrate was concentrated and the residue was distilled at 124 °C. The ^1H NMR spectrum of this liquid showed signals at 9.67 (due to Me_3Si) and 8.57 (due to $tert$-butyl group) in the ratio of 1:1.

Preparation of Bis(dialkylamino)magnesium Compounds by the Reaction of $(CH_3)_2Mg$ with Dialkylamines in 1:2 Molar Ratio. Dialkylamines in THF were added dropwise to a well stirred solution of $(CH_3)_2Mg$ in diethyl ether in 2:1 molar ratio at room temperature. The reaction mixture was refluxed overnight and its completion was checked by the absence of any hydrolyzable gas. The solution was then standardized by magnesium analysis.

Preparation of MgH_2 slurry in THF was performed according to the procedure described in paper 1 of this series.

Preparation of Dialkylaminomagnesium Hydrides by the Reaction of Bis(dialkylamino)magnesium Compounds with MgH_2 Slurry in THF. A solution of bis(dialkylamino)magnesium compounds in THF was added dropwise to a well-stirred slurry of MgH_2 in THF at room temperature. The reaction mixture was further stirred to give a clear solution. The resulting solution was analyzed for magnesium (EDTA) and hydrolyzable gas (Table I).

Preparation of Diisoproplylaminomagnesium Hydride by the Reaction of Diisopropylamine with MgH_2 in 1:1 Molar Ratio in THF. Diisopropylamine (6.06 g, 6.0 mmol) in THF (15 mL) was added dropwise to a slurry of MgH_2 (6.0 mmol) in THF (50 mL) at room temperature. The reaction mixture was stirred for 15 h to give a clear solution. Anal. Calcd for $HMgN(i\text{-Pr})_2$: Mg:H = 1.00:1.00. Found: 1.00:0.96.

Acknowledgment. We are indebted to the National Science Foundation (Grant No. MPS 7504127) and the Office of Naval Research (Grant No. N00014-67-A-0419-005AD) for financial support of this work.

Registry No.—4-$tert$-Butylcyclohexanone, 98-53-3; 3,3,5-trimethylcyclohexanone, 873-94-9; 2-methylcyclohexanone, 583-60-8; camphor, 76-22-2; trimethylsilyl($tert$-butyl)amine, 5577-67-3; $tert$-butylamine, 75-64-9; Me_3SiCl, 75-77-4; diisopropylamine, 108-18-9.

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Stereochemistry of the Hydroboration of Alkenes

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The reactions of (*E*)- and (*Z*)-1-hexene-*1,2-d*$_2$ with dialkylboranes (dicyclohexylborane and 9-BBN) produce *threo*- and *erythro*-(1,2-dideuteriohexyl)dialkylboranes, respectively. Further, the reactions of (*E*)- and (*Z*)-1-hexene-*1-d*$_1$ with di(2-deuteriocyclohexyl)borane-*B-d*$_1$ produce *erythro*- and *threo*-(1,2-dideuteriohexyl)di(deuteriocyclohexyl)borane, respectively. These results constitute direct evidence that the hydroboration reaction involves the cis addition of the boron hydrogen moiety to the alkene.

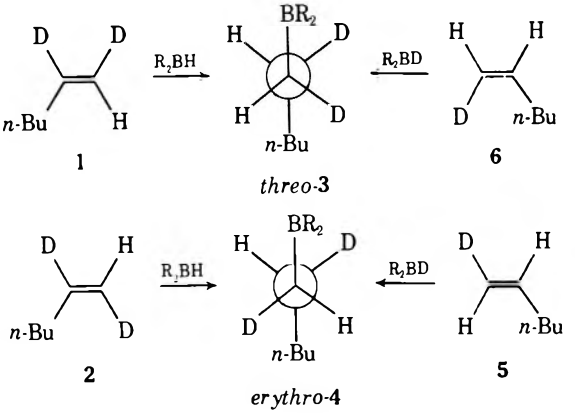
The hydroboration of alkenes has become increasingly important in organic chemistry primarily due to the synthetic versatility of the resultant organoboranes.[2-5] The reaction is generally believed to involve the cis addition of the boron hydrogen moiety to an alkene.[6,7] However, the basis for this belief rests primarily on the fact that hydroboration–oxidation sequences are known to lead to stereospecific cis hydration of alkenes,[8-10] e.g., (*Z*)-2-butene yields *erythro*-2-butanol-*3-d*$_1$ upon deuterioboration (BD_3), oxidation, and saponification. The hydroboration reaction, per se, is of sufficient importance to warrant the unambiguous determination of its stereochemistry.

Nuclear magnetic resonance spectroscopy was chosen as the appropriate analytical method due to its proven utility in stereochemical investigations.[11-14] The NMR analysis of organoboranes is (in the present case) complicated by at least three factors: first, the chemical shifts of the hydrogens on the 1- and 2-carbons are essentially isochronous such that first-order coupling constants are not observable; second, symmetric 1-deuteriotrialkylboranes, i.e., those arising from hydroboration of 1-deuterioalkenes, exist as mixtures of diastereomers giving rise to multiple overlapping resonances in the relevant high-field region of their proton spectra; and, third, the pertinent (1 and 2) resonances in the proton spectra are in a spectral region encumbered by other resonances. These difficulties were circumvented by the utilization of a complexing agent and by employing symmetric hydroborating agents. The use of a simple Lewis base, methylamine, as a complexing agent resulted in a diamagnetic shift of the 1-hydrogen of the product boranes such that vicinal coupling (to the 2-proton) was directly observable in a spectral region unencumbered by other resonances.[15] The use of symmetrical hydroborating agents, e.g., dicyclohexylborane and 9-borabicyclo[3.3.1]nonane (9-BBN), produced enantiomeric rather than diastereomeric products which significantly simplified the NMR analysis.

Results and Discussion

(*E*)- and (*Z*)-1-hexene-*1,2-d*$_2$ (**1** and **2**, respectively) were hydroborated with dicyclohexylborane and with 9-BBN. The addition of these (symmetric) dialkylboranes to the diastereomeric hexenes would produce the *threo*- and *erythro*-organoboranes (**3** and **4**, respectively) if the addition of the boron hydride were cis.[16] Trans addition would produce the opposite stereochemical results. In order to present a complete analysis, (*E*)- and (*Z*)-1-hexene-*1-d*$_1$ (**5** and **6**, respectively) were reacted with di(2-deuteriocyclohexyl)borane-*B-d*$_1$ [(c-$C_6H_{10}D)_2BD$]. In these reactions, the resultant organoborane products would be the erythro and threo diastereomers, **4** and **3**, respectively, if cis addition were to occur.

The steric bulk of the *n*-butyl and the (complexed) dialkylborane groups ensures that the anti conformer of each product is predominantly populated. The experimental results are summarized in Table I. The magnitudes of the vicinal



($^3J_{HH}$) coupling constants provide compelling evidence[17] for the assigned configurations assuming that the *anti-n*-butyldialkylborane comformation predominates.[18] Thus, the ^1H NMR results clearly demonstrate that cis addition occurs, i.e., **1** and **6** both produce the threo diastereomer upon addition of the appropriate dialkylborane while **2** and **5** produce the erythro diastereomer. The high-field regions of the proton NMR spectra of the dicyclohexylborane addition products of (*E*)- and (*Z*)-1-hexene-*1,2-d*$_2$ are presented in Figure 1.

Analysis of the hydrogen decoupled deuterium spectra supports the conclusions drawn from the deuterium decoupled proton spectra concerning the stereospecificity of the reaction; only two ^2H resonances are observed in the high-field region of the various spectra, one corresponding to the observed 1-H spectrum and the other at the appropriate chemical shift such that computed ^1H spectra exhibit the observed relative intensities in the ^1H spectrum.

It must be concluded that hydroboration of alkenes proceeds predominantly in a cis manner in accordance with Brown's original proposition.[19]

Experimental Section

All reactions were carried out in flame-dried, nitrogen-flushed glassware. Diglyme (Ansul) was distilled from calcium hydride prior to use. All other solvents were dried over sodium. Borane–methyl sulfide (Aldrich), 9-BBN (Aldrich), 1-hexyne (Farchan), acetic acid-*d*$_1$ (Norell Chemical Co., Inc.), deuterium oxide (Aldrich), and lithium deuteride (Alfa) were used as received.

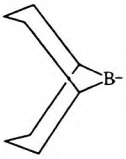
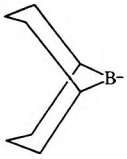
Routine NMR spectra were recorded on Varian T-60 and HA-100 spectrometers; chemical shifts are reported in ppm relative to Me_4Si unless otherwise indicated. ^2H decoupled proton and ^1H decoupled deuterium NMR spectra were recorded on a Bruker HX-90 spectrometer at 90 and 13.8 MHz, respectively. For proton and ^2H spectra the lock signal was benzene. Chemical shifts are referred to benzene and benzene-d_6, respectively.

1-Hexyne-*1-d*$_1$. 1-Hexyne (300 mmol, 34 mL) was added dropwise to a solution of *n*-butyllithium (350 mmol) in 180 mL of hexane which was contained in a dry, nitrogen-flushed flask cooled to 0 °C. D_2O was added slowly to the lithium salt and the reaction mixture was stirred overnight. Distillation afforded 29 mL (85%) of 1-hexyne-*1-d*$_1$: bp 72 °C; NMR (CCl_4) δ 2.13 (t, 2), 1.46 (m, 4), 0.90 (t, 3).

Di(2-deuteriocyclohexyl)borane-*B-d*$_1$ [(c-$C_6H_{10}D)_2BD$].

0022-3263/78/1943-1567$01.00/0

Table I. ^{1}H NMR Parameters of *n*-BuCHDCHDBR$_2$[a,b]

Alkene	R_2B–	Registry no.	δ 1-H[c]	δ 2-H[d]	$^3J_{1H-2H}$[e]
1[f] or 6[h]	(c-$C_6H_{10}D)_2B$–	65253-12-5	7.00	6.13	3.6
2[g] or 5[i]	(c-$C_6H_{10}D)_2B$–		6.99	6.12	12.4
1		65253-14-7	6.74	6.17	3.6
2		65253-15-8	6.77	6.18	13.3

[a] Deuterium decoupled. [b] Methylamine added as complexing agent (see Experimental Section). [c] Relative to internal benzene. [d] Position determined from ^{2}H derivative relative to internal benzene-d_6. [e] Hz. [f] Registry no. 65253-10-3. [g] Registry no. 65253-11-3. [h] Registry no. 18963-99-0. [i] Registry no. 18963-98-9.

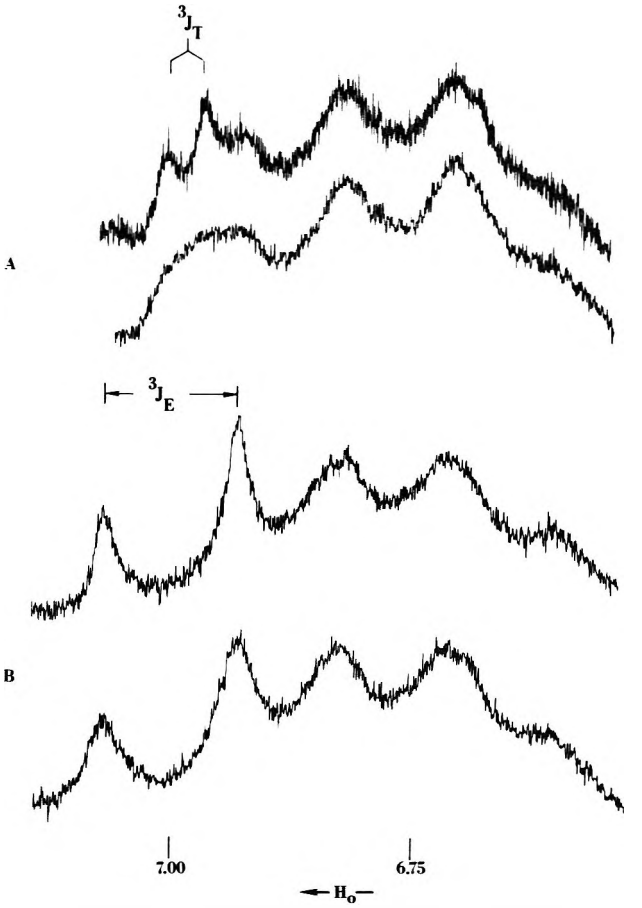


Figure 1. Proton spectra (90 MHz) of 1,2-dideuteriohexyldicyclohexylboranes: (A, upper) ^{2}H decoupled threo diastereomer; (A, lower) normal (undecoupled) spectrum; (B, upper) ^{2}H decoupled erythro diastereomer; (B, lower) normal (undecoupled) spectrum. Chemical shifts relative to benzene; field increasing to left. The low-field resonances arise from the cyclohexyl proton B–CH.

Lithium deuteride (300 mmol, 2.7 g), cyclohexene (200 mmol, 20 mL), and diglyme (100 mL) were placed in a dry, nitrogen-flushed, 250-mL flask equipped with a magnetic stirring bar, reflux condenser, pressure equilizing dropping funnel, and a gas exit tube. A solution of BF_3 in diglyme (400 mmol, 70 mL) was prepared by dissolving BF_3·etherate (400 mmol) in 70 mL of diglyme and distilling the diethyl ether at ambient temperature (20 Torr). This BF_3 solution was added dropwise (1 h) to the reaction mixture which was maintained at 0 °C. Dicyclohexylborane-*B*-d_1 precipitated from the reaction mixture. To ensure complete reaction, the mixture was stirred for 1 h at room temperature and was subsequently utilized for the preparation of deuterated alkenes.

Dicyclohexylborane. Cyclohexene (200 mmol, 20 mL) and 100 mL of diglyme were placed in a dry, nitrogen-flushed, 250-mL flask fitted with a magnetic stirring bar, reflux condenser, septum inlet, and a gas exit tube. The solution was cooled to 0 °C and BH_3·SMe_2 (100 mmol, 9.6 mL) was added via a syringe (10 min). The dicyclohexylborane precipitated during a 1-h period.

(*E*)-1-Hexene-*1,2-d*$_2$. 1-Hexyne (100 mmol, 11.4 mL) was added to dicyclohexylborane-*B*-d_1 (100 mmol) in diglyme, vide supra. After 1 h, the reaction was complete (the solid dicyclohexylborane dissolves) and the reaction mixture was solvolyzed by addition of acetic acid-d_1 (150 mmol, 7.0 mL). The product (9 mL, 70%) was isolated by fractional distillation: bp 66 °C; NMR (neat) δ 4.90 (broad singlet, 1), 2.00 (t, 2), 1.33 (m, 4), 0.90 (t, 3); mass spectra M$^+$ 86.

(*Z*)-1-Hexene-*1,2-d*$_2$ was prepared in a manner analogous to the preparation of (*E*)-1-hexene-*1,2-d*$_2$. 1-Hexyne-d_1 (100 mmol) was reacted with dicyclohexylborane-*B*-d_1 and then protonolyzed with acetic acid. The product (8 mL, 65%) was isolated by fractional distillation: bp 66 °C; NMR (neat) δ 4.90 (broadened singlet, 1), 2.00 (t, 2), 1.33 (m, 4), 0.90 (t, 3); M$^+$ 86.

(*E*)-1-Hexene-*1*-d_1. 1-Hexyne (100 mmol, 11.4 mL) was added to dicyclohexylborane (100 mmol) (vide supra) in diglyme at 0 °C. The reaction mixture was stirred for 1 h and dimethyl sulfide was distilled from the mixture (N_2 atmosphere maintained). The mixture was cooled to room temperature and solvolyzed with acetic acid-d_1 (150 mmol, 7.0 mL). The product (9 mL, 70%) was isolated by fractional distillation: bp 65 °C; NMR (CCl_4) δ 5.73 (m, 1), 4.90 (d, 1, $^3J_{HH}$ = 18.0 Hz), 2.00 (m, 2), 1.33 (m, 4), 0.90 (t, 3); mass spectra M$^+$ 85.

(*Z*)-1-Hexene-*1*-d_1 was prepared in a manner analogous to the preparation of (*E*)-1-hexene-*1*-d_1. 1-Hexyne-*1*-d_1 was hydroborated with dicyclohexylborane followed by protonolysis with acetic acid. The product (8 mL, 65%) was isolated by fractional distillation: bp 65 °C; NMR (neat) δ 5.73 (m, 1), 4.83 (d, 1, $^3J_{HH}$ = 10.0 Hz), 2.00 (m, 2), 1.33 (m, 4), 0.90 (t, 3); M$^+$ 85.

***threo*-1,2-Dideuteriohexyldicyclohexylborane. Method A.** Cyclohexene (4 mmol, 0.4 mL), BH_3·$S(CH_3)_2$ (2 mmol, 0.20 mL), and dioxane (0.5 mL) were added to a nitrogen-flushed, dry NMR tube fitted with a rubber septum. After 30 min, (*E*)-1-hexene-*1,2-d*$_2$ (2 mmol, 0.20 mL) was added via a syringe and the reaction was allowed to proceed for 1 h at room temperature. (The solid dicyclohexylborane dissolves during this period.) Methylamine (0.50 mL of a 40% aqueous solution) was added and the water layer which formed was removed with a syringe. The ^{2}H decoupled proton spectrum exhibited a doublet (J = 3.6 Hz) centered at 7.00 ppm upfield from internal benzene. The ^{1}H-decoupled ^{2}H spectrum exhibited two broad resonances at 7.00 and 6.13 ppm from internal benzene-d_6. The absence of ^{1}H signals at 6.99 ppm (J = 12.4 Hz) reflects the absence of the erythro diastereomer (vide infra).

Method B. Di(2-deuteriocyclohexyl)borane-*B*-d_1 (2 mmol) (vide supra) in diglyme was added to a nitrogen-flushed, dry NMR tube via syringe. Dioxane (0.5 mL) was added followed by (*Z*)-1-hexene-*1*,d_1 (2 mmol, 0.20 mL). After standing for 1 h at room temperature (the dicyclohexylborane dissolves), methylamine (0.50 mL of a 40% aqueous solution) was added and the water layer was removed with a syringe. The NMR spectrum duplicated that obtained by method A except for the solvent peaks.

***erythro*-1,2-Dideuteriohexyldicyclohexylborane. Method A.** (*Z*)-1-Hexene-*1,2-d*$_2$ was hydroborated using the procedure outlined for the (*E*) diastereomer, method A. The ^{2}H-decoupled ^{1}H spectrum exhibited a doublet (J = 12.4 Hz) centered at 6.99 ppm upfield from internal benzene. The ^{1}H-decoupled ^{2}H spectrum exhibited two broad resonances at 6.99 and 6.12 ppm relative to internal benzene-d_6. The absence of additional resonances in the ^{1}H spectrum at 7.00 ppm (J = 3.6 Hz) (vide supra) reflects the absence of the threo diastereomer.

Method B. (*E*)-1-Hexene-*1*-d_1 was reacted with di(2-deuteriocyclohexyl)borane-*B*-d_1 using the procedure outlined for the (*Z*) diastereomer, method B. The NMR spectrum duplicated that obtained by method A except for the solvent peaks.

***threo*-1,2-Dideuteriohexyl-9-BBN.** In a nitrogen-flushed glove box, 9-BBN (1.5 mmol, 0.17 g) was placed into an oven-dried NMR tube. Dioxane (0.5 mL) was added followed by (*E*)-1-hexene-*1,2-d*$_2$ (1.5 mmol, 0.15 mL). After 1 h, methylamine (0.5 mL of a 40% aqueous

solution) was added. The water layer was removed with a syringe. The NMR spectrum indicated that the threo diastereomer had formed exclusively. The ^{2}H-decoupled ^{1}H spectrum exhibits a doublet (J = 3.6 Hz) at 6.74 ppm upfield from internal benzene. The ^{1}H-decoupled ^{2}H spectrum exhibits two broad singlets at 6.74 and 6.17 ppm, respectively, from internal benzene-d_6. The absence of additional ^{1}H signals at 6.77 ppm (J = 13.3 Hz) indicates the absence of the erythro diastereomer (vide infra).

***erythro*-1,2-Dideuteriohexyl-9-BBN.** (*Z*)-1-Hexene-*1,2*-d_2 (1.5 mmol, 0.15 mL) was reacted with 9-BBN (1.5 mmol, 0.17 g) as described for the (*E*) diastereomer. NMR analysis indicated that only the erythro diastereomer was produced. The ^{2}H-decoupled ^{1}H spectrum exhibits a doublet (J = 13.3 Hz) at 6.77 ppm relative to internal benzene. The ^{1}H-decoupled ^{2}H spectrum consists of two broad singlets at 6.77 and 6.18 ppm relative to internal benzene-d_6. The absence of additional ^{1}H signals at 6.74 ppm (J = 3.6 Hz) indicates the absence of the threo diastereomer (vide supra).

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Registry No.—9-BBN, 280-64-8; BH_3·$S(CH_3)_2$, 13292-87-0; 1-hexyne, 693-02-7; 1-hexyne-*1*-d_1, 7299-48-1; di(2-deuteriocyclohexyl)borane-*B*-d_1, 65253-16-9; dicyclohexylborane, 1568-65-6; cyclohexene, 110-83-8.

References and Notes

(1) (a) University of Tennessee; (b) Clemson University.
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Synthesis of 9,9-Dimethyl-2-methoxy-5-benzosuberone. An Unexpected Failure of Benzylic Oxidation

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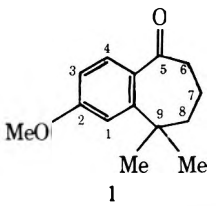
Attempts to prepare 9,9-dimethyl-2-methoxy-5-benzosuberone (**1**) by benzylic oxidation of 9,9-dimethyl-2-methoxybenzosuberan (**9**) proved unsuccessful. The problems associated with this oxidation are consistent with severe nonbonded interactions associated with the *gem*-dimethyl group in **9** which make formation of an initial benzylic radical difficult. Both nuclear magnetic resonance and ultraviolet data indicate a tendency of an sp^2-hybridized center adjacent to the aromatic nucleus in benzosuberans not to attain planarity with the phenyl ring, in contrast to the corresponding tetralin systems. An efficient synthesis of the ketone **1** from 4,4-dimethyl-6-methoxy-1-tetralone (**3**) is described.

During a study of synthetic approaches to the himachalene class of sesquiterpenes,[1] 9,9-dimethyl-2-methoxy-5-benzosuberone (**1**) was a desired intermediate. Initial attempts to synthesize ketone **1** involved McMurry's ring expansion



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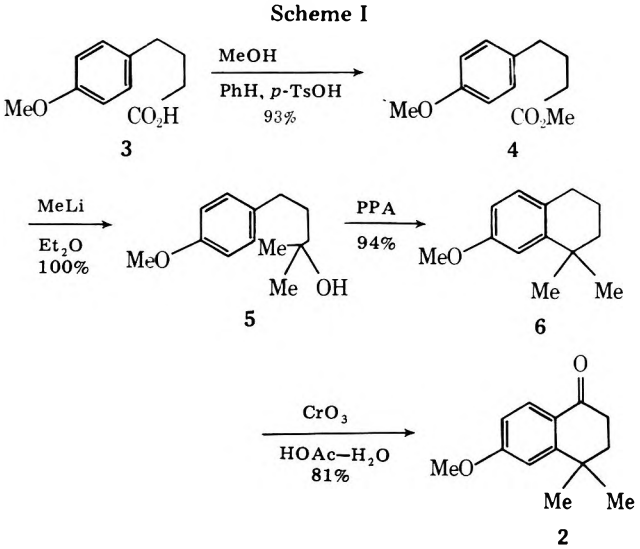
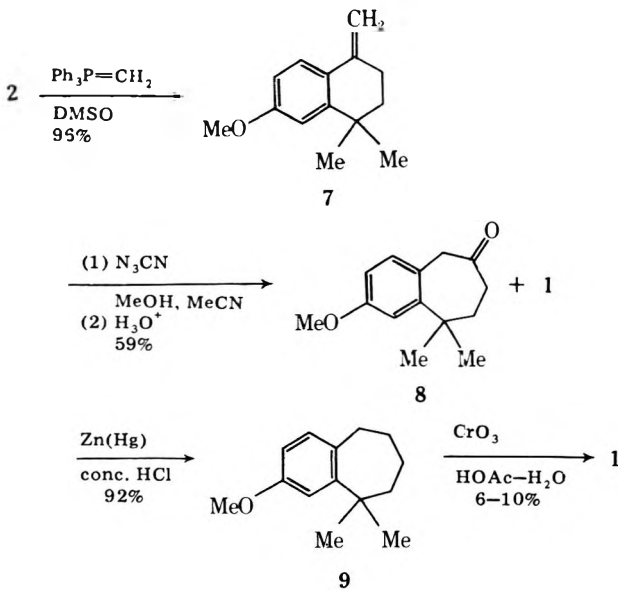
procedure[2] on 4,4-dimethyl-6-methoxy-1-tetralone (**2**) whose straightforward preparation is shown in Scheme I. For future consideration, it should be noted that the benzylic oxidation of tetralin **6** using chromium trioxide–acetic acid–water[3] proceeded in good yield. Treatment of tetralone **2** in dimethyl sulfoxide with methylenetriphenylphosphorane gave a 96% yield of the exocyclic olefin **7** which proved to be very labile.[4] Therefore, the crude exocyclic olefin **7** was subjected to cy-

Scheme I



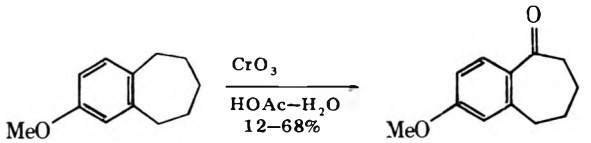
Scheme II



anogen azide ring expansion[2] to give a mixture of benzosuberones 8 and 1 (see Scheme II). The ratio of ketonic products 8 and 1 was found to be dependent on the method of preparation of the cyanogen azide solution.[5] If no precautions were taken to exclude sodium bromide (formed in situ by reaction of equimolar amounts of sodium azide and cyanogen bromide in acetonitrile) from the solution, the product distribution was 65:35 8/1.[6] However, if the cyanogen azide solution was filtered prior to use, the ratio shifted to 92:8 8/1.[6] Chromatography of the crude product obtained using the filtered cyanogen azide solution gave a 59% yield of the mixture of ketones 8 and 1. This mixture was subjected to Clemmensen reduction to give the benzosuberan 9 in 92% yield (see Scheme II).

Attempted benzylic oxidation of 9 → 1 with chromium trioxide–acetic acid–water in a similar manner to the successful oxidation of 6 → 2 resulted in poor mass recovery and only 6% yield of the desired ketone 1. Variation of reaction times, temperatures, and molar ratios gave an optimum yield of benzosuberone 1 of only 10%. Several other oxidative procedures also failed to give improved yields of ketone 1.[7]

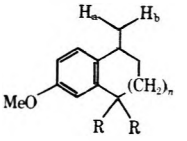
In order to determine whether the dramatic difference in the oxidation of tetralin 6 and benzosuberan 9 was due to the presence of the seven-membered ring or a combination of the seven-membered ring and the *gem*-dimethyl group, 2-methoxybenzosuberan (10)[8] was oxidized with chromium



10 11

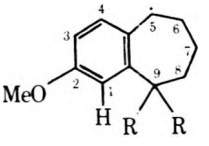
trioxide–acetic acid–water at 0 °C for 24 h, again the conditions used successfully for the transformation of 6 → 2. Examination of the reaction products revealed largely starting material and 12% of desired ketone 11. By optimizing the reaction conditions (28 h at room temperature) the yield of ketone 11 was raised to 68% (63% conversion).[9] When *gem*-dimethylbenzosuberan 9 was reacted under these conditions, a 10% yield of ketone 1 was obtained. Although this is higher than the 6% yield observed originally, the amount of starting material was very much reduced in the second case. The above observations indicate that a combination of the seven-membered ring and the *gem*-dimethyl group influence the yield in the benzylic oxidation but that the presence of the *gem*-dimethyl group is the dominant factor.

Table I. NMR Comparison of Exocyclic Olefins

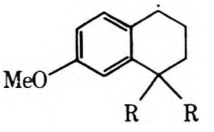


Compound	*n*	R	δ H_a, ppm	δ H_b, ppm
7	1	Me	5.21	4.75
15	2	Me	4.87	4.87
16	1	H	5.20	4.68
17	2	H	4.91	4.91

One explanation of these observations is that the benzylic radical, the initial species in the benzylic oxidation,[10] is more difficult to form in going from compounds 6 to 10 to 9. Resonance stabilization of the benzylic radical would be most effective if the carbon containing the odd electron were in the same plane as the phenyl ring, allowing for maximum overlap of the aromatic π system and the orbital bearing the lone electron. Examination of space-filling models of benzylic radical 12 where C-5 is assumed sp^2 hybridized and held rigidly in the plane of the aromatic ring shows a severe peri interaction between a C-9 methyl and a C-1 hydrogen. Holding the C-5 carbon in the aromatic plane also causes some torsional strain in the seven-membered ring. Inspection of models corresponding to radical 13, again holding the C-5 carbon rigid for maximum orbital overlap with the aromatic system, indicates that the C_9–H to C_1–H interaction is quite minimal. The main source of strain in this molecule is torsional, and this strain can be relieved if the C-5 carbon is not planar.[11] However, planarity can be easily attained if required. Models of radical 14 show it to be a relatively strain-free system.



12, R = Me
13, R = H

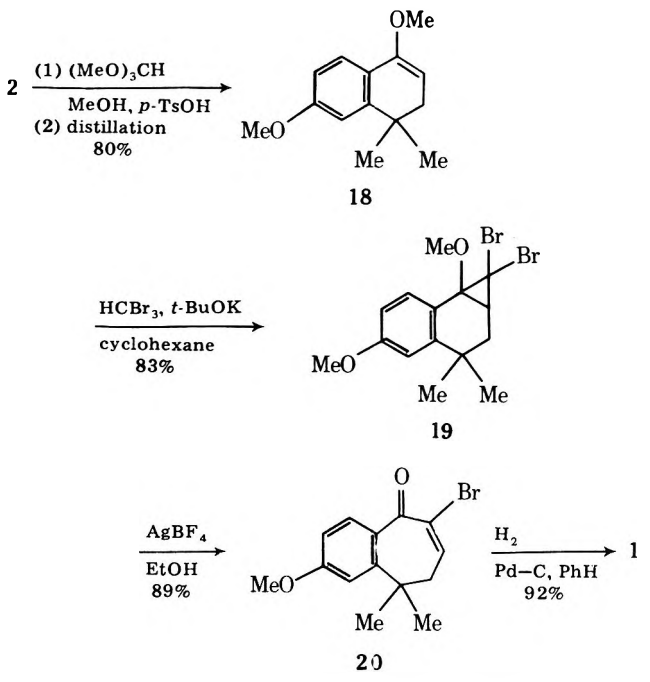


14

The tendency of an sp^2-hybridized center adjacent to the aromatic nucleus in benzosuberans *not* to attain planarity with the phenyl ring is consistent with an examination of the nuclear magnetic resonance spectra of compounds 7 and 15, and also 16[12] and 17 (see Table I). In the tetralin system 7, the two vinyl protons absorb at quite different fields due to H_a being in the deshielding portion of the induced magnetic field caused by the aromatic ring current while H_b is not.[13,14] In compound 15 the two exocyclic protons give rise to a single absorption at δ = 4.87 ppm, close to the δ = 4.80 ppm absorption for protons on an isolated exocyclic double bond on cyclohexane.[15] That H_a in compound 15 does not feel the diamagnetic anisotropic deshielding of the aromatic ring implies that the double dond and the phenyl nucleus are not in the same plane. Examination of space-filling models of this compound shows that indeed the double bond and the aromatic ring lie in intersecting planes with a substantial dihedral angle between them. Examination of the pair of compounds 16 and 17 shows a similar effect.

Further evidence that the exocyclic double bond in compound 15 is not coplanar with the aromatic ring is indicated from examination of its ultraviolet spectrum, which exhibits an absorption at 244 mμ (ε 8100) in 95% EtOH. This band appears at approximately 260 mμ in normal *p*-methoxystyrene systems.[16] The shift to shorter wavelength is consistent with

Scheme III



there being little π overlap between the exocyclic double bond and the phenyl nucleus in **15**. On the other hand, the ultraviolet absorption at 265 mμ (ϵ 13 700)[12] in 95% EtOH of compound **16** is consistent with the nuclear magnetic resonance data indicating that the exocyclic olefinic linkage in this compound is coplanar with the aromatic ring.

Our failure to functionalize the aromatic hydrocarbon **9** in any acceptable way forced us to look for an alternative route to benzosuberone **1** needed in our synthetic plan. An efficient solution to this problem is given in Scheme III.

Conversion of tetralone **2** to its methyl enol ether **18** was accomplished by treatment with methyl orthoformate and a catalytic amount of *p*-toluenesulfonic acid.[17] The crude reaction product was a mixture of dimethoxy ketal and enol ether **18**. However, distillation, during which the ketal underwent pyrolytic loss of methanol, afforded an 80% yield of the desired enol ether **18**. Addition of dibromocarbene to this olefin gave the crystalline tricyclic dibromocyclopropane **19**. The dibromocarbene was generated by either of two methods: (1) action of potassium *tert*-butoxide on bromoform in cyclohexane[17] or (2) use of 33% aqueous sodium hydroxide, bromoform, and Cetrimide (a phase reversal catalyst).[18] The yields of **19** were 83 and 69%, respectively, when the former and latter procedures were employed. The dibromide was ring expanded to bromoenone **20** in 89% yield by refluxing in ethanol in the presence of silver tetrafluoroborate.[19] Conversion of **20** to the much awaited benzosuberone **1** was accomplished in one step by concurrent saturation of the double bond and hydrogenolysis of the carbon–bromine bond by hydrogenation in benzene over palladium on charcoal catalyst using sodium carbonate to neutralize liberated hydrobromic acid. The transformation was accomplished in 92% yield. This scheme represents a 54% yield from tetralone **2** to benzosuberone **1**. It was found that when purification of intermediates, except enol ether **18**, was avoided an overall yield of 66% was obtained.

Experimental Section

Melting points are reported uncorrected. Boiling points were recorded at gauge pressure and are reported uncorrected. GLPC purifications are performed on a Varian Aerograph gas chromatograph Model 90P with 20% S.E.-30 on 60/80 Chrom WHDMS in a ¼ in. × 12 ft stainless steel column. Nuclear magnetic resonance spectra were recorded on either a Varian A-60A or Varian EM 360 instrument. Chemical shifts are reported in δ values (ppm) relative to tetramethylsilane as an internal standard. Infrared spectra were recorded on a Beckman IR-8 instrument, using polystyrene calibration points; only selected absorptions are reported. Ultraviolet spectra were recorded on a Cary 14 recording spectrophotometer. Low resolution mass spectra were recorded on a Consolidated Electrodynamics Corporation mass spectrometer. High resolution mass spectra were determined by Mr. Kei Miyano on a Varian M-60 mass spectrometer. Analytical samples for high resolution mass spectroscopic analysis were prepared by preparative GLPC. Combustion analyses were determined by Chemalytics, Inc., Tempe, Ariz. Solvents were dried by standard methods and stored over Linde 4A molecular sieves prior to use. Organic extracts from reaction mixtures were dried by washing with brine and swirling with anhydrous sodium sulfate. All reactions were run under a dry nitrogen atmosphere.

Methyl 4-(*p*-Methoxyphenyl)butyrate (4). To a 500-mL round-bottomed flask was added 72.6 g (0.37 mol) of 4-(*p*-methoxyphenyl)butyric acid (**3**),[20] 60 mL of methanol, 200 mL of benzene, and 0.2 g of *p*-toluenesulfonic acid monohydrate. The resulting solution was magnetically stirred under reflux for 18 h. The solution was cooled, neutralized with solid sodium bicarbonate, and extracted with ether. The combined organic layers were washed with water until neutral and then dried. Evaporation of the solvent gave a yellow-brown oil which was distilled at reduced pressure to give 72.2 g (93% yield) of water-white ester **4**: bp 111 °C (0.7 mm); IR (neat) 1737 cm^{-1} (ester >C=O); NMR (CCl_4) δ 1.65–2.64 (m, 6 H), 3.55 (s, 3 H), 3.68 (s, 3 H), and 6.59–7.13 ppm (symmetric m, 4 H); high resolution mass spectrum, calculated (*m/e*) for $C_{12}H_{16}O_3$, 208.1099; found, 208.1103.

2-Methyl-5-(*p*-methoxyphenyl)pentan-2-ol (5). A magnetically stirred solution of 50.0 g (0.24 mol) of ester **4** in 450 mL of anhydrous diethyl ether in a 2-L flame-dried round-bottomed flask was cooled to 0 °C. To the chilled solution was slowly added 352 mL of 1.5 M (0.53 mol) methyllithium in ether dropwise over a 1.5-h period. The reaction mixture was allowed to warm to room temperature and stirred 24 h. At this time excess methyllithium was decomposed by dropwise addition of water-saturated diethyl ether. Water (300 mL) was then added to dissolve the lithium salts and the mixture was extracted with ether. The combined organic layers were washed with water until neutral and then dried. Evaporation of the solvent gave 50.0 g (100%) of tertiary alcohol **5**: IR (neat) 3435 (-OH), 1375, and 1365 cm^{-1} [$(CH_3)_2C<$]; NMR (CCl_4) δ 1.12 (s, 6 H), 1.37–166 (m, 4 H), 2.90 (broad s, 1 H), 2.34–2.65 (m, 2 H), 3.68 (s, 3 H), and 6.57–7.10 ppm (symmetric m, 4 H); high resolution mass spectrum, calculated (*m/e*) for $C_{13}H_{20}O_2$, 208.1463; found, 208.1468.

1,1-Dimethyl-7-methoxytetralin (6). A 1-L round-bottomed flask was charged with 49.5 g (0.24 mol) of tertiary alcohol **5**. To this was added 900 g of commercial polyphosphoric acid (Matheson Coleman and Bell, Inc.). The resultant mixture was mechanically stirred for 9 h at 50 °C during which time the color changed from clear to yellow to red. The mixture was cooled to room temperature and then poured into 800 mL of ice water. The aqueous layer was extracted four times with ether. The combined organic layers were washed with water until neutral and then dried. Evaporation of the solvent at reduced pressure gave a brown oil which was distilled to give 42.2 g (94% yield) of dimethyltetralin **6** as a water-white oil: bp 85–87 °C (0.5 mm); IR (neat) 1381 and 1365 cm^{-1} [$(CH_3)_2C<$]; NMR (CCl_4) δ 1.23 (s, 6 H), 1.47–2.03 (m, 4 H), 2.44–2.80 (m, 2 H), 3.68 (s, 3 H), and 6.37–7.14 ppm (unsymmetrical m, 3 H); high resolution mass spectrum, calculated (*m/e*) for $C_{13}H_{18}O$, 190.1357; found, 190.1344.

4,4-Dimethyl-6-methoxy-1-tetralone (2). Into a 500-mL three-necked round-bottomed flask equipped with a mechanical stirrer and an addition funnel was placed 15.0 g (0.0788 mol) of dimethyltetralin **6** in 160 mL of glacial acetic acid. The solution was cooled to 10 °C. A solution of chromium trioxide, 23.7 g (0.237 mol) in 18 mL of water and 70 mL of acetic acid, was introduced into the addition funnel and two drops of this solution were added to the reaction mixture. At this time the reaction mixture was cooled to 0 °C and the chromium trioxide solution added dropwise over a 45-min period, maintaining the temperature at 0–5 °C. After addition was complete, the mixture was stirred at 0 °C for 24 h. The reaction was diluted with 200 mL of water and the mixture extracted five times with ether. The combined organic layers were washed with 5% sodium hydroxide until the aqueous washes were alkaline. The organic phase was washed with water until neutral and then dried. Removal of solvent gave a dark orange oil which was distilled to give 13.0 g (81% yield) of tetralone **2** as a pale yellow oil: bp 120–122 °C (0.1 mm); IR (neat) 1675 (conjugated >C=O), 1383 and 1362 cm^{-1} [$(CH_3)_2C<$]; NMR (CCl_4) δ 1.32 (s, 6 H), 1.74–2.09 (m, 2 H), 2.35–2.70 (m, 2 H), 3.78 (s, 3 H), and 6.54–7.94 ppm (m, 3 H); high resolution mass spectrum, calculated

for (*m/e*) $C_{13}H_{16}O_2$, 204.1150; found, 204.1146.

1-Methylene-4,4-dimethyl-6-methoxytetralin (7). To a flame-dried 50-mL three-necked round-bottom flask equipped with an efficient magnetic stirrer and a reflux condenser was added 1.26 g (0.030 mol) of sodium hydride as a 57% dispersion in mineral oil. This was washed three times with dry pentane, decanted, and then induced to react with 4 mL of dimethyl sulfoxide by heating to 70–75 °C until hydrogen evolution ceased (~40 min). The slurry was cooled to room temperature and 5 mL of dimethyl sulfoxide was added, followed by 12.18 g (0.030 mol) of methyltriphenylphosphonium iodide over a 15-min period. An additional 5 mL of dimethyl sulfoxide was added to make the mixture easier to stir. The mixture was stirred for 10 min, and then 3.06 g (0.015 mol) of tetralone **2** in 3 mL of dimethyl sulfoxide was added. The reaction mixture was stirred at 60–65 °C for 8 h. The material was then poured into a 125-mL Erlenmeyer flask containing 30 mL of ice water and 30 mL of pentane. The resulting mixture was vigorously stirred for 15 min, until the triphenylphosphine oxide precipitated. The mixture was filtered and the solid washed with pentane. The combined organic layers were washed with dimethyl sulfoxide–water (1:1) and water, and then dried. Removal of the solvent at reduced pressure gave 2.91 g (96% yield) of exocyclic olefin **7**: IR (neat) 1622 (ar >C=C<) and 875 cm^{-1} (>C=CH_2); NMR (CCl_4) δ 1.27 (s, 6 H), 1.54–1.84 (m, 2 H), 2.30–2.66 (m, 2 H), 3.71 (s, 3 H), 4.75 (m, 1 H), 5.21 (m, 1 H), and 6.45–7.53 ppm (m, 3 H); high resolution mass spectrum, calculated (*m/e*) for $C_{14}H_{18}O$, 202.1357; found, 202.1333.

Mixture of 9,9-Dimethyl-2-methoxy-6-benzosuberone (8) and 9,9-Dimethyl-2-methoxy-5-benzosuberone (1). (a) Using Filtered Cyanogen Azide Solution. To a 100-mL round-bottomed flask were added 2.95 g (0.0146 mol) of exocyclic olefin **7** and 30 mL of methanol–acetonitrile (1:1). To this was added 14.60 mL (0.0585 mol) of freshly prepared and filtered 4 M cyanogen azide solution[2] in acetonitrile. The solution was magnetically stirred for 72 h at ambient temperature during which time nitrogen evolution was noticeable. To the reaction mixture was added 15 mL of 6 M hydrochloric acid and the material was vigorously stirred at 50 °C for 4 h. This was cooled and extracted with ether. The ethereal extracts were washed with water until neutral and then dried. The dry organic phase was then percolated through a column of basic alumina capped with a layer of Celite to remove the explosive azide residues. Evaporation of the solvent gave 2.50 g of an orange oil which was then chromatographed. Elution with 50% dichloromethane–50% pentane from Florisil gave 1.89 g (59% yield) of ketone mixture **8** and **1**. Analysis of the crude product by NMR[4] prior to chromatography indicated a ratio of 92:8 **8/1**. Ketone **8** could be obtained in pure form by careful chromatography: IR (neat) 1711 cm^{-1} (>C=O); NMR (CCl_4) δ 1.37 (s, 6 H), 1.85–2.14 (m, 2 H), 2.28–2.55 (m, 2 H), 3.60–3.80 (m, 5 H including singlet at 3.69), and 6.38–6.98 ppm (m, 3 H); high resolution mass spectrum, calculated (*m/e*) for $C_{14}H_{18}O_2$, 218.1307; found, 218.1303.

(b) Using Unfiltered Cyanogen Azide Solution. In a manner exactly analogous to the one described above except that the cyanogen azide solution was not filtered prior to use, 0.404 g (0.002 mol) of exocyclic olefin **7** was subjected to ring expansion. Analysis by NMR[4] of the crude product after workup indicated a ratio of 65:35 **8/1**.

9,9-Dimethyl-2-methoxybenzosuberan (9). Amalgamated zinc was prepared by shaking 20.0 g of zinc powder, 2.0 g of mercuric chloride, 20 mL of water, and 1 mL of concentrated hydrochloric acid in a 100-mL round-bottomed flask for 10 min. The mixture was decanted. To the amalgamated zinc were added 1.39 g (0.00637 mol) of ketone mixture **8** and **1** and 60 mL of concentrated hydrochloric acid. After refluxing for 3 h, the mixture was cooled and extracted with ether. The organic layers were washed with water until neutral and then dried. Evaporation of the solvent gave a tan oil which was chromatographed. Elution from neutral alumina with pentane gave 1.19 g (92% yield) of benzosuberan **9**: IR (neat) 1385 and 1360 cm^{-1} [$(CH_3)_2C$<]; NMR (CCl_4) δ 1.34 (s, 6 H), 1.50–1.95 (m, 6 H), 2.72–3.00 (m, 2 H), 3.70 (s, 3 H), and 6.35–7.00 ppm (m, 3 H); high resolution mass spectrum, calculated (*m/e*) for $C_{14}H_{20}O$, 204.1514; found, 204.1536.

Benzylic Oxidation of 9,9-Dimethyl-2-methoxybenzosuberan (9). (a) In a manner analogous to that described for preparation of compound **2**, 0.530 g (0.0026 mol) of benzosuberan **9** was oxidized at 0 °C for 24 h with chromium trioxide–acetic acid–water. Chromatography of the crude product on neutral alumina (50% dichloromethane–50% pentane) gave 0.035 g (6% yield) of benzosuberone **1**: IR (neat) 1673 cm^{-1} (conjugated >C=O); NMR (CCl_4) δ 1.38 (s, 6 H), 1.65–2.01 (m, 4 H), 2.35–2.79 (m, 2 H), 3.79 (s, 3 H), and 6.52–7.40 ppm (m, 3 H); high resolution mass spectrum, calculated (*m/e*) for $C_{14}H_{18}O_2$, 218.1307; found, 218.1313.

(b) The above experiment was repeated at room temperature for 28 h. Starting with 0.651 g (0.00319 mol) of benzosuberan **9**, the reaction yielded 0.073 g (10.5% yield) of desired benzosuberone **1** and only 0.117 g of unreacted starting material **9**.

Benzylic Oxidation of 2-Methoxybenzosuberan (10). (a) In a manner analogous to that described for preparation of compound **2**, 1.030 g (0.00585 mol) of benzosuberan **10** was oxidized at 0 °C for 24 h with chromium trioxide–acetic acid–water. The crude product was chromatographed on neutral alumina. Elution with 50% dichloromethane–50% pentane gave 0.133 g (12% yield) of crystalline benzosuberone **11**, which was identical with an authentic sample (Aldrich Chemical Co.): mp 60.5–61.0 °C; IR (CCl_4) 1673 cm^{-1}; NMR (CCl_4) 1.54–1.90 (m, 4 H), 2.53 (distorted t, 2 H), 2.79 (distorted t, 2 H), 3.70 (s, 3 H), and 6.46–7.70 ppm (m, 3 H).

(b) The above oxidation, using the same molar ratios, was performed on 0.995 g (0.00565 mol) of benzosuberan **10**. In this case the addition of the chromium trioxide solution was carried out between 25 and 30 °C and the reaction was allowed to go for 28 h at room temperature. Workup as before gave 0.791 g of gummy material which was chromatographed. Elution from neutral alumina with pentane gave 0.075 g of benzosuberan **10**. Further elution with 50% dichloromethane–50% pentane gave 0.676 g (63% conversion, 68% yield based on recovered starting material) of compound **11**.

9,9-Dimethyl-5-methylene-2-methoxybenzosuberan (15). In a manner analogous to that described for the preparation of compound **7** using the same molar ratios, 2.900 g (0.0133 mol) of benzosuberone **1** was reacted with the Wittig reagent derived from methyltriphenylphosphonium iodide to give 2.502 g (87% yield) of olefin **15**: IR (neat) 1625 (ar >C=C<) and 890 cm^{-1} (>C=CH_2); UV $\lambda_{max}^{95\%\ EtOH}$ 244 mμ (ϵ 8100); NMR (CCl_4) δ 1.23 (s, 6 H), 1.49–1.98 (m, 4 H), 2.05–2.44 (m, 2 H), 3.74 (s, 3 H), 4.85 (m, 2 H), and 6.32–7.07 ppm (m, 3 H); high resolution mass spectrum, calculated (*m/e*) for $C_{15}H_{20}O$, 216.1514; found, 216.1507.

5-Methylene-2-methoxybenzosuberan (17). In a manner analogous to that described for the preparation of compound **7** using the same molar ratios, 2.00 g (0.0105 mol) of benzosuberone **11** was reacted with the Wittig reagent derived from methyltriphenylphosphonium iodide. Workup as for exocyclic olefin **7** gave, after evaporation of the solvent, 1.88 g (95%) of olefin **17**: IR (neat) 1615 (ar –C=C) and 895 cm^{-1} (>C=CH_2); NMR (CCl_4) δ 1.55–2.86 (m, 8 H), 3.67 (s, 3 H), 4.93 (m, 2 H), and 6.41–7.15 ppm (m, 3 H); low resolution mass spectrum, parent peak (*m/e*) = 188.

Enol Ether 18. To a solution of 4.70 g (0.023 mol) of *gem*-dimethyl tetralone **2** in 75 mL of anhydrous methanol (in a 250-mL round-bottomed flask) were added 10 mL of methyl orthoformate and 0.1 g of *p*-toluenesulfonic acid. After the mixture was stirred at room temperature for 12 h, enough solid sodium methoxide was added to make the mixture slightly alkaline. The mixture was stirred 10 min. The methanol was removed at reduced pressure and the residue extracted with ether. The organic layers were combined and washed with water until neutral and then dried. Evaporation of the solvent gave 5.56 g of a thick red oil which was distilled to give 4.03 g (80% yield) of enol ether **18**: bp 113 °C (0.08 mm); IR (neat) 1648 cm^{-1} (>C=COR); NMR (CCl_4) δ 1.20 (s, 6 H), 2.14 (d, 2 H, J = 4.5 Hz), 3.55 (s, 3 H), 3.62 (s, 3 H), 4.54 (d, 1 H, J = 4.5 Hz), and 6.30–7.38 ppm (m, 3 H); high resolution mass spectrum, calculated (*m/e*) for $C_{14}H_{18}O_2$, 218.1307; found, 218.1313.

Dibromocyclopropane 19. Method A. To a 500 mL round-bottomed three-necked flask (equipped with a mechanical stirrer and an additional funnel) was introduced 4.01 g (0.0184 mol) of enol ether **18** in 90 mL of freshly distilled cyclohexane. Then 20 g of potassium *tert*-butoxide was added and the solution was chilled to 10 °C in an ice–water bath. To the cool solution was added 50 g of freshly distilled bromoform dropwise over a period of 2 h, maintaining the reaction temperature at or less than 20 °C. The mixture was allowed to warm to room temperature and stirred 12 h. After addition of 100 mL of water, the reaction mixture was extracted with dichloromethane. The combined organic layers were washed with water until neutral and then dried. Evaporation of the solvent gave 7.25 g of a thick brown oil which was then chromatographed. Elution from Florisil with 20% dichloromethane–80% pentane gave 5.60 g (78% yield) of white crystalline dibromocyclopropane **19**. Other fractions rich in the desired product but containing varying amounts of impurities were combined and rechromatographed to give an additional 0.35 g of product (combined yield 83%). An analytical sample was recrystallized from pentane: mp 88.0–88.5 °C; IR (CCl_4) 1115 cm^{-1} (COC); NMR (CCl_4) δ 1.27 (s, 6 H), 1.46–2.43 (m, 3 H), 3.27 (s, 3 H), 3.69 (s, 3 H), and 6.41–7.38 ppm (m, 3 H). Anal. Calcd for $C_{15}H_{18}Br_2O_2$: C, 46.18; H, 4.65; Br, 40.96. Found: C, 45.99; H, 4.66; Br, 40.72.

Method B. In a 25-mL three-necked pear-shaped flask equipped

with a mechanical stirrer was placed 0.411 g (0.00189 mol) of enol ether **18** in 3 mL of freshly distilled bromoform and 0.020 g of Cetrimide. To this was added 3 mL of 33% aqueous sodium hydroxide dropwise over a 15-min period. The resulting two-phase mixture was vigorously stirred for 34 h at ambient temperature. Workup as in method A gave 0.715 g of a brown oil which on Florisil (elution with 20% dichloromethane–80% pentane) gave 0.507 g (69% yield) of crystalline material identical with that produced by method A.

Bromoenone 20. A solution of silver tetrafluoroborate was perpared along the lines of Birch and Keeton.[19] To 4.6 g of 37–40% aqueous hydrofluoroboric acid in a 10-mL Erlenmeyer flask equipped with a magnetic stirrer was slowly added 0.506 g (0.00218 mol) of silver oxide in small portions. The black silver oxide dissolved to give a clear pale gray solution, which was stirred an additional 10 min. At this time the silver tetrafluoroborate solution was slowly added to a 50-mL round-bottomed flask equipped with a magnetic stirrer and containing a solution of 0.850 g (0.00218 mol) of dibromocyclopropane **19** in 15 mL of ethanol. The mixture was stirred at reflux for 2 h. During the course of the reaction, silver bromide was formed as a granular precipitate. The solution was cooled to room temperature and transferred to a 125-mL Erlenmeyer flask and made alkaline (cautiously) with solid sodium carbonate. The solution was filtered to remove silver salts and the filtrate extracted with dichloromethane. The combined organic layers were washed with water until neutral and then dried. Evaporation of the solvent gave 0.640 g of a brown oil which was chromatographed on Florisil. Elution with 20% dichloromethane–80% pentane gave 0.572 g (89% yield) of bromoenone **20** as a pale yellow oil: IR (neat) 1645 cm^{-1} (conjugated >C=O); NMR (CCl_4) δ 1.31 (s, 6 H), 2.41 (d, 2 H, J = 5.5 Hz), 3.71 (s, 3 H), 6.40–7.50 (m, 3 H), and 6.89 ppm (t, 1 H, J = 5.5 Hz); low resolution mass spectrum, parent peak: (m/e) = 204 (^{79}Br) and 206 (^{81}Br).

9,9-Dimethyl-2-methoxy-5-benzosuberone (1). A 25-mL round-bottomed flask was charged with 0.471 g (0.0016 mol) of bromoenone **20.** To this were added 0.150 g of 5% palladium on charcoal catalyst and 0.20 g of sodium carbonate, followed by 10 mL of benzene. The mixture was magnetically stirred as it was hydrogenated at room temperature and pressure for 8 h. At this time, the reaction mixture was filtered to remove the catalyst and excess sodium carbonate. The filtrate was evaporated at reduced pressure to give a yellow oil, which upon chromatography on Florisil (50% dichloromethane–50% pentane) gave 0.320 g (92% yield) of ketone **1.** This material was identical with that obtained from the direct oxidation of benzosuberan **2** with chromium trioxide in aqueous acetic acid.

When 7.63 g (0.035 mol) of enol ether **18** was subjected to the sequence **18** → **19** → **20** → **1** using the same molar ratios and conditions, but not isolating the intermediate products, a yield of 6.33 g of ketone **1** was produced after column chromatography as above. This represents a yield of 83% from enol ether **18** (or 66% from tetralone **2**).

Acknowledgment. The authors wish to thank the Committee on Research, University of California, Davis, for partial support of this work.

Registry No.—**1**, 65275-82-3; **2**, 23203-51-2; **3**, 4521-28-2; **4**, 20637-08-5; **5**, 4586-90-7; **6**, 23203-50-1; **7**, 65275-83-4; **8**, 65275-77-6; **9**, 65275-78-7; **10**, 21336-18-5; **11**, 6500-65-8; **15**, 65275-79-8; **16**, 13587-99-0; **17**, 64746-51-6; **18**, 65275-80-1; **19**, 65354-45-2; **20**, 65275-81-2; methyllithium, 917-54-4; methyltriphenylphosphonium iodide, 2065-66-9; bromoform, 75-25-2.

