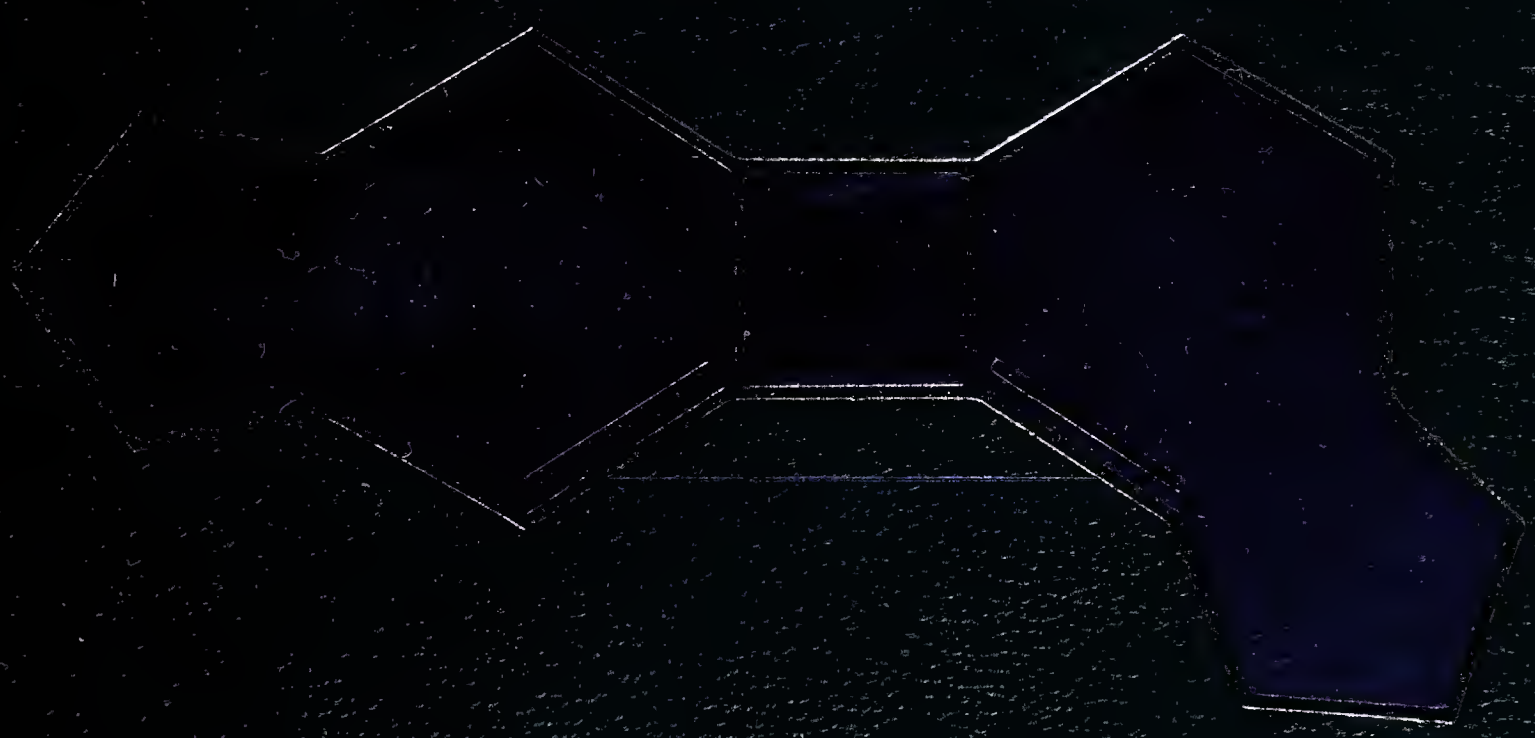
ALLENES IN ORGANIC SYNTHESIS



Herbert R. Schuster
Gary M. Coppola

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To
my wife Maro
and my parents
Heidi and Frank Schuster

H.F.S.

To
my parents
Richard and Josephine Coppola

G.M.C.

PREFACE

Within the last 25 years allene chemistry has progressed from intermittent experimental investigations of physical and chemical properties to development of modern methodologies that provide synthetically useful applications of the allene function to a variety of desirable intermediates and natural products. This veritable explosion of allene chemistry is evidenced by weekly reports appearing in the current chemical literature.

The purpose of this book is to describe the synthesis of a variety of functionalized allenes and their applications to the preparation of a variety of interesting chemical intermediates and natural products. Various synthetic approaches to a particular allene are discussed to make available to the chemist the optimal conditions for the desired results. Our aim is to demonstrate synthetic uses of allenes in almost all areas of organic synthesis with the hope of making the reader aware of alternate and sometimes superior avenues for an approach to a target compound. Consequently this book is geared for the organic chemist (whether in an industrial or academic environment) who is interested in the construction of complex molecules and natural products. We feel that this book will be a valuable addition to the chemist's library. To this end we dedicate our efforts.

The authors wish to thank Rosalie Piegario and Jean McCarthy for efficiently typing the manuscript, and Honora Lukas for assistance in the drawing of the structures.

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East Hanover, New Jersey
August 1984

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ABBREVIATIONS

Ac	Acetyl
AIBN	Azobisisobutyronitrile
Ar	Aryl
9-BBN	9-Borabicycyclo[3.3.1]nonane
BTA	Benzyltriethylammonium chloride
Cp	Cyclopentadiene
CSI	Chlorosulfonyl isocyanate
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DIBAH	Diisobutylaluminum hydride
DMAP	4-Dimethylaminopyridine
DME	Dimethoxyethane
DMF	N,N-dimethylformamide
DMSO	Dimethyl sulfoxide
DPIBF	1,3-Diphenylisobenzofuran
ee	Enantiomeric excess
HMPA	Hexamethylphosphoramide
LDA	Lithium diisopropylamide
LDCA	Lithium dicyclohexylamide
LTMP	Lithium 2,2,6,6-tetramethylpiperidide
MCPBA	*m*-Chloroperoxybenzoic acid
MSA	Methanesulfonic acid
NBS	N-bromosuccinimide
PCC	Pyridinium chlorochromate
PNPBA	*p*-Nitroperoxybenzoic acid
PPA	Polyphosphoric acid
PTSA	*p*-Toluenesulfonic acid
PTSH	*p*-Toluenesulfonyl hydrazide
Py	Pyridine
TBS	*t*-Butyldimethylsilyl
TBTH	Tri-*n*-butyltin hydride
TCNE	Tetracyanoethylene
TEA	Triethylamine
THF	Tetrahydrofuran
THP	2-Tetrahydropyran
TMEDA	N,N,N′,N′-tetramethylethylenediamine
TMS	Trimethylsilyl
Ts	*p*-Toluenesulfonyl (Tosyl)

Throughout this book the empirical formula for straight chain alkyl substituents is written without the *n* preceeding. For example, *n*-butyllithium is C_4H_9Li. All other branched alkyl groups have the corresponding letter included (*i*, *t*, *s*, etc.).

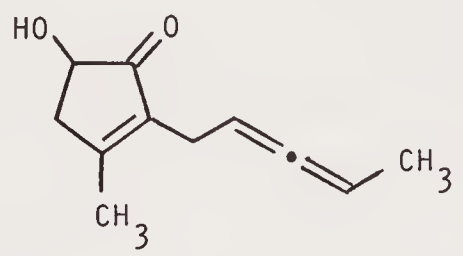
ALLENES IN ORGANIC SYNTHESIS

CHAPTER ONE

ALLENES: AN INTRODUCTION

1.1. HISTORICAL

Allenes comprise that class of compounds characterized by a 1,2-diene grouping. In 1887 Burton and Pechmann[1] prepared the first allenic acid, but it was not until 1954 that Jones confirmed its structure.[2] As a result of the mistaken belief that such a cumulated system would be unstable, allenes were mostly regarded as chemical curiosities. This, as well as insufficient methodology available for their syntheses, hindered the growth of allene chemistry.



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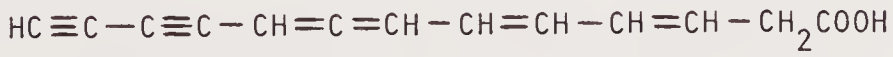
The first naturally occurring allene, pyrethrolone (**1**), was isolated by Staudinger and Ruzicka[3] in 1924. It was not until 1952 that a second naturally occurring allene, mycomycin (**2**), was isolated and characterized.[4] Subsequently, nearly 20 allenic metabolites were found in the Basidomycete fungi.[5] Allenes have also been found in higher organisms such as brown algae[6] and the seed oil of the Chinese tallow tree.[7] Most recently, several interesting haloallenes have been isolated and characterized from the red alga *Laurencia okamurai* Yamada.[8]

At present allenic compounds are being synthesized and chemically transformed



2

in a wide variety of ways. The strange and curious have become the familiar and useful.

1.2. STRUCTURE AND SPECTRA

This section briefly summarizes the spectral properties associated with the allenic structure to familiarize the reader with their intrinsic characteristics. An extremely thorough review presenting detailed physical properties of allenes has recently been published[9] and is an excellent source for additional information. Selected excerpts from that review are blended into this section.

A π-bond, as in olefins, results from the overlapping of the two parallel p-orbitals of each sp^2-hybridized carbon atom of the alkene. In the case of the cumulated 1,2-diene system, the central carbon is now sp-hybridized with two sets of orthogonal p-orbitals available for bonding with the remaining p-orbitals of the two terminal sp^2-carbon atoms of the diene. For maximum overlap to occur between these p-orbitals, the resulting π-bonds must be orthogonal to each other, as shown in Figure 1. Since the a and b groups attached to the trigonal carbon lie in a plane at right angles to the plane of the adjacent π-bond, their planes are also orthogonal to each other.[10] Hence there is a lack of conjugation owing to this perpendicular orientation of the π-bonded electrons in the two double bonds. The allene bond acts as a insulator between conjugated systems. However, each double bond of the allene portion will conjugate with a π-system directly attached to it. The correlation of the ultraviolet absorption of mycomycin (**2**) and some model compounds with this theory has been demonstrated.[4]

For the identification of allenes, the infrared spectrum is most useful. There are two significant bands; the first at 1950–1960 cm^{-1} is due to an antisymmetrical stretching vibration, whereas the second at 850 cm^{-1} is a result of the torsional motion of the allenic terminal methylene.[11] The absence of the second band is good evidence for the lack of a terminal allene group. The examination of the infrared spectra of 58 allenic compounds provides the following useful correlations[11]:

1. The asymmetric stretch at 1950 cm^{-1} appears as a doublet when the allene group is terminal and substituted with an electron-withdrawing group, such as an ester, amide, or ketone.
2. The intensity of this absorption band decreases with increasing substitution of the allene with electronically similar groups and is not greatly affected by groups with different electronic substituents.

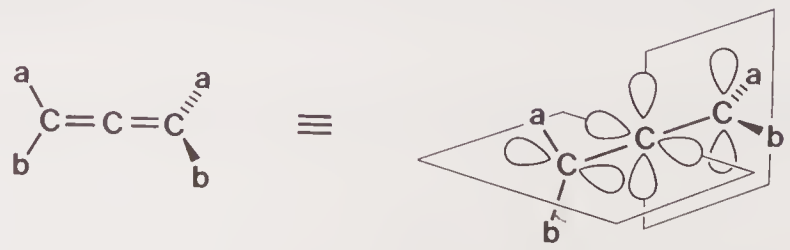


Figure 1. Orthogonal bonding of allene orbitals.

3. The substitution of fluorine atoms for hydrogen in allenes shifts the asymmetric stretch to longer wavelengths.[12]

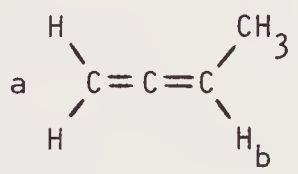
Proton magnetic resonance spectroscopy (^{1}H-nmr) is very useful for establishing the presence of an allene as well as providing information on the substituents attached to the allene. The chemical shifts of some alkylated allenes are shown in Table 1.1.[13]

When an allene is substituted by a halogen atom, an upfield shift occurs both in the proton on the same carbon atom as the halogen and in the proton at the other terminal position.[14] A phenyl ring results in a downfield shift of the proton on the same allene carbon atom as the phenyl ring.[15] The allenic protons of cyclic allenes are shifted slightly downfield from those of the acyclic systems.[16]

Carbon-13 nuclear magnetic resonance spectroscopy (^{13}C-nmr) provides an excellent method for the structural analysis of allenes. In general, for allenes bonded to a nonfunctionalized carbon, the central sp-hybridized carbon is found at extremely low field, in the range of 201–220 ppm.[17] Table 1.2 illustrates typical shifts for a variety of substituted allenes.

Most recently, an empirical method for the calculation of carbon-13 chemical shifts of allene carbons has been developed.[19] Using a multiple linear regression

Table 1.1. ^{1}H-NMR Chemical-Shift Data for Simple Allenes[a]



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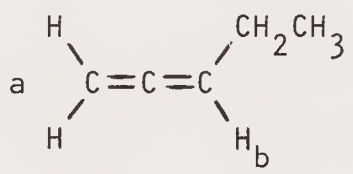

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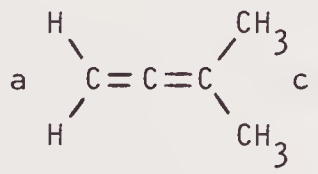

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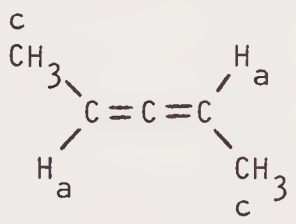

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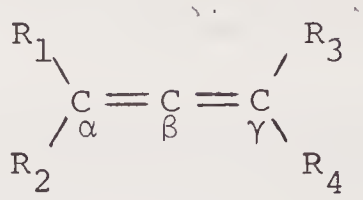
Compound	Chemical Shifts, δ (ppm) (TMS Standard) a	b	c	d	J_{HH} (Hz) (4-bond)	J_{H,CH_3} (5-bond)
I (1,2-Butadiene)	4.49	4.94	1.58	—	6.67	3.47
II (1,2-Pentadiene)	4.54	5.03	1.95	0.99	—	—
III (3-Methyl-1,2-butadiene)	4.40	—	1.62	—	—	3.15
IV (2,3-Pentadiene)	4.89	—	1.56	—	6.35	3.20

[a]Reprinted from Reference 13 with permission from John Wiley & Sons.

Table 1.2. ^{13}C-NMR Shifts of Substituted Allens[a,b]



Substituents				Chemical Shifts (TMS Standard)		
R_1	R_2	R_3	R_4	Cα	Cβ	Cγ
H	H	H	H	74.8	213.5	74.8
CH_3	H	H	H	84.4	210.4	74.1
H	H	CH_3	CH_3	72.1	207.3	93.4
CH_3	CH_3	CH_3	CH_3	92.6	200.2	92.6
C_2H_5	H	H	H	91.7	208.9	75.3
SCH_3	H	H	H	90.0	206.1	81.3
OCH_3	H	H	H	123.1	202.0	90.3
C_6H_5	H	H	H	94.5	210.3	78.7
Br	H	H	H	72.7	207.6	83.8
COOH	H	H	H	88.1	217.7	80.0
CN	H	H	H	80.5	218.7	67.2
CH_2SCH_3	H	H	H	88.6	210.5	76.1
H	H	CH_3	SCH_3	80.1	203.6	99.9
H	H	*i*-C_3H_7	SC_2H_5	80.8	201.9	110.0
C_6H_5	C_6H_5	C_6H_5	C_6H_5	113.6	209.5	113.6

[a]See Reference 18.
[b]Reprinted from Reference 18 with permission from John Wiley & Sons, Inc.

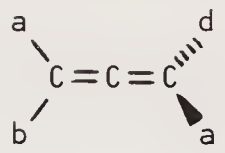
computer program (Algol-60), a set of substituent parameters was calculated for a number of most commonly occurring groups.

1.3. OPTICAL PROPERTIES AND CHIRALITY

As early as 1875 van't Hoff predicted that unsymmetrically substituted allenes should exist in two enantiomeric forms.[20] This has been confirmed by resolution of an allenic acid with a variety of alkaloids,[21] by synthesis with dissymmetric catalysts[22,23] and reagents,[24,25] and by use of reactions of active compounds containing asymmetric atoms.[26–29]

Asymmetric allenes contain no element of symmetry and can be represented in general by three cases[30]:

1. The ends of the allenic group bear three or four different types of achiral substituents as in **3** and **4**.



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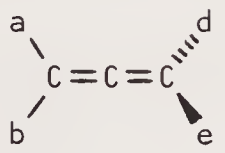

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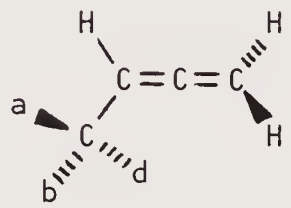
2. The allene possesses a chiral substituent as in **5**.



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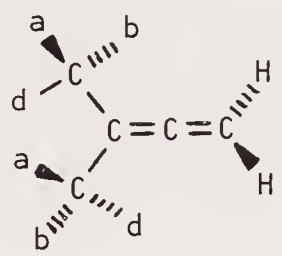
3. The allene contains two chiral substituents as in **6** or **7**.



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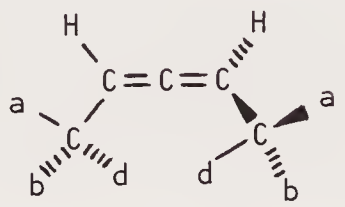

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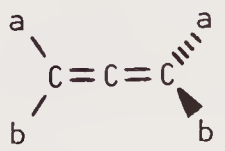
Allenes containing a C_2 proper axis of rotation are defined as ''dissymmetric'' and occur when[30]:

1. Both ends of the allene group bear two different achiral groups, **8**.
2. The substitution on different carbons of the allene is by two configurationally and structurally identical groups, each containing one or more chiral centers, **9**.



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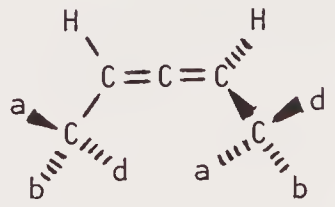

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Both asymmetric and dissymmetric allenes can exist in two enantiomeric forms. The configurational symbol for each enantiomer is assigned on the basis of the Cahn, Ingold, and Prelog[31] nomenclature. Consider, for example, allene **10**. If

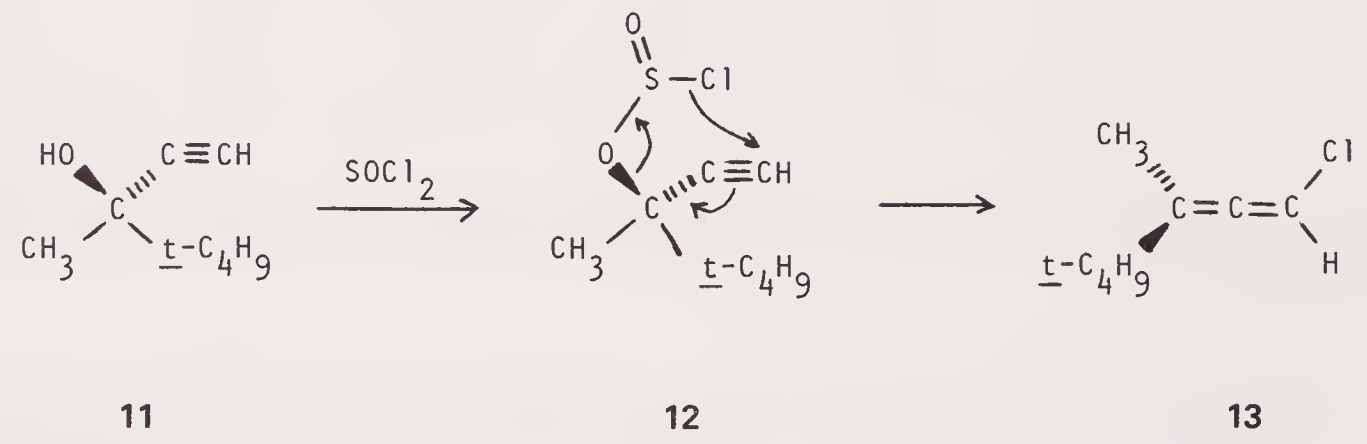
10 **10a**

viewed from the end of the molecule with a rotation of 90° about its longitudinal axis, projection **10a** results. The substituents located on the vertical axis take precedence over groups on the horizontal axis, with the order of precedence being

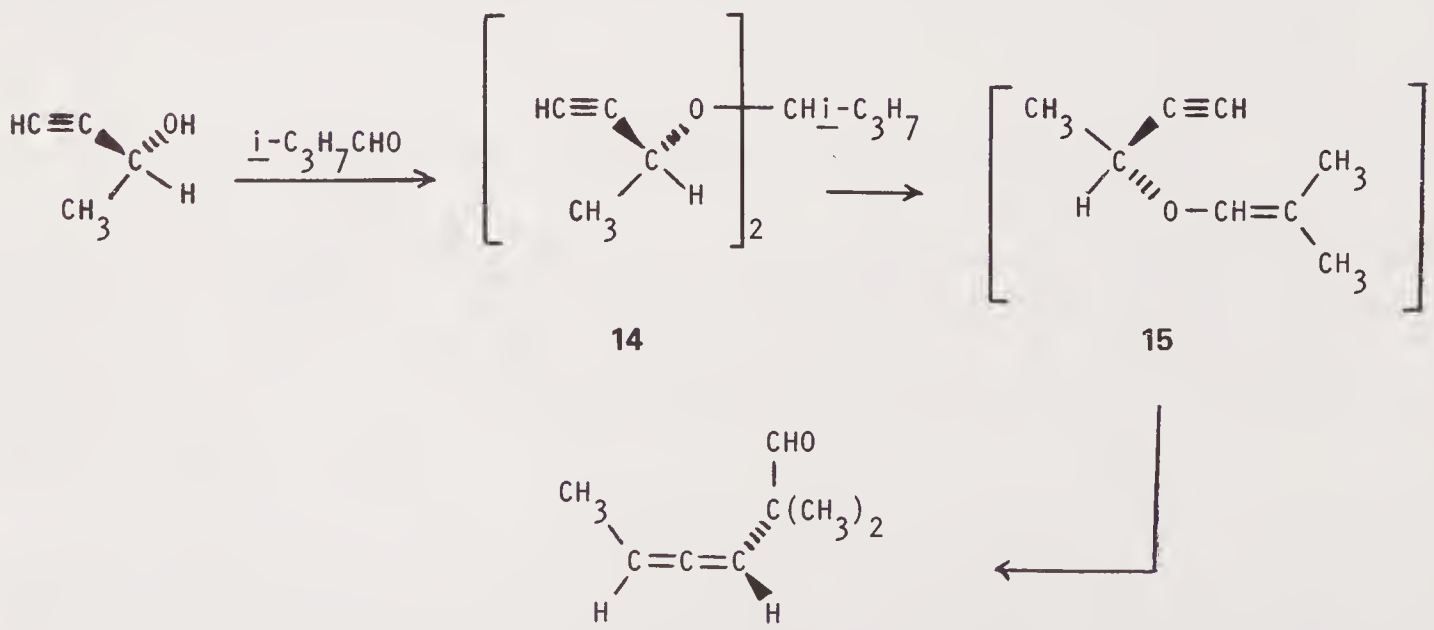
$$CH_3 > H > COOH > C_4H_9$$

Therefore, owing to the counterclockwise direction, allene **10** is assigned the (S)-configuration.[30]

Compounds containing asymmetric carbon atoms are known as "centroasymmetric or centrodissymmetric."[30] The determination of the absolute configuration of chiral allenes involves chemical correlations of the centrodissymmetric molecules of known configuration. For example, the stereospecific synthesis of (R)-(+)-1-chloro-3,4,4-trimethylpenta-1,2-diene (**13**) is correlated with (S)-(+)-3-hydroxy-3,4,4-trimethylpent-1-yne (**11**) through a cyclic S_Ni mechanism **12**.[26,33,34]



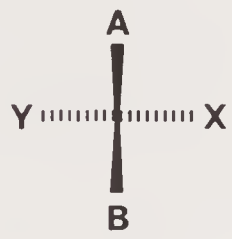
11 **12** **13**



14 **15** **16**

Another configurational correlation developed by Jones[27] is based on knowledge of the stereochemistry involving the transformation of a centrodissymmetric compound into an asymmetric chiral allene. This is illustrated by the stereospecific Claisen-type rearrangement of the enol ether **15**, derived from acetal **14**. If the acetal is dextrorotatory, then the allene **16** must be the (R)-(−) configuration.

The assignment of absolute configuration to allenic compounds can be accomplished by chemically transforming the allene, through stereospecific reactions, into derivatives, whose absolute configuration can easily be determined.[35,36] The Lowe–Brewster rule[37,38] relates the absolute configuration of a chiral allene to the sign of its rotatory power at the sodium D-line. The rule states that if the most polarizable substituent of a chiral allene is placed uppermost on the vertical axis of projection **17** and the more polarizable of the two rear substituents on the horizontal axis is to the right, a clockwise screw pattern of polarizability will be obtained and the enantiomer will be dextrorotatory; if the more polarizable of the two rear substituents is on the left side, the allene will be levorotatory.



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The rule is useful in predicting the absolute configuration of many chiral synthetic and "natural" allenes; however, (+)-1,2-cyclononadiene does not conform because the phase relationships between the induced dipoles along each C—C bond are such that the $A_1 \rightarrow B_2$ allene transition has an overall positive rotational strength.[39]

One highly successful determination of absolute configuration by physical methods is accomplished by observing the ultraviolet and circular dichroism spectra of an allene and applying the coupled-oscillator method.[40] Recently a sector rule for the absolute configuration of chiral allenes has been developed[39] from circular dichroism data of some chiral allenes with established configuration and the static and dynamic coupling theory of optical activity. The stereochemical configuration is predicted on the basis of the Cotton effect associated with the lowest energy absorption band of the allenic chromophore (220–250 nm).

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CHAPTER TWO

ALKYL, ARYL, AND CYCLIC ALLENES

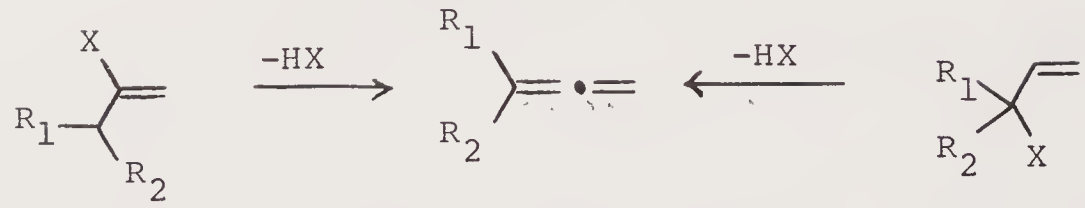
Allenic hydrocarbons serve as extremely useful precursors in the synthetic endeavors of the organic chemist. Allenes and their unique chemistry have been successfully applied to the preparation of pharmaceuticals, dyes, and elastomers as well as highly complex and strained molecules synthesized specifically for the investigation of their physical properties and reactivities. Appropriately substituted allenes which contain no element of symmetry are asymmetric. Reactions using these optically active substrates usually result in the transfer of chirality to the respective products and are therefore desirable in transformations leading to natural products.

Various examples of reactions using these starting materials are presented in subsequent portions of the book. Therefore, this chapter is devoted to the methods most amenable to the preferential, if not exclusive, formation of alkyl, aryl, or cyclic allenes over their acetylenic isomers. Several of the earlier examples are presented to keep the allene chemistry in perspective with the more modern methodologies and to demonstrate how their syntheses have progressed from those accepting virtually inseparable isomeric mixtures to elegantly orchestrated molecular manipulations generating pure allenes in reasonable yield. Several excellent reviews containing more detailed presentations including the historical aspects of the development of allenes and their chemistry are listed at the end of this chapter.

2.1. TERMINAL ALLENES

2.1.1. Elimination Reactions

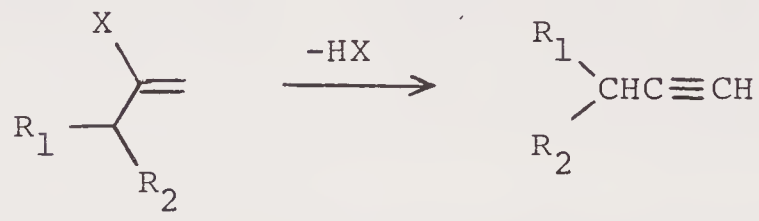
In considering the allene structure, a reasonable approach for the construction of the propadiene framework would be the elimination of HX from a suitably substituted alkene as shown in equation (1). Classically, transformations such as these have been performed by base-induced dehydrohalogenation of appropriate haloalkenes. The initial step of the reaction requires that the proton α to the leaving group be removed, therefore vinyl halides are more conducive to allene formation than



(1)

are the corresponding allylic halides (where vinylic deprotonation occurs less readily).

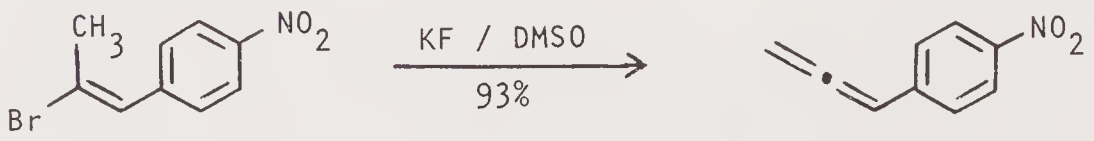
Since the reaction requires the use of a strong base (usually in excess), the method suffers from competing side reactions which render the allenic product severely contaminated and in relatively low yield. As shown in equation (2) the



(2)

contaminant is usually an acetylene. Its formation can also be rationalized by the base-promoted elimination of HX initiated by terminal vinylic deprotonation. Another source of the acetylene may be attributed to the base-catalyzed isomerization of the allene after its formation.[11,12] Usually the allene and the isomeric acetylene have similar boiling ranges and are extremely difficult to separate by distillation. However, the acetylene may be removed from the mixture by extraction with aqueous silver nitrate.[13]

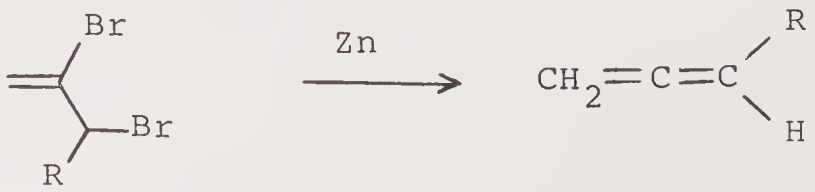
Fluoride ion may also be used as a promoting base for the elimination of halogen from a vinyl halide such as **1**, and the resulting *p*-nitrophenylallene (**2**) is isolated in excellent yield.[14]



(3)

1 **2**

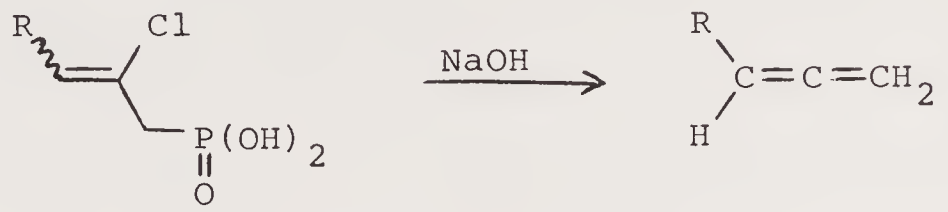
A generally reliable method for the preparation of allenes is the reductive elimination of two vicinal halogen atoms from a 1,3-dibromoalkene with zinc (equation 4).[15,16] An important feature of the reaction is that the position of the olefin remains intact, however, a possible drawback of the multistep sequence required to prepare the necessary dibromoalkene.