References and Notes

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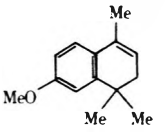
(4) Exocyclic olefin **8** isomerizes to endocyclic olefin **i** on contact with acid or on attempted distillation or chromatography.



i

(5) McMurry has noted minor changes in product distribution upon the addition of $AgBF_4$; see ref 2.
(6) These ratios were determined by integration of the NMR spectrum of the crude reaction product. Integration of the aromatic proton ortho to the carbonyl function in ketone **1** (δ = 7.29 ppm) relative to the remaining aromatic protons (no absorption past δ = 7.00 ppm) gave the reported ratios.
(7) Some conditions which failed were sodium dichromate–acetic acid in benzene both at room temperature and at reflux, and chromium trioxide in pyridine.
(8) Compound **10** was prepared from 6-methoxy-1-tetralone (Aldrich Chemical Co.) by a completely analogous route to that used for the preparation of compound **9** (see Scheme II). The yields of the individual steps were very similar in each case.
(9) Starting material disappeared after 36 h at room temperature but only a 52% yield of **11** was realized.
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Synthesis and Novel Physical Properties of a Biphenoquinoquinocyclopropane

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The synthesis and physical properties of 1-(3,5-di-*tert*-butyl-4-hydroxy-4′-biphenylyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)cyclopropene (**8**) are described. Upon oxidation with either PbO_2 or alkaline $K_3Fe(CN)_6$ **8** yields two major products. One of the products is tentatively identified as the fully quinoid system **4**, which displays a λ_{max} well into the near-infrared at 1300 nm. The other oxidation product is identified as the biradical **10**. The dianion of **8** can be electrochemically oxidized in an ESR cell to yield an anion radical identical with that obtained upon electrochemical reduction of **10**.

The quinocarbons (polyquinocycloalkanes) represent a class of radialenes in which each exocyclic double bond comprises either the ylidene linkage of a 4-oxo-2,5-cyclohexadien-1-ylidene moiety or a carbonyl group. Since the synthesis of the first quinocarbon, triquinocyclopropane **1**,[1] a number of other quinocarbons and related radialenes have been re-

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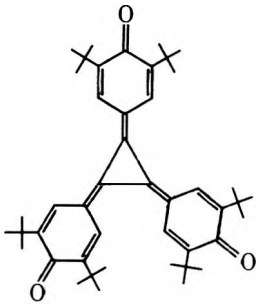

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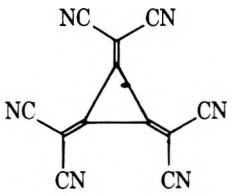
ported.[2-5] Among the more noteworthy advances in this area are the syntheses of hexacyanomethylenecyclopropane **2**[6] and tetraquinocyclobutane **3**.[3]



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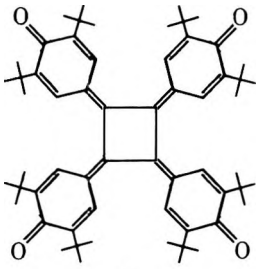

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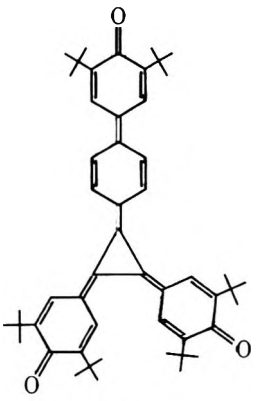
Recent interest in the possible uses of the highly conjugated, brightly colored quinocarbons as dyes, organic semiconductors, photographic materials, and charge-transfer salts has stimulated our endeavors to design and synthesize molecules having potentially useful electronic and magnetic properties. Since triquinocyclopropane **1** has an extremely intense electronic absorption in the near-infrared at about 770 nm (log ϵ 4.71),[1] we have directed our efforts toward the syntheses and investigation of the physical properties of molecules with even lower energy first electronic transitions. In this report we describe results of attempts to synthesize the biphenoquinonoid compound 1,2-bis(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)-3-(3,5-di-*tert*-butyl-4-oxobiphen-4′-ylidene)cyclopropane (**4**).



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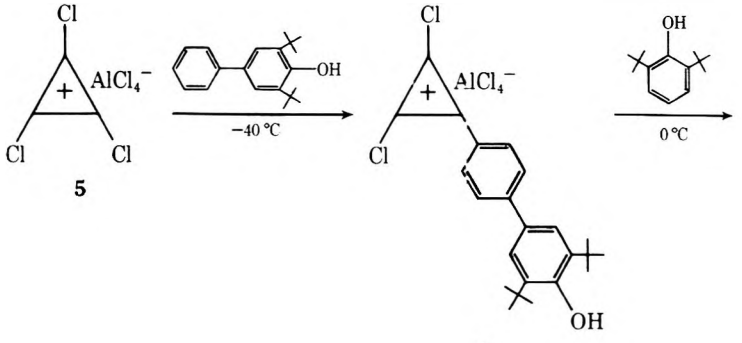
Based on analogy to the straightforward preparation of triquinocyclopropane **1**,[1] we employed the synthetic route outlined in Scheme I. 2,6-Di-*tert*-butyl-4-phenylphenol (1 equiv), prepared by the method of Koser and Pirkle,[7] was slowly added to trichlorocyclopropenium aluminate at −40 °C. The reaction was allowed to warm slowly to 0 °C, and 2 equiv of 2,6-di-*tert*-butylphenol was added to generate the triarylcyclopropenium aluminate **7**. An attempt to first generate the 1,2-bis(2,6-di-*tert*-butyl-4-hydroxyphenyl)-3-chlorocyclopropenium aluminate followed by addition of the 2,6-di-*tert*-butyl-4-phenylphenol proved unsuccessful. Apparently the 2,6-di-*tert*-butyl-4-phenylphenol is unreactive towards electrophilic attack by diarylcyclopropenium ion. Similar behavior has been observed upon the attempted addition of other unactivated aromatics, such as benzene, to diarylcyclopropenium salts.[8] Hydrolysis of **7** followed by

Scheme I



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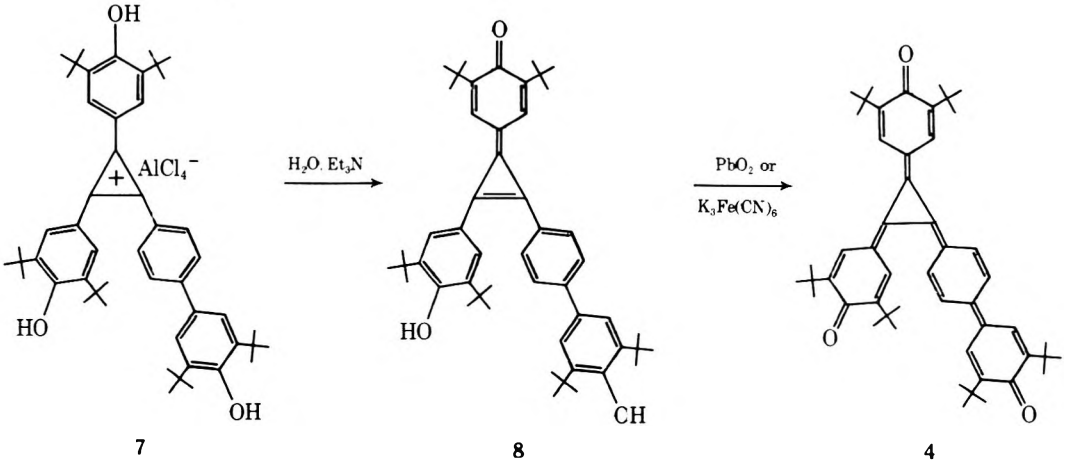

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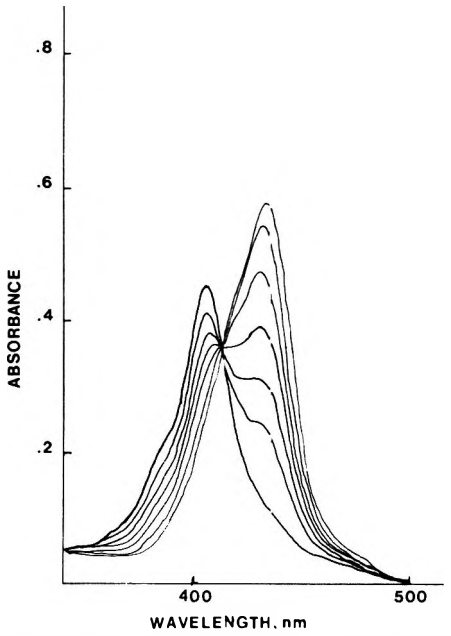
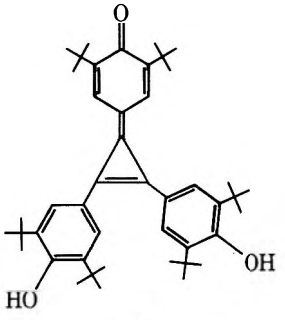


Figure 1. Electronic spectra of 8 (1×10^{-4} M MeOH) showing the conversion to its dianion upon titration with 3.34×10^{-4} N NaOH.

treatment with triethylamine produced 8 in about 30% yield after column chromatography.

The ^{1}H NMR spectrum of 8 displays two *tert*-butyl absorbances with intensity ratios of 2:1. This pattern is attributed to hydrogen exchange between the 3,5-di-*tert*-butyl-4-hydroxyphenyl and the 3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadiene moieties. Apparently the 1-(3,5-di-*tert*-butyl-4-hydroxybiphenyl) substituent does not participate in this hydrogen exchange since two distinct hydroxyl ^{1}H NMR absorbances of equal intensity (one sharp and one broad) are observed. Similar hydrogen exchange is observed for the diarylquinocyclopropene precursor to **1**, compound **9**, which



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shows only one *tert*-butyl absorbance in its ^{1}H NMR spectrum.[9] The aryl region of the ^{1}H NMR spectrum of 8 shows the expected pattern of two singlets in a 2:1 intensity ratio as well as a doublet of doublets (4 H, $J_1 = 11.0$, $J_2 = 1.7$ Hz).

The orange–red colored 8 has λ_{max} 405 nm (log ϵ 4.65) in methanol, closely paralleling that of **1**, λ_{max} 406 nm (log ϵ 4.86).[1] Compound 8 also shows a bathochromic shift from polar to nonpolar solvents (λ_{max} 413 nm in cyclohexane), which suggests a dipolar ground state with significant cyclopropenium ion character. A spectrophotometric titration of 8 using sodium hydroxide in methanol was performed (Figure 1). All intermediate curves passed through one set of isosbestic points, implying that the monoanion is unstable with respect to the dianion under the titration conditions. The dianion has λ_{max} 432 nm (log ϵ 4.77).

The infrared spectrum of 8 shows the characteristic 1822-cm^{-1} absorbance from the carbon–carbon double-bond

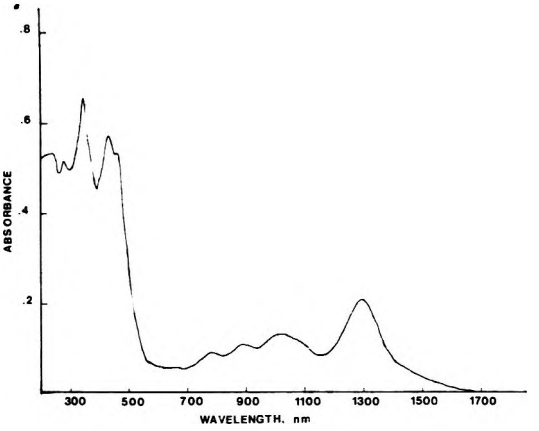


Figure 2. Electronic spectra of freshly oxidized 8 in CCl_4 (4.3×10^{-5} M).

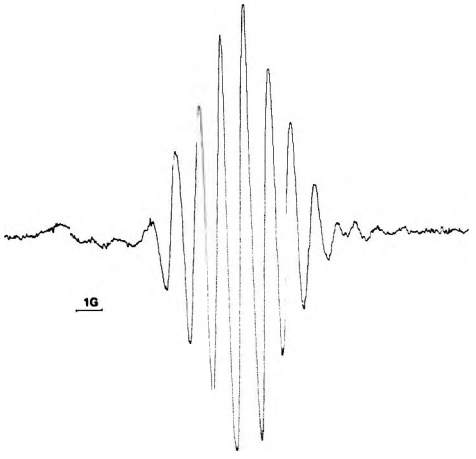


Figure 3. Electronic spin resonance spectrum of the biradical **10** in toluene at room temperature. The spectrum was obtained by PbO_2 oxidation of 8.

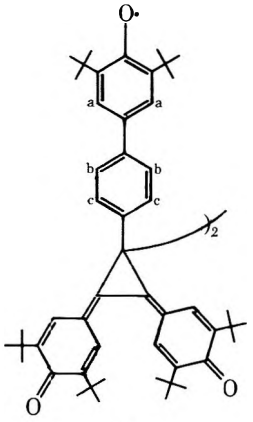
stretch of cyclopropenes. An intense band near 1600 cm^{-1}, attributed to the quinoid group, is also observed.

Further structural proof of 8 includes conversion to its ionic perchlorate salt by treatment with perchloric acid. The infrared spectrum of the perchlorate salt shows an intense 1365-cm^{-1} band, characteristic of cyclopropenium ions, as well as the 1070-cm^{-1} broad band from O_4Cl^-. The 1822-cm^{-1} stretching is no longer present.

Upon oxidizing 8 with an excess of either PbO_2 or alkaline $K_3Fe(CN)_6$, we observed absorptions well into the near-infrared at 1300 nm, 1030, 880 sh, and 770 sh (Figure 2). The 1300-nm absorption represents an extremely low-energy first electronic transition. However, all four of the long wavelength absorptions decayed at room temperature, following first-order kinetics ($\tau_{1/2}$ = 92 min).

The oxidized solution displays a strong nine-line signal in the ESR spectrum (Figure 3), whose intensity remains constant as the near-infrared absorptions decay. In addition to the low-energy absorption bands, the oxidized solution also displays λ_{max} at 467 nm, 434, 347, and 283. After the 1300-nm absorption has disappeared, only the 467-nm band remains, implying that it is from the paramagnetic species.

Our interpretation of these observations is that the fully quinoid structure **4**, having λ_{max} 1300 nm, is produced upon oxidation of 8 and this compound decomposes via an unspecified route. Assuming the extinction coefficient of **4** to be similar to that of triquinocyclopropane (log ϵ 4.71), **4** is formed in about 10% yield. The paramagnetic species is probably best represented as the biradical dimer **10**.



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The ESR signal can be simulated as the central nine lines of an 11-line pattern from a pentet of triplets with respective coupling constants of 1.78 and 0.80 G and a line width of 0.25 G, g = 2.0039. The pentet arises from coincidentally equivalent couplings with the four a and b protons (see structure **10**) and the triplet from the two c protons. This spectrum closely parallels that of the 2,6-di-*tert*-butyl-4-phenylphenoxyl radical, which has analogously equal a and b proton splittings of 1.77 G and c splitting of 0.88 G.[10]

A sample of **8** was oxidized with excess alkaline $K_3Fe(CN)_6$ in chloroform; after removal of the oxidizing agent and solvent, a polycrystalline black solid was isolated. The magnetic susceptibility (μ) of this solid was 1.10 μ_B, based on *moles of starting material* **8**. This μ is consistent with the dimer biradical **10** and rules out any possible monomeric biradical structure which would have a predicted μ of 3.46 μ_B. (The deviation of the observed μ (1.10 μ_B) from the theoretical value for **10** of 1.73 μ_B can be accounted for by the uncorrected possible diamagnetic impurities from the decomposition products of **4** and the relatively large diamagnetic correction necessary for **10**.)

The absence of a sharp O–H stretching band in the IR spectrum of **10** suggests that it is fully oxidized. Further proof that no monoradical of **8** is present was obtained by treatment of **8** with less than 0.25 equiv of PbO_2. A complicated and uninterpretable ESR spectrum is obtained, presumably from overlap of the signals from the two possible monoradicals of **8**.

While any discussion of the nature of the immediate precursor to **10** can only be speculative, several important inferences should be emphasized. **10** must be formed from rapid dimerization of an oxidized form of compound **8**. The oxidized form of **8** is most likely either the singlet state quinoid structure **4**, the triplet state of **4**, or a biradical. Oxidations carried out at −70 °C followed by low-temperature ESR experiments failed to show any signals other than those observed for **10**. No enhanced ESR signal intensity was observed during the decay of **4** at any temperature. **4** decays with first-order kinetics and consequently cannot be an immediate precursor to **10**; however, it could cross to a triplet state or biradical which dimerizes. Considering the relatively small proportion of **4** which is detected upon oxidation of **8**, it is most reasonable to assume that the primary source of **10** is from rapid dimerization of short-lived triplet or biradical species, which are formed concomitantly with **4**.

The biradical **10** can be cleaved by electrochemical reduction in an ESR cell to yield the corresponding anion radical. The ESR spectrum shows the central 11 lines of a 13-line pattern (Figure 4). The spectrum can be simulated assuming two sets of pentets with respective coupling constants of 1.62 and 0.81 G and a line width of 0.25 G, g = 2.0045. The same anion radical spectrum was generated by electrochemical

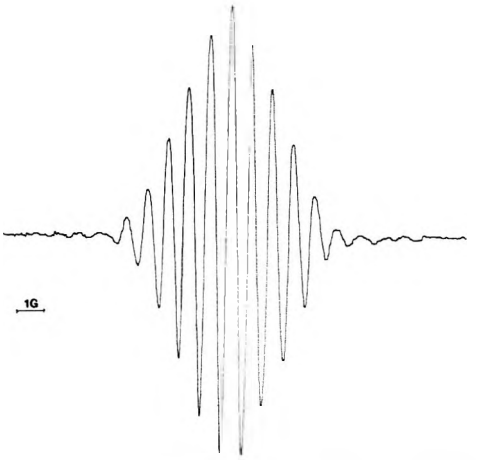
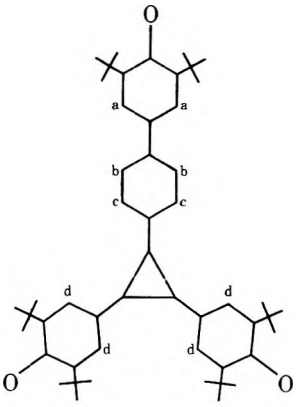


Figure 4. Electronic spin resonance spectrum of the radical anion **11** in CH_2Cl_2 at room temperature. The spectrum was obtained by electrolytic oxidation of the dianion of **8**.

oxidation of the dianion of **8** in an ESR cell. The anion radical spectrum suggests complete delocalization of the unpaired electron over the conjugated π system. McLachlan-type Hückel molecular orbital calculations[11] are in agreement with the major pentet arising from interaction of the unpaired electron with the coincidentally equivalent four a and b protons (see structure **11**) and the minor pentet arising from in-



11

teraction with the four equivalent d protons. The calculations predict interaction with the c protons to be negligible. This spin delocalization closely parallels the anion radicals of triquinocyclopropane **1** and other quinocarbons which also show the unpaired electron to be completely delocalized throughout the conjugated π system.[1,4,5]

Experimental Section

General Procedures. All syntheses were performed using purified grades of commercially available starting materials. Combustion analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Spectra were recorded by means of the following instruments: IR, Perkin-Elmer 237; ^{1}H NMR, Jeol MA-100; UV–vis near-infrared, Cary 14; ESR, Varian 4502-B.

1-(3,5-Di-*tert*-butyl-4-hydroxy-4′-biphenylyl)-2-(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)cyclopropene (8). Trichlorocyclopropenium aluminate (**5**) was generated by the rapid addition of 5.34 g (0.030 mol) of tetrachlorocyclopropene to a slurry of 3.99 g (0.030 mol) of $AlCl_3$ and 5 mL of methylene chloride. After the initial exothermicity, the reaction was heated at 60 °C for 15 min as a beige paste formed. An additional 10 mL of methylene chloride was added, and the reaction was cooled to −40 °C. The monoarylcyclopropenium aluminate **6** was formed by the addition of 8.46 g (0.030 mol) of 2,6-di-*tert*-butyl-4-phenylphenol in 10 mL of methylene chloride over the course of 1 h while maintaining the reaction temperature at −40 °C. After the addition was completed, the reaction was allowed to

warm to −20 °C for 30 min, to −10 °C for 30 min, and then to 0 °C for 30 min. The triarylcyclopropenium aluminate **7** was formed by the rapid addition of 12.36 g (0.060 mol) of 2,6-di-*tert*-butylphenol in 10 mL of methylene chloride at 0 °C. After the addition was completed, the reaction was allowed to warm to room temperature over the course of 1 h. At this time the reaction mixture was poured into 200 mL of ice water, and 5 mL of triethylamine was added. Chloroform (50 mL) was added, and the organic and aqueous phases were separated. The organic phase was thoroughly washed with water and dried over $MgSO_4$. After filtration and solvent evaporation, the crude burgundy residue was chromatographed on 360 g of silica gel ($CHCl_3$–CCl_4, 1:1) to isolate 6.54 g (30.0%) of **8** as a red powder, mp 135–139 °C dec. A small amount of the tautomer of **8** was also present, and it can be converted entirely to **8** by acid catalysis and warming at 50 °C for 30 min. Analytical samples of **8** were obtained by additional preparative TLC on silica gel (Skelly B–diethyl ether, 1:1): ^1H NMR ($CDCl_3$) δ 1.26 (s, 18 H), 1.41 (s, 36 H), 5.22 (s, 1 H), 5.34 (s, 1 H, broad), 7.26 (s, 2 H), 7.52 (s, 4 H), 7.93 (d of d, 4 H, J = 1.0, 1.7 Hz); IR ($CHCl_3$) 3622 m, 2960 s, 2875 m, 1822 m, 1600 s, 1483 s, 1432 s, 1357 s, 1330 s, 1156 m, 906 m, 886 w cm^{-1}; UV–vis (MeOH) 405 nm (log ϵ 4.65), 385 sh (4.34), 310 (4.06), 265 (4.12); UV–vis (cyclohexane) 413 nm (log ϵ 4.83), 392 (4.79), 371 (4.55), 3.15 (4.56), 275 (4.57).

Anal. Calcd for $C_{51}H_{66}O_3$: C, 84.24; H, 9.16; O, 6.60. Found: C, 84.10; H, 9.01; O, 6.89.

Perchlorate Salt of 8. A 1.00-g amount of **8** was dissolved in 5 mL of benzene and treated with 2.5 mL of 60% $HClO_4$. After 10 min a light green precipitate was filtered off and thoroughly washed with water followed by Skelly B. This material was precipitated from CH_3CN–diethyl ether to give 0.35 g of a light yellow powder, mp 171–175 °C dec. This perchlorate could be converted back to **8** by treatment with triethylamine in a chloroform–water mixture: ^1H NMR (acetone-d_6) δ 1.57 (s, 18 H), 1.67 (s, 36 H), 3.16 (s, 3 H, broad), 7.72 (s, 2 H), 8.47 (s, 4 H), 8.47 (d of d, 4 H, J = 9.0, 2.0 Hz); IR ($CHCl_3$) 3600 m, 2960 s, 1590 s, 1365 s, 1332 m, 1070 s, broad, 720 m, 660 w, 620 w cm^{-1}; UV (MeOH) 360 nm (log ϵ 4.79), 232 (4.09).

Titration of 8 to Its Dianion. A solution of 14.5 mg (0.020 mmol) of **8** in 200 mL of spectroquality MeOH was titrated with 3.34×10^{-4} N NaOH. Base was added to the solution of **8** in 2-mL aliquots. Aliquots were withdrawn for each UV–vis spectrum and returned after each reading. An isosbestic point was observed at 412 nm throughout the titration. The dianion has λ_{max} 432 nm (log ϵ 4.77), 318 (4.08), and 254 (4.08); see Figure 1. After the dianion was completely formed, it was converted back to the original full intensity spectrum of **8** by the addition of 1 equiv of aqueous HCl.

Oxidation of 8. PbO_2 and alkaline $K_3Fe(CN)_6$ oxidations of **8** were performed by adding at least a fourfold excess of oxidizing agent to a solution of **8** in a variety of different solvents, including toluene, methylene chloride, chloroform, and carbon tetrachloride. PbO_2 was always centrifuged from the oxidized solution, and $K_3Fe(CN)_6$ oxidations were always thoroughly washed with water. **4**: UV–vis near-infrared (CCl_4) λ_{max} 1300 nm, 1030, 880, 770, 434, 347. No extinction coefficients were calculated since the exact amount of **4** in solution was not determined.

Electron Spin Resonance Experiments: Biradical 10. In a typical ESR experiment 2 mg of **8** was placed in the bottom of an ESR cell and 6 mg of PbO_2 was placed in a side arm in the cell. Degassed solvent (either toluene, 2-methyl THF, or methylene chloride) was vacuum transferred into the bottom of the degassed cell. The solution of **8** was mixed with the PbO_2 in the side arm just prior to recording the spectrum. The spectrum in Figure 3 was obtained at room temperature: a_H = 0.88 G; g = 2.0039.

Anion Radical of 8. The dianion of **8** was generated from 2 mg of **8** and an excess of DBU in dichloromethane. A small amount of (n-Bu)$N^+ClO_4^-$ was added to the solution which was transferred to an electrochemical ESR cell. A small piece of glass wool was placed between the electrodes to slow diffusion, and the cell was degassed. A minimal current was passed through the cell to develop a strong signal: a_H = 0.81 G; g = 2.0045. An identical spectrum was generated by starting with the biradical prepared from **8** and excess PbO_2 in dichloromethane followed by electrochemical reduction.

Acknowledgment. We are sincerely grateful to Mr. Cliff Feldmann for performing magnetic susceptibility measurements. This work was supported by Grants CHE74-01345A02 and CHE76-80374 from the National Science Foundation and by a grant from the 3M Company.

Registry No.—**5**, 10438-65-0; **6**, 65276-06-4; **7**, 65276-08-6; **8**, 65276-77-9; **8** perchlorate, 65276-78-0; tetrachlorocyclopropene, 6262-42-6; 2,6-di-*tert*-butyl-4-phenylphenol, 2668-47-5; 2,6-di-*tert*-butylphenol, 128-39-2.

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Synthesis and Physical Properties of a Quinoiminocyclopropane

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The syntheses and physical properties of two quinoiminocyclopropanes, **1a** and **1b**, are described. These brightly colored, extensively conjugated quinoid compounds display an intense λ_{max} at 539 nm (log ϵ 4.85). The anion radicals of **1a** and **1b** were generated electrochemically in an ESR cell, and their spectra show the unpaired spin density to be primarily localized in the quinoimine ring. Cyclic voltammetry shows that **1a** and **1b** are relatively strong oxidizing agents, each having $E_{1/2}$ values of +0.075 and −0.505 V.

In light of the interesting physical properties of tris-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)cyclopropane (**2**)[1,2] and other related quinocarbons,[3-6] we wished to observe the effect of replacing one of the 4-oxo moieties of **2** with a different heteroatom group, the imino substituent. In this paper we report the synthesis and characterization of the first quinoiminocyclopropanes, **1a** and **1b**.

Although quinomonoimines and -diimines have been known for many years, their study has been hampered by their sensitivity to light, water, and air.[7] In addition to our primary objective of synthesizing a new quinocarbon, we hoped our approach would also offer a novel route to sterically hindered, less labile quinomonoimine compounds.

Synthesis. The syntheses of **1a** and **1b** are accomplished

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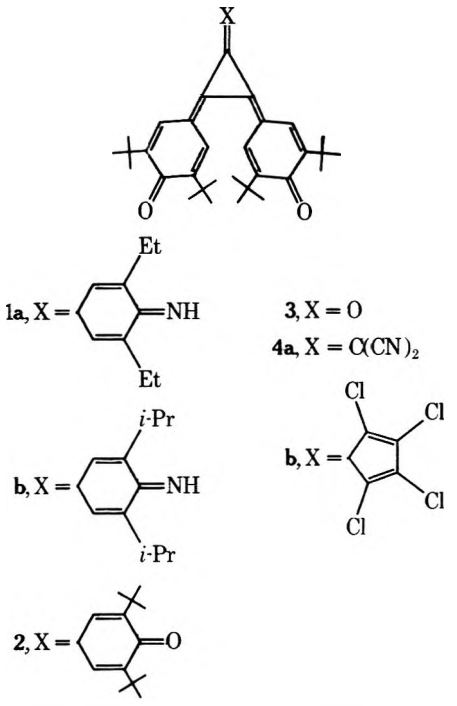


by the sequence depicted in Scheme I. The appropriate 2,6-dialkyl-substituted aniline is treated with 1-chloro-2,3-bis(3,5-di-*tert*-butyl-4-hydroxyphenyl)cyclopropenium aluminate (**5**)[8] followed by hydrolysis and treatment with triethylamine to yield a mixture of the isomeric quinocyclopropenes **6** and **7** in 60–70% isolated yield. The lead dioxide oxidation of **6** and **7** to the stable quinoiminocyclopropane **1** is effected in quantitative yield.

Analytical samples of both **6** and **7** can be isolated by dry column chromatography. The ^{1}H NMR spectra of **7a** and **7b** clearly show *tert*-butyl absorbances with the expected 2:1:1 intensity ratios. While the alkyl portion of the ^{1}H NMR spectra of **6a** and **6b** is not clearly resolved, two types of *tert*-butyl absorbances with the anticipated 1:1 intensity ratios can be discerned. **6** and **7** display medium intensity IR absorbances at 1870 and 1845 cm^{-1}, respectively; these bands are characteristic for the quinodiarylcyclopropene C=C bond stretch.[1]

The fully oxidized quinoiminocyclopropanes **1a** and **1b** display ^{1}H NMR absorbances from four magnetically nonequivalent *tert*-butyl groups, indicating that N–H inversion is slow on the ^{1}H NMR time scale. Consistent with slow N–H inversion, the aryl region of the ^{1}H NMR spectra for these compounds shows four broad[10] doublet[11] absorbances and one sharper absorbance with relative intensities of 1:1:1:1:2. The two quinoid hydrogens furthest away from the imino function are coincidentally equivalent and give rise to the singlet absorbance.

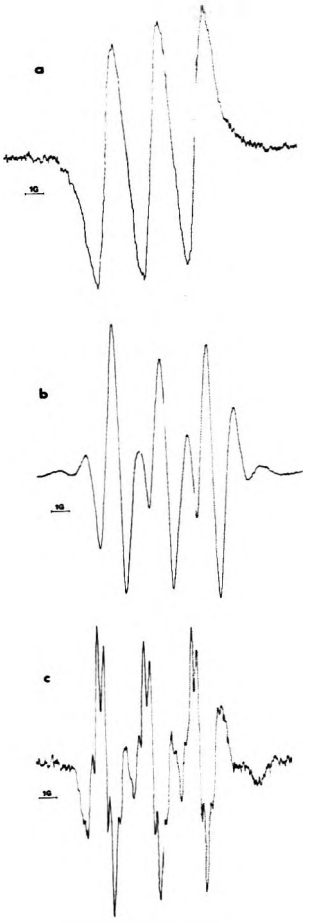
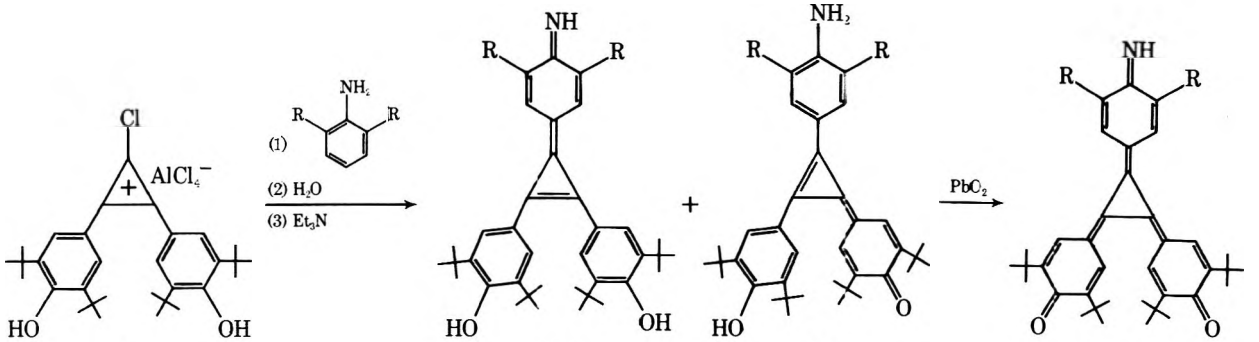


Figure 1. Electron spin resonance of the anion radical of **1a** with decreasing (a → c) modulation. The spectra were obtained by electrolytic reduction of **1a** in dichloromethane.

Physical Properties. One of the more striking physical properties of the quinocarbons is their intense color in solution. These extensively π-conjugated systems have electronic transitions in the visible and near-infrared region with extremely large extinction coefficients. For example, triquinocyclopropane **2** has λ_{max} 770 nm (log ε 4.71),[1] diquinocyclopropanone **3** has λ_{max} 542 nm (log ε 5.08),[4] and the diquinodicyanomethylenecyclopropane **4a** has λ_{max} 640 nm (log ε 4.25).[6] Like the other quinocarbons, **1a** and **1b** are brilliantly colored in solution (violet), having λ_{max} 539 nm (log ε 4.85).

The radical anions of **1a** and **1b** were electrochemically generated in an ESR cell. Each anion spectrum initially displayed three lines of equal intensity: a = 2.64 G; g = 2.0027 (Figure 1a). Utilizing the line-sharpening technique described by Glarum,[9] each of the three lines was shown to be split into doublets of equal intensity to give a six-line pattern, a = 1.35

Scheme I



a, R = Et; b, R = *i*-Pr

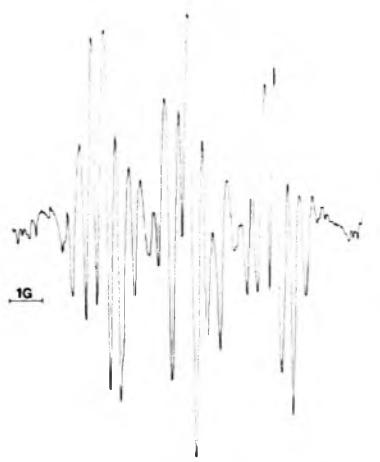
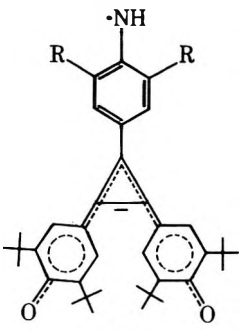


Figure 2. Electron spin resonance of the anion radical of **1b**. The spectrum was obtained by electrolytic reduction of **1b** in dichloromethane.

G (Figure 1b). Each of the doublets of the anion radical spectrum of **1b** has further couplings of about 0.30 G, splitting each doublet peak into a six-line pattern (Figure 1c). Similar fine structure in the spectrum of **1a** shows each doublet to be split into an eight-line pattern, a = 0.41 G, with approximate relative intensities of 1:4:6:5:5:6:4:1 (Figure 2).

These spectra are consistent with the major triplet splitting arising from coupling with the nitrogen nucleus and the doublets from coupling with the imino hydrogen. The six-line fine structure of **1b** is attributed to the coupling of the unpaired electron with the two methine hydrogens of the isopropyl groups, further splitting each line into nonoverlapping sets of triplets. Similarly, the fine structure of **1a** arises from the splitting of each line of the sextet by the four equivalent methylene hydrogens of the ethyl substituents to give partially overlapping pentets having predicted intensities of 1:4:6:5:5:6:4:1.

The ESR spectra suggest that the anion radical of **1** can be represented by structure **10**. The unpaired electron appears



10

to be primarily localized on the nitrogen nucleus, with the negative charge delocalized mainly over the more electron-withdrawing aryloxy groups. Since no coupling from the meta hydrogens of the quinoid rings is observed (0.1-G couplings would be discernible), the spin density at these positions must be very small. The triquinocyclopropane anion radical **2**, in which the unpaired electron is delocalized over three *equivalent* quinoid rings, displays couplings of 0.43 G from the quinoid hydrogens.[2] Diquinocyclopropanone **3** and diquinotetrachlorocyclopentadien-1-ylidenecyclopropane **4b**, which contain *more* strongly electron-withdrawing substituents than the quinoid group, have anion radicals with quinoid hydrogen couplings of 0.63 and 0.85 G, respectively.[6] The larger coupling constants for these two compounds are consistent with greater localization of the negative charge on the electron-withdrawing carbonyl and tetrachlorocyclopentadiene substituents, with consequently greater spin density on the quinoid groups.

The coupling constants of the anion radicals of **2**, **3**, **4b**, and other quinocarbons have been accurately predicted by the method of McLachlan,[10] using Hückel molecular orbitals as reported elsewhere.[2,6] Similar calculations on **1** show very little spin density for the quinoid meta positions, in agreement with the negligible coupling from the hydrogens at these positions. The quinoiminocyclopropanes are the first quinocarbons which contain a more electron-releasing substituent than the quinoid group; a further test of our explanation awaits the synthesis and study of other such quinocarbons.

Cyclic voltammetry of **1a** and **1b** displays well-defined reversible voltammograms having two waves of similar height, corresponding to two discrete one-electron transfers to form the respective radical anions and dianions. For both **1a** and **1b**, $E_{1/2}$ values of −0.075 and −0.505 V were recorded. The quinocarbons in general have high positive values for $E_{1/2}$, suggesting their potential use as organic oxidizing agents. The $E_{1/2}$ values of **1a** and **1b** are not as positive as values reported for other quinocarbons; for example, triquinocyclopropane **2** has $E_{1/2}$ values of +0.05 and −0.33 V, and 1,2-bis(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)-3-dicyanomethylenecyclopropane (**4a**) has $E_{1/2}$ values of +0.30 and −0.24 V.[11] The more positive $E_{1/2}$ values of **2** and **4a** reflect the greater electron affinities of the quino and dicyanomethylene substituents relative to the quinoimino group.

Experimental Section

General Procedures. All syntheses were performed using purified grades of commercially available starting materials. Combustion analyses were performed by Galbraith Laboratories, Knoxville, Tenn. Spectra were recorded by means of the following instruments: IR, Perkin-Elmer 237; ^{1}H NMR, Jeol MH-100; UV–vis, Cary 14; MS, CEC 21-103C; ESR, Varian 4502-B; cyclic voltammetry, PAR Model 170 electrochemistry system.

1,2-Bis(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(3,5-diethyl-4-imino-2,5-cyclohexadien-1-ylidene)cyclopropene (6a) and 1-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2-(3,5-diethyl-4-aminophenyl)-3-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)cyclopropene (7a). Tetrachlorocyclopropene (1.78 g, 0.010 mol) was added to 1.33 g (0.010 mol) of aluminum chloride slurried in 3 mL of dichloromethane under nitrogen. After initial exothermicity the reaction was stirred for 15 min at 60 °C, forming a brown paste. The slurry was diluted with 10 mL of dichloromethane and cooled to −40 °C. At this point 4.12 g (0.020 mol) of 2,6-di-*tert*-butylphenol in 15 mL of dichloromethane was added dropwise over the course of 30 min while maintaining the temperature at −40 °C. The mixture was allowed to warm to −20 °C for 30 min and then to 0 °C for 30 min, forming a brownish-green solution. 2,6-Diethylaniline (1.49 g, 0.010 mol) in 5 mL of dichloromethane was rapidly added, and the reaction was warmed to room temperature and brought to reflux for 4 h. After cooling the mixture to room temperature and diluting with 20 mL of chloroform, 15 mL of water was added dropwise with stirring, followed by the addition of 2 mL of triethylamine. The organic layer was separated, washed with water and a saturated aqueous sodium chloride solution, and then dried over $MgSO_4$. After filtration and solvent removal the remaining orange residue was triturated with hot benzene and 1.4 g of a yellow powder consisting mostly of **6a** with some **7a** was filtered off. The filtrate was concentrated and chromatographed on silica gel (benzene–diethyl ether, 9:1) to give 2.9 g of a yellow powder consisting mostly of **7a** with some **6a** present. The combined product represents a yield of 70.0%. Analytical samples of **6a** and **7a** were obtained by dry column chromatography on silica gel (hexane–diethyl ether, 1:1). **6a:** ^{1}H NMR (THF-d_8) δ 1.17–1.41 (multiplet, 24 H), 1.61 (s, 18 H), 2.79 (q, 4 H, broad), 7.21–7.33 (multiplet, 7 H, broad), 7.81 (s, 2 H); IR (KBr) 3600 m, sh, 3400 w, broad, 3040 m, 2950 s, 2870 s, 1870 m, 1585 s, 1453 m, 1380 s, 1310 s, 1190 m, 1135 m, 975 m, 924 m, 890 w, 776 m, 750 w cm^{-1}; UV (MeOH) 420 nm (log ε 4.59), 330 (4.12), 280 (4.36).

Anal. Calcd for $C_{41}H_{53}NO_2$: C, 82.91; H, 9.34; N, 2.36; O, 5.39. Found: C, 82.85; H, 9.27; N, 2.41; O, 5.47.

7a: ^{1}H NMR (CCl_4) δ 1.12 (t, 6 H), 1.32 (s, 18 H), 1.35 (s, 9 H), 1.48 (s, 9 H), 2.61 (q, 2 H), 7.00 (multiplet, 5 H, broad), 7.24 (s, 2 H), 7.43 (d, 2 H, broad); IR ($CHCl_3$) 3600 m, 3300 w, broad, 3200 w, broad, 2960

s, 2867 m, 1845 m, 1590 s, 1560 s, 1350 s, 1290 s, 909 s, 890 m, 639 m, 629 m cm^{-1}; UV (MeOH) 430 nm (log ϵ 4.49), 320 (4.36); MS Calcd for $C_{41}H_{55}NO_2$, 593.42327; MS Obsd, 593.42387.

1,2-Bis(3,5-di-*tert*-butyl-4-hydroxyphenyl)-3-(3,5-diisopropyl-4-imino-2,5-cyclohexadien-1-ylidene)cyclopropene (6b) and 1-(3,5-Di-*tert*-butyl-4-hydroxyphenyl)-2-(3,5-diisopropyl-4-aminophenyl)-3-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)cyclopropene (7b). These compounds were synthesized and purified by the method described for **6a** and **7a**.

6b: ^1H NMR(Me_2SO-d_6 and $CDCl_3$,1:1) δ 1.04–1.24 (multiplet,30 H), 1.48 (s, 18 H), 3.16 (septet, 2 H, broad), 6.96 (s, 2 H), 7.08–7.36 (multiplet, 5 H, broad), 7.62 (s, 2 H); IR (KBr) 3600 m, sh, 3400 w, broad, 3050 m, 2950 s, 2860 s, 1870 m, 1587 s, 1460 s, 1380 s, 1300 s, 1190 s, 1140 m, 972 m, 925 m, 890 m, 860 w, 877 m, 850 m cm^{-1}; UV (MeOH) 420 nm (log ϵ 4.54), 330 (4.07), 280 (4.26); MS Calcd for $C_{43}H_{59}NO_2$, 621.45457; MS Obsd, 621.45350.

Anal. Calcd for $C_{43}H_{59}NO_2$: C, 83.04; H, 9.56; N, 2.25; O, 5.15. Found: C, 82.80; H, 9.42; N, 2.20; O, 5.58.

7b: ^1H NMR ($CDCl_3$) δ 1.07 (d, 12 H), 1.25 (s, 18 H), 1.31 (s, 9 H), 1.47 (s, 9 H), 3.21 (septet, 2 H), 4.23 (s, 3 H, broad), 7.07 (s, 2 H), 7.09 (s, 2 H), 7.43 (d, 2 H, broad); IR ($CHCl_3$) 3610 m, sh, 3300 w, broad, 3200 w, broad, 2955 s, 2860 s, 1845 m, 1590 s, 1560 s, 1460 s, 1365 s, 1325 m, 1150 s, 1130 s, 908 s, 890 m, 638 m, 630 m cm^{-1}; MS Calcd for $C_{43}H_{59}NO_2$, 621.45457; MS Obsd, 621.45364.

Anal. Calcd for $C_{43}H_{59}NO_2$: C, 83.04; H, 9.56; N, 2.25; O, 5.15. Found: C, 83.06; H, 9.48; N, 2.14; O, 5.32.

1-(3,5-Diethyl-4-imino-2,5-cyclohexadien-1-ylidene)-2,3-bis-(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)cyclopropane (1a). In a typical preparation, 0.200 g (0.3 mmol) of the combined mixture of **6a** and **7a** was slurried in 30 mL of benzene in an Erlenmeyer flask under a nitrogen atmosphere. To this slurry was added 0.200 g of lead dioxide, and the reaction mixture was stirred for 30 min. The lead dioxide was then filtered from the brilliant purple solution and the solvent was removed, leaving a metallic golden solid. The product was chromatographed on silica gel (hexane–ethyl ether, 9:1), giving **1a** in quantitative yield: ^1H NMR (CCl_4) δ 0.92–1.16 (multiplet, 15 H), 1.34 (s, 9 H), 1.40 (s, 9 H), 1.42 (s, 9 H), 2.40 (q, 4 H, broad), 6.18 (d, 1 H, broad), 6.92 (s, 3 H), 7.19 (d, 1 H, broad), 7.24 (d, 1 H, broad), 7.44 (d, 1 H, broad); IR ($CHCl_3$) 2963 s, 2880 w, 1750 m, 1610 s, 1600 s, 1485 m, 1410 m, 1365 m, 1255 m, 1093 s, 905 w, 881 w cm^{-1}; UV (cyclohexane) 539 (log ϵ 5.84), 500 sh (4.25), 280 (4.17); MS Calcd for $C_{41}H_{53}NO_2$, 591.40762; MS Obsd, 591.40682.

1-(3,5-Diisopropyl-4-imino-2,5-cyclohexadien-1-ylidene)-2,3-bis(3,5-di-*tert*-butyl-4-oxo-2,5-cyclohexadien-1-ylidene)cyclopropane (1b). **1b** was synthesized and purified by the method described for **1a**: ^1H NMR (CCl_4) δ 0.92 (s, 9 H), 1.08 (d, 6 H), 1.16 (d, 6 H), 1.33 (s, 9 H), 1.38 (s, 9 H), 1.40 (s, 9 H), 2.96 (septet, 2 H, broad), 6.26 (d, 1 H, broad) 7.14 (s, 3 H), 7.30 (d, 1 H, broad), 7.40 (d, 1 H, broad), 7.60 (d, 1 H, broad); IR ($CHCl_3$) 2965 s, 2878 w, 1750 m, 1610 sh, 1593 s, 1484 m, 1409 m, 1364 m, 1254 m, 1093 s, 905 w, 881 w, 810 w cm^{-1}; UV (cyclohexane) 539 nm (log ϵ 4.85), 500 sh (4.57), 280 (4.17).

Anal. Calcd for $C_{43}H_{57}NO_2$: C, 83.04; H, 9.24; N, 2.25; O, 5.47. Found: C, 83.09; H, 9 33; N, 2.14; O, 5.44.

Cyclic Voltammetry. A PAR Model 170 electrochemistry system was used with a three-electrode cell having platinum wire working and auxiliary electrodes and a saturated calomel reference electrode. All sample solutions were 1 mM in quinoid compound with 0.1 M tetrabutylammonium perchlorate as a supporting electrolyte in dichloromethane.

Electron Spin Resonance. About 2 mg of the quinoid compound and a small amount of tetrabutylammonium perchlorate were placed in an electrolytic ESR cell. A small piece of glass wool was placed between the electrodes to slow diffusion, and approximately 0.25 mL of dichloromethane was added as solvent. The cell was thoroughly degassed, and a minimal current necessary for a satisfactory signal was passed through the cell. Identical g values of 2.0027 were obtained for the anion radicals of **1a** and **1b**. The ESR spectra of the anion radicals of **1a** and **1b** are shown in Figures 1 and 2 and are described in the text.

Acknowledgment. We wish to thank Mr. John Jorgensen for stimulating discussions throughout the course of this work. This work was supported by Grants CHE74-01345A02 and CHE76-80374 from the National Science Foundation and by a grant from the 3M Company.

Registry No.—**1a**, 65276-72-4; **1b**, 65338-73-0; **6a**, 65276-73-5; **6b**, 65276-74-6; **7a**, 65276-75-7; **7b**, 65276-76-8; tetrachlorocyclopropene, 6262-42-6; 2,6-di-*tert*-butylphenol, 128-39-2; 2,6-diethylaniline, 579-66-8.

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Synthesis of Morphinandienones, a Dihydrophenanthrone, and Pummerer's Ketones by Anodic Coupling[1]

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Anodic oxidations of several 1-benzyltetrahydroisoquinolines, laudanosine derivatives, were performed at platinum in acetonitrile containing sodium bicarbonate. Morphinandienones, flavinantine derivatives, were obtained in high yield. Oxidation of 4,4′-dimethoxy-2-methylbibenzyl anodically or with VOF_3 produced a dihydrophenanthrone. The anodic oxidation of several 4-alkylphenols to the corresponding Pummerer's ketones has been investigated, and improved yields are reported using aqueous acetonitrile as solvent and a carbon anode.

We have been interested for some time in the synthetic utility of anodic reactions which couple together activated aromatic rings. In this paper we explore three aspects of such anodic couplings. The first is an intramolecular coupling which produces morphinandienones. An improved procedure which gives very high yields is reported, and several approaches to compounds with the morphine substitution pattern are discussed. Second, the intramolecular coupling of 4,4′-dime-

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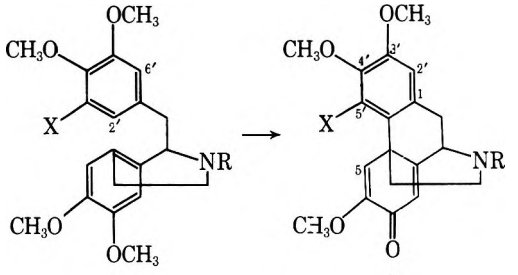
thoxy-2-methylbibenzyl is described. This cyclization produces a dihydrophenanthrone with an angular methyl group, a structure equivalent to the steroidal A, B, C ring system. Finally, the intermolecular coupling of simple phenols to provide complex dimers known as Pummerer's ketones is described. This is a well-known oxidative process which normally proceeds in low yield. A more satisfactory electrochemical procedure is detailed.

Results and Discussion

Morphinandienone Syntheses. In previous papers[2,3] we have shown that anodic oxidation of 1-benzyltetrahydroisoquinolines (1) produces morphinandienones (**2**). This bio-



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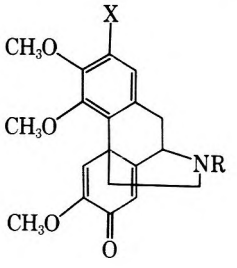

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mimetic reaction revealed the unrecognized synthetic possibilities available from nonphenolic oxidative coupling. This work has been followed by studies from several groups, using both chemical[4] and electrochemical[5] oxidations of suitable phenol ethers to procure alkaloid products. Our previous work produced morphinandienones in 30–50% yield by oxidation at platinum or carbon anodes in acetonitrile containing an electrolyte like lithium perchlorate or tetraethylammonium fluoroborate. The potential was controlled at ca. 1.1 V vs. Ag/Ag^{I},[6] and sodium carbonate was included to buffer the acid formed during oxidation. More detailed studies of this reaction have been undertaken.[7,8] Cyclic voltammetry revealed two waves for compounds **1**. The first at ca. 0.5 V was assigned to oxidation of the amine function, and the second at ca. 1.1 V was assigned to oxidation of a dimethoxy aromatic moiety. Most interestingly preparative oxidation of **1a** (see Table I) at the first wave led to aromatic coupling, and **2a** was isolated as usual. The mechanistic significance of this observation has been noted,[8] and it led to experiments in which weak acids, e.g., $NaHCO_3$, were added to the anolyte. We have shown using cyclic voltammetry that in the presence of 1% water $NaHCO_3$ protonates the amine functionality, protecting it from oxidation.

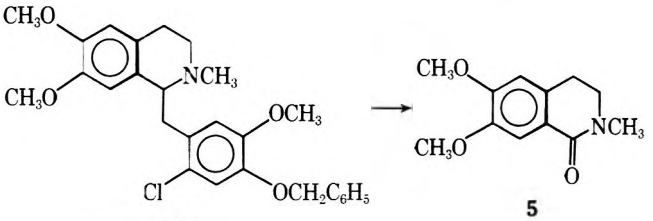
In the present study several 1-benzyltetrahydroisoquinolines were synthesized and preparative oxidations were performed in the presence of $NaHCO_3$. The synthesis generally followed the classical Bischler–Napieralski route. The compounds **1a–f, 3,** and **4** were isolated and identified spectrally. The new compounds **1c–f** gave satisfactory elemental analyses as well. Preparative oxidations were performed using a divided cell, a platinum anode, and a solvent mixture of 0.5% water in acetonitrile containing sodium bicarbonate and lithium perchlorate. Preparative oxidation of 1–5 mmol of **1a** at 1.1 V gave

Table I. Substituents for 1 and 2 and Yield of 2[a]

Registry no.	1	R	X	Yield of 2, %
1699-51-0	1a	CH_3	H	93
26642-09-1	b	H	H	91
65293-02-9	c	$CH_2CH{=}CH_2$	H	84
65293-03-0	d	*b*	*b*	94
65293-04-1	e	CH_3	Br	89
65293-05-2	f	CH_3	I	29

[a] Yield of **2** isolated from anodic oxidation of **1** in $NaHCO_3/H_2O/CH_3CN$ system; based on added starting material. Current yields were similar. [b] **1d** is 1-(2-bromo-3-benzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline. It was oxidized to the corresponding bromomorphinandienone.

a 93% yield of **2a.** In comparison, the sodium carbonate procedure gave 55%. In Table I there are several other examples, all of which proceeded in satisfactory yield. Note, in particular, the oxidation of norlaudanosine (**1b**), which provides a general route to N-substituted derivatives. It seems clear that the utility of $NaHCO_3$ comes from some crude buffering capacity which prevents both amine oxidation and also acid-catalyzed rearrangements.[9] The product **2** is known to be quite sensitive to acid[10] and could be destroyed since two protons are produced at the anode per product molecule. A divided cell is used so that the anolyte acidity can become very high.



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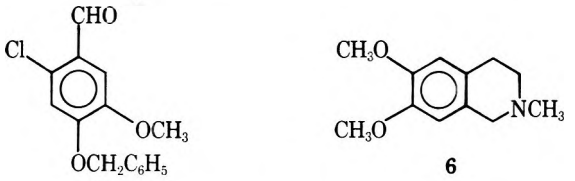

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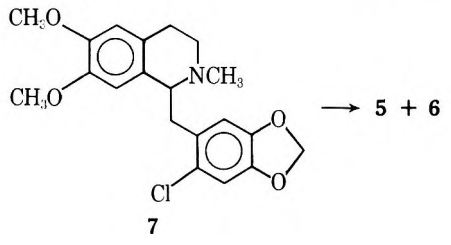

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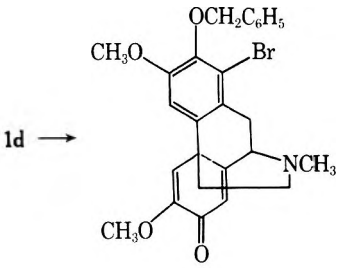
All oxidations of this type lead to the flavinantine substitution pattern of **2** via coupling at the 2′ position. Perturbing the coupling route to provide compounds with the morphine substitution pattern, e.g., **3,** via coupling at 6′[11] is obviously desirable. We have approached this problem by varying substituents on the benzyl ring. Because halogen substituents are easily attached and can be removed at some later stage, several halogenated analogues were synthesized and oxidized. Initial attempts involved 6′-halogen-substituted compounds which might block the usual coupling route. The use of 6′-bromolaudanosine was previously shown[3] not to produce the desired bromomorphinandienone, and this has now been affirmed for oxidation in the presence of sodium bicarbonate. Instead, cleavage of the bromo substituent, yielding **2a,** is the major route. In addition, an unsymmetrical dimer (NMR and mass spectra) was isolated but not fully characterized. The 6′-chloro compounds **4** and **7** were also prepared and oxidized. In each

case only cleavage products, e.g., **5, 6,** and the aldehyde, were found after oxidation in either the sodium carbonate or bicarbonate media. Oxidations of **4** were also made at platinum in methylene chloride/trifluoroacetic acid. After workup the mixture appeared to contain no morphinandienone. It was reduced with sodium borohydride, and **6** was identified as a major component. Apparently the electron-withdrawing chlorine atom sufficiently deactivates the ring so that coupling at 2′ does not occur, and cleavage of the benzyl moiety takes over. This alternative pathway has many analogies in anodic chemistry[12] and mass spectroscopy. In particular, the mass spectra of the compounds **1a,d–f** show *m/e* 206, with the dimethoxytetrahydroisoquinolinium ion as the base peak.

The three halo analogues **1d–f** have been prepared and oxidized. The 2′-bromo compound **1d** cyclized without cleavage of bromine, indicating that the debromination previously found for 6′-bromolaudanosine came after the C–C bond formation of coupling.



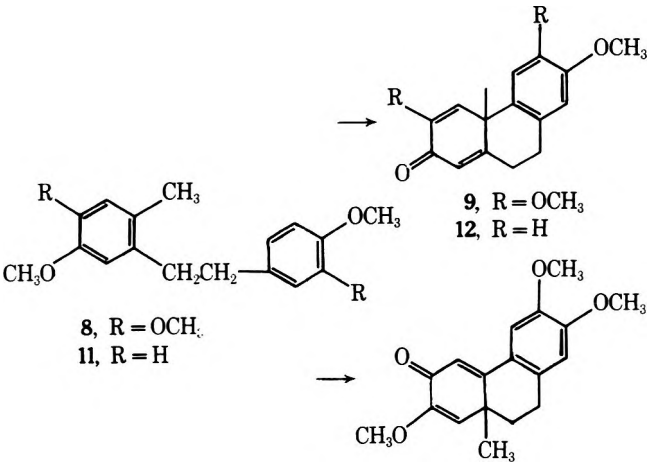
2d

The 5′ analogues were examined because it was hoped that the halo substituents would not be cleaved and would sterically impede coupling at the 6′ position. Morphinandienones were obtained in good yield from both the 5′-bromo and 5′-iodo compounds. The NMR spectra of these dienones suggested the structures **2e** and **2f** instead of the isomers **3.** In particular, the chemical shift of the vinyl proton in the 5 position of the dienone (δ 8.2) was taken into consideration. The structure **3** has a methoxy group in the 4 position which should deshield the proton at the 5 position to a value of δ 7.3.[13] Structure **2f** is, however, consistent with the spectrum since the presence of bulky iodine in the 4 position would have a larger deshielding effect on the C-5 proton. This assignment was confirmed by chemical reactions. Thus, the same reduction product, namely, *O*-methylflavinantinol, was obtained from the dienones **2e** and **2a** upon lithium aluminum hydride reduction.

The distinct preference for flavinantine-type coupling at the 6′ position rather than 2′ coupling can be explained by a combination of electronic and steric arguments. Coupling at the 6′ position is activated by a *p*-methoxy group and coupling at the 2′ position by an o-methoxy group. Coupling at 2′ is, however, disfavored by the *o*-methoxy inductive effect. Furthermore, coupling at 2′ should be sterically inhibited by the neighboring 3′-methoxy group. This might be especially severe since the methyl of the 3-methoxy needs to be in the plane of the ring to provide stabilization of incipient charge, and the most favorable conformation places the methyl of 3′-methoxy in front of the 2′ position. It is, nevertheless, surprising that the 5′-iodo compound still preferred cyclization at 6′ rather than 2′. As the NMR spectrum demonstrates, the steric requirements of iodine in **2f** are substantial.

It will be noted that the electrochemical route to morphinandienones of the type **2** is the only useful synthetic method to date. These compounds in turn serve as a useful starting point for the preparation of aporphines and dibenzazonines.[10]

Dihydrophenanthrone Synthesis. In a previous study the electrooxidation of **8** was performed with the intent of preparing **9.**[14] In fact, a 90% yield of the rearranged product **10** was obtained. Kupchan and co-workers reported the same reaction occurred during oxidation of **7** with vanadium oxyfluoride in trifluoroacetic acid.[15] Consideration of the proposed mechanism for rearrangement suggested that the oxidation of **11** would produce an unrearranged product. This product is of interest because of its close relationship to several medicinal compounds[16] and because it represents a route to the A, B, C steroid rings[17] with the angular methyl group intact. Synthesis of **11** was achieved as detailed in the Experimental Section. Anodic oxidations at platinum in acetonitrile and in trifluoroacetic acid media were performed under several conditions. The cyclic voltammetric peak potential for 1 mM **11** in CH_3CN is 1.18 V. However, the most successful preparative oxidations were carried out at 1.8 V in acetonitrile with 2% water and solid sodium carbonate at 0 °C; Et_4NBF_4 was used as the electrolyte. After electrolysis, workup by evaporation, extraction with chloroform/water, and preparative thin-layer chromatography gave the product. Further purification by passage through a Sephadex column gave a pale yellow solid. The assignment of structure **12** is based on the compound's spectroscopic characteristics and by analogy to the coupling reactions reported in the literature. The $C_{16}H_{16}O_2$ molecular formula was indicated by mass spectroscopy and combustion analysis. The IR spectrum indicated the presence of a cross-conjugated cyclohexadienone system, and the NMR spectrum was consistent with structure **12.** Ultraviolet spectroscopy showed maxima at 233 and 272 nm. No absorption bands occurred beyond 300 nm, and this rules out the possibility of a conjugated, rearranged cyclohexadienone. The isolated yield of **12** was 22%, and 28% starting material was recovered when a charge of 3 F/mol was passed. In the absence of water or sodium carbonate, the current yield of dienone decreased to about 10% with 3 F/mol of electricity passed.



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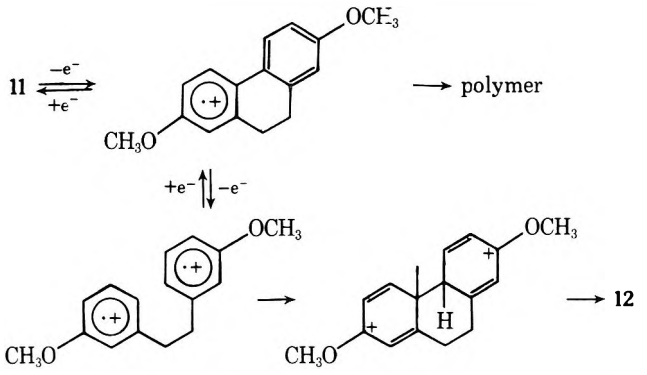
When the oxidation was performed at 1.20 V, the peak potential of the first wave, the current passing was only about 5 mA even with pulsing the anode potential to 0.0 V for 0.5 s every 30 s. The electrode was heavily coated with brown material. The same electrode coating problem occurred when nitromethane or a 1:2 mixture of trifluoroacetic acid and dichloromethane was used as solvent at 1.20 V.

Only 3% of **12** was obtained when **11** was oxidized at 1.2 V at a platinum electrode in acetonitrile with 0.1 M fluoroboric acid[5] as the supporting electrolyte after the passage of 2.2 F/mol. The electrode was also heavily coated with brown material. At 1.8 V, 18% of **12** was obtained after the passage of 3 F/mol and the electrode coating was less serious. In all cases, 1.8 V was the lowest potential at which a reasonable current could be passed.

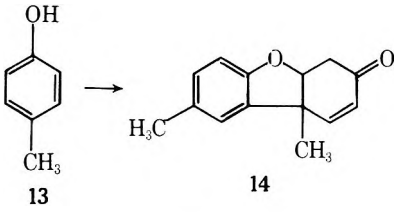
The need for high potentials can be understood if intermolecular coupling via cation radicals predominates at 1.2 V and intramolecular cyclization of a dication takes over at 1.8



V. These results and the explanation have analogy in the work of Parker and Ronlan on anodic oxidation of 3,4-dimethoxy-4′-methoxybibenzyl.[18] It should be noted that because of the high potential required for cyclization, the product **12** will not be totally stable and therefore the yields cannot be high.

Vanadium oxytrifluoride was also used. When **11** was stirred in trifluoroacetic acid with VOF_3 at either room temperature or at 0 °C for 45 min, only tar and trace amounts of starting material were obtained. At −15 °C, 30% of dienone **12** and 22% of **11** were isolated after stirring for 2.5 h. It seemed to be useful to go to even lower temperatures, and in order to bring the temperature down to −30 °C[15] a 1:9 mixture of fluorosulfonic acid (FSO_3H) and CF_3COOH was used. **11** does not seem to survive in this solvent since neither it nor any dienone was detected after it was stirred in the solvent for 25 min without VOF_3.

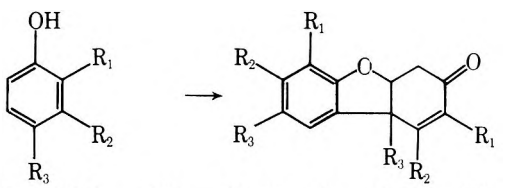
Ortho–Para Coupling of 4-Alkylphenols. Phenol oxidation reactions have held the interest of organic chemists for over a century. In addition to the intrinsic interest which was fed by the ease of oxidation of phenolate ions, phenol oxidations are thought to be important in the biosynthesis[19] of numerous natural products. In particular, the oxidative coupling of *p*-cresol (**13**) to Pummerer's ketone **14** has been often



13 **14**

cited as an analogue to usnic acid and morphine biosyntheses.[19]

Curiously there are to our knowledge no examples of high-yield conversions of **13** to **14**. Reported electrochemical routes give no more than a 10% yield of the ortho–para-coupled product. Recent advances in anodic coupling reactions have led us to further explore this route for several simple phenols;



13, $R_1 = R_2 = H$; $R_3 = CH_3$ **14**, $R_1 = R_2 = H$; $R_3 = CH_3$
15a, $R_1 = H$; $R_2 = R_3 = CH_3$ **16**, $R_1 = H$; $R_2 = R_3 = CH_3$
b, $R_1 = R_3 = CH_3$; $R_2 = H$ **17**, $R_1 = R_3 = CH_3$; $R_2 = H$
c, $R_1 = R_2 = H$; $R_3 = Et$ **18**, $R_1 = R_2 = H$; $R_3 = Et$

the results are given in Table II. The conditions used here, a carbon anode in 5% aqueous acetonitrile containing 1 equiv of base, are analogous to those used by Bobbitt for phenolic alkaloid oxidations.[20] We note that the yields based on reacted phenols are consistently higher than other methods, and in most cases pure crystalline compounds are readily obtained by simple column chromatography. The procedure described is the best of several evaluated. In particular, a carbon anode is important. Platinum is useless as an anode because it is rapidly passivated by a polymeric film. Reactions in which the phenoxide was produced using tetraethylammonium hydroxide in dry acetonitrile were unsuccessful as were reactions in aqueous sodium hydroxide.

Table II. Yield of Ketone Products

Registry no.	Reactant	Charge, F/mol	Product	Yield, %	Recovered reactant, %
106-44-5	**13**	1.0	**14**	37	50
95-65-8	**15a**	1.0	**16**	31	50
105-67-9	**b**	1.0	**17**	20	27
123-07-9	**c**	0.3	**18**	25	

The oxidation of 4-alkylphenols has been studied using a variety of chemical and electrochemical oxidizing systems.[21-23] The nature of the oxidant, the solvent, and pH are all important in determining the types of products formed. Strong chemical oxidants, nucleophilic solvents, and low pH favor nucleophilic trapping routes. In this manner it is possible to obtain good yields of synthetically useful 4-methyl-4-hydroxycyclohexadienones or 4-methyl-4-methoxycyclohexadienones.[24,25] Various mixtures of other products apparently derived from phenoxonium ions have also been described. Oxidations of *p*-cresol using a lead dioxide anode have been reported by Parker and Ronlan and produce high yields of hydroxycyclohexadienones.[24] Again cationic intermediates seem likely.

Reaction of phenols in basic media with mild oxidizing agents ($E_{1/2} < 1.0$ V) produces more dimeric products, and such conditions are employed here. The further problem in producing good yields of Pummerer's ketones is positional selectivity. In the present case it seems likely that surface chemistry on the anode is important. Bobbitt has reached a similar conclusion in his study of phenolic alkaloid oxidations performed under comparable conditions.[20]

Experimental Section

1-Benzyltetrahydroisoquinolines. Compounds **1a**, **1b**, and **4** have been previously reported.[2,3] Data confirming the structural assignments are provided for compounds **1c–f** and **7**. Spectra of the intermediates are not reported, but were consistent with the proposed structures. An exemplary procedure is given below for the synthesis of 5′-bromolaudanosine.

***N*-(3,4-Dimethoxyphenethyl)-3-bromo-4,5-dimethoxyphenylacetamide.** To 24.1 g of 3-bromo-4-hydroxy-5-methoxybenzaldehyde in 75 mL of dimethylformamide (DMF) was added 20 mL of CH_3I and 25 g of anhydrous K_2CO_3. The mixture was heated at reflux for 3 h, poured into water, and extracted with $CHCl_3$. The $CHCl_3$ solution was dried over Na_2SO_4 and evaporated in vacuo to yield 25.5 g (98%) of crude 3-bromo-4,5-dimethoxybenzaldehyde.

To 24.5 g of this benzaldehyde in 150 mL of ethanol was added excess $NaBH_4$ in small portions. After the addition was complete, the ethanol was removed in vacuo and a mixture of 5% aqueous NH_4Cl and $CHCl_3$ was added. The $CHCl_3$ layer was separated, dried, and evaporated to yield 24.1 g (97.5%) of crude 3-bromoveratryl alcohol.

A solution of 40 g of crude bromoveratryl alcohol in 500 mL of ether was treated with 9.8 mL of pyridine, and 49 g of $SOCl_2$ was added dropwise. The mixture was stirred for 3 h and then poured into 1 L of water. The aqueous solution was extracted with ether, and the ether was dried and evaporated to yield 50.6 g (96%) of crude 3-bromoveratryl chloride.

The crude chloride (49.6 g) in 250 mL of Me_2SO was heated for 1 h with 27.5 g (3 equiv) of NaCN. The solution was poured into water and extracted with $CHCl_3$. The $CHCl_3$ solution was washed five times

with H_2O, dried, and evaporated in vacuo to yield 43.9 g (91%) of crude 3-bromoveratronitrile.

The crude veratronitrile (43.3 g) was heated to reflux in 400 mL of 2 N NaOH for 12 h. The cooled solution was extracted with $CHCl_3$, acidified to pH 1, and reextracted with $CHCl_3$. This $CHCl_3$ solution was dried and evaporated in vacuo to yield 38.1 g (88%) of crude 3-bromo-4,5-dimethoxyphenylacetic acid.

A mixture of 25 g of this crude acid and 7.29 g (1.05 equiv) of 3,4-dimethoxyphenethylamine was heated at 160–180 °C for 3 h under a flow of argon. The black residue was dissolved in $CHCl_3$, extracted with 1 N NaOH and 1 N HCl, dried, and evaporated. The residue was dissolved in 70:30 EtOAc/cyclohexane, and the solution was passed through a silica gel plug. Evaporation of the solution yielded 32.4 g (81.3%) of *N*-(3,4-dimethoxyphenethyl)-3-bromo-4,5-dimethoxyphenylacetamide, mp 120–121 °C.

Anal. Calcd for $C_{20}H_{24}NO_5Br$: C, 54.93; H, 5.30; N, 3.20. Found: C, 54.89; H, 5.61; N, 3.18.

1-(3-Bromo-4,5-dimethoxybenzyl)-3,4-dihydro-2-methyl-6,7-dimethoxyisoquinolinium Iodide. The amide (20 g) was dissolved in 200 mL of CH_3CN, and 27 g of $POCl_3$ (6.5 equiv) was added dropwise over a 20-min period. The mixture was heated at reflux for 1 h, and the solution was evaporated in vacuo. The residue was dissolved in $CHCl_3$, and this solution was washed with water and 5% $NaHCO_3$. The $CHCl_3$ solution was dried and evaporated to give 19.7 g (96%) of crude product. This (18.2 g) was dissolved in 100 mL of EtOH and 25 mL of CH_3I, and the solution was heated at reflux for 12 h. The yellow 1-(3-bromo-4,5-dimethoxybenzyl)-3,4-dihydro-2-methyl-6,7-dimethoxyisoquinolinium iodide precipitated and was collected by filtration, mp 166–167 °C.

Anal. Calcd for $C_{21}H_{25}BrINO_4 \cdot H_2O$: C, 43.46; H, 4.69; N, 2.41. Found: C, 42.62; H, 4.39; N, 2.35.

1-(3-Bromo-4,5-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline. The quinolinium iodide (5.0 g) was suspended in 50 mL of EtOH, and 1.0 g of $NaBH_4$ was added in portions with vigorous stirring. The solvent was removed in vacuo and the residue treated with 5% NH_4Cl and $CHCl_3$. The $CHCl_3$ layer was separated, dried, and evaporated to yield 3.72 g (96%) of 1-(3-bromo-4,5-dimethoxybenzyl)-6,7-dimethoxy-2-methyl-1,2,3,4-tetrahydroisoquinoline (**1e**) as a yellow oil: NMR δ 2.50 (s, 3 H), 2.6–3.5 (m, 7 H), 3.63–3.95 (m, 12 H), 6.20 (s, 1 H), 6.50 (2 H), 6.95 (1 H).

Anal. Calcd for $C_{21}H_{26}BrNO_4 \cdot H_2O$: C, 55.76; H, 6.19; N, 3.10. Found: C, 56.14; H, 6.03; N, 2.93.

***N*-Allylnorlaudanosine (1c).** Allyl bromide (1.0 g) was added in drops to a stirring mixture containing 3 g of norlaudanosine **1a**, 3 g of anhydrous K_2CO_3, and 20 mL of dimethylformamide maintained at 45 °C. After stirring for 1 h the excess dimethylformamide was evaporated and the residue was taken up in 100 mL of $CHCl_3$. The $CHCl_3$ layer was washed six times with 100-mL portions of H_2O, dried, and evaporated to give 2.5 g of a pale yellow oil. Crystallization from ethanol gave a white solid, mp 80–80.5 °C. The overall yield was 90%: NMR δ 3.6 (s, 3 H), 3.8 (s, 3 H), 3.85 (s, 6 H), 5.1 (broad, 1 H), 5.3–5.4 (broad d, 2 H), 6.1 (s, 1 H), 6.6–6.8 (m, 4 H); mass spectrum, *m/e* 385 (M^+), 355, 340, 246, 233 (base peak), 206, 176, 133.

Anal. Calcd for $C_{23}H_{29}NO_4$: C, 72.06; H, 7.57; N, 3.66. Found: C, 71.82; H, 7.85; N, 3.59.

1-(2-Bromo-3-benzyloxy-4-methoxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (1d). This was prepared as above starting from 3,4-dimethoxyphenethylamine and 2-bromo-3-benzyloxy-4-methoxyphenylacetic acid in an overall yield of 58%: mp 101–101.5 °C; NMR δ 2.5 (s, 3 H), 3.55 (s, 3 H), 3.78 (broad s, 6 H), 5.05 (s, 2 H), 6.03 (s, 1 H), 6.63 (s, 1 H), 6.7 (s, 2 H), 7.2–7.7 (m, 5 H).

6′-Chlorolaudanosine. This was prepared as above and recrystallized from absolute ethanol: mp 130–130.5 °C (lit.[26] mp 130 °C); NMR δ 2.55 (s, 3 H), 3.65 (s, 3 H), 3.75 (s, 3 H), 3.85 (s, 3 H), 6.1 (s, 1 H), 6.55 (s, 1 H), 6.6 (s, 1 H), 6.9 (s, 1 H); mass spectrum, *m/e* 391, 248, 207, 190, 177.

1-(6-Chloro-3,4-methylenedioxybenzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-methylisoquinoline (7). Prepared as above, recrystallization from absolute ethanol gave a white powder: mp 152–153 °C; NMR δ 2.55 (s, 3 H), 3.7 (s, 3 H), 3.9 (s, 3 H), 5.95 (s, 2 H), 6.25 (s, 1 H), 6.6 (s, 2 H), 6.9 (s, 1 H); mass spectrum, *m/e* 375 (M^+), 337, 338, 190, 169.

Anal. Calcd for $C_{20}H_{22}ClNO_4$: C, 63.92; H, 5.80; N, 3.73; Cl, 9.44. Found: C, 63.96; H, 5.68; N, 3.27; Cl, 9.43.

Morphinandienone Synthesis. The procedure and equipment have been previously described.[2,3] It is noted that the anolyte usually consisted of ca. 100 mL of 0.5% H_2O in CH_3CN (twice distilled from P_2O_5) containing 0.1 M $LiClO_4$ and 2 g of $NaHCO_3$. Most of the $NaHCO_3$ is insoluble. The mixture is stirred with a magnetic stirring bar. In contrast to runs using Na_2CO_3, the anode usually did not "film" to any extent. After the passage of 2 F/mol at 1.1 V, the anolyte was worked up by evaporation of most of the CH_3CN and extraction with $CHCl_3/H_2O$. The crude $CHCl_3$-soluble mixture was separated by column chromatography.

The morphinandienones **2a–f** were characterized by IR, NMR, and mass spectrometry. **2a** and **2b** gave spectra superimposable on those from authentic samples.[2] Products **2c–f** have not been previously described. In each case the IR spectrum showed a characteristic set of three dienone bands with intensities decreasing in the order 1670, 1640, and 1615 cm^{-1}. The mass spectra showed the proper parent ion and M − 15 and M − 43 ions.

***N*-Allyl-*O*-methylflavinantine (2c)** was obtained as a colorless oil from the oxidation of **1c**: NMR δ 1.9 (m, 2 H), 2.65 (t, 2 H), 3.3 (m, 4 H), 3.8 (s, 3 H), 3.85 (s, 3 H), 3.9 (s, 3 H), 5.1 (broad s, 1 H), 5.3–5.4 (broad d, 2 H), 6.3 (s, 1 H), 6.4 (s, 1 H), 6.7 (s, 1 H), 6.9 (s, 1 H); UV λ_{max} (EtOH) 215, 245, 290 nm; mass spectrum, *m/e* 367 (M^+), 240, 175, 159, 145. The molecular formula was confirmed by high-resolution mass spectrometry as $C_{22}H_{25}NO_4$.

The **2′-bromo-*O*-methylflavinantine 3′-*O*-benzyl analogue 2d** was obtained as an oil from the oxidation of **1d**: NMR δ 1.95 (m, 2 H), 2.5 (s, 3 H), 3.8 (s, 3 H), 4.0 (s, 3 H), 5.05 (s, 2 H), 6.4 (s, 2 H), 7.0 (s, 1 H), 7.8–7.3 (m, 5 H); mass spectrum, *m/e* 497 (M^+), 495 (M^+), 406, 404, 331, 260, 206, 91.

Anal. Calcd for $C_{26}H_{26}BrNO_4$: C, 58.60; H, 5.27; N, 2.63. Found: C, 58.51; H, 5.23; N, 2.81

5′-Bromo-*O*-methylflavinantine (2e) was obtained as a white solid on recrystallization from ethyl acetate/methanol: mp 214–216 °C; NMR δ 1.9 (m, 2 H), 2.45 (s, 3 H), 2.5–3.4 (m, 5 H), 3.85–3.95 (three s, 9 H), 6.35 (s, 1 H), 6.65 (s, 1 H), 8.0 (s, 1 H).

Anal. Calcd for $C_{20}H_{22}BrNO_4$: C, 57.15; H, 5.28; N, 3.33. Found: C, 56.87; H, 5.07; N, 3.26

5′-Iodo-*O*-methylflavinantine (2f) was obtained as a white solid: mp 202–205 °C; NMR δ 1.9 (m, 2 H), 2.40 (s, 3 H), 2.5–3.4 (m, 5 H), 3.75–3.85 (three s, 9 H), 6.35 (s, 1 H), 6.65 (s, 1 H), 8.20 (s, 1 H); mass spectrum, *m/e* 467.056; mass spectrum calcd, *m/e* 467.060.

Oxidation of the 6′-Chlorolaudanosine 4′-Benzyloxy Analogue 4. The oxidation of this compound was carried out under many different conditions as described above. In all cases only cleavage products **5** and **6** were observed. A typical oxidation and isolation procedure involved oxidation of **4** (360 mg, 0.9 mmol) in the presence of Na_2CO_3 at 1.25 V at platinum for 250 min. During this period about 4 F/mol of electricity was consumed. At the end the volume of the anolyte was reduced to 15 mL, 100 mL of water was added, and the organic material was extracted with three 100-mL portions of chloroform (extract A). The aqueous layer was neutralized with 0.1 N HCl and extracted three times with 50-mL portions of chloroform (extract B). Extract A was dried and evaporated to give a pale brown gum whose TLC analysis showed the presence of four compounds besides the starting material. These compounds had R_f values of 0.0, 0.3, 0.8, and 0.9 and were separated by chromatography and identified spectroscopically.

The compound with R_f 0.9 was identified as 3,4-dimethoxy-6-chlorobenzaldehyde from spectral data: NMR δ 3.95 (s, 3 H), 4.0 (s, 3 H), 6.9 (s, 1 H), 7.4 (s, 1 H), 10.3 (s, 1 H); IR ($CHCl_3$) 1730 cm^{-1}.

The compound with R_f 0.8 was identified as *O*-methylcorypaldine (**5**) from its spectral data: NMR δ 2.95 (t, 2 H), 3.15 (s, 3 H), 3.95 (s, 6 H), 6.65 (s, 1 H), 7.65 (s, 1 H); IR ($CHCl_3$) 3600–3200 (broad), 2980, 2920, 2820, 1630, 1590 cm^{-1}; mass spectrum, *m/e* 221 (M^+), 178, 163, 150 (base peak), 135, 107, 92.

The spectral and TLC properties of the compound with R_f 0.3 were identical with a known sample of *O*-methylcorypalline (**6**):[27] NMR δ 2.8 (s, 3 H), 3.9 (s, 6 H), 6.6 (s, 1 H), 6.7 (s, 1 H); mass spectrum, *m/e* 207 (M^+), 206, 190, 164 (base peak), 149 (metastable), 135, 121, 103.

Reduction of the R_f 0.0 product with sodium borohydride in ethanol gave O-methylcorypaldine.

Extract B was dried and evaporated to give a dirty white solid whose spectral properties corresponded to 6-chloro-3,4-dimethoxybenzoic acid: mp 86–88 °C (lit.[28] mp 85–87 °C); NMR δ 3.9 (s, 3 H), 3.95 (s, 3 H), 6.92 (s, 1 H), 7.45 (s, 1 H).

Oxidation of 7. This compound was oxidized under several conditions as described above. In a typical electrooxidation, **7** (320 mg, 0.85 mmol) was oxidized in the presence of sodium carbonate at 1.25 V at platinum for 180 min. The usual workup led to 290 mg of crude products. The TLC analysis showed the presence of four products at R_f values of 0.0, 0.3, 0.8, and 0.9. Compounds at R_f values of 0.3 and 0.8 were identified as *O*-methylcorypalline and O-methylcorypaldine, respectively, by comparing their spectral and TLC properties with authentic samples.

α-Hydroxy-5,4′-dimethoxy-2-methylbibenzyl. 2-Bromo-4-nitrotoluene was prepared by the method of Bunnett and Rauhut[29] and then converted on a 100-g scale to 3-bromo-4-methylaniline sulfate (127 g). 2-Bromo-4-hydroxytoluene was then produced in a standard fashion by diazotization.[30] Methylation of this phenol using 2 N NaOH and dimethyl sulfate gave 51 g of 2-bromo-4-methoxytoluene.[31]

2-Bromo-4-methoxytoluene was converted to the Grignard reagent and reacted with 3-methoxyphenylacetaldehyde as follows. In a 250-mL three-neck flask fitted with a reflux condenser, a dropping funnel, an adapter for passing in nitrogen, and a magnetic stirrer was placed 2.4 g (0.1 mol) of magnesium turnings. A mixture of 2.0 g of 2-bromo-4-methoxytoluene and 10 mL of dry ether was run into the flask. The flask was warmed until the reaction began. Stirring was started and the flask was surrounded by a dish of cold water. A mixture of 18 g of 2-bromo-4-methoxytoluene (total 20 g, 0.1 mol) and 50 ml of dry ether was added at such a rate as to cause refluxing. When the addition was complete, the mixture was stirred until the magnesium turnings disappeared. The Grignard solution was cooled in an ice bath, and 12 g (0.08 mol) of 3-methoxyphenylacetaldehyde in 30 mL of ether was added dropwise; white solid appeared near the end of the addition. The solution was stirred at room temperature for 1 h. The product was decomposed by pouring the reaction mixture into 300 g of cracked ice. A 50-mL amount of 2 N sulfuric acid was added. The ether solution was separated, and the aqueous layer was extracted with two 150-mL portions of ether. The ether solution was dried, the mixture was filtered, and the ether was removed. The product was purified by passing through an 18 × 1 in alumina column eluted by chloroform. The α-hydroxy-5,4′-dimethoxy-2-methylbibenzyl (17.5 g, 65%) was collected from fractions 12–20 (50 mL/fraction): NMR δ 2.00 (d, 1 H), 2.20 (s, 3 H), 2.90 (m, 2 H), 3.80 (s, 3 H), 3.82 (s, 3 H), 5.18 (m, 1 H), 7.00 (m, 7 H); IR ν_{max} (neat) 3450, 1615 cm^{-1}; mass spectrum, *m/e* (% of base) 272 (10), 151 (70), 123 (100), 122 (100), 108 (50).

5,4′-Dimethoxy-2-methylbibenzyl (11). To a solution of 10 g (0.037 mol) of the α-hydroxy compound in 200 mL of dry ether and 50 mL of dry THF containing 0.5 mL of pyridine was added dropwise a solution of 10 mL of thionyl chloride in 20 mL of dry ether during 30 min with stirring. After an additional 20 min at room temperature, the reaction was cautiously quenched with cold water. Separation and evaporation of the ethereal layer gave 10 g of α-chloro-5,4′-dimethoxy-2-methylbibenzyl as a pale yellow, mobile oil. The infrared spectrum showed no OH absorption.

A solution of 2 g of this chloro compound in 10 mL of dry THF was added dropwise to a stirred solution of 600 mg of $LiAlH_4$ in 100 mL of dry THF at room temperature. After refluxing for 5 h, the reaction was cautiously quenched with wet THF. The separated aluminate was filtered off and washed with ether. The organic filtrate was washed with water, dried, and evaporated to give 1.6 g (92%) of 11 as a yellow oil: NMR δ 2.20 (s), 2.84 (s, 4 H), 3.76 (s, 3 H), 3.80 (s, 3 H), 6.80 (m, 7 H); mass spectrum, *m/e* (% of base) 256 (35), 135 (100), 121 (21).

Anal. Calcd: C, 79.69; H, 7.81. Found: C, 79.43; H, 7.72.

Electrolysis of 5,4′-Dimethoxy-2-methylbibenzyl (11). The three-compartment cell has been described. This compound (256 mg, 1.0 mmol) was oxidized at 0 °C in 150 mL of acetonitrile with 2% water and 1 g of anhydrous Na_2CO_3. The potential was set at 1.80 V vs. $Ag/AgNO_3$. The initial current was 40 mA. The potential was pulsed to 0.0 V for 0.5 s in every 30-s period. The electrolysis was discontinued when a 3-F/mol charge had passed, which took 2.5 h. The usual workup of the anolyte solution led to a light brown residue. TLC analysis on silica gel developed with chloroform showed one component with R_f 0.15 and starting material. The component was isolated by preparative TLC and purified by preparative liquid chromatography using 40 psi of pressure with a 12 × 1 in Sephadex column. Gradient elution was performed with $CHCl_3$/1% methanol, taking 5-mL fractions. From fractions 36–40 was isolated 53 mg (22%) of compound **12** as a pale yellow solid: mp 57–59 °C; NMR δ 1.60 (s, 3 H), 2.40–3.25 (m, 4 H), 3.90 (s, 3 H, OCH_3), 6.20–7.60 (m, 6 H); IR ν_{max} ($CHCl_3$) 1665, 1630, 1625, 1600 cm^{-1}; UV (ethanol) λ_{max} (log ε) 233 (4.71), 272 (3.85) nm; mass spectrum, *m/e* (% of base) 240 (46), 225 (100).

Anal. Calcd for $C_{16}H_{16}O_2$: C, 80.00; H, 6.67. Found: C, 79.61; H, 7.00.

VOF_3 Oxidation of 11. In a 100-mL three-neck flask equipped with a calcium chloride drying tube and an inlet for passing nitrogen was placed 30 mL of CF_3COOH, 256 mg (1 mmol) of **11**, and a magnetic stirring bar. The flask was put into a benzyl alcohol–dry ice bath to keep the temperature at −14 °C, and VOF_3 (0.9 g, 7 mmol) was added. After 3 h of stirring, the mixture was poured into 60 mL of cold water containing 5 g of citric acid. The solution was basified with 5% NH_4OH and extracted with chloroform. The chloroform extracts were dried and concentrated. A compound with R_f 0.15 on silica gel developed by chloroform was isolated by preparative TLC. After purification by liquid chromatography as described above, 72 mg (30%) of a pale yellow solid with spectra identical with **12** was obtained.

Phenoxide Oxidations. All reactions were carried out in a three-compartment electrolysis cell using a stainless steel cathode, six carbon rods (0.25 × 4 in) as the anode, and a SCE of commercial design as the reference electrode. The anode potential was controlled using a PAR model 173 potentiostat. Reactions were carried out at room temperature with magnetic stirring under a nitrogen atmosphere. The solvent-supporting electrolyte solution was prepared by dissolving 5.0 g of sodium or lithium perchlorate or 7.0 g of tetraethylammonium fluoborate in 300 mL of distilled acetonitrile containing from 10 to 20 mL of H_2O. The phenoxides were prepared by reaction with 1 equiv of sodium methoxide in methanol followed by removal of the methanol or in situ by the dropwise addition of 1 equiv of NaOH in 5 mL of H_2O.

Workup consisted of removal of the acetonitrile in vacuo followed by partitioning the residue between 200 mL of chloroform and 100 mL of 10% aqueous NaOH. The organic layer was washed with saturated sodium chloride solution, dried over calcium chloride, filtered, and reduced in vacuo. Product analysis was carried out by either GLPC on a Carbowax 20 M on Chromosorb W, N.A.W. 10 ft × 0.25 in column at 250 °C or via HPLC (ALTEX) using Woelm silica gel (0.032–0.063 mm) and eluting with benzene/ethyl acetate (85:15).

1,2,10,11-Tetrahydro-6,11-dimethyl-2-oxodibenzfuran (14). *p*-Cresol (1.05 g) was oxidized at 0.25 V in the presence of 1 equiv of NaOH. After the passage of 1 F/mol, the current had dropped to 5 mA and the reaction was worked up. **13** (0.54 g) was recovered from the basic extracts, and GLPC indicated a 35% yield of **14**. The use of lithium perchlorate in place of sodium perchlorate in the above procedure gave a 37% yield of **14**. Pure **14** was obtained by passing the crude reaction mixture through a short (15 × 150 cm) silica gel column using benzene eluant followed by recrystallization from ether, mp 123 °C (lit.[22] mp 123 °C). The ^1H NMR, ^{13}C NMR, IR, and mass spectra were consistent with the proposed structure.

1,2,10,11-Tetrahydro-3,6,8,11-tetramethyl-2-oxodibenzfuran (17). 2,4-Dimethylphenol (3.75 g) was oxidized at 0.2 V in the presence of 2 equiv of NaOH. The initial current was 200 mA, and it dropped to 10 mA before completion of the reaction. The electrodes were then cleaned by wiping them with paper. Resumption of electrolysis gave an initial current of 120 mA. After the passage of 1 F/mol, the reaction was terminated and the anolyte worked up, yielding 1.97 g of $CHCl_3$-soluble material, 1.0 g of alkali-soluble material and 0.28 g of a red oil found between the $CHCl_3$ and aqueous layers. GLPC of the $CHCl_3$-soluble fraction showed the presence of 0.76 g of isohomo Pummerer's ketone (**17**), and HPLC yielded 0.74 g (20%) of this product, mp 137–139 °C (lit.[22] mp 137 °C). The ^1H NMR, ^{13}C NMR, IR, and mass spectra were consistent with the proposed structure. Minor amounts of four other unidentified compounds were also present.

1,2,10,11-Tetrahydro-4,6,7,11-tetramethyl-2-oxodibenzfuran (16). A mixture of 1.55 g of 3,4-dimethylphenol and 1.0 g of sodium methoxide in 10 mL of methanol was oxidized at 0.25 V in 200 mL of anolyte. The reaction was worked up after the passage of 1 F/mol to yield 0.77 g of 3,4-dimethylphenol and 0.45 g of crude product, which upon crystallization from ether yielded 0.24 g (31%) of homo Pummerer's ketone (**16**), mp 155 °C (lit.[22] mp 156 °C). The ^1H NMR, ^{13}C NMR, IR, and mass spectra were consistent with the proposed structure.

1,2,10,11-Tetrahydro-6,11-diethyl-2-oxodibenzfuran (18). 4-Ethylphenol was oxidized at 0.25 V and worked up after the passage of 0.3 F/mol. The ^1H NMR spectrum of the crude reaction product showed a long-range proton coupling pattern very similar to that observed in Pummerer's ketone. Integration of the NMR spectrum showed that the crude reaction mixture contained about 50% of compound **18** which was not further purified.

Oxidation of *p-tert*-Butylphenol. Attempts to dimerize *p-tert*-butylphenol under conditions similar to those used above gave only starting material and polymeric materials. This material was brown to tan in color and only slightly soluble in polar solvents. No distinct spots could be detected by TLC.

Registry No.—**2c,** 65354-46-3; **2d,** 65354-47-4; **2e,** 65354-48-5; **2f,** 65354-49-6; **4,** 65293-06-3; **5,** 6514-05-2; **6,** 16620-96-5; **7,** 65293-07-4; **11,** 61582-79-4; **12,** 36126-09-7; **14,** 546-24-7; **16,** 62156-65-4; **17,** 62156-64-3; **18,** 62224-30-0; 3-bromo-4-hydroxy-5-methoxybenzaldehyde, 2973-76-4; 3-bromo-4,5-dimethoxybenzaldehyde, 6948-30-7; 3-bromoveratryl alcohol, 52783-74-1; 3-bromoveratryl chloride,

52783-75-2; 3-bromoveratronitrile, 59116-12-0; 3-bromo-4,5-dimethoxyphenylacetic acid, 56982-10-6; 3,4-dimethoxyphenethylamine, 120-20-7; *N*-(3,4-dimethoxyphenethyl)-3-bromo-4,5-dimethoxyphenylacetamide, 65292-97-9; 1-(3-bromo-4,5-dimethoxybenzyl)-3,4-dihydro-2-methyl-6,7-methoxyisoquinolinium iodide, 65292-98-0; allyl bromide, 106-95-6; 2-bromo-3-benzyloxy-4-methoxypheny acetic acid, 38849-42-2; 3,4-dimethoxy-6-chlorobenzaldehyde, 18083-05-5; 6-chloro-3,4-dimethoxybenzoic acid, 6003 2-95-3; 3-methoxyphenylacetaldehyde, 65292-99-1; α-hydroxy-5,4'-dimethoxy-2-methylbibenzyl, 65293-00-7; α-chloro-5,4'-dimethoxy-2-methylbibenzyl, 65293-01-8; 6'-chlorolaudanosine, 55954-20-6; 2-bromo-4-methoxytoluene, 36942-56-0.

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Methano-Bridged 14π-Electron Aromatic Annulenes. 1. 1,6-Methanofluorenyl and 9-Methyl-1,6-methanofluorenyl Anions

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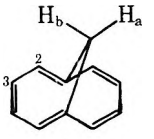
The syntheses of 1,6-methanofluorene, *syn*- and *anti*-9-methyl-1,6-methanofluorene, and their monoanions are described. The anions were shown by proton NMR to be delocalized aromatic systems existing in "cycloheptatriene" rather than "norcaradiene" forms.

Several methano-bridged 14π-electron aromatic systems have been described, namely *syn*-1,6-methano-8,13-oxido[14]annulene,[2] *syn*-1,6-methano-8,13-bismethano[14]annulene,[3] 3,4-benzo-1,6-methano[10]annulene,[4] 1,7-methanododecapentaenyl dianion,[5] 1,6-methanododecapentaenyl dianion,[5] the dianion of 1-aza-2-methoxy-5,10-methano[12]annulene,[6] 2,3-benzo-1,6-methano[10]annulene,[7] and the 1,6-methanocarbazoyl anion.[8] Proton NMR spectroscopy showed delocalized aromatic π systems for all of these except the [11]annulene dianion, which decomposed before a spectrum could be recorded. In our initiation of a study of the effects of methano bridges on the physiological properties of psychoactive compounds (via reduction in aromaticity and alteration of steric factors) we found it necessary to investigate bridging procedures for various types of similar parent species. Included among them was fluorene, which can be considered a benzoannelated indene.

Benzoannelation reduces aromaticity of a molecule and its diamagnetic ring current. For example, Vogel[7] showed such a reduction for 2,3 annelation of 1,6-methanonaphthalene, **1**, with the observation that resonance signals for protons H_a and H_b are shifted 0.5 and 1.9 ppm, respectively, downfield on introduction of the additional ring.



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We now wish to report the syntheses of 1,6-methanofluorene (**2**) and 9-methyl-1,6-methanofluorene (**3**), and their corresponding anions **4** and **5**. The anions exhibited electron delocalization over the entire π system, but a decided downfield shift of bridge protons relative to those in the methanoindenyl anion[9] indicated a reduced diamagnetic ring current due to the additional ring.[10]

The key intermediate for the synthesis of 1,6-methanofluorene,[11] **2**, was ketone **6**, whose preparation from indene was already described.[13] It was readily reduced to the epimeric alcohols, **7**, which then were converted successively to the bridged *syn*-alcohol **8**, mesylate **9**, and mixture of elimination products **10** and **11**.

Previous experience showed that **10** should be preferred for the conversion to diene **2**. Since the **10**/**11** ratio from mesylate **9** was 60:40 (somewhat more favorable after chromatography

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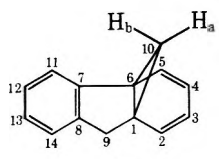
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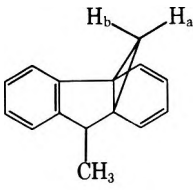
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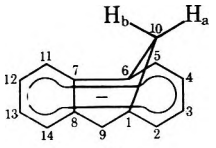
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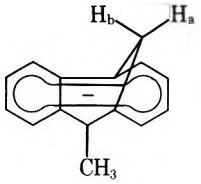
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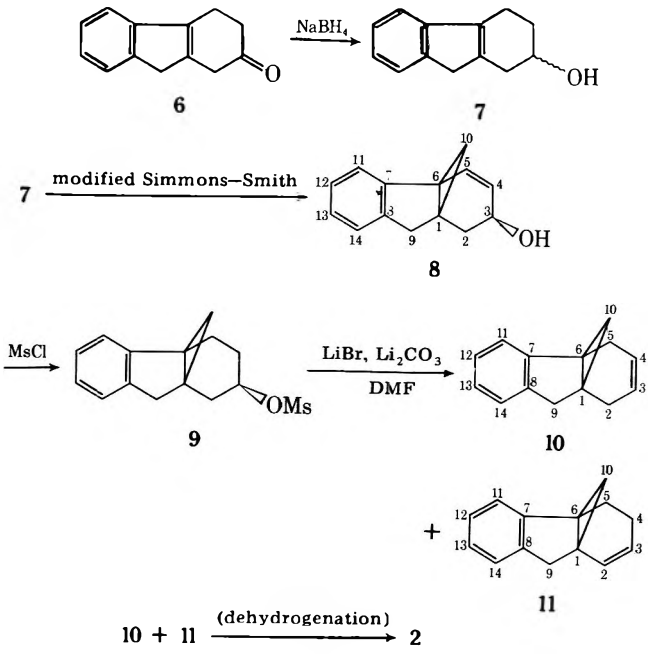
with silver nitrate on silica gel), attempts were made to improve the yield of the preferred monoene by carrying out eliminations on anti halides derived from **9**. Even though



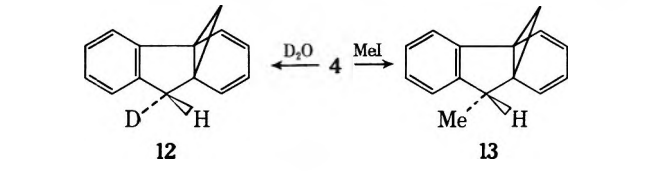
6 7 8 9 10 11 10 + 11 → 2

elimination by DBN in the iodo species yielded a 75:25 ratio, the overall yield of **10** was less than that directly obtained from the mesylate.

Among the unsuccessful routes for converting **11** to 1,6-methanofluorene were NBS bromination/elimination, DDQ dehydrogenation, and epoxidation/ring opening/elimination. However, addition of bromine to **10** at −78 °C followed by dehydrohalogenation with DBN/THF at 60 °C gave **2** in 75% distilled yield.

The bridged anion, **4**, was prepared by deprotonation of **2** with dimsyl-d_5 sodium in Me_2SO-d_6 using a modified procedure described originally by Rosen.[14] A 90-MHz proton NMR spectrum of the resulting solution thus prepared gave good resolution because of low concentration and viscosity.

Quenching of 4. Treatment of **4** with water regenerated **2** in near-quantitative yield, confirming the integrity of the carbon skeleton during proton transfers. Quenching instead with deuterium oxide gave *anti*-9-deuterio-1,6-methanofluorene, **12**. Similarly, methyl iodide converted **4** stereospecifically to *anti*-9-methyl-1,6-methanofluorene, **13**. These reactions are analogous to those previsouly described for the 1,6-methanoindenyl anion.[14] A difference between the methanoindenyl and methanofluorenyl systems appeared in the acidity of the remaining 9-proton of **13**. Even with a great excess of base no deprotonation of the methylated methanoindene had been noted, but under the same conditions **13** could be converted to its anion, **5**. Subsequent protonation of **5** yielded *syn*-9-methyl-1,6-methanofluorene, **14**, providing an interesting sequence for the generation of a pair of isomers.

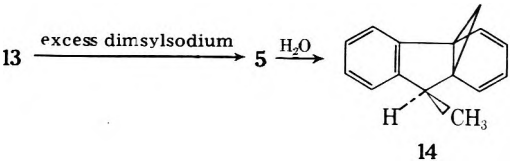


12 13

Table I. 90-MHz Proton NMR Data for 4

Proton	Splitting pattern	Chemical shift, δ	Coupling constants, Hz
11	Double doublet	7.62	J = 7.55 J' = 1.46
14	Doublet	7.25	J = 8.06
5	Doublet	7.04	J = 7.18
2	Doublet	6.80	J = 8.21
13	Doublet of triplets	6.70	J = 8.21 J' = 1.46
12	Triplet	6.38	J = 7.20
3	Triplet	6.29	J = 8.35
9	Unresolved multiplet[a]	5.63	
4	Triplet	5.60	J = 7.62
10b	Doublet	−0.29	J = 7.33
10a	Double doublet	−0.84	J = 7.33 J' = 1.32

[a] W-coupled to 10a as shown by some sharpening of the band on decoupling.



13 5 14

Discussion

As in Rosen's observation with methanoindene,[15] deprotonation and subsequent anion quenching are stereospecific processes. This is confirmed in several ways. Of primary importance is the reported observation[16] that a proton syn to a methylene bridge is farther upfield than that of its anti counterpart. The benzylic proton that remains in **12** appears at δ 3.03, near the center of the doublet for the *syn*-benzylic proton of **2**. Furthermore, successive deprotonation and protonation of **12** resulted in virtually complete removal of the deuterium (only a small amount of **12** could be detected), demonstrating stereospecificity in both the original deuteration and subsequent deuterium loss. Finally, the clean inversion of the 9-methyl from syn to anti was consistent with preferential attack by the anion at its position opposite the bridge, and both isomers on deprotonation yielded the same anion as demonstrated by NMR spectra.

The 1,6-Methanofluorenyl Anion, 4. The pertinent proton NMR data for **4** are given in Table I. Assignments were made by comparison of chemical shifts with those of model systems that included the indenyl anion (**15**),[17] fluorenyl anion (**16**),[18] and 1,6-methanoindenyl anion (**17**).[9,14]

The cyclopropyl protons H_b and H_a of **4** are found at δ −0.29 and −0.84 as compared with δ −0.45 and −0.95 in **17**. The

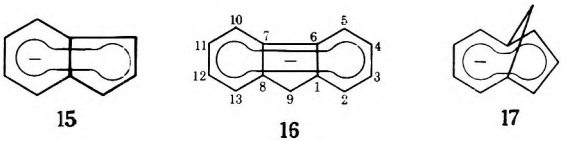

15 16 17

Table II. 90-MHz Proton NMR Data for 2

Proton	Splitting pattern	Chemical shift, δ
2,5	Complex multiplet	6.42
11,12,13,14	Sharp multiplet	6.87–7.53
3,4	Sharp multiplet	5.85
10b	Doublet (J = 3.6 Hz)	1.45
10a	Doublet (J = 3.6 Hz)	0.20
9a,9b	Doublets (J = 16.5 Hz)	2.90, 3.27

Table III. 90-MHz Proton NMR Data for 5

Proton	Splitting pattern	Chemical shift, δ	Coupling constants, Hz
11	Double doublet	7.55	J = 7.47, J' = 1.32
14	Double doublet	7.18	J = 7.91, J' = 1.17
2,5	Doublet	6.98	J = 7.18
13	Doublet of triplets	6.81	J = 8.06, J' = 1.47
12	Triplet	6.43	J = 6.96
3	Triplet	6.34	J = 8.50
4	Triplet	5.56	J = 7.69
Methyl	Singlet	1.93	
10b	Doublet	−0.26	J = 7.62
10a	Doublet	−0.88	J = 7.62

change is not as dramatic as that observed for the 2,3-benzo-annelation of **1**, which causes shifts of 1.9 and 0.5 ppm.[7] Delocalization of charge over the 14 π system is shown by the downfield shift for protons in the six-membered aromatic ring when **2** is converted to **4**. In **2**, protons 11, 12, 13, and 14 appeared as a very complex multiplet at δ 6.87–7.53 (Table II) but shifted to as low as δ 6.38 for H-12 (Table I) in **4**. This kind of shift was described by Cox[18] when fluorene was converted to its anion, **16**.

HMO theory[17] predicted that, next to C-9, carbons C-4 and C-11 in **16** should have the highest electron density and C-5 and C-10 the lowest. Introduction of the methano bridge into **16** to give **4** caused an upfield shift in protons attached to positions 2, 3, 4, and 5 due to higher charge density, but relative density arrangements remained the same.

The 9-Methyl-1,6-methanofluorenyl Anion, 5. The proton NMR spectrum (Table III) for **5** is very similar to that of **4**. The inductive effect of the methyl group produced a downfield shift for H-2 and H-13, and the bridge proton over the six-membered ring no longer shows W coupling as it did in **4** because of the absence of any 9 proton.

During the interconversion of the anti to the syn form of 9-methylmethanofluorene via **5**, the methyl protons shifted from δ 1.49 to δ 1.18, showing that the cyclopropyl proton H-10b does have a shielding effect on the methyl group. This shielding concept is consistent with all of the stereochemical consequences proposed for all proton removals and quenchings in the methanofluorene system.

The structure for the methano-bridged fluorenyl anions (**4** and **5**) is shown in cycloheptatriene rather than norcaradiene (**18**) form. Primary justification for the assignment comes from ^{13}C NMR spectra. Pertinent data are given in Table IV.

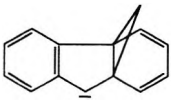


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Table IV. Carbon-13 Chemical Shifts for Bridged Fluorenes and Related Compounds

Compound	Registry no.	Chemical shifts, δ at 22.638 MHz C-1	C-6	C-10
Methano-indene[a]	174-44-7	40.07	48.07	28.01
Fluorene[19]	86-73-7	143.1	141.6	
2[a]	19540-84-2	39.57	45.57	26.47
15[b]	65150-09-6	128.1	(128.1)	
17[b]	65150-10-9	113.73	(113.76)	42.07
16[a]	12257-35-1	136.04	121.48	
4[b]	65150-11-0	119.17	101.30	39.83
8[a]	65150-12-1	32.76	26.54	24.60
10[a]	65167-98-8	32.67	26.15	24.62
11[a]	65150-13-2	36.59	26.32	26.09

[a] In chloroform/Me_4Si. [b] In Me_2SO-d_6/Me_4Si.

The effect of change in charge state is illustrated by the relatively small change in transforming fluorene to its anion, **16**. The very large change in the opposite direction in converting methanofluorene, **2**, to the methanofluorenyl anion, **4**, or methanoindene to methanoindenyl anion, **15**, must be ascribed to a change in hybridization of the carbon atoms at C-1 and C-6. Thus, a large reduction in s character in the anion would preclude consideration of a norcaradiene structure for these products.

Experimental Section

Spectra were obtained as follows: 60-MHz NMR spectra on Varian A-60, A-60d, or T-60 spectrometers; 90-MHz ^1H NMR and 22.63-MHz ^{13}C NMR spectra on a Brüker HX-90 FT multinuclear spectrometer; infrared spectra on a Perkin-Elmer Model 137 spectrometer; ultraviolet spectra on a Cary-14 spectrometer; and mass spectra on a Finnigan mass spectrometer. Microanalyses were performed by C. F. Geiger and Chemalytics, Inc. High-resolution mass spectra were recorded by Dr. Kai Fang on an AEI MS-9 spectrometer.

Melting points, obtained on a Thomas-Hoover capillary melting point apparatus, are uncorrected. Evaporative bulb-to-bulb distillations were carried out on a Jumo SSP-O apparatus. High-pressure liquid chromatography was carried out on a Waters Associates liquid chromatograph Model 6000-A.

Grace-Davison grade 62 neutral silica gel, EM precoated PLC plates (silica gel 60 F-254) and 0.25-mm plates (EM silica gel 60 F-254) were used for preparative scale chromatography. Analytical thin-layer chromatography was performed using EM precoated TLC sheets (silica gel F-254, 0.25 mm on plastic support).

Tetrahydrofuran was redistilled from potassium benzophenone ketyl under nitrogen just prior to use; hexane and methylene chloride were distilled; all other solvents were used as obtained from Mallinckrodt.

2-Hydroxy-1,2,3,4-tetrahydrofluorene (7). To a stirred 0 °C solution of 33.5 g (0.182 mol) of ketone **6** (prepared from indene[13]) in 1200 mL of absolute ethanol was added 20.7 g (0.546 mol) of sodium borohydride (cautiously and slowly). The mixture was warmed to room temperature and kept there for 7.25 h. After solvent removal, the residue was taken up in 25% aqueous sodium hydroxide and stirred at room temperature overnight. The organic material was extracted into ether and washed with dilute hydrochloric acid and water. Drying over $MgSO_4$ followed by solvent removal and crystallization (hexanes/chloroform) gave 25.6 g (76%) of **7** as off-white plates: mp 103.5–104.5 °C; IR (KBr) 3.00 (OH), 3.45, 6.90, 9.70, 13.28, 14.00 μm; NMR ($CDCl_3$/Me_4Si) δ 6.97–7.49 (m, 4 H), 3.88–4.31 (m, 1 H), 3.16 (broad s, 2 H), 2.31–2.79 (m, 5 H, allylic and hydroxyl protons), 1.74–2.18 (m, 2 H); MS m/e (rel intensity) 186 (16), 115 (100). Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; H, 7.58. Found: C, 83.47; H, 7.57.