(4)

R = C_2H_5, C_3H_7, *i*-C_3H_7, C_4H_9, *i*-C_4H_9

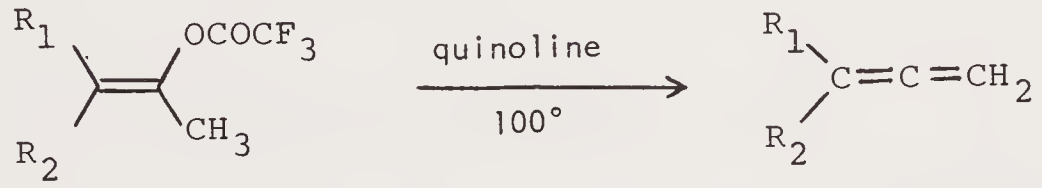
The fragmentation of 2-chloroalkyl-2-enylphosphonic acids in the presence of sodium hydroxide (equation 5) affords 1,2-alkadienes in moderate yields.[17]



(5)

$$R = C_3H_7,\ C_5H_{11},\ C_7H_{15}$$

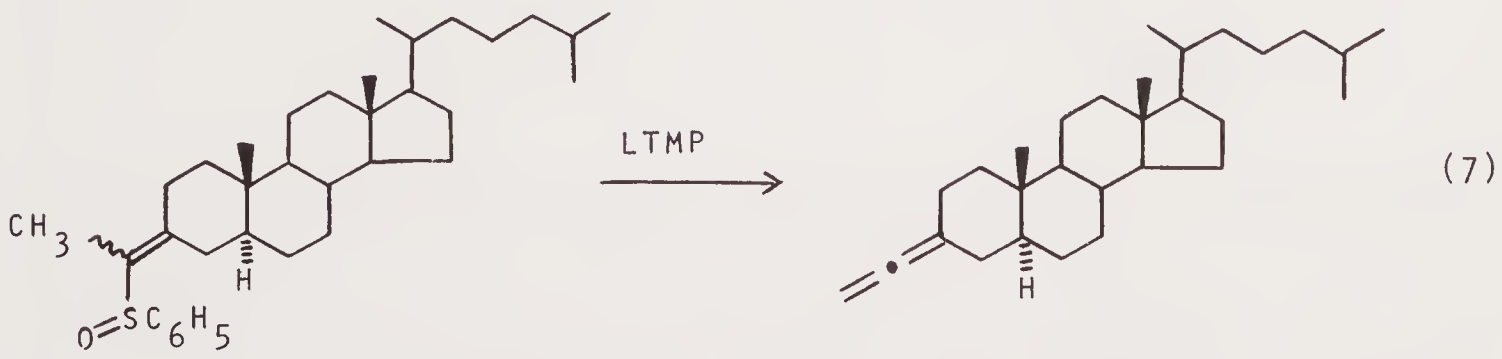
Elimination reactions involving the O-trifluoroacetyl (triflate) group are also suitable for the preparation of allenes, and, as shown in equation (6), the conversion can be realized by heating a vinyl triflate in quinoline at 100°C.[18] The only limitation is that R_1 or R_2 cannot be H because elimination of triflate from an alkene containing a vinyl proton produces the isomeric acetylene as the major product.



(6)

R_1	R_2	Yield (%)
CH_3	CH_3	70
C_2H_5	CH_3	85

With the advent of lithium dialkylamides elimination reactions can be performed at much lower temperatures and with stoichiometric proportions of the base. Recently Posner[19] described a method for terminal allene formation by way of sulfoxide elimination from 2-alkenyl aryl sulfoxides. Treatment of sulfoxide **3** with LTMP at -100°C affords the steroidal allene **4** in 60% yield; none of the corresponding acetylene is formed.

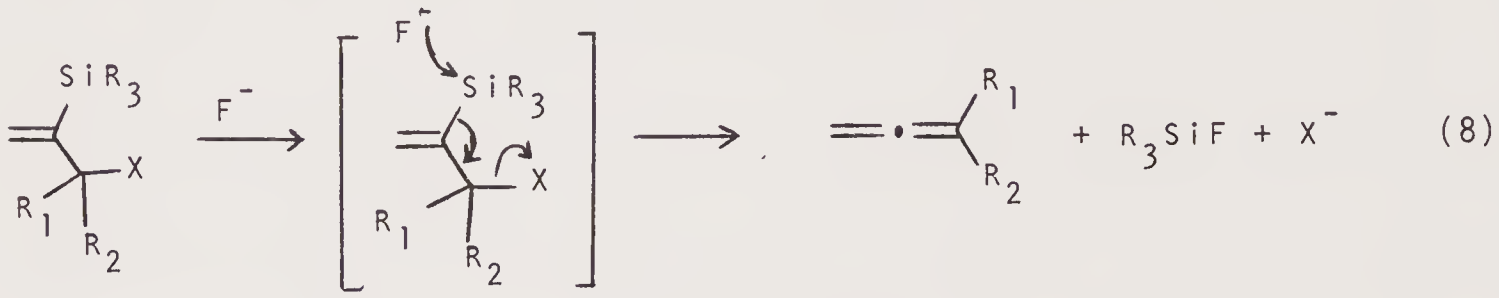


3 **4**

(7)

Chan[20,21] has taken advantage of the high affinity of the silicon and fluorine atom for each other to promote elimination of X from the vinylsilane illustrated in equation (8). The order of reactivity of the fluoride salt is $R_4N^+F^-$(R = alkyl) > CsF > KF,

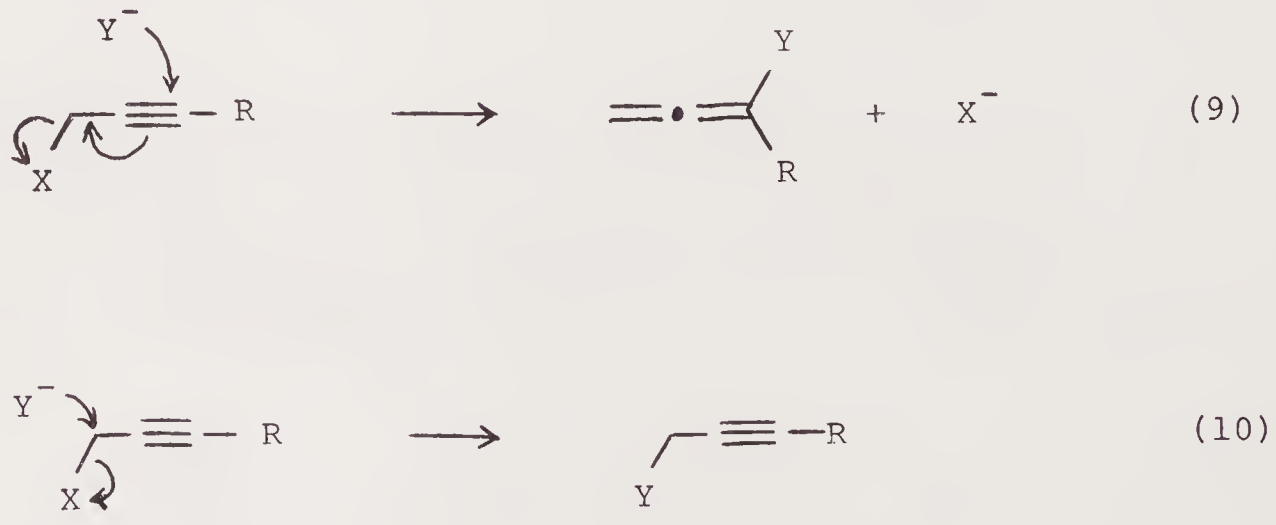
which may be a function of their solubilities in organic solvents. The rate of elimination is also governed by the nature of the silyl group. Allene formation is five times faster with a triphenylsilyl alkene than with the corresponding trimethylsilyl derivative. Additionally, the leaving group X exerts some influence on the rate of reaction as evidenced by the faster elimination of chlorine in comparison to a triflate group. Allenes prepared by this route are usually isolated in moderate yield, but in the case of phenylallene the conversion is quantitative.



$X = Cl, OCOCF_3$

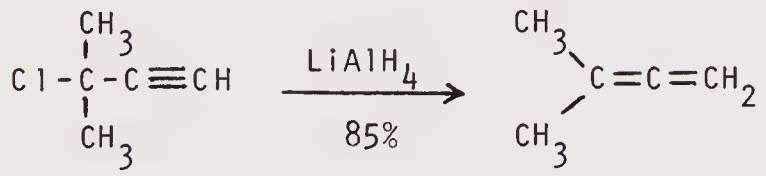
2.1.2. Addition to Acetylenes

Propargylic rearrangement reactions have been a valuable asset in gaining entry into the propadiene system. One such transformation is a displacement reaction which can generally be categorized as an S_N2' reaction and is depicted in equation (9). In the presence of a strong base, such as an organometallic, the reaction can also proceed through a carbenoid species generated by α elimination. The reaction may be complicated by a competing direct substitution of the propargylic substrate by way of an S_N2 pathway (equation 10) which ultimately results in the formation of mixtures containing both allenic and acetylenic products. The nature of X requires that it must function as a suitable leaving group, and generally a halogen, hydroxyl, acetate, or tosylate is employed. The nucleophile Y may be represented by a hydride or organometallic species.



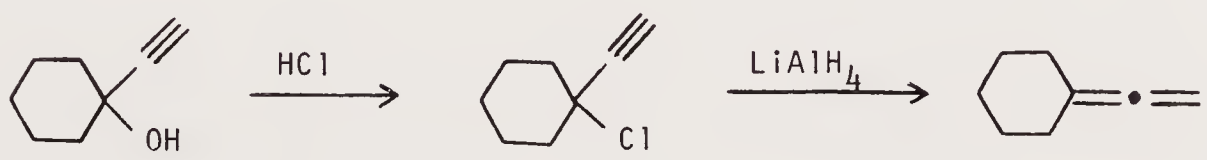
In reactions where a hydride source is employed (usually lithium aluminum hydride), allenes can be generated from either primary, secondary, or tertiary propargyl halides. 3-Methyl-1,2-butadiene (**6**) is formed in high yield, with only traces

of acetylenic contamination, by the treatment of 3-chloro-3-methyl-1-butyne (**5**) with $LiAlH_4$.[22,23] The method, although fairly general, is limited by the inherent instability of tertiary acetylenic halides. This is demonstrated in the conversion of 1-ethynylcyclohexanol (**7**) to pentamethylene allene (**9**) where the low yield is a direct result of the preparation of **8**.[22]



(11)

5 **6**

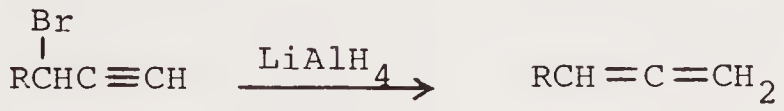


(12)

7 **8** **9**

15% yield(2 steps)

Secondary propargyl bromides are readily converted to monosubstituted allenes (equation 13). Early investigators[24] used ether as the medium for their reactions, and conversions could only be described as moderate with products being contaminated to the extent of 10% with the corresponding 1-alkyne. However, if a higher-boiling ether such as triethyleneglycol dimethyl ether is used as the solvent, the allene can be distilled directly from the reaction mixture in yields exceeding 95%.[25]

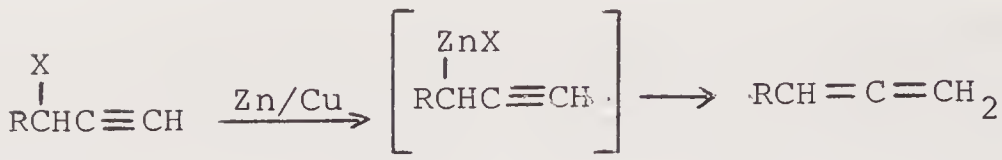


(13)

R= CH_3, C_2H_5, i-C_3H_7

Primary propargyl bromides are unsatisfactory in this type of transformation because the allene is usually produced as the minor component of the reaction mixture, the major portion of which is the corresponding 2-alkyne.[24]

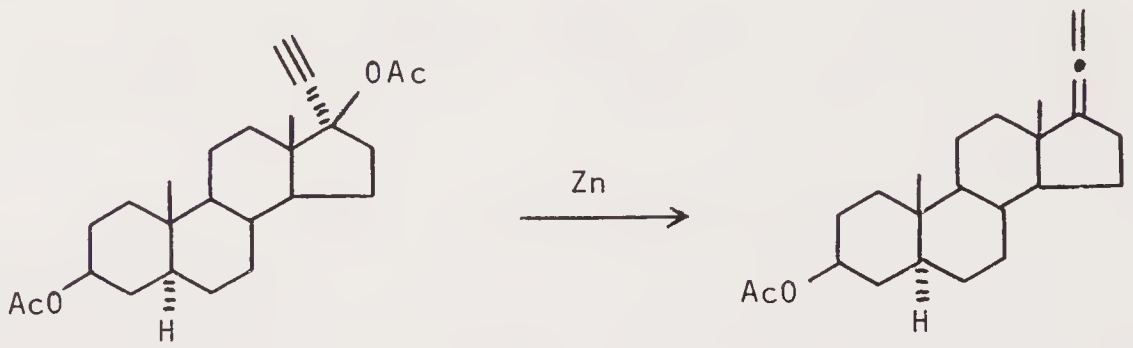
An alternate method for the conversion of 3-haloalkynes to allenes is that originally pioneered by Ginsburg[26,27] which employs zinc–copper couple in ethanol. Mechanistically, the reaction presumably proceeds through an organozinc intermediate (equation 14) which is subsequently protonated by the solvent. The method has the advantage of producing allenes contaminated with only very minor quantities of acetylenes.[24,28,29]



(14)

X	R	Yield (%)
Cl	C_3H_7	71
Br	C_4H_9	77

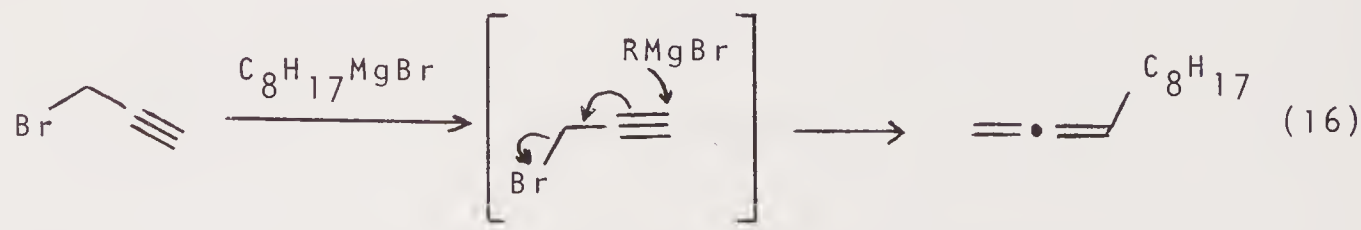
Crabbé and co-workers[30] have used a somewhat similar approach to prepare the allenyl steroid **11** which serves as a useful precursor to the pregnane and corticosteroids. When **10** is refluxed in diglyme in the presence of zinc dust, the reduction is accompanied by rearrangement and elimination to give **11** in 86% yield.



10 **11**

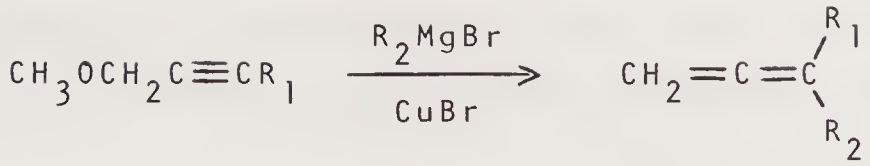
(15)

Propargyl bromide is susceptible to 1,3-substitution by the nucleophilic attack of a Grignard reagent as shown in equation (16). When one equivalent of *n*-octylmagnesium bromide is allowed to react with propargyl bromide at −40°C in ether, 1,2-undecadiene is isolated in 90% yield.[31] The high yield and stoichiometry of the reactants favors an S_N2' mechanism over a pathway involving a carbenoid intermediate (where two equivalents of the alkylmagnesium halide are required).



(16)

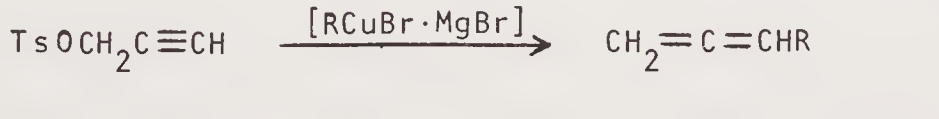
The method can also be extended to include propargylic ethers (equation 17). In general, the ether function is less suitable as a leaving group, and higher reaction temperatures (>100°) and longer times are required to effect the conversion. However, the addition of a catalytic amount of cuprous bromide (10 mole %) accelerates the reaction and allows the conversion to proceed at room temperature within a one- to two-hour period.[32] The addition of cuprous bromide to the Grignard reagent presumably leads to the formation of an organocuprate species which is the active participant in the reaction.[33]



(17)

R_1	R_2	Yield (%)
H	C_7H_{15}	70
H	C_8H_{17}	78
H	i-C_5H_{11}	80
H	C_6H_5	65
CH_3	C_7H_{15}	81
CH_3	C_8H_{17}	84
CH_3	C_6H_5	82
C_8H_{17}	C_2H_5	70

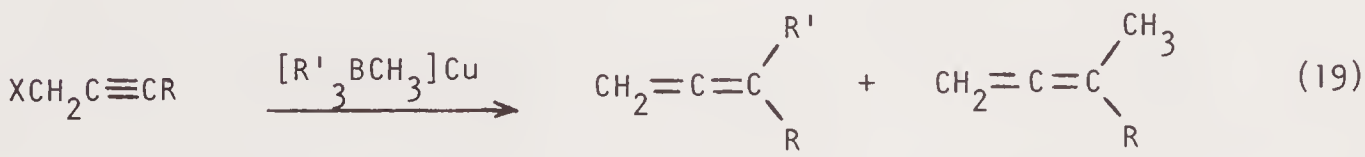
The tendency of organocuprates to initiate S_N2' reactions in propargylic compounds is remarkably high. When the cuprate is prepared from at least equimolar quantities of cuprous bromide and an organomagnesium halide, reaction with a propargylic substrate (e.g., tosylate) affords allenes (equation 18) in 80–90% yield with less than 5% acetylenic contamination. However, when the CuBr/RMgX ratio is decreased, the amount of the acetylenic component increases.[34]



(18)

R= C_6H_5, 1-naphthyl, 2-thienyl

Copper(I) methyltrialkylborates (**12**) induce 1,3-substitution in propargylic halides and afford 1,2-alkadienes **13** by the transfer of an alkyl function from the boron atom to the allene framework. A competing transfer of the methyl group attached to the boron produces significant quantities of the methyl-substituted allene **14** at the expense of the desired product **13**. The reported yields of the reaction range from 31 to 59%.[35]



(19)

12 **13** **14**

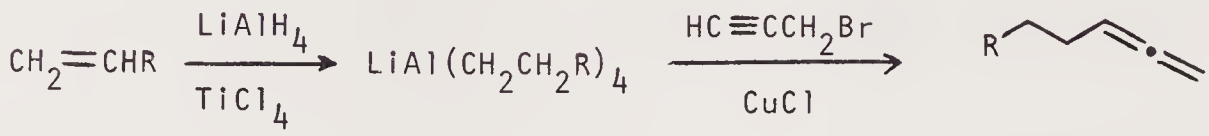
X= Cl, Br

R= H, C_6H_5

R'= C_5H_{11}, C_8H_{17}, C_4H_9

Since the organocuprate methodology is primarily used in the synthesis of internal allenes, the mechanistic implications as well as the effect of the organocuprate species and leaving group on the ultimate yield of the allenes are discussed in the internal allene section of this chapter.

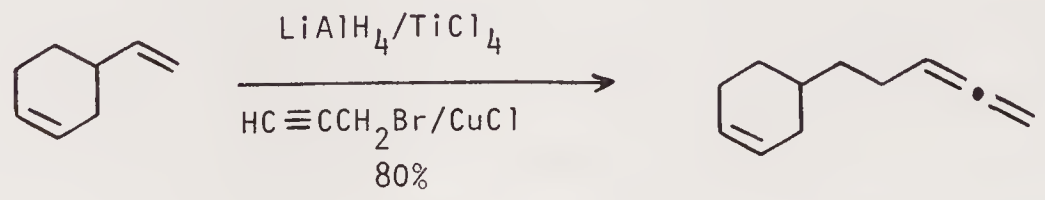
A convenient route to terminal allenes, developed by Sato and co-workers,[36] involves a hydroalumination of a 1-olefin followed by treatment with propargyl bromide in the presence of a catalytic amount of cuprous chloride (equation 20). Since many 1-alkenes are readily available, this reaction offers an attractive method for the simple preparation of a wide variety of terminal allenes. It should be noted that the allenes are virtually free of all by-products and their purity usually exceeds 99%.



(20)

R	Yield (%)
H	88
C_3H_7	76
C_4H_9	80

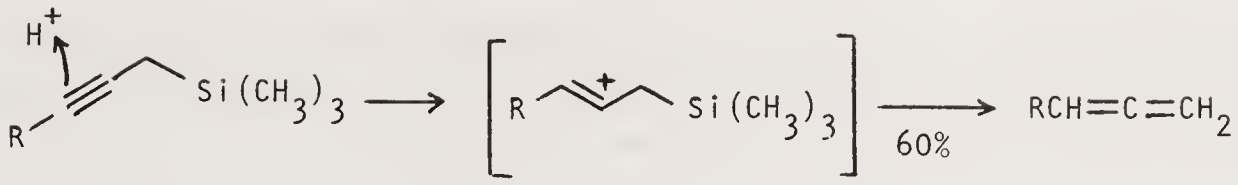
This method possesses an additional advantage in that a second site of unsaturation in the olefinic starting material remains unaffected by the hydroalumination step, and therefore a propadiene with an isolated double bond can be synthesized as illustrated by the two examples in equations (21) and (22). The only requirement is that the additional olefinic site cannot be monosubstituted.



(21)

(22)

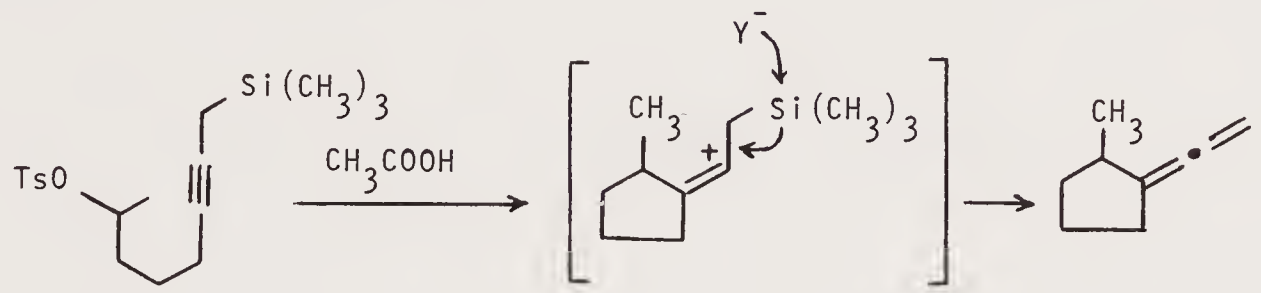
Propargyltrimethylsilanes, upon electrophilic attack of H^+, furnish terminal allenes (equation 23) by way of a cationic transition state. The silanes remain intact under mildly acidic conditions (glacial acetic acid) and require the stronger trifluoroacetic acid for a smooth conversion to the allene.[37] When the analogous reaction is performed under basic conditions (sodium ethoxide), a mixture of 2-nonyne and 1,2-nonadiene is formed in a ratio of 1.5:1.



(23)

R= C_6H_{13}

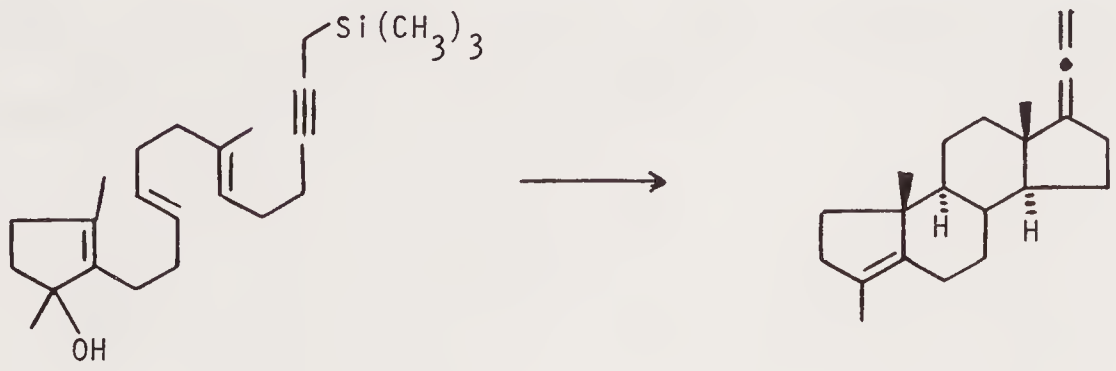
Olefin–acetylene cyclizations that contain a tosylate initiator and a propargylsilane function as a terminator group lead to exocyclic allenes. The presence of a trimethylsilyl group directs cyclization toward five-membered ring formation by β stabilization of the intermediate **15**, which then fragments to the allenic structure.[38] Solvolysis of tosylate **15** proceeds, in this case with acetic acid, and affords allene **17** as the only cyclic product.



(24)

15 **16** **17**

Johnson,[39] in a truly amazing reaction, has applied this methodology in a spectacular one-step polyene cyclization of the propargyl silane **18**. Treatment of **18** with trifluoroacetic acid at −35°C results in the isolation of the steroidal type allene **19** in 58% yield where the only impurity is a small amount of the *cis* C/D ring fusion.

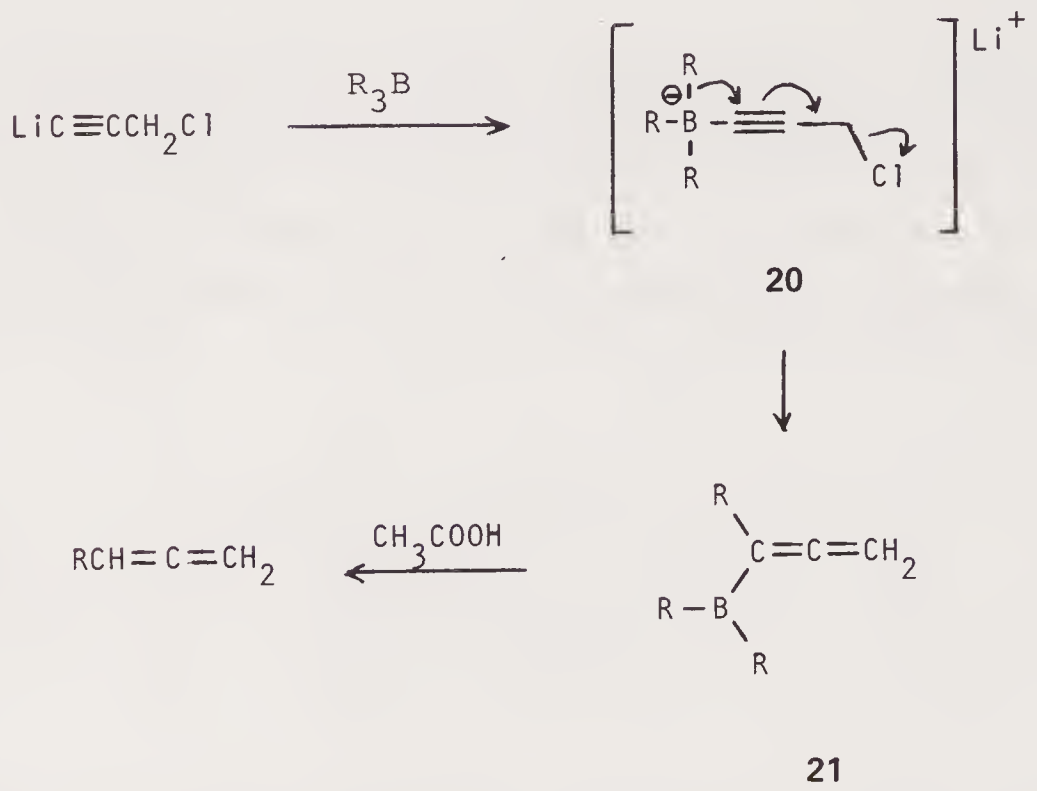


(25)

18 **19**

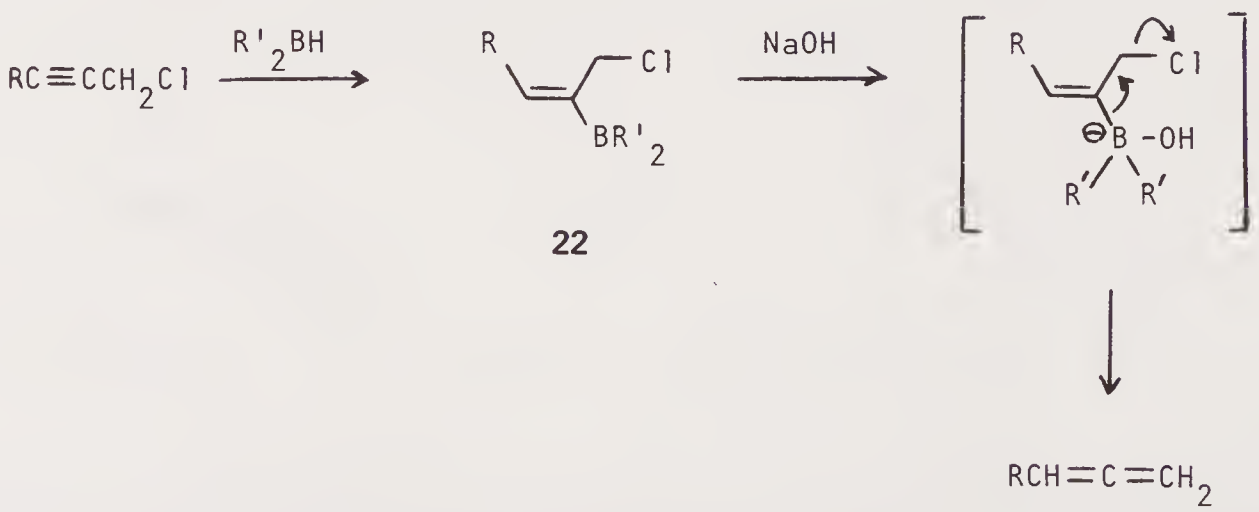
Anionotropic rearrangements, where the leaving group is induced to migrate by a negatively charged species in close proximity or directly attached to an acetylene, generally do not lend themselves to the preparation of alkyl allenes in a high state of purity. However, rearrangements involving alkynylboranes do produce terminal allenes in excellent yields and almost free of acetylenes.