***syn*-3-Hydroxy-7,8-benzotricyclo[4.3.1.0^{1,6}]dec-7-ene (8).** A zinc–copper couple[20] was prepared by heating to reflux 35.8 g (0.548 mol) of 30 mesh zinc and 0.5 g (0.0015 mol) of cupric acetate monohydrate in 125 mL of acetic acid for 10 min. After the acetic acid was decanted, the couple was washed five times with boiling ether and dried under nitrogen. The zinc–copper couple was transferred to a three-necked flask equipped with a mechanical stirrer, addition funnel, reflux condenser, and nitrogen inlet/outlet. The couple was

covered with 100 mL of ether. To the addition funnel was added 25.5 g (0.137 mol) of **7**, 147.0 g (0.548 mol) of methylene iodide, and 600 mL of ether. One crystal of iodine was added to the zinc–copper couple mixture and the addition of methylene iodide/**7** solution was started. The flask was heated (heat lamp) for 5 min to start the reaction. Then the addition rate was regulated to maintain a gentle reflux. After the addition was complete (50 min), the mixture was refluxed for an additional 10.5 h. The flask was cooled to 0 °C and saturated ammonium chloride solution was added. The aqueous phase was extracted with ether and the combined organic phases were washed twice with saturated ammonium chloride, twice with saturated sodium bicarbonate solution, and water. This extract was dried over $MgSO_4$, filtered, and concentrated. Chromatography (silica gel) of the residue gave 21.3 g (78%) of **8** as a viscous, yellow oil which could not be induced to crystallize. An analytical sample was obtained by preparative thick-layer chromatography (light yellow oil): R_f = 0.499 (100% ethyl ether); IR (film) 3.00 (OH), 3.31, 3.45, 3.53, 6.81, 9.55, 9.77, 10.28, 13.20, 13.70, 14.09 μm; NMR ($CDCl_3$/Me_4Si) δ 7.00–7.22 (m, 4 H), 3.35–3.90 (10-line m, 1 H), 3.11 (d, J = 17 Hz, 1 H, benzylic H anti to cyclopropane), 2.91 (d, J = 17 Hz, 1 H, benzylic proton syn to cyclopropane), 0.91–2.64 (m, 7 H), 1.05 (d, J = 4.4 Hz, 1 H, H-10b), 0.31 (d, J = 4.4 Hz, 1 H, H-10a); MS m/e (rel intensity) 200(56), 167(91), 128(61), 115(100). Anal. Calcd for $C_{14}H_{16}O$: C, 83.96; H, 8.05. Found: C, 83.73; H, 7.93.

Methanesulfonate Ester 9. To a stirred solution (−5 to −10 °C) of 18.7 g (0.094 mol) of alcohol **8** and 15.6 g (0.154 mol) of triethylamine in 125 mL of methylene chloride was added 15.0 g (0.103 mol) of methanesulfonyl chloride over a period of 30 min. The mixture was kept at −5 to 0 °C for an additional 30 min and then stirred at room temperature for 2 h. The solution was cooled to 0 °C, 150 mL of water was added, and the mixture was warmed to room temperature. The aqueous phase was reextracted with methylene chloride. The combined organic phases were washed successively with water, 3 M hydrochloric acid (three times), saturated sodium bicarbonate solution (twice), and saturated sodium chloride solution. The organic extract was dried over $MgSO_4$, filtered, and evaporated to yield 24.4 g (94%) of an orange-yellow, viscous oil (R_f = 0.701 in 100% diethyl ether). A sample was purified by preparative thick-layer chromatography (eluting with 100% diethyl ether, run up twice) to yield a colorless oil which solidified to a near-colorless, waxy solid: mp 81–83 °C; IR (film) 3.34, 3.45, 6.83, 6.95, 7.51 (O=S=O), 8.58 (O=S=O), 10.62, 13.18, 13.73 μm; NMR ($CDCl_3$/Me_4Si) δ 6.94–7.34 (m, 4 H), 4.37–4.92 (m, 1 H), 3.10 (d, J = 17 Hz, 1 H), 2.94 (d, J = 17 Hz, 1 H), 2.87 (s, 3 H), 1.24–2.64 (m, 6 H), 1.08 (d, $J \cong$ 4.5 Hz, 1 H), 0.35 (d, $J \cong$ 4.5 Hz, 1 H); MS m/e (rel intensity) 278(9), 182(90), 167(100), 141(83). Anal. Calcd for $C_{15}H_{18}O_3S$: mol wt, 278.0976. Found: mol wt (MS), 278.0975.

7,8-Benzotricyclo[4.3.1.0^{1,6}]deca-3,7-diene (10) and 7,8-Benzotricyclo[4.3.1.0^{1,6}]deca-2,7-diene (11). Mesylate Method. A mixture of 16.2 g (0.058 mol) of mesylate **9**, 21.6 g (0.292 mol) of lithium bromide, and 7.6 g (0.088 mol) of lithium carbonate in 400 mL of dimethylformamide was stirred under nitrogen for 4 h at 125 °C. At room temperature water was added. An ether extract was washed four times with water, dried over $MgSO_4$, filtered, and evaporated to give 9.3 g (88%) of a dark brown oil. The crude product was chromatographed on 10% silver nitrate-impregnated silica gel. Elution with 2% diethyl ether/98% hexanes gave 4.07 g (44%) of **10** as a light yellow oil (R_f = 0.730, 3:1 benzene/diethyl ether on 10% silver nitrate-impregnated silica gel). An analytically pure sample was obtained by evaporative bulb-to-bulb distillation (92.5 °C, 0.075 mm). Compound **10** was obtained as a colorless oil: IR (film) 3.30, 3.46, 3.53, 6.73, 6.97, 13.13, 13.76 μm; NMR (CCl_4/Me_4Si) 6.84–7.41 (m, 4 H, aromatic), 5.53 (m, 2 H, vinyl), 3.09 (d, J = 17 Hz, 1 H, benzylic H anti to cyclopropane), 2.80 (d, J = 17 Hz, 1 H, benzylic H syn to cyclopropane), 1.89–2.92 (m, 4 H, allylic), 1.06 (d, J = 3.8 Hz, H-10b), 0.24 (d, J = 3.8 Hz, 1 H, H-10a); MS m/e (rel intensity) 182(31), 167(40), 165(22), 128(100). Anal. Calcd for $C_{14}H_{14}$: C, 92.23; H, 7.74. Found: C, 92.15; H, 8.06.

Continued elution with 4% diethyl ether/96% hexanes yielded 2.48 g (27%) of **11** as an orange-red oil. This oil was purified by short-path distillation to give 1.76 g (17%) of a colorless oil: bp 58–60 °C (0.1 mm); R_f = 0.651, 3:1 benzene/ether on 10% silver nitrate-impregnated silica gel; IR (film) 3.34, 3.48, 3.55, 5.85, 6.33, 13.18, 13.80, 14.28 μm; NMR (CCl_4/Me_4Si) δ 6.87–7.33 (m, 4 H, aromatic), 6.10 (dd, J = 10 Hz, J' = 2 Hz, 1 H, vinyl), 5.37 (ddt, J = 10 Hz, J' = 6 Hz, J'' = 2 Hz, 1 H, vinyl), 3.14 (d, J = 16.5 Hz, 1 H, benzylic H anti to cyclopropane), 2.97 (d, J = 16.5 Hz, 1 H, benzylic H syn to cyclopropane), 1.50–2.60 (m, 4 H), 1.38 (d, J = 4.2 Hz, 1 H, H-10b), 0.49 (d, J = 4.2 Hz, 1 H, H-10a); MS m/e (rel intensity) 182(100), 167(66), 165(50), 141(80). Anal. Calcd for $C_{14}H_{14}$: C, 92.26; H, 7.74. Found: C, 91.94; H, 8.02.

An attempted elimination reaction on mesylate **9** using potassium *tert*-butoxide in dimethyl sulfoxide yielded a 41:59 mixture of **10** and **11** and other unidentified materials.

Halide Method for 10 and 11. A solution of 218 mg (0.784 mmol) of mesylate **9** and 420 mg (3.136 mmol) of lithium iodide in 10 mL of acetone was refluxed under nitrogen for 20 h. Acetone was removed under reduced pressure, water was added to the residue and the organic materials were extracted into methylene chloride. The extracts were dried over $MgSO_4$, filtered, and concentrated to give 219 mg (90%) of a green oil. Preparative thick-layer chromatography of this crude product yielded 120 mg (49%) of a yellow oil (R_f = 0.642 in 100% ether). This oil was shown by proton NMR analysis to be a mixture of *anti*-3-iodo-7,8-benzotricyclo[4.3.1.0^{1,6}]dec-7-ene (**19**) and **10** (minor component). The IR (film) showed bands at 3.45, 3.58, 3.65, 6.82, 6.90, 6.98, 7.05, 13.13, 13.40, and 13.68 μm.

The mixture of iodide **19** and **10** was reacted with 120 mg (1.07 mmol) of DBN in 10 mL of dry tetrahydrofuran at 60 °C for 11.3 h under nitrogen. After tetrahydrofuran was removed under reduced pressure, water was added and the organic materials were extracted into methylene chloride and washed with dilute hydrochloric acid (three times), dilute aqueous sodium hydroxide (twice), water (twice), and saturated sodium chloride solution. The methylene chloride extracts were dried over $MgSO_4$, filtered, and concentrated to give 75 mg (53%) of an orange oil. Proton NMR (CCl_4/Me_4Si) analysis of this material showed it to be a 70.5:29.5 mixture of **10** and **11** (this corresponded to a 37% unisolated yield of **10** from **9**). The same general procedure was used for the preparation of **10** and **11** from **9** via the bromide and chloride.

1,6-Methanofluorene (2). To a stirred solution (−78 °C) of 546 mg (3.0 mmol) of olefin **10** in 30 mL of methylene chloride under nitrogen was added 600 mg (3.3 mmol) of bromine in 25 mL of methylene chloride over a period of 45 min (the stirring bar was treated successively with fuming nitric acid, 50% aqueous sodium hydroxide, and water before use to minimize iron-catalyzed aromatic substitution). After an additional 20 min at −78 °C about 2 g of sodium sulfite and 5 mL of methanol were added. The mixture was allowed to warm to room temperature and 20 mL of water was added. The organic phase was washed with water (twice) and saturated sodium chloride solution. Drying over $MgSO_4$ followed by filtration and concentration gave 966 mg (94%) of **19** (the dibromide of **10**) as a yellow oil: R_f = 0.653 in 1:1 benzene/ether; IR (film) 3.48, 6.84, 7.05, 8.58, 13.18, 13.78 μm; NMR (CCl_4/Me_4Si) δ 7.08 (m, 4 H), 4.12–4.64 (m, 2 H), 3.15 (d, J = 15.5 Hz, 1 H), 2.95 (dd, J = 15.5 Hz, J' = 3 Hz, 1 H), 1.70–2.93 (m, 4 H), 1.43 (dd, J = 4.4 Hz, J' = 2.2 Hz, 1 H), 0.49 (d, J = 4.4 Hz, 1 H).

A mixture of 966 mg (2.82 mmol) of **19**, 1414 mg (12.64 mmol) of DBN and 45 mL of tetrahydrofuran was stirred at 60 °C under argon for 40.8 h. After 5 mL of water was added the tetrahydrofuran was removed under reduced pressure. The residue was treated with methylene chloride and water and the aqueous phase was further extracted twice with methylene chloride. The combined organic phases were washed with dilute hydrochloric acid (twice), 10% sodium hydroxide solution (twice), water (twice), and saturated sodium chloride solution, dried over $MgSO_4$, filtered, and concentrated to give 483 mg (91%) of a brown oil. This crude product was purified by evaporative bulb-to-bulb distillation (92 °C (0.075 mm)) to give 407 mg (80%) of **2** as a light yellow oil (R_f = 0.625, 1:1 benzene/ether). Alternatively, purification could be accomplished by short-path distillation to give **2** as a colorless oil (51%) (bp 64–66 °C (0.09 mm)) which subsequently solidified, mp 57.0–58.5 °C. The residue of this distillation was subjected to evaporative bulb-to-bulb distillation (103–112 °C (0.075 mm)) to yield additional **2** as a yellow oil, which raised the overall yield to 64%. The spectral data for **2** are as follows: IR (film) 3.28, 3.43, 3.51, 6.76, 6.87, 6.99, 9.85, 13.72, 13.92 μm; NMR (CCl_4/Me_4Si) δ 6.87–7.53 (m, 4 H, aromatic), 6.42 (m, 2 H, vinyl), 5.85 (m, 2 H, vinyl), 3.21 (d, J = 16.5 Hz, 1 H, benzylic H anti to cyclopropane), 2.94 (d, J = 16.5 Hz, 1 H, benzylic H syn to cyclopropane), 1.45 (d, J = 3.6 Hz, 1 H, H-10b), 0.20 (d, J = 3.6 Hz, 1 H, H-10a); UV (THF) 236 (ε 5140), 268 (sh, ε 4260), 273 (ε 4380), 300 nm (sh, ε 1470); MS m/e (rel intensity) 180 (100), 179(51), 165(90). Anal. Calcd for $C_{14}H_{12}$: C, 93.29; H, 6.71. Found: C, 93.32; H, 6.52.

Generation of the 1,6-Methanofluorenyl Anion (4). To a dry, thin-walled (5 mm) NMR tube covered with a septum was added 28 mg (0.154 mmol) of diene **2** in 0.4 mL of Me_2SO-d_6. This solution was degassed by repetitive freeze–thaw cycles and the air replaced by argon. Dimsyl-d_5 sodium was prepared by heating 5 mg (0.21 mmol) of sodium hydride in 0.6 mL of degassed Me_2SO-d_6 for 1 h at 70–80 °C (under nitrogen). After the solution cooled to room temperature it was transferred to the tube via syringe and kept under argon. Immediately a deep orange-red color formation was noted and the NMR tube was shaken a few times to ensure complete mixing. The 90-MHz

proton NMR was recorded within 15–30 min. The anion was stable at room temperature for approximately 4 h, after which extensive polymerization began. The 90-MHz ^1H NMR (Me_2SO-d_6/Me_4Si) is summarized in Table I. The UV spectrum (*n*-BuLi/THF) showed λ_{max} at 250 (ε 69 700), 297 (ε 86 900), and 340 nm (sh, ε 20 500).

***anti*-9-Methyl-1,6-methanofluorene (13).** To a stirred solution of 100 mg (0.556 mmol) of diene **2** in 15 mL of tetrahydrofuran (under argon) were added successively 0.20 mL (1.112 mmol) of HMPA and 0.16 mL (1.112 mmol) of diisopropylamine. The resulting solution was cooled to 0 °C and 0.71 mL (1.112 mmol) of a 1.56 M solution of *n*-butyllithium/hexane was added. With continuous stirring the cooling bath was removed after 21 min at 0 °C and 0.49 mL (1.51 mmol) of methyl iodide was added; then after an additional 75 min at room temperature, 5 mL of saturated ammonium chloride solution was added. The aqueous phase was separated and extracted with ether. The combined organic phases were washed with water (four times) and saturated sodium chloride, dried over $MgSO_4$, filtered, and concentrated to give 103 mg (96%) of an orange oil. Purification was accomplished by evaporative bulb-to-bulb distillation (96 °C (0.02 mm)) to yield 57 mg (53%) of **13** as a pale yellow oil: R_f = 0.606 in 10% ethyl acetate/90% hexanes; IR (film) 3.30, 3.38, 3.42, 3.49, 6.78, 6.88, 8.37, 9.82, 12.58, 13.35, 13.79, 14.29 μm; UV (THF) 236 (ε 5430), 273 (ε 4100), 301 nm (sh, ε 1670); 90-MHz NMR ($CDCl_3$/Me_4Si) δ 7.44 (m, 1 H, aromatic), 7.15 (m, 3 H, aromatic), 6.49 (m, 2 H, vinyl), 5.93 (m, 2 H, vinyl), 3.03 (m, 1 H, benzylic), 1.55 (d, J = 3.52 Hz, 1 H, H-10b), 0.26 (d, J = 3.52 Hz, 1 H, H-10a); MS *m/e* (rel intensity) 194(39), 180(12), 179(100), 178(57). Anal. Calcd for $C_{15}H_{14}$: mol wt, 194.1095. Found: mol wt (MS), 194.1098.

***anti*-9-Deuterio-1,6-methanofluorene (12).** Diene **2** (23 mg, 0.128 mmol) in 0.5 mL of Me_2SO-d_6 was treated with about 0.1 mL of 5.2 M dimsyl-d_5 sodium/Me_2SO-d_6 (about 0.5 mmol) under argon until no further color change could be detected. After approximately 30 min, 0.5 mL (27.7 mmol) of deuterium oxide was added and the mixture was allowed to stand for an additional 30 min. An ether extract was washed three times with water, dried over $MgSO_4$, filtered, and concentrated, to give 11 mg (48%) of a yellow oil. Purification was accomplished by preparative thin layer chromatography to yield 4.4 mg (19%) of **12** as a light yellow oil: IR (film) 3.43, 3.57, 4.71 (C–D), 6.82, 6,93, 8.42, 9.58, 9.85, 13.05, 13.90 μm; NMR ($CDCl_3$/Me_4Si) δ 6.94–7.54 (m, 4 H, aromatic), 6.15–6.79 (m, 2 H, vinyl), 5.75–6.11 (m, 2 H, vinyl), 3.36 (q, J = 7 Hz, 1 H, benzylic), 1.49 (d, J = 7 Hz, 3 H, methyl), 1.45 (d, J = 3.6 Hz, 1 H, H-10b), 0.09 (d, J = 3.6 Hz, 1 H, H-10a); UV (THF) 236 (ε 4820), 273 nm (ε 3580). Anal. Calcd for $C_{14}H_{11}D$: mol wt, 181.1002. Found: mol wt (MS), 181.0999.

Preparation of 1,6-Methanofluorene (2) from *anti*-9-Deuterio-1,6-methanofluorene (12). To a dry, thin-walled (5 mm) NMR tube covered with a septum was added 51 mg (0.282 mmol) of **12** (91% deuterated as estimated by NMR) in 0.4 mL of Me_2SO-d_6 under argon. The NMR tube was degassed as outlined for generation of **4**, and 0.15 mL (0.757 mmol) of 5.05 M dimsyl-d_5 sodium in Me_2SO-d_6 was added (solution immediately turned deep red). Proton NMR analyses showed that the resulting anion, which contained very little deuterium as determined from integration of the spectrum, consisted mainly of **4**. After water (0.5 mL, 0.02 mol) was added, the mixture was extracted into ether, washed with water (four times), dried over $MgSO_4$, filtered, and concentrated, to yield 33 mg (62%) of a light orange oil. Proton NMR analysis ($CDCl_3$/Me_4Si) indicated that this oil contained only a small amount of **12** (less than 10%) and was comprised mainly of **2**.

Generation of the 9-Methyl-1,6-methanofluorenyl Anion (5) from *anti*-9-Methyl-1,6-methanofluorene (13). Anion **5** was prepared in an analogous manner to **4** using 37 mg (0.191 mmol) of **13** in 0.2 mL of Me_2SO-d_6 and 0.20 mL (1.01 mmol) of 5.05 M dimsyl sodium in Me_2SO-d_6 solution. The deep red anion generation was considerably slower than that of **4**. Anion **5** was stable at room temperature for approximately 1 h and exhibited the 90-MHz NMR data summarized in Table III.

***syn*-9-Methyl-1,6-methanofluorene (14).** *anti*-9-Methyl diene **13** (37 mg, 0.191 mmol) in 0.2 mL of Me_2SO-d_6 was treated with 0.20 mL of 5.05 M dimsyl-d_5 sodium in Me_2SO-d_6 (1.01 mmol) under argon. After about 30 min, 0.5 mL (0.022 mol) of water was added. The mixture was extracted into ether, washed with water (four times), dried over $MgSO_4$, filtered, and concentrated, to yield 23 mg (62%) of an orange oil. Evaporative bulb-to-bulb distillation (95–130 °C (0.037–0.080 mm)) followed by preparative thin-layer chromatography (silica gel, run up three times) yielded 5 mg (14%) of a near-colorless oil: R_f = 0.667 in 15% ethyl acetate/85% hexanes; IR (film) 3.40, 3.43, 3.50, 6.65, 6.77, 12.98, 13.18, 13.40, 13.66 μm; 90-MHz NMR ($CDCl_3$/Me_4Si) δ 7.39 (m, 1 H), 7.14 (m, 3 H), 6.51 (m, 2 H), 5.96 (m, 2 H), 3.41 (q, J = 7.35 Hz, 1 H), 1.54 (d, J = 3.52 Hz, 1 H), 1.18 (d, J = 7.04 Hz, 3 H), 0.24 (d, J = 3.52 Hz, 1 H); MS *m/e* (rel intensity) 194(9), 167(100). Anal. Calcd for $C_{15}H_{14}$: mol wt, 194.1095. Found: mol wt (MS), 194.1101.

Generation of the 9-Methyl-1,6-methanofluorenyl Anion (5) from *syn*-9-Methyl-1,6-methanofluorene (14). Anion **5** was prepared in the same manner outlined for **4** using 4.0 mg (0.021 mmol) of the *syn*-methyl diene **14** in 0.4 mL of Me_2SO-d_6 and about 0.1 mL (0.053 mmol) of 5.3 M dimsyl-d_5 sodium in Me_2SO-d_6 under nitrogen at room temperature. Proton NMR analysis (90 MHz) showed that the anion generated was identical with that from *anti*-9-methyl diene **13**.

Generation of the Fluorenyl Anion (16). Anion **16** was prepared in a manner analogous to that for **4** using a saturated solution of fluorene in 0.5 mL of Me_2SO-d_6 and about 0.2 mL (0.106 mmol) of 5.3 M dimsyl-d_5 sodium in Me_2SO-d_6 under argon at room temperature. The 90-MHz proton NMR is summarized in Table IV. This spectrum was identical with that published by Cox[18] except for slight solvent-induced chemical shift changes.

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Registry No.—**5**, 65150-14-3; **6**, 26726-28-3; **7**, 65150-15-4; **9**, 65150-16-5; **12**, 65150-17-6; **13**, 65150-18-7; **14**, 65206-89-5; **19**, 65150-19-8; methanesulfonyl chloride, 124-63-0.

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Notes

Asymmetric Induction in the Synthesis of Thiophene-Containing Steroidlike Molecules via Olefinic Cyclization. 2.[1] Evidence for Precoiling As Model Description for the Cyclization

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Recently, we demonstrated the occurrence of asymmetric induction in the preparation of thiophene-containing steroids via olefinic cyclization.[1] With the chiral center at *pro*-C-5 far from the reaction initiator, a 97 and 100% asymmetric induction in favor of the α isomer was realized on cyclizing **1b** and **1c** respectively (Scheme I). These high stereospecificities were ascribed to nonbonded interactions between R and the hydrogen atoms at *pro*-C-7 and *pro*-C-9 that bring about the initial stereospecific C–D ring closure.

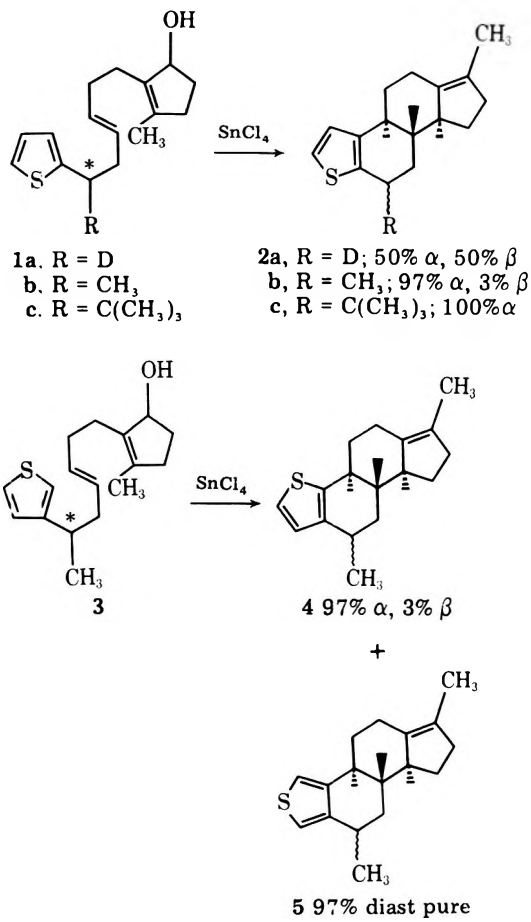
To gain further insight into such cyclization processes, we examined the reaction of deuterio derivative **1a** as well as the 3-substituted thiophene derivative **3**. From racemic **1a**, both the 5α as the 5β enantiomeric pairs of diastereomers were formed in equal amounts. Cyclization of racemic **3** gave compounds **4** and **5** each being 97% diastereomerically pure.

The starting materials **1a** and **3** were prepared according to Scheme II. 2-Thiophenecarboxylic acid, on esterification and reduction with $LiAlD_4$, gave 2-thienyldideuteriomethanol (**6a**). Oxidation with pyridinium chlorochromate[2] afforded aldehyde **7a**. 3-Thienyllithium reacted with acetaldehyde to afford 1-(3-thienyl)ethanol (**6b**) which, on oxidation with lead tetraacetate, furnished ketone **7b**. Wittig condensation of **11a,b** with phosphonium salt **12**[3] under Schlosser conditions[4] afforded *E* alkenes, a geometric prerequisite for cyclization.[5] The structures were confirmed with ^{13}C NMR by a method developed by de Haan and van de Ven.[6]

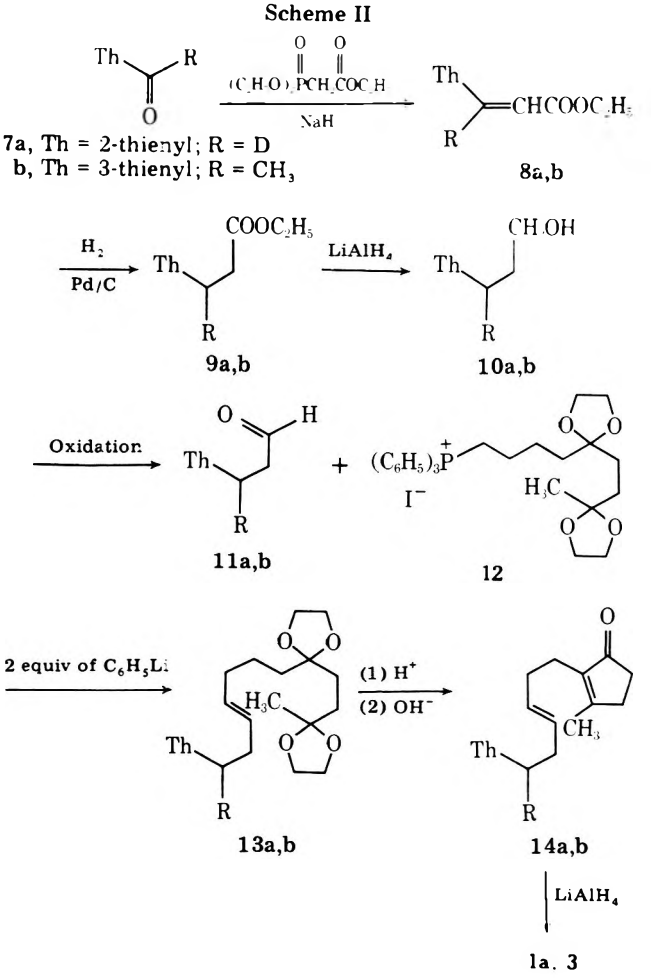
Upon cyclization of **1a**, both enantiomeric pairs of diastereomers **2a** were formed in equal amounts (±5%); in ^1H NMR (360 MHz) the integrals of the signals from the C-5–αH and C-5–βH at δ 2.74 and 2.84 ppm respectively were of equal magnitude.

Cyclization of the 3-substituted thiophene **3** afforded a mixture of tetracyclic products. ^{13}C NMR data revealed that approximately 70% consisted of a product in which ring closure has occurred at the 2 position of thiophene (**4**). The α configuration of the 5-methyl substituent in **4** was determined by the δ values of C-7 and C-8.[1] In the remaining 30% ring closure has taken place at the 4 position of thiophene to form compound **5** (see Table I). Also a singlet at 6.70 ppm in the ^1H-NMR spectrum for the two aromatic protons corroborates this structure. The TLC pure material could be separated partially by analytical HPLC, which showed both **4** and **5** to be 97% diastereomerically pure. The diastereomers in the mixture could be assigned by mass spectroscopy; the products show a two by two corresponding specific mass fragmentation.

Scheme I[a]



Scheme II



[a] The enantiomers are not drawn.

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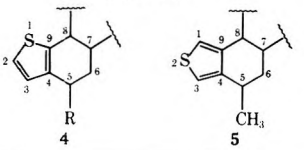
Table I[a]



4 5

Compd	Registry no.	C-1	C-2	C-3	C-4	C-5	C-6	C-7	C-8	C-9
4, R = H[b]	65166-17-8		122.63	128.16	135.25	26.78	28.89	42.52	50.42	141.16
4, R = CH_3	65121-19-9		122.73	126.73	141.16	32.28	38.91	42.83	50.68	140.63
5	65121-20-2	119.20		118.40	142.97	33.22	39.10	43.27	49.98	144.38

[a] Values in parts per million downfield from Me_4Si. [b] The values of this compound are obtained from ref 7.

The absolute configuration of the 5-methyl substituent in **5** could not be determined. The similarities of asymmetric induction with the different substrates suggest that the 5-methyl group in **5** also occupies the α position (for 97%). The different cyclization experiments show the diastereomeric purity to be the same (97%) regardless of the cyclization occurring at the 2, 3, or 4 position of thiophene.

To the best of our knowledge the formation of **5** represents an unusual mode of cyclization in the thiophene series. The only known electrophilic cyclizations of achiral 3-substituted thiophene analogues take place at the 2 position exclusively.[5] Moreover, the 4 position of 3-alkylthiophenes is the least reactive one toward substitution reactions. In our opinion the isomer formation finds its cause in a considerably retarded or stopped conformer exchange A ⇌ B (Scheme III) at the low reaction temperature (−95 °C) due to a steric interaction between the methyl substituent at *pro*-C-5 and the hydrogen atoms at *pro*-C-3 and *pro*-C-9.

The cyclizations proceed concertedly, as already has been confirmed by Johnson for phenyl analogues,[11] via a distinct productlike transition state. Cyclization of **1a–c** demonstrates how slight steric variation of substituents can effectively influence the 1,3-diaxial interactions which ultimately govern the asymmetric induced stereospecific C–D ring closure. The cyclization of **3** to the least reactive 4 position of thiophene implies that the reaction is initiated from a fixed conformer. *All these results confirm strongly our earlier proposal to describe the stereochemical course of the reaction by precoiling of the initial formed allylic cation.*[1]

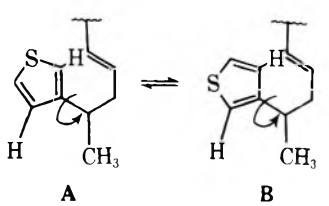
Experimental Section

The ^1H NMR data were obtained on a Varian EM-360 spectrometer using Me_4Si as internal standard (δ 0.00). The ^{13}C data were recorded on a Varian HA-100 equipped with a Digilab FTS-NMR-3. Microanalyses were carried out in our laboratories by Messrs. P. van den Bosch and H. Eding. HPLC analyses were carried out by Mr. G. J. Bezemer. 3-Bromothiophene was prepared according to the literature.[8]

2-Thienyldideuteriomethanol (6a). To 1.4 g of $LiAlD_4$ in 50 mL of ether 7.5 g (53 mmol) of 2-thiophenecarboxylic acid methyl ester was added dropwise at 0 °C. After 2 h of refluxing 1 N NaOH was added. Filtering and extracting with ether followed by distillation yielded 6 g of **6a** (100%): bp 96–98 °C (12 mm); NMR (CCl_4) δ 4.53 (s, 1, OH), 6.69–7.18 (m, 3, ThH).

2'-Thienyl-1-deuteriocarbaldehyde (7a). A solution of 4 g (35 mmol) of **6a** in 25 mL of dichloromethane was rapidly added to a suspension of 11.4 g (53 mmol) of pyridinium chlorochromate[9] in 50 mL of dichloromethane at room temperature. After 3 h of stirring no alcohol could be monitored. A fivefold excess of ether was added and the solution was filtered over Florisil. Distillation afforded 3.7 g of aldehyde **7a** (94%): bp 67–68°C (13 mm); NMR (CCl_4) δ 7.00–7.67 (m, 3, ThH).

Scheme III



A B

1-(3-Thienyl)ethanol (6b). To a solution of 20 g (122 mmol) of 3-bromothiophene in 150 mL of ether at −78 °C, 80.9 mL of butyllithium (15% in hexane) in 50 mL of ether was added dropwise. After 1 h 20 mL (350 mmol) of acetaldehyde in 100 mL of ether was added. After being stirred for 4 h at −78 °C, the mixture was poured into water and the product was extracted into ether. The combined ether layers were dried with $MgSO_4$ and concentrated. The alcohol **6b** was immediately oxidized to 3-acetylthiophene (**7b**): NMR (CCl_4) δ 1.27 (d, 3, CH_3), 3.72 (s, 1, OH), 4.70–5.00 (m, 1, $CHCH_3$), 6.76–7.22 (m, 3, ThH).

3-Acetylthiophene (7b). To a solution of 4.8 g (38 mmol) of **6b** in 100 mL of pyridine 20 g (130 mmol) of lead tetraacetate was added in small portions at such a rate that the temperature did not exceed 35 °C. After 60 h the mixture was poured into a solution of 150 g of K_2CO_3 in 800 mL of water and the product was extracted into benzene. Chromatography yielded 4.6 g of **7b** (95%): mp 57.0–57.8 °C; NMR (CCl_4) δ 2.39 (s, 3, CH_3), 6.90–8.03 (m, 3, ThH).

3-(2-Thienyl)-3-deuterioprop-2-enoic Acid Ethyl Ester (8a). To a solution of 3 g (0.1 mol) of sodium hydride (80% in paraffin) in 100 mL of dimethoxyethane (under a nitrogen atmosphere) was added 21.2 g (0.1 mol) of triethyl phosphonoacetate at a temperature below 20 °C. After the solution was stirred for 1 h 11.3 g (0.1 mol) of aldehyde **7a** was added and refluxed for 16 h. The mixture was poured into water and the product was extracted into ether. After the combined ether layers were dried with $MgSO_4$, the solvent was stripped off. Distillation gave 14.5 g of **8a** (79%): bp 155–159 °C (25 mm); NMR (CCl_4) δ 1.21 (t, 3, CH_3), 4.18 (q, 2, CH_2), 6.17 (s, 1, CH), 6.17–7.38 (m, 3, ThH).

3-(3-Thienyl)but-2-enoic Acid Ethyl Ester (8b) was prepared as for **8a** with benzene as solvent. The product was obtained as a mixture of *Z* and *E* isomers (*Z*/*E* = 3/7): yield 92%; NMR (CCl_4) δ 1.02–1.43 (2t, 3, CH_3), 2.13–2.52 (m, 3, $C{=}CCH_3$), 3.80–4.40 (2q, 2, CH_2), 5.70 and 6.07 (m, 1, CH), 7.02–7.40 (m, 3, ThH).

3-(2-Thienyl)-3-deuteriopropanoic Acid Ethyl Ester (9a). A mixture of 10 g of **8a** (54.6 mmol) was hydrogenated in 75 mL of ethanol with 3 g of Pd on carbon (10%) as catalyst. After 20 h the mixture was filtered to yield after distillation 8.5 g (84%) of **9a:** bp 102 °C (9 mm); NMR (CCl_4) δ 1.21 (t, 3, CH_3), 2.48–3.17 (m, 3, $CDHCH_2$), 4.03 (q, 2, CH_2CH_3), 6.70–7.11 (m, 3, ThH).

3-(3-Thienyl)butanoic Acid Ethyl Ester (9b) was prepared analogous to **9a:** yield 89%; bp 125 °C (18 mm); NMR (CCl_4) δ 1.15 (t, 3, CH_2CH_3), 1.27 (d, 3, CH_3), 2.35–2.55 (AA'B, 2, $CHCH_2$), 3.03–3.63 (m, 1, CH), 3.98 (q, 2, CH_2CH_3), 6.70–7.18 (m, 3, ThH).

3-(2-Thienyl)-3-deuteriopropanol (10a). A solution of 3.7 g (0.02 mol) of **9a** in 10 mL of ether was added dropwise to a suspension of 0.02 mol (0.76 g) of $LiAlH_4$ in 30 mL of ether at 0 °C. After 1 h of stirring at room temperature and 1 h of refluxing, 1 N sodium hydroxide was added. Filtering, drying, and distillation yielded 2.30 g (80%) of **10a:** bp 85 °C (4 mm); NMR (CCl_4) δ 1.77 (q, 2, CH_2CH_2OH), 1.72 (t, 1, CDH), 3.50 (t, 2, CH_2OH), 4.80 (s, 1, OH), 6.68–6.90 (m, 3, ThH).

3-(3-Thienyl)butanol (10b) was prepared as for **10a:** yield 90%; bp 126–129 °C (15 mm); NMR (CCl_4) δ 1.20 (d, 3, $CHCH_3$), 1.51–1.91 (m, 2, CH_2CH_2OH), 2.63–3.17 (m, 1, $CHCH_3$), 3.40 (t, 2, CH_2OH), 3.95 (s, 1, OH), 6.72–7.18 (m, 3, ThH).

3-(2-Thienyl)-3-deuteriopropanal (11a). This compound was prepared analogous to **7a:** yield 95%; bp 60 °C (0.8 mm).

3-(3-Thienyl)butanal (11b) was also prepared analogous to **7a:** yield 90%; bp 112 °C (16 mm).

2,5-Bis(ethylenedioxy)-12-(2-thienyl)-12-deuterio-(*E*)-dodec-9-ene (13a). To 20.23 g (32 mmol) of phosphonium salt **12**[3] in 75 mL of tetrahydrofuran (THF) was added 16 mL of phenyllithium (2 N solution) at 0 °C under a nitrogen atmosphere. At −70 °C 5.0 g (32 mmol) of **11a** in 5 mL of THF was added, followed by a second equivalent of C_6H_5Li. The mixture was maintained between −30 and −50 °C during 1 h, after which 7 mL of ethanol was added. The mixture was poured into water from which the product was extracted with petroleum ether. Chromatography yielded 4.7 g (40%) of **13a**: NMR (CCl_4) δ 1.23 (s, 3, diox CH_3), 1.65 (s, 4, $O_2CCH_2CH_2CO_2$), 3.79 (s, 8, 4 OCH_2), 5.20–5.50 (m, 2, CH=CH), 6.62–7.04 (m, 3, ThH).

2,5-Bis(ethylenedioxy)-12-(3-thienyl)-(*E*)-tridec-9-ene (13b) was prepared as for **13a**: yield 42%; NMR (CCl_4) δ 1.22 (d, 3, $CHCH_3$), 1.23 (s, 3, diox CH_3), 1.62 (s, 4, $O_2CCH_2CH_2CO_2$), 2.48–3.17 (m, 1, $CHCH_3$), 3.88 (s, 8, 4 OCH_2), 5.20–5.40 (m, 2, CH=CH), 6.77–7.28 (m, 3, ThH).

2-[6-(2-Thienyl)-6-deuterio-(*E*)-hex-3-enyl]-3-methylcyclopent-2-enone (14a). A mixture of 2.75 g (7.5 mmol) of diketal **13a**, 30 mL of 0.5 N HCl, and 60 mL of ethanol was refluxed under a nitrogen atmosphere of 1.5 h, whereupon the solution was rendered alkaline with 1 g of sodium hydroxide and refluxed for another 1.5 h. After evaporation of the ethanol and extraction with pentane, chromatography yielded 1.7 g (88%) of pure product **14a**: NMR (CCl_4) δ 1.30–2.52 (m, 13, aliphatic H), 2.52–3.04 (m, 1, CHD), 5.20–5.47 (m, 2, CH=CH), 6.45–7.20 (m, 3, ThH). Anal. Calcd for $C_{16}H_{19}DOS$: C, 73.51; H, 8.10. Found: C, 73.45; H, 7.82.

2-[6-(3-Thienyl)-(*E*)-hept-3-enyl]-3-methylcyclopent-2-enone (14b) was prepared as for **14a**: yield 80%; NMR (CCl_4) δ 1.18 (d, 3, $CHCH_3$), 1.67–2.52 (m, 13, aliphatic H), 2.52–3.00 (m, 1, $CHCH_3$), 5.12–5.37 (m, 2, CH=CH), 6.72–7.17 (m, 3, ThH). Anal. Calcd for $C_{17}H_{22}OS$: C, 74.40; H, 8.08. Found: C, 74.25; H, 8.18.

2-[6-(2-Thienyl)-6-deuterio-(*E*)-hex-3-enyl]-3-methylcyclopent-2-enol (1a). 2-[6-(3-Thienyl)-(*E*)-hept-3-enyl]-3-methylcyclopent-2-enol (3). At −30 °C 2 mmol of $LiAlH_4$ was added in small portions to a solution of 2.0 mmol of ketone **14a** or **14b**. After 1 h 0.5 N sodium hydroxide was added. The mixture was filtered, dried, and concentrated at low temperature. Due to their susceptibility to dehydration, the cyclopentenols were used immediately for cyclization experiments.

5-Methyl-11-deuterio-12,13[*b*]-thienotricyclo[7.4.0.0^{4,8}]tridec-4-ene (2a). To a solution of 500 mg of unsaturated alcohol **1a** in 10 mL of dichloromethane at −95 °C, 1.2 equiv of $SnCl_4$ was added dropwise. After 1 h the solution was poured into saturated ammonium chloride and the product was extracted with dichloromethane. Chromatography yielded 230 mg of product (50%): NMR (CCl_4) δ 1.60 (s, 3, CH_3), 1.80–2.65 (m, 14, aliphatic H), 6.66–6.95 (AB, 2, ThH). Anal. Calcd for $C_{16}H_{19}DS$: C, 78.31; H, 8.62. Found: C, 78.47; H, 8.67.

The cyclization of **3** was analogous to **1a**: yield 50%; NMR (CCl_4) δ 1.00–3.00 (m, 14, aliphatic H), 1.22 (d, 3, $CHCH_3$), 1.60 (s, 3, C=CH_3), 6.60–6.90 (AB, 2, ThH), 6.70 (s, 2, ThH). Anal. Calcd. for $C_{17}H_{22}S$: C, 79.07; H, 8.53. Found: C, 79.42; H, 8.85.

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Registry No.—**1a**, 65121-21-3; **2a** α-isomer, 65121-22-4; **2a** β-isomer, 65166-18-9; **3**, 65121-23-5; **6a**, 42006-95-1; **6b**, 14861-60-0; **7a**, 42007-08-9; **7b**, 1468-83-3; **8a**, 65121-24-6; (*E*)-**8b**, 65121-25-7; (*Z*)-**8b**, 65121-26-8; **9a**, 65121-27-9; **9b**, 65121-28-0; **10a**, 65121-29-1; **10b**, 65121-30-4; **11a**, 65121-31-5; **11b**, 65121-32-6; **12**, 33548-59-3; **13**, 65121-33-7; **13b**, 65121-34-8; **14a**, 65121-35-9; **14b**, 65121-36-0; 2-thiophenecarboxylic acid methyl ester, 5380-42-7; 3-bromothiophene, 872-31-1; acetaldehyde, 75-07-0; triethyl phosphonoacetate, 867-13-0.

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Methylation of Pyrimidines, the Corresponding Nucleosides, and Inosine with Trimethyloxosulfonium Hydroxide

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The methylation of nucleic acid components is being actively pursued. The most interesting aspects of the problem have arisen from the discovery of various kinds of methylated ribonucleosides from RNA,[1-3] and from studies of the interaction of alkylating agents with nucleic acids and their components.[4-6]

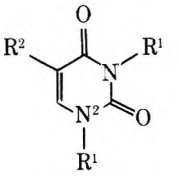
We wish to describe the methylation of pyrimidines (**1, 2,** and **5**), the corresponding nucleosides (**7, 10,** and **16**), and inosine (**13**), using trimethyloxosulfonium hydroxide (MOSH) as a new alkylating agent. Although the preparation of MOSH was reported about two decades ago,[7] its chemistry has been little studied. We prepared MOSH in methanol by a modified procedure, finding that this reagent is potentially very useful for methylation of a wide variety of compounds.

Results and Discussion

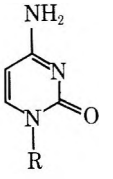
The general procedure consists of heating pyrimidines or nucleosides with MOSH at 40–140 °C in dimethylformamide (DMF). The reaction was followed by thin-layer chromatography and the products were isolated through a very simple workup of the reaction mixture. The results are summarized in Table I.

This method converted uracil (**1**), thymine (**2**), and cytosine (**5**) to the corresponding *N*-methylated derivatives in excellent yields.

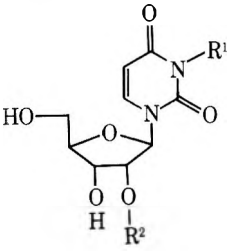
Similarly, uridine (**7**), thymidine (**10**), and inosine (**13**)



1, $R^1 = R^2 = H$
2, $R^1 = H$; $R^2 = Me$
3, $R^1 = Me$; $R^2 = H$
4, $R^1 = R^2 = Me$



5, R = H
6, R = Me



7, $R^1 = R^2 = H$
8, $R^1 = Me$; $R^2 = H$
9, $R^1 = R^2 = Me$

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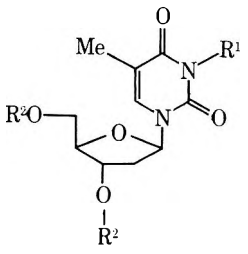
Table I. Methylation of Pyrimidines, the Corresponding Nucleosides, and Inosine with MOSH

Compound	Registry no.	Mole ratio,[a] MOSH/compd	React. temp, °C	React. time, h	Product[b]	Registry no.	Yield,[c] %	λ_{max} (log ϵ)[d] (pH 7)	R_f'/R_f[e]
Uracil (1)	66-22-8	4 (DMF)	80	2	1,3-Me_2-Ura (3)	874-14-6	96 (31)	267.0 (3.92)	3.4
Thymine (2)	65-71-4	4 (DMF)	80	2	1,3-Me_2-Thy (4)	4401-71-2	92 (77)	272.0 (3.97)	4.5
Cytosine (5)	71-30-7	4 (DMF)	80	2	1-Me-Cyt (6)	1122-47-0	87 (80)	275.0 (4.02)	2.1
Uridine (7)	58-96-8	1.4 (DMF)	60	3	3-Me-Urd (8)	2140-69-4	78 (60)	262.0 (3.95)	2.0
					3,$O^{2'}$-Me_2-Urd (9)[f]	7103-27-7	12	262.0 (3.95)	3.1
7		3 (Me_2SO)	60	3	8		83		
					9		5		
7		4 (MeOH)	64	5	8		56		
					9		4		
Thymidine (10)	50-89-5	1.4 (DMF)	60	4	3-Me-dThd (11)	958-74-7	90 (75)	269.5 (3.96)	1.6
					3,$O^{3'}$,$O^{5'}$-Me_3-dThd (12)	65150-68-7	2	270.0 (3.88)	2.6
Inosine (13)	58-63-9	1.4 (DMF)	60	7	1-Me-Ino (14)	2140-73-0	67 (50)	249.5 (4.00)	1.3
					1,$O^{2'}$-Me_2-Ino (15)[f]	65150-69-8	5	250.0 (4.01)	1.7
Cytidine (16)	65-46-3	3 (DMF)	100	5	$O^{2'}$-Me-Cyd (17)[f]	2140-72-9	53 (43)	270.0 (3.96)	1.9
16		2 (DMF)	60	8	17		40 (31)		

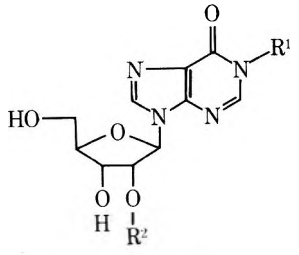
[a] Solvents used are shown in parentheses: DMF, dimethylformamide; Me_2SO, dimethyl sulfoxide. [b] Ura, Thy, Cyt, Urd, dThd, Ino, and Cyd refer to uracil, thymine, cytosine, uridine, thymidine, inosine, and cytidine, respectively. [c] Yields were calculated by spectroscopic method. Yields in parentheses were obtained based on isolated amounts of purified products. [d] UV spectra in acidic (pH 1) and basic (pH 13) conditions were identical with those reported in the literature. [e] R_f and R_f' refer to mobilities of starting materials and products, respectively: aluminum oxide TLC, solvent B for the reaction mixtures of 1 and 2; silica gel TLC, solvent A for the reaction mixtures of 7 and 10; solvent C for the reaction mixtures of 5, 13, and 16. [f] A trace of the $O^{3'}$-methyl isomer was present in the reaction mixture.

underwent smooth methylation with MOSH to produce the corresponding *N*-methylated nucleosides (**8**, **11**, and **14**) in good yields and the *O'*-methylated nucleosides (**9**, **12**, and **15**) in small amounts. Here, the use of high reaction temperature and a large excess of MOSH gave numerous products which might have arisen from random methylation of nitrogen atoms and carbohydrate hydroxyls. In general, however, *N*-methylated nucleosides were formed exclusively when the reactions were conducted at 40–60 °C, using about 40% excess of MOSH.

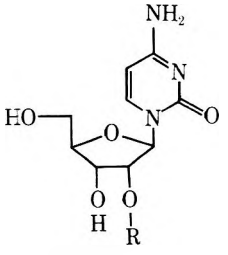
In cytidine (**16**), on the other hand, methylation did not take place on the pyrimidine ring, but MOSH methylated selectively the 2′ OH group, furnishing $O^{2'}$-methylcytidine (**17**) in fairly good yield. Failure of MOSH to methylate the 3 position of **16** is also shown by the absence of 1,3-dimethylcytosine in the reaction of **5** with excess reagent.



10, $R^1 = R^2 = H$
11, $R^1 = Me$; $R^2 = H$
12, $R^1 = R^2 = Me$

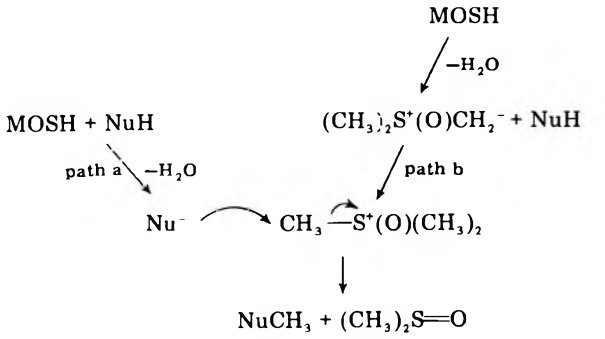


13, $R^1 = R^2 = H$
14, $R^1 = Me$; $R^2 = H$
15, $R^1 = R^2 = Me$



16, R = H
17, R = Me

Scheme I



There was no evidence of methylation of the carbonyl group oxygen or the external amino groups of the pyrimidines and nucleosides examined.

The above results are comparable with or superior to methylations by other alkylating agents such as dimethyl sulfate,[8] methyl iodide,[9] diazomethane,[10] etc.[11,12] The present method is unique in the highly selective formation of **17** from **16**; by contrast, all other methods have been reported to convert **16** inefficiently to a mixture of **17**, $O^{3'}$-methyl-, and $O^{5'}$-methylcytidines, and di- and tri-*O'*-methylated cytidines.[13–16]

Me_2SO as a reaction medium gave results similar to those observed in DMF. Less polar solvents such as acetone and dioxane were unsuitable because of solubility problems. Employment of protic solvents such as methanol and ethanol decreased the yields.

Although kinetics were not examined, methylation occurs most likely in a bimolecular fashion between trimethyloxosulfonium ion and anionized forms (Nu^-) of pyrimidines or nucleosides (NuH) (path a of Scheme I). Involvement of an ylide, $[(CH_3)_2S^+(O)CH_2^-]$, as an alkylating agent[17] (path b) is not likely since its formation would require the action of a very strong base such as sodium hydride on $(CH_3)_3S^+{=}O$ in an anhydrous environment, a condition which would not be realized because methylation would result in formation of water in amounts equal to the concentration of NuH.

Experimental Section

Melting points were uncorrected. Thin-layer chromatography was performed on silica gel [GF_{254} (Type 60), Merck] or aluminum oxide [GF_{254} (Type 150), Merck], using a mixture of chloroform and methanol in the following volume ratios: solvent A, 17:3; B, 5:1; C, 5:2. Column chromatography was carried out using silica gel [Merck (art. 7734), 70–230 mesh].

Commercially available uracil (**1**), thymine (**2**), cytosine (**5**), uridine (**7**), thymidine (**10**), inosine (**13**), and cytidine (**16**) were used without further purification.

Preparation of Trimethyloxosulfonium Hydroxide (MOSH). Trimethyloxosulfonium iodide[7] (5.0 g, 22.7 mmol) was dissolved in a hot mixture of methanol and water (500 mL–1 mL). Excess silver oxide (5.3 g, 23.0 mmol) was added to the solution and the mixture was stirred at room temperature. After 1 h, a few drops of the supernatant was removed, acidified with dilute nitric acid, and tested for iodide with a silver nitrate solution. The checking was repeated until the reaction was complete. The reaction mixture was filtered, concentrated to 100 mL, and used for the subsequent methylation reactions. The concentration of MOSH was determined by titration with 0.1 N hydrochloric acid to be 0.216 N; the yield was calculated as 95%. MOSH was stable in methanol for several months upon storage in a refrigerator.

The neat sample of MOSH gave the following spectral data: IR (KBr) 3350 (s), 2950 (m), 1645 (bm), 1480 (m), 1210 (s), 1105 (s), 1047 (s), and 950 (m) cm^{-1}; NMR (Me_2SO-d_6) τ 2.98 (s, CH_3); mass spectrum (75 eV) *m/e* 92 ($M - H_2O$), 78 ($92 - CH_2$), 77 ($92 - CH_3$) and 63 ($CH_3S{=}O$).

Reaction of the methanol solution of MOSH with equivalent amounts of hydrochloric acid or hydroiodic acid gave trimethyloxosulfonium chloride or iodide, respectively, in quantitative yields.

Methylation Reactions. The following are isolation procedures. The mobilities (R_f) of products in thin-layer chromatography are shown in Table I with references on the UV spectral peak at pH 7. UV spectra at pH 1 and 13 as well as the melting points of all known compounds agreed in most cases with literature values. The NMR spectra were obtained in all compounds and coincided with the assigned structures. Yields are calculated after recrystallization and are based on the isolated amounts of products. Spectroscopic yields of products in reaction mixtures were determined in a manner similar to that employed in our previous study.[18]

Products (**9**, **12**, and **15**) were identified by a comparison of R_f values and UV spectra of the aqueous extracts of the corresponding spots in thin-layer chromatography of reaction mixtures with those of authentic samples.[19]

Reaction conditions and results are summarized in Table I.

A. Pyrimidines (1, 2, and 5). These heterocycles (5.0 mmol) were dissolved in the methanol solution of MOSH prepared as above (20.0 mmol). The solvent was removed under reduced pressure and the residues were dissolved in DMF (30 mL) and warmed at 80 °C for 2 h. The reaction mixtures were concentrated and the resulting substances were purified by recrystallization from suitable solvents (ethanol–diethyl ether, ethanol–water, and water for **3**, **4**, and **6**, respectively).

B. Uridine (7). The nucleoside (1.22 g, 5.0 mmol) was mixed with the methanol solution of MOSH (7.0 mmol). The solvent was removed from the mixture and the residue in DMF (30 mL) was heated at 60 °C for 3 h. The reaction mixture was concentrated under reduced pressure and applied to a silica gel chromatograph (1.5 × 55 cm) using chloroform–methanol (8:1 v/v) as a solvent. The fraction (200–530 mL) gave crude 3-methyluridine (**8**), which was recrystallized from ethyl acetate–methanol: 0.78 g (60%); mp 118.5–119 °C (lit.[20] 119–120 °C).

C. Thymidine (10). The treatment of **10** (1.21 g, 5.0 mmol) with MOSH (7.0 mmol) in DMF (30 mL) at 60 °C for 4 h provided 3-methylthymidine (**11**) after processing the reaction mixture in a manner similar to that mentioned above: 0.95 g (75%); mp 130–131 °C (chloroform) (lit.[21] 128.5–132 °C).

D. Cytidine (16). Compound **16** (1.22 g, 5.0 mmol) was allowed to react with the methanol solution of MOSH (7.0 mmol) in DMF (30 mL) at 100 °C for 1 h. Thereafter, 3 mmol, 3 mmol, and 2 mmol of the reagent solution were added at hourly intervals to the reaction mixture. After the last of the MOSH solution was added, heating was continued for 2 h. The resulting solution was concentrated and applied to a silica gel column chromatograph (1.5 × 70 cm), using a mixture of chloroform and methanol (3:1 v/v) as a solvent. $O^{2'}$-Methylcytidine (**17**) was eluted in the fraction (70–110 mL): 0.54 g (43%); mp 257–258 °C (ethanol) (lit.[14] 256–257 °C).

E. Inosine (13). The nucleoside (1.34 g, 5.0 mmol) was treated with MOSH (7.0 mmol) in DMF (30 mL) at 60 °C for 7.5 h. The reaction mixture was concentrated under reduced pressure to give the residue, which was washed with diethyl ether and then extracted with hot acetone. 1-Methylinosine (**14**) was obtained as a white precipitate from the cooled extract: 0.70 g (50%); mp 207–208 °C (ethanol–methanol) (lit.[22] 209–210 °C).

Registry No.—3-Methylcytidine, 2140-64-9; trimethyloxosulfonium hydroxide, 65150-70-1; trimethyloxosulfonium iodide, 1774-47-6.

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(*Z*)-2-Ethoxyvinyllithium: A Remarkably Stable and Synthetically Useful 1,2-Counterpolarized Species[1]

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(*Z*)-2-Ethoxyvinyllithium ((*Z*)-**1**) can easily be prepared by halogen/metal exchange between (*Z*)-2-ethoxyvinyl bromide and butyllithium in diethyl ether at −80 °C.[2] Addition of an aldehyde or a ketone followed by hydrolysis leads to the formation of (*Z*)-3-hydroxy enethers (**2**) which may be alkylated to afford alkenyl diethers (**3**) or to be converted, by acid treatment, into α,β-unsaturated aldehydes (**4**). Examples are listed in Table I.

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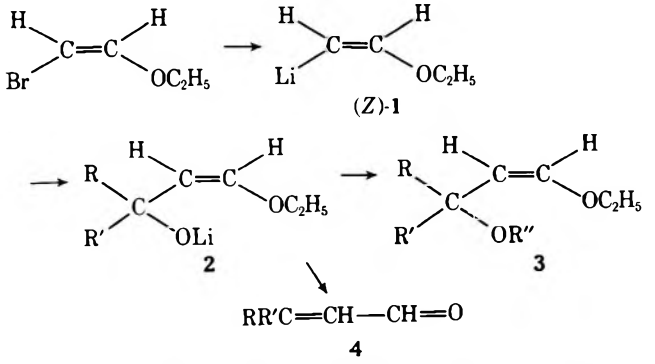
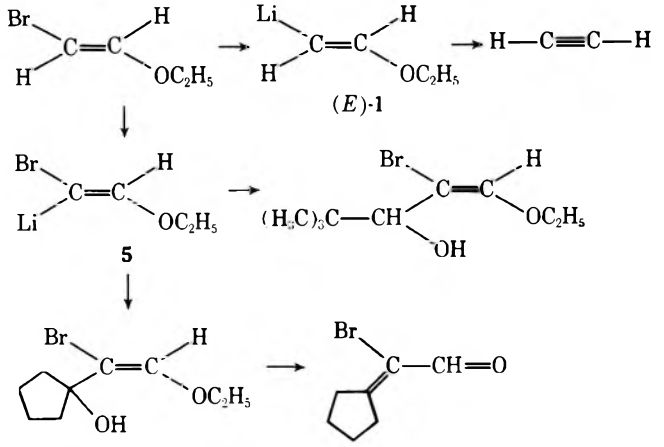
Table I. Products Derived from (*Z*)-2-Ethoxyvinyllithium[g] and Carbonyl Compounds RR'C=O

	Formula	Registry no.	Yield[a,b]
2,[c]	R = C_6H_5; R' = H	65275-94-7	84%
3,	R = C_6H_5; R' = H; R'' = CH_3	65275-93-6	63%[d]
3,	R = C_6H_5; R' = H; R'' = $CH_2C_6H_5$	65392-07-6	54%[d]
4,	R = C_6H_5; R' = H	14371-10-9	46% (62%)[e]
4,	R = $C(CH_3)_3$; R' = H	926-37-4	60% (70%)
4,	R = $C(CH_3)_3$; R' = CH_3	65275-95-8	25% (30%)[f]
4,	R, R' = $-(CH_2)_4-$	5623-82-5	44% (50%)

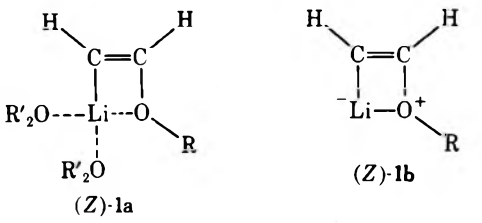
[a] Yield of pure, distilled product; values in parentheses are yields as determined by GC techniques. [b] All (*Z*)-3-hydroxy enethers (**2**) are fairly unstable, the favorite decomposition mode being the loss of water. [c] After hydrolysis, i.e., OH instead of OLi. [d] With respect to **2**. [e] The product (cinnamaldehyde) was compared with an authentic sample by GC on two different columns; it had exclusively the *E* configuration. [f] The product, apparently being homogeneous (see Experimental Section), is supposed to possess the thermodynamically favored *E* configuration. [g] Registry no.: 64724-28-3.



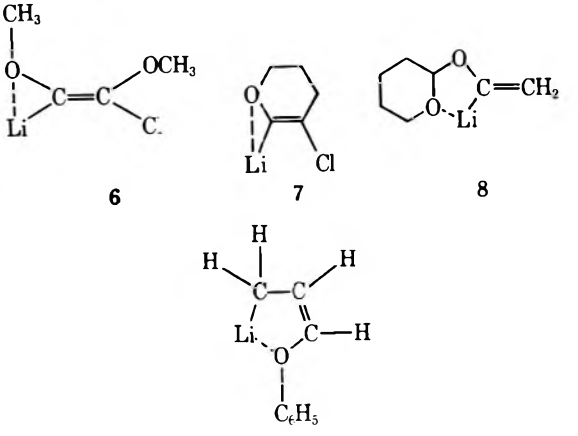
On the contrary, (*E*)-2-ethoxyvinyl bromide undergoes hydrogen/lithium rather than bromine/lithium exchange when treated with butyllithium. The resulting (*E*)-1-bromo-2-ethoxyvinyllithium[4] (**5**) was trapped by addition



onto pivalaldehyde (yielding 58% (*E*)-1-ethoxy-2-bromo-4,4-dimethyl-1-penten-3-ol) and cyclopentanone (yielding 30% cyclopentylidene-α-bromoacetaldehyde, mp 91–92 °C, after acid hydrolysis). Upon interaction of lithium dihydrobiphenylylide ("biphenyl/lithium 1:1 adduct"), (*E*)-2-ethoxyvinyl bromide does produce (*E*)-2-ethoxyvinyllithium ((*E*)-1) which cannot, however, be intercepted. At −80 °C it instantaneously decomposes to afford lithium ethoxide and acetylene, the latter being identified by its conversion to 2,2,7,7-tetramethyl-4-octyne-3,6-diol (22%, after consecutive addition of 2 equiv of butyllithium and pivalaldehyde). (*Z*)-1 is stable in diethyl ether up to −50 °C or even to −30 °C in the presence of tetrahydrofuran and 1,2-dimethoxyethane. This exceptional stability may be contrasted with the lability of (*E*)-1 or that of 2-methoxyethyllithium (trapped in only 5.3% yield at −130 °C[5]) and can be attributed to the interplay of two factors: the lack of a favorable trans-(anti-) elimination mode[6,7] and an optimum geometry for intramolecular solvation. The latter effect may be depicted in terms of an oxygen–lithium partial bond[3] ((*Z*)-**1a**, externally solvated by two ether molecules) or an ate complex[8] ((*Z*)-**1b**).



Intramolecular solvation of lithium by an oxygen atom is well established, the hetero element being either directly attached to the metal-bearing carbon atom or situated in the next position but one. 1-Ethoxyvinyllithium,[9,10] (*E*)-2-chloro-1,2-dimethoxyvinyllithium (**6**),[11] 1,2-dimethoxyvinyllithium (configuration undefined)[12] or 3-chloro-2-lithio-5,6-dihydro-4*H*-pyran (**7**),[13] and 1-(2-tetrahydropyranyloxy)vinyllithium (**8**)[14] or (*Z*)-3-phenoxyallyllithium (**9**)[15] represent typical examples for each pattern of interaction.



As the formation of α,β-unsaturated aldehydes demonstrates, (*Z*)-1 is equivalent to the acetaldehyde anion. Other substitutes for this unaccessible species are α-metalated ethylideneamines[13,17] or bromomagnesium ethoxyacetylide[18] (when allowed to perform a carbon–carbon linking step followed by a Lindlar hydrogenation). Because of the ease of its preparation and the mild reaction conditions (*Z*)-1 compares favorably with those reagents.

Experimental Section

For general remarks, see ref 15 and 19.

1-Bromo-2-ethoxyethylene. The isomeric mixture was prepared according to a modified literature procedure.[20] Bromine (160 g, 1.00 mol) was added dropwise to ethyl vinyl ether (72 g, 1.00 mol) in dichloromethane (100 mL) at −78 °C. The slightly yellow solution was slowly added to tributylamine (200 g, 1.08 mol) kept at 100 °C and under 75 mmHg over a period of 4 h. A distillate was continuously collected in a cold trap. Distillation of this liquid through a Vigreux column (30 cm) afforded two fractions: 59 g, bp 56–61 °C (46 mmHg), *Z*:*E* = 64:36 and 66.8 g, bp 62–64 °C (46 mmHg), *Z*:*E* = 95:5, total yield 84%; GC (3 m, 15% UCC-W, glass column, 70 °C) permitted clean separation of the isomers; NMR (CCl_4) of the *Z* isomer, δ 6.65 (d, *J* = 4 Hz, 1 H), 5.10 (d, *J* = 4 Hz, 1 H), 4.02 (q, *J* = 7.5 Hz, 2 H), 1.36 (t, *J* = 7.5 Hz, 3 H); NMR (CCl_4) of the *E* isomer, δ 6.78 (d, *J* = 12 Hz, 1 H), 5.38 (d, *J* = 12 Hz, 1 H), 3.82 (q, *J* = Hz, 2 H), 1.31 (t, *J* = 7 Hz, 3 H).

(Z)-3-Ethoxy-1-phenyl-2-propen-1-ol and Its Derivatives. (Z)-1-Bromo-2-ethoxyethylene (3.57 g, 23.7 mmol) was dissolved in diethyl ether (10 mL) and treated at −80 °C under nitrogen with a 1.56 N hexane solution (16.7 mL) of butyllithium (26.1 mmol). The mixture was kept 24 h at −80 °C before benzaldehyde (1.55 g, 14.6 mmol) was added. At 25 °C it was hydrolyzed with water (20 mL). The aqueous phase was extracted with diethyl ether (2 × 10 mL); the combined organic fractions were washed with water (2 × 10 mL), dried ($MgSO_4$), and concentrated. Careful bulb-to-bulb (Kugelrohr) distillation gave 3.55 g (84%) of colorless (Z)-3-ethoxy-1-phenyl-2-propen-1-ol, bp 120–125 °C (0.5 mmHg); IR (film) 3380 (br), 1665 (s) cm^{-1}; NMR (CCl_4) δ 7.5 (m, 5 H), 6.00 (d × d, J = 6, 1.5 Hz, 1 H), 5.68 (d × d, J = 8.5, 1.5 Hz, 1 H), 4.64 (d × d, J = 8.5, 6 Hz, 1 H), 3.80 (q, J = 7 Hz, 2 H), 1.23 (t, J = 7 Hz, 3 H); mass spectrum *m/e* 132 (100%, $M^+ - H_2O, C_2H_4$).

The alcohol (3.38 g, 19.0 mmol) was added to a vigorously stirred suspension of sodium hydride sand (0.52 g, 21.7 mmol) in 20 mL of diethyl ether. After 3 h the reaction mixture was treated with methyl iodide (12 g, 85 mmol), first at 25 °C and then 2 h at reflux temperature. After filtration the liquid was concentrated and distilled to afford 2.31 g (63%) of (Z)-1-ethoxy-3-methoxy-3-phenylpropene: bp 58.0–58.5 °C (0.5 mmHg); IR (film) 3120–2810 (m), 1660 (s) cm^{-1}; NMR (CCl_4) δ 7.4 (m, 5 H), 6.12 (d × d, J = 6.5, 1.5 Hz, 1 H), 5.21 (d × d, J = 9.5, 1.5 Hz, 1 H), 4.50 (d × d, J = 9.5, 6.5 Hz, 1 H), 3.31 (s, 3 H), 3.85 (q, J = 7 Hz, 2 H), 1.25 (t, J = 7 Hz, 3 H); mass spectrum *m/e* 192 (34%, M^+), 121 (100%).

Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 75.09; H, 8.23.

Analogously, by consecutive treatment with sodium hydride (0.33 g, 14 mmol) and benzyl bromide (2.35 g, 13.7 mmol) in tetrahydrofuran (15 mL), (Z)-3-ethoxy-1-phenyl-2-propen-1-ol was converted into (Z)-3-benzyloxy-1-ethoxy-3-phenylpropene, yield 1.89 g (54%): bp 120–125 °C (0.5 mmHg); IR (film) 3080–2860 (s), 1660 (s) cm^{-1}; NMR (CCl_4) δ 7.3 (m, 10 H), 6.08 (d × d, J = 6.5, 1.5 Hz, 1 H), 5.44 (d × d, J = 9.5, 1.5 Hz, 1 H), 4.6 (m, br, 3 H), 3.78 (q, J = 7 Hz, 2 H), 1.21 (t, J = 7 Hz, 3 H); mass spectrum *m/e* 197 (100%, $M^+ - C_4H_7O$).

In another experiment the (Z)-3-ethoxy-1-phenyl-2-propen-1-ol, without being isolated, was acidified to pH 2. After 2 h of stirring, the reaction mixture was extracted with diethyl ether (2 × 10 mL). The combined organic layers were washed with saturated aqueous sodium hydrogen carbonate solution (10 mL) and water (10 mL), dried, and concentrated. Distillation of the residual oil gave pure cinnamaldehyde. The yield, based on (Z)-1-bromo-2-ethoxyethylene, was 0.89 g (46%): bp 145–150 °C (4 mmHg).

4,4-Dimethyl-2-pentenal.[21] To a solution of *tert*-butyllithium (35.2 mmol) in tetrahydrofuran (75 mL) and hexane (25 mL), cooled to −80 °C, (Z)-1-bromo-2-ethoxyethylene (2.57 g, 17.0 mmol) and, after 30 min, pivaldehyde (2.9 g, 40 mmol) were added. After the mixture had reached room temperature, it was hydrolyzed (20 mL of 15% hydrochloric acid) and worked up by extraction (2 × 20 mL of diethyl ether) and distillation. The crude product (1.15 g, 60%; bp 138–140 °C) was further purified by GC (3 m, 15% Carbowax 20M, glass column, 90 °C): IR (film) 2900 (s), 2880 + 2830 + 2740 (m), 1700 (s), 1130 (s), 995 (m) cm^{-1}; NMR ($CDCl_3$) δ 9.53 (d, J = 7.5 Hz, 1 H) 6.83 (d, J = 16 Hz, 1 H), 6.04 (d × d, J = 16 + 7.5 Hz, 1 H), 1.13 (s, 9 H); mass spectrum *m/e* 112 (14%, M^+), 97 (100%).

Anal. Calcd for $C_7H_{12}O$: C, 74.95; H, 10.78. Found: C, 74.71; H, 10.83.

In a series of similar runs (Z)-2-ethoxyvinyllithium (prepared as usual at −80 °C) was kept 15 min at a given temperature in the range between −60 and −20 °C before being treated with pivalaldehyde. As evidenced by the yields of 4,4-dimethyl-2-pentenal, (Z)-2-ethoxyvinyllithium is stable in tetrahydrofuran solution up to −45 °C; in an ethylene glycol dimethyl ether/tetrahydrofuran mixture (1:1) it is perfectly stable up to −35 °C and fairly stable up to −30 °C.

3,4,4-Trimethyl-2-pentenal. Consecutive treatment of (Z)-1-bromo-2-ethoxyethylene (2.86 g, 18.9 mmol) in diethyl ether (10 mL) with butyllithium (20.8 mmol in 16.5 mL of hexane, 24 h at −78 °C), 2,2-dimethyl-3-butanone (pinacolone, 1.80 g, 18.0 mmol, at −78 °C) and hydrochloric acid (10%, 24 h at 25 °C) gave 3,4,4-trimethyl-2-pentenal, which was purified by preparative GC (6 m, 20% C-20-M, glass column, 130 °C): IR (film) 2960 (s), 2870 (m), 1680 (s) cm^{-1}; NMR (CCl_4) δ 10.08 (d, J = 7.5 Hz, 1 H), 5.91 (d × q, J = 7.5, 1.5 Hz, 1 H), 2.19 (d, J = 1.5 Hz, 3 H), 1.15 (s, 9 H); mass spectrum *m/e* 126 (50%, M^+), 111 (100%).

Anal. Calcd for $C_8H_{14}O$: C, 76.14; H, 11.18. Found: C, 76.05; H, 10.99.

Cyclopentylideneacetaldehyde. Using the same procedure described above and starting out with (Z)-1-bromo-2-ethoxyethylene (1.44 g, 9.5 mmol), butyllithium (10.5 mmol), and cyclopentanone (0.76 g, 9.1 mmol), 0.44 g (44%) cyclopentylideneacetaldehyde was obtained; bp 30–35 °C (0.5 mmHg); IR (film) 2960 (m), 2885 (m), 1685 (s) cm^{-1}; NMR (CCl_4) δ 9.92 (d, J = 7.5 Hz, 1 H), 6.01 (d × pentet, J = 7.5, 2.5 Hz, 1 H). 3.3–2.2 (m, 4 H), 2.2–1.3 (m, 4 H); mass spectrum *m/e* 110 (100%, M^+).

Anal. Calcd for $C_7H_{10}O$: C, 76.33; H, 9.15. Found: C, 76.46; H, 9.07.

Cyclopentylidene-α-bromoacetaldehyde. (E)-1-Bromo-2-ethoxyethylene (1.0 g, 6.6 mmol) in diethyl ether (5 mL) and butyllithium (7.4 mmol) in hexane (6 mL) were mixed at −78 °C. After 6 h at −50 °C, cyclopentanone (0.53 g, 6.3 mmol) was added. At 25 °C the reaction mixture was acidified with 10% hydrochloric acid to pH 2 and stirred for 5 h. Extraction with ether (2 × 10 mL), washing (10 mL of $NaHCO_3$ solution, 10 mL of water), drying ($MgSO_4$), and solvent evaporation yielded a viscous oil which was taken up in 20 mL of petroleum ether and stored at −5 °C. The white crystalline solid formed overnight was recrystallized from pentane: yield, 0.37 g (30%); mp 91–92 °C; IR (KBr) 2970 (m), 2880 (m), 1700 (s), 1675 (s), 1610 (s) cm^{-1}; NMR (CCl_4) δ 9.63 (s, 1 H), 2.8 (m, 4 H), 2.0 (m, 4 H); mass spectrum *m/e* 190 (95%, M^+), 109 (100%).

Anal. Calcd for C_7H_9BrO: C, 44.50; H, 4.80. Found: C, 44.10; H, 5.25.

(E)-1-Ethoxy-2-bromo-4,4-dimethyl-1-penten-3-ol.[21] At −80 °C a hexane solution (2.1 mL) of butyllithium (3.2 mmol) was added dropwise to (E)-1-bromo-2-ethoxyethylene (0.44 g, 2.9 mmol) in diethyl ether (5 mL). After 16 h at −60 °C, pivalaldehyde (0.44 g, 6.0 mmol) was added. The reaction mixture was briefly shaken with 5 N hydrochloric acid (5 mL), washed, dried, and evaporated. The residual, almost colorless oil (0.4 g) was purified by GC (3 m, 15% UCC-W, 145 °C): IR (film) 3450 (s), 2950 + 2870 (s), 1645 (s), 1190 + 1075 (s) cm^{-1}; NMR ($CDCl_3$) δ 6.49 (s, 1 H), 4.33 (s, 1 H), 3.86 (q, J = 7 Hz, 2 H), 2.47 (s, 1 H), 1.26 (t, J = 7 Hz, 3 H), 0.99 (s, 9 H).

Anal. Calcd for $C_9H_{17}BrO_2$: C, 45.58; H, 7.23. Found: C, 45.30; H, 6.41.

2,2,7,7-Tetramethyl-4-octyne-3,6-diol.[21] Upon dropwise addition of (E)-1-bromo-2-ethoxyethylene (0.21 g, 1.4 mmol) to a fresh solution of lithium dihydrobiphenylylide[22] (3 mmol) in tetrahydrofuran (15 mL) at −80 °C, the deep-blue "radical-anion" color changed to light red. The reaction mixture was consecutively treated with butyllithium (2.8 mmol) in hexane at −80 °C and pivalaldehyde (1.1 g, 15 mmol) at −30 °C and then hydrolyzed (10 mL of 1 N hydrochloric acid). According to GC (2 m, 15% Carbowax 20M, glass column, 80–200 °C; 2 m, 15% UCC-W, 130–200 °C; octanol as an "internal standard") the organic layer contained *meso*- and *dl*-2,2,7,7-tetramethyl-4-octyne-3,6-diol (22% yield), identified by comparison with an authentic sample.[23]

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Registry No.—(Z)-1-Bromo-2-ethoxyethylene, 23521-49-5; (E)-1-bromo-2-ethoxyethylene, 16339-88-1; benzaldehyde, 100-52-7; benzyl bromide, 100-39-0; pivaldehyde, 630-19-3; 2,2-dimethyl-3-butanone, 75-97-8; cyclopentanone, 120-92-3; cyclopentylidene-α-bromoacetaldehyde, 65275-96-9; (E)-1-ethoxy-2-bromo-4,4-dimethyl-1-penten-3-ol, 65275-97-0; *meso*-2,2,7,7-tetramethyl-4-octyne-3,6-diol, 54277-04-2; *dl*-2,2,7,7-tetramethyl-4-octyne-3,6-diol, 54277-05-3.

References and Notes

(1) Part 7 of the series "Selective Syntheses with Organometallics." For the preceding paper see M. Stähle, J. Hartmann, and M. Schlosser, *Helv. Chim. Acta*, **60**, 1730 (1977).

(2) Previously (Z)-1 had been only obtained as a by-product (10%) accompanying (Z)-1-bromo-2-ethoxyvinyllithium when (Z)-2-ethoxyvinyl bromide was treated with butyllithium in a tetrahydrofuran/hexane mixture at −100 °C (J. Ficini and J. C. Depezay, *Tetrahedron Lett.*, 937 (1968)). It is a general rule[3] that low temperatures and solvent polarity facilitate the hydrogen/metal exchange more than other reactions including halogen/metal exchange. Tetrahydrofuran, however, turned out to be a very suitable solvent if *tert*-butyllithium is applied to bring about the bromine/lithium exchange (see Experimental Section: preparation of 4,4-dimethyl-2-pentenal). According to two reports which have just appeared (R. H. Wollenberg, K. F. Albizati, and R. Peries, *J. Am. Chem. Soc.*, **99**, 7365 (1977); J. Ficini, S. Falou, A. M. Touzin, and J. d'Angelo, *Tetrahedron Lett.*, 3589 (1977)), (Z)-1 can also be obtained by metal/metal exchange between tributyl-(Z)-2-ethoxyvinyltin and butyllithium at −70 °C.

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(4) A mixture of (Z)- and (E)-1-bromo-2-ethoxyvinyllithium had previously been generated by treatment of 1,1-dibromo-2-ethoxyethylene with butyllithium (J. Ficini, personal communication; see J. C. Depezay, Ph.D. thesis, Université de Paris, 1969).

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Chemistry of Alkali Metal Tetracarbonylferrates. Synthesis of Aldehydes and Reductive Dehalogenation by a Polymer-Supported Iron Carbonyl Complex

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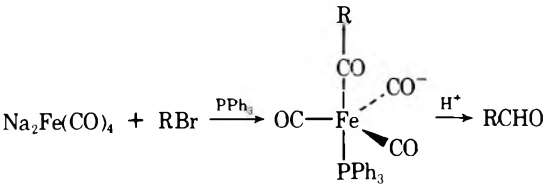
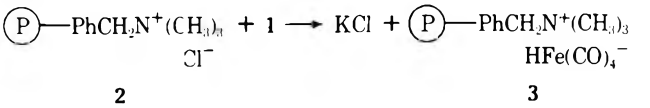
Recently several works have demonstrated that alkali metal tetracarbonylferrates ($M_2Fe(CO)_4$) and the corresponding alkali metal tetracarbonylhydridoferrates ($MHFe(CO)_4$) are useful reagents in organic synthesis.[1] The treatment of an aldehyde or a ketone containing the partial structure CH_3COR or $R'CH_2COR$ with an aldehyde in the presence of $MHFe(CO)_4$ in ethanol or water results in reductive alkylation of the carbonyl compound in high yield.[2] Moreover, $M_2Fe(CO)_4$ is able to convert alkyl halides, acid chlorides, and carboxylic anhydrides into ketones and carboxylic acid derivatives.[3] Aldehydes are also obtained in high yield from alkyl halides in the presence of added triphenylphosphine or CO.[4] We now find that similar results can be obtained supporting the reagent on a polymeric matrix by an exchange process with an ion-exchange resin (Amberlyst A-26) in the chloride form. The tetracarbonylhydridoferrate anion, prepared in alcoholic solution from iron pentacarbonyl and potassium hydroxide as described elsewhere,[5] rapidly and quantitatively exchanges, under an inert atmosphere, with the chloride ion simply on stirring the resin **2** a few minutes with the solution of hydride **1**. The resin **3** prepared by this method, filtered off and washed



$$Fe(CO)_5 + 3KOH \longrightarrow KHFe(CO)_4 + K_2CO_3 + H_2O$$

1



2 **3**

$$RX + 3 \longrightarrow RCHO$$

as indicated in the Experimental Section, was directly utilized to convert alkyl halides to homologous aldehydes in THF solution under reflux. The choice of the solvent is critical to avoid side reactions. In fact, in benzene, isooctane, and petroleum ether the autocondensation of aldehyde was prevailing. Hexane seems to be useful, although the yield is, in this case, lower. The results of the application of this system to several alkyl halides are summarized in Table I. The yields of the aldehydes are very high and the ease and simplicity of the method seem to provide an improvement over other existing procedures. We have to note, however, that alkyl chlorides fail to react while secondary alkyl halides are subjected to E2 elimination in the presence of the basic iron complex **3**.

The most remarkable advantages of our technique are the possibility of a facile drying of the reagent and the ease of separation of the reaction products, which are simply recovered by filtering off the resin while the iron complex remains bound to the polymer. As a matter of fact the separation of iron-containing byproducts from the organic compounds constitutes a hard to solve problem which limits the usefulness of the usual procedure in solution.[4] Moreover, with our resin **3** there is no need for added ligand to perform the reaction as is necessary with Cooke's procedure.[4]

A possible explanation of this remarkable difference is that on the resin the migratory insertion required is induced by the halogen anion formed. It has been indeed demonstrated that the nucleophilicity of halogen ions is strongly enhanced if they are bonded on the resin.[6]

Table I. Reaction of the Polymer-Supported $FeH(CO)_4^-$ Anion with Alkyl Halides

Alkyl halide	Registry no.	Product[a]	Registry no.	Solvent[b,c]	Yield, %[d]
n-$C_7H_{15}Br$	629-04-9	n-$C_7H_{15}CHO$	124-13-0	THF	90
n-$C_8H_{17}Br$	111-83-1	n-$C_8H_{17}CHO$	124-19-6	THF	90
n-$C_8H_{17}Br$		n-$C_8H_{17}CHO$		Hexane[e]	60
n-$C_8H_{17}I$	629-27-6	n-$C_8H_{17}CHO$		THF	95
$C_6H_5CH_2CH_2Br$	103-63-9	$C_6H_5CH_2CH_2CHO$[f]	104-53-0	THF	80
$EtOCO(CH_2)_3Br$	2969-81-5	$EtOCO(CH_2)_3CHO$[g]	22663-36-6	THF	85

[a] All products were identified by comparison with authentic samples and by spectroscopic data. [b] At reflux for 4 h. [c] The use of other solvents as benzene, isooctane, and petroleum ether (75–120) caused the formation of autocondensation products. [d] Yields were determined by GLC using an internal standard. [e] At reflux for 10 h. [f] Product isolated and identified as 2,4-dinitrophenylhydrazone.

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Table II. Reductive Dehalogenation by Polymer-Supported $FeH(CO)_4^-$ Anion

Alkyl halide	Registry no.	Product[b]	Registry no.	Yield,[c] %
$C_6H_5COCH_2Br$	70-11-1	$C_6H_5COCH_3$	98-86-2	90
	822-85-5		108-94-1	92
$CH_3(CH_2)_3CH(Br)COOCH_3$		$CH_3(CH_2)_4COOCH_3$	106-70-7	81
$C_6H_5CH(Br)C_6H_5$	776-74-9	$C_6H_5CH_2C_6H_5$	101-81-5	85
$C_6H_5CH(Br)CH(Br)C_6H_5$	5789-30-0	*trans*-$C_6H_5CH{=}CHC_6H_5$	103-30-0	85

[a] The reaction were performed in THF at room temperature for 5 h. [b] Products were identified by comparison with authentic samples. [c] Yields were determined by GLC internal standard method. [d] At reflux.

We have also found that the reaction of polymer-supported $HFe(CO)_4^-$ anion **3** with certain types of halides gives the dehalogenated product in good to excellent yields (Table II): α-bromo ketones, esters, and aromatic bromide functionalities are employed as substrates.[7]

The reaction is performed in THF at room temperature for 5 h and once more the product is easily recovered from the mixture by simple filtration.

We can conclude that ease of workup and greater effectiveness are the general features of the reactions described above, which were developed as part of a program carried out in our laboratory with the trend to demonstrate the usefulness of polymer-supported anions in organic synthesis.

Experimental Section

General. ^1H NMR spectra were measured in $CDCl_3$ solution by a Perkin-Elmer R1 2B instrument with tetramethylsilane as internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 7108 infrared spectrophotometer and the mass spectra (MS) were taken on a Varian Mat III (70 eV). Vapor-phase chromatography was performed on a Hewlett-Packard 5750 instrument equipped with 5% SE 30 stainless steel column (10 ft × 0.25 in.). Anhydrous diethyl ether and tetrahydrofuran (THF) were obtained by distillation from sodium wires and then from $LiAlH_4$.

Preparation of the Polymer-Supported $HFe(CO)_4^-$ Reagent. To a stirred solution of KOH (5.6 g, 100 mmol) in water–ethanol 50:50 (100 mL) pentacarbonyliron (4.5 mL, 33 mmol) was added under argon. The mixture was stirred for 2 h under reflux. To this red-brown solution 24 g of Amberlyst A-26 (chloride form ion-exchange resin, Rohm and Haas, as purchased) was added.

After stirring for 15 min the exchange was complete and the tetracarbonylhydridoferrate anion was bound on the polymer support and the liquid phase appeared colorless: we can hence assume for our resin a capacity of about 1.5 mmol/g. After rinsing with deaerated water to neutrality and then with dry methanol and dry ether, the resin was dried by blowing with argon and then was directly used for the reaction in order to avoid traces of iron complexes in the solution.

Efforts to regenerate the resin, at the moment, failed to give useful, reproducible results.

Pelargonaldehyde from *n*-Octyl Bromide (General Procedure). The polymer-supported tetracarbonylhydridoferrate anion (**3**; 33 mmol), obtained as previously described, was transferred into a reaction flask equipped with a mechanical stirrer, reflux condenser, and argon inlet. *n*-Octyl bromide (11 mmol) was added along with THF (50 mL) and the mixture was refluxed for 4 h, following the starting material conversion by GLC. As soon as the reaction was complete, the resin was filtered off and the filtrate slowly distilled under reduced pressure to remove the solvent. Bulb-to-bulb distillation of the residue affords 1.40 g of pelargonaldehyde (90%): IR (neat) 1720 (C=O); NMR ($CDCl_3$) δ 0.9 (m, CH_3), 1.2–1.9 (m, $(CH_2)_6$), 2.1–2.5 (m, CH_2CHO), 9.8 (CHO); MS *m/e* 142 (M^+).

Acetophenone from ω-Bromoacetophenone (General Procedure). The polymer-supported tetracarbonylhydridoferrate anion (**3**; 33 mmol) was added to ω-bromoacetophenone (11 mmol) in THF (50 mL). After stirring for a 4 h at room temperature, the resin was filtered off and the solvent carefully removed by distillation under reduced pressure. Bulb-to-bulb distillation of the residue affords 1.2 g of acetophenone (90%) identified by comparison with an authentic sample.

Registry No.—Iron carbonyl complex, 18716-80-8.

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m-Chloroperbenzoic Acid Oxidation of 2-Trimethylsilyloxy-1,3-dienes. Synthesis of α-Hydroxy and α-Acetoxy Enones

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Synthetic methods for the introduction of oxygen functionality to the α-carbon of enone systems have relied almost exclusively upon treatment of the appropriate enone with lead(IV) acetate (LTA).[1] However, erratic yields as well as high reaction temperatures mitigate against the general use of this procedure. Since α-oxygenated enones continue to serve as important synthetic intermediates, as evidenced by recent syntheses of acorenone-B,[2] pyroangolensolide,[3] and prostaglandin anologues,[4] improved methods for the production of these useful compounds should be welcomed.

We report an efficient and extremely mild method for the preparation of both α-hydroxy enones (**1**) and α-acetoxy enones (**2**). Treatment of 2-trimethylsilyloxy-1,3-dienes (**3**) with *m*-chloroperbenzoic acid (MCPBA), followed by hydrolysis or acetylation, affords **1** or **2**, respectively. In the former instance, the crude reaction mixture resulting from the treatment of **3** with MCPBA is separated from the *m*-chlorobenzoic acid and the solvent (hexane) removed in vacuo. Treatment of the crude residue with a a methylene chloride solution of triethylammonium fluoride,[5] followed by aqueous workup,

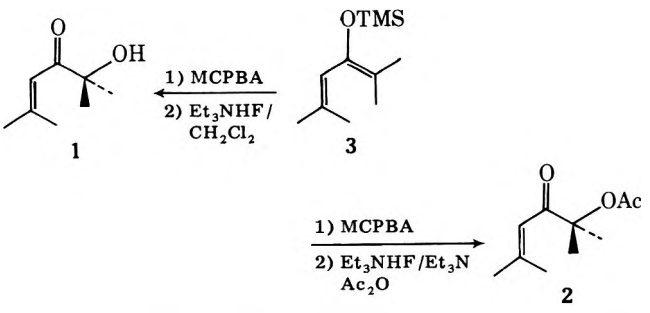

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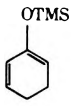
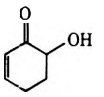
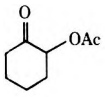
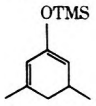
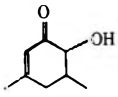
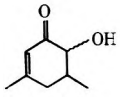
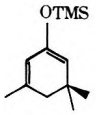
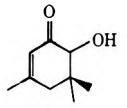
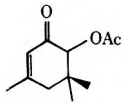
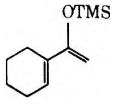
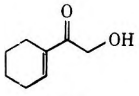
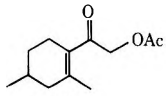
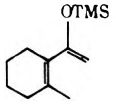
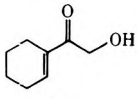
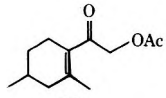
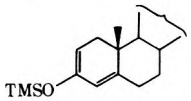
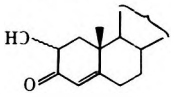
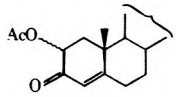
Table I. MCPBA Oxidation of 2-Trimethylsilyloxy-1,3-dienes 3

Isolated 3 from corresponding enone (% yield)	Registry no.	Isolated 1 (% yield)	Registry no.	Isolated 2 (% yield)	Registry no.
 a(80)	54781-19-0	 a(70)	65311-22-0	 a(60)	55444-14-9
 b(86)	65311-20-8	 b/b'[a](87)		 b/b'[a](80)	
 c(81)	54781-28-1	 c(82)	61592-66-3	 c(98)	19019-49-9
 d(85)	54781-35-0	 d(83)	65311-19-5	 d(74)	65311-23-1
 e(82)	65311-21-9	 e(68)	65311-18-4	 e(89)	65311-14-0
 f[b]	62017-99-60	 f(2α)/f(2β)'[a](80)[c]		 f(2β)/f'(2α) (44);[c] (29)[c]	

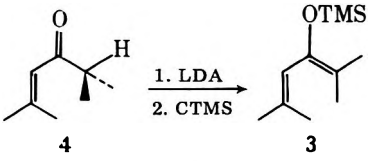
[a] Mixture of cis/trans isomers; registry no.: **1b**, 65311-16-2; **1b'**, 65311-17-3, **1f**(2α)571-15-3; **1f**(2β)', 65375-81-7; **2b**, 55519-03-4; **2b'**, 55444-10-5. [b] Not isolated; see Experimental Section. [c] Yield based on cholest-4-en-3-one; registry no.: **2f**, 65311-15-1; **2f'** 2066-08-2.

affords **1** in excellent yields (see Table I). If, on the other hand, the crude reaction mixture, free of *m*-chlorobenzoic acid and hexane, is allowed to react with a solution of triethylammonium fluoride and triethylamine in acetic anhydride, excellent yields of **2** result (see Table I).

In all examples, oxidation occurred only at the 1,2-double bond in **3**. This phenomenon is general for these systems, as evidenced by the reaction of **3** with Simmons–Smith reagent[6] and halogen.[7] It should be noted that lead(IV) benzoate, in certain cases, adds to **3** in a 1,4 manner.[8] Further, in the present work, no evidence of products arising from the oxidation of both double bonds in **3** was obtained.

Yields of **2f** and **2f'** represent a substantial increase over those reported for the LTA reaction with Δ^4-cholestenone,[9] and the mildness of the procedures outlined allows isolation of labile compounds such as **1a,b,b'**, and **2a,b,b'**, again in high yield. Although the regiospecificity of the transformation is excellent, **3b** and **3f** gave cis–trans mixtures of both the α-hydroxy enones as well as the α-acetoxy enones (see Experimental Section). With **3f**, the less stable 2β-acetoxy-Δ^4-cholestenone (**2f**) predominated (44%), while the more stable 2α-isomer **2f'** was obtained in 29% yield. The isolation of **2** represents the highest reported yield for the transformation of a steroidal enone into its 2β-acetoxy derivative.[10]

Starting materials **3** were conveniently prepared by a modification of the method used by Ainsworth for the production of alkyl trimethylsilyl ketene ketals[11] (eq 1). Kinetically controlled proton removal from **4** was effected with strong base (LDA) and the resulting carbanions were quenched with chlorotrimethylsilane (CTMS). Nonaqueous



4 **3** (1)

workup affords **3** in excellent yields (see Experimental Section).

The lability of **3f** led us to conduct the oxidation reactions on the crude diene. Yields of **1f/1f'** and **2f/2f'** indicate that isolation of **3** is not necessary in the work reported.

Although no mechanstic studies were attempted, the MCPBA reactions of **3** most likely follow a pathway previously noted for the reaction of trialkylsilyl enol ethers with MCPBA.[12]

Experimental Section

General. Melting points were determined with a Thomas-Hoover capillary melting-point apparatus and are uncorrected. Proton magnetic resonance (NMR) spectra were recorded at 60 MHz on a Varian Anaspect EM 360 spectrometer using tetramethylsilane as an internal standard. Infrared spectra (IR) were obtained on a Perkin-Elmer 621 grating infrared spectrometer. Low-resolution mass spectral data (MS) were obtained with a Perkin-Elmer RMU 6E instrument at 15 eV and are recorded as *m/e* with the relative abundance in parentheses. Elemental microanalysis were determined with a Perkin-Elmer 240 elemental analyzer. For column chromatography, silica gel Woelm, 0.032–0.063 mm (ICN Pharmaceuticals GmbH & Co.), was used. The MCPBA (tech, 85%) was purchased from Aldrich Chemical Co., Inc. The triethylammonium fluoride was obtained as a white solid (very hygroscopic) by the procedure of Hunig.[13] Anhydrous magnesium sulfate was employed as a drying agent.

Preparation of 2-Trimethylsilyloxy-1,3-dienes (3).[11] General Procedure. To a solution of 5.10 g (50.5 mmol) of diisopropylamine in 100 mL of dry DME under an atmosphere of nitrogen was added, at −15 °C (ice-methanol bath), 20.6 mL (49.5 mmol) of *n*-butyllithium (2.4 M in hexane). Then, 45.4 mmol of enone 4 was added dropwise over 5 min. After 10 min of stirring at −15 °C, 11 mL (87 mmol) of CTMS was added rapidly. After stirring for 2 h at room temperature, the solvent was removed in vacuo (rotoevaporation), followed by the addition of 75 mL of pentane. Filtration and removal of the pentane in vacuo yielded crude **3**. Reduced pressure distillation afforded pure **3**.

4,6-Dimethyl-2-trimethylsilyloxycyclohexa-1,3-diene (3b): 86%; bp 81.5–85.0 °C (9.5 mm); IR (neat) 1660, 1605 cm^{-1}; NMR (CCl_4) δ 0.18 (s, 9 H), 1.00 (d, 3 H, J = 7 Hz), 1.80 (s, 3 H), 2.00 (br d, 2 H, J = 7 Hz), 2.25 (m, 1 H), 4.40 (m, 1 H); MS *m/e* 197 (15), 196 (M^+, 88), 182 (17), 181 (100), 165 (23), 82 (14), 75 (10), 73 (21), metastables 167.5, 151.

Anal. Calcd for $C_{11}H_{20}OSi$: C, 67.28; H, 10.27. Found: C, 67.11; H, 10.56.

4,6,6-Trimethyl-2-trimethylsilyloxycyclohexa-1,3-diene (3c): 81%; bp 54–57 °C (1.5 mm); lit.[7] bp 45–47 °C (0.05 mm).

1-(α-Trimethylsilyloxyvinyl)cyclohexene (3d): 85%; bp 85–89 °C (4.8 mm) lit.[14] bp 111–115 °C (18 mm).

1-(α-Trimethylsilyloxyvinyl)-2-methylcyclohexene (3e): 82%; bp 67–70 °C (1.6 mm); IR (neat) 1620 (sh), 1610 cm^{-1}; NMR (CCl_4) δ 0.19 (s, 9 H), 1.4–2.3 (m, 11 H), 4.00 (s, 1 H), 4.23 (s, 1 H); MS *m/e* 211 (18), 210 (M^+, 100), 196 (18), 195 (84), metastable 181.5.

Anal. Calcd for $C_{12}H_{22}OSi$: C, 68.50; H, 10.54. Found: C, 68.62; H, 10.71.

2-Trimethylsilyloxcyclohexa-1,3-diene (3a). Prepared by the method outlined by Conia.[6] A detailed procedure is given in reference 8: 80%; bp 56–58 °C (6.0 mm); lit.[9a] bp 33–37 °C (0.01 mm).

The MCPBA Oxidation–Hydrolysis of 2-Trimethylsilyloxy-1,3-dienes (3). General Procedure. To a prestirred solution (20 min at room temperature) of 450 mg (2.2 mmol) of MCPBA in 30 mL of hexane at −15 °C (ice–methanol bath) was added 2.0 mmol of **3** in 1 mL of hexane. After stirring for 1 h at room temperature, the reaction mixture was filtered and the hexane removed in vacuo. The residual MCPBA precipitated and was removed by filtration with the aid of 3–5 mL of pentane. Then, 75 mL of methylene chloride and 725 mg (6.0 mmol) of triethylammonium fluoride were added. After 5–10 h at room temperature, the reaction mixture was extracted sucessively with 15 mL of aqueous sodium bicarbonate, 15 mL of 1.5 N hydrochloride acid, and 15 mL of aqueous sodium bicarbonate. Drying, filtration, and removal of solvent in vacuo afforded crude **1**. Pure **1** was obtained via the methods noted for the specific cases below.

6-Hydroxy-2-cyclohexen-1-one (1a). Molecular distillation of crude **1a** at 100 °C (20 mm) gave 158 mg (70%) of **1a**: IR (neat) 3485, 1685, 1615 cm^{-1}; NMR (CCl_4) δ 1.5–2.8 (m, 4 H), 3.66 (s, 1 H–OH), 4.04 (AB q, 1 H, J = 6, 15 Hz), 5.98 (br d, 1 H, J = 10 Hz), 6.73–7.10 (m, 1 H); MS *m/e* 112 (M^+, 28), 84 (29), 68 (10), 67 (100), metastable 63.

Anal. Calcd for $C_6H_8O_2$: C, 64.27; H, 7.19. Found: C, 64.51; H, 7.13.

***cis*/*trans*-3,5-Dimethyl-6-hydroxy-2-cyclohexen-1-one (1b/1b').** Molecular distillation of crude **1b/1b'** at 130 °C (15 mm) yielded 244 mg (87%) of a 60:40 mixture of *cis*-**1b**/*trans*-**1b** (NMR analysis): IR (neat) 3470, 1670, 1630 cm^{-1}; NMR (CCl_4) δ 0.87 (d, J = Hz, cis 3 H), 1.19 (d, J = 7 Hz, trans 3 H), 1.7–3.0 (m, 3 H), 1.99 (s, 3 H), 3.56 (br s, 1 H, –OH), 3.60 (d, J = 5 Hz, cis 1 H), 5.85 (br s, 1 H); MS *m/e* 140 (M^+, 15), 83 (10), 82 (100).

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.62, H, 8.83.

6-Hydroxy-3,5,5-trimethyl-2-cyclohexen-1-one (1c). Molecular distillation of crude **1c** at 100 °C (5 mm) gave 248 mg (82%) of **1c**: mp 43–44 °C (hexane); lit.[15] mp 45–46 °C.

1-(α-Hydroxyacetyl)cyclohexene (1d). Molecular distillation of crude **1d** at 140 °C (15 mm) yielded 231 mg (83%) of **1d**: IR (neat) 3480, 1670, 1628 cm^{-1}; NMR (CCl_4) δ 1.4–2.5 (m, 8 H), 3.2 (s, 1 H, –OH), 4.37 (s, 2 H), 6.80 (m, 1 H); MS *m/e* 140 (M^+, 12), 110 (10), 109 (100), 81 (25), metastable 60.

Anal. Calcd for $C_8H_{12}O_2$: C, 68.54; H, 8.63. Found: C, 68.64; H, 8.75.

1-(α-Hydroxyacetyl)-2-methylcyclohexene (1e). Column chromatography (silica gel; hexane/ethyl acetate, 7:1) yielded 210 mg (68%) of **1e**. An analytical sample was obtained by molecular distillation of 150 °C (15 mm): IR (neat) 3440, 1676, 1607 cm^{-1}; NMR (CCl_4) δ 1.43–1.80 (m, 4 H), 1.98 (s, 3 H), 2.0–2.4 (m, 4 H), 3.3 (br s, 1 H, –OH), 4.19 (s, 2 H); MS *m/e* 154 (M^+, 8), 124 (10), 123 (100), 111 (8), 95 (32), 67 (8), metastable 73.

Anal. Calcd for $C_9H_{14}O_2$: C, 70.10; H, 9.15. Found: C, 70.08; H, 9.39.

2α/2β-Hydroxycholest-4-en-3-one (1f/1f').[16] The general procedure cited for the synthesis of **3** was applied using 1.15 g (2.97 mmol) of cholest-4-en-3-one (mp 80.5–81.5 °C) to prepare a pentane solution of **3f** (10 mL) which was used directly in the MCPBA reaction. Crystallization from hexane yielded 950 mg (80%) of **1f/1f'**, mp 124–130 °C. Recrystallization from methanol furnished an analytical sample of the 2α/2β mixture: mp 139.0–139.5 °C; IR (KBr) 3400, 1675, 1610 cm^{-1}; NMR ($CDCl_3$) δ 0.72 (s), 0.80 (s), 0.98 (s), 1.30 (s), 4.0–4.6 (m, 8 lines, 1 H), 5.79 (s, 1 H), 3.55 (br s, 1 H, –OH); MS *m/e* 401 (31), 400 (M^+, 100), 357 (28), 356 (93).

Anal. Calcd for $C_{27}H_{44}O_2$: C, 80.69; H, 11.02.

The MCPBA Oxidation–Acetylation of 2-Trimethylsilyloxy-1,3-dienes (3). General Procedure. To a prestirred solution (20 min at room temperature) of 450 mg (2.2 mmol) of MCPBA in 30 mL of hexane at −15 °C (ice–methanol bath) was added 2.0 mmol of **3** in 1 mL of hexane. After stirring for 1 h at room temperature, the reaction mixture was diluted with 50 mL of hexane and extracted with aqueous sodium bicarbonate (2×, 20 mL). After drying, filtration, and removal of solvent in vacuo, 8 mL of acetic anhydride, 725 mg (6.0 mmol) of triethylammonium fluoride, and 1 mL of triethylamine were added. This solution was stirred for 12 h and then partitioned between 50 mL of aqueous sodium bicarbonate and 75 mL of ether. Additional solid sodium bicarbonate was added as required to complete the hydrolysis of the acetic anhydride. The ethereal solution was washed with 20 mL of water, 20 mL of 1.5 N hydrochloric acid, and 20 mL of aqueous sodium bicarbonate. The aqueous washes were extracted with an additional 30 mL of ether. The ether extracts were combined, dried, filtered, and concentrated in vacuo to afford crude **2**. Pure **2** was obtained as noted below.

6-Acetoxy-2-cyclohexen-1-one (2a). Molecular distillation of crude **2a** at 100 °C (10 mm) yielded 185 mg (60%) of **2a**: NMR (CCl_4) δ 5.20 (AB q, 1 H, J = 7, 12 Hz), lit.[1b] 5.20 (AB q, 1 H, J = 6.6, 12.0 Hz).

***cis*/*trans*-6-Acetoxy-3,5-dimethyl-2-cyclohexen-1-one (2b/2b').** Molecular distillation of crude **2b/2b'** at 150 °C (5 mm) afforded 291 mg (80%) of **2b/2b'** as a 60:40 mixture: NMR (CCl_4) δ 5.07 (2d, 1 H, J = 5, 13 Hz), lit.[17] 5.07 (2d, 1 H, J = 4.7, 12.5 Hz).

6-Acetoxy-3,5,5-trimethyl-2-cyclohexen-1-one (2c). With the acetylation reaction time extended to 48 h, removal of solvent yielded 385 mg (98%) of crystalline **2c**: mp 76.5–77.5 °C (hexene); lit.[15] mp 76–78 °C.

1-(α-Acetoxyacetyl)cyclohexene (2d). Molecular distillation of crude **2d** at 160 °C (5 mm) yielded 270 mg (74%) of **2d**: IR (neat) 1750, 1685, 1635 cm^{-1}; NMR ($CDCl_3$) δ 1.5–1.8 (m, 4 H), 2.0–2.45 (m, 4 H), 2.20 (s, 3 H), 5.03 (s, 2 H), 6.85 (m, 1 H); MS *m/e* 182 (M^+, 3), 140 (18), 109 (100), 81 (33), 43 (26).

Anal. Calcd for $C_{10}H_{14}O_3$: C, 65.91; H, 7.74. Found: C, 65.75; H, 7.93.

1-(α-Acetoxyacetyl)-2-methylcyclohexene (2e). Molecular distillation of crude **2e** at 160 °C (1 mm) afforded 347 mg (89%) of **2e**: IR (neat) 1750, 1695, 1610 cm^{-1}; NMR (CCl_4) δ 1.5–1.75 (m, 4 H), 1.84 (br s, 3 H), 2.0–2.2 (m, 4 H), 2.10 (s, 3 H), 4.62 (s, 2 H); MS *m/e* 196 (M^+, 5), 136 (7), 123 (100), 95 (26), metastable 73.5.

Anal. Calcd for $C_{11}H_{16}O_3$: C, 67.32; H, 8.22. Found: C, 67.33; H, 8.25.

2β-Acetoxycholest-4-en-3-one (2f) and 2α-Acetoxycholest-4-en-3-one (2f'). The procedure cited for the preparation of **1f/1f'** was followed. Methylene chloride was used as a solvent (enough to produce a homogeneous solution) in the acetylation procedure (48 h). Column chromatography of 24% of the crude material (silica gel; hexane/ethyl acetate, 9:1) afforded 136 mg (44%) of **2f** and 89 mg (29%) of **2f'**.

Compound 2f: mp 104.5–105.5 °C (petroleum ether); IR (KBr) 1748, 1680, 1620 cm^{-1}; NMR ($CDCl_3$) δ 0.70 (s), 0.08 (s) 1.18 (s), 2.12 (s, 3 H), 5.30 (AB q, 1 H, J = 12, 6 Hz), 5.76 (s, 1 H); MS *m/e* 442 (M^+, 16), 383 (27), 382 (87) 356 (26), 270 (13), 123 (10), 122 (100), metastable 331.

Anal. Calcd for $C_{29}H_{46}O_3$: C, 78.68; H, 10.47. Found: C, 78.85; H, 10.62.

Compound 2f': mp 137–138 °C (lit.[18] 140.5–141.5 °C); NMR ($CDCl_3$) δ 5.45 (AB q, 1 H, J = 14, 6 Hz), lit.[18] 5.44 (AB q, 1 H, J = 14, 6 Hz).

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Registry No.—**4a**, 930-68-7; **4b**, 1123-09-7; **4c**, 78-59-1; **4d**, 932-66-1; **4e**, 2047-97-4; **4f**, 601-57-0; CTMS, 75-77-4; MCPBA, 937-14-4.

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Reactions of 2-Methyl-2*H*-cyclopenta[*d*]pyridazines with Nitration Reagents, Mercuric Acetate, and Tetracyanoethene[1,2]

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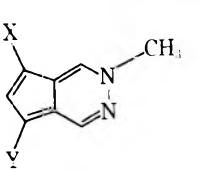
Azulene readily underwent mononitration on reaction with cupric nitrate and acetic anhydride,[5] tetranitromethane,[6] or nitric acid and acetic anhydride[6] with the last reagent also effecting dinitration. Mononitration of cyclopenta[*c*]thiapyran was accomplished with tetranitromethane.[7] Studies on the reactions of 2*H*-cyclopenta[*d*]pyridazines have shown that this system is also very reactive to electrophilic acylation,[8] halogenation,[9] and diazonium coupling,[10] so it was anticipated that direct nitration would occur with difficulty.

Treatment of 2-methyl-2*H*-cyclopenta[*d*]pyridazine (**1**) with tetranitromethane in methanol and pyridine gave extensive decomposition. Me_2SO alone gave > 90% recovery of unchanged **1**, and Me_2SO plus triethylamine gave 10% recovered **1** and 7% of a mixture. The NMR spectrum showed the major components to be the 5- and 7-nitro derivatives (**2** and **3**) in a ratio of 1:3. Attempts to separate pure **2** and **3** failed. Attempts to introduce the nitro group with a mixture of nitric, acetic, and sulfuric acids gave unchanged **1** at room temperature and complete decomposition when warmed. Reaction with cupric nitrate and acetic anhydride at −78 °C gave a very low yield of an impure mixture of **2** and **3** and longer periods formed a tar, as did treatment of **1** with nitronium tetrafluoroborate in acetonitrile.