The addition of a trialkylborane to the lithio derivative of propargyl chloride (equation 26) results in the initial formation of an ate complex **20**. Spontaneous rearrangement and alkyl group migration generates the boron-substituted allene **21**, which upon protonation with acetic acid furnishes the desired allene in 73–77% yield.[40]



(26)

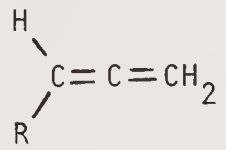
Alternately, the hydroboration of 1-chloro-2-alkynes with either disiamylborane or dicyclohexylborane furnishes the unsaturated chloroorganoborane **22** which, upon treatment with aqueous sodium hydroxide, undergoes a β-elimination to give the monosubstituted allene in high yields (equation 27).[41]

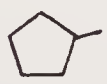
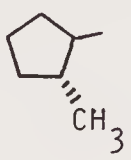
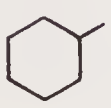


(27)

In rearrangements of the acetylenic system, the prototropic rearrangement is the least favorable for the preparation of alkyl allenes. The basic conditions required for the allene formation also promote further isomerization leading to a 2-alkyne or regeneration of the starting 1-alkyne.[42] This process, however, is more applicable

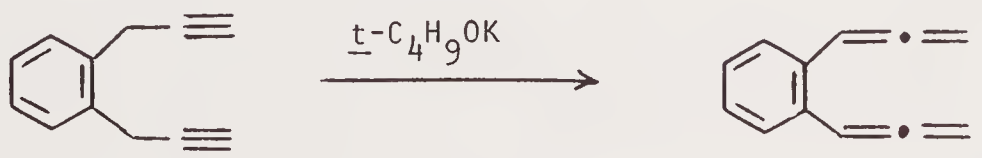
Table 2.1. Terminal Allenes Prepared from Boron-Substituted Alkynes (Method A, Equation 26) or Alkenes (Method B, Equation 27)[a]



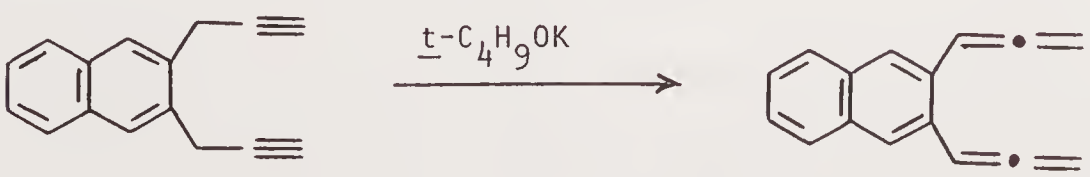
R	Method	Yield, %	Reference
C_4H_9	B	64 (83)	41
t-C_4H_9	B	65 (92)	41
C_6H_{13}	A	73	40
C_2H_5-CH-C_3H_7	A	74	40
	A	75	40
	A	76	40
	A	77	40
	B	72 (93)	41
C_6H_5	B	73 (91)	41

[a]The table lists isolated yields. Those in parenthesis denote the actual yields of the reaction as determined by glpc analysis.

for the preparation of arylallenes. The novel *o*-dipropadienylbenzene (**24**) and 2,3-dipropadienylnaphthalene (**26**) are readily obtained by the isomerizations of **23** and **25** with potassium *t*-butoxide in ether at $-78°C$.[43]



23 **24** (28)



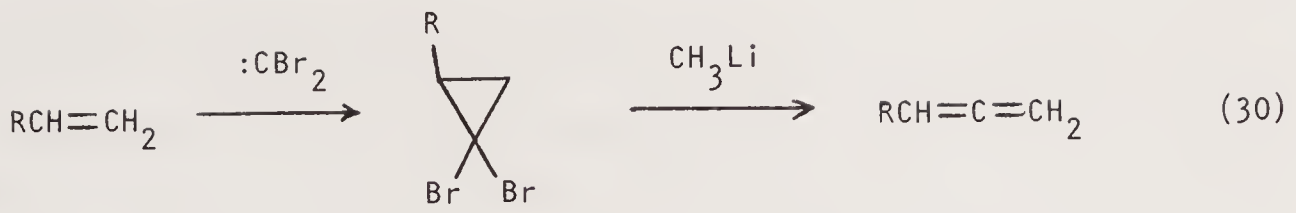
25 **26** (29)

2.1.3. Reactions of 1,1-Dihalocyclopropanes

Dihalocarbenes react with alkenes to give 1,1-dihalocyclopropanes by way of insertion into the double bond. Doering and LaFlame[44] first investigated the action of sodium and magnesium on such systems and found that allenes are generated in varying yields. Other researchers have successfully employed zinc,[45] chromium(II) chloride (Hiyama's reagent),[46] copper (0)-isonitrile complex,[47] sodium triethylborohydride,[48] Grignard reagents,[49] phenyllithium,[50] and alkyllithium reagents[51] to effect the conversion. In general, 1,1-dibromocyclopropanes are preferred over the corresponding dichloro analogs[51] with best results being obtained if *n*-butyllithium or methyllithium is employed as the base (equation 30). An overwhelming advantage of this method over the others previously mentioned is the complete absence of acetylenic by-products. A variety of terminal allenes prepared by these methods are listed in Table 2.2.

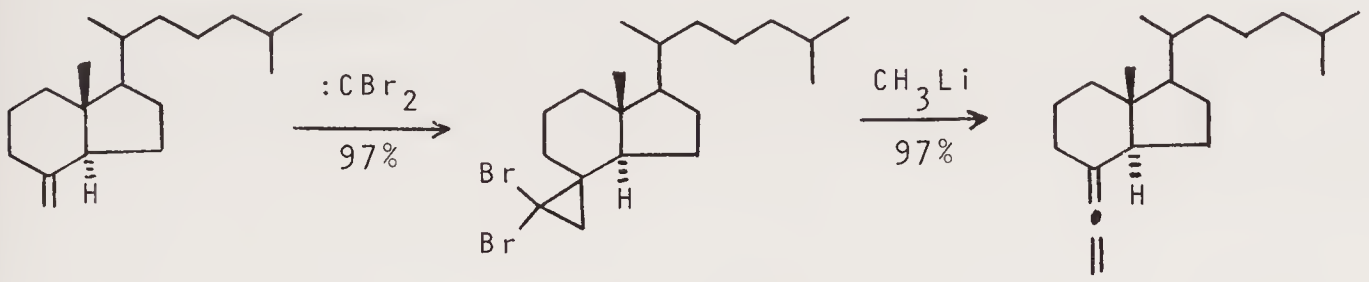
Table 2.2. Terminal Allenes Prepared from 1,1-Dibromocyclopropanes

R_1	R_2	Reagent	Yield, %	Reference
CH_3	H	CH_3Li	92	52
CH_3	CH_3	$Na[(C_2H_5)_3BH]$	42	48
C_3H_7	H	Mg	62	44
		Na	64	44,45
$\underline{t}$-C_4H_9	H	$Cu(0)(C_6H_{11}NC)_n$	58	47
C_6H_{13}	H	Na	87	45
		Zn	61	45
		$Cu(0)(C_6H_{11}NC)_n$	50	47
$C_{10}H_{21}$	H	C_2H_5MgBr	44	49
	H	Mg	30	53
C_6H_5	H	$CrCl_2$	62	46
		CH_3Li	82	51
C_6H_5	C_6H_5	CH_3Li	43	51



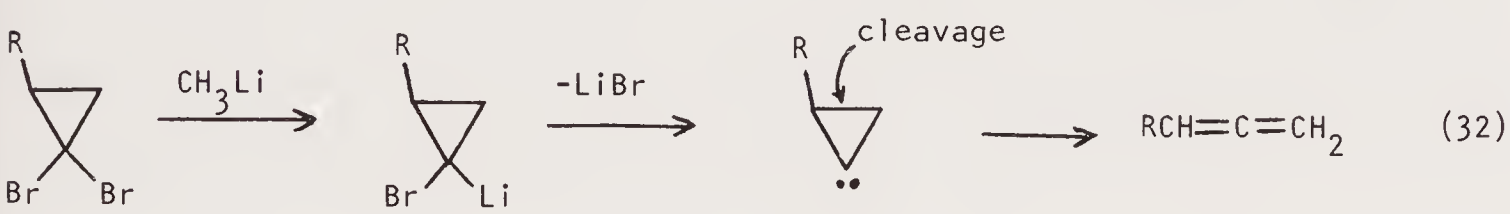
(30)

Okamura,[54] in his studies on vitamin D (calciferol) and its analogs, successfully employed this methodology to synthesize its C/D ring fragment (equation 31) which ingeniously contains the allene moiety in the proper position for further elaboration to the desired products.



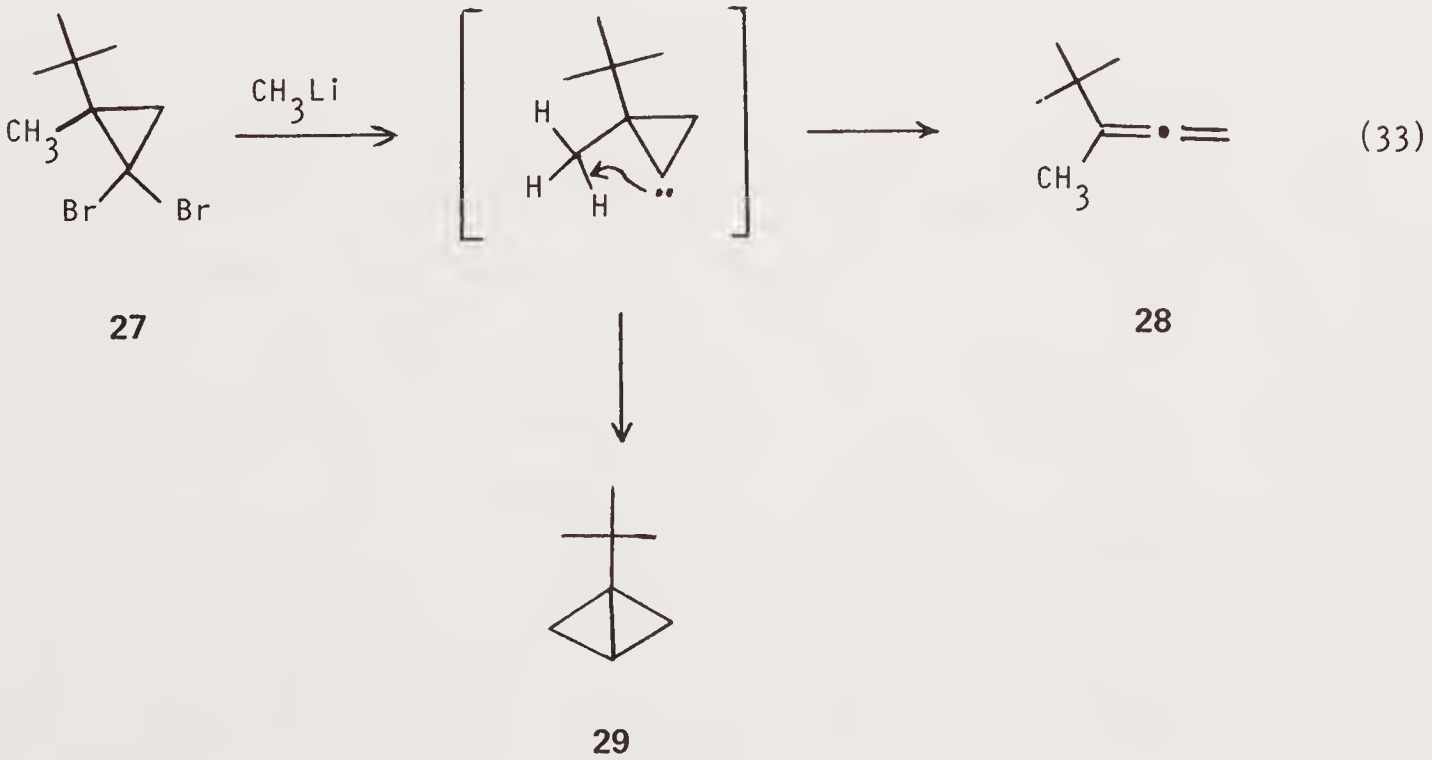
(31)

A generally accepted mechanism for this type of transformation (equation 32) involves the initial formation of an α-bromolithium intermediate (by metal–halogen exchange) which subsequently eliminates lithium bromide to generate a carbene. Rupture of the cyclopropane ring gives rise to the allenic structure.[55]



(32)

In cases where the dibromocyclopropane is sterically crowded as in **27**, both 1-*t*-butyl-1-methylallene (**28**) and 1-*t*-butylbicyclo [1.1.0]butane (**29**) are formed in a combined yield of 70% (3:2 ratio).[56]



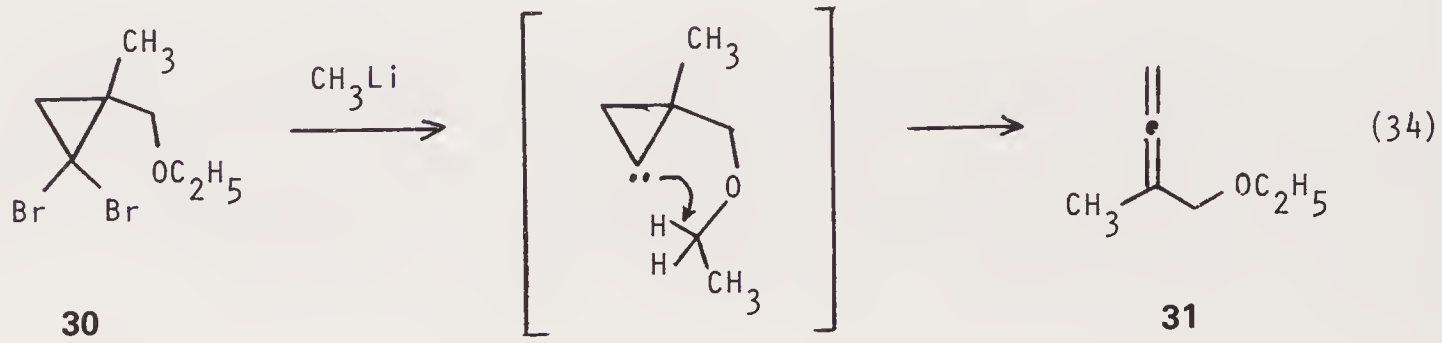
27 **28**

29

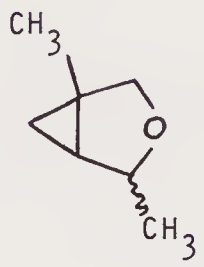
(33)

The formation of the bicyclobutane can be rationalized by the steric repulsion exerted on the geminal methyl and *t*-butyl groups, which may widen the angle between the two. This would force the CH from the methyl group into a favorable orientation for insertion of the carbene. This mechanism is somewhat supported by an analogous reaction with the 2-methyl-2-neopentylcyclopropane which gives only 10–20% of the bicyclobutane system. Further reduction in the size of the groups (e.g., 2,2-diethyl) results only in allene formation.

Another cyclopropane system suitably functionalized to favor carbene insertion reactions is the ether **30**. When this is treated with methyllithium at −30 to −32°C, the major volatile product isolated from the reaction mixture is the 3-oxabicyclo[3.1.0]hexane (**32**), which is formed from insertion into the CH bond α to the oxygen (the allene **31** only represents 5% of the mixture). Higher reaction temperatures (25–35°) still favor **32** (48%), but now larger quantities of the allene **31** are produced (32%).[57]

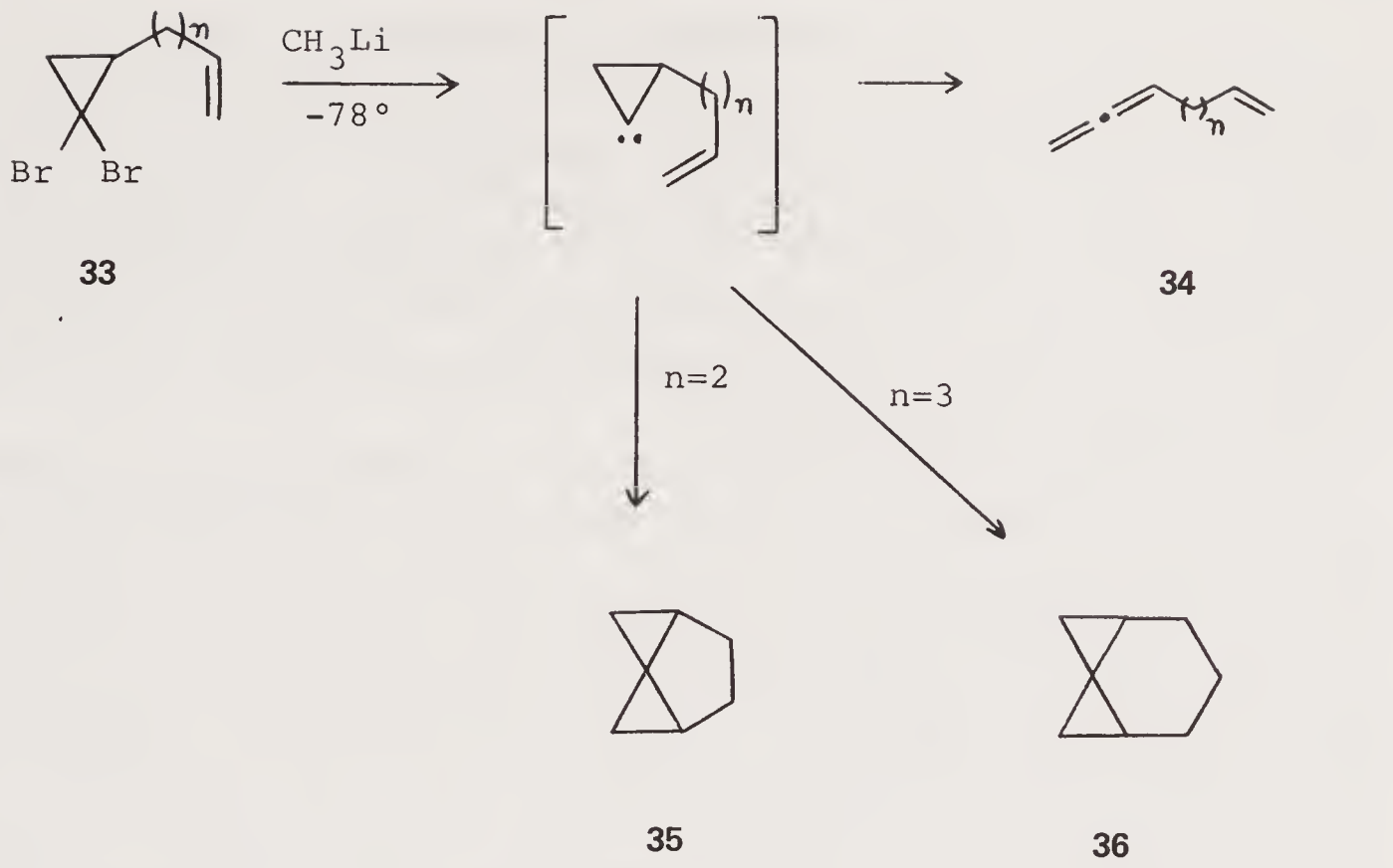


30 **31** (34)



32

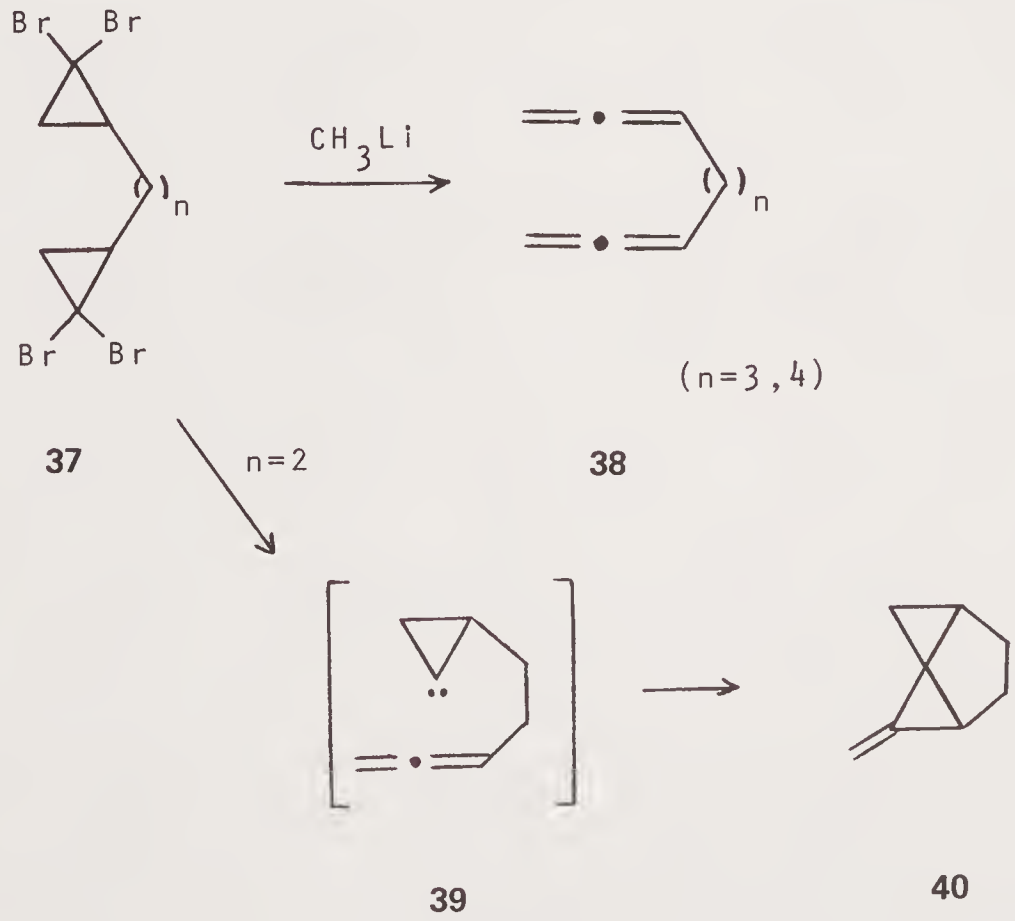
Dibromocyclopropanes that have an isolated olefinic site attached to the 2-position (e.g., **33**) produce allenes of type **34** upon reaction with methyllithium at −78°C. When $n = 1$, 1,2,5-hexatriene is the only product isolated (46% yield), however, as the number of carbons between the cyclopropane ring and olefin increases, the positioning of the double bond becomes more favorable for the insertion of the carbene into the alkene. When $n = 2$ (the optimum distance), an 85% yield of a mixture of 1,2,6-heptatriene (**34**, $n = 2$) and tricyclo[4.1.0.0]heptane (**35**) (52:48 ratio) is produced. The ratio of allene can be increased to 84:16 by performing the reaction at 0°C. Extending the carbon linkage to three methylene units, reaction at −78° provides an 85% yield of a mixture of 1,2,7-octatriene (**34**, $n = 3$) and tricyclo[5.1.0.0]octane (**36**) in a ratio of 90:10, and finally, when $n = 4$, only 1,2,8-nonatriene (**34**, $n = 4$) is isolated in 80% yield.[58,59]



33 34 35 36

Scheme 1

Bisdibromocyclopropylalkanes (**37**) are converted in good yields to the diallenic systems **38**. When $n = 3$ or 4, the only products isolated are 1,2,7,8-nonatetraene (83%) and 1,2,8,9-decatetraene (86%). Reducing the alkane bridge to two methylene units places the intermediate carbene **39** in a position to insert into the more substituted double bond on the preformed allene and results in the formation of a mixture of 1,2,6,7-octatetraene (**38**, $n = 2$) and 5-methylenebicyclo [4.1.0.0] heptane (**40**) in a ratio of 68:28[58] (71% total yield).



37 38 39 40

Scheme 2

2.2. INTERNAL ALLENES

Allenes that bear substituents in both the 1 and 3 positions serve as useful intermediates in organic synthesis. This nature of substitution, in addition to the orthogonality of the cumulated double bonds of the propadiene framework enables the molecule to exist in two possible enantiomeric configurations. The enrichment or asymmetric synthesis of either antipode furnishes intermediates with potential for the preparation of chiral molecules.

In the previous discussion on the preparation of terminal allenes, it was shown that the primary by-product of many of the reactions is an isomeric acetylene. Various reactions producing internal allenes, in addition to forming acetylenic impurities, may be further complicated by prototropic rearrangement of the allene to a 1,3-diene system.[60] In general, the methods discussed previously are not reexamined in detail in their applications to internal allene preparations, although several of the reactions have been extensively studied in order to provide optimal yields of allenes and they deserve additional discussion. Selected examples of various transformations leading to a variety of internal allenes are listed in Table 2.3 at the end of this section.

Table 2.3. Alternate Preparations of Internal Allenes

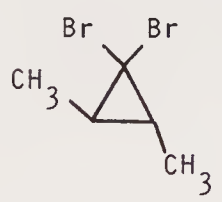
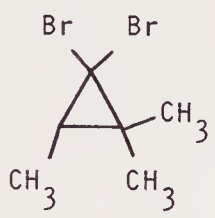
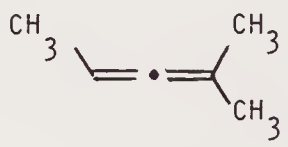
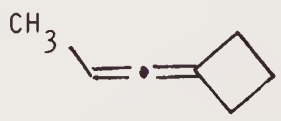
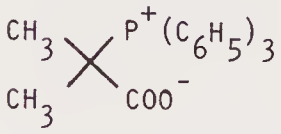
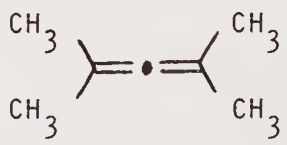
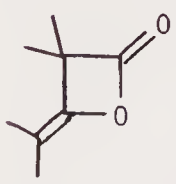
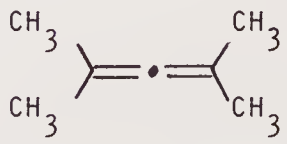
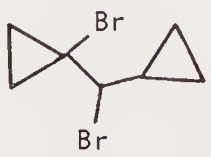
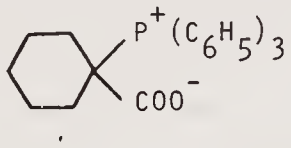
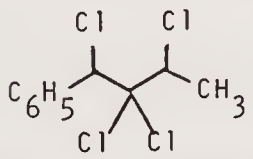
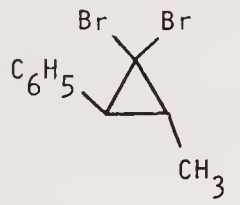
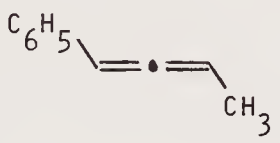
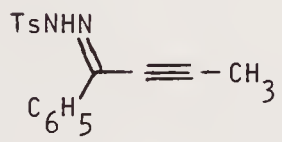
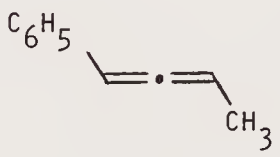
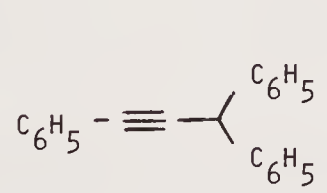
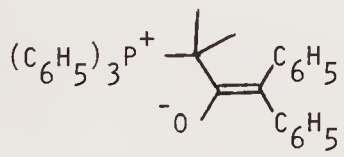
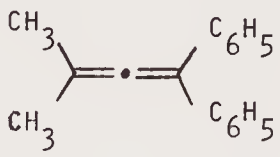
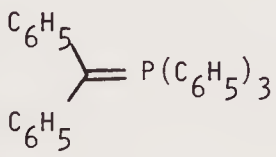
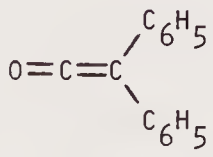
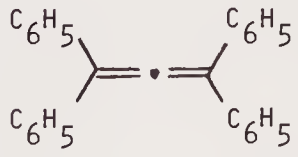
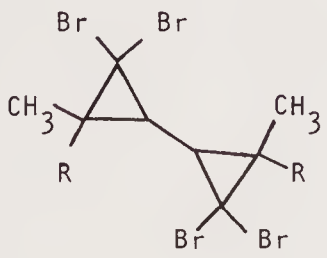
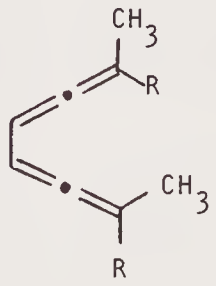
Substrate	Reagent(conditions)	Product	Yield, %	reference
	Na/Al_2O_3		44	44
	Mg		34	44
	CH_3MgI		28	120
	heat		30	121
	450°, 6 hrs		94	122
	$t\text{-}C_4H_9OK$		58	112

Table 2.3. (*Continued*)

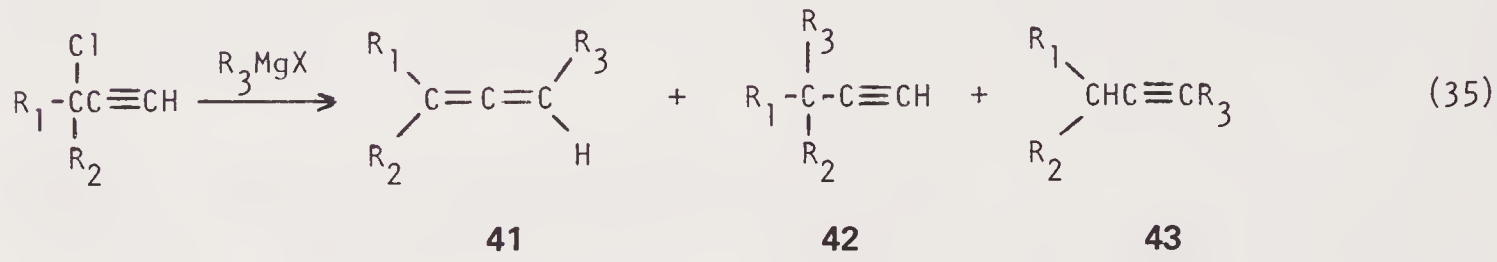
Substrate	Reagent(conditions)	Product	Yield, %	reference
	heat		36	121
	Zn		77	123
	$CrCl_2$		58	46
	catechol borane		84	124
	Al_2O_3 (run on a column)		74.5	125
	Al_2O_3 (run on a column)		83.5	126
	145-160° 0.2mm		64	127
			100	128
	CH_3Li		82-93	129, 130

R= CH_3, C_2H_5, $\underline{t}$-C_4H_9, C_6H_5

2.2.1. Allenes from the Addition of Grignard Reagents to Acetylenes

The history of the reaction of Grignard reagents with propargyl derivatives is fraught with inconsistencies, and a wide variety of mechanisms have been proposed to explain the product distributions obtained from various reactions. Although these mechanistic proposals are not considered at this time, Pasto, et al.[61] have conveniently summarized them and offer a clarification of the mechanism for the reaction of terminal propargylic chlorides with alkyl Grignard reagents.

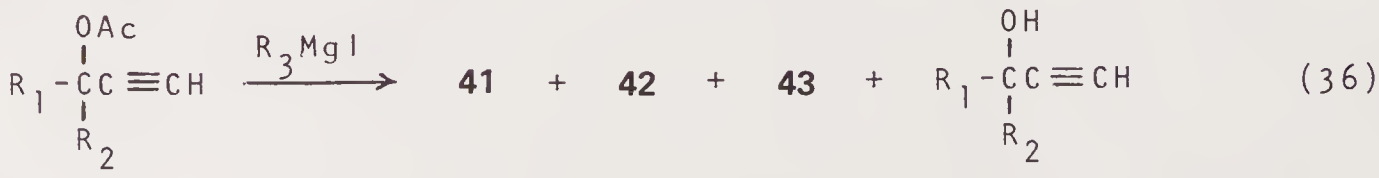
The action of an alkylmagnesium halide on a tertiary propargyl chloride in the absence of a transition metal catalyst affords mixtures of allene (**41**) and alkynes (**42** and **43**) along with varying amounts of 1,3-dienes[61,62] (equation 35). If the reaction is performed in refluxing ether, the allene **41** is produced as a minor component of the mixture while the acetylene **42**, the primary product, accounts for as much as 75% of the total. Lowering the temperature to 0°C shifts the distribution in favor of the allene, but **42** still forms in significant quantities (up to 40%).



(35)

As shown in equation (36), the use of an acetate function as the leaving group introduces a tertiary propargyl alcohol (**44**) as an additional by-product of the reaction (up to 30%) at the expense of the desired allene. It can be rationalized as forming by way of direct attack of the organometallic on the acetoxy group. A limitation of this reaction is that R_1 or R_2 cannot be a proton, and conditions require that ether (at reflux temperature) be used as the solvent. Deviations from these conditions usually result in the quantitative recovery of the starting material.[62]

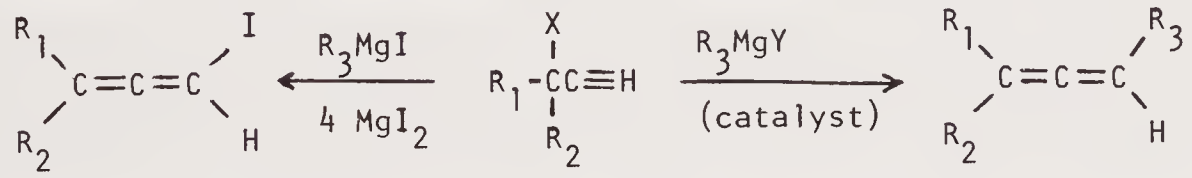
The allene content of the mixture can be increased by the addition of certain metals or their salts. The introduction of either four equivalents of magnesium bromide,[63,64,65] one equivalent of magnesium iodide,[66] or 6 mole % of cobalt(II) chloride[66] into the acetate solution prior to the addition of the organomagnesium halide allows the allene **41** to be isolated in 50–70% yield along with 5–15% of acetylenes **42** and **43**. In the case of magnesium iodide, if larger quantities of salt



(36)

are employed, mixtures of alkylallenes **41** and iodoallenes **45** result until the ratio reaches 4 moles of magnesium iodide per mole of acetate. At this point only **45** is produced as the allenic component of the reaction mixture.[67] In these types of reactions, Grignard reagents derived from secondary halides perform less satisfactorily than those of primary halides, with iodides giving better results than bromides.