1, X = Y = H
2, X = H; Y = NO_2
3, X = NO_2; Y = H
4, X = Br; Y = NO_2
5, X = NO_2; Y = Br
6, X = NO_2; Y = I
7, X = I; Y = NO_2
8, X = Y = HgOAc
9, X = C(CN)=C(CN)$_2$; Y = H
10, X = H; Y = C(CN)=C(CN)$_2$

The sole route to a pure nitro derivative of **1** found was the reaction of the 7-bromo compound with silver nitrite, a method which had been discovered with 1,3-dibromoazulene and 5,7-dichlorocyclopenta[c]thiapyran in earlier work.[7] In the present case a 75% yield of **3** was obtained. Attempts to achieve dinitration of **3** led to decomposition. As was found for the dibromoazulene and dichlorocyclopenta[c]thiapyran compounds, treatment of the 5,7-dibromo derivative of **1** with excess silver nitrite effected the substitution of only one bromine per molecule and a mixture of the 5-nitro-7-bromo (**4**) and 5-bromo-7-nitro (**5**) products (79%) was obtained. That the presence of the strongly electron-withdrawing group in **5** and **6** was responsible for the inertness of the second bromine[7] was reaffirmed by the fact that the 5-trifluoroacetyl-7-bromo compound[9] gave no reaction with silver nitrite in 30 h. The 5,7-diiodo derivative of **1** also gave a mixture of the 5-nitro-7-iodo (**7**) and 5-iodo-7-nitro (**6**) products. Attempts to separate **4** from **5** and **6** from **7** were not successful.

The reaction of **1** with mercuric chloride gave a product which appeared to be a complex of the expected 5,7-bis(chloromercuri) derivative[11] with mercuric chloride. Reaction with 2 equiv of mercuric acetate, however, gave a 65% yield of the 5,7-diacetoxymercuri compound (**8**). The use of excess mercuric acetate resulted in no separation of **8** from the solution, and **8** was redissolved by the reagent, again indicating complexation. An attempt to convert **8** to the 5,7-dibromo derivative by reaction with NBS gave a small amount of impure material which contained (spectral identification) the expected product.

Azulene reacts with tetracyanoethene to give the substitution product, 1-azulyltricyanoethene.[12] This mode of reaction was also found for **1** and the 7-tricyanoethenyl compound (**9**) was isolated in 41% yield. Also obtained was a small amount (4%) of product spectrally (NMR, IR, mass spectrum) characterized as the isomeric 5-tricyanoethenyl derivative (**10**). The low solubility of **9** and **10** made their separation difficult. The immediate and pronounced darkening of the color observed upon contact of **1** with tetracyanoethene was consistent with the intermediacy of a charge transfer or π complex,[13] and it is suggested that the nonsubstitution reactions of **1** with the reagents for direct nitration wherein darkening also occurred might have involved an electron transfer from **1** to the electrophilic species.

Experimental Section[14]

7-Nitro-2-methyl-2*H*-cyclopenta[*d*]pyridazine (3). A mixture of 34.5 mg (0.164 mmol) of 7-bromo-2-methyl-2*H*-cyclopenta[*d*]-pyridazine[9] and 575.7 mg (3.74 mmol) of $AgNO_2$ in 14 mL of Me_2SO was heated (steam bath) for 16 h under a N_2 atmosphere and then shaken with 50 mL of H_2O and 50 mL of CH_2Cl_2. The resultant mixture was filtered and the filtrate phases were separated. The aqueous layer was extracted with CH_2Cl_2 and the solvent was removed from the combined, washed (H_2O), dried, and filtered organic solutions. Chromatography (silica gel plate, 4:1 $HCCl_3$–ether) separated two fractions, the first of which was unchanged starting material. The second yielded 21.7 mg (75%) of **3** as yellow needles: softening and sublimation at 164–169 °C; mp 170–171 °C; NMR (acetone) δ 9.72 (s, 1, H-4), 9.18 (s, 1, H-1), 7.9 (d, 1, H-6, J = 4 Hz), 6.77 (d, 1, H-5, J = 4 Hz), and 4.60 (s, 3, N–CH_3); UV (ether) ($\epsilon \times 10^{-3}$) 243 (24), 267 (12), 272 (sh, 11), 292 (5.3), 336 (8.3), 349 (sh, 6.4), and 416 nm (11). Anal. Calcd for $C_8H_7N_3O_2$: C, 54.24; H, 3.95. Found: C, 54.07; H, 4.12.

Reaction of 1 with Tetranitromethane. A solution of 3.0 mL (1.5 mmol) of 0.5 M tetranitromethane in methanol was added (30 min) to 109.3 mg (0.829 mmol) of **1** in 3 mL of Me_2SO and 0.5 mL of tri-

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ethylamine. After 5 min the mixture was poured into 100 mL of H_2O and 100 mL of CH_2Cl_2 and the phases were separated. The aqueous layer was extracted with CH_2Cl_2 and the solvent was removed from the combined, washed (H_2O) and dried organic solutions. Chromatography (silica gel column, 50:1 CH_2Cl_2–acetone) separated a yellow-orange solid which on rechromatography (silica gel plate, CH_2Cl_2) gave two fractions. The first yielded 11.3 mg (10.3%) of unchanged **1**: mp 123–125 °C (lit.[15] 128–129 °C); UV and visible spectrum identical with those of authentic sample. The second gave 10.5 mg (7.17%) of yellow solid, mp 152–154 °C, indicated to be a 3:1 mixture of **3** and **2** by its spectra: NMR (acetone) δ 9.63 (s, 3, H-4, **3**), 9.47 (s, 1, H-4, **2**), 9.35 (s, 1, H-1, **3**), 9.08 (s, 1, H-1, **2**), 7.86 (d, 3, H-6, **3**, J = 4 Hz), 7.73 (d, 1, H-6, **2**, J = 4 Hz), 6.80 (d, 1, H-7, **2**, J = 4 Hz), 6.70 (d, 3, H-5, **2**, J = 4 Hz), 4.53 (s, 9, N–CH_3, **3**), and 4.45 ppm (s, 3, N–CH_3, **2**); UV (ether) (D_{max}) 267 (1.58), 292 (0.80), 338 (0.97), 350 (sh, 0.84) 408 (1.10). and after dilution 243 (0.77) and 267 nm (0.40).

Reaction of 5,7-Dibromo-2-methyl-2*H*-cyclopenta[*d*]pyridazine with Silver Nitrite. A mixture of 69.6 mg (0.24 mmol) of the 5,7-dibromo compound[9] and 223.5 mg (1.45 mmol) of $AgNO_2$ in 5 mL of Me_2SO was heated (steam bath) under N_2 for 48 h and then shaken with 125 mL of H_2O and 30 mL of CH_2Cl_2. The separated aqueous layer was extracted with CH_2Cl_2 and the solvent was removed from the combined, washed (H_2O), dried, and filtered organic solutions. Chromatography (silica gel column, CH_2Cl_2) of the residue separated a yellow band which yielded 48.2 mg (78.5%) of yellow solid, mp 236–238 °C dec, indicated to be a 1:1 mixture of **4** and **5** by its spectra: NMR (Me_2SO) δ, 9.85 (s, 1 H), 9.55 (s, 1 H), 9.47 (s, 1 H), 9.08 (s, 1 H), 7.93 (s, 1 H), 7.82 (s, 1 H), 4.44 (s, 3 H) and 4.40 ppm (s, 3 H); UV (ether) ($\epsilon \times 10^{-3}$) 249 (18), 274 (12), 362 (sh 4.7), and 408 nm (6.7). Anal. Calcd for $C_8H_6N_3O_2Br$: C, 37.50; H, 2.34. Found: C, 37.66; H, 2.50.

Reaction of 5,7-Diiodo-2-methyl-2*H*-cyclopenta[*d*]pyridazine with Silver Nitrite. To a solution of the 5,7-diodo compound[9] prepared from the reaction of 31.9 mg (0.27 mmol) of **1** and 241.9 mg (1.06 mmol) of NIS in 11 mL of CH_2Cl_2 was added 5 mL of Me_2SO and a large excess of $AgNO_2$. The procedure (above) for the reaction with the 5,7-dibromo compound was followed except the reaction time was 4.5 h. The yellow solid (28.1 mg, 38.6% yield from **1**), mp 214–215 °C, was indicated to be a 1:1 mixture of **6** and **7** by its spectra: NMR (trifluoroacetic acid) δ 9.54 (s, 1 H), 8.95 (s, 0.5 H), 8.85 (s, 0.5 H), 8.07 (s, 0.5 H), 7.97 (s, 0.5 H), and 4.62 ppm (s, 3 H); UV (ether) ($\epsilon \times 10^{-3}$) 250 (16), 275 (13), 365 (4), and 410 nm (6.2). Anal. Calcd for $C_8H_6N_3O_2I$: C, 31.68; H. 1.98; N, 13.85. Found: C, 31.83; H, 2.11; N, 13.70.

5,7-Di(acetoxymercuri)-2-methyl-2*H*-cyclopenta[*d*]pyridazine (8). A mixture of 190.2 mg (0.597 mmol) of mercuric acetate and 35.8 mg (0.271 mmol) of **1** in 7 mL of methanol was stored in the dark for 18 h. The dried yellow crystals which formed amounted to 112.6 mg (65%) of **8** after washing with methanol and ether: darkening above 100 °C but no melting up to 265 °C; NMR (Me_2SO) δ 9.14 (s, 1 H), 8.92 (s, 1 H), 7.27 (broad, 1 H), and 4.19 ppm (s, 3 H); UV (THF) (D_{max}) 321 (1.74), 322 (1.80), 389 (0.41), and after dilution 260 nm. Anal. Calcd for $C_{12}H_{12}N_2O_4Hg_2$: C, 22.19; H, 1.89; N, 4.31. Found: C, 22.28; H, 2.15; N, 4.41.

Reaction of 1 with Tetracyanoethene. The addition of a mixture of 296 mg (2.24 mmol) of **1** and 10 mL of benzene to 283 mg (2.21 mmol) of tetracyanoethene in 10 mL of benzene at reflux temperature caused immediate darkening of the solution. After the addition of 3 drops of pyridine and 45 min under reflux, removal of the solvent and chromatography (silica gel column, 1:1 dry ether–ethyl acetate) gave as the first fraction 213 mg (41%) of **9** as maroon crystals, mp 244–248 °C after recrystallization from ethyl acetate and 247–248 °C after two further recrystallizations from acetone: NMR (acetone, CAT) 9.56 (s, 1 H), 9.09 (s, 1H), 8.29 (d, 1 H, J = 4.5 Hz), 7.06 (d, 1 H, J = 4.5 Hz), and 4.59 (s, 3 H); UV (ether)(D_{max}) 496 (0.70), 469 (0.44), 388 (0.09), and 261 nm (0.30); IR ($HCCl_3$) 2203 cm^{-1} (CN). Anal. Calcd for $C_{13}H_7N_5$: C, 66.95; H, 3.02; N, 30.03. Found: C, 66.96; H, 3.28; N, 30.21.

The second fraction was a mixture of **9** and other compounds and, after **9** was absent (TLC), 29.3 mg of red solid was obtained which after rechromatography (ethyl acetate) gave 18.6 mg (4%) of crystals, mp 227–231 °C, partially characterized as **10**: mp 229–230 °C after recrystallization from acetone; NMR (acetone, CAT) δ 9.51 (s, 1 H), 9.37 (s, 1 H), 8.12 (d, 1 H, J = 5 Hz), 7.07 (d, 1 H, J = 5 Hz), and 4.52 (s, 3 H); UV (ether)(D_{max}) 477 (0.26) and 4.54 nm (0.18); IR ($HCCl_3$) 2197 cm^{-1} (CN); mass spectrum m/e 233.076 (calcd for $C_{13}H_7H_5$: 233.070).

Registry No.—**1**, 22291-85-6; **2**, 65275-84-5; **3**, 65275-85-6; **4**, 65275-86-7; **5**, 65275-87-8; **6**, 65275-88-9; **7**, 65275-89-0; **8**, 65275-90-3; **9**, 65275-91-4; **10**, 65275-92-5; $AgNO_2$, 7783-99-5; 7-bromo-2-methyl-2*H*-cyclopenta[*d*]pyridazine, 55268-19-4; tetranitromethane, 509-14-8; 5,7-dibromo-2-methyl-2*H*-cyclopenta[*d*]pyridazine, 55268-20-7; 5,7-diodo-2-methyl-2*H*-cyclopenta[*d*]pyridazine, 55268-23-0; mercuric acetate, 1600-27-7; tetracyanoethene, 670-54-2.

References and Notes

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(2) From the Ph D. Theses of D.M.F. and L.D.G., University of Washington.
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(4) National Science Foundation Trainee, 1965–1966; National Defense Education Art Fellow, 1966–1968; National Institutes of Health Fellow, 1968–1970.
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2-Aminomethylimidazole and Imidazole-2-carboxaldehyde: Two Facile Syntheses

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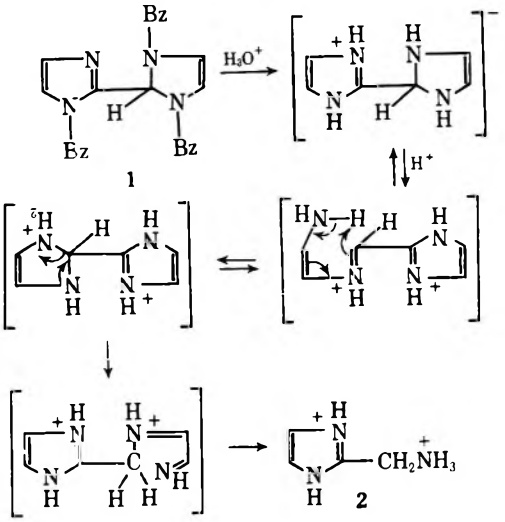
Interest in our laboratories has been directed toward elaborating methodologies for introducing functionality onto imidazoles available in bulk.[1,2] In a recent publication Regel described the reaction of imidazole with 3 equiv of benzoyl chloride; this led to compound **1**. The functionality latently



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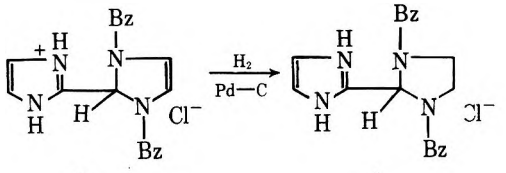
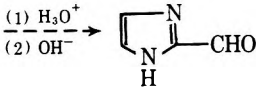
present in 1 was thought to be exploitable toward providing some key 2-substituted imidazoles, thus prompting us to examine some of its properties.

Efforts at bringing about total hydrolysis under the usual aqueous acidic or basic conditions were unrewarding or unpromising. On the other hand, refluxing 1 in methanol containing ca. 20% 2-propanolic hydrochloride readily afforded 2-aminomethylimidazole dihydrochloride (2) in 63% yield. The mechanism almost certainly involves a 1,5-hydrogen shift.

By the same token, 1 may be viewed as a derivatized aminal stemming from imidazole-2-carboxaldehyde (5). It was therefore hydrolyzed to dibenzoyl derivative 3.[3] Subsequent hydrogenation afforded 4, which, in refluxing aqueous HCl gave, besides benzoic acid and ethylenediamine dihydrochloride, aldehyde 5 cleanly and in consistently better than 85% yield.



3 4



5

Compound 5 has previously been obtained by MnO_2 oxidation of the appropriate carbinol[4] or via a multistep procedure centering on treatment of N-substituted 2-imidazolelithium reagents with dimethylformamide,[5] or by acid-promoted cyclization–deacetalization of *N*-(2,2-diethoxyethyl)-2,2-diethoxyacetamidine.[6] The amine (2) has been shown to be derivable from 5 through an oximation–reduction sequence.[7] Considering, however, both the yields and the ease of operation, the approach offered herein may well constitute the method of choice for synthesizing the title compounds.

Experimental Section

General. Melting points were measured with a Fisher-Johns apparatus and are uncorrected. The NMR spectra were recorded in a Varian EM 360A apparatus using Me_4Si as internal standard (δ 0.00). The analytical data furnished by Messrs. P. van den Bosch and H. Eding and the technical assistance of Miss Wilma Oomens are gratefully acknowledged.

2-Aminomethylimidazole Dihydrochloride (2). A solution of 3.96 g (0.02 mol) of 1[3] in 100 mL of methanol containing 20 mL of 2-propanol previously saturated with HCl gas was refluxed for 22 h. Solvents were then removed and the semicrystalline residue was triturated with acetone to give 2.16 g (63.5%) of 2, mp 240–242 °C, and spectrally identical to material reported earlier.[7] An analytical sample was prepared from methanol/isopropyl ether. Anal. Calcd for $C_4H_7N_3 \cdot 2HCl$: C, 28.25; H, 5.33; N, 24.71. Found: C, 28.15; H, 5.38; N, 24.72.

2-(1,3-Dibenzoyl-4-imidazolin-2-yl)imidazole Hydrochloride (3). This compound, previously prepared as the base by Regel[3] by aminolyzing 1, was obtained by us as follows.

Compound 1, 4.48 g (0.01 mol), in 25 mL of methanol containing 2.5 mL of 2-propanol saturated with HCl gas gave a green solution. After 18 h at room temperature the mixture had turned colorless; it was poured onto 200 mL of ethyl ether to give 3.54 g (93%) of 3, mp 240–242 °C; analytical material (methanol/isopropyl ether) gave mp 241–243 °C. Anal. Calcd for $C_{20}H_{16}N_4O_2 \cdot HCl$: C, 63.07; H, 4.56; N, 14.71. Found: C, 63.02; H, 4.60; N, 14.79.

2-(1,3-Dibenzoylimidazolidin-2-yl)imidazole Hydrochloride (4). A solution of 4.5 g (0.0118 mol) of 3 in 50 mL of methanol was hydrogenated in the presence of 0.1 g of Pd–C at room temperature and at atmospheric pressure till 1 equiv of H_2 was taken up. Catalyst and solvent were then successively removed to leave a solid residue. Recrystallization from ethanol–isopropyl ether gave 3.9 g of material: mp 215–217 °C; ^{1}NMR (CD_3OD) AA'BB' system centered around δ 4.17 (4, CH_2CH_2). Anal. Calcd for $C_{20}H_{18}N_4O_2 \cdot HCl$: C, 62.74; H, 5.00; N, 14.64. Found: C, 62.96; H, 4.98; N, 14.42.

Imidazole-2-carboxaldehyde (5). Two grams (0.0052 mol) of 4 in 30 mL of concentrated HCl was refluxed for 22 h. The resulting benzoic acid was removed on chilling and filtration; the filtrate was then evaporated. Addition of a minimum of ethanol to the residue gave 0.63 g (91%) of ethylenediamine dihydrochloride which was removed by filtration. Aqueous dilution of the filtrate, basification (NaOH), extraction with methylene dichloride, drying of the organic phase, and solvent removal left 0.44 g (88%) of 5, melting at 200–202 °C and spectrally identical to material reported earlier.[4,5]

Registry No.—1, 62457-77-6; 2, 22600-77-7; 3, 65276-00-8; 4, 65276-01-9; 5, 10111-08-7.

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Synthesis of 2-Cyanophenyl Thiocyanates and Related Disulfides by Nitro Displacement. A Novel Synthesis of 3-Chloro-1,2-benzisothiazole

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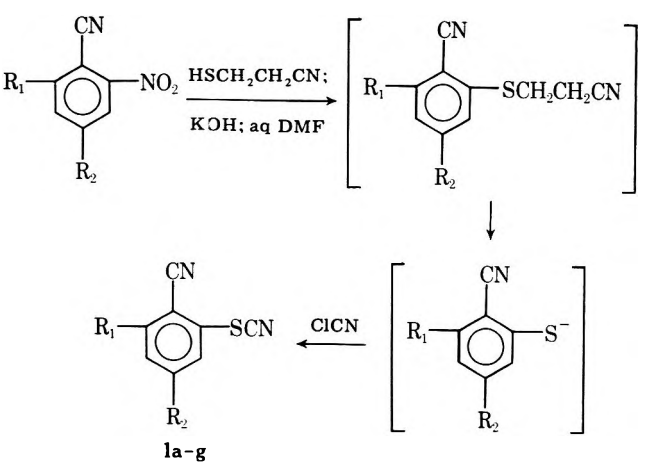
The conversion of a nitro group to a thiocyanate function ordinarily involves reduction, diazotization, and displacement with thiocyanate ion. In the case of a nitro group activated by an *o*-cyano function, a direct displacement by thiocyanate ion should be possible. However, in a previous report[1] we were unable to find conditions for this process, apparently because of the weak nucleophilicity of thiocyanate ion. We wish to report an alternate approach, which involves an initial displacement by 3-mercaptopropionitrile[2] anion to give a cyano ethyl thioether[3] (Scheme I). This intermediate is rapidly converted to the thiol anion by loss of acrylonitrile under the basic reaction conditions or, less likely, through direct displacement by hydroxide ion. Addition of cyanogen chloride then yields the thiocyanic acid ester 1.

Scheme I



1a-g

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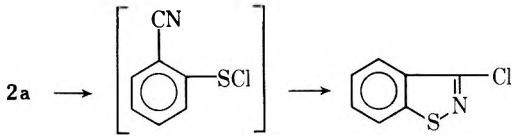
Table I. 2-Cyanophenyl Thiocyanates

Compd[a]	Registry no.	R_1	R_2	Mp, °C	Yield, %	Crystn solvent[b]
1a	34263-66-6	H	H	79–81[c]	72	A
1b	65275-70-9	Cl	H	127–128[d]	65	B
1c	65275-71-0	OMe	H	162.5–164	77	C
1d	65275-72-1	OMe	CF_3	54–55	53	C
1e	65275-73-2	NO_2	CF_3	101–102	54	C
1f	65275-74-3	NO_2	H	91–92	67	C
1g	65275-75-4	H	Cl	149–151	70	C

[a] Satisfactory analytical data (±0.3% for C, H, and N) were reported for all compounds in the table. [b] A = alcohol–water; B = benzene–hexane; C = alcohol. [c] Lit.[4] mp 83 °C. [d] Lit.[5] mp 125–126 °C.

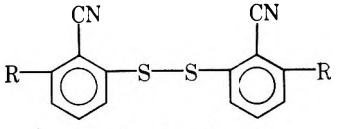
Scheme II



3

For example, *o*-nitrobenzonitrile was allowed to react with 3-mercaptopropionitrile anion in aqueous DMF for 15 min at ice bath temperature. Cyanogen chloride was added, and after an additional 30 min the reaction was quenched. The product isolated (72% yield) was shown to be 2-cyanophenyl thiocyanate (**1a**).[4] Similarly prepared were **1b–g** (Table I), and the yields were in the range of 50–75%. An attempt was made to isolate the intermediate thiophenol. The reaction mixture containing o-nitrobenzonitrile and 3-mercaptopropionitrile anion was stirred at room temperature for 1.5 h and then carefully acidified. The product isolated was not the thiophenol but rather the disulfide **2a** (61%).[6] Similar treatment of 2-chloro-6-nitrobenzonitrile yielded the disulfide **2b** (87%).

When **2a** was allowed to react with chlorine in DMF, the product obtained was 3-chloro-1,2-benzisothiazole (**3**, 36%),[7] apparently formed through the intermediacy of the sulfenyl chloride (Scheme II). Sulfenyl halides are known to undergo addition reactions with nitriles.[8] Two reported examples[9] proceeded by intramolecular cyclization, although neither involved an aromatic nitrile function.



2a, R = H
b, R = Cl

Experimental Section[10]

Materials. 6-Nitro-o-anisonitrile,[1] α,α,α-trifluoro-2,6-dinitro-*p*-tolunitrile,[11] α,α,α-trifluoro-2-methoxy-6-nitro-*p*-tolunitrile,[1] and 3-mercaptopropionitrile[2] were prepared by procedures described in the literature. All other chemicals were commercially available.

2-Cyanophenyl Thiocyanate 1a. To a cold solution (ice bath) containing 13.3 g of 2-nitrobenzonitrile (90 mmol) and 9.3 g of 3-mercaptopropionitrile (107 mmol) in 120 mL of DMF was added dropwise a solution containing 15 g of potassium hydroxide in 30 mL of water. The mixture was stirred in the cold for 15 min, and then cyanogen chloride was bubbled into the solution for 10 min. After the mixture had been stirred for a further 30 min, the mixture was poured into ice water. The solid was collected and crystallized from alcohol–water to yield 10.35 g (72%) of product, mp 78–81 °C. An analytical sample, mp 79–81 °C (lit.[4] mp 83 °C), was recrystallized. Anal. Calcd for $C_8H_4N_2S$: C, 59.98; H, 2.52; N, 17.49. Found: C, 59.69; H, 2.77; N, 17.19.

General Procedure for Preparation of Esters 1b–g. To a cold solution (ice bath) of 30 mmol of the appropriate *o*-nitrobenzonitriles and 36 mmol[12] of 3-mercaptopropionitrile in 60 mL of DMF was added dropwise a solution of 5 g of potassium hydroxide in 15 mL of water. The mixture was stirred in the cold for 15 min, and then cyanogen chloride was bubbled in for 5 min. After an additional 1 h, the mixture was poured into ice water. The crude solid was collected and crystallized from the appropriate solvent (Table I). Melting points and yields are summarized in Table I.

2,2′-Dithiobis(benzonitrile) (2a). A solution containing 10 g of potassium hydroxide in 25 mL of water was added dropwise to a cold solution (ice bath) containing 8.9 g of 2-nitrobenzonitrile (60.1 mmol) and 6.2 g of 3-mercaptopropionitrile (71.2 mmol) in 100 mL of DMF. The ice bath was removed and the mixture was stirred for 1.5 h and then carefully acidified with 30 mL of concentrated hydrochloric acid. After 5 min the mixture was poured into ice water. The solid was collected and crystallized from alcohol to yield 4.9 g (61%) of product, mp 105–106 °C (lit.[6] 103–104 °C). Anal. Calcd for $C_{14}H_8N_2S_2$: C, 62.66; H, 3.00; N, 10.44. Found: C, 62.42; H, 2.77; N, 10.38.

2,2′-Dithiobis(6-chlorobenzonitrile) (2b). To a cold solution (ice bath) of 5.5 g of 2-chloro-6-nitrobenzonitrile (30.1 mmol) and 3.1 g of 3-mercaptopropionitrile (35.6 mmol) in 60 mL of DMF was added dropwise a solution of 5 g of potassium hydroxide in 20 mL of water. The mixture was stirred in the cold for 1.5 h and then 15 mL of concentrated hydrochloric acid was added dropwise. The solution was stirred for an additional 5 min and then poured into ice water. The solid was collected and crystallized from DMF–water to yield 4.4 g (87%) of product, mp 183–185 °C. Anal. Calcd for $C_{14}H_6Cl_2N_2S_2$: C, 49.86; H, 1.79; N, 8.31. Found: C, 49.65; H, 1.50; N, 8.12.

3-Chloro-1,2-benzisothiazole (3). Chlorine was bubbled into 50 mL of DMF for several minutes. To this solution was added portionwise 5.6 g of **2a** (20.9 mmol) and the resulting mixture was stirred for 17 h. Chlorine was again bubbled in for several minutes, and the solution was stirred for an additional 4 h. The mixture was poured into ice water, which was then extracted twice with ether. The combined ether extract was washed three times with water and dried. Removal of the solvent and crystallization from alcohol–water yielded 1.5 g of product, mp 40–41 °C (lit.[7] 40 °C). Concentration of the mother liquor yielded 1.05 g of product, mp 39–40 °C. The combined yield was 2.55 g (36%). A mixture melting point with an authentic sample showed no depression. Anal. Calcd for C_7H_4ClNS: C, 49.56; H, 2.38; Cl, 20.90; N, 8.26; S, 18.90. Found: C, 49.27; H, 2.40; Cl, 21.20; N, 7.98; S, 19.20.

Acknowledgments. The authors thank Mr. Paul Unger and associates for spectral measurements and Mr. George Maciak and associates for microanalytical data.

Registry No.—**2a**, 33174-74-2; **2b**, 65275-76-5; **3**, 7716-66-7; 2-nitrobenzonitrile, 612-24-8; 6-chloro-2-nitrobenzonitrile, 6575-07-1; 6-methoxy-2-nitrobenzonitrile, 38469-85-1; 6-methoxy-4-trifluoromethyl-2-nitrobenzonitrile, 51271-38-6; 4-trifluoromethyl-2,6-dinitrobenzonitrile, 35213-02-6; 2,6-dinitrobenzonitrile, 35213-00-4; 4-chloro-2-nitrobenzonitrile, 34662-32-3; 3-mercaptopropionitrile, 1001-58-7; cyanogen chloride, 506-77-4.

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Reaction of Aryllithium Reagents with Nitriles. Synthesis of 1-Substituted 3,4-Dihydroisoquinolines[1,2]

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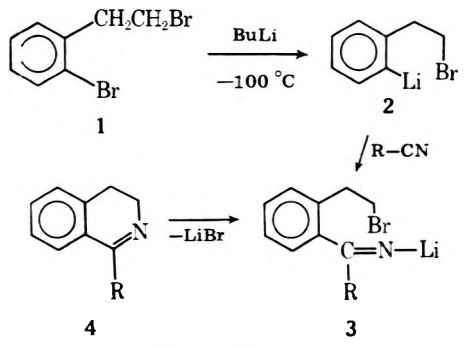
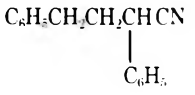
Parham and his students have shown that formation of functionalized organolithium reagents at low temperature (−100 °C), followed by reaction with either an internal or external electrophile, provides an excellent route to various cyclization products, many of which were heretofore difficult to obtain.[3]

A previously unexplored possibility was that *o*-lithiophenethyl bromide (**2**), obtained by selective lithiation of *o*-bromophenethyl bromide (**1**),[3c] might react with nitriles to



a, R = C_6H_5
b, R = *p*-$CH_3OC_6H_4$
c, R = CH_3OCH_2
d, R = cyclohexyl



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form imine salts which could undergo intramolecular alkylation, affording a new route to 3,4-dihydroisoquinolines. It seemed likely that the cyclization step would occur since it is known[4] that intermolecular alkylation of the lithio salts of imines can be accomplished.

Predictably the best success was had with aryl nitriles. Using *tert*-butyllithium as the reagent for transmetalation, yields of 63 and 43% of the 1-aryl-3,4-dehydroisoquinoline (**4a,b**) were obtained from benzonitrile and 4-methoxybenzonitrile, respectively. For nitriles having an α hydrogen the yields ranged from 18% for methoxyacetonitrile to essentially zero for phenylacetonitrile (Table I). In the latter case the anion formed was alkylated by the phenethyl bromide present in the reaction mixture to provide a 35% yield of 1,3-diphenylbutyronitrile (**5**).

1-Adamantylnitrile which has no α hydrogens and has been shown[5] to react normally with organolithium reagents likewise failed, probably because the rate of attack on the sterically hindered nitrile was slower than the competing cyclization of **2** to afford benzocyclobutene.[3c]

Table I. Reaction of β-(*o*-Lithiophenyl)ethyl Bromide (2) with Nitriles to Afford 3,4-Dihydroisoquinolines (4)

RCN	Registry no.	Yield 4, %[a]	RLi	Picrate, mp, °C
C_6H_5	100-47-0	63	*t*-C_4H_9	177–178[b]
p-$CH_3OC_6H_4$	874-90-8	43	*t*-C_4H_9	162[c]
CH_3OCH_2	1738-36-9	18	*n*-C_4H_9	206–207
Cyclohexyl	766-05-2	16	*t*-C_4H_9	167–168[d]
Adamantyl	23074-42-2	0	*t*-C_4H_9	
C_6H_5–CH_2	140-29-4	0	*n*-C_4H_9	

[a] Determined by GLC analysis. [b] Lit.[11] mp 175 °C. [c] Lit.[12] mp 155–156 °C. [d] Lit.[13] mp 169–170 °C.

The new isoquinoline synthesis would appear inferior to the classical Bischler–Napieralski[6] synthesis unless possibly one were interested in the synthesis of a 1-arylisoquinoline having acid-sensitive groups.

Experimental Section

All reactions involving organolithium reagents were carried out under an atmosphere of nitrogen. Tetrahydrofuran was distilled from lithium aluminum hydride prior to use. Reaction temperatures of −100 °C were obtained via a diethyl ether–liquid nitrogen bath. All organic residues were dried with anhydrous magnesium sulfate. NMR data were obtained from a JEOL Model JNM-MH-100 100-MHz spectrometer using 1–2% tetramethylsilane as an internal standard; IR data were obtained from either a Perkin-Elmer Model 127 or Model 297 spectrometer; and GLC analyses were performed with a Varian Model 920 gas chromatograph (thermal conductivity detector). Microanalyses were performed by MHW Laboratories, Garden City, Mich. All melting points were determined on a Mel-Temp heating block apparatus and are uncorrected.

General Procedure for Halogen–Metal Exchange. β-(o-Bromophenyl)ethyl bromide (**1**, 5.28 g, 0.02 mol, bp 67–68 °C (0.2 Torr) [lit.[7] bp 65–66 °C (0.15 Torr)]) and tetrahydrofuran (125 mL)–hexane[3c] (30 mL) were introduced, under nitrogen, into a 250-mL three-neck flask equipped with a low-temperature thermometer, pressure-equalizing addition funnel, nitrogen inlet, and mechanical stirrer. The reaction mixture was cooled to −100 °C and either *n*-butyllithium (1.0 equiv) or *tert*-butyllithium (2.0 equiv)[8] was added at such a rate that the temperature did not exceed −95 °C. Ten minutes after the addition of *n*-butyllithium was completed, a solution of the nitrile (0.02 mol) in tetrahydrofuran (25 mL) was added at a rate such that the temperature did not exceed −95 °C. After an additional 45 min at −100 °C,[9] the reaction mixture was allowed to warm to room temperature (2 h) and was poured into 250 mL of 5% hydrochloric acid. If butyllithium was used, upon reaching room temperature, the reaction mixture was then refluxed under nitrogen (1 h), at which time the mixture was allowed to cool to room temperature and was quenched in 250 mL of 5% hydrochloric acid. The neutral organics were separated from the acidic solution and the organics were then extracted with 5% hydrochloric acid. The acid wash was then combined with the original acidic aqueous solution, which was then made basic with 20% sodium hydroxide solution. The basic aqueous solution was extracted with benzene (3 × 100 mL), and after drying ($MgSO_4$) and concentration (rotary evaporation), the crude product was purified by preparative GLC.[10]

1-Phenyl-3,4-dihydroisoquinoline (4a) (63% yield) was obtained as a light yellow oil: IR (neat) 1613 cm^{-1}; NMR ($CDCl_3$) δ 2.80 (t, 2, CH_2), 3.92 (t, 2, benzylic CH_2), 7.20–7.80 (m, 9, ArH). Anal. Calcd for $C_{15}H_{13}N$: C, 86.96; H, 6.28; N, 6.76. Found: C, 86.84; H, 6.33; N, 6.52.

1-(*p*-Methoxyphenyl)-3,4-dihydroisoquinoline (4b) (43% yield) was obtained as a light yellow oil: IR (neat) 1620, 1590 cm^{-1}; NMR ($CDCl_3$) δ 2.70 (t, 2, CH_2) 3.79–3.82 (singlet overlapping triplet, 5, OCH_3, benzylic CH_2), 6.74–7.90 (m, 8, ArH). Anal. Calcd (picrate) for $C_{22}H_{18}N_4O_8$: C, 56.65; H, 3.89; N, 12.01. Found: C, 56.48; H, 3.88; N, 12.12.

1-Methoxymethyl-3,4-dihydroisoquinoline (4c) (18% yield) was obtained as a light yellow oil: IR (neat) 1600, 1070 cm^{-1}; NMR ($CDCl_3$) δ 2.68 (t, 2, CH_2), 3.40 (s, 3, OCH_3), 3.74 (t, 2, benzylic CH_2), 4.45 (s, 2, CH_2OCH_3), 7.05–7.62 (m, 4, ArH). Anal. Calcd for $C_{11}H_{13}NO$: C, 75.43; H, 7.43; N, 8.00. Found: C, 75.23; H, 7.70; N, 7.84.

1-Cyclohexyl-3,4-dihydroisoquinoline (4d) (16% yield) was

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obtained as a light yellow oil: IR (neat) 1610 cm^{-1}; NMR ($CDCl_3$) δ 0.90–2.08 (m, 10, cyclohexyl CH_2), 2.58 (t, 2, CH_2), 2.80 (m, 1, cyclohexyl CH), 3.60 (t, 2, benzylic CH_2), 6.95–7.65 (m, 4, ArH). Anal. Calcd for $C_{15}H_{19}N$: C, 84.51; H, 8.92; N, 6.57. Found: C, 84.58; H, 9.03; N, 6.36.

Reaction of (2) with Phenylacetonitrile. The general procedure was followed except that an excess (0.6 mol) of phenylacetonitrile was added to 0.2 mol of **2**. The basic fraction was negligible but the neutral fraction on vacuum distillation yielded phenylacetonitrile (88% recovery) and 1,3-diphenylbutyronitrile (**5**) (1.55 g, 35% yield based on **1**, bp 126–128 °C (0.10 Torr)): IR (neat) 2230 cm^{-1}; NMR ($CDCl_3$) δ 2.12 (m, 2, CH_2CH), 2.80 (t, 2, benzylic CH_2), 3.64 (t, 1, CH), 7.00–7.68 (m, 10, ArH). Anal. Calcd for $C_{16}H_{15}N$: C, 86.88; H, 6.79; N, 6.33. Found: C, 86.63; H, 7.00; N, 6.35.

Acknowledgment. The authors wish to thank Dr. Y. Sayed for helpful discussion and suggestions.

Registry No.—**1**, 1074-15-3; **2**, 57918-65-7; **4a**, 52250-50-7; **4b**, 59224-73-; **4b** picrate, 65071-49-0; **4c**, 65071-50-3; **4c** picrate, 65071-51-4; **4d**, 65071-52-5; **5**, 5558-42-9.

References and Notes

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(9) The low temperature was employed to make halogen–metal exchange more selective and to hold at a minimum the formation of benzocyclobutene (ref 3c).
(10) GLC analyses were carried out on a column of 20% SE-30 on 60/80 Chromosorb W [4 ft × 0.25 in., 250 °C, 30 mL/min He]. Preparative GLC appeared preferable to distillation in dealing with small volumes of product. Positive identification of the products was effected by NMR as well as by elemental analysis on either the picrate or the free base.
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Selenium in Synthesis. Conjugated Vinylic Ethers, Esters, and Halides from α-Hetero-Substituted Selenides

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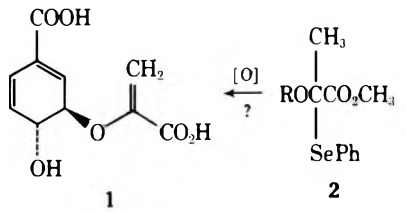
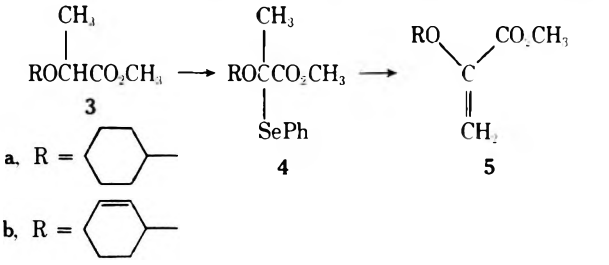
Recent work in our laboratory aimed at the total synthesis of chorismic acid **1**[1] has led us to investigate the oxidative fragmentation of α-oxygenated α-phenylseleno carboxyl derivatives **2** as an approach to the sensitive enol pyruvyl functionality in **1**.[2] Although there have been numerous reports of arylseleno carbonyl compounds serving as precursors for α,β-unsaturated ketones and esters,[3] the effect of an additional heteroatom on such selenoxide eliminations appears not to have been studied. In this note we disclose that α-alkoxy as well as α-acyloxy and α-chloro-unsaturated esters can be prepared from appropriately substituted selenides at neutral pH and below room temperature.



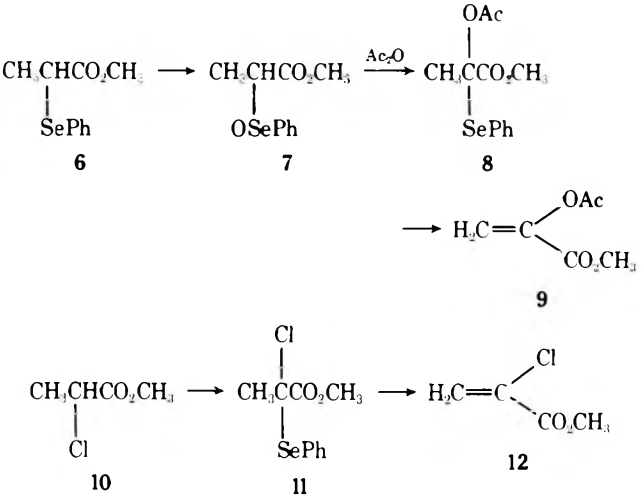
1 2

Cyclohexanol and 2-cyclohexen-1-ol were converted to α-alkoxypropionates **3a** and **3b** by the classical Williamson ether synthesis. Selenation of the corresponding ester enolates



(LDA, THF–HMPA, −70 °C) using phenylselenenyl bromide or diphenyl diselenide afforded **4a** and **4b** without complication. When solutions of these arylseleno esters in ethyl acetate were treated with 30% H_2O_2 (4–6 equiv) at 0 °C for 2 h, the enol pyruvates **5a** and **5b** were produced in 30 and 36% yields, respectively, after column chromatography.

In related experiments we had occasion to prepare two other hetero-substituted selenides. Acyloxyseleno ester **8** arose from the low-temperature Pummerer reaction of selenoxide **7**.[4]



Chloroseleno ester **11** was synthesized by metalation and selenation of methyl α-chloropropionate. Both **8** and **11** underwent smooth oxidation and rapid elimination at 0 °C to produce the known α-acetoxy and α-chloroacrylic esters **9**[5] and **12**.[6]

Unsaturated carbonyl compounds bearing α-oxygen or α-halogen substituents are relatively unstable substances. The very gentle reaction conditions we have delineated constitute a convenient access to these structures.[7,8]

Experimental Section[9]

Selenation of Methyl 2-Cyclohexyloxypropionate. Preparation of 4a and Oxidation to 5a. A solution of LDA (1.2 mmol) was prepared in THF (5 mL) from diisopropylamine (0.168 mL) and *n*-BuLi (0.83 mL of a 1.45 M solution in hexane), then cooled to −70 °C under N_2. To it was added a solution of **3a** (0.186 g, 1.0 mmol) and HMPA (0.358 g, 2 mmol) in THF (1 mL) and the reaction mixture was stirred for 1 h. Meanwhile a solution of PhSeBr was prepared from PhSeSePh (0.47 g, 1.5 mmol) and Br_2 (0.24 g, 1.5 mmol) in THF (3.5 mL). A portion of this solution (1.4 mL, ca. 1.2 mmol of PhSeBr) was added by syringe to the enolate anion at −60 to −70 °C and the dark

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mixture was stirred for 3 h at −70 °C. After warming to room temperature, 10% NH_4Cl was added and the aqueous layer extracted 3 times with ether. The combined organic layers were washed with 5% HCl, 5% $NaHCO_3$, and water, then dried over $MgSO_4$. Filtration and evaporation yielded 0.31 g of yellow oil: NMR δ 1.75 (s, 3 H), 3.56 (s, 3 H), 3.6–3.7 (m, 1 H), 7.30, 7.52 (2m, 5 H); IR λ_{max} 5.77 μm.

The crude selenoester was dissolved in ethyl acetate (6 mL) and with ice-cooling, 30% H_2O_2 (0.6 mL, 5.3 mmol) was added cautiously. After stirring for 2 h at 0 °C, the reaction mixture was diluted with water (10 mL) and extracted twice with ether. The organic extracts were washed with 10% $NaHSO_3$, 5% $NaHCO_3$, and water. Drying ($MgSO_4$), filtration, and concentration afforded 0.11 g of an oil. Column chromatography (10 g silica gel, $CHCl_3$) was used to elute the desired product **5a** (55 mg, 30%) having R_f = 0.6 in $CHCl_3$: NMR δ 5.37 (d, 1 H, J = 2 Hz), 4.58 (d, 1 H, J = 2 Hz), 3.76 (s, 3 H), 3.8–4.05 (m, 1 H); IR λ_{max} 5.80, 6.16 μm. This material was identical in every respect with an authentic sample of **5a** prepared by the anionic condensation of methyl cyclohexyloxyacetate with formaldehyde, then dehydration.

Selenation of Methyl 2-(2-Cyclohexen-1-yl)oxypropionate. Preparation of 4b and Oxidation to 5b. A solution of LDA (1.8 mmol) was prepared as usual from diisopropylamine (0.252 mL) and n-BuLi (1.125 mL of a 1.6 M solution) in THF (6.5 mL), then cooled to −70 °C under N_2. A mixture of **3b** (0.276 g, 1.5 mmol) and HMPA (0.537 g, 3 mmol) in THF (1.5 mL) was added slowly and the colorless solution was stirred for 1 h at −70 °C. Then PhSeSePh (0.562 g, 1.8 mmol) in THF (1.5 mL) was introduced and after 1 h at −70 °C followed by 3 h at −40 °C, the reaction was terminated by adding 10% NH_4Cl (10 mL). Three ether extracts were combined and washed with 5% HCl, 5% $NaHCO_3$, and water. Drying ($MgSO_4$), filtration, and concentration afforded 0.60 g of yellow oil: NMR δ 1.80 (s, 3 H), 3.55 (s, 3 H), 4.4–4.5 (broad m, 1 H), 5.75 (broad s, 2 H), 7.33, 7.55 (2 m, 5 H); IR λ_{max} 5.77 μm.

The crude product was dissolved in ethyl acetate (9 mL) and cooled to 0 °C. Thirty percent H_2O_2 (0.8 ml, 7 mmol) was added slowly, the reaction mixture stirred 2 h at 0 °C, then worked up by diluting with water (10 mL) and extracting twice, with ether. The combined ether layers were washed with cold $NaHCO_3$ and water, then dried over $MgSO_4$. Filtration and evaporation furnished 0.199 g of oil. TLC showed a UV active spot having R_f = 0.5 in $CHCl_3$. The crude product was chromatographed on a column of silica gel (10 g) using $CHCl_3$ to afford 0.099 g of clear, colorless **5b** (36%): NMR δ 5.82 (broad s, 2 H), 5.38 (d, 1 H, J = 2 Hz), 4.63 (d, 2 H, J = 2 Hz), 4.50 (broad m, 1 H), 3.77 (s, 3 H); IR λ_{max} 5.79, 6.17 μm. This substance was identical in every respect with an authentic sample of **5b** prepared by the condensation of methyl cyclohexenyloxyacetate with formaldehyde, then dehydration.

Preparation of Acetoxyselenide 8. Oxidation of 8 to 9. A solution of methyl 2-phenylselenopropionate (0.30 g, 1.24 mmol) in THF (3 mL) was cooled to −22 °C under N_2 and treated with powdered m-chloroperoxybenzoic acid (85%; 0.251 g, 1.24 mmol). After 30 min, acetic anhydride (0.152 g, 1.49 mmol) was added by microsyringe followed by pyridine (0.216 g, 2.73 mmol). The contents of the flask were stirred for 1 h at −20 °C then 2 h at 0 °C. Ether was added and the organic layer separated, washed with 5% $NaHCO_3$ and water, and finally dried ($MgSO_4$). Filtration and concentration afforded 0.40 g of an oil. This crude product was chromatographed on a column of silica gel (15 g) eluting with $CHCl_3$. Two major fractions were collected. First, 0.050 g (11%) of oil having R_f = 0.65 in $CHCl_3$ was eluted whose structure was shown to be methyl 2-(m-chlorobenzoyloxy)-2-phenylselenopropionate. Continued elution afforded 0.120 g (32%) of **8** as a colorless oil: NMR δ 1.83 (s, 3 H), 2.03 (s, 3 H), 3.59 (s, 3 H), 7.32, 7.60 (2m, 5 H); IR λ_{max} 5.78 μm (broad).

The above sample of **8** was dissolved in ethyl acetate (2.5 mL) and oxidized at 0 °C for 2 h with 30% H_2O_2 (0.3 mL). Workup as described above afforded 0.025 g of pure acetoxyacrylic ester **9** (44%): NMR δ 6.05 (d, 1 H, J = 2 Hz), 5.46 (d, 1 H, J = 2 Hz), 3.82 (s, 3 H), 2.23 (s, 3 H); IR λ_{max} 5.65, 5.78, 6.09 μm. These values are essentially identical with those reported[6] for an authentic sample of **9**.

Preparation of Chloroselenide 11. Oxidation of 11 to 12. A THF (30 mL) solution of LDA was prepared as usual from diisopropylamine (1.54 mL) and n-BuLi (6.9 mL of a 1.6 M solution) and cooled to −78 °C under N_2. To it was added a solution of methyl α-chloropropionate (1.225 g, 10 mmol) in THF (10 mL) with stirring over 1 h. Meanwhile PhSeBr was prepared from PhSeSePh (1.72 g, 5.5 mmol) and Br_2 (.88 g, 5.5 mmol) in THF (10 mL) at 0 °C. The selenating agent was then taken up in a syringe and added rapidly dropwise to the −70 °C enolate solution. After an additional hour at −70 °C the reaction mixture warmed slowly to room temperature and was poured into cold 10% NH_4Cl. Three ether extractions were performed and the combined organic layers were washed with 5% HCl, H_2O, 5% $NaHCO_3$, and saturated NaCl solution. Drying ($MgSO_4$), filtration, and concentration afforded 2.9 g of yellow oil. Using silica gel column chromatography, the major product 11 (R_f 0.6 in $CHCl_3$) was isolated (0.69 g, 69%) as a very pale yellow oil: NMR δ 2.05 (s, 3 H), 3.65 (s, 3 H), 7.35, 7.65 (2m, 5 H); IR λ_{max} 5.76 μm.

A portion of this sample (0.15 g, .54 mmol) was dissolved in ethyl acetate (3 mL) and treated with 30% H_2O_2 (0.31 mL) at 0 °C for 2 h. Workup in the standard fashion with precautions to prevent loss of the low-boiling product gave a concentrate of **12** containing some diethyl ether solvent: NMR δ 6.47 (d, 1 H, J = 2 Hz), 5.97 (d, 1 H, J = 2 Hz), 3.74 (s, 3 H), 1.97 (s, 3 H). These spectral data were identical with an authentic sample of **12** prepared according to Nield.[10]

Acknowledgment. We thank the National Institutes of Health and Eli Lilly & Company for partial support of this research.

Registry No.—**3a**, 65275-60-7; **3b**, 65275-61-8; **4a**, 65275-62-9; **4b**, 65275-63-0; **5a**, 65275-64-1; **5b**, 65275-65-2; **6**, 65275-66-3; **7**, 686-46-4; **8**, 65275-67-4; **10**, 17639-93-9; **11**, 65275-68-5; **12**, 80-63-7; PhSeBr, 34837-55-3; PhSeSePh, 1666-13-3; methyl 2-(m-chlorobenzoyloxy)-2-phenylselenopropionate, 65275-69-6.

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Nitration of *N*-Alkylphthalimides

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The nitration of *N*-methylphthalimide (**1a**) and *N*-ethylphthalimide (**1b**) has been reported to give "almost exclusively" the 4-nitro derivative, **2**.[1] However, no details of reaction conditions, actual isomer distributions, or the yields of nitrated products were presented. We recently investigated this reaction in an effort to develop a high-yield synthesis of 4-nitro-*N*-alkylphthalimides,[2] and we wish at this time to report our results.

We initially nitrated **1a**, slightly modifying the conditions described for the nitration of phthalimide,[3] to give an 85–90% yield of pure **2a**. If the reaction time was reduced from 16 to 2 h, similar results were obtained (see Table I), but a small amount of 3-nitro isomer, **3a**, was obtained. Although the re-

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Table I. The Nitration of *N*-Methylphthalimide (1, R = CH_3)

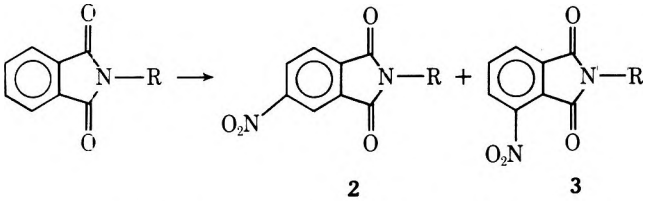
HNO_3 (equiv)[a]	H_2SO_4 (mL)[b]	Temp (°C), time (h)	% unreacted 1	% 2[c]	% 3[c]	Ratio 2/3
90 (3.5)	96 (6)	15–25, 16	0	90[i]	0	100/0
90 (3.5)	96 (6)	15–25, 5	0	92	3	97/3
90 (3.5)	96 (6)	15–25, 2	1	81	5	94/6
			0	91	0	100/0
90 (1.2)	96 (1.8)	70, 2	36	43	3	93/7[d]
90 (1.2)	96 (1.8)	90, 2	24	40	1	98/2
90 (1.5)	96 (1.8)	70, 2	18	57	4	93/7
90 (2.0)	96 (1.8)	70, 2	0	77[j]	7	92/8[e]
90 (3.0)	96 (1.8)	70, 2	0	80	5	94/6[f]
90 (1.5)	100 (1.8)	70, 2	0.5	72	7	91/9[g]
90 (2.0)	100 (1.8)	70, 1	0	82	6	93/7
90 (3.0)	100 (1.8)	70, 1	0	80	6	93/7[h]
98 (2.0)	100 (1.8)	70, 1	0	79	7	92/8

[a] The first number is the percentage of the nitric acid solution used. The second number is the molar equivalent of nitric acid used per 1 mol of **1**. [b] The first number is the percentage of the sulfuric acid solution used. The second number is the mL of sulfuric acid solution used per mL of nitric acid solution. [c] The percent yield of this compound in the isolated mixture of products. [d] Stirring 1 g of this material with 4 mL of methanol resulted in a 72% recovery of material containing 71% of **2** and 29% of **1**. [e] Extraction of the filtrate with a combination of methylene chloride and diethyl ether gave 0.58 g of material consisting of 3% phthalic anhydride, 41% 4-nitrophthalic anhydride, 4% 3-nitrophthalic anhydride, 15% of **1a**, 9% of **2a**, and 28% of **3a** by VPC analysis. [f] Ratio from ^{13}C NMR was 95/5. [g] Stirring 1 g of this material with 4 mL of methanol resulted in an 89% recovery of material containing 100% of **2a**. [h] Ratio from ^{13}C NMR was 97/3. [i] The reaction was repeated on 10× this scale (50 g of **1a**) and the crude product was treated with methanol to give an 88% yield of pure **2a**. [j] The reaction was repeated on 10X this scale (50 g of **1a**) and the crude product was treated with methanol to give an 81% yield of pure **2a**.

Table II. *N*-Alkylphthalimide Nitrations

R	HNO_3 (equiv)[a]	H_2SO_4 (mL)[b]	Temp (°C), time (h)	% unreacted 1	% 2[c]	% 3[c]	Ratio 2/3
CH_3CH_2	90 (2.0)	96 (1.8)	70, 2	3	84[i]	5	94/6
CH_3CH_2	90 (3.5)	96 (6.0)	15–25, 5	0	86[g]	0	100/0
$CH_3(CH_2)_3$	90 (2.0)	96 (1.8)	70, 2	1	76[j]	4	95/5
$CH_3(CH_2)_3$	90 (3.5)	96 (6.0)	15–25, 5	0	78[k]	5	94/6
$CH_3(CH_2)_5$[d]	90 (2.0)	96 (1.8)	70, 2	40	21	2	91/9
$CH_3(CH_2)_5$[d]	90 (3.5)	96 (6.0)	15–25, 5	14	13	0.6	96/4
$CH_3(CH_2)_7$[d,e]	90 (2.0)	96 (1.8)	70, 2	65	6	1	90/10
$CH_3(CH_2)_7$[d,e]	90 (3.5)	96 (6.0)	15–25,[f] 5	33	4	0	100/0

[a] The first number is the percentage of the nitric acid solution used. The second number is the molar equivalents of nitric acid used per 1 mol of **1**. [b] The first number is the percentage of the sulfuric acid solution used. The second number is the mL of sulfuric acid solution used per mL of nitric acid solution. [c] The percent yield of this compound in the isolated mixture of products. [d] Large amount of bubbling took place during the reaction. [e] Isolated product contained unidentified side products. [f] Extremely exothermic reaction; reaction temperature rose to 140 °C in 10 s even with ice bath cooling. [g] Mp 113–114 °C (lit.[h] 114–115 °C). [h] J. H. Billman and R. V. Cash, *J. Am. Chem. Soc.*, **75**, 2499 (1953). [i] Mp of material after MeOH treatment (63% recovery) 114–115 °C (lit.[h] 114–115 °C). [j] Mp of material after MeOH treatment (70% recovery) 94–95 °C (lit.[h] 95–96 °C). [k] Mp of material after MeOH treatment (65% recovery) 94–95 °C (lit.[h] 95–96 °C).