In a study of reactions of propargyl halides with Grignard reagents, inconsistencies were found regarding the amount of allenes, alkynes, and 1,3-dienes formed. Some reactions produce mixtures of all three whereas others afford only the allene. The anomalous results were traced to two different sources of magnesium used to prepare the Grignard reagents. The reactions producing large quantities of allenes result from catalysis due to minor amounts of transition metals present in the magnesium.[61] When various transition metals are purposely added to the reaction mixture prior to the introduction of the organomagnesium halide, a tremendous acceleration of the rate of the reaction occurs, and high yields of allenes uncontaminated with alkynes are obtained.[68,69] The catalytic efficiency decreases in the sequence Fe > Co > Ni > Cu. In reactions catalyzed with iron, both terminal and nonterminal propargyl halides react with primary or secondary Grignard reagents in the presence of 5×10^{-5} M ferric chloride to produce allenes in excellent yield. Ferric acetonylacetonate may also be used in place of ferric chloride. In a separate report[70] [Pd°], which is generated *in situ* by the reduction of palladium chloride with diisobutylaluminum hydride in the presence of triphenylphosphine, is also shown to be an effective catalyst in these types of reactions. Again, allenes are produced virtually free of acetylenes.



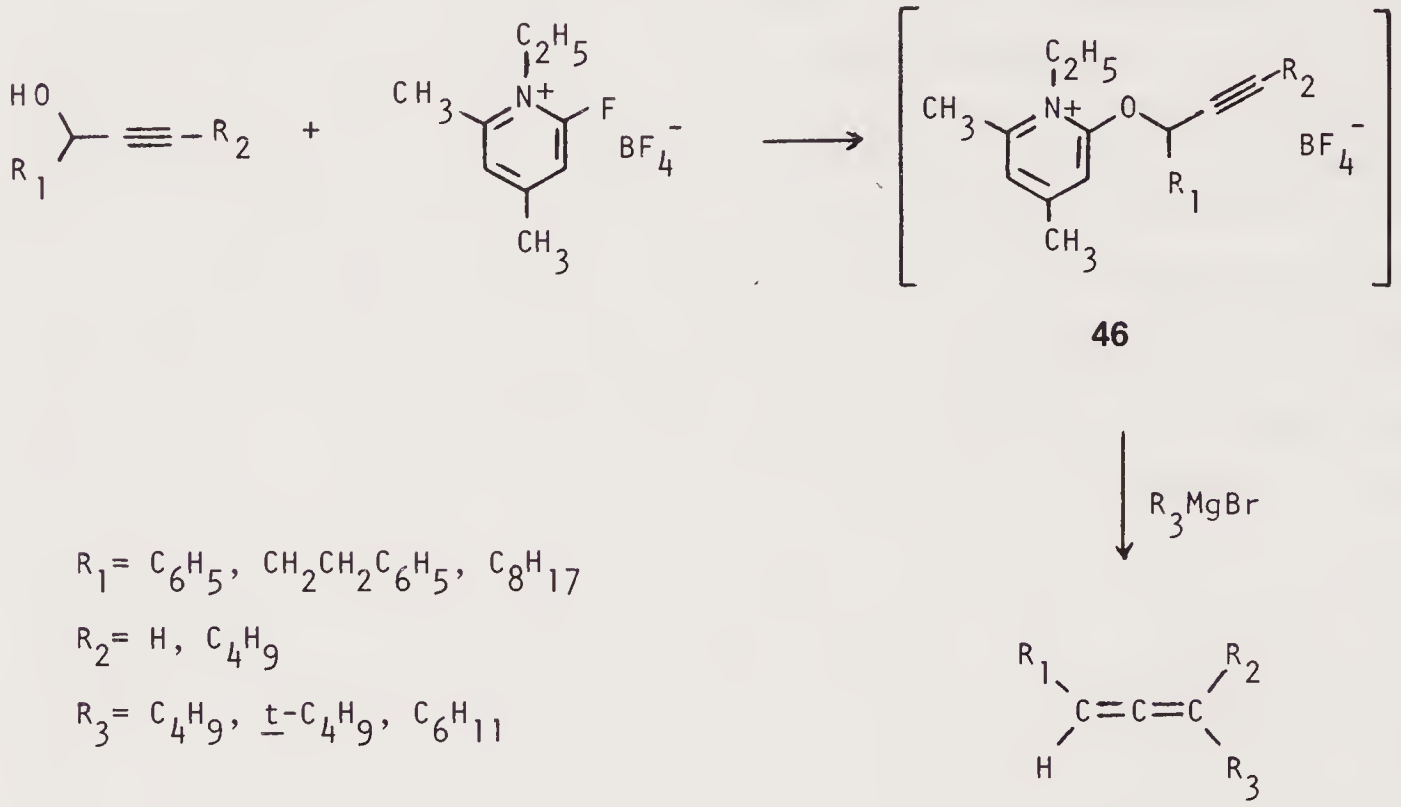
(37)

45 **41**

R_1	R_2	R_3	X	Y	Catalyst	Yield (%)	Reference
H	CH_3	C_8H_{17}	Cl	Cl	[Pd°]	62	70
CH_3	CH_3	C_8H_{17}	Cl	Cl	[Pd°]	77	70
CH_3	CH_3	C_4H_9	Cl	Br	$FeCl_3$	90	69
$—(CH_2)_5—$		CH_3	Cl	Br	$FeCl_3$	84	69
H	CH_3	C_4H_9	Cl	Br	$FeCl_3$	80	68
CH_3	CH_3	C_8H_{17}	OAc	I	$MgBr_2$	64	65
$—(CH_2)_5—$		CH_3	OAc	I	MgI_2	50	67

In a high-yielding reaction, propargylic alcohols can be converted directly to allenes in a one-pot procedure by sequential treatment with 1-ethyl-2-fluoro-4,6-dimethylpyridinium tetrafluoroborate (which provides the intermediate 2-propar-

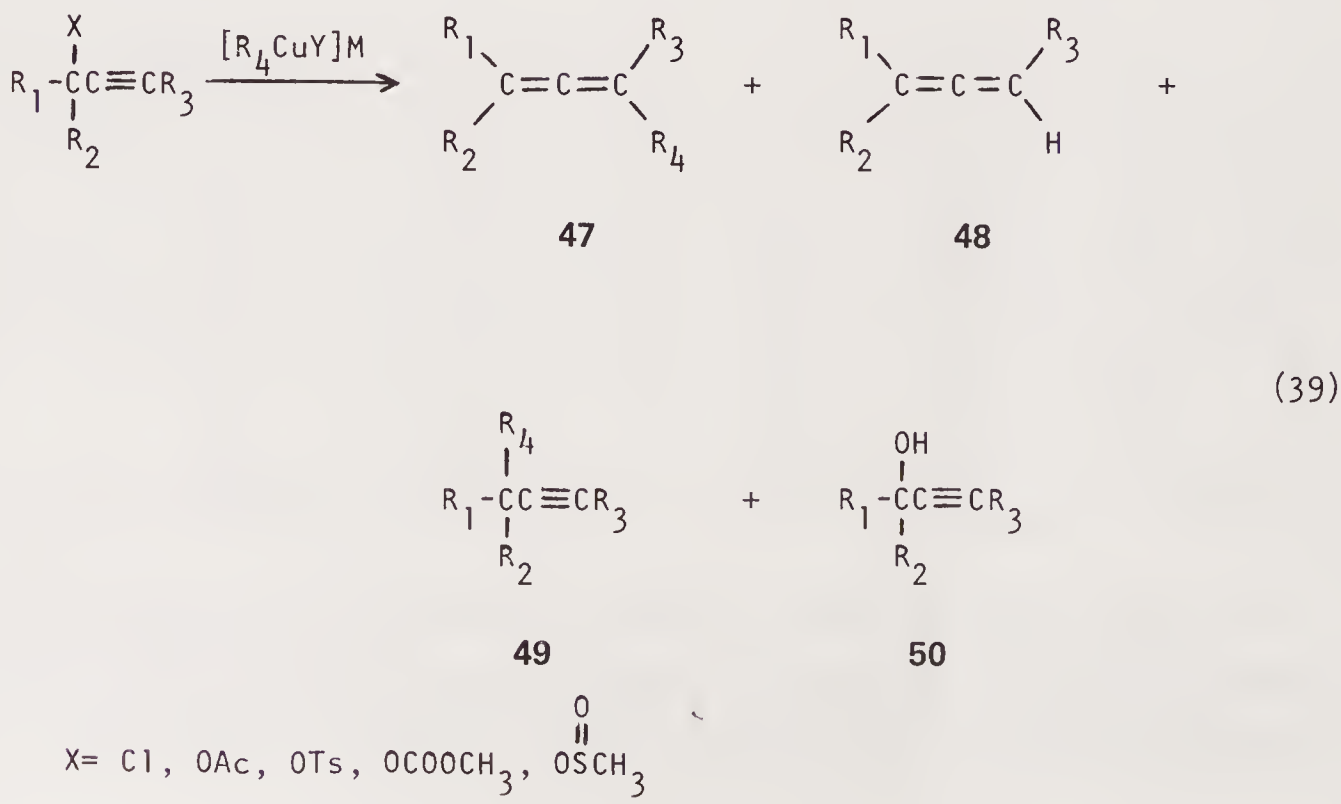
gyloxypyridinium salt **46**) followed by a Grignard reagent in the presence of a catalytic amount of copper(I) iodide[71] (equation 38). Either primary, secondary, or tertiary Grignard reagents are acceptable and afford acetylene-free allenes in 77–99% yields.



(38)

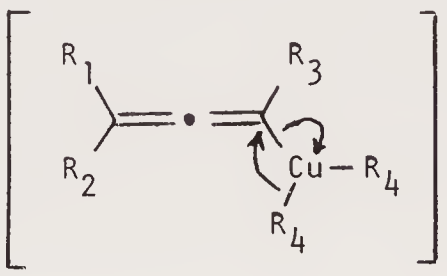
2.2.2. Allenes from the Addition of Organocuprates to Acetylenes

Organocopper reagents are extremely versatile in 1,3-substitution reactions of propargylic substrates. Early investigations into such reactions favor propargyl acetates and lithium dialkylcuprates (R_2CuLi) as the primary reactants[72,73] (equation 39, X = OAc).

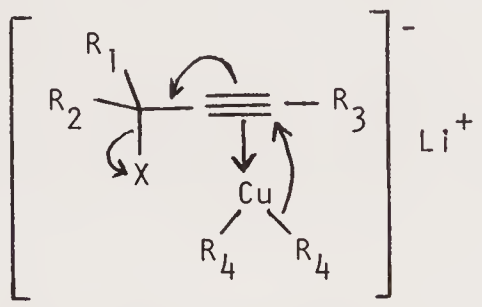


(39)

In addition to the desired allene **47**, a nonalkylated or ''reduced'' allene **48** is sometimes formed and can amount to as much as 50% of the allenic hydrocarbon fraction. Crabbé and co-workers[74] have suggested the copper(III) intermediate **51** as a likely precursor to allenes **47** and **48**. A 1,2-shift which effectively transfers an R from copper to the allenic skeleton results in the formation of **47**, whereas hydrolytic protonation of **51** affords **48**. In separate reports, both Landor[75] and Pasto[76] postulate a π complex such as **52** as an alternate transition state leading to the formation of **47**.



51



52

Thermal considerations are crucial in the product distribution of **47** and **48**. Reaction temperatures between $-10°$ and $+22°$ favor the 1,2-shift and give **47** with less than 5% contamination of **48**. The ''reduced'' allenes can be preferentially formed by performing the reaction at $-50°$ then quenching with 1N HCl at $-75°C$.[77]

Manipulation of the organocopper reagent, the leaving group of the acetylene, the steric bulk at either R_1 or R_3, or the solvent causes significant changes in the total product distribution in equation (39). The most dominant factor in determining the site of displacement leading to allenes **47** or acetylenes **49** is the nature of the organocopper reagent. In general, homocuprates R_2CuMgX tend to generate **49**, whereas alkylheterocuprates (RCuBr)MgX or the complex organocopper species [$CH_3Cu \cdot LiBr \cdot MgBrI$] favor allene formation (''reduced'' allenes **48** very rarely occur with these reagents).[78,79] The solvent of choice in these reactions is THF, whose polarity favors very high yields (>90%) of allenes **47**. Similar reactions performed in ether produce significant amounts of **49** at the expense of **47**.[79]

The leaving group appears not to alter dramatically the distribution of displacement products generated by way of attack on the propargylic structure but instead influences the relative proportion of **50** formed in the reaction.[78]*

Steric considerations also play an important role in allene/alkyne product ratios. Increasing the bulk at R_3 enhances S_N2 displacement leading to the formation of **49**, whereas increasing the size of R_1 limits access to the propargylic site, therefore invoking an S_N2' process which favors **47**. The constraints, however, can be circumvented by the use of [$CH_3Cu \cdot LiBr \cdot MgBrI$] in THF which provides allene **47** exclusively regardless of steric factors[78] (e.g., $R_3 = t\text{-}C_4H_9$).

An alternate route which allows the conversion of propargyl alcohols directly to

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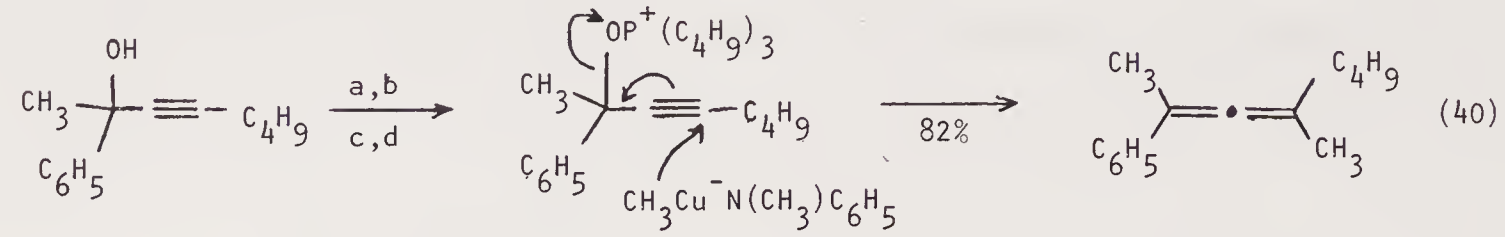
allenes in a one-pot procedure is shown in equation (40) and involves an *in situ* generation of the heterocuprate. The reaction is general and completely regiospecific, furnishing allenes from either primary, secondary, or tertiary propargyl alcohols regardless of steric influences.[80]

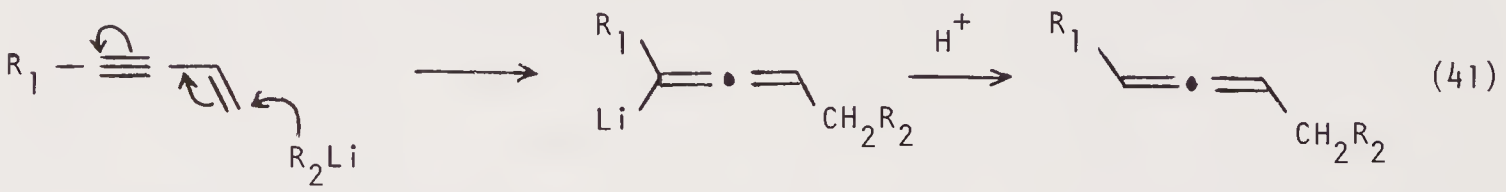


(40)

(a) CH_3Li; (b) CuI; (c) CH_3Li; (d) $(C_4H_9)_3P^+N(CH_3)C_6H_5I^-$

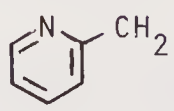
2.2.3. Addition of Organolithium Reagents to Vinylacetylenes

Conjugated enynes are susceptible to 1,4-addition of organolithium compounds and furnish internal allenes in good yields[81] (equation 41). At temperatures below $-30°C$ extremely clean reactions ensue and only allenic hydrocarbons are obtained regardless of the nature of the organolithium. The initially formed allenyllithium intermediate[82] **53** is protonated by the addition of water to give the product. The anion **53** can also be treated with a variety of other electrophiles to furnish highly diversified propadienes and is presented in chapters that deal with those specifically functionalized allenes.



(41)

53

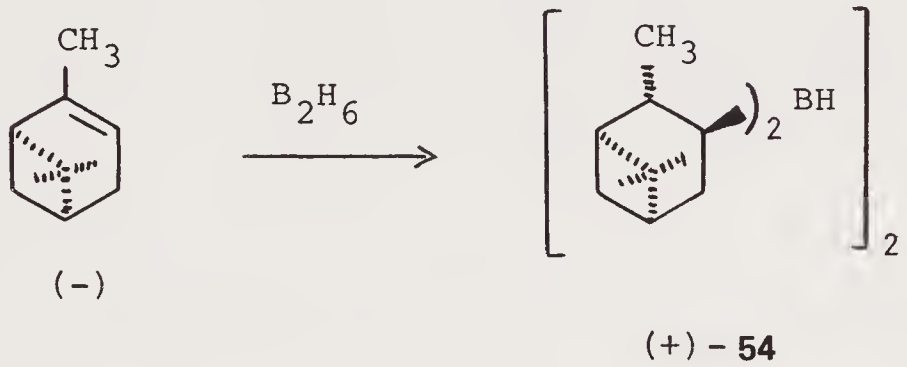
R_1	R_2	Yield,%	reference
CH_3	C_2H_5	72	81
C_2H_5	i-C_3H_7	80.5	81
C_2H_5	t-C_4H_9	52	81
t-C_4H_9	C_4H_9	70	83
CH_3	C_6H_5	25	84
CH_3		80	84

2.2.4. Optically Active Allenes

Optically active allenes can be obtained in various states of enantiomeric purity by two basic methods:

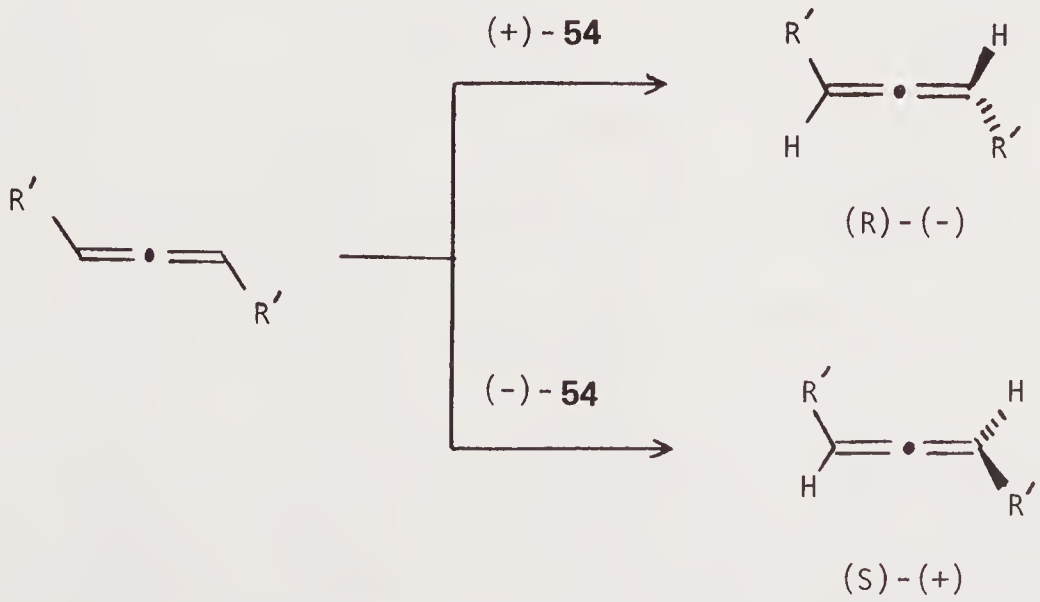
1. Resolution of a racemic mixture of the allene.
2. Asymmetric synthesis from chiral intermediates.

The least efficient of the two is the resolution method. A simple one-step procedure for such a process involves a kinetic resolution, by way of partial asymmetric hydroboration of an excess of the racemic mixture, which leads to recovery of allenes with induced optical rotations. One of the most versatile reagents developed for such transformations is (+)-*sym*-tetraisopinocamphenyldiborane[85] (**54**) which is derived from the hydroboration of (−)-α-pinene[86] (equation 42).



(42)

The resolution using (+)-**54** is generally performed at 0°C in diglyme with a twofold excess of the racemic allene. The (S)-allene enantiomer is the more reactive of the two, therefore, leaving the unreacted portion of the allene mixture optically enriched (from 4 to 25%) with the (−) enantiomer of R configuration[85,87,88] (equation 43). Increasing the size of the groups attached to the allene framework results in attaining substantially higher ee with the optical purity decreasing in the order 1,3-dipropylallene > 1,3-diethylallene > 1,3-dimethylallene.[89] Resolutions using an analogous borane reagent derived from (+)-α-pinene result in an excess of the (S)-allene.[87,89]

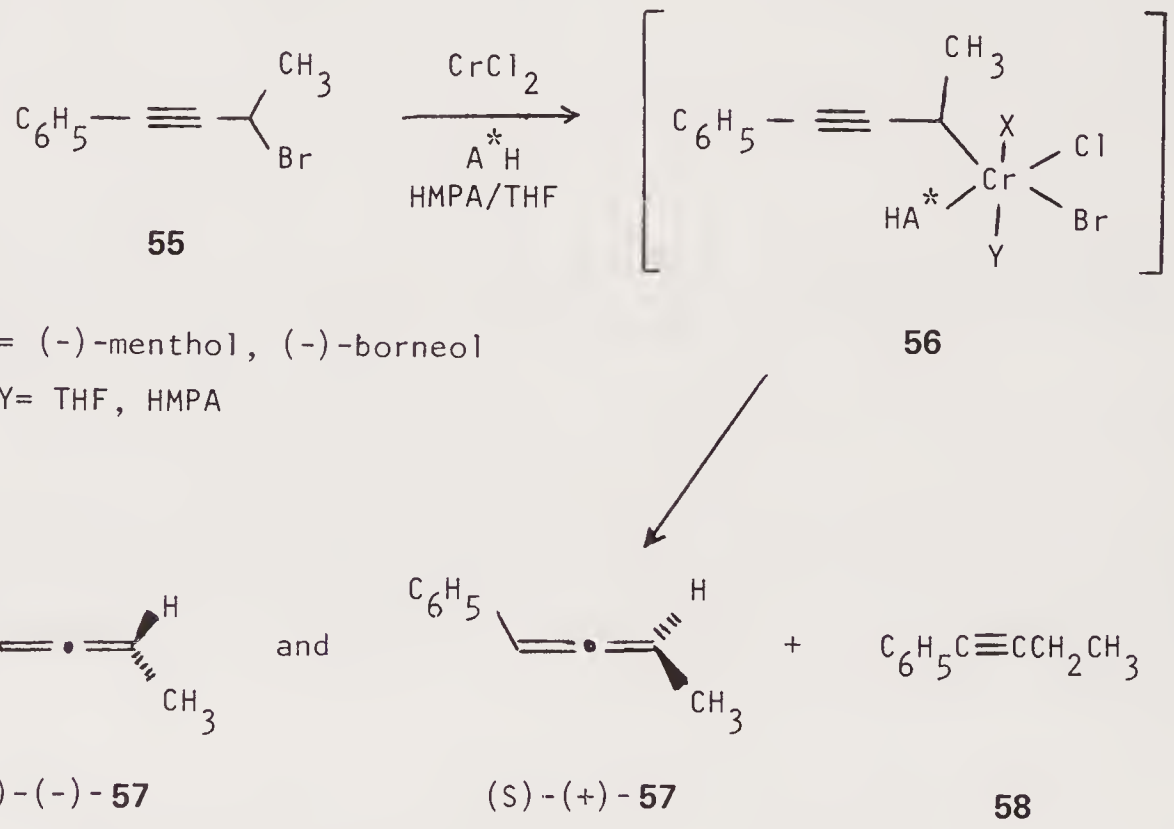


(43)

$$R = CH_3,\ C_2H_5,\ C_3H_7,\ t\text{-}C_4H_9,\ C_6H_5$$

A potential drawback to the described resolution method is the irreversible consumption of half of the allene (assuming complete recovery of the unreacted portion of the mixture). In the case of an extremely valuable allene intermediate, this may not be a satisfactory choice. An alternate approach is to induce asymmetry in the allene-forming reaction either by using chiral starting materials or optically active reagents.

The asymmetric reduction of racemic propargyl bromide **55** can be accomplished with chromium(II) chloride (Hiyama's reagent) modified by the addition of a protonic chiral auxiliary [A*H, such as (−)-menthol or (−)-borneol] along with varying amounts of HMPA.[90,91] The optically enriched allene results from an enantioselective intramolecular protonation of the organochromium intermediate **56**. When (−)-menthol is used in the absence of HMPA, a 50:50 mixture of **57** and **58** is obtained, with the allene portion being enriched 12.2% in the (S)-(+) enantiomer. Introduction of HMPA augments the allene segment of the mixture, however, the direction of optical rotation is changed to give an excess of the (R)-(−) enantiomer (maximum 15.6% ee). Employing (−)-borneol only produces an excess of the (R)-(−) allene (maximum 22.5% ee).

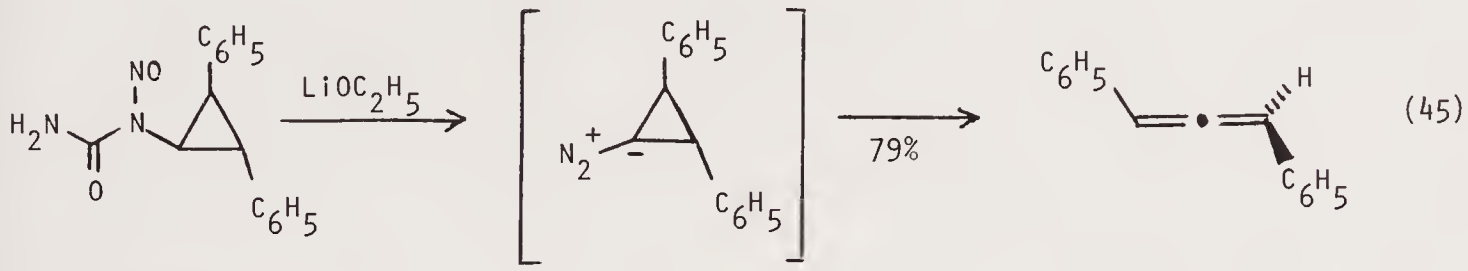


(44)

A*H	HMPA/Cr	Yield (%) (**57** + **58**)	Ratio (**57**:**58**)	Enantiomer (% ee)	
(−)-Menthol	0	64	50:50	(S)-(+)	(12.2)
(−)-Menthol	1	86	76:24	(S)-(+)	(2.7)
(−)-Menthol	2	77	73:27	(R)-(−)	(8.6)
(−)-Menthol	3	41	100:0	(R)-(−)	(15.6)
(−)-Borneol	0	46	55:45	(R)-(−)	(14.7)
(−)-Borneol	3	39	65:35	(R)-(−)	(22.5)
(−)-Borneol	5	39	80:20	(R)-(−)	(20.7)

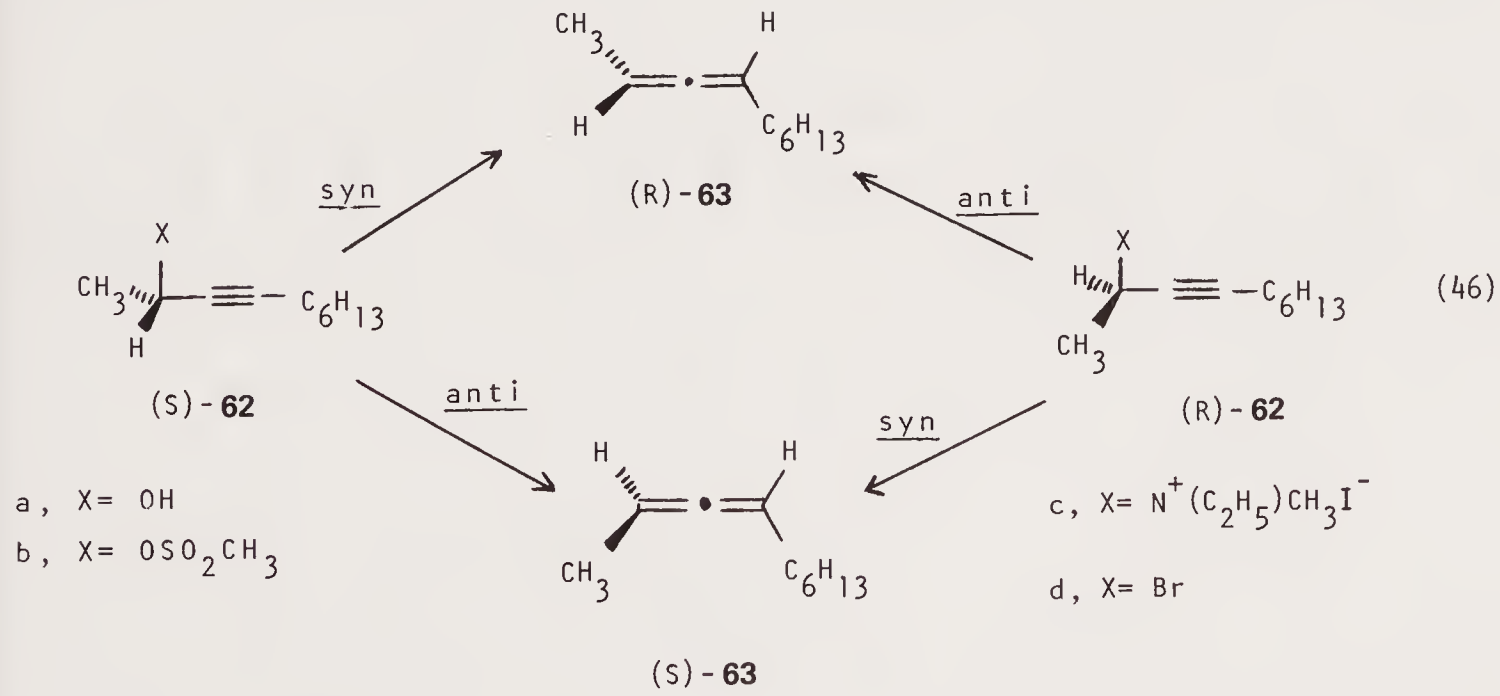
Material from equation (44) reprinted in part with permission from C. Verniere, B. Cazes and J. Gore, *Tetrahedron Lett.*, 103 (1981), Pergamon Press.

Optically active *N*-nitroso-*N*-(*trans*-2,3-diphenylcyclopropyl) urea (**59**) is readily converted to (S)-(+)-1,3-diphenylallene (**61**, 70% enantiomerically pure) by treatment with lithium ethoxide in heptane.[92,93] A likely mechanism involves a concerted collapse of the initially formed diazocyclopropane (**60**) and subsequent fission of the resulting cyclopropylcarbenoid species.[94]



(-)-**59** **60** **61** (45)

Chiral 3-decyn-2yl derivatives (**62a–d**) when treated with aluminum hydride reagents give high yields of 2,3-decadiene (**63**) (equation 46).[95*] The use of hydroxy, tertiary amine, or bromide as the leaving group X (compounds **62a, 62c,** and **62d**) produces the allene in a preferred *syn* mode of substitution, the degree of which increases with temperature. Alternately, the mesylate **62b** with lithium trimethoxyaluminum hydride produces the (S)-allene by way of an *anti* displacement which is more preferred at lower temperatures. The percent ee of the optically active allenes produced by this reaction is fairly high and generally falls between 70 and 80%.



(46)

hydride reagents: AlH_3, $LiAlH_4$, $LiAlH_4$—$AlCl_3$, $LiAlH_4$—$AlCl_3$—LiCl, $LiAlH(OCH_3)_3$

Chiral allenes are also obtained in high yield from organocuprate-induced 1,3-substitution of optically active propargylic derivatives such as acetates,[74] methane sulfinates,[96] or mesylates[97] (equation 47). Enantiomeric purities of the allenic prod-

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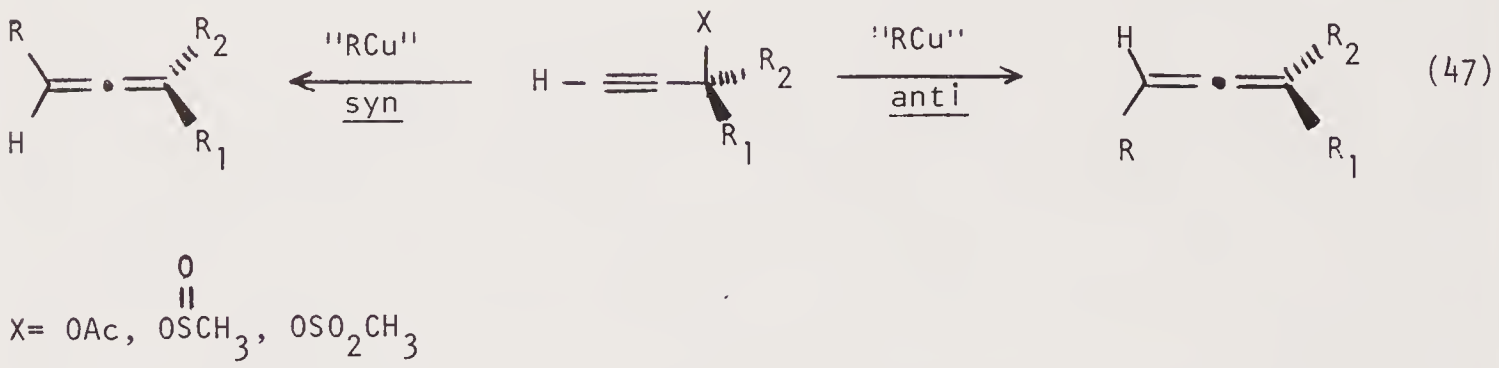
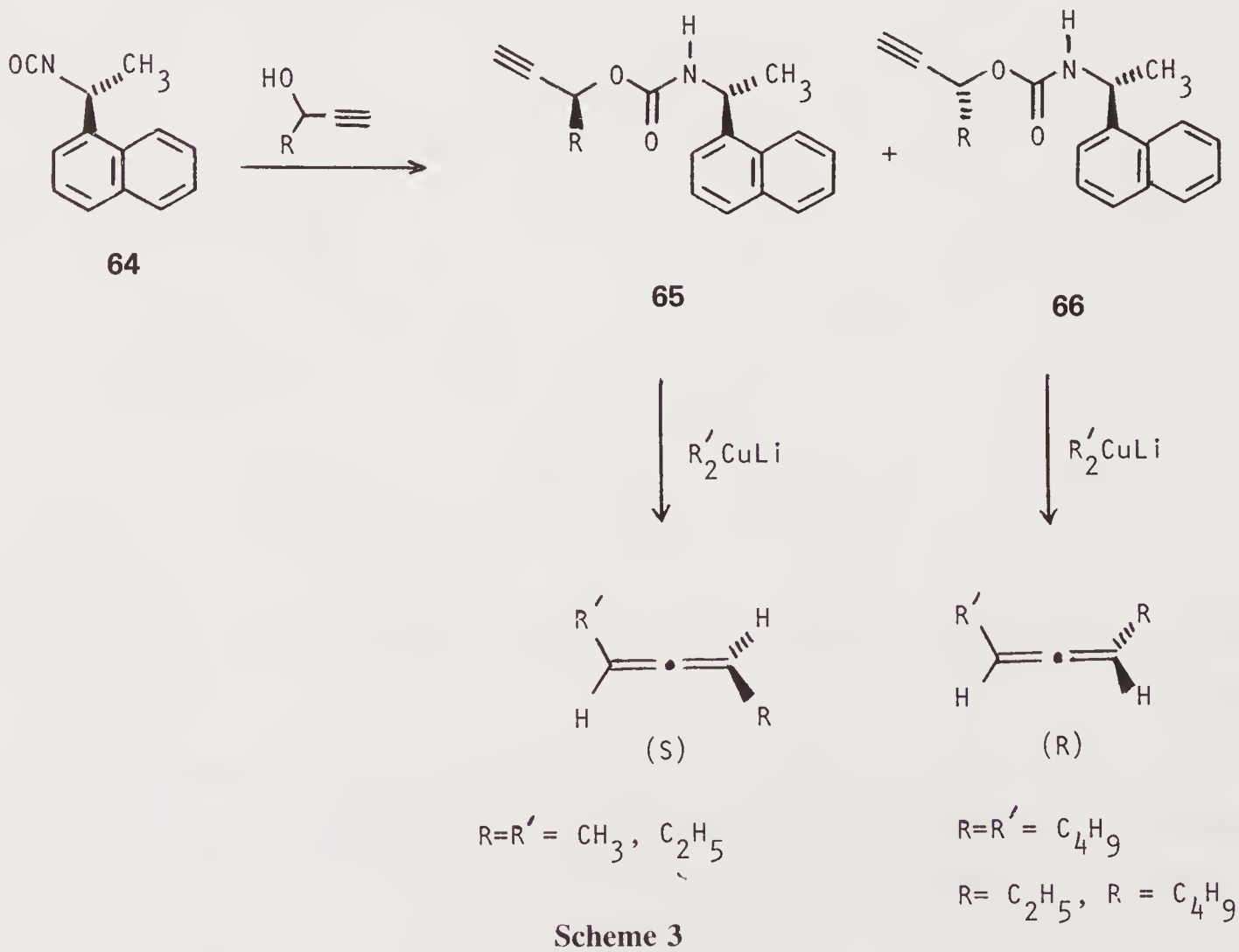
ucts are generally 65–80% (35–60% ee) and in the case of (R)-(−)-1,3-diphenylallene,[96] 88%. Highest ee's are obtained when reaction times are kept relatively short (less than 15 minutes).[97] Longer contact times with the organocopper reagent result in considerable racemization of the allene.[98]



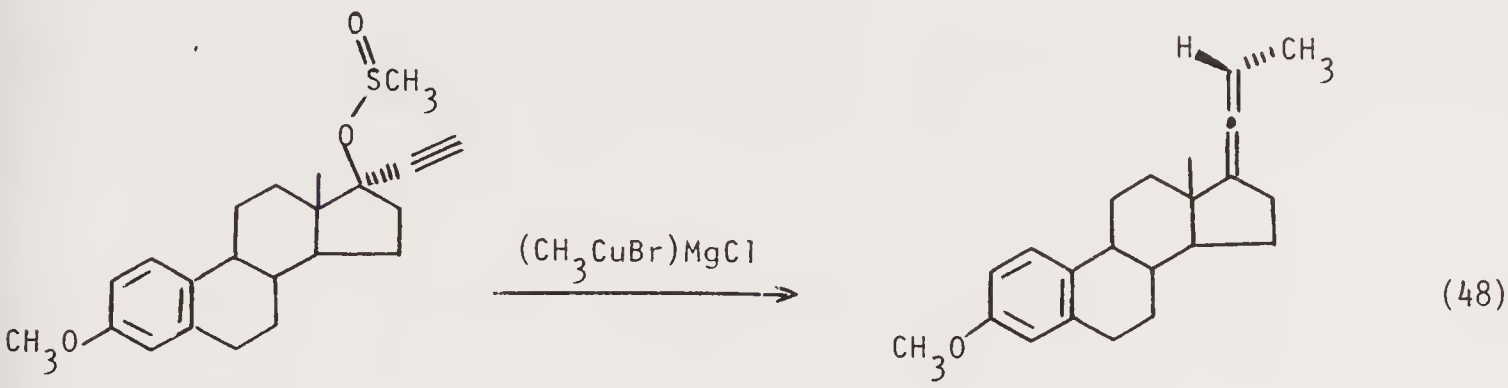
The difficult resolution of the chiral propargylic substrate presents a potential problem in the production of synthetically useful quantities of the enantiomeric allene. Pirkle and Boeder[99] circumvent this situation by converting a racemic propargyl alcohol to a mixture of diastereomeric carbamates by reaction with (R)-1-(1-naphthyl)ethylisocyanate (**64**). The mixture is readily separable into its enantiomers **65** and **66** by chromatography, and each reacts with lithium dialkylcuprates to give the (R) or (S)-1,3-dialkylallenes (60–80% ee) in high yields.

Early investigations into the mechanism of the transformation illustrated in equation (47) led to the belief that for nonsteroids the substitution preferentially proceeds by an *anti* mode[96] whereas steroids prefer *syn* addition.[79,100] Recently, however, Vermeer[101] has shown that reactions in the steroid series also proceed by an *anti*



Scheme 3

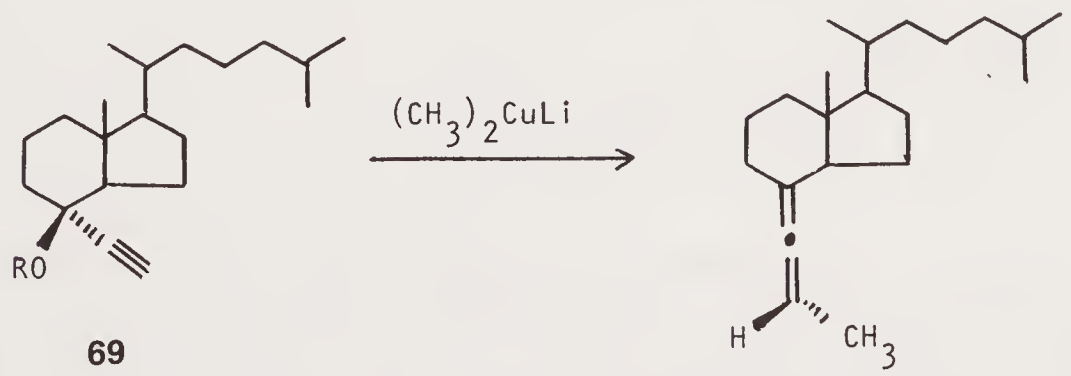
displacement, a violation of the Lowe–Brewster rules. The allenic steroid **68**, prepared from mestranol methane sulfinate (**67**), was elucidated unambiguously by X-ray analysis.



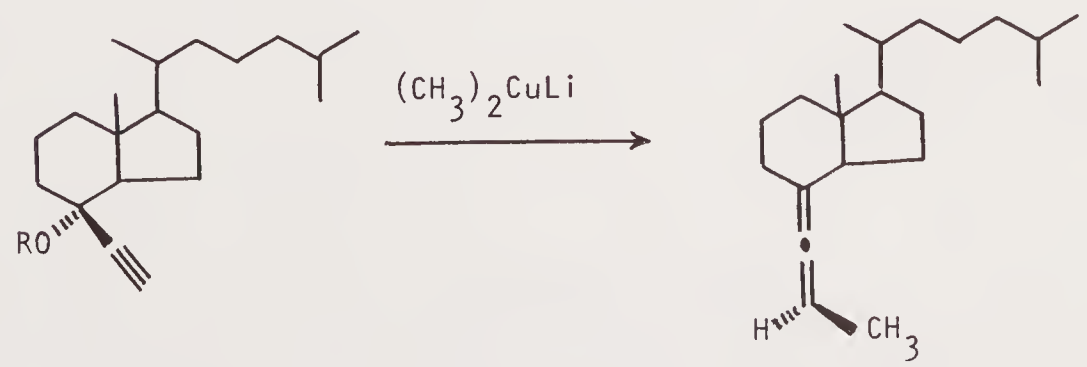
67 **68** (48)

Further corroboration for this selectivity is furnished from reactions of C-8 propargylic esters (**69** and **71**) which are derived from Grundmann's ketone, a C/D steroidal fragment originating from Vitamin D_3.[102] Treatment of either **69** or **71** with lithium dimethylcuprate in ether furnishes allenes **70** or **72** by way of an *anti* 1,3-substitution.

Therefore due caution should be exercised when surveying literature reports on stereospecific organocuprate-induced allene syntheses in steroidal or steroidlike series that suggest *syn* substitution[103] when in actuality the *anti* mode is preferred.



69 **70** (49)

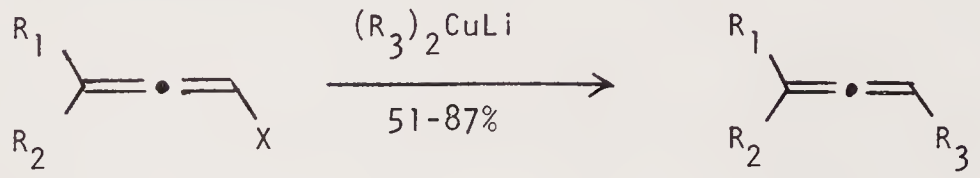


71 **72** (50)

R= $\overset{O}{\overset{\|}{C}}C_6H_5$, Ac, $\overset{O}{\overset{\|}{S}}CH_3$

2.2.5. Miscellaneous Preparations

Lithium dialkylcopper reagents serve as useful alkylating agents for direct replacement of halogen atoms attached to the allene skeleton[104,105] (equation 51).



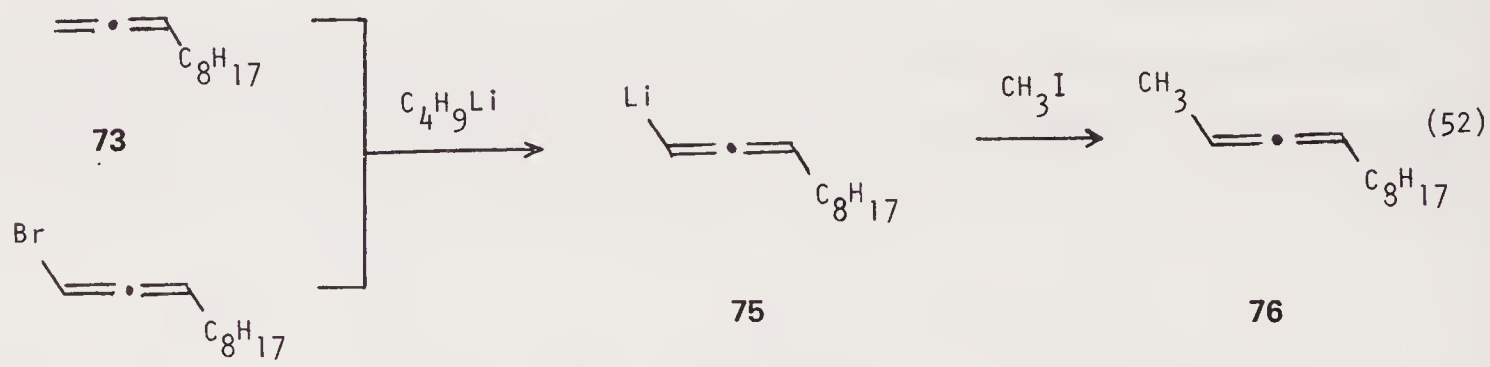
(51)

X= Br, I

R_1, R_2= H, CH_3, C_2H_5, C_3H_7, t-C_4H_9

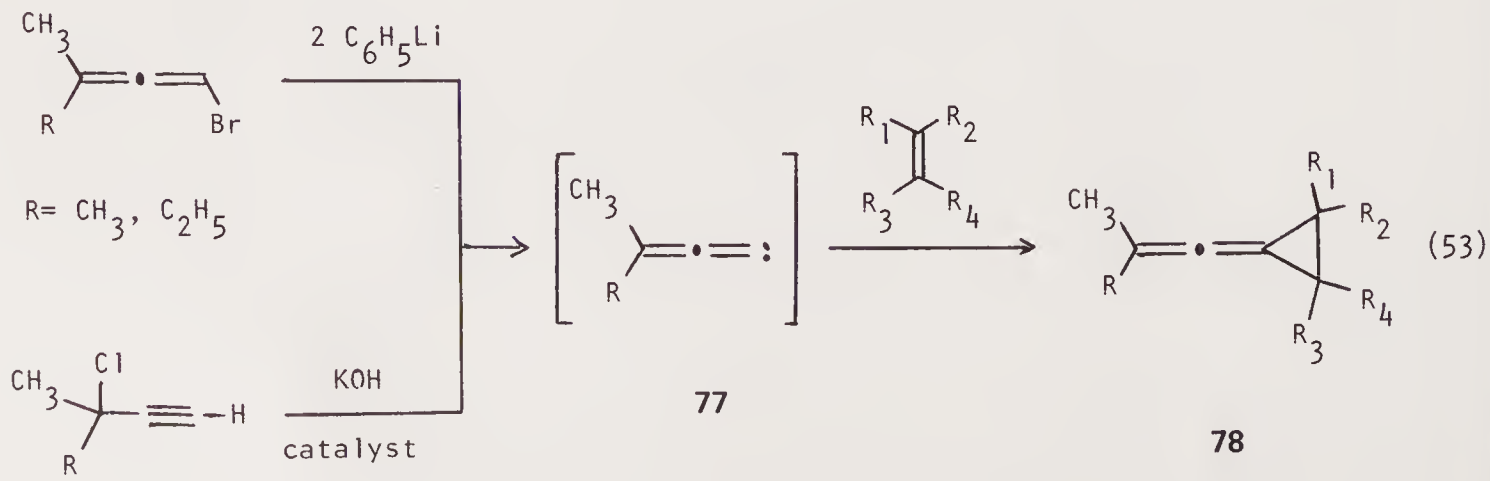
R_3= CH_3, C_2H_5, C_4H_9

Monosubstituted allenes such as 1,2-undecadiene (**73**) can be lithiated regiospecifically at the terminal position to give **75**. Subsequent treatment with methyl iodide furnishes 2,3-dodecadiene (**76**) in 93% yield. Alternately, the same lithioallene **75** can be generated by the action of one equivalent of *n*-butyllithium on 1-bromo-1,2-undecadiene (**74**). Similar treatment with methyl iodide gives **76** in 90% yield.[106]



(52)

When 1-bromo-3,3-disubstituted allenes are treated with two equivalents of an organolithium reagent, an allenic carbene (**77**) is generated which can be intercepted with olefins to produce dialkylvinylidenecyclopropane derivatives[107] (**78**) (equation 53). Higher carbene conversions are obtained by the base-promoted elimination of

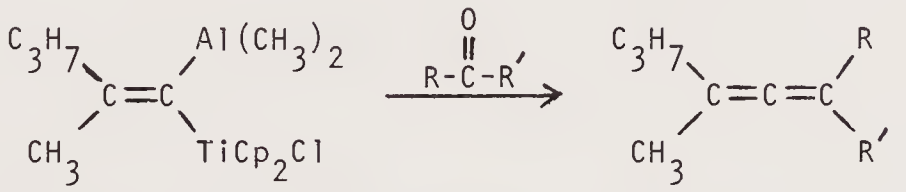


(53)

$R_1 - R_4$ = H, alkyl, aryl

hydrogen chloride from a 3-chloro-1-alkyne. Aqueous sodium or potassium hydroxide is generally employed, and catalysts such as quaternary ammonium salts[108–110] (phase transfer conditions) or crown ethers[111] markedly influence the rate of the reaction.

The interestingly substituted 1,1-dimetallated olefin (**79**), formed in greater than 90% yield by the addition of a 1:1 complex of trimethylaluminum and Cl_2TiCp_2 to 1-heptynyldimethylalane,[112] reacts with aldehydes (at $-30°C$) or ketones (at 0°C) to give allenes **80** in good yield.[113]



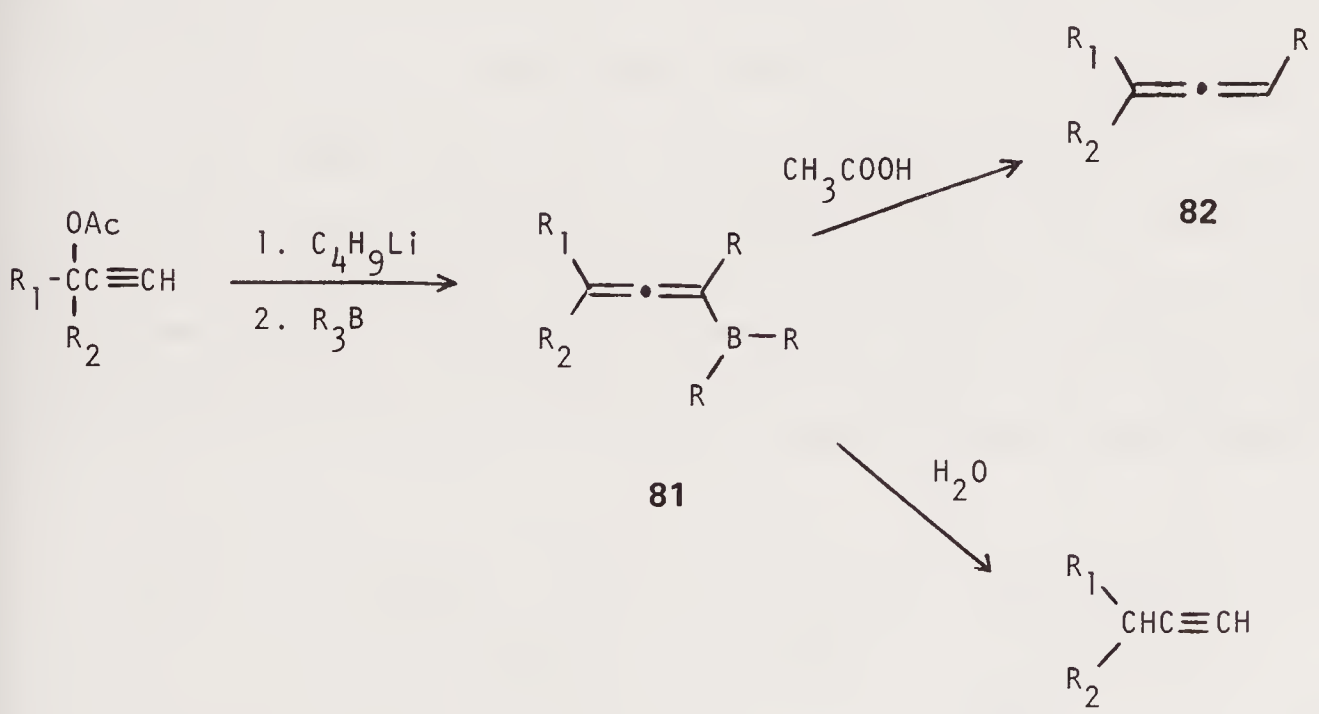
(54)

79

80 a, R, R′ = $(CH_2)_5$ 83%

b, R = C_6H_5, R′ = H 67%

Propargyl acetates, when sequentially treated with *n*-butyllithium and a trialkylborane at $-78°$, produce an allenic borane **81** by way of an alkyl migration similar to that illustrated in equation (26). Protonation of **81** with dry acetic acid results in the formation of an allene (**82**), whereas addition of water gives an acetylene exclusively (**83**).[114]



(55)

81

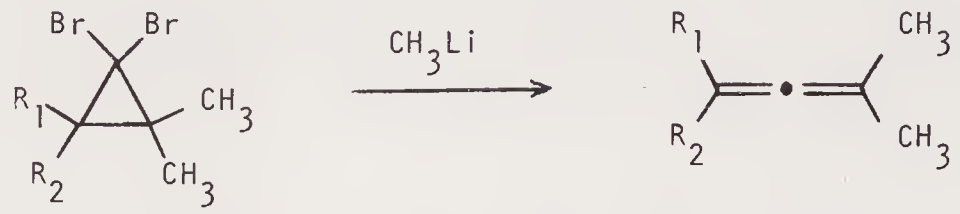
82

83

R_1, R_2 = alkyl, alkenyl, C_6H_5

An effective method for allene synthesis, previously discussed in the terminal allene section of this chapter, is the base-promoted rearrangement of 1,1-dibromocyclopropanes (e.g., equation 32). This methodology can also be applied to the synthesis of internal allenes, however, a curious result appears. The treatment of **84a, 84b,** or **87** with methyllithium gives the expected allenes **85** and **88** in good yields.[51,115,116] When the identical reaction is performed using the tetramethyl de-

rivative **84c**, only 1,2,2-trimethylbicyclobutane (**86**) is produced in quantitative yield.[117,118] It appears that extremely subtle steric differences inhibit cyclopropane fission of the carbene intermediate (leading to the allene) and favor carbene insertion into an alpha CH bond (affording **86**).[119]



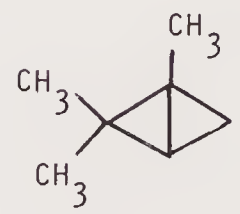
(56)

85a, b

84 a, R_1= H, R_2= CH_3

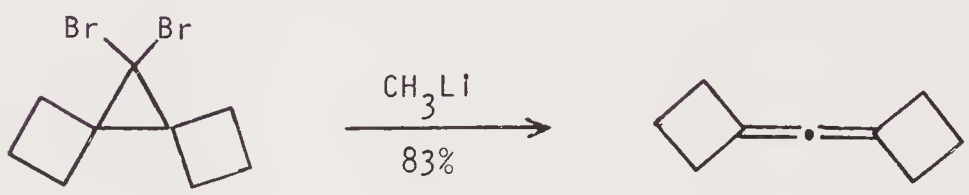
b, R_1, R_2= $(CH_2)_4$

c, R_1= R_2= CH_3



(57)

86



(58)

87 **88**

2.3. CYCLIC ALLENES

The incorporation of the propadiene unit into a cyclic system (**89**) creates a topologically interesting moiety which enables the chemist to perform stereoselective transformations on the allene portion of the molecule. Depending on the size of the ring and its conformation, the carbon chain bridging the 1 and 3 positions of the propadiene effectively shields one side of the allene, therefore directing chemical reactions from the unencumbered face.

89

The smallest ring that can accommodate a propadiene unit in a relatively strain-free environment is a nine-membered ring. As the size of the ring is decreased, deformation of the allene function is necessary to relieve the subsequent ring strain. The first mode of deformation consists of bending the allene linkage at the central carbon atom thereby reducing the angle θ from the normal value of 180° (Figure 2). The second mode of deformation retains the linearity of the allene function

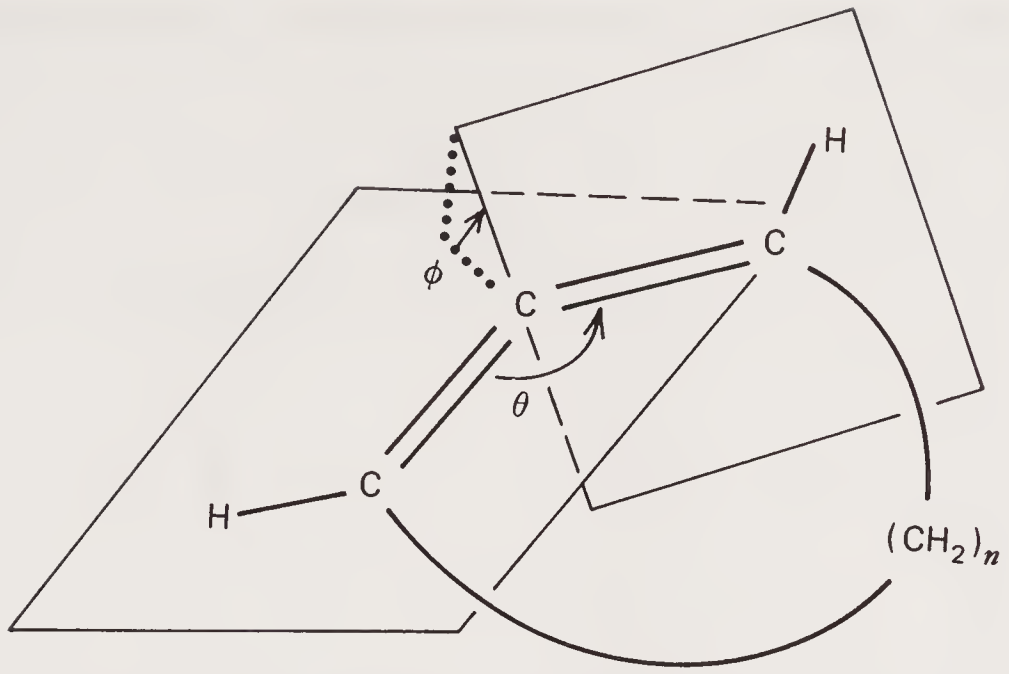


Figure 2. Modes of deformation of strained cyclic allenes. (Reprinted in part with permission from reference 131. Copyright 1974 American Chemical Society.)

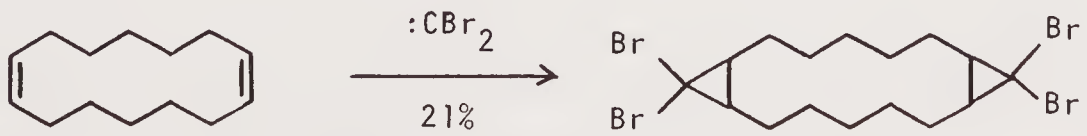
($\theta = 180°$) but requires one of the methylene groups of the bridging chain to twist causing the angle ϕ to diminish from its theoretical value of 90°.[131] In the case of seven- or eight-membered rings, both the bending and twisting mode may occur.

Initially, cyclic allenes were synthesized as laboratory curiosities to study their physical characteristics. As preparative allene methodology became more sophisticated and reliable, many of these techniques were applied to the cyclic systems, and synthetically useful quantities of cyclic allenes became available for chemical manipulations.

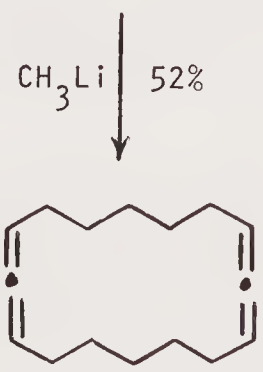
This section presents cyclic allenes starting with the larger stable rings and proceeds sequentially to the smaller rings of limited stability.

2.3.1. Sixteen Membered Rings

The novel monocyclic bisallene **91** can be conveniently prepared by the method perfected by Skattebol.[52] The treatment of cyclotetradeca-1,8-diene with dibromocarbene gives the tetrabromotricyclohexadecane derivative **90**, which is debrom-



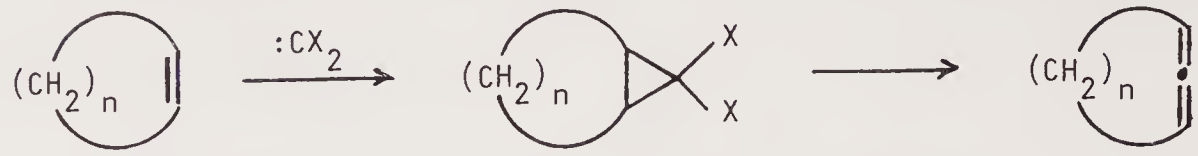
90



(59)

91

Table 2.4. Simple Monocyclic Allenes Prepared from 1,1-Dihalocyclopropanes



(60)

n	X	Reagent	Yield (%)	Reference
12	Cl	C_4H_9Li	80	133
11	Cl	C_4H_9Li	79	133
10	Cl	CH_3Li	86	133
10	Br	CH_3Li	76	134
10	Br	$NaCH_2SOCH_3$	46	134
10	Br	$CrSO_4$	85	135
8	Br	C_4H_9Li	89	136
7	Br	C_4H_9Li	78	136
7	Br	Na/Al_2O_3	64	137
6	Br	Na/Al_2O_3	44	137
6	Br	CH_3Li	90	138
6	Br	Mg	59	139
6	Br	$CrCl_2$	100	46
6	Br	$NaCH_2SOCH_3$	66	140

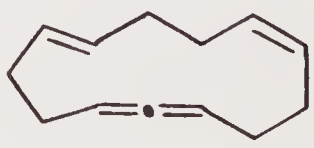
inated with methyllithium at $-30°C$ to give the product.[51,52] Compound **91** is of interest because of its ability to undergo intramolecular transannular cyclization upon reaction with iron carbonyls.[132]

2.3.2. Fifteen → Eleven-Membered Rings

Throughout the cyclic allene series, the reductive dehalogenation of 1,1-dihalocyclopropanes proves to be one of the most effective methods for generating such species (equation 60). The procedure has been successfully applied to the synthesis of nearly all the stable ring sizes down to 1,2-cyclononadiene. Table 2.4 includes various reagents used to effect the conversions and also includes 1,2-cyclodecadiene and 1,2-cyclononadiene for the purpose of comparison.