2 **3**

a, R = CH_3
b, R = CH_2CH_3
c, R = $(CH_2)_3CH_3$
d, R = $(CH_2)_5CH_3$
e, R = $(CH_2)_7CH_3$

action did produce a high yield of pure **2a**, we felt it suffered from several disadvantages. Foremost was the potential danger of a delayed exotherm during the nitration at these low temperatures. We wished to develop a procedure in which such an exotherm could be controlled and in which the large excess of nitric and sulfuric acid could be avoided.

Reactions were carried out in which a mixture of *N*-methylphthalimide and sulfuric acid was heated to 70 °C and, after removal of the heat, nitric acid was added at such a rate to maintain the temperature at 70–75 °C. The mixture was then stirred at the indicated temperature for the desired time and added to ice to precipitate the product. As shown in Table I, under these reaction conditions, the molar equivalents of nitric acid could be reduced from 3.5 to 2.0 and the volume of sulfuric acid could also be greatly reduced. The use of 90% nitric acid and 96% sulfuric acid was adequate for carrying out the nitrations; the only exception to this was when only 1.5 molar equivalents of nitric acid was used. In this case the use of 100% sulfuric acid gave much less unreacted starting material.

Using this procedure the nitric acid was consumed as soon as it was added and the danger of delayed exotherm was removed. However, by carrying out these reactions at elevated temperatures, we did produce small amounts of the isomer **3a**. Fortunately we found that if the isolated mixture was simply stirred with methanol, the 3-nitro isomer, **3a**, and the starting imide, **1a**, could be removed and pure **2a** could be obtained.

As shown in Table II, we also investigated the nitration of *N*-ethyl-, *N*-butyl-, *N*-hexyl-, and *N*-octylphthalimide using both sets of nitrating conditions. The *N*-ethyl system gave results very similar to the *N*-methyl system; however, as the size of the R group was further increased, the yield of nitrated products greatly decreased although the ratio of 4-nitro/3-nitro product remained relatively constant. By stirring the mixture of products obtained from the nitration of **1b** and **1c** with methanol, pure **2b** and **2c** could be obtained although the percent recovery of pure **2** was lower in each case than for the *N*-methyl system. Nitration of the *N*-hexyl and *N*-octyl system resulted in severe bubbling which was thought to arise

from oxidation of the alkyl chain by the nitric acid.[4] In the *N*-octyl system this side reaction is especially critical and when the reaction is carried out at room temperature, an extremely rapid and dangerous exothermic reaction takes place.

In summary, high yields of pure 4-nitro-*N*-methylphthalimide can be obtained from the nitration of *N*-methylphthalimide. Although the nitration of **1a** at 15–25 °C gives excellent yields of pure **2a**, we feel that it is much safer to carry out these reactions under conditions which provide for a controlled exotherm. The small amount of 3-nitro isomer which is isolated in the product under these conditions can easily be separated by methanol treatment to give pure **2a**. The nitration of *N*-ethyl- and *N*-butylphthalimide gives reaction mixtures containing primarily the corresponding 4-nitro compounds which can also be isolated by a methanol treatment although the yields of the recovered products **2** are lower than for the *N*-methyl system. The nitro group of these compounds is extremely labile to nucleophilic displacement which makes these nitro imides useful starting materials for the synthesis of a variety of new phthalimide derivatives.[5]

Experimental Section

All ^1H spectra were recorded with a Varian Associates T-60 NMR spectrometer using tetramethylsilane as an internal standard and deuteriochloroform or Me_2SO-d_6 as a solvent. All ^{13}C NMR spectra were recorded with a Varian Associates CFT-20 NMR spectrometer using complete ^1H decoupling at 79.5 MHz with simultaneous ^{13}C observation at 20.0 MHz. Chemical shifts were measured from internal tetramethylsilane or calibrated to this standard using known chemical shifts of solvent peaks. Mass spectra were determined on a CEC 21-104 analytical mass spectrometer at 70 eV. Vapor phase chromatography (VPC) was carried out on a Hewlett Packard 5750 instrument using a 6 ft 10% UC-W98 on 80/100 Chromosorb W column with temperature programming between 150 and 300 °C at 8 °C/min. Melting points were determined on a Thomas-Hoover instrument and are uncorrected.

All N-substituted phthalimides were prepared by reacting the appropriate alkylamine with either phthalic anhydride, 3-nitrophthalic anhydride, or 4-nitrophthalic anhydride in refluxing acetic acid. The structures of these imides were confirmed by ^{13}C NMR (see Supplemental Material Available paragraph), mass spectral analysis, and by a comparison of the melting points with literature values. The nitric and sulfuric acid solutions were purchased commercially and were used as received.

Analysis of the *N*-methyl system was done by both ^{13}C NMR and VPC. All other systems were analyzed only by VPC. VPC yields were obtained using an internal standard and correcting for detector response differences. Integrations were done on a Spectra Physics SP4000. The ^{13}C NMR analyses were done in Me_2SO-d_6 with the ratios of the products being determined from the average relative peak heights of the carbons for the 4 isomer at 129.4, 124.5, and 117.6 and for the 3 isomer at 136.1, 128.0, and 126.6 ppm.

Typical Nitration Procedure. The Nitration of *N*-methylphthalimide (1a). A. At Lower Temperature. A mixture of 30.8 mL of 96% sulfuric acid and 5.13 mL of 90% nitric acid was cooled to 15 °C. To this well-stirred solution was added 5.00 g of **1a** at such a rate to maintain the reaction temperature between 15 and 20 °C. When addition was complete, a clear bright yellow-orange solution was obtained. The mixture was allowed to slowly warm to room temperature and then to stand overnight at room temperature. The reaction mixture was then poured into ca. 600 mL of ice and the resulting precipitate was filtered, washed with cold water, and dried to give 5.80 g (90%) of **2a** which was pure by VPC analysis.

This reaction was repeated using 50 g of **1a** to give a crude product containing 98.5% of **2a** and 1.5% of **3a**. This material was stirred with 250 mL of methanol and filtered to give 56.53 g (88%) of pure **2a**, mp 175–176 °C (lit.[1] 177–178 °C).

B. At Elevated Temperature. A mixture of 5.0 g of **1a** and 5.28 mL of 96% sulfuric acid was heated at 70 °C with an oil bath. The bath was removed and 2.93 mL of 90% nitric acid was added at such a rate as to maintain the internal temperature at 70 °C (ca. 20 to 30 min). The reaction mixture was then heated at 70 °C for an additional 1.5 h, cooled to room temperature, and added to 200 mL of ice. The resulting precipitate was collected by filtration and dried to give 5.39 g of material. Analysis of this material by VPC showed it to consist of 92% of **2a** and 8% of **3a** for an isolated yield of 77% **2a** and 7% **3a**.

The reaction was repeated using 50 g of **1a**. The nitric acid was added over a period of ca. 100 min. Workup gave a crude product which contained 1% of **1a**, 88% of **2a**, and 11% of **3a**. This crude product was stirred with 250 mL of methanol to give 51.5 g (80.5%) of **2a** which was pure by VPC analysis, mp 175–177 °C (lit.[1] 177–178 °C).

Acknowledgments. We would like to thank N. C. Cook, G. C. Davis, and J. M. Gasaway for their many helpful suggestions and interesting discussions concerning this work.

Registry No.—**1a**, 550-44-7; **1b**, 5022-29-7; **1c**, 1515-72-6; **1d**, 20320-48-3; **1e**, 59333-62-9; **2a**, 41663-84-7; **2b**, 55080-56-3; **2c**, 54395-37-8; **2d**, 65311-53-7; **2e**, 65311-54-8; **3a**, 2593-81-9; **3b**, 2778-84-9; **3c**, 54395-36-7; **3d**, 2593-84-2; **3e**, 2593-54-6.

Supplementary Material Available: Tabulated ^{13}C NMR chemical shifts for all the *N*-alkylphthalimides studied (1 page). Ordering information is given on any current masthead page.

References and Notes

(1) J. Tirouflet and R. Dabard, *C. R. Hebd. Seances Acad. Sci.*, 916 (1956); R. Dabard and J. Tirouflet, *Bull. Soc. Chim. Fr.*, 565 (1957).
(2) Both 3- and 4-nitro-substituted phthalimides can easily be prepared from the reaction of the appropriate alkyl amine with either 3- or 4-nitrophthalic anhydride. Unfortunately, the nitration of phthalic anhydride results in an ca. 50/50 mixture of 3- and 4-nitro isomers which are very difficult to separate.
(3) E. H. Huntress and R. L. Shriner report that the nitration of phthalimide at 10–25 °C gives a 52% yield of the pure 4-nitro isomer ("Organic Syntheses", Collect. Vol. 2, John Wiley, New York, N.Y., 1943, p 459). L. F. Levy and H. Stephen (*J. Chem. Soc.*, 79 (1931)) report that if the nitration mixture is allowed to warm tc 80 °C for 30 min, 78% of the pure 4-nitro isomer could be obtained.
(4) N. C. Cook and G. C. Davis have shown that some oxidation of the alkyl group takes place even when R = CH_3 (private communication, General Electric Co., Corporate Research and Development).
(5) For examples of these types of reactions, see: F. J. Williams and P. E. Donahue, *J. Org. Chem*, **42**, 3414 (1977); F. J. Williams and P. E. Donahue, *ibid.*, **43**, 250 (1978); and R. L. Markezich and O. S. Zamek, *ibid.*, **42**, 3431 (1977).

Convenient Synthesis of a Highly Efficient and Recyclable Chiral Director for Asymmetric Induction

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Asymmetric syntheses utilizing the menthyloxy group as a chirality director have been reported frequently; however, optical yields are generally too low to be really useful.[2] Although Lewis-acid catalyzed Diels–Alder reactions of menthyl acrylate are unusually efficient (optical yields approach 80%[3]), the menthyloxy group is still far from ideal.

As a result of a study directed toward the enantioselective synthesis of intermediates useful for the preparation of naturally occurring prostaglandins we introduced the use of (1*S*,2*R*,5*S*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexanol, (+)-**1**, which proved to be an exceptionally efficient chirality director.[4]

The reaction of the acrylate ester of (−)-**1** with cyclopentadiene afforded the *endo*-norbornenecarboxylic ester **2** in 82% yield with 99% enantiselectivity.[5] Similarly, the acrylate ester of (+)-**1**, on reaction with 5-benzyloxymethylcyclopentadiene, resulted in the formation of **3** in 89% yield and 97% enantioselectivity.[4]

The preparation of (−)-**1** in 71% yield from (*R*)-(+)-pule-

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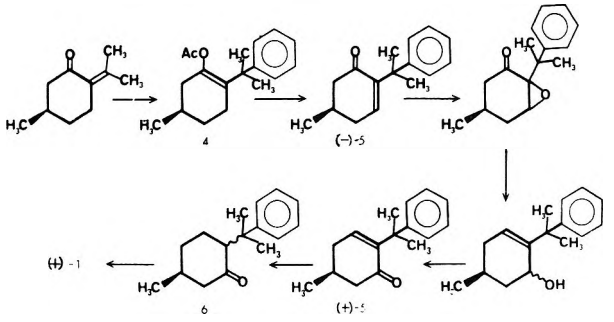
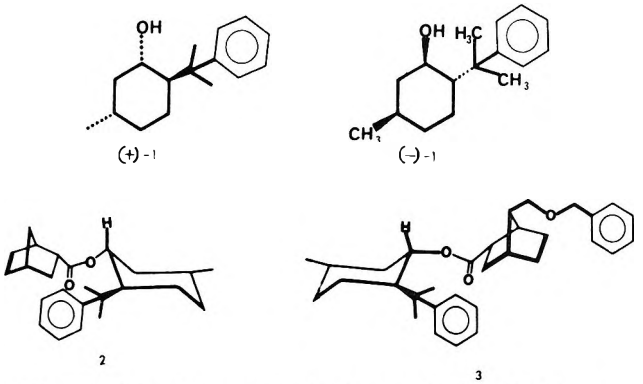
Scheme I



gone provides a convenient route to this enantiomer. Previously, (+)-1 has been prepared in an identical fashion from (*S*)-(−)-pulegone.[5] However, due to the lesser availability of (*S*)-(−)-pulegone,[6] a more convenient preparation of (+)-1 was desirable.



We report herein a convenient procedure (which is amenable to large scale reactions) for the preparation of (+)-1 directly from (*R*)-(+)-pulegone (Scheme I).

Cuprous iodide catalyzed conjugate addition of phenylmagnesium bromide to (*R*)-(+)-pulegone followed by trapping the resulting enolate with excess acetyl chloride affords a 91% yield of the enolacetate **4**.[7] Conversion of **4** to the desired α-bromo ketone (as an epimeric mixture) could be accomplished by regiospecific generation of the lithium enolate followed by addition of bromine[8] (88% yield) or more conveniently by direct bromination of **4** in methylene chloride at −78 °C (89% yield).[9] Treatment of the α-bromo ketone with a slurry of lithium bromide and sodium carbonate in refluxing dimethylformamide[10] gave an 89% yield (from **4**) of the α,β-unsaturated ketone (−)-**5**. Conversion of (−)-**5** to its enantiomer was accomplished in 78% yield by base-catalyzed epoxidation with hydrogen peroxide,[11] treatment with hydrazine in the presence of a catalytic amount of acetic acid,[12] and in situ Collins' oxidation[13] of the allylic alcohol. Birch reduction of (+)-**5** followed by Jones oxidation affords **6** as a 1:1 mixture of cis and trans isomers in 85% yield. Base treatment of the ketones gives an equilibrium mixture comprised of 85% trans and 15% cis forms. Reduction of this mixture with sodium in isopropyl alcohol produces (+)-1 in 91% yield.

Experimental Section

(5R)-1-Acetoxy-2-(1-methyl-1-phenylethyl)-5-methylcyclohexene (4). A slurry of 5.8 g (0.03 mol) of purified cuprous iodide in 70 mL of ether was cooled to −20 °C and treated with 300 mL (0.45 mol) of 1.5 M phenylmagnesium bromide. The resulting solution was stirred at −20 °C for 15 min and a solution of 40 g (0.263 mol) of (*R*)-(+)-pulegone, $[\alpha]^{23}D$ +24° (c 2, EtOH), in 100 mL of ether was added dropwise at −20 °C. After the addition, the reaction mixture was stirred for 3 h at 25 °C. The reaction mixture was cooled to −20 °C and a solution of 100 g (1.27 mol) of acetyl chloride in 250 mL of ether was added dropwise. The solution was stirred for 1 h at 0 °C and overnight at 25 °C and then poured into 2 L of ice-cold, saturated ammonium chloride. The mixture was filtered, the organic layer was separated, and the aqueous layer was extracted with 300 mL of ether. The combined organic layers were dried (Na_2SO_4) and evaporated and the residue was distilled at reduced pressure to give 64.8 g (0.238 mol, 90%) of **4**: bp 106–110 °C (0.3 mm); $[\alpha]^{22}D$ +46.18° (*c* 2.39, EtOH); IR 1750 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 7.2–7.0 (m, 5 H, aromatic), 2.3–0.9 (m, 7 H), 1.52 (s, 3 H, O_2CCH_3), 1.37 (s, 6 H, CH_3CPh), 0.96 (d, J = 6.5 Hz, 3 H, $CHCH_3$). Anal. Calcd for $C_{18}H_{24}O_2$: C, 79.37; H, 8.88. Found: C, 79.14; H, 8.62.

(5*R*)-2-(1-Methyl-1-phenylethyl)-5-methylcyclohex-2-enone [(−)-5]. To a solution of 25.0 g (91.0 mmol) of **4** in 250 mL of methylene chloride at −78 °C was added dropwise a solution of 14.8 g (92.5 mmol) of bromine in 100 mL of methylene chloride. The reaction mixture was quenched 5 min after completion of the addition with 50 mL of saturated sodium bicarbonate at −78 °C. The organic layer was separated and the aqueous layer was extracted with 100 mL of methylene chloride. The combined organic layers were dried (Na_2SO_4) and the solvent was evaporated at 40 °C (20 mm) to give 28.6 g (101%) of crude α-bromo ketone which was dehydrobrominated without further purification. The crude α-bromo ketone was dissolved in 50 mL of dry dimethylformamide and added dropwise to a heated (150 °C) slurry of 20 g (230 mmol) of lithium bromide and 20 g (241 mmol) of sodium carbonate in 200 mL of dry dimethylformamide. The solution was heated at 150 °C for 2 h, cooled, filtered, diluted with 500 mL of water, and extracted twice with 200 mL of benzene. The combined benzene extracts were evaporated and the residue was distilled at reduced pressure to afford 18.6 g (81.6 mmol, 89%) of (−)-**5**: bp 110–111 °C (0.2 mm); $[\alpha]^{22}D$ −57.35° (c 1.36, EtOH); IR 1680 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 7.4–6.9 (m, 5 H, aromatic), 6.83–6.70 (m, 1 H, vinyl), 2.56–0.9 (m, 8 H), 1.44 (s, 6 H, CH_3CPh). Anal. Calcd for $C_{16}H_{20}O$: C, 84.16; H, 8.82. Found: C, 84.21; H, 8.61.

(5*S*)-2-(1-Methyl-1-phenylethyl)-5-methylcyclohex-2-enone [(+)-5]. To a cooled (0 °C) solution of 18 g (78.9 mmol) of (−)-**5** in 250 mL of ethanol was added a solution of 1.6 g (40 mmol) of sodium hydroxide in 6 mL of water and 50 mL (580 mmol) of 30% hydrogen peroxide. The solution was stirred at 25 °C for 24 h and an additional 1.0 g (25 mmol) of sodium hydroxide in 5 mL of water and 25 mL (290 mmol) of 30% hydrogen peroxide was added. The solution was stirred for 24 h at 25 °C and then concentrated to 150 mL at reduced pressure. The residue was diluted with 200 mL of water and extracted twice with 200 mL of benzene. The combined layers were dried (Na_2SO_4), evaporated, and distilled to give 18.5 g (75.8 mmol, 96%) of epoxy ketone: bp 110–113 °C (0.3 mm); $[\alpha]^{22}D$ + 20.74° (c 3.76, EtOH); IR 1710 (C=O) cm^{-1}; NMR ($CDCl_3$) δ 7.22–6.95 (m, 5 H, aromatic), 3.54 (bs, 1 H, oxirane), 2.5–1.08 (m, 5 H), 1.50 (s, 3 H, CH_3CPh), 1.12 (s, 3H, CH_3CPh), 0.86 (d, J = 6.5 Hz, 3 H, $CHCH_3$). Anal. Calcd for $C_{16}H_{20}O_2$: C, 78.65; H, 8.25. Found: C, 78.52; H, 7.98.

A solution of 15.7 g (64.3 mmol) of epoxy ketone in 250 mL of methanol was cooled to 0 °C and 60 mL (1.70 mol) of 95% hydrazine was added. The solution was warmed to 25 °C and 0.5 g (8.3 mmol) of acetic acid was added. Additional 0.5-g portions of acetic acid were added at 12-h intervals (2.0-g total, 30 mmol) and after 2 days at 25 °C the reaction mixture was warmed to 50 °C for 12 h. The solvent and excess hydrazine were evaporated at reduced pressure and the residue was taken up in 150 mL of benzene. The benzene solution was washed twice with 100 mL of water and twice with 50 mL of 10% sodium dihydrogen phosphate. The benzene solution was dried (Na_2SO_4) and evaporated to give 13.3 g (57.9 mmol, 90%) of the allylic alcohol as a mixture of epimers.

To a solution of 58 g (720 mmol) of pyridine in 600 mL of methylene chloride at 0 °C was added 36 g (360 mmol) of chromium trioxide. The solution was stirred for 15 min at 20 °C and then treated with 14.0 g (60 mmol) of the mixture of epimeric allylic alcohols in 50 mL of methylene chloride. After stirring 45 min at 20 °C, the solution was filtered and the residue was washed several times with ether. The combined filtrate and washings were washed twice with 100 mL of 10% sodium hydroxide, dried (Na_2SO_4), concentrated, and distilled to give 12.6 g (55 mmol, 92%) of (+)-**5**: bp 110–112 °C (0.2 mm); $[\alpha]^{22}D$ +56.31° (c 1.15, EtOH); IR and NMR identical to authentic (−)-**5**. Anal. Calcd for $C_{16}H_{20}O$; C, 84.16; H, 8.82. Found: C, 84.24; H, 8.91.

(1*S*,2*R*,5*S*)-2-(1-methyl-1-phenylethyl)-5-methylcyclohexanol [(+)-1]. To 100 mL of liquid ammonia at −78 °C was added 0.56 g (0.08 g-atom) of lithium wire. Then a solution of 4.56 g (20 mmol) of (+)-**5** and 3.00 g (40.5 mmol) of *tert*-butyl alcohol in 20 mL of tetrahydrofuran was added. The solution was stirred at −78 °C for 30 min and then quenched by addition of solid ammonium chloride. The excess ammonia was evaporated and the semisolid residue was washed twice with 50 mL of benzene. Filtration and evaporation of the solvent gave 4.52 g of an oil consisting of saturated ketone and

alcohol. The residue was dissolved in 50 mL of acetone and excess 8 N chromic acid was added at 0 °C. The oxidation mixture was diluted with 100 mL of water and extracted twice with 100 mL of benzene. The combined organic extracts were dried (Na_2SO_4) and evaporated to afford 3.91 g (17 mmol, 85%) of **6** as a 1:1 mixture of cis and trans isomers. Equilibration of the mixture by heating at 70 °C in 100 mL of ethanol containing 1 equiv of 3 N sodium hydroxide gave 3.90 g (17 mmol, 100%) of **6** as an 85:15 mixture of trans to cis ketone.

To 2.30 g (0.100 g-atom) of sodium in 75 mL of refluxing toluene was added 3.80 g (16.5 mmol) of the 85:15 mixture of trans- and cis-6 in 8.4 g (140 mmol) of isopropyl alcohol. After 2 h at reflux the sodium had dissolved. After another 15 min the solution was cooled and quenched with 50 mL of saturated sodium dihydrogen phosphate. The layers were separated and the aqueous layer was extracted with 50 mL of toluene. The combined organic layers were dried (Na_2SO_4) and concentrated and the residue was chromatographed on silica gel (5% ether/petroleum ether) to afford 3.37 g (14.5 mmol, 88%) of (−)-1 as an oil: $[\alpha]^{22}D$ +26.3° (c 2.30, EtOH); IR 3420 (OH) cm^{-1}; NMR ($CDCl_3$) δ 7.33–7.08 (m, 5 H, aromatic), 3.50 (d of t, J = 3.5 Hz, J = 10.5 Hz. 1 H, HCO), 2.00–1.02 (m, 9 H), 1.40 (s, 3 H, CH_3CPh), 1.27 (s, 3 H, CH_3CPh), 0.85 (d, J = 5 Hz, 3 H, $CHCH_3$).

Acknowledgment. We are grateful to the donors of the Petroleum Research Fund, administered by the American Chemical Society, and the National Science Foundation for partial support of this work.

Registry No.—(+)-1, 57707-91-2; **4**, 65253-05-6; (−)-**5**, 65253-06-7; (+)-**5**, 65253-07-8; **5** epoxy ketone. 65253-08-9; **5** alcohol isomer I, 65253-09-0; **5** alcohol isomer II, 65337-05-5; **6** isomer I, 65337-06-6; **6** isomer II, 57707-92-3; phenyl bromide, 108-86-1; (*R*)-(+)-pulegone, 89-82-7; acetyl chloride, 75-36-5.

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Synthesis of Heavily Substituted Cyclopropylethylenes by Titanium(0) Catalyzed Cross-Coupling of Ketones. Restricted Rotation in 1,1-Dicyclopropyl-2,2-di(2-propyl)ethylene

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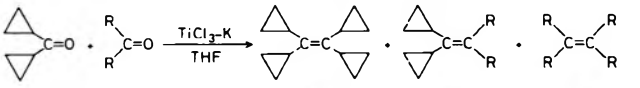
Carbonyl coupling reaction employing low-valent titanium[1] is a valuable method for preparing sterically hindered olefins.[2-4] Recently, McMurry and Krepski[5] have demonstrated further that the method is equally effective for cross-couplings between aryl ketones and aliphatic carbonyl compounds. We investigated the cross-couplings between dicyclopropyl ketone and aliphatic ketones in the hope that heavily substituted cyclopropylethylenes could be prepared. Although we were not without doubts regarding the survival of the cyclopropane ring under the reaction conditions, cross-coupled cyclopropylethylenes as well as tetracyclopropylethylene[6,7] were obtained in satisfactory yields.

The cross-coupling was performed by refluxing a 1:1 mixture of dicyclopropyl ketone and 2,4-dimethyl-3-pentanone with the titanium(0) reagent[1] in tetrahydrofuran under a nitrogen atmosphere for 12 h. As a result, an olefinic fraction composed of three components was obtained in a 29% yield. The major component (ca. 60%) was characterized as a cross-coupled olefin, 3-dicyclopropylmethylene-2,4-dimethylpentane (1,1-dicyclopropyl-2,2-di(2-propyl)ethylene, **2a**). The other two were homocoupled products, namely tetracyclopropylethylene (**1**) and 2,5-dimethyl-3,4-di(2-propyl)hex-3-ene (**3a**). Similarly, the reaction of dicyclopropyl ketone with 3-pentanone produced cross-coupled 3-dicyclopropylmethylenepentane (**2b**) as the major olefinic product. All olefins produced were separated and purified by column chromatography and GLC. The amounts of the crossed olefins were somewhat greater than the statistical value.[8]



		1	2	3
a	R = $CH(CH_3)_2$	29% (2.5	6	1.5)[9]
b	R = CH_2CH_3	31% (1	6.5	2.5)[10]

An application of the titanium(0) coupling procedure for the reaction of cyclopropyl phenyl ketone was fruitless. However, *trans*- and *cis*-1,2-dicyclopropylstilbenes (**4a** and **4b**) were satisfactorily prepared by the coupling of the ketone with $TiCl_4$–Zn reagent[11] in dioxane.

Olefin **3a** has been reported to exhibit temperature-dependent NMR[2,3] and a suggestion has been made that olefin **1** should behave similarly.[2] However, in our observations, we noted that olefin **1** showed practically no change in its NMR down to −160 °C. We in fact noted that olefin **2a** lies between **1** and **3a**. It was found that the methyl signal in the 2-propyl group coalesced at −105 °C (168 K) in Freon 12. At −140 °C or below, it split into a pair of doublets at δ 0.94 and 1.22.[12] From these results, $\Delta G_c^{\ddagger}$ at 168 K is calculted to be 8.3 kcal/mol.[13] Further, signals due to the cyclopropyl ring protons in **2a** also appeared to coalesce,[14] suggesting that the cogwheel effect[15] including all four substituents was in operation.

The present results clearly demonstrated that the size of the cyclopropyl group is significantly smaller than that of the 2-propyl. It is natural, therefore, that the coalescence temperature for **1** should be lower than −160 °C.

Experimental Section

IR spectra were recorded on a Hitachi 215 grating infrared spectrophotometer, UV were recorded on a Cary Model 17 spectrometer, and NMR were recorded on a JEOL PS-100 high-resolution spectrometer. Both preparative and analytical GLC were carried out on a Hitachi 063 gas chromatograph. All boiling and melting points are uncorrected.

Cross-Coupling between Dicyclopropyl Ketone and Aliphatic Ketone with Titanium(0) Reagent. Under a nitrogen atmosphere, the titanium(0) reagent[1] was prepared from 19.5 g (126 mmol) of titanium trichloride and 14.0 g (358 mg-atom) of potassium in 350 mL of dry tetrahydrofuran. Under ice-cooling, a solution of 1.65 g (15 mmol) of dicyclopropyl ketone, 1.71 g (15 mmol) of 2,4-dimethyl-3-pentanone, and 255 mg of dodecane (internal standard for GLC analysis) in 70 mL of dry tetrahydrofuran was added slowly to the reagent, and the resulting mixture was stirred at room temperature for 1 h and then at reflux for 12 h. The cooled reaction mixture was treated with a small amount of ethanol and then poured onto a mixture of 300 mL of water and 500 mL of hexane. After filtration to remove resinous precipitates, the hexane layer was separated. The water layer was extracted with two portions of hexane. The combined hexane solution was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. The solvent was removed and the resulting oily product was analyzed by GLC (Apiezon L 20%

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on Chromosorb with temperature programming from 80 to 250 °C). The yields of **1**, **2a**, and **3a**, determined by GLC with respect to the internal standard, were 8, 16, and 5%, respectively. In a separate experiment, the product mixture was separated briefly by column chromatography (silica gel with low boiling petroleum ether as eluant). Each component was purified by GLC. Olefin **1** was characterized by comparison against authentic specimen.[6] Olefin **3a** melted at 119.5–121 °C (lit. 116–117 °C,[2] 125–125.5 °C[3]) and gave the same NMR as that reported.[2]GLC purified **2a** gave the following spectral and analytical data: IR (liquid film) 3090, 3020, 1630 (broad and weak), 1035 cm^{-1}; NMR ($CDCl_3$) δ 0.4–0.7 (m, 8), 1.07 (d, 12, J = 7 Hz), 1.1–1.5 (m, 2), 3.05 (heptet, 2, J = 7 Hz). Anal. Calcd for $C_{14}H_{24}$: C, 87.4; H, 12.6. Found: C, 87.5; H, 12.3.

Similar treatment of dicyclopropyl ketone (2.09 g, 19 mmol) and 3-pentanone (1.64 g, 19 mmol) with the titanium(0) reagent gave 1.30 g of an olefinic fraction, bp 40–82 °C at 4 mmHg. GLC analysis of the fraction showed the existence of three major components (74% of the total peak area) and many minor components. The three components were characterized as **1** (3%), **2b** (21%), and **3b** (7%). GLC purified **2b** gave the following data: IR (liquid film) 3080, 3020, 1635, 1010 cm^{-1}; NMR (CCl_4) δ 0.3–0.8 (m, 8), 0.95 (t, 6, J = 7.5 Hz), 1.0–1.4 (m, 2), 2.23 (quartet, 4, J = 7.5 Hz). Anal. Calcd for $C_{12}H_{20}$: C, 87.7; H, 12.3. Found: C, 87.7; H, 12.2.

In both coupling reactions, the ratio of **1:2:3** given in the text is an average of two to four runs.

1,2-Dicyclopropylstilbene. To 26.6 g (140 mmol) of titanium tetrachloride in 300 mL of dry dioxane 10.2 g (70 mmol) of cyclopropyl phenyl ketone was added. Under a nitrogen atmosphere, 18.3 g (280 mg atom) of zinc powder was then added in one portion and the resulting mixture was refluxed for 8 h.[11] After cooling down the mixture, 400 mL of water was added and organic material was extracted with three portions of benzene. The combined benzene solution was washed with saturated sodium chloride solution and dried over anhydrous magnesium sulfate. Evaporation of the solvent gave a solid residue which was recrystallized from ether to give 2.09 g (23%) of crystalline product **4a**, mp 147.5–148.5 °C. The mother liquid of the recrystallization was concentrated and the residue was placed on top of a silica gel column (50 g), and elutions were carried out with hexane. From relatively later fractions, the second product **4b**, mp 78–79 °C (from ethanol), 1.85 g (20%), was obtained. Olefins **4a** and **4b** were characterized as isomeric 1,2-dicyclopropylstilbene from the following data. Olefin **4a**: NMR ($CDCl_3$) δ 0.0–0.6 (m, 8), 1.2–1.6 (m, 2), 7.0–7.5 (m, 10); mass m/e 260 (M^+); UV_{max} (hexane) 242 nm (ε 6400). Anal. Calcd for $C_{20}H_{20}$: C, 92.3; H, 7.7. Found: C, 92.2; H, 7.8. Olefin **4b**: NMR (CCl_4) δ 0.1–0.4 (m, 4), 0.5–0.8 (m, 4), 2.0–2.3 (m, 2), 6.6–7.0 (m, 10); mass m/e 260 (M^+); UV_{max} (hexane) 254 nm (ε 8400). Anal. Calcd for $C_{20}H_{20}$: C, 92.3; H, 7.7. Found: C, 92.5; H, 7.9. Olefin **4a**, which may be the same substance as that described by Bennett and Bunce (mp 139.8–140.2 °C),[16] is assigned as a trans isomer. Heating of either **4a** or **4b** in 1,2-dichloroethane[17] at 100 °C for 44 h resulted in the formation of a mixture with the same composition (**4a**/**4b** = 75:25). Regarding the UV data, it is reported that the trans isomer of 1,2-dialkylstilbenes exhibits the maximum at wavelengths shorter than that for the cis isomer.[18]

NMR Examination of 2a and 1. Forty-six milligrams of **2a** was placed in an NMR tube and ca. 0.8 mL of Freon 12 was condensed in the tube. The tube was sealed and NMR measurements were performed at several temperatures (down to −160 °C). The methyl signal coalesced at −105 °C as described in the text. The signals due to the methine protons coalesced at −95 °C and they appeared at δ 2.44 and 3.57 at −140 °C or below. Thus, $\Delta G_c^{\ddagger}$ at 178 K is calculated to be 8.5 kcal/mol.[13] The signals due to the cyclopropyl groups also changed their shapes and split at least into four signals at ca. δ 0.3, 0.6, 0.9, and 1.7 at −140 °C or below.

On the other hand, NMR signals of **1** remained practically unchanged down to −160 °C. Slight line broadenings observed may be due to the viscosity increase.

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Registry No.—**1**, 23534-93-2; **2a**, 65045-41-2; **2b**, 65045-42-3; **3a**, 7090-88-2; **3b**, 868-46-2; **4a**, 65045-43-4; **4b**, 65045-44-5; titanium trichloride, 7705-07-09; potassium, 7440-09-7; dicyclopropyl ketone, 1121-37-5; 2,4-dimethyl-3-pentanone, 565-80-0; 3-pentanone, 96-22-0; titanium tetrachloride, 7550-45-0; cyclopropylphenyl ketone, 3481-02-5.

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Sesquiterpenoids from the Hawaiian Marine Alga *Laurencia nidifica*. 7. (+)-Selin-4,7(11)-diene

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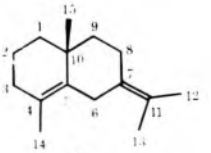
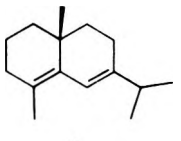
The selinane skeleton is one of the most common in sesquiterpenoids of terrestrial origin. Its presence in marine organisms has also been noted in a gorgonian,[1] a sponge,[2] and a brown alga.[3] Very recently the prolific *Laurencia* genus has been found to produce (−)-selin-7-ene derivatives.[4] We report here the isolation of (+)-selin-4,7(11)-diene (**1**) from the green variety of the Hawaiian marine alga *Laurencia nidifica*. To our knowledge this material has not been previously recorded as naturally occurring.

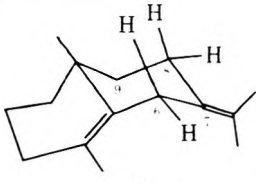
(+)-Selin-4,7(11)-diene (**1**) was isolated as an unstable



1



2



3

colorless oil in 0.08% yield from the dry alga. High resolution mass spectroscopy established its molecular formula as $C_{15}H_{24}$. Its infrared spectrum showed only carbon–hydrogen absorptions. ^{13}C NMR indicated the presence of four quaternary olefinic carbons (119.8, 123.7, 131.7, 135.2) and a fifth quaternary center at 34.8. ^1H NMR confirmed the absence of

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olefinic protons and revealed one quaternary (1.11) and three vinyl methyl groups [1.71 (3 H) and 1.64 (6 H)].

The skeletal structure of **1** was determined by its isomerization to (+)-δ-selinene (**2**) on treatment with *p*-toluenesulfonic acid. The optical[5] and spectral properties of **2** were identical to those reported in the literature.[5,6]

Since **1** possesses a selinane carbon skeleton its two double bonds must be placed at the 4,5 and the 7,11 positions as both olefinic links are quaternary. The configuration at C-10 is fixed by the formation of dextrarotatory δ-selinene on isomerization. Double resonance experiments at 270 MHz permitted the assignment of the chemical shifts and *J* values for several protons in **1**. H-6β absorbs at δ 2.32 and appears as a broad doublet coupled by 15 Hz to H-6α. The latter occurs as a doublet of doublets at δ 3.16, coupled to H-6β by 15 Hz and to H-8α by 2 Hz. A near coplanar W arrangement is present between H-6α and H-8α in conformer **3**, accounting for the long-range coupling. The location of H-6α in the deshielding region of both double bonds[7] explains its rather large downfield shift. H-8α appears at δ 2.44 as a broad doublet ($J_{8\alpha,6\alpha}$ = 2 Hz, $J_{8\alpha,8\beta}$ = 13 Hz, $J_{8\alpha,9}$ = 5 Hz) and H-8β at 2.05 as a broad triplet ($J_{8\beta,8\alpha} = J_{8\beta,9\alpha}$ = 13 Hz).

Experimental Section

IR spectra were taken on a Perkin-Elmer 700 spectrophotometer as neat liquids. ^{1}H NMR were recorded on a Perkin-Elmer R-24B spectrometer at 60 MHz and a Bruker 270 HX spectrometer at 270 MHz in C_6D_6. ^{13}C NMR spectra were obtained with a JOEL PFT-100 spectrometer in $CDCl_3$. Low-resolution mass spectra were recorded on a Finnigan 1015 D GC–mass spectrometer and high-resolution mass spectra on a CEC-21-110B spectrometer. Ultraviolet spectra were determined with a Perkin-Elmer 202 spectrophotometer in 95% EtOH. Optical rotations were measured in $CHCl_3$ on a Zeiss type VDr Na polarimeter. Brinkman silica gel HF-254 + 366, Type 60 (500 μm, activated 0.5 h at 100 °C), was used for TLC. All solvents were reagent grade.

Isolation of (+)-Selin-4,7(11)-diene. (1). Approximately 160 mg of the 3:1 hexane–benzene eluant of the crude algal extract[8] was dissolved in ether and spotted on TLC plates. The plates were developed three times in hexane, drying between developments, and the spots were extracted with ether to give 89 mg of **1** as a colorless oil (0.08%, dry weight of alga): R_f 0.84; $[\alpha]^{24}_D$ +34° (c 0.90); UV λ_{max} 218 nm (ε 4800); IR ν_{max} 2960, 2920, 2860, 1450, 1370, 1230, 1120, 875 cm^{-1}; ^{1}H NMR (270 MHz) δ 1.1–1.6 (m), 1.11 (3 H, s), 1.64 (6 H, s), 1.71 (3 H, s), 1.87 (br m), 2.05 (1 H, br t, *J* = 13 Hz), 2.32 (1 H, br d, *J* = 15 Hz), 2.44 (1 H br d, *J* = 2, 5, 13 Hz), 3.46 (1 H, dd, *J* = 2, 15 Hz); ^{13}C NMR δ 19.1, 19.4, 20.1 (2), 24.5, 26.1, 29.9, 32.9, 34.8,[9] 39.7, 42.2, 119.8,[9] 123.7,[9] 131.7,[9] 135.2;[9] mass spectrum *m/e* 204 (68), 189 (76), 161 (60), 147 (28), 133 (72), 119 (60), 105 (88), 91 (84), 81 (40), 79 (40), 77 (40), 67 (36), 55 (56), 41 (100). High-resolution mass spectrum Calcd for $C_{15}H_{24}$: 204.1878. Found: 204.1891.

Isomerization of (+)-Selin-4,7(11)-diene (1). (+)-δ-Selinene (2). A solution of 50 mg of **1** and a crystal of *p*-toluenesulfonic acid monohydrate in 5 mL of benzene was heated at reflux for 1 h. The benzene was removed and the residue was purified by TLC (hexane) to give 39 mg (78%) of (+)-δ-selinene as a colorless oil: R_f 0.65; $[\alpha]^{24}_D$ +196° (c 4.6); UV λ_{max} 248 (ε 14 300); IR ν_{max} 2960, 2920, 2870, 1620, 1480, 1370, 1210, 870 cm^{-1}; ^{1}H NMR (270 MHz) δ 0.94 (3 H, s), 1.05 (3 H, d, *J* = 7 Hz), 1.06 (3 H, d, *J* = 7), 1.24–1.57 (m), 1.69 (3 H, s), 1.95–2.31 (m), 6.12 (1 H, s); ^{13}C NMR[10] δ 18.7 (2), 21.4, 21.9, 23.3 (2), 32.8, 35.6, 37.7, 38.1, 117.0; mass spectrum *m/e* 204 (57), 189 (70), 161 (100), 147 (18), 133 (43), 119 (41), 105 (63), 91 (59), 81 (39), 67 (23), 55 (33), 43 (53), 41 (53). High-resolution mass spectrum Calcd for $C_{15}H_{24}$: 204.1878. Found: 204.1885.

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Registry No.—**1**, 41071-31-2; **2**, 28624-28-4.

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Marine Natural Products: Cembrene-A and Cembrene-C from a Soft Coral, *Nephthea sp.*

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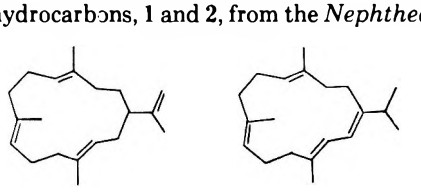
Previously we reported the isolation of two new cembrene derivatives, nephthenol and epoxynephthenol acetate, from a soft coral, *Nephthea* species.[2] Since then, nephthenol has been identified as a component in another soft coral[3] and also synthesized.[4] In this paper we report the isolation of two cembrene hydrocarbons, **1** and **2**, from the *Nephthea sp.* that



1 **2**

yielded nepthenol. Many oxygenated diterpenoids having a cembrane skeleton have been obtained from marine organisms, but the only report to date of a cembrene hydrocarbon from marine sources is the recent paper by Herin and Tursch,[5] wherein the isolation of cembrene-A from another soft coral is described. Cembrene-A (**1**) has been isolated previously from several terrestrial sources.[6] The hydrocarbon **2** was initially reported as a component of the oleoresin of *Pinus koraiensis*,[7a] but later work[7b] revealed that it was an artifact; **2** has also been obtained in trace amounts from strong base-catalyzed isomerization of cembrene-A.[6b]

The hydrocarbon **1** has earlier been assigned various names: neocembrene,[6a] cembrene-A,[6c] and neocembrene-A.[6b] Although neocembrene has chronological precedence in the literature, we have chosen to use the name cembrene-A. This name allows for convenient construction of trivial names for still other double-bond isomers of cembrene in a manner

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analogous to the suggestions[8] for nomenclature of germacrenes, the corresponding biogenetically equivalent sesquiterpene hydrocarbons. Similarly, we suggest that compound **2** be designated cembrene-C[9] rather than α-pinacene, the name assigned to this hydrocarbon when it was first reported.[7a]

The hydrocarbons cembrene-A (**1**) and cembrene-C (**2**) were obtained from soft coral collected at Enewetak, Marshall Islands. Freshly collected specimens were preserved immediately in isopropyl alcohol and later recovered by filtration, air-dried, and soaked in hexane at room temperature. The concentrate of the isopropyl alcohol extract was extracted with benzene. These benzene and hexane extracts were combined and chromatographed over Florisil. One of the chromatographic fractions was a clear oil that was shown by gas chromatography to consist predominantly of only two components (**1** and **2**) present in approximately equal amounts. Chromatography of part of this fraction over silica gel yielded a pure sample of cembrene-A but led to complete loss of the second component. Cembrene-A was identified by comparison of its spectral and gas chromatographic properties with those of an authentic sample.[10]

Cembrene-C (**2**), isolated by preparative GC, was optically inactive and had the same elemental composition as cembrene-A, $C_{20}H_{32}$ (M^+, 272). On catalytic hydrogenation both compounds yielded the same saturated hydrocarbon, thus establishing that cembrenes-A and -C have the same carbon skeleton. The NMR spectrum of cembrene-C appeared identical with that reported for α-pinacene[7] and revealed that the molecule possessed an isopropyl group and four double bonds: two isolated trisubstituted double bonds and two conjugated double bonds, UV max 252 nm (ε 18 403) and shoulders at 246 (16 230) and 260 (13 350). The conjugated double bonds had associated with them a two-proton NMR signal at δ 5.98 (AB quartet with intense overlapping central lines and very weak outer members, J = 10–12 Hz) that was coupled to one vinyl methyl signal (δ 1.73). In order to account for the three vinyl methyl groups and the allylic nature of the isopropyl methine proton (δ 2.26), the conjugated double-bond unit must be positioned as in **2**. Confirmation of this structure was obtained by oxidative degradation. Both Lemieux–von Rudloff oxidation[11] and ozonolysis of cembrene-C yielded levulinic acid as the only isolable acidic product and 6-methyl-2,5-heptanedione as the sole neutral product. A micro-ozonolysis experiment[12] led to the identification of glyoxal as the remaining oxidation fragment. Cembrene-C thus has the same overall structure as proposed for the stereoisomeric α-, β-, and γ-pinacene and corresponds by NMR to α-pinacene. The isomeric pinacenes are reported[7a] to differ only in configuration at the conjugated diene site, but no specific geometry has been assigned to any of the isomers. Our data do not permit assignment of this stereochemistry either.

Cembrenes-A and -C appear to be present in the crude extract and are not just artifacts derived from nephthenol during the isolation process. Thus, the low-boiling distillate from a falling film distillation [110 °C (2–3 mm)] of the original hexane extract exhibits the diagnostic low-field NMR signals for the conjugated diene (δ 5.98) of cembrene-C and for the exo-methylene of cembrene-A (δ 5.8). Furthermore, nephthenol survives chromatographies over Florisil and silica gel, as does synthetic nephthenol. Although chromatography over silica gel led to a complete loss of **2**, both **1** and **2** survived chromatography over Florisil (very little separation), and no isomerization of **1** to **2** appeared to occur on the latter adsorbent, as judged by GC analysis of eluted material.

All attempts to prepare a Diels–Alder addition product of **2** failed (maleic anhydride, sulfur dioxide, 4-phenyl-1,2,4-triazoline-3,5-dione[13]). This indicates that the conjugated diene system in **2** is s-trans.

Experimental Section

Infrared spectra were taken on a Beckman IR-8 spectrophotometer and Ultraviolet spectra on a Carey Model 118 spectrophotometer using 1-cm matched quartz cells. NMR spectra were acquired on Varian T-60 and XL-100 spectrometers in the solvents specified; signals are reported in parts per million (δ) downfield from internal tetramethylsilane. Mass spectra were obtained on Hitachi RMU-7 and Finnigan Model 1015 spectrometers and optical rotations on Perkin-Elmer 141 digital readout or Gaertner polarimeters. Microanalyses were obtained from Mr. E. Meier, Department of Chemistry, Stanford University, Palo Alto, Calif. Chromatographic adsorbents used were Florisil (Fischer, 100–200 mesh) and silicic acid (Mallinckrodt, SilicAR CC-7 and Brinkman TLC mesh). Gas chromatographic analyses were conducted on Varian Aerograph Models 1200 and 1700 using the following columns: A, 6 ft × 0.5 in, 10% FFAP on 60–80 mesh Chromosorb W (Applied Science Laboratories, State College, Pa.); B, 10 ft × 0.25 in, 20% FFAP on 60–80 Chromosorb W; C, 6 ft × 0.125 in, 3% OV-225 on 100–120 mesh Gas-Chrom Q (Applied Science Laboratories, State College, Pa.); D, 6 ft × 0.125 in, OV-1 on 100–120 mesh Gas-Chrom Q.

Isolation of Cembrene-A and Cembrene-C. *Nephthea sp.*, 3 kg, was obtained preserved in isopropyl alcohol from Enewetak, Marshall Islands. The specimens were recovered by filtration, air-dried, and then soaked in hexane at room temperature for 1 week. The isopropyl alcohol solution was concentrated on a rotary evaporator, and the aqueous concentrate was extracted with benzene. Evaporation of the combined hexane and benzene solutions gave 172 g of dark, viscous residue. This entire extract was chromatographed on Florisil (900 g). Elution was initiated with hexane, and from the first 2 L of eluate, 55 g of oil was recovered. Rechromatography of this material over Florisil (900 g), employing hexane as solvent (250-mL fractions), afforded 2.7 g (fraction 9) of a colorless oil, which was shown by gas chromatographic analysis to consist of only two components present in approximately equal amounts.

Chromatography of 75 mg of this two-component fraction on 10 g of TLC-mesh silica gel yielded 35 mg of pure cembrene-A; the second hydrocarbon was not recovered from this adsorbent. The purified sample of cembrene-A exhibited IR and NMR spectra identical with those reported[6a,c] and also obtained from an authentic sample, but it showed a negligible rotation,[14] $[\alpha]_D$ −0.37°. Cembrene-A from *Nephthea* was indistinguishable from an authentic sample by gas chromatography, and the two samples gave virtually the same mass spectra under similar conditions on the same instrument.

Purification and Identification of Cembrene-C. Cembrene-C was isolated by preparative gas chromatography, column B, 155 °C; UV max (isooctane) 252 nm (ε 18 403), with shoulders at 246 (16 230) and 260 (13 500); IR (neat) 3060, 1660, 1605, 1440, 1375, 1355, 860, 840 cm^{-1}; NMR ($CDCl_3$) δ 1.04 (d, 6, J = 7 Hz, isopropyl methyls), 1.52, 1.58 (s, 3 each, vinyl methyls of isolated double bonds), 1.73 (s, 3, vinyl methyl, conjugated double bond), 2.12 (allylic methylene H's), 2.26 (heptet, isopropyl methine), 5.02 (br m, 2, nonconjugated vinyl protons), 5.98 (AB q. with intense overlapping inner members, 2, J = 10–12, vinyl protons, conjugated double bond); mass spectrum (70 eV), m/e (relative intensity) 272 (39, M^+), 257 (2), 229 (7), 189 (5), 161 (16), 137 (23), 136 (100), 135 (13), 121 (86), 119 (13), 107 (22), 105 (20), 93 (73), 91 (23), 81 (23), 79 (21), 77 (23), 67 (21), 55 (18), 53 (18).

Anal. Calcd for $C_{20}H_{32}$: C, 88.16; H, 11.84. Found: C, 87.98; H, 11.62.

Hydrogenation of Cembrene-C. A small sample of cembrene-C (5 mg, 83% cembrene-C and 17% cembrene-A by GC analysis) in 95% ethanol was added to a suspension of prereduced PtO_2 in a few milliliters of ethanol and stirred under hydrogen (1 atm) for 48 h. Gas chromatographic analysis on columns A and D showed only one peak, and this was found to have the same retention time (peak enhancement) on both columns as the product obtained from hydrogenation of cembrene-A under the above conditions.

Permanganate–Periodate Oxidation of Cembrene-C. A solution of cembrene-C (32 mg) in 1 mL of *tert*-butyl alcohol was added to a solution prepared by adding 19 mL of *tert*-butyl alcohol and 75 mg of K_2CO_3 to 38.3 mL of Lemieux–von Rudloff reagent.[11] The mixture was then stoppered and shaken (Parr apparatus) for 24 h with occasional checks to ensure that the pH was maintained at 8–9. The reaction was quenched by the addition of 1.6 g of $K_2S_2O_5$, whereupon a clear yellow solution was obtained. The pH was adjusted to 8 with K_2CO_3 (0.3 g more of $K_2S_2O_5$ was added to discharge the brown color),

and the *tert*-butyl alcohol was removed on a rotary evaporator at 40 °C. The concentrated aqueous solution was extracted with peroxide-free ether to obtain neutral fragments and then acidified and extracted continuously with ether for 14 h to isolate the acidic products.

The neutral fraction was shown by GC analysis to contain only one component. A few milligrams of this was purified by preparative GC and identified as 6-methyl-2,5-heptanedione from the following spectral data: NMR (100 MHz, CCl_4, Fourier transform) 1.08 (d, 6), 2.11 (s, 3), 2.58 (5) [lit.[15] 1.05 (d, 6), 2.06 (s, 3), 2.54 (5)]; mass spectrum (11 eV) *m/e* 142 (0.5, M^+), 99 (100), 71 (7), 43 (5) chemical ionization MS, 183 $(M + 43)^+$, 171 $(M + 29)^+$, 143 $(M + 1)^+$ (base peak), 125 $[(M + 1) - 18]^+$, 99 $(M - 43)^+$, 71 $(M - 71)^+$.

The sole significant acidic product was identified as levulinic acid by the GC retention times of the acid and its methyl ester (from diazomethane treatment) on columns A and B, respectively, in comparison to authentic reference samples.

Ozonolysis of Cembrene-C. Ozone was bubbled through a solution of 1 mg of cembrene-C in 2 mL of ethyl acetate at −70 °C for 6 min, at which time the solution remained blue. Part of the ozonolysis mixture was treated with *o*-phenylenediamine according to the procedure of Moore and Brown[12] to convert any glyoxal to quinoxaline. The latter was identified in the final reaction mixture by GC analysis on columns A and C (peak enhancement using an authentic sample).

Acknowledgment. This work was supported in part by Commerce Department Sea Grant Project 3-158-56. We are grateful to the Mid-Pacific Marine Laboratory, Enewetak, Marshall Islands, for the use of its facilities, to Drs. R. E. Middlebrook, R. A. Gross, and R. E. Schroeder for collecting *Nephthea*, and to Dr. C. Shew, Kerr Environmental Laboratories, Ada, Oklahoma, for MS analyses. We gratefully acknowledge grants from the National Science Foundation (GP-38410) and the Phillips Petroleum Co., Bartlesville, Okla., which aided in the purchase of NMR spectrometers and accessories.

Registry No.—1, 31570-39-5; 2, 64363-64-0; 6-methyl-2,5-heptanedione, 13901-85-4.

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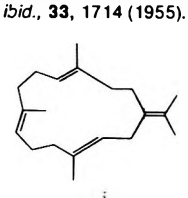

i

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Controlled-Potential Reduction of Cyclopropyl Ketones

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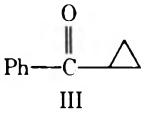
There are many instances of cyclopropyl systems reacting in a manner similar to double bonds. For example, addition reactions to cyclopropanes resulting in ring opening to 1,3-disubstitution products have been found with iodine,[1] bromine,[2] hydrogen bromide,[2,3a,b] hydrogen,[3b] and malonic ester anion.[4] Cyclopropyl rings have been used as double bond equivalents in Friedel–Crafts alkylations[5] and in Diels–Alder reactions.[6] Spectral studies have shown that cyclopropyl rings can affect absorption maxima in the ultraviolet region in much the way as does a double bond.[7]

We wished to see if this analogy could be realized in the electrochemical reduction of cyclopropyl ketones as compared to α,β-unsaturated ketones. Although there have been polarographic studies[8] of such systems there are no reported controlled potential reductions *with product isolation*. The polarography carried out revealed that the half-wave reduction potentials for cyclopropyl ketones is in between that of saturated ketones and α,β-unsaturated ketones, thus indicating a possible interaction of the cyclopropyl ring with the carbonyl group.

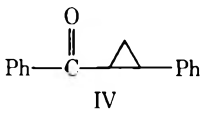
The reduction of α,β-unsaturated ketones follows the scheme shown in Scheme I. Which of the pathways obtains depends on the structure of the ketone and the potential at which the reduction is carried out. In some cases it is only possible to effect 2-e additions.

A similar scheme for cyclopropyl ketones would be Scheme II. Products B′, C′, and E′ could reflect interactions between the initially formed 1-e addition product and the cyclopropyl ring, I ↔ II, and would indicate an analogy to the olefinic system. The behavior of radicals of type I produced by chemical means has been studied by Neckers et al.[9]

Two ketones were subjected to polarography and controlled potential reduction, phenyl cyclopropyl ketone, III, and *trans*-1-benzoyl-2-phenylcyclopropane, IV.