Analogs that contain additional olefinic sites in the ring can also be synthesized by this two-step method; 1,2,6Z,10E-cyclotridecatetraene (**92**) from 1E,5Z,9E-dodecatriene,[134,135] and 1,2,7-cycloundecatriene (**93**) from 1Z,6Z-cyclodecadiene.[141]

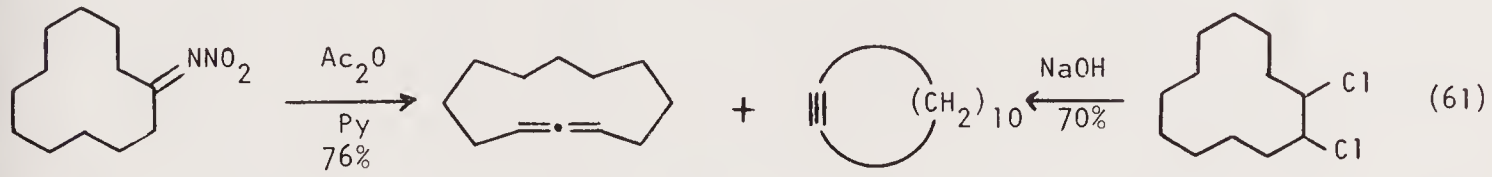
Only two low-yielding syntheses are reported for the formation of 1,2-cyclododecadiene (**95**). Dehydrohalogenation of 1,2-dichlorocyclododecane (**97**) with



92

93

alcoholic sodium hydroxide at 120–150°C furnishes pure cyclododecyne (**96**) in 70% yield. If the reaction is performed at 180°C a mixture of **95** and **96** is produced (ratio 28:72) as a result of isomerization of **96**.[42] Alternately, the base-catalyzed rearrangement of the *N*-nitroenamine **94** affords a similar mixture of **95** and **96** (ratio 19:81).[143] The use of either pyridine (100°, 2 hr) or DMAP (30°, 24 hr) does not significantly change the ratio of the products.



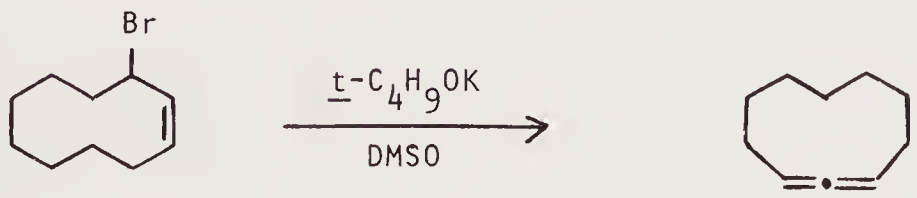
(61)

94 **95** **96** **97**

2.3.3. Ten-Membered Rings

Several classical approaches have been used in the synthesis of 1,2-cyclodecadiene (**98**). Among them are the treatment of 1-chlorocyclodecene with either potassium hydroxide[144] or sodium amide,[137] and the dehalogenation of 1-bromo-2-chlorocyclodecene with sodium.[145] The yields of allene are moderate at best (39–60%), and contamination with the isomeric cyclodecyne represents up to 40% of the product mixture. However, the unwanted acetylene can be removed easily by extraction with aqueous silver nitrate.[144]

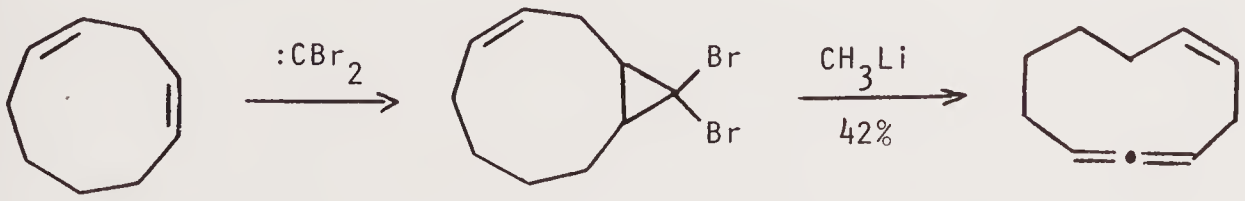
A noteworthy preparation of **98** involves a regiospecific dehydrobromination of *cis*-3-bromocyclodecene with potassium *t*-butoxide in DMSO (equation 62). The cyclic allene, which forms at room temperature in 5 minutes, is isolated in 78% yield and is 95% pure.[146]



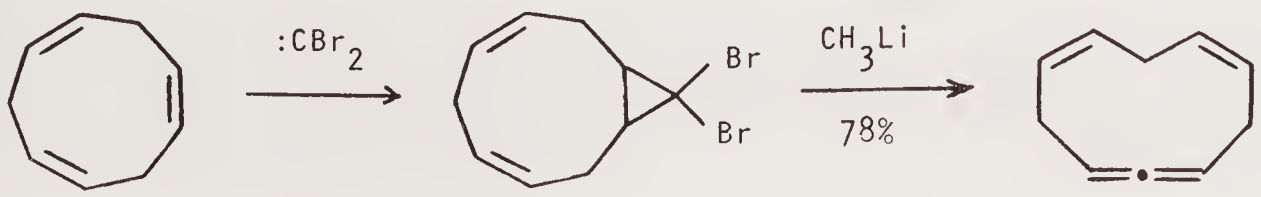
(62)

98

Cyclic ten-membered allenes that contain isolated double bonds are readily prepared from the appropriately unsaturated cyclononene by reaction with dibromocarbene then with methyllithium[147] (equations 63 and 64).

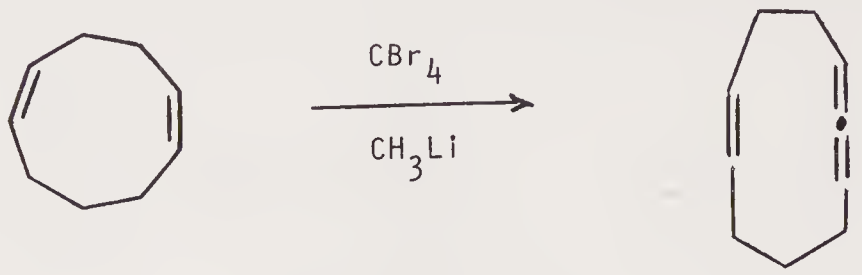


(63)



(64)

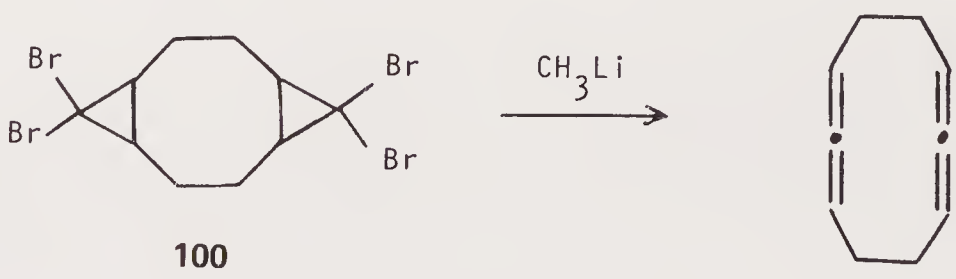
This method can be shortened to one step by employing methodology developed by Untch.[148] The treatment of a fourfold excess of 1Z,5Z-cyclononadiene with one equivalent of carbon tetrabromide and two equivalents of methyllithium at −65°C furnishes 1,2,6-cyclodecatriene (**99**) in 60% yield.[149]



(65)

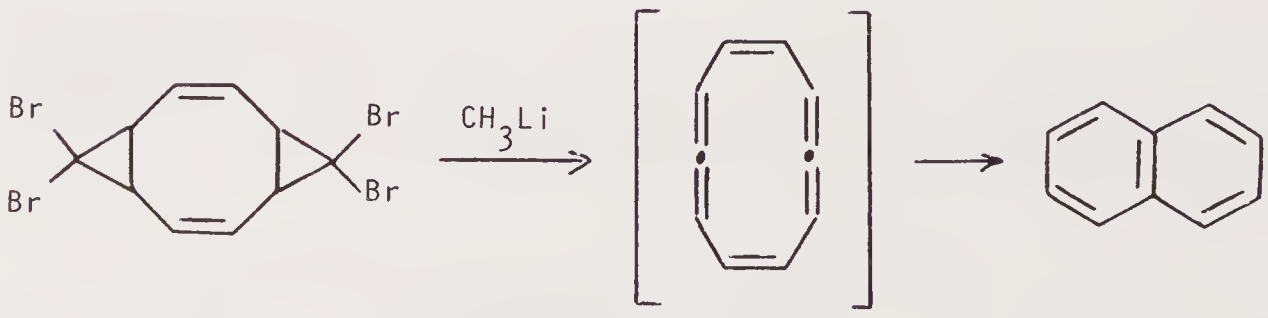
99

A 10-membered ring can accept two propadiene units in three possible isomeric positions. The symmetrical 1,2,6,7-cyclodecatetraene (**101**) is prepared in low yield by the action of methyllithium on **100**.[51,52] The stereochemical nature of this molecule enables it to exist in either a *meso* or *dl* configuration.[150] In practice, the reaction outlined in equation (66) affords the *meso* isomer, and its structure is substantiated by X-ray analysis. The two allenic linkages exert some degree of strain in the ring which causes a small amount of bending at their central carbon atoms ($\theta = 174°$).[151] Introduction of additional unsaturation into the system (e.g., **102**) results in the direct isolation of naphthalene which presumably forms by way of the cyclodecahexaene **103** (equation 67).[150]



(66)

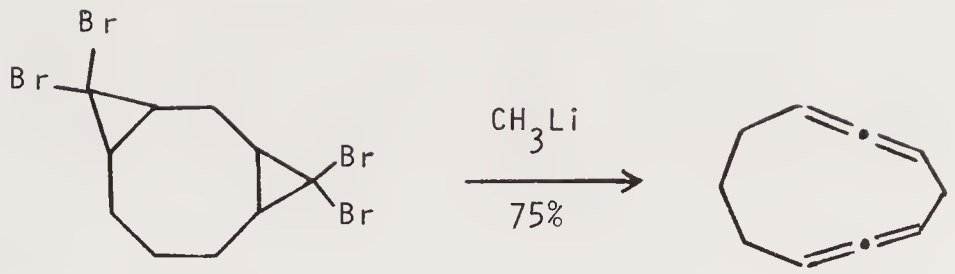
100 **101**



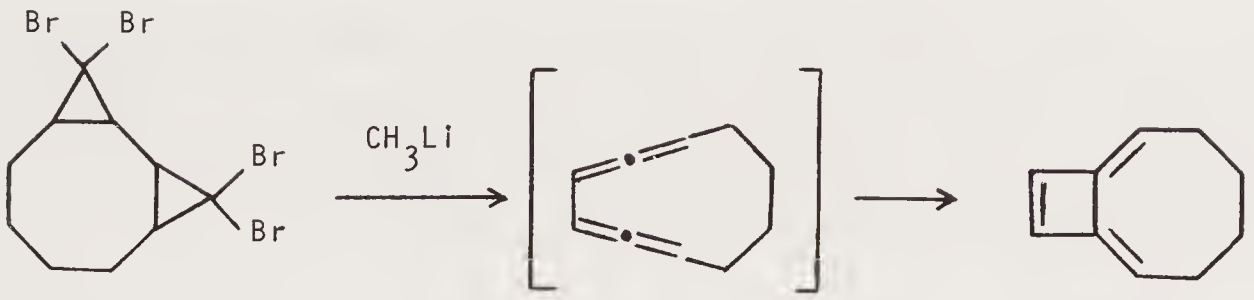
(67)

102 **103**

Analogous reactions of **104** and **106** furnish 1,2,5,6-cyclodecatetraene (**105**, equation 68) and 1,2,4,5-cyclodecatetraene (**107**, equation 69).[152] Bisallene **107**, however, is thermally unstable, and only bicyclo[6.2.0]deca-1,7,9-triene (**108**) is isolated in good yield.[153]



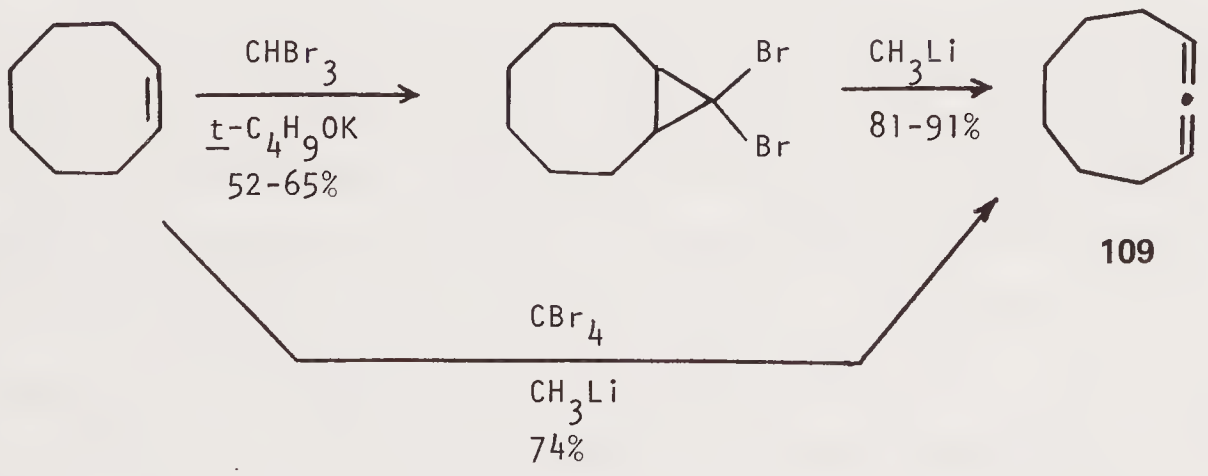
104 105 (68)



106 107 108 (69)

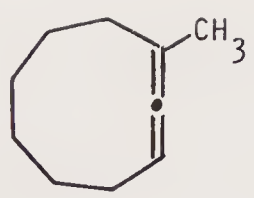
2.3.4. Nine-Membered Rings

The most popular cyclic allene employed in chemical manipulations is 1,2-cyclononadiene (**109**). Its high-yielding synthesis from readily available cyclooctene is amenable to large-scale preparation[138,148] (equation 70). Its formation can also be realized by the dehydrohalogenation of 1-chlorocyclononene with either sodium amide in ammonia,[137] potassium hydroxide,[144,154] or sodium on alumina,[137] however, yields are generally lower, and cyclononyne is also formed as a by-product.



109 (70)

Several derivatives of **109** have been prepared by the methods mentioned before. These include 1-methyl-1,2-cyclononadiene (**110**) from 1-methylcyclooctene,[155] bicyclo[7.1.0]deca-4,5-diene (**111**) from bicyclo[6.1.0] cyclonon-4-ene,[156] 1,2,6-cyclononatriene (**112**) from either 1,5-cyclooctadiene,[148,157] 9,9-dibromobicyclo[6.1.0]non-4-ene[51,140] or 1,9-dibromocyclonona-1,5-diene,[158] 1,2,5,7-cyclononatetraene (**113**) from the dibromocarbene adduct of 1,4,6-cyclooctatriene,[152] and 1,2,5-cyclononatriene (**114a**) and its 7-methoxy analog **114b** from the appropriate dibromobicyclononenes.[152]



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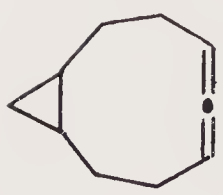
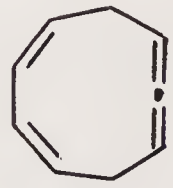
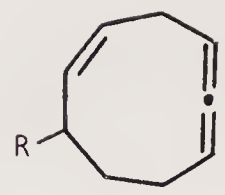


111

112

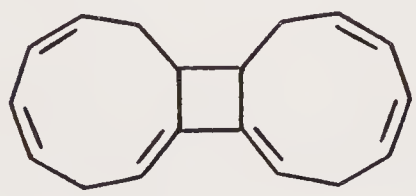


113

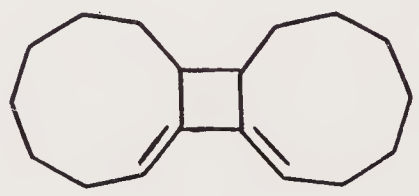


114 a, R= H
b, R= OCH_3

With the exception of **113**, allenes **109–114** are stable at room temperature. Compound **113** is relatively unstable and slowly dimerizes at 0°C with a half-life of 10–20 minutes, to **115**.[152] In comparison, **109** requires heating at 130° for 18 hours to effect nearly quantitative dimerization to **116**.[159,160]



115



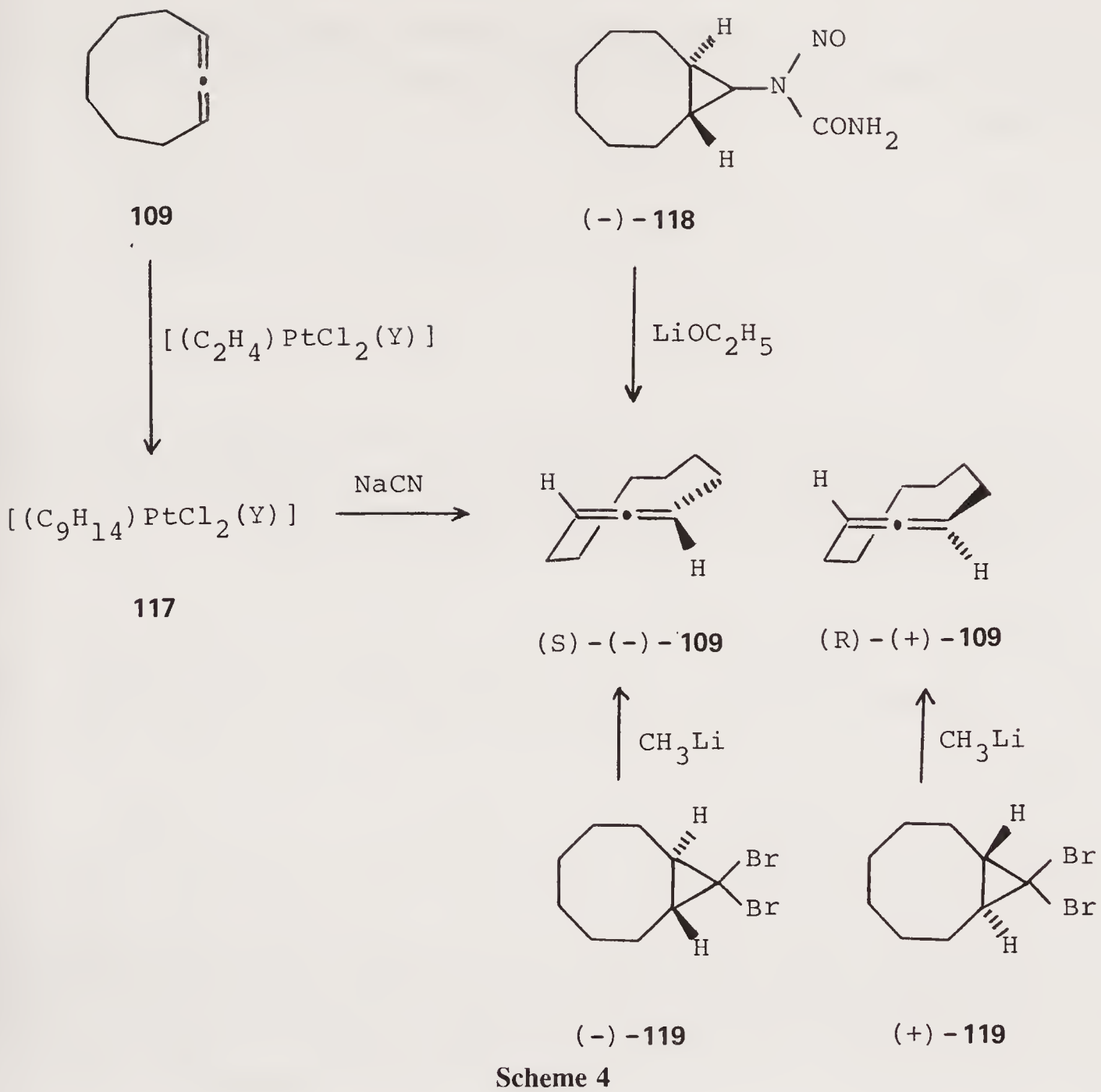
116

Optically active 1,2-cyclononadiene can be obtained by a kinetic resolution by way of partial asymmetric hydroboration with (+)-**54**.[88,161] The resulting (+)enantiomer, of 15% optical purity, has the R absolute configuration.[162,163] Alternately, partial resolution of racemic **109** can be accomplished by complexation with $[(C_2H_4)PtCl_2(Y)]$ where Y represents either optically active α-methylbenzylamine or *p*-nitro-α-methylbenzylamine.[164] Fractional crystallization of the diastereomeric platinum complexes **117** (Scheme 4) followed by decomposition with sodium cyanide furnishes either enantiomer of **109** with an optical purity of 44%.

Both enantiomers of **109** are available in high optical purity by asymmetric synthesis. The decomposition of (−)-**118** with lithium ethoxide at 0°C gives (S)-(−)-**109** whose rotation of $[\alpha]^{25}D$-159° corresponds to an optical purity of approximately 93%.[165] By a shorter overall route, (S)-(−)-**109** can be obtained in two steps by the treatment of (+)-*trans*-cyclooctene with bromoform and potassium *t*-butoxide to give (−)-**119** which, upon reaction with methyllithium at 0°, affords the product in 89% yield with an optical purity of 85–88%.[164,165] The optical yield can be increased to greater than 96% by performing the reaction at −78°, however, the yield of allene is reduced. By similar transformations, (−)-*trans*-cyclooctene is converted to (R)-(+)-**109** with comparable optical activity.[164]

2.3.5. Eight-Membered Rings

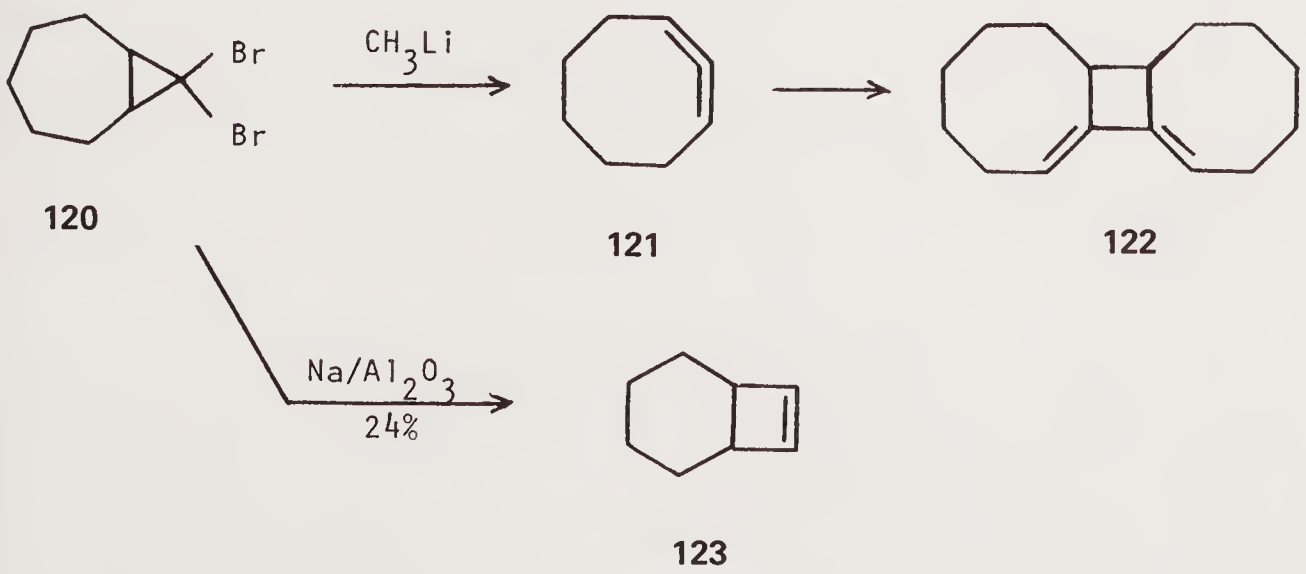
The strained 1,2-cyclooctadiene system (**121**) borders on the limit of stability. The methyllithium-induced α-elimination of 8,8-dibromobicyclo[5.1.0]octane (**120**) at 0° forms a mixture containing approximately 8% of **121** which can be detected (by infrared spectroscopy) immediately after quenching the reaction mixture with water.[166]



(-)-119 (+)-119

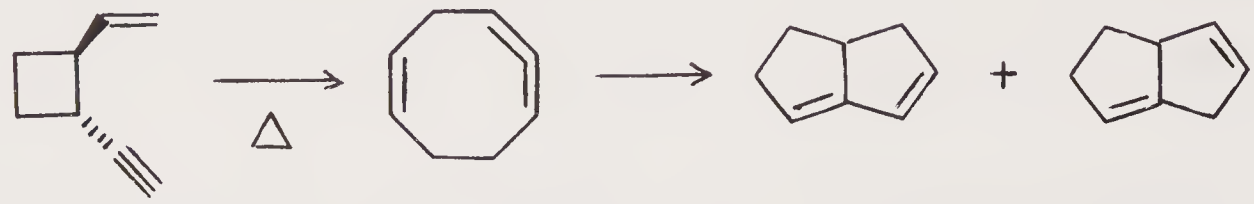
Scheme 4

If the mixture is allowed to stand, the stable allene dimer **122** can be isolated in 32% (Scheme 5). If **121** is generated by the interaction of **120** with sodium on alumina, the reaction takes a different course. When held on the solid surface of the alumina, **121** rearranges internally to give **123** instead of following the normal dimerization route.[137]



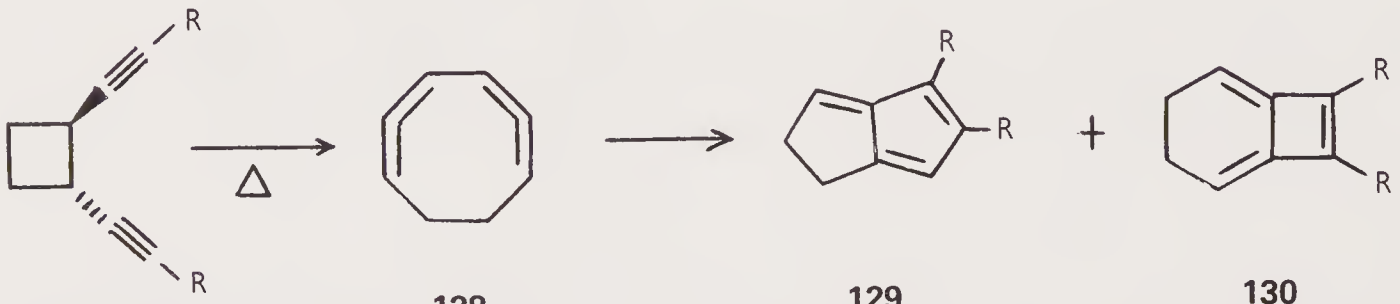
Scheme 5

Thermolysis of *trans*-1-ethynyl-2-vinylcyclobutane at 460°C produces a mixture of bicyclooctadienes **125** and **126** presumably from the transient 1,2,5-cyclooctatriene (**124**).[167]



124 **125** **126** (71)

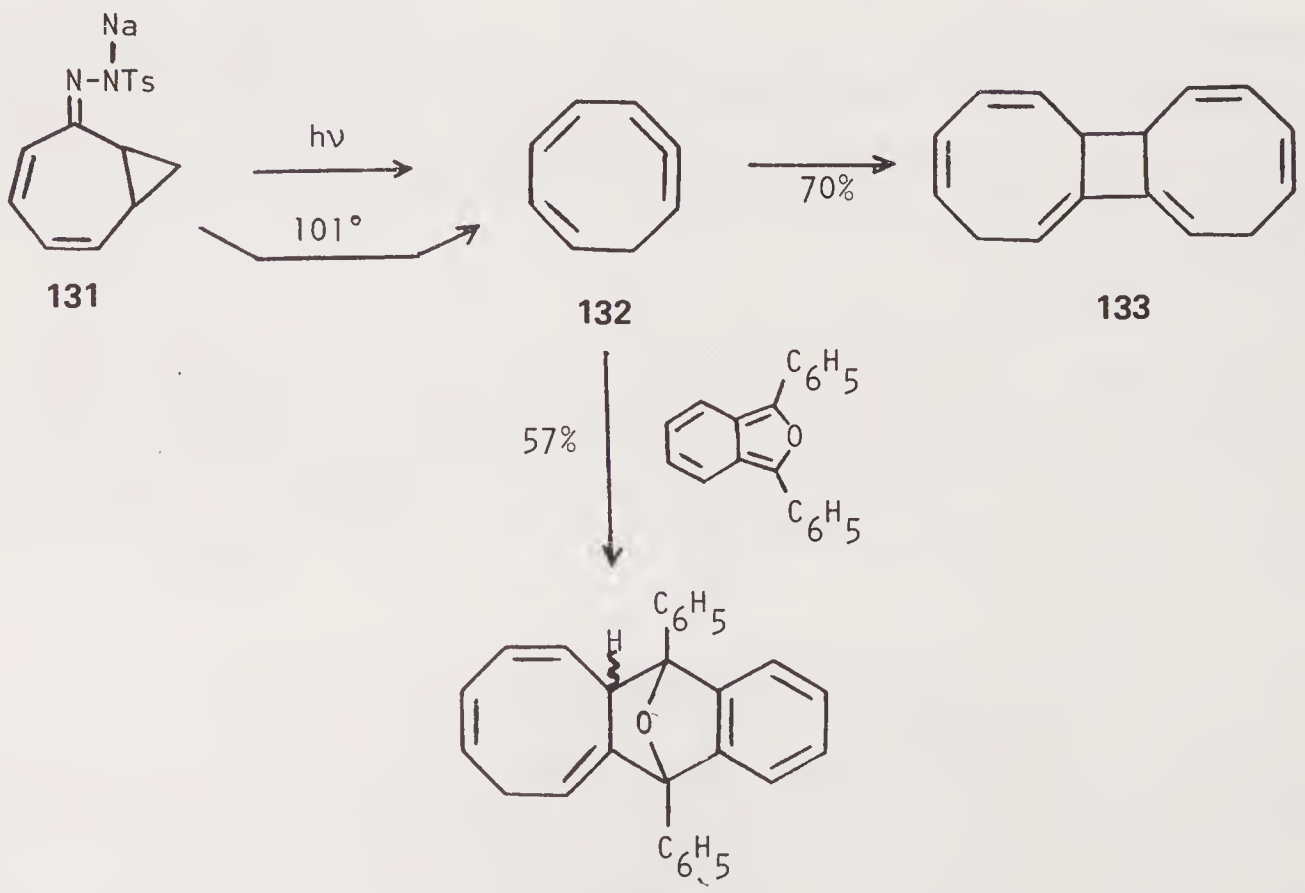
Analogous pyrolyses of *trans*-1,2-diethynylcyclobutanes (**127**) at 430°C yields a mixture of 1,2-dihydropentalenes (**129**, major product) and bicyclo[4.2.0]octa-1,5,7-trienes (**130**) by way of 1,2,4,5-cyclooctatetraene (**128**).[168]



127
R= H, CH_3

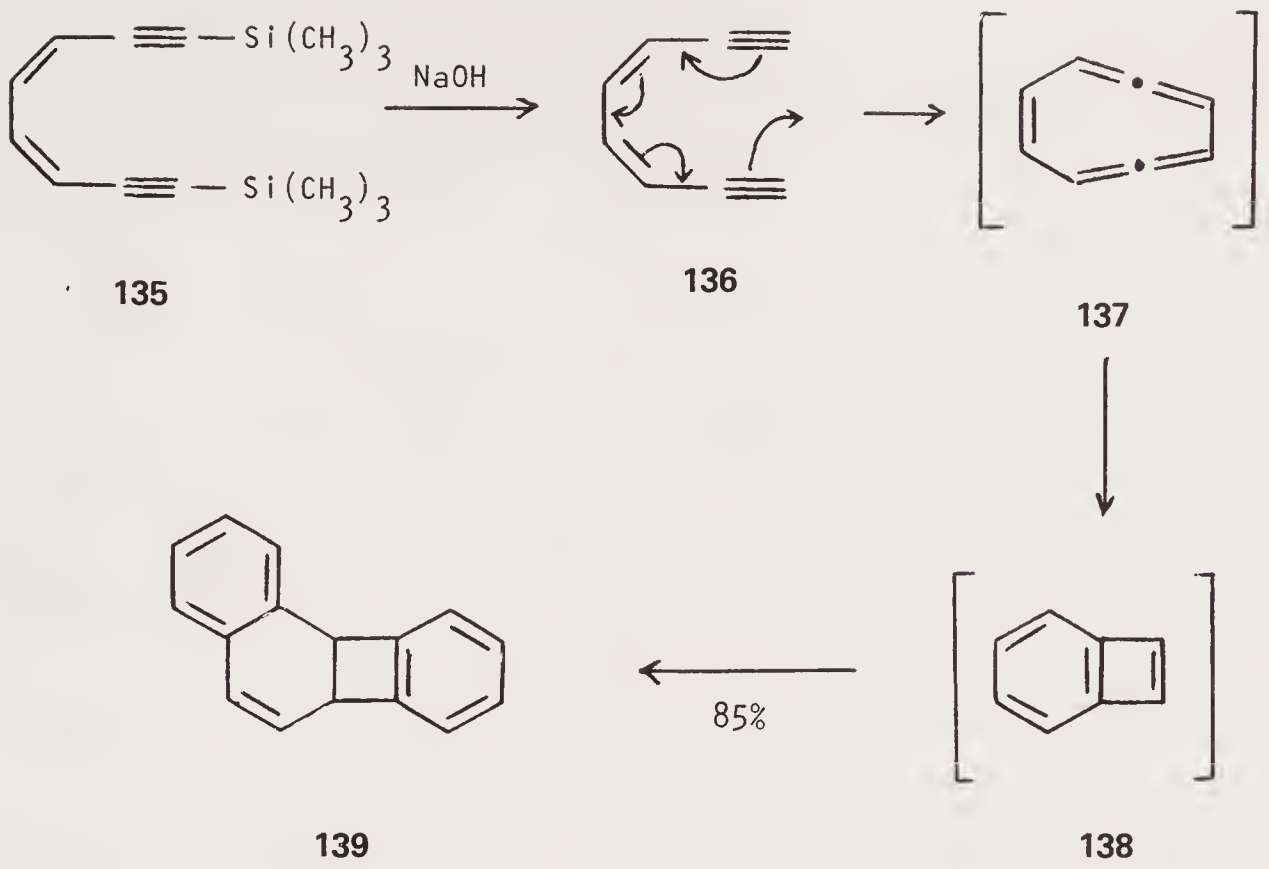
128 **129** **130** (72)

Photoirradiation of the sodium salt of 2,3-homotropone *p*-toluenesulfonylhydrazone (**131**) in THF results in the isolation of dimer **133** as the sole product. Thermal decomposition of **131** in the presence of 1,3-diphenylisobenzofuran gives the Diels–Alder adduct (**134**) of 1,2,4,6-cyclooctatetraene (**132**)[169] (Scheme 6).