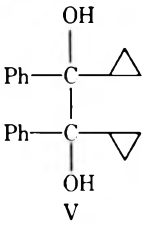


III

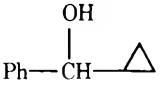


IV

From the controlled-potential reduction of ketone III, an 80% material balance was obtained which consisted of 40% starting ketone, III, 43% dimeric glycol, V, and 17% of the 2-e reduction product, cyclopropylphenylcarbinol, VI. These products provide no evidence for the interaction I ↔ II nor the analogy of this system with the double bond counterpart.



V



VI

The ketone IV on controlled-potential reduction provided (90% recovery) a mixture of the starting material, 25%, and γ-phenylbutyrophenone, VII. This result can be explained in terms of the increased importance of the type of interaction shown above, I ↔ II, when a phenyl is present to stabilize radical character as in IIa.

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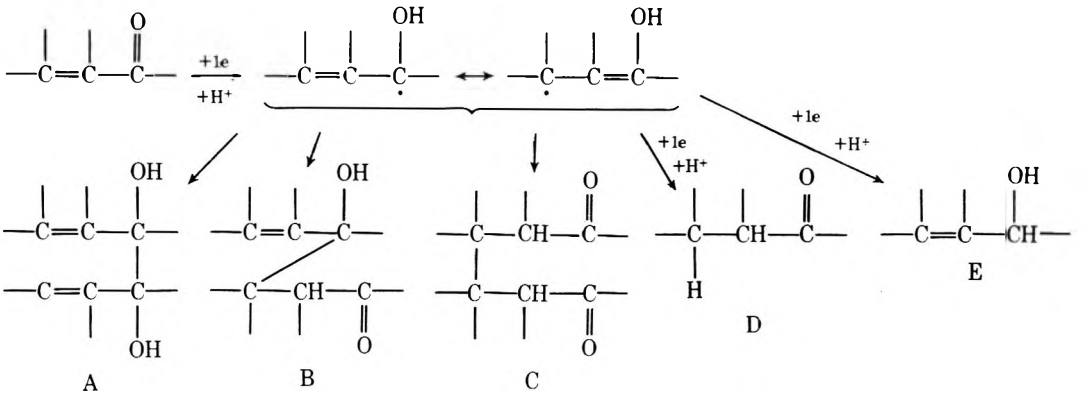
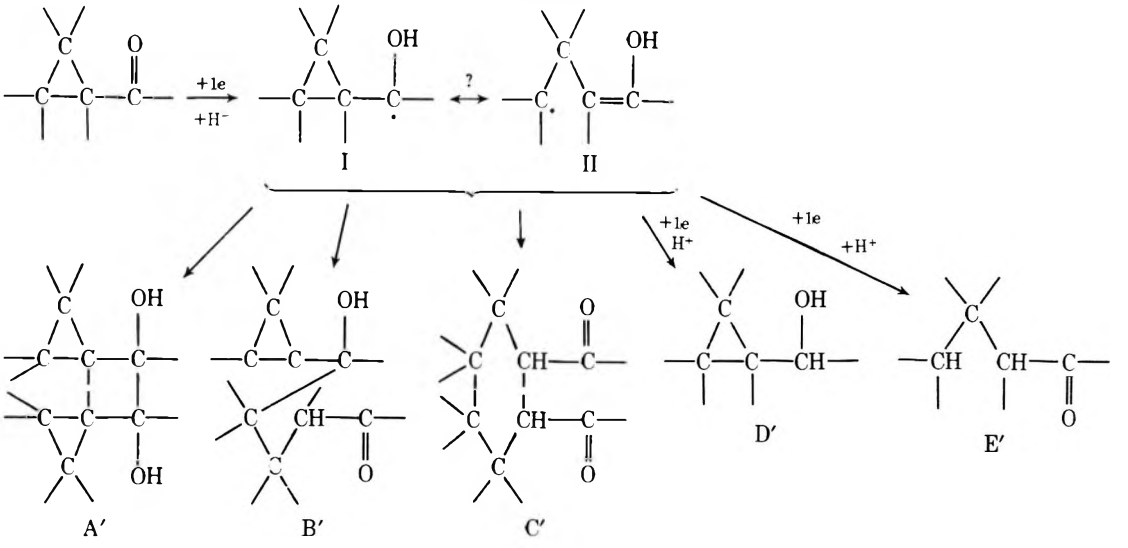
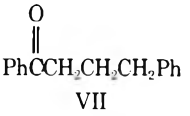
Scheme I

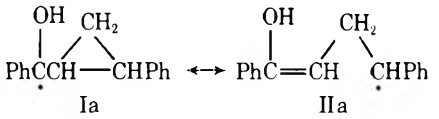


Scheme II





VII



Ia IIa

Experimental Section

Melting points are not corrected. NMR spectra were recorded on the Varian Model EM-360 using $CDCl_3$ as solvent and tetramethylsilane as an internal standard. IR spectra were taken on the Perkin-Elmer Model 257 spectrometer in spectral grade $CHCl_3$ as solvent. Gas chromatographic analysis was done on the Hewlett Packard Model 5712A. UV spectra were run on a Cary 14 recording spectrophotometer. The pH of solutions were measured with a Corning Digital 110 pH meter. Polarographic runs and controlled potential electrolyses were done on a Princeton Applied Research Model 170 Electrochemistry system (dropping mercury electrode and a saturated calomel electrode, SCE, for the polarography).

Preparation of Buffer. Na_2HPO_4 (14.196 g, 0.10 mol) was dissolved in 200 mL of distilled water. Enough water was then added to make 500 mL of 0.20 M Na_2HPO_4 solution. To this solution was added, with stirring, enough solid citric acid to bring the pH to approximately 3. Distilled water was added to increase the volume to 950 mL and then the pH was brought to exactly 3 with 1 M citric acid solution. Finally, the total volume was brought to 1 L.

Polarography of Ketones III and IV. The polarography was carried out in a 20-mL H-type polarographic cell. Solutions were purged with N_2 for 15 min before polarograms were run. The half-wave potential ($E_{1/2}$) for III (2.82×10^{-3} M in 1:1 EtOH/buffer) was -1.32 V vs. SCE for the addition of the first electron and -1.40 V for the addition of the second electron. For ketone IV (4.33×10^{-4} M in 3:2 EtOH/buffer) one wave with $E_{1/2} = -1.0$ V was observed.

Controlled-Potential Electrolysis of Ketones III and IV. The electrolysis cell was a convential three-electrode system, namely, mercury (instrument grade) pool working electrode (cathode), a saturated calomel reference electrode, and a Ag|AgCl auxiliary electrode (anode) which was separated from the solution by a fritted glass disk. Both reductions were carried out under N_2 atmosphere and with the mercury pool being stirred rapidly by a magnetic stirrer. Prior to each electrolysis the system was purged with N_2 for 30 min until a steady current for the system was reached.

Ketone III. EtOH/buffer (1:1, 220 mL) was placed in the electrolysis cell and purged with N_2 and the reduction potential was set at -1.38 V. After a steady background current was obtained 1.46 g (0.01 mol) of cyclopropyl phenyl ketone (III) in 30 mL of EtOH was added. The current returned to background level after 5 h. The pH of the solution was adjusted to 8 with saturated $NaHCO_3$ solution and the resulting solution was then extracted four times with 100-mL portions of $CHCl_3$. The $CHCl_3$ extracts were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated to a cloudy oil.

Ketone IV. EtOH/buffer (3:2, 200 mL) was placed in the electrolysis cell and purged with N_2 and the reduction potential was set at -1.20 V and a steady background current obtained. *trans*-1-Benzoyl-2-phenylcyclopropane (IV) (2.15 g, 9.69×10^{-3} mol) in 50 mL of EtOH was added. After 21 h the current returned to background level. The solution was distilled under reduced pressure on a rotary evaporator to remove the ethanol. The pH of the aqueous solution which remained was brought to 8 by the addition of saturated $NaHCO_3$ solution and the solution was extracted five times with 100-mL portions of $CHCl_3$. The organic extracts were combined, dried over anhydrous $MgSO_4$, filtered, and concentrated to a cloudy, viscous oil (2 g, 90% recovery).

Product Isolation and Identification

Products of Electrolysis of Ketone III. The cloudy oil

obtained from work-up of the reduction of cyclopropyl phenyl ketone (III) was chromatographed on 85 g of Silicar CC-7, eluting with 10% ether in hexane. Three peaks totaling 1.0427 g were obtained. The first peak, 418 mg (40.09%), was the starting ketone III. The second peak, 447.6 mg (42.93%), was identified as the dimeric glycol (V). The final peak, 177.1 mg (16.98%), was determined by NMR analysis to be the 2-e reduction product, cyclopropylphenylcarbinol (VI).

Peak 2. Glycol: NMR δ 0.43 (m, 8 H), 1.55 (m, 2 H), 2.20 (s, 1 H, exchangeable with D_2O), 2.40 (s, 1 H, exchangeable with D_2O), 7.14 (m, 10 H); IR 1440 (w) 3580 (m); mp 115–120 °C. Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.63; H, 7.48. Found: C, 81.56; H, 7.52. This material is a mixture of *dl* and meso diols.

Peak 3. Cyclopropylphenylcarbinol: NMR δ 0.48 (m, 4 H), 1.22 (m, 1 H), 2.04 (s, 1 H, exchangeable with D_2O), 3.98 (d, 1 H, J = 8 Hz), 7.22 (m, 5 H).

Products of Electrolysis of Ketone IV. Thin-layer chromatography and GC analysis showed the viscous oil isolated from the reduction of 1-benzoyl-2-phenylcyclopropane (IV) contained only two products. One of the products had the same retention times as the starting material, and the NMR of the mixture indicated the presence of the ketone (IV). Area calculations of the GC trace showed the starting material comprised 24.8% of the mixture. The viscous oil was recrystallized from hexane to give a white crystalline substance that still contained some of the starting ketone. The crystals were chromatographed twice on Silicar CC-7, eluting with 15% ether in hexane. The only pure product isolated from the column, other than starting material, proved to be the 2-e reduction product, γ-phenylbutyrophenone, VII. Several fractions contained mixtures (by NMR and GC) of IV and VII. Evidence for the structure of VII is given below.

γ-Phenylbutyrophenone (VII): NMR δ 2.10 (m, 2 H), 2.82 (m, 4 H), 7.05–7.98 (m, 10 H); IR 1450 (m), 1580 (m), 1600 (m), 1680 (s), 2940 (m), 3000–3090 (m); UV λ_{max} 228 nm, ϵ 15 068 (1.46×10^{-5} M in hexane); mass spectrum, molecular ion peak at 224, intense peaks at 120 and 105, base peak at 77. Anal. Calcd for $C_{16}H_{16}O$: C, 85.68; H, 7.19. Found: C, 85.52; H, 7.20; mp 51–52 (lit.[10] mp 56–57 °C).

Registry No.—III, 3481-02-5; IV, 1145-92-2; V, 60079-97-2; VI, 1007-03-0; VII, 5407-91-0.

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Communications

Palladium Hydrides in Organic Synthesis. Reduction of Aryl Halides by Sodium Methoxide Catalyzed by Tetrakis(triphenylphosphine)palladium

Summary: Aryl halides react with sodium methoxide and catalytic amounts of tetrakis(triphenylphosphine)palladium in DMF at ~100 °C to produce arenes.

Sir: We have undertaken the investigation of new applications of transition metal hydrides as intermediates in organic synthesis.[1] Of the several methods for the generation of these hydrides, the most common are reactions of transition metal complexes with hydrogen or main group hydrides. Another common method, the reaction of various complexes with alcohols in the presence of base or with alkoxides,[2] is especially attractive because of the ready availability and low cost of these materials as sources of hydride.

For our initial studies, we chose to examine the reduction of organic halides. In synthesis, the need occasionally arises to remove a halogen atom that has been introduced to temporarily block a given position, as an activating group, or as the side result of other synthetic operations.[3] We now wish to report a new method for the reduction of aryl halides to arenes catalyzed by tetrakis(triphenylphosphine)palladium(0) (**1**)[4] with sodium methoxide as the source of hydride (eq 1). Typical results of this reaction are summarized in Table I.

$$\mathrm{ArX} + \mathrm{NaOCH_3} + 0.05\ \underset{\mathbf{1}}{\mathrm{Pd(PPh_3)_4}} \xrightarrow[\mathrm{DMF}]{\sim 100\ ^\circ\mathrm{C}} \mathrm{ArH} \qquad (1)$$

Commercially available sodium methoxide is satisfactory for this reaction. Normally, an excess (50%) is employed in order to allow for possible decomposition during storage and handling, although if adequate precautions are taken, the use of this excess is not necessary. Both this reagent and the catalyst (**1**) may be weighed conveniently in the air and then transferred to the reaction vessel which is then placed under an inert atmosphere for the duration of the reaction. *N,N*-Dimethylformamide (DMF) is normally used as the solvent for this reaction, but other polar solvents may also be employed. For example, with either ethanol or methanol as the solvent, ~80% yields of benzene are obtained from bromobenzene. Also, methoxide is not the only alkoxide which may be employed in the reduction. For example, sodium isopropoxide[5] reacts with 2-bromonaphthalene in DMF at 60 °C for 6 h to give naphthalene in 62% yield (94% conversion of the bromide). Despite the higher reaction temperature required for the use of methoxide, we have chosen to emphasize the use of this reagent in our initial studies because of the convenience provided by its air stability and commercial availability.

The principal utility of the reaction is the reduction of aryl bromides. Chlorobenzene (run 13) undergoes only a very low conversion under our usual conditions. The presence of a nitro substituent (runs 9 and 10) increases the rate of the reaction, but the reduction product is accompanied by a considerable amount of coupling product, the corresponding biaryl (Ar–Ar). Coupling is also observed for a substrate bearing a carbomethoxy substituent (run 8) and for iodobenzene (run 12). For the remaining cases, the yields of biaryls are generally quite low (0–2%). Other side products are *N,N*-dimethylanilines ($\mathrm{ArNMe_2}$, 0–5%) and anisoles ($\mathrm{ArOCH_3}$, 0–1%). Also, small amounts of benzene (~10% yields based upon the amounts of aryl halides) have been detected in several cases (e.g., runs 2–4) in which this product could not be formed from the starting aryl halide.[6]

Table I. Reduction of Aryl Halides

Run	Aryl halide	Time, h	Temp, °C	Conversion, %	Yield of ArH, %[a]
1	Bromobenzene	4.5	95	100	89
2	2-Bromotoluene	5.0	95	100	89
3	4-Bromotoluene	4.5	100	100	70
4	2-Bromonaphthalene	4.0	100	100	85[b]
5	1-Bromonaphthalene	4.0	120	78	84
6	4-Bromophenyl phenyl ether	4.0	100	100	81[b]
7[c]	Sodium 3-bromobenzoate	3.5	140	58	100
8	Methyl 3-bromobenzoate	4.0	100	95	54[d]
9	4-Chloronitrobenzene	4.0	100	100	43[d]
10	4-Bromonitrobenzene	4.5	100	100	39[d]
11[c]	Sodium 4-bromophenoxide	4.0	100	[e]	36
12	Iodobenzene	4.0	80	100	44[d]
13	Chlorobenzene	3.0	100	1	50

[a] Unless otherwise noted, the yields were determined by GLC with an internal standard. All yields are based upon the amounts of aryl halides consumed. [b] This value is an isolated yield. [c] The sodium salt was formed in situ from the neutral compound by use of an additional equivalent of sodium methoxide. [d] This product was accompanied by large amounts of the corresponding biaryl (~30–50% yield). [e] The conversion was not determined in this case.

A number of other methods have been reported for the reduction of aryl halides,[7] some of the more important methods being the use of catalytic hydrogenolysis,[8] Raney nickel,[9] lithium aluminum hydride,[10] organotin hydrides,[11] and copper hydrides.[12] The advantages of our method over these earlier approaches are the use of a very simple, readily available, inexpensive, and comparatively nonhazardous source of hydride, better functional group compatibility than several of the other methods (see runs 7–10), the catalytic use of the metal species, and the simplicity and convenience of performing the reaction using routine laboratory glassware.

A likely pathway for the reaction is outlined in Scheme I. Oxidative addition[13] of the aryl halide to a coordinatively unsaturated zerovalent palladium complex is followed by metathetical displacement of halide from the adduct **2** to give the methoxo complex **3**, which then forms the hydride complex **4** and formaldehyde. Finally, reductive elimination of the arene from **4** regenerates the catalyst. The steps leading from **2** to the arene are well-precedented in earlier work,[2c,14] including the oxidation of alcohols to carbonyl compounds by palladium salts.[15] Because we have been unable to detect formaldehyde in our reaction mixtures, we doubt whether it is produced in free form, but it probably undergoes further oxidation as has been reported for other systems.[16] To date we have made no attempts to identify other products derived

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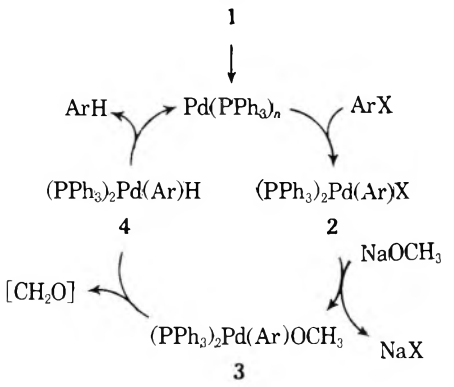
Scheme I



from the formaldehyde or possibly from the solvent, DMF. Also, the nature of the palladium species remaining after completion of the reaction has not been investigated. Therefore, we cannot rule out other possible mechanisms at this time.

The formation of the various side products is explainable on the basis of Scheme I. Biaryls have previously been obtained from arylpalladium complexes.[17] Reductive elimination from 3 would produce anisoles, and metathetical displacement of halide from 2 by the *N,N*-dimethylamide ion derived from DMF would lead to anilines. Formation of benzene may result from cleavage of a carbon–phosphorus bond of the triphenylphosphine ligand, a process for which several other workers have reported evidence.[18]

A typical procedure is given for the reduction of 2-bromonaphthalene (run 4). Into a round-bottom flask equipped with a magnetic stirring bar were placed 2-bromonaphthalene (0.414 g, 2.00 mmol), sodium methoxide (0.162 g, 3.00 mmol), and 1 (0.116 g, 0.100 mmol) at 25 °C. The mixture was then placed under nitrogen, DMF (4 mL) was added, and the heterogeneous yellow mixture was heated at 100 °C for 4 h. The resulting orange solution was cooled to 25 °C and diluted with ether, water, and pentane. The crude product was isolated from the organic layer and was purified by sublimation [75–140 °C (16 Torr)] to afford 0.218 g (85%) of naphthalene as white crystals, mp 79–80 °C (lit.[19] mp 80.2 °C).

Further work is in progress to explore other conditions for performing the reduction,[20] the generation of the catalyst in situ, the use of other transition metal species as catalysts, and the reduction of other types of organic halides and of other classes of compounds. We also intend to investigate conditions for obtaining the biaryls as the major products because of the important potential of this reaction to provide a metal-*catalyzed* method for the coupling of aryl halides as opposed to the usual methods which employ stoichiometric amounts of metal-containing reagents.[21–23]

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(22) An approach to optimization of biaryl formation is to employ a reducing agent which is capable of reducing Pd(II) to the catalytically active Pd(0) species but which does not lead to reduction of the aryl halides.
(23) Because the biaryls could conceivably have been formed from the arenes (the reduction products) by the well-known Pd(II)-catalyzed arene coupling reaction,[24] a control experiment was performed in which 2-bromotoluene was reduced under the usual conditions but in the presence of 1 equiv of benzene. No (<0.1%) biphenyl or methylbiphenyls were formed. Therefore, the biaryl side products are probably formed by a direct coupling of the aryl halides.
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1,2-Transposition of Ketones via Vinylsilanes

Summary: New methodology for shifting a ketone carbonyl by one carbon is described. The scheme, which involves sequential vinylsilane generation from an arenesulfonyl hydrazone, epoxidation, hydride reduction, and chromic acid oxidation, is both simple and efficient.

Sir: The carbonyl group plays a pivotal role in bringing latitude to organic synthesis. The need to relocate this functional group within a molecule occurs with such frequency that interest in efficient methods of carbonyl transposition remains high. Various procedures have been developed for effecting site exchange within saturated[1–9] and α,β-unsaturated ketones,[10–13] sometimes in tandem with an alkylation step,[14–17]

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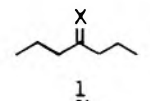
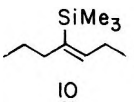
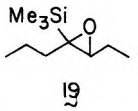
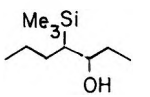
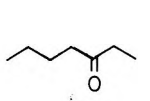
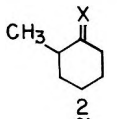
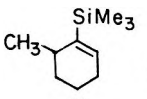
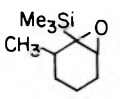
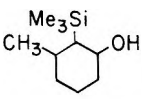
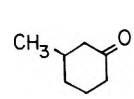
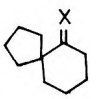
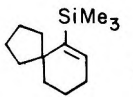
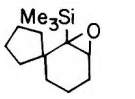
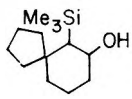
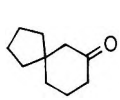
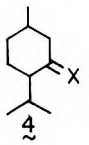
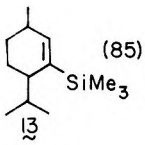
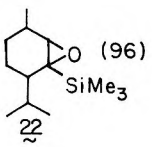
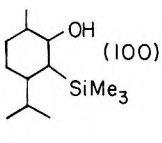
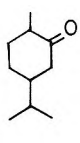
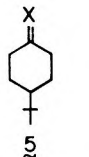
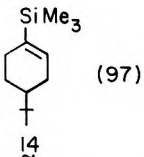
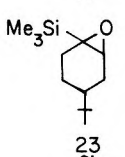
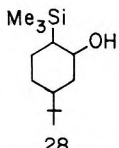
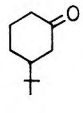
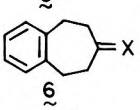
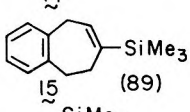
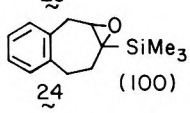
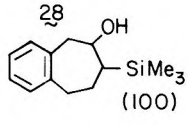
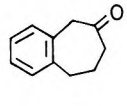
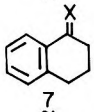
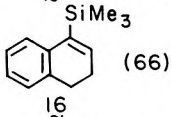
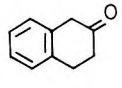
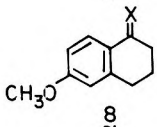
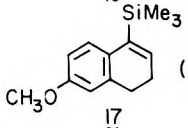
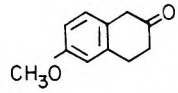
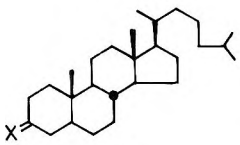
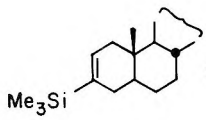
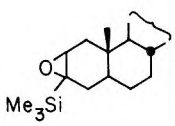
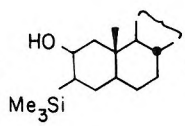
Table I. Carbonyl Transposition Data[a,b]

Substrate[c]	Vinylsilane	Epoxysilane	β-Silanol	Ketone
 1	 (96) 10	 (97.5) 19	 (88)	 (84)
 2	 (91) 11	 (89) 20	 (83) 26	 (84)
 3	 (67) 12	 (91) 21	 (95)	 (66)[f]
 4	 (85) 13	 (96) 22	 (100)	 (90)
 5	 (97) 14	 (87) 23	 (e) 28	 (83)
 6	 (89) 15	 (100) 24	 (100)	 (63)[g]
 7	 (66) 16	d	d	 (83)
 8	 (67) 17	d	d	 (96)
 9	 (33) 18	 (100) 25	 (43)[h]	(87)

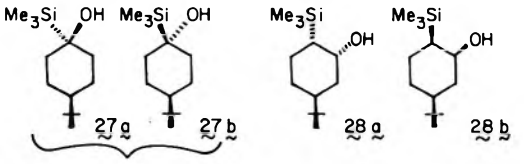
[a] All compounds were identified by IR, NMR, and accurate mass spectral measurements. Additionally, the vinylsilanes were characterized by combustion analysis. The transposed ketones were identified by comparison with authentic samples of the ketones or derivatives thereof. [b] The percentage yields which are provided in parentheses represent the isolated yields at each step. [c] For convenience purposes, these structures will be further defined as follows: **a**, X = O; **b**, X = $NNHSO_2C_6H_5$. [d] These intermediates were not isolated under the conditions employed (see text). [e] See text for discussion of results. [f] Reference 5. [g] G. Bodennec and M. St. Jacques, *Can. J. Chem.*, **55**, 1199 (1977). [h] The remainder of the product was the α-silyl alcohol.

and these have met with varying degrees of accepted usage. We now wish to describe a quite different approach to the 1,2-transposition of ketones which takes advantage of the chemical properties associated with covalently bonded silicon.

Previous work in this laboratory[18] and elsewhere[19] has demonstrated that vinyl carbanions generated through reaction of ketone arenesulfonyl hydrazones with alkyllithium reagents in TMEDA solution[20] condense with chlorotrimethylsilane to deliver vinylsilanes in very good yield. Where relevant, this transformation is regiospecific, deprotonation occurring perferentially for electronic reasons at the lesser substituted α position.[21] A representative selection of such conversions is provided in Table I.

The vinylsilanes undergo smooth oxidation to their epoxides[22] at 0 °C in dichloromethane solution with 1.1 equiv of *m*-chloroperbenzoic acid. Subsequent reductions with lithium aluminum hydride were performed in anhydrous tetrahydrofuran at room temperature (**19, 20,** and **23**) or under reflux conditions. In early work, Eisch and Trainor discovered that hydride attack on α-silyl epoxides occurs preferentially at the silicon-bearing carbon.[23] More recently, Robbins and Whitham have demonstrated that hydride reduction of the conformationally flexible 1,2-epoxy-1-trimethylsilylcyclohexane molecule is stereospecific as well, *cis*-2-trimethylsilylcyclohexanol being the only product isolated.[24] In the present study, we have found that the electronic directing effect of silicon is inadequate to overcome the normal kinetic bias for trans diaxial ring opening in conformationally rigid systems. When ring inversion is not severely impeded as in **20, 21, 22,**

Table II. Specificity of Mixed Hydride Reductions of 23a and 23b[a]



$LiAlH_4/AlCl_3$	Probable effective reagent	27a + 27b	28a	28b
1:0	$LiAlH_4$	76	24	
1:1.2	$AlHCl_2$	23	59	18
1:1	AlH_2Cl	5	64	31
2:1	$AlH_2Cl + AlH_3$	9	50	41
3:1	AlH_3	11	57	32

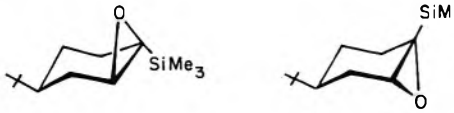
[a] Reactions conducted in anhydrous ether at 0 °C to room temperature. The percentage composition values given were obtained by vapor-phase chromatography (thermal conductivity detector), are uncorrected as to relative response to detection, and are normalized to exclude small amounts of recovered epoxide. [b] Structural assignments to these alcohols were made chiefly on the basis of their ^1H NMR spectra [W. K. Musker and G. L. Larson, *Tetrahedron Lett.*, 3481 (1968)].

and **24**, ring opening occurs by regiospecific α attack in the usual manner. For example, vinylsilane **11**, which is presumed to exist as a pair of rapidly equilibrating conformational isomers,[25] is converted to the epoxide mixture **20a** and **20b**

20a 20b

(38:62). These isomers were separated by vapor phase chromatography, identified by $Eu(fod)_3$ shifting of their ^1H NMR spectra,[26] and separately reduced to give only β-trimethylsilylated alcohol.

When the identical reduction procedure is applied to more rigid α-silyl epoxides such as **23** and **25**, mixtures result. Our findings with **23** are exemplary (Table II). Upon epoxidation of **14**, there was produced a 40:60 mixture of **23a** and **23b**



23a 23b

which, because it proved difficultly amenable to separation, was utilized as such. It is, of course, not feasible to estimate accurately the ground- and transition-state conformational interaction energies which gain importance within **23a** and **23b** as reduction proceeds. Nor can some degree of anomalous mechanistic behavior be ruled out in such reactions.[27] However, the level to which **27a** and **27b** are produced in the presence of $LiAlH_4$ alone is clearly not at all acceptable for our synthetic purposes. As a means of enhancing the electrophilic nature of the α carbon in such epoxides, we have examined the efficacy of various "mixed hydrides"[28] and uncovered remarkably enhanced specificity for α attack, particularly with AlH_2Cl (95% combined yield of **28a** and **28b**).[29]

Application of similar methodology to **25** likewise results in higher levels of α-bond fission, thereby illustrating the versatility of this modification.

Typically, the β-silylethanols are oxidized with a stoichiometric quantity of chromic acid under two-phase (ether/water) conditions[31] to deliver the pure transposed ketone. The rate of acid-promoted desilylation[32] of the intervening α-silyl ketones was found to be accelerated by increased amounts of acid and therefore 10 molar equiv of H_2SO_4 were routinely utilized.

In the case of the activated vinylsilanes **16** and **17**, treatment with buffered ($NaHCO_3$) *m*-chloroperbenzoic acid in dichloromethane led directly to the corresponding β-tetralone in high yield and there was no need for the customary reduction–oxidation sequence. The precise course of these one-step reactions has not been elucidated.

The present approach to 1,2-carbonyl transposition complements the existing methods. It employs a different substrate, a vinylsilane, as the relay intermediate. Since the ready availability of the latter from ketones is now well documented,[18,19] and since their subsequent chemical manipulation is exceptionally efficient, the scheme serves as a promising means for effecting the 1,2 migration of a carbonyl group. It is also minimally time consuming, since the intermediate products need not be isolated, but simply freed of solvent prior to further manipulation.

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(29) Reduction of **23** with AlD_2Cl afforded **28a** containing the isotopic label only at C_1, α to the silicon atom (^1H NMR analysis). Structural assignment to this alcohol was further secured by its reaction with sodium hydride in tetrahydrofuran to give 4-*tert*-butylcyclohexene-*1-d* (>92.5% d_1 by mass spectroscopy). Accordingly, the stronger Lewis acid character of AlH_2Cl and AlD_2Cl does not appear to bring into play a new mechanism such as initial electrophilic α C–O fission with concomitant intramolecular 1,2-hydride shift and subsequent normal reduction of 3-*tert*-butylcyclohexanone. The possible intervention of a pentacoordinated silicon hydride intermediate[30] which provides directionality to this epoxide-opening process has been neither established nor disproven.
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Peptide-Gap Inhibitors.[2] 2. Stereoselective Synthesis of Enantiomeric Dipeptide Analogues of Glycylleucine Which Contain Methylene Thioether Groups Substituted for Peptide Linkages

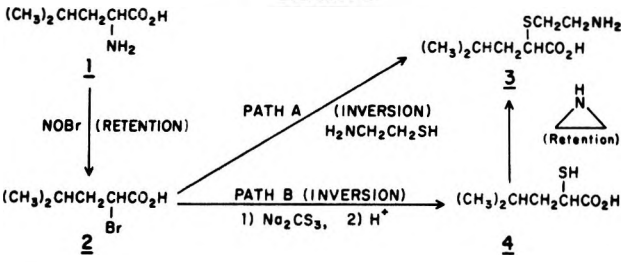
Summary: Stereoselective syntheses of (*R*)- and (*S*)-(*S*-cysteaminyl)-4-methylpentanoic acids have been developed which involve: (a) displacement of bromide in the appropriate enantiomers of 2-bromo-4-methylpentanoic acid by cysteamine; or (b) displacement of bromide of these substrates with thiocarbonate followed by aminoethylation of the resulting 2-mercapto-4-methylpentanoic acids.

Sir: Recently we reported from this laboratory that the dipeptide analogue *S*-2-(*S*-cysteaminyl)-4-methylpentanoic acid (**3**) binds several times more tightly to aminopeptidase M than the natural substrate glycyl-L-leucine.[1] **3** is a member of a class of peptide analogues which contain methylene thioether groups substituted for the peptide bond atoms. Model building as well as enzymatic studies indicate that such analogues may satisfy binding requirements while being resistant to enzymatic hydrolysis.[1] It is, therefore, clear that practical routes to such analogues would permit access to a broad new avenue for study and modulation of biological control. Accordingly, the purpose of this communication[2] is to describe for the first time two complementary synthetic paths which provide a general basis for gram scale preparation of peptide analogues of Gly–X, where X may be a variety of amino acids. The syntheses described are for the instances where X is L- or D-Leu.

Scheme I summarizes the routes. Treatment of D-leucine (**1**) (16.4 g, 125 mmol) with nitrosyl bromide,[3] followed by distillation of the crude product, gave 15.1 g (77.4 mmol) of purified (*R*)-2-bromo-4-methylpentanoic acid (**2**)[4]: bp 97–98 °C (0.25 mm); $[\alpha]_D^{22}$ +38.2 ± 1.8° (c 2, methanol) [lit. (*S* isomer),[4a] $[\alpha]_D^{27}$ −34° (methanol)]. The (*R*)-bromo acid (5.3 g, 27 mmol) was dissolved in 530 mL of nitrogen-purged 0.5 M $NaHCO_3$ and a threefold molar excess of 2-mercaptoethylamine hydrochloride (9.2 g, 81 mmol) was added (path A, Scheme I). The reaction vessel was flushed with nitrogen for 1 h and then sealed. After standing 24 h at room temperature, automatic amino acid chromatography revealed that 70% of **2** had been converted to **3**.

The solution was acidified with 6 N HCl and extracted twice

Scheme I



with ether. The ether extracts were discarded. The aqueous portion was neutralized with 2 N NaOH and diluted to 2 L with deionized water. This solution was desalted on a 5.5 × 30 cm column of Dowex 2-X8 resin according to Dréze et al.[5] The fractions from the 1 M acetic acid wash containing **3** were pooled and evaporated to dryness under reduced pressure. The residue was triturated with 20 mL of acetone (discarded) and then crystallized from 47.5% ethanol to give white needles (yield: 2.34 g, 12.1 mmol, 44.5%): mp 205–210 °C dec. For analytical purposes, **3** was subjected to gel filtration on Sephadex G-15 using 0.1 M acetic acid as eluent and was further crystallized: anal. ($C_8H_{17}NO_2S$) C, H, N, S; mol wt 191, QM^+ (*m/e*) 192; $[\alpha]_D^{21}$ −23.2 ± 1.2° (c 2, H_2O); ^1H NMR (90 MHz, 2 N DCl in D_2O) multiplets centered at δ 0.902 (6 H), 1.622 (3 H), 2.919 (2 H), 3.221 (2 H), 3.475 (1 H) ppm (DSS as standard); TLC R_f 0.48 (1-butanol–acetic acid–H_2O, 12:3:5, silica gel). **3** is resistant to 6 N HCl hydrolysis (24 h, 110 °C, 91% recovery) and elutes near the position of arginine during automatic amino acid chromatography of the single column type[6] (ninhydrin constant, 0.82 times that of leucine).

Alternatively, the same enantiomer of **3** may be prepared in two steps (path B) from the bromo acid **2**. Bromide was displaced with trithiocarbonate and the resulting thioester was decomposed with acid.[7] The product was extracted with ether and the ether extract was dried over sodium sulfate. Removal of the ether at reduced pressure left an oil which was subjected to vacuum distillation to give purified (*S*)-2-mercapto-4-methylpentanoic acid (**4**): $[\alpha]_D^{22}$ −23.8 ± 1.8° (c 1.8, ether) [lit[4b] $[\alpha]_D^{20}$ −15.6° (ether)]. Treatment of **4** with ethylene imine[8] gave crude **3**. Purification by Dowex 2-X8 column chromatography and recrystallization from 47.5% ethanol gave a 56% yield of **3** based on **4** or an overall yield from D-leucine of 34%, $[\alpha]_D^{22}$ −16.3° (c 1, H_2O). This compound was otherwise indistinguishable in all respects from that prepared by path A.

When L-leucine was substituted for D-leucine in path A the enantiomeric (*R*) form of **3** was obtained: $[\alpha]_D^{22}$ +24.1 ± 1° (c 2, H_2O).

The assignment of the *S* configuration to the product (**3**) derived from D-leucine, which exhibits a negative rotation at 589 nm, is supported by the following. (1) Substitution of 2-bromo acids branched at C-4 with nitrogen as the nucleophilic atom produces inversion of configuration.[9] Accordingly, treatment with mercaptoethylamine, where displacement by sulfur predominates over nitrogen, would also be expected to cause inversion as would trithiocarbonate. Aminoethylation of the mercapto acid **4** would not be expected to alter the configuration. The properties of **3** obtained by paths A and B are indistinguishable with the exception of the specific rotation. The greater magnitude of the rotation of **3** obtained from the single step synthesis suggests that this product is of higher optical purity. (2) Brewster's studies[10] suggest that the (*S*)-2-mercapto-3-methylpentanoic acid would have a negative rotation at the sodium D line as would the final product **3**. (3) The conclusion that both paths involve a predominant overall inversion of configuration is consistent with the observed binding patterns of the *S* and *R* analogues with aminopeptidase M. This enzyme is known to cleave only those

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peptides which contain L-amino acid residues.[11] As reported earlier the *S* form of **3** competitively inhibits aminopeptidase M with a K_I of 1.2 mM.[1] More recent studies have shown that the *R* form of **3** also inhibits competitively, but with a K_I of 9.2 mM, reflecting an eightfold preference for the *S* form. The corresponding constants for Gly-L-Leu and Gly-D-Leu were found to be 4.8 and 24 mM, respectively.[12]

When considering the preparation of other Gly–X analogues, it appears that if the displacement of bromide from the 2-bromo acid precursor is facile, then the preferred nucleophile is 2-mercaptoethylamine. However, in some instances the more powerful nucleophile, trithiocarbonate, may be required. The combination of the two synthetic approaches provides the basis for preparation of Gly–X analogues of substantial biochemical interest.

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(2) The term "peptide-gap inhibitor" (alternatively "pseudopeptide") is used to describe compounds whose structures are identical with dipeptides with the exception that the atoms of the peptide linkage (–CONH–) have been replaced by a methylene thioether linkage (–CH_2S–). Thus, any peptide containing this alteration exhibits a "gap" in its peptide backbone at the position of replacement. The support of this research by Grant EY 00969 from the National Eye Institute is gratefully acknowledged. Thanks are due to Dr. Arno F. Spatola of the Department of Chemistry for determination of the NMR spectra reported in this communication.

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(11) A. Light, *Methods Enzymol.*, **25**, 253 (1972).

(12) The methods employed for these determinations are described in ref 1.

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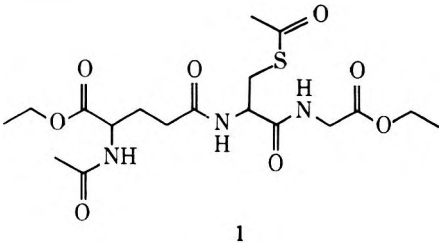
Thiazoles from Cysteinyl Peptides

Summary: Certain thiazoles are obtained via dehydrative cyclization of the corresponding cysteinyl peptides and oxidation of the resulting thiazolines with NiO_2; the biomimetic syntheses of two natural products are reported, as is the potential of NiO_2 as an oxidant for other partially reduced heterocycles.

Sir: Thiazolines and thiazoles are structural components of a number of peptide-derived natural products; among these are the antibiotics siomycin,[1] thiostrepton[2] and micrococcin P,[3] the antitumor antibiotics phleomycin[4] and bleomycin[4] (elaborated by *Streptomyces verticillus*), and Jadot's novel dicarboxylic amino acid (**4**),[5] isolated from the mushroom *Xerocomus subtomentosus*. Several lines of evidence suggest that the biosyntheses of these natural products proceed via the dehydrative cyclization of the corresponding cysteinyl peptides and subsequent oxidation to thiazoles.[6] The facility with which polypeptides may now be assembled makes the biomimetic preparation of peptide-derived thiazoles an attractive synthetic approach; the cysteinyl peptide → thiazoline → thiazole transformation has also been of interest as a possible peptide sequencing tool.[7] However, in spite of the potential utility of such transformations, and the likelihood that biosynthesis proceeds in this fashion, attempted chemical syntheses of all but the simplest thiazoles have failed during dehydrative cyclization[8] or subsequent dehydrogenation.[9] Our interest in the total synthesis of the thiazole-containing antibiotic bleomycin prompted us to reinvestigate the conversion of cysteinyl peptides to their corresponding thiazoles. We report herein the realization of this transformation in a synthetically useful fashion.

Cyclization of glutathione to the corresponding thiazoline was first reported by Calvin,[10] who observed its formation in strong mineral acid by monitoring changes in the ultraviolet spectrum of the reaction mixture. This observation has been verified by others, but it has not been possible to isolate the product.[11] Indeed, Hirotsu et al.[12] reported that their "attempt to secure a pure thiazoline compound by dehydration of *N*-acylglutathione dibenzyl ester in nonaqueous acidic medium . . . failed". In spite of the reported experimental difficulties, we observed that the slow addition of anhydrous hydrogen chloride to *N*,*S*-diacetylglutathione diethyl ester (**1**)[13] in a 5% ethanolic chloroform solution over a period of 24 h effected its cyclization to thiazoline **2**. Treatment of the reaction mixture with solid sodium bicarbonate, followed by filtration, concentration of the filtrate, and trituration of the residue with benzene afforded the thiazoline as a white solid in 70% yield. The proton NMR spectrum of thiazoline **2** included signals characteristic[14] of Δ^2-thiazolines at δ 3.61 (d, 2, J = 9.5 Hz) and 5.07 (t, 1, J = 9.5 Hz) and the UV spectrum had the expected[12] λ_{max} (1:1 C_2H_5OH–HCl) 267 nm (ϵ 5400); $[\alpha]^{25}_D$ +40° (*c* 2.0, $CHCl_3$). Dehydrative cyclization of several cysteinyl peptides not requiring prior ethanolysis of S-protecting groups has been accomplished conveniently in chloroform solution;[6,15] the choice of protecting groups was important in such cases, since better yields were generally obtained when the desired thiazolinium chlorides were insoluble in the reaction medium.



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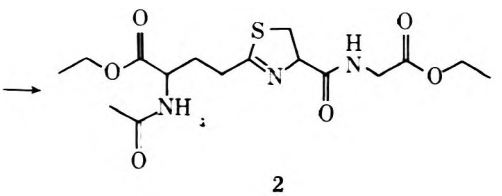

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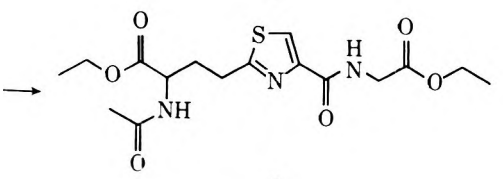

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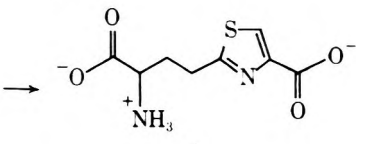

4

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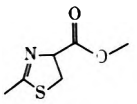
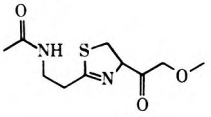
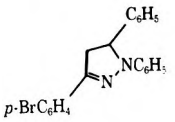
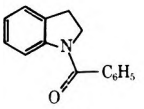
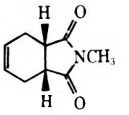
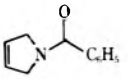
Table I. Nickel Peroxide Oxidations of Partially Reduced Heterocycles

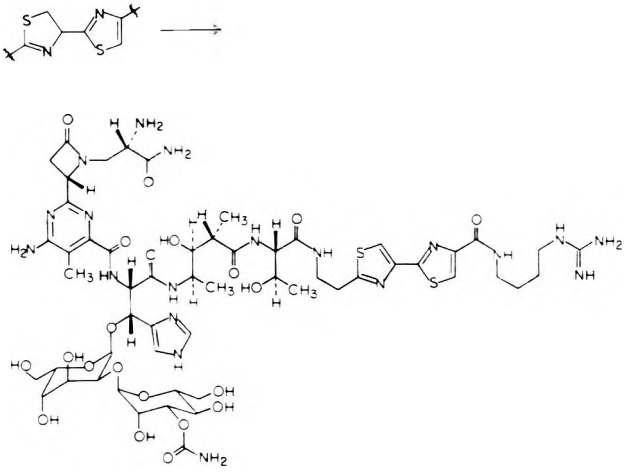
Heterocycle	NiO_2 (equiv O_2/equiv substrate)	Solvent	Conditions	% yield[a]
	2.0	$CHCl_3$	3 days, room temperature	81[b]
	3.7	C_6H_6	4 h, reflux	60
	2.4	$CHCl_3$	3 days, room temperature	93[c]
		C_6H_6	3 h, reflux	95[d]
	2.2	C_6H_6	11 h, reflux	52
	4.4[e]	C_6H_6	24 h, reflux	54
	2.3	C_6H_6	7 h, reflux	62[f]
	3.4	C_6H_6	3.5 h, reflux	59

[a] Isolated yields. The products were obtained by filtration of the catalyst through Celite, concentration of the filtrate, and purification where necessary by chromatography or crystallization. [b] Previously oxidized with phenanthrenequinone in 45% yield. [c] Oxidized in 65% yield with MnO_2. [d] Reference 16. [e] Oxidant was added in three equivalent portions. [f] Product was *N*-methylphthalimide.

The oxidation of several peptide-derived thiazolines was attempted using each of the reagents reported to have utility for this type of transformation,[9] and others not previously used for this purpose. Of the reagents tested, only manganese dioxide effected the desired transformation in a synthetically useful fashion, giving moderate yields of the corresponding thiazoles. In an effort to improve the yields, we considered the use of nickel peroxide[16] as oxidant, since this reagent is believed to function mechanistically in similar fashion to MnO_2.[17] Although preparations of nickel peroxide contain fewer oxidizing equivalents per gram of catalyst than does tion, we reasoned that the greater oxidizing power (or possibly instability) of Ni(IV) as compared with Mn(IV) should make NiO_2 the more effective oxidant.[18] In fact, treatment of thiazoline **2** with NiO_2 afforded the corresponding thiazole (**3**) as a clear oil in 75% yield; λ_{max} 232 nm; NMR ($CDCl_3$, $(CH_3)_4Si$) δ 1.28 (2t, 6), 2.05 (s, 3), 2.27 (bm, 2), 3.07 (t, 2, J = 7.5 Hz), 4.0–4.5 (m, 6), 4.77 (dd, 1, J = 7.5 Hz), 6.55 (bd, 1, J = 7.5 Hz), 7.90 (bs, 1), 8.00 (s, 1). As shown in Table I, the efficient oxidation of other thiazolines has also been achieved with NiO_2. Acid hydrolysis of thiazole **3** afforded a new compound (**4**) in 95% yield, identical with Jadot's mushroom acid.[19]

The mild, selective nature of the dehydrogenations achieved with NiO_2 can be judged by the successful conversion of

Scheme I



phleomycin A_2 to bleomycin A_2 (Scheme I).[20] The phleomycin molecule, which has substantial solubility only in water and stability only at neutral pH, is a complex, densely functionalized molecule.[4] Exacting requirements are thus made of any oxidant utilized for the conversion of phleomycin to bleomycin, since it must have a high degree of selectivity under a narrow range of conditions. Phleomycin A_2 was oxidized in neutral, aqueous solution by stirring with portions of nickel peroxide at room temperature. The course of the dehydrogenation was monitored by the increase in λ_{max} 290 nm and concomitant decrease in λ_{max} 242 nm;[21] analysis of the supernatant revealed 83% conversion to bleomycin A_2. The purified reaction product was shown to be identical with bleomycin A_2, as judged by proton NMR and chromatography on paper and cellulose TLC in five different solvent systems.[22] Parallel oxidation with MnO_2 revealed <30% conversion of phleomycin A_2 to bleomycin A_2 and much more extensive loss of material by irreversible adsorption to the oxidant.

Since NiO_2 has not been utilized as a reagent for heterocyclic dehydrogenations, we have begun to examine its reaction with partially unsaturated heterocycles. Several examples are included in Table I.

Acknowledgments. We thank Dr. H. Umezawa for samples of phleomycin A_2 and bleomycin A_2. This investigation was supported in part by contract NO1-CM-43712 from the Division of Cancer Treatment, National Cancer Institute, National Institutes of Health, Department of Health, Education, and Welfare.

Supplementary Material Available: Details of preparation procedures for compounds **1**, **2**, **3**, and **4** and for oxidation of compounds listed in Table I (4 pages). Ordering information is given on any current masthead page.

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(8) Reversible cyclization of simple *N*-acylcysteines in concentrated, aqueous mineral acid has been demonstrated repeatedly [see, e.g., ref 7; W. Stoffel and L. C. Craig, *J. Am. Chem. Soc.*, **83**, 145 (1961); H. A. Smith and G. Gorin, *J. Org. Chem.*, **26**, 820 (1961)]. However, decomposition of the thiazolines upon neturalization or dilution renders the procedure preparatively useless [see also R. E. Barnett, *Acc. Chem. Res.*, **6**, 41 (1973)].

Several Lewis acids have also been utilized for the preparation of relatively simple thiazolines [e.g., phosphorous pentachloride: S. Gabriel, *Ber.*, **24,** 1110 (1891); S. Gabriel and W. Coblentz, *ibid.*, **24,** 1122 (1891); phosphorous pentoxide: S. Gabriel, *ibid.*, **49,** 1110 (1913); phosphorous oxychloride[14]], but were found to be ineffective for the dehydrative cyclization of cysteinyl peptides. See, however, Y. Hirotsu, T. Shiba, and T. Kaneko, *Bull. Chem. Soc. Jpn.*, **40,** 2950 (1967); **43,** 1564 (1970).

(9) Reagents employed have included sulfur [F. Asinger, H. Diem, and A. Sin-Gun, *Justus Liebigs Ann. Chem.*, **643,** 186 (1961)], potassium ferricyanide,[7] mercuric acetate,[7] hydrogen peroxide, potassium dichromate [F. Asinger, M. Thiel, and L. Schroeder, *ibid.*, **610,** 49 (1957)], cupric sulfate,[14] ferric chloride [W. D. McElroy, E. H. White, F. McCapra, and G. F. Field, *J. Am. Chem. Soc.*, **83,** 2402 (1961)], MnO_2, and various quinones [M. A. Barton, G. W. Kenner, and R. C. Sheppard, *J. Chem. Soc. C,* 1061 (1966)].

(10) M. Calvin, "Symposium on Glutathione", Academic Press, New York, N.Y., 1954, p 3.

(11) E.g., an attempt to isolate the thiazoline by concentration of the acidic solution over P_2O_5 resulted in a mixture consisting of at least four products: I. Goodman and L. Salce, *Biochim. Biophys. Acta,* **100,** 283 (1955).

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(13) Compound **1** was prepared in 70% yield by treatment of glutathione with acetic anhydride and 1 M NaOH, followed by esterification with acetyl chloride in ethanol.

(14) J. C. Vederas, Ph.D. Thesis, M.I.T., 1973.

(15) Workup was simplified in these cases, involving only partition of the reaction mixture with aqueous carbonate and subsequent concentration of the organic layer.

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(18) F. A. Cotton and G. Wilkinson, "Advanced Inorganic Chemistry", 2nd ed, Wiley-Interscience, New York, N.Y., 1966, pp 798, 837, 838. Consistent with this suggestion was the greater activity of NiO_2 in the conversion of benzaldehyde to benzoic acid and the single report of the use of NiO_2 for the oxidation of nitrogen heterocycles.

(19) The new compound, isolated as the acetate, had the expected NMR spectrum in D_2O [δ 1.93 (s, 3), 2.35 (bd, 2) 3.17 (t, 2), 3.82 (m, 1), 7.97 (s, 1)] and infrared and ultraviolet spectra identical with those reported. (The structures of **2–4** were also verified by low- and high-resolution mass spectrometry). The synthesis of compound **4** in seven steps was reported previously;[5] however, no experimental details or yields were given and both the thiazoline- and thiazole-forming steps involved procedures which we have found to be of marginal utility in related cases.

(20) Conversions of phleomycins D_1 and E to bleomycins B_2 and B_4, respectively, with MnO_2 in unspecified yield has been reported by Umezawa and his co-workers: T. Takita, Y. Muraoka, A. Fujii, H. Itoh, K. Maeda, and H. Umezawa, *J. Antibiot.*, **25,** 197 (1972); H, Umezawa, *Biomedicine,* **18,** 459 (1973).

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(22) After destruction of the remaining phleomycin A_2 with acid, bleomycin A_2 was treated with copper(II) chloride and purified by chromatography on Sephadex C-25.[21] The product was identical with authentic bleomycin A_2, but not with phleomycin A_2, in five chromatographic systems. See ref 11b; H. Umezawa, K. Maeda, T. Takeuchi, and Y. Okami, *J. Antibiot., Ser. A,* **19,** 200 (1966); T. Takita, Y. Muraoka, A. Fujii, M. Itoh, K. Maeda, and H. Umezawa, *J. Antibiot.*, **25,** 197 (1972). After removal of copper,[21b] the conversion was also verified by proton NMR.

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(25) National Science Foundation Predoctoral Fellow, 1976–1979.

(26) National Cancer Institute Career Development Awardee, 1975–1980. Alfred P. Sloan Research Fellow, 1975–1977. John Simon Guggenheim Fellow, 1977–1978.

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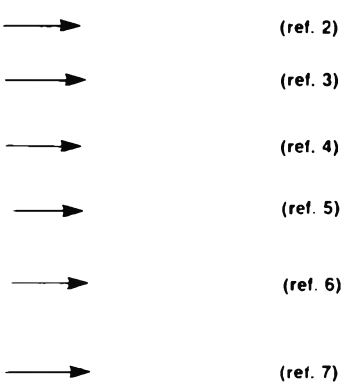
The reduction of aldehydes, ketones, and acid chlorides with **$NaBH_4$** is well known. However, numerous other interesting reductions have been reported using this reagent. The following are a few examples:



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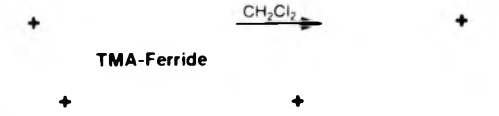
500g $38.50; 2kg $121.00

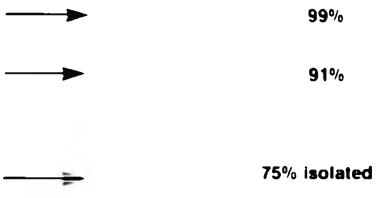
TMA-Ferride™

Recently, Cole and Pettit described the preparation and utility of a new reducing agent, **tetramethylammonium hydridoirontetracarbonyl**.[1] Aldrich now offers this reagent under the trade name **TMA-Ferride.™**

TMA-Ferride provides a mild and facile method for the reduction of acid chlorides to aldehydes in excellent yields.



This procedure was applied to several acid chlorides, including the following:



The ease and simplicity of this conversion of acid chlorides to aldehydes provides an improvement over existing methods.

Sodium and potassium hydridoirontetracarbonyl are useful for reductive alkylations,[2] hydroacylations,[3] dehydrogenations,[4] desulfurizations,[5] and hydrogenations.[6] However, the alkali metal hydridoirontetracarbonyl reagents can only be prepared and utilized in concentrated alkaline solutions. **TMA-Ferride** now provides a neutral source of the interesting hydridoirontetracarbonyl anion.

References:

1) T.E. Cole and R. Pettit, *Tetrahedron Lett.*, 781 (1977).
2) G.P. Boldrini, *et al.*, *Chem. Commun.*, 359 (1974), and *Synthesis*, 733 (1974); Y. Watanabe, *et al.*, *Tetrahedron Lett.*, 1879 (1974), and *Chem. Lett.*, 1265 (1974).
3) T. Mitsudo, *et al.*, *ibid.*, 1385 (1974).
4) H. Alper, *Tetrahedron Lett.*, 2257 (1975).
5) H. Alper, *J. Org. Chem.*, **40**, 2694 (1975); H. Alper and H.-N. Paik, *ibid.*, **42**, 3522 (1977).
6) R. Noyori, *et al.*, *ibid.*, **37**, 1542 (1972).

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