131 **132** **133** **134**

Scheme 6



135 136 137 138 139

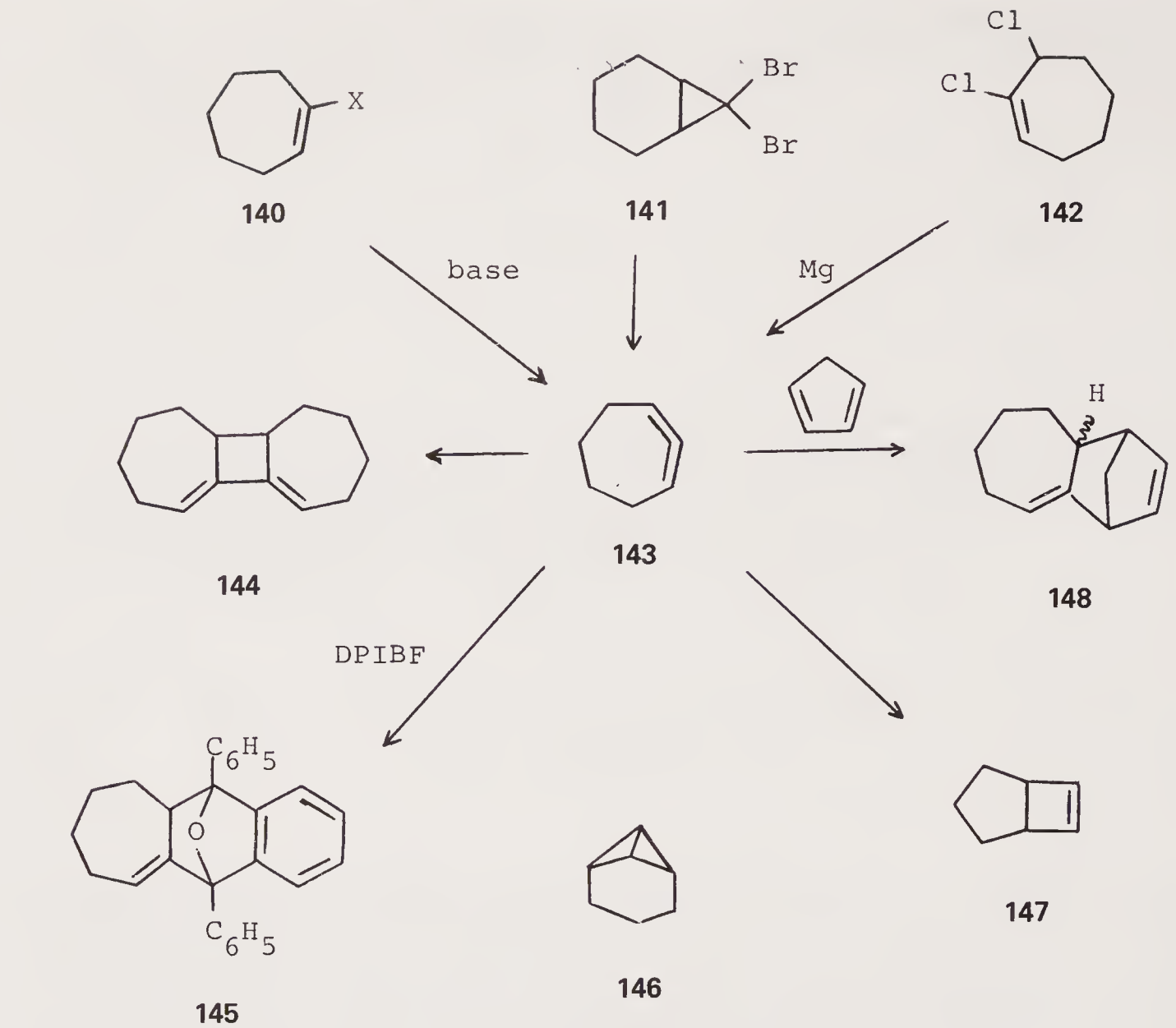
Scheme 7

The hydrolysis of 1,8-di(trimethylsilyl)-3Z,5Z-octadiene-1,7-diyne (**135**) with aqueous sodium hydroxide in ethanol at room temperature produces benzocyclobutadiene dimer (**139**) in high yield (Scheme 7). The initial conversion of **135** to **136** occurs within a few seconds then proceeds through 1,2,4,5,7-cyclooctapentaene (**137**). Further cyclization of **137** then gives benzocyclobutadiene (**138**) which spontaneously dimerizes to the observed product.[170]

2.3.6. Seven-Membered Rings

The 1,2-cycloheptadiene homolog **143** possesses enough ring strain to preclude its isolation or detection. When **143** is generated (Scheme 8) by dehydrohalogenation of **140** (X = Cl, Br) with either sodium amide[137,171] or potassium *t*-butoxide[172,173] in the absence of a trapping agent, its dimer **144** is isolated in good yield. In the presence of 1,3-diphenylisobenzofuran[172] or cyclopentadiene,[174] the [4 + 2] cycloadducts **145** and **148** are formed in 54% and 85% yields, respectively. In the reaction of 7,7-dibromobicyclo[4.1.0]heptane (**141**) with methyllithium, the steric constraints are such that intramolecular insertion of the intermediate carbene into the CH bond of the 2-position is favored over ring opening, and tricyclo[4.1.0.$0^{2,7}$]heptane (**146**) is formed in 45% yield.[175,176] Alternately, when **141** is adsorbed on alumina impregnated with sodium, internal reorganization of the initially formed 1,2-cycloheptadiene occurs producing **147** in 50% yield.[137]

In contrast to the carbene insertion pathway which leads to the formation of **146**, it is apparent that steric factors alone do not dictate the course of the reaction. The interaction of the methoxy derivative **149** with methyllithium favors the cyclopropane fission route leading to 1-methoxy-1,2-cycloheptadiene (**150**) with its dimer



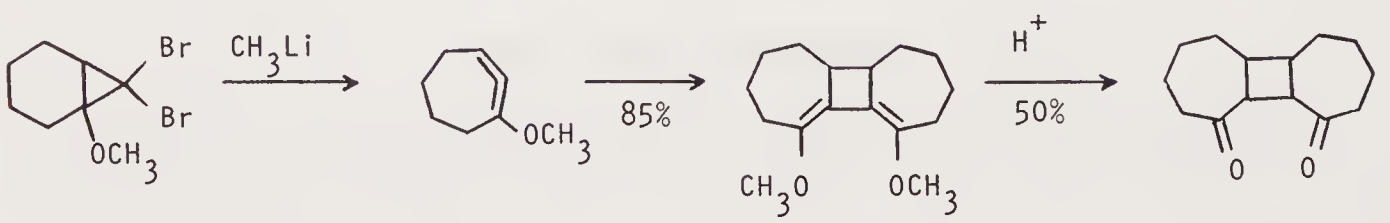
140 **141** **142**

143

144 **145** **146** **147** **148**

Scheme 8

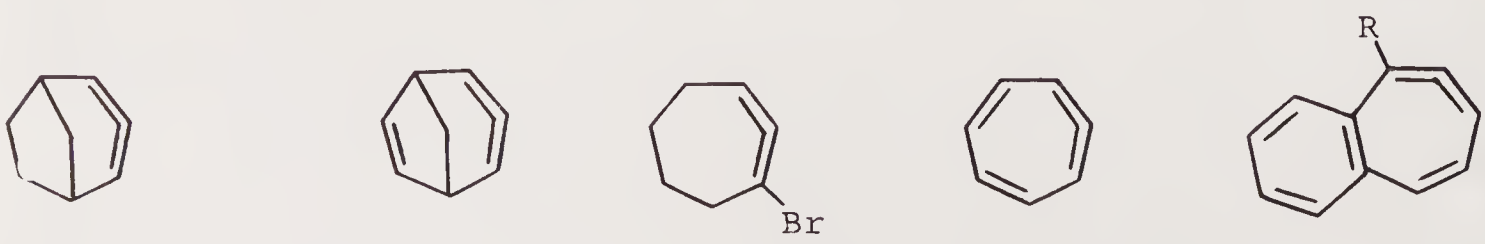
151 being isolated in 85% yield.[177] Acidic hydrolysis furnishes the interesting diketone **152**.



(73)

149 **150** **151** **152**

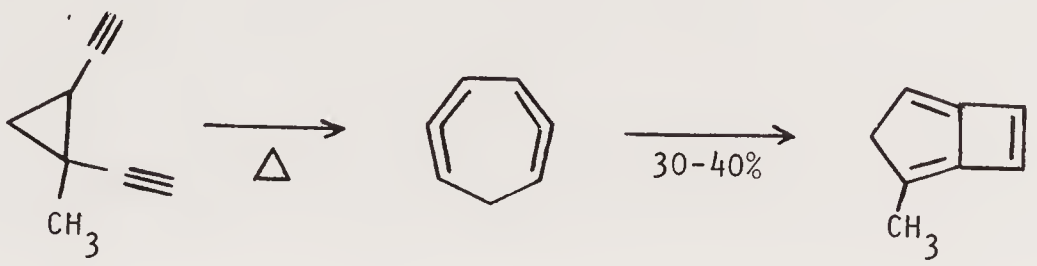
A variety of other transient seven-membered allenes **153–157** have also been reported and follow. They have been isolated either as their dimers or trapped as [4 + 2] or [2 + 2] cycloadducts by reaction with dienes or olefins.



153[174,178,179] **154**[180] **155**[172] **156**[181,182] **157**[182,183]

R= H, CH_3

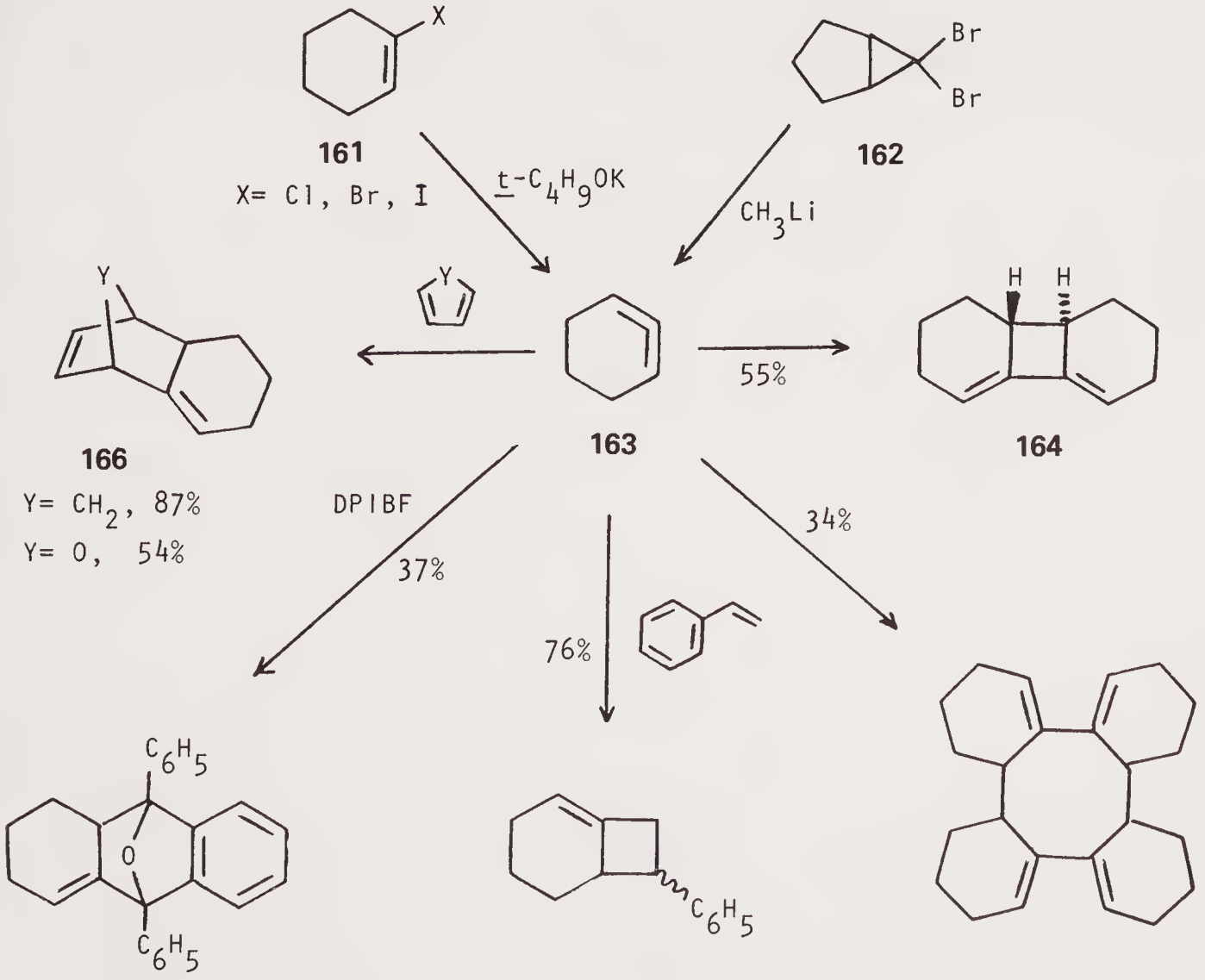
The highly strained 2-methylbicyclo[3.2.0]hepta-1,4,6-triene (**160**) is readily formed by flow pyrolysis of **158** at 350°C.[184] This remarkably stable bicyclic system (the only isolable product from the reaction) is conjecturally formed by internal dimerization of the bisallene **159**.



158 159 160 (74)

2.3.7. Six-Membered Rings

The 1,2-cyclohexadiene system is the smallest ring size in which any products relating to its intermediacy have been isolated. The constraints imposed by such a ring size result in a bent allene whose most stable geometry would be approximately $\theta = 120°$ and $\phi = 0°$ (Figure 2). This will introduce s-character into the p orbital of the central allene carbon which is perpendicular to the bending axis and therefore weaken that π bond.[131] The actual structure of 1,2-cyclohexadiene has been the



Scheme 9

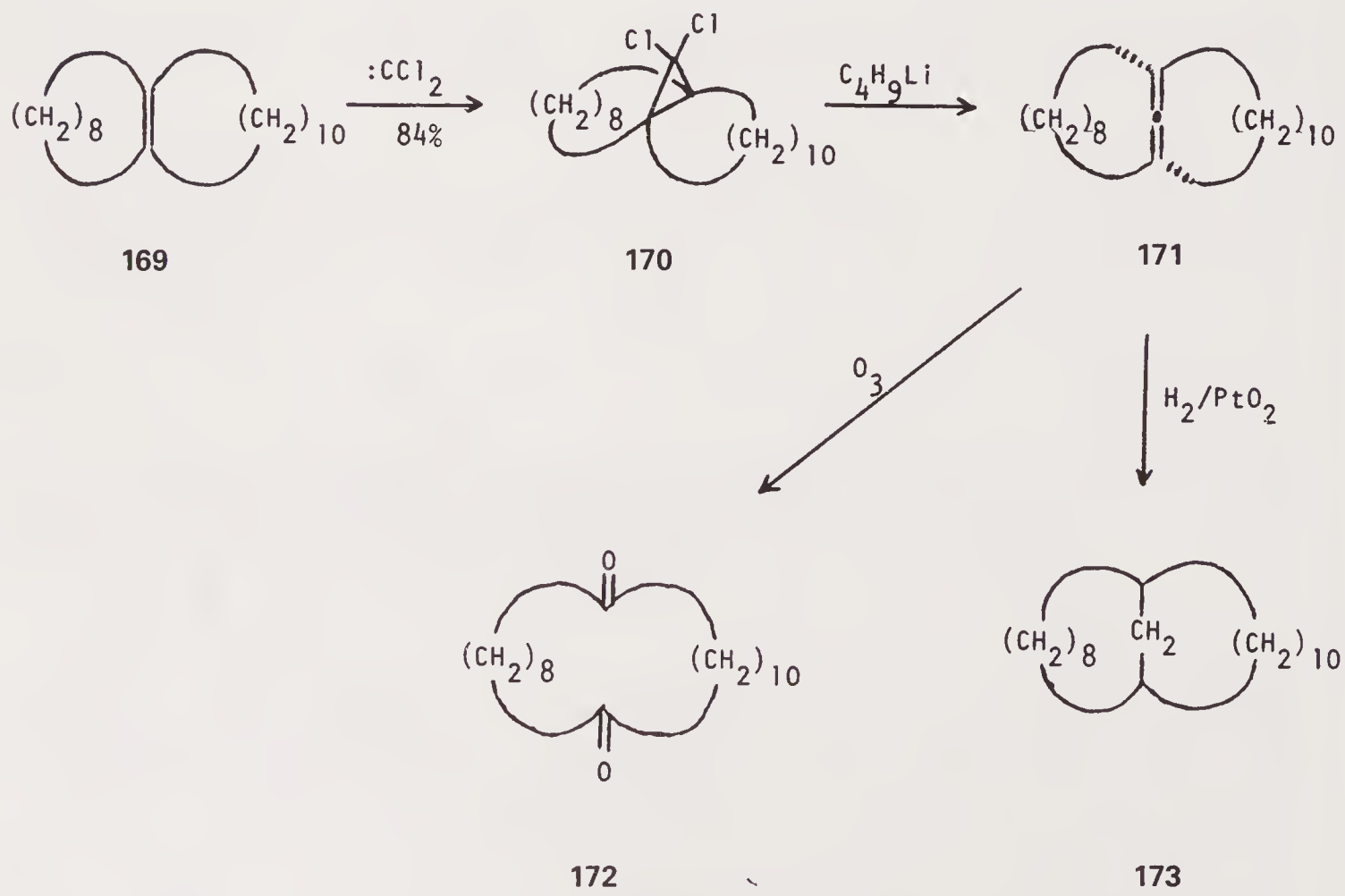
topic of several studies. INDO-MO calculations suggest the allene may be considered as an allyl cation with an anion located at the central carbon in the in-plane sp^x orbital,[131] however, the formation of chiral Diels–Alder adducts indicate that it may exist as a somewhat twisted bent allene[185] where $\phi \neq 0°$.

1,2-Cyclohexadiene (**163**), available from the dehydrohalogenation of 1-haloalkenes (**161**, Scheme 9) with potassium *t*-butoxide, is readily trapped with 1,3-diphenylisobenzofuran to give the [4 + 2] adduct **167**.[186,187] In the absence of a trapping reagent the dimer **164** is isolated in 7% yield. Competitive formation of 1-*t*-butoxycyclohexene by nucleophilic attack of butoxide at the central allene carbon is responsible for the low yield of **164**. In THF the yield of 1-*t*-butoxycyclohexene can reach as high as 63%.[188–190]

The preferred method for the generation of **163** is the reaction of 6,6-dibromobicyclo[3.1.0]hexane (**162**) with methyllithium. In contrast to the formation of **146**, no products derived from a carbene insertion pathway are observed and **163** is produced exclusively.[176] When 1,2-cyclohexadiene is generated in refluxing ether, **164** is formed, whereas at −80°C the tetramer **165** predominates (61% yield by glpc analysis, 34% isolated).[55,191] At −15°, **163** can be trapped with cyclopentadiene, furan, or styrene to give the respective adducts **166** and **168** in good yields.[192,193]

2.3.8. Bicyclic Allenes

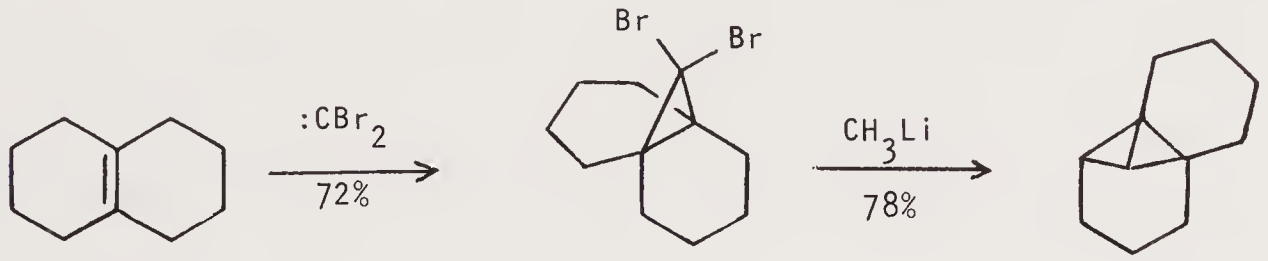
The incorporation of a propadiene unit into a system where it is mutually shared endocyclically by two rings constitutes a bicyclic allene. To date, only one example of a stable allene fitting into this category has been reported[194] (Scheme 10). The



169 **170** **171** **172** **173**

Scheme 10

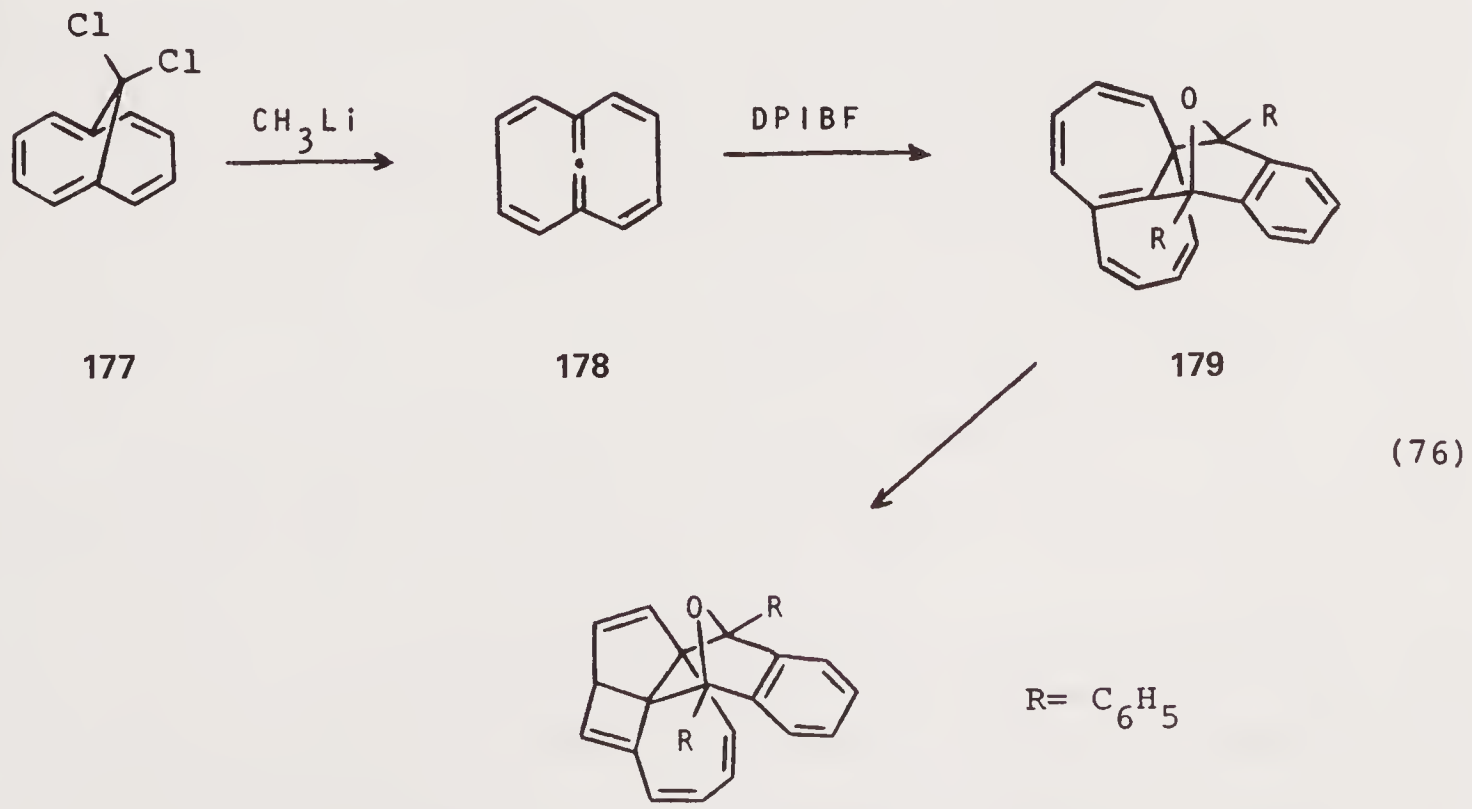
insertion of dichlorocarbene, under phase transfer conditions, into bicyclo[10.8.0]-eicos-1(12)-ene (**169**) provides the dichlorocyclopropane derivative **170** in high yield. The treatment of **170** with *n*-butyllithium furnishes (±)-bicyclo[10.8.1]-heneicos-1(21),12(21)-diene (**171**) in 5% yield. An analogous reaction with (−)-spartiene-modified butyllithium affords (+)-(R)-**171** (9% yield). In addition to spectral elucidation of **171**, its ozonolysis to 1,10-cycloeicosanedione (**172**) and hydrogenation to **173** adds support to its structural integrity. To circumvent the awkward nomenclature associated with these gyrochirally symmetrical molecules, the interesting name [8][10]screw[2]ene has been proposed for **171**.[194]



174 **175** **176** (75)

When 9,10-octalin (**174**) is subjected to similar manipulations (equation 75), only the highly strained tetracyclo [5.3.$0^{1,6}$.$0^{6,11}$]undecane (**176**) is formed, presumably by an intramolecular carbene insertion into one of the CH bonds in position 2.[195]

The treatment of 11,11-dichloro-1,6-methano[10]annulene (**177**) with methyllithium in the presence of 1,3-diphenylisobenzofuran gives a 65% yield of **180**. This 1:1 adduct may arise from a Diels–Alder addition to the initially formed unstable bicyclic allene **178** to give **179** followed by internal cyclization to the observed product.[196]



177 **178** **179** (76)

180

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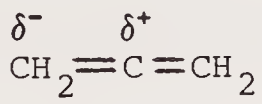
CHAPTER THREE

ADDITIONS TO ALLENE HYDROCARBONS

The ability of allenes to enter into reactions as either a nucleophile or an electrophile provides the chemist with a variety of methods for the preparation of synthetic precursors or desired end products. The accessibility to an attacking species of the cumulated diene system of allenic compounds lead to facile addition reactions. When reagents react with an allene by a mechanism involving charged intermediates, the polarization of the allene is represented as **1** where the central carbon atom is electrophilic in nature.[8] However, the allene framework is so delicately balanced that small changes in steric or electronic factors greatly affect the orientation of addition.



1

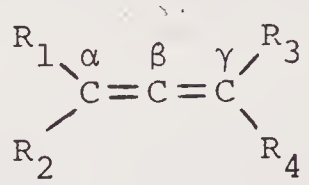
In an interesting study of methoxymercuration of methylated allenes, Waters and Kiefer[9] show that the ratio of electrophilic attack of the reagent depends on the degree of alkylation (see Table 3.1). As the allene is progressively methylated, the character of the central carbon atom changes from electrophilic to nucleophilic.

This chapter serves as an introduction to various types of additions to allenes that lead to synthetically interesting and useful substances. Only reactions of alkyl and cyclic allenes are presented here. Additions to allenes containing a specific functional group are discussed in the respective chapter dealing with that class of allene.

3.1. HYDROGENATION

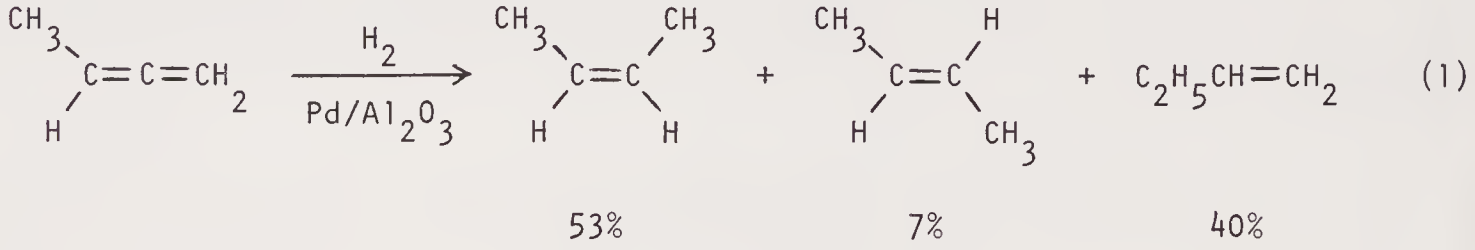
Catalytic hydrogenation of allenes to the parent hydrocarbons has been a useful technique for structural characterization.[10,11] In the presence of Adams catalyst (platinum oxide) the uptake of two equivalents of hydrogen occurs rapidly, and the

Table 3.1. Electrophilic Attack in Methoxymercuration of Allenes



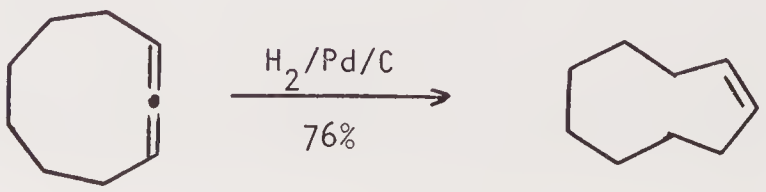
R_1	R_2	R_3	R_4	β-Attack (%)	α + γ Attack (%)
H	H	H	H	—	95
H	H	H	CH_3	60	35
H	CH_3	H	CH_3	93	—
H	H	CH_3	CH_3	84	—
CH_3	CH_3	CH_3	CH_3	90	—

totally saturated hydrocarbon is isolated.[11–14] In contrast, when the reduction is performed over palladium, the addition of hydrogen occurs in a distinct stepwise manner: the first equivalent adds very rapidly; the second equivalent then adds slowly.[15,16] With terminal allenes the regioselectivity of such hydrogenations favors addition to the less substituted double bond but, as seen in equation (1), complete stereospecificity is not assured.[17]



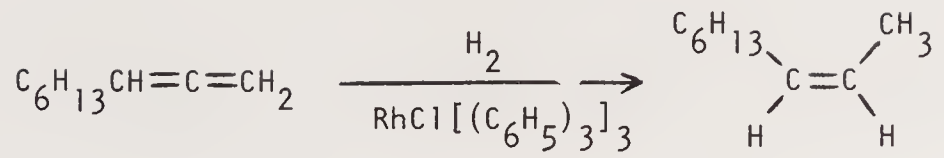
(1)

In cyclic systems catalytic hydrogenation occurs in a stereospecific fashion owing to the blocking of one face of the allene linkage by the bridging methylene chain. This allows the molecule to contact the surface of the catalyst from the less hindered side, and, as shown in equation (2), only the *cis*-isomer is formed.[18] This transformation can also be effected in quantitative yield by a chemical reduction using diimide.[19]



(2)

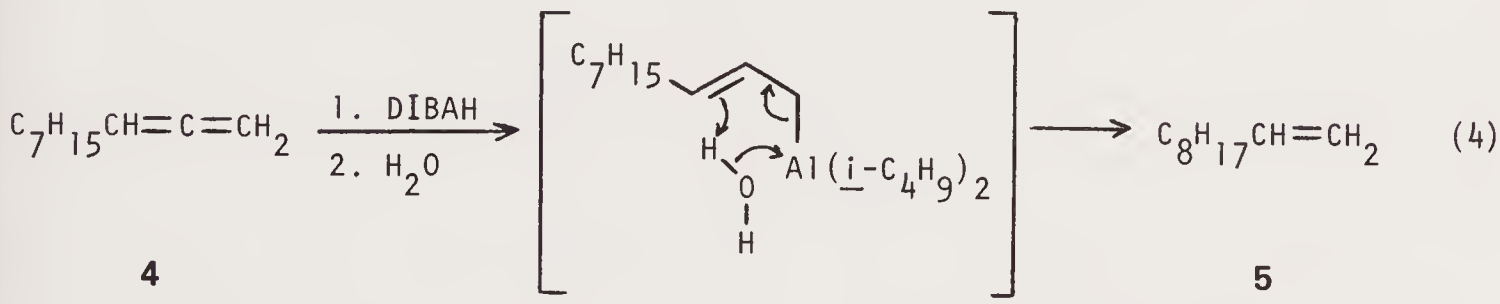
The regio- and stereospecific reduction of terminal allenes can be accomplished by partial homogeneous hydrogenation using chlorotris(triphenylphosphine) rhodium catalyst. In the hydrogenation of 1,2-nonadiene (**2**), only reduction of the less substituted double bond occurs and furnishes *cis*-2-nonene (**3**) in 90–95% yield based on the allene consumed.[20]



(3)

2 **3**

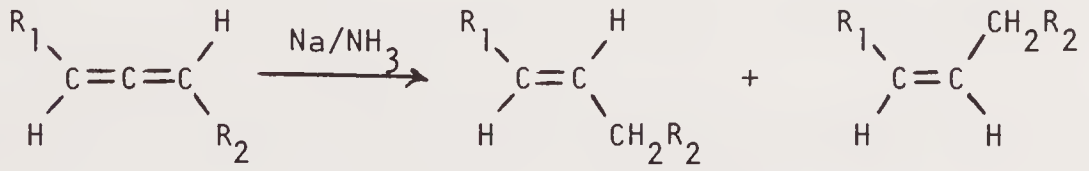
Reversed regiospecificity, where the more highly substituted double bond of the allene is reduced, can be achieved by a hydroalumination with DIBAH followed by aqueous hydrolysis[21] (equation 4). When 1,2-decadiene (**4**) is subjected to these conditions, 1-decene (**5**) is produced in 83% yield and is 96% pure (the remaining 4% is represented by the totally saturated *n*-decane).



(4)

4 **5**

The action of sodium–ammonia on acyclic terminal allenes produces *trans*-olefins in high yields (usually contaminated with less than 7% of the corresponding *cis*-olefin) (equation 5).[22] Internal allenes, unless symmetrically substituted, afford a statistical mixture of regioisomers. For example, the reduction of 2,3-nonadiene gives an 85% yield of a mixture of *trans*-2-nonene (49.2%) and *trans*-3-nonene (47.9%) with less than 3% contamination of the corresponding *cis*-isomers.[23]

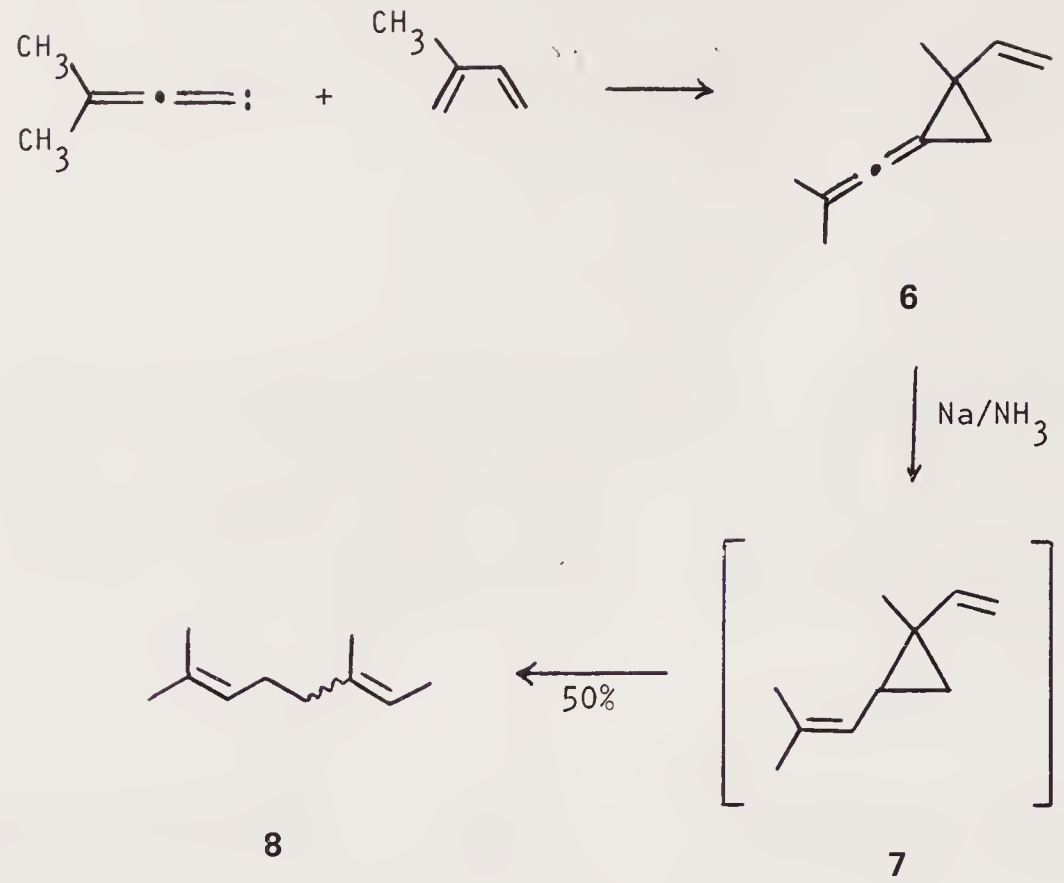


(5)

R_1	R_2	Yield (%)	*trans* (%)	*cis* (%)
C_5H_{11}	H	77	96.8	2.5
C_6H_{13}	H	80	92.8	7.2
C_3H_7	C_3H_7	82	96.6	3.4

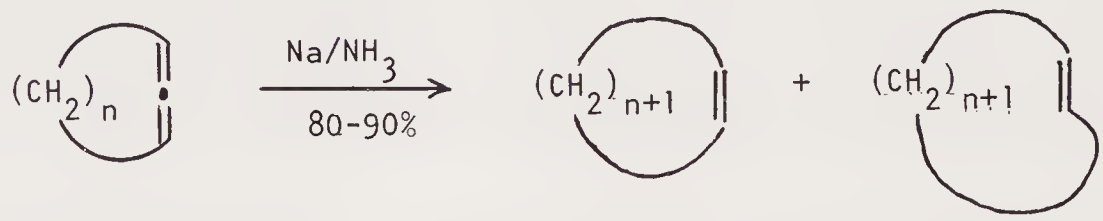
The monoterpene dihydromycene (**8**) is readily prepared by this method and is outlined in Scheme 1. The reduction of the vinylcyclopropane **6** leads initially to the divinylcyclopropane **7**. Subsequent 1,4-addition of an electron followed by cyclopropane ring opening provides the observed product **8**.[24]

In cyclic systems, the steric constraints imposed upon the molecule result in the formation of a *cis*-cycloolefin. However, as shown in equation (6), as the size of



Scheme 1

the ring becomes progressively larger, the ratio of the *trans*-cycloolefin increases proportionately.[25] The values in parenthesis are the percentages obtained when the reaction is performed in the presence of a proton donor such as ethanol.

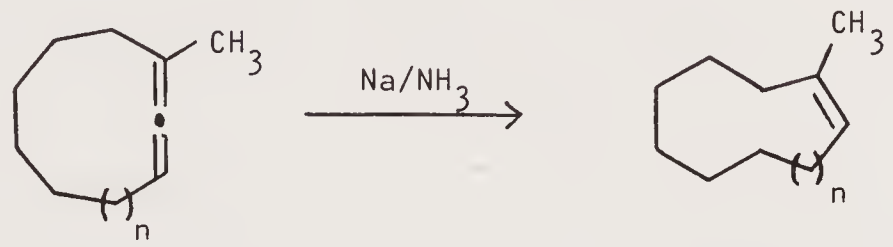


(6)

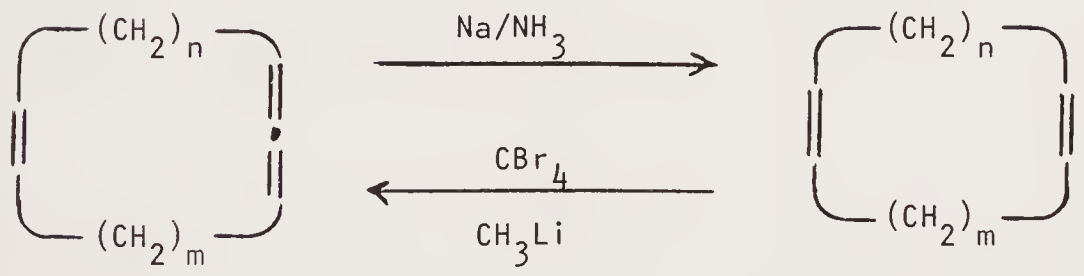
n	*cis* (%)	*trans* (%)
6	100(100)	0(0)
7	100(66)	0(34)
8	73(45)	27(55)
9	75(46)	25(54)
10	50(17)	50(83)
11	27(14)	73(86)

The method can be conveniently applied to the stepwise homologation of cyclic olefins. In equation (7) the reduction of 1-methyl-1,2-cyclononadiene (**9a**) gives *cis*-1-methylcyclononene (**10a**) in 85% yield. Treatment of **10a** with carbon tetrabromide and methyllithium furnishes 1-methyl-1,2-cyclodecadiene (**9b**), then reduction of **9b** produces *cis*-1-methylcyclodecene (**10b**) in 80% yield.[26] The prep-

aration of *cis,cis*-cyclic dienes can analogously be accomplished by the allene/reduction/allene methodology (equation 8) which starts with *cis,cis*-1,5-cyclooctadiene and sequentially proceeds to **11** → **12**[27] → **13** → **14**[28] → **15** and ends with *cis,cis*-1,6-cycloundecadiene (**16**).[29]



9 **a**, n = 1 **b**, n = 2 **10** (7)



(8)

11; n=2, m=2 **12**; n=3, m=2 (84%)

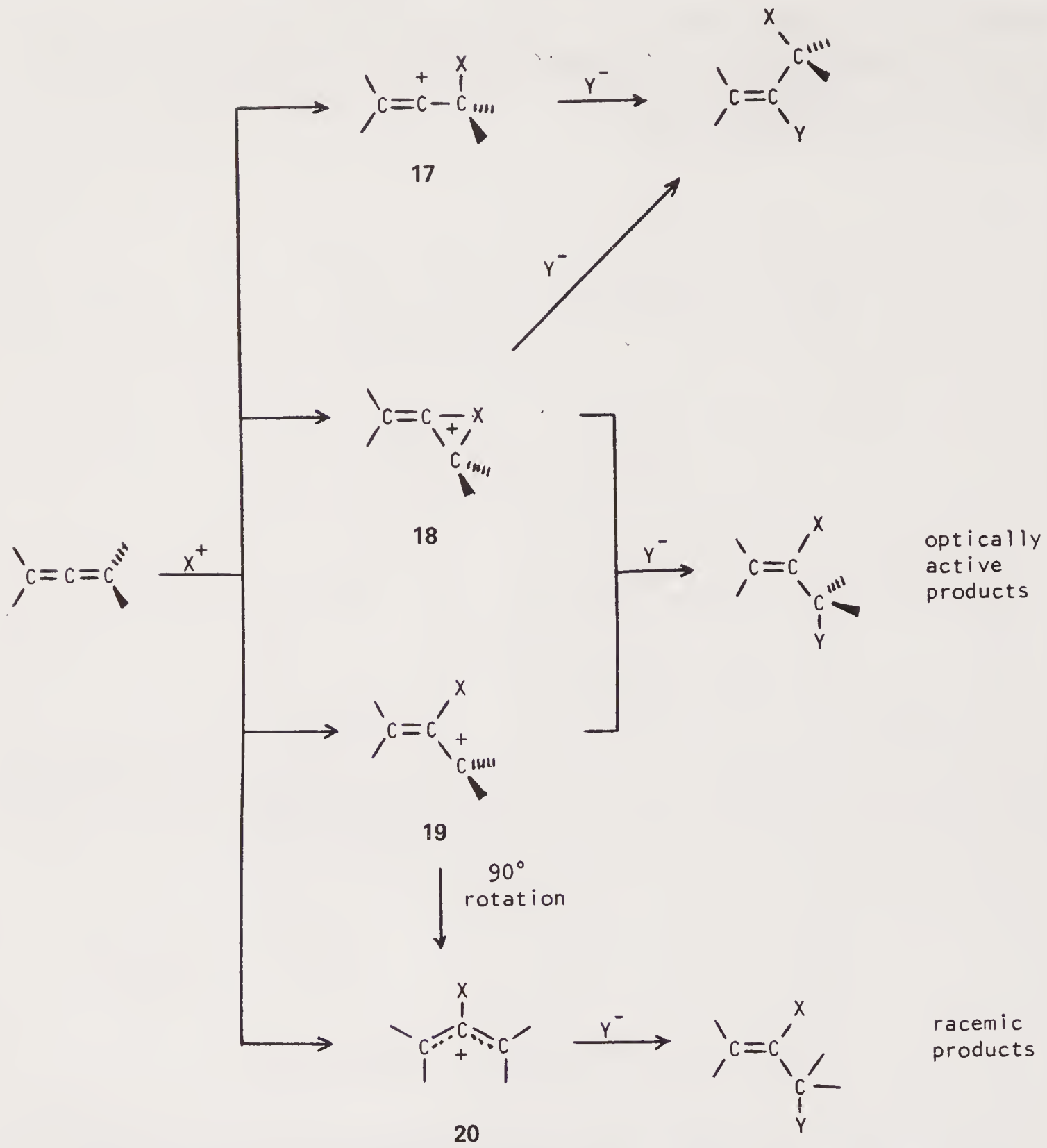
13; n=3, m=2 **14**; n=3, m=3 (76%)

15; n=3, m=3 **16**; n=3, m=4 (95%)

3.2. ELECTROPHILIC ADDITIONS

Allenes lacking an activating functionality are highly susceptible to electrophilic substitution reactions. In the addition of an electrophilic reagent $X^{\delta+}Y^{\delta-}$ to an allene, the electrophile X^+ may attack the terminal carbon of the cumulated system to give a vinyl cation **17**. The stereospecificity in various reactions suggest that bridged ions **18** also may be initially formed. Alternately, attack at the central carbon gives rise to an allyl cation **19** (Scheme 2). To maximize electron delocalization and achieve allylic resonance stabilization, the nonplanar ion **19** must rotate 90° about the σ bond and consequently form the planar species **20**.

The use of chiral allenes is of great assistance in determining which of the charged species **17–20** is operative in the mechanistic pathway. If planar allylic intermediates **20** are formed to any extent prior to the product-forming step, the products are expected to be racemic. If, however, the initially formed nonplanar intermediates **18** or **19** react to form products faster than they can interconvert to **20**, optically active products could result.[5]



Scheme 2. Reprinted from ref. 5 with permission from the author and John Wiley & Sons.

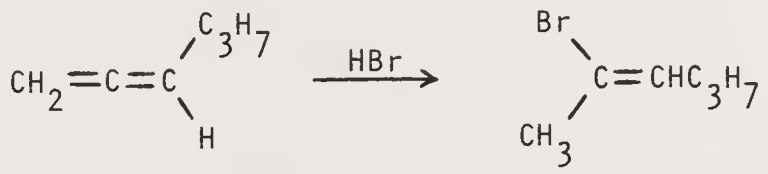
3.2.1. Addition of Acids

The addition of HX to allene obeys Markovnikov's rule to give 2-halopropenes and/or 2,2-dihalopropanes (equation 9). The addition of hydrogen bromide occurs at a markedly faster rate than that of hydrogen chloride.[30]

$$CH_2{=}C{=}CH_2 \xrightarrow{HX} \underset{CH_3}{\overset{X}{\diagdown}}\!\!C{=}CH_2 \quad + \quad CH_3\text{-}\overset{X}{\underset{X}{C}}\text{-}CH_3 \tag{9}$$

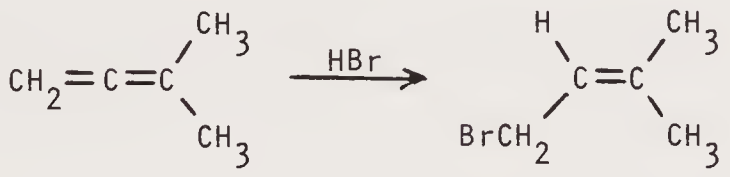
The hydrobromination of monosubstituted terminal allenes (e.g., 1,2-hexadiene) behaves analogously as shown in equation (10). However, when 3-methyl-1,2-

butadiene is subjected to the same reaction conditions, the anti-Markovnikov product 1-bromo-3-methyl-2-butene is isolated as the principal constituent of the reaction mixture[31,32] (equation 11). Symmetrically substituted allenes give products derived from both modes of addition.[33]



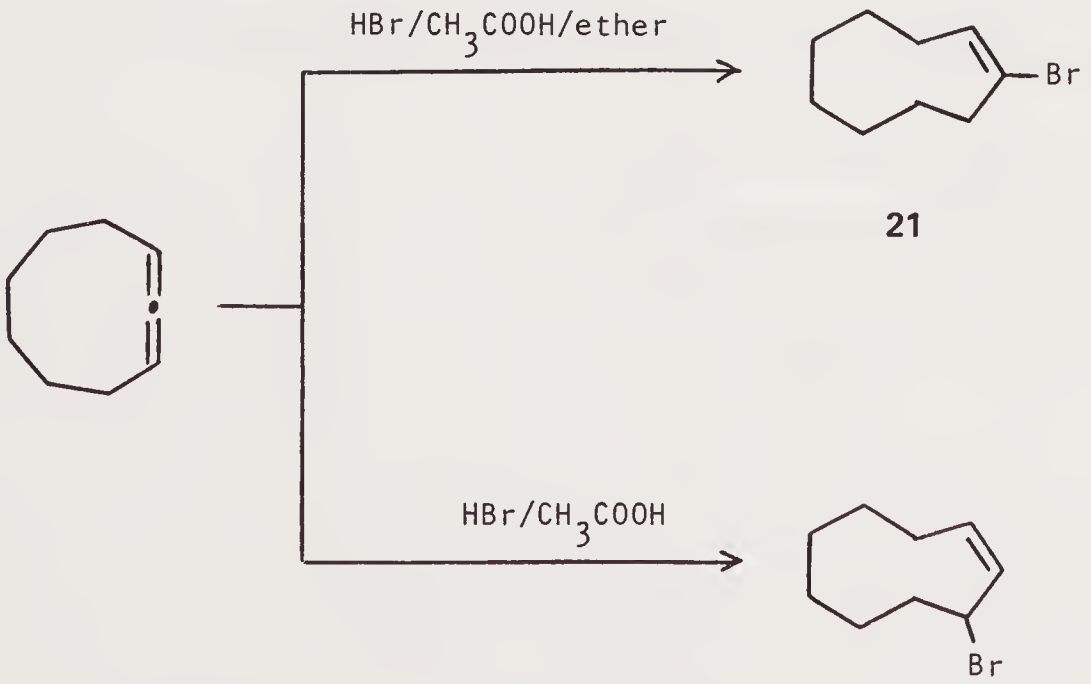
(10)

Solvent has a profound effect on the regioselectivity of the addition of hydrogen bromide to allenes. When a solution of 1,2-cyclononadiene in ether or petroleum ether is treated with hydrogen bromide/acetic acid at room temperature, *cis*-1-bromocyclononene (**21**) is obtained in high yield as the sole product. In the absence



(11)

of ether, only *cis*-3-bromocyclononene (**22**) is obtained.[34] In a similar manner, 1,2-cyclodecadiene is converted to *cis*-3-bromocyclodecene in 75% yield. 1,2-Cyclotridecadiene, however, produces a mixture of 1-bromocyclotridecene and 3-bromocyclotridecene in a ratio of 45:55.[35]



(12)

The addition of hypochlorous acid to allene hydrocarbons introduces both a chlorine and a hydroxyl substituent into the resulting olefinic product (equation 13). The chlorine atom becomes fixed to the central allene carbon while the hydroxy is attached to the more substituted terminal carbon.[36] Reactions involving monosubstituted terminal allenes produce minor amounts (less than 10%) of the regioisomeric primary alcohols, and nonsymmetrical 1,3-disubstituted allenes give a 50:50 mix-

ture of alcohols resulting from hydroxyl substitution on either of the terminal carbon atoms of the allene.

(13)

R_1	R_2	R_3	Yield (%)
CH_3	H	CH_3	60
H	CH_3	CH_3	85
CH_3	CH_3	CH_3	72

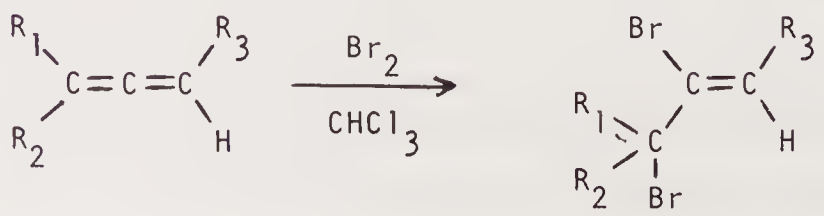
Allenes are readily converted to ketones in good yields by hydration with aqueous sulfuric acid (equation 14). The keto group, formerly the central allene carbon, may be derived from the tautomerism of an initially formed enol.

(14)

R_1	R_2	Reference
H	C_3H_7	10
CH_3	C_3H_7	37
CH_3	$CH_2CH(CH_3)CH_3$	37
H	CH_2Cl	38
	$-(CH_2)_{10}-$	39
	$-(CH_2)_{11}-$	39
	$-(CH_2)_{12}-$	39

3.2.2. Addition of Halogen

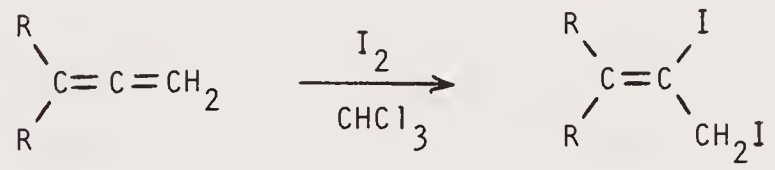
The addition of halogens to allenes proceeds rapidly and can be controlled so that the reaction may be terminated after one equivalent of the reagent is absorbed. Terminal allenes preferentially add bromine across the more substituted double bond.[31]



(15)

R_1	R_2	R_3	Yield (%)	Reference
H	H	H	77	40
C_3H_7	H	H	50	31
CH_3	H	CH_3	100	41
CH_3	CH_3	H	42	31

The addition of iodine, however, produces vinylic iodides with opposite regioselectivity (equation 16). For example, when 3-methyl-1,2-butadiene (**23a**) is treated with an equimolar quantity of iodine, 1,2-diiodo-3-methyl-2-butene (**24a**) is isolated in 95% yield.[42,43]



(16)

23 **24** a, R=CH_3; b, R=C_2H_5

Upon halogenation, internal allenes that are 1,3-disubstituted can form *cis*- or *trans*-monoadducts, depending on the structure of the allene and the nature of the electrophile. If the halogen approaches the allene from above the plane (or less hindered side) of the terminal R group, the *cis*-isomer will be formed (Figure 3). On the other hand, approach on the same side as the R group will produce the *trans*-isomer.[44]

The orientation and stereochemical outcome from the addition of various halogens to optically active 2,3-pentadiene gives some insight into the possible mechanism of the reaction. Bromine, bromine chloride, and iodine add to (R)-(−)-2,3-pentadiene (**25**) to give a mixture of optically active *trans*- and *cis*-dibromopentenes **28** and **29** with the major adduct being the *trans*-isomer[45,46] (Scheme 3). Halogenations with iodine tend to racemize the chiral allene.

Evidently, steric effects do not play a major role in influencing the course of the reaction as evidenced by the preferential formation of the *trans*-isomer by way of attack from the more hindered side of the allene. The retention of optical activity in the products **28** and **29** suggest that they are derived from a nucleophilic attack of Y^- on the initially formed nonplanar halonium ions **26** and **27**[5] (Scheme 3).

When the allene is incorporated into a cyclic system, the *trans* side attack is hindered by the bridging methylene chain [Figure 3, R,R′ = $(CH_2)_6$], and therefore

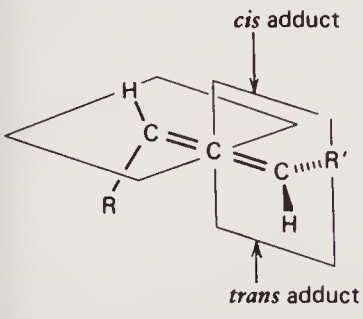
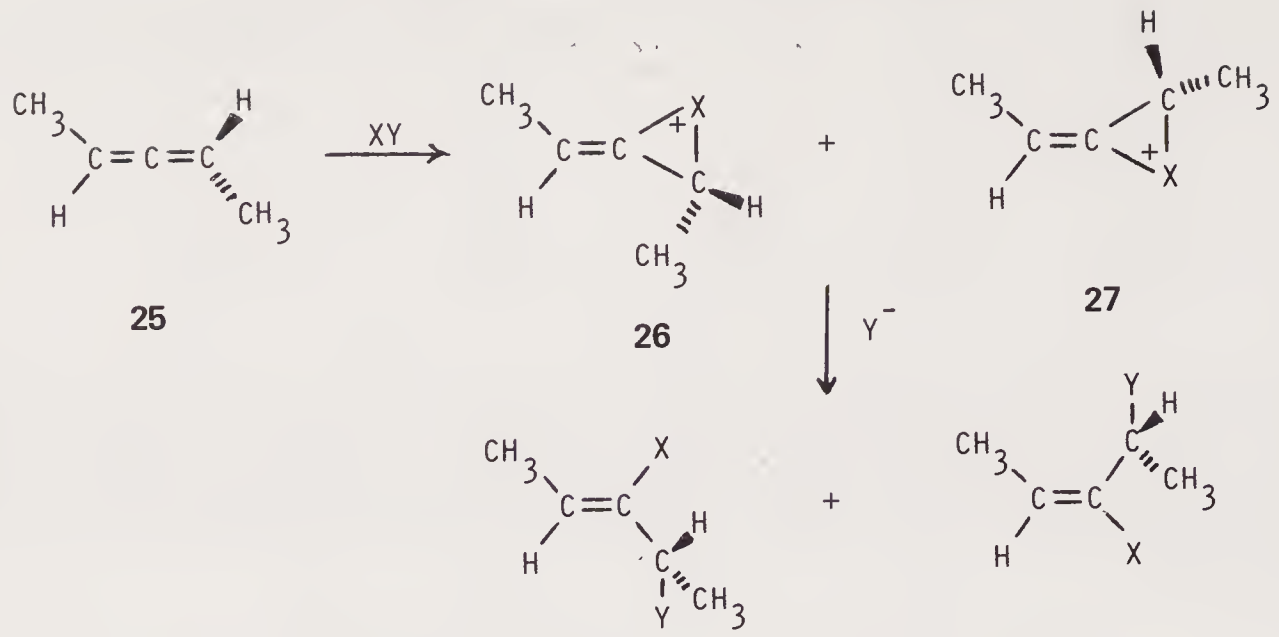


Figure 3. Directions of approach of an electrophile leading to cis or trans isomers.



25 **26** **27**

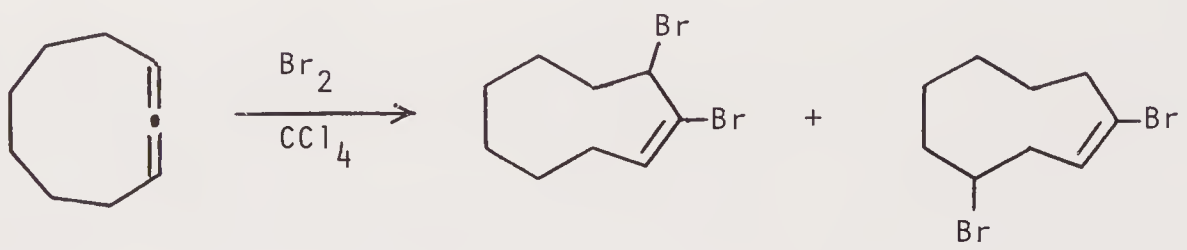
28a, X=Y=Br (83:17) **29a**, X=Y=Br

28b, X=Br, Y=Cl (72:28) **29b**, X=Br, Y=Cl

28c, X=I, Y=Cl (85:15) **29c**, X=I, Y=Cl

Scheme 3

only *cis*-products are produced. When treated with bromine, 1,2-cyclononadiene gives a mixture of *cis*-2,3-dibromocyclononene (**30**) and *cis*-1,4-dibromocyclononene (**31**) in a 40:60 ratio.[47,48] The major product **31** is speculatively produced by a transannular 1,5-hydride shift.[44]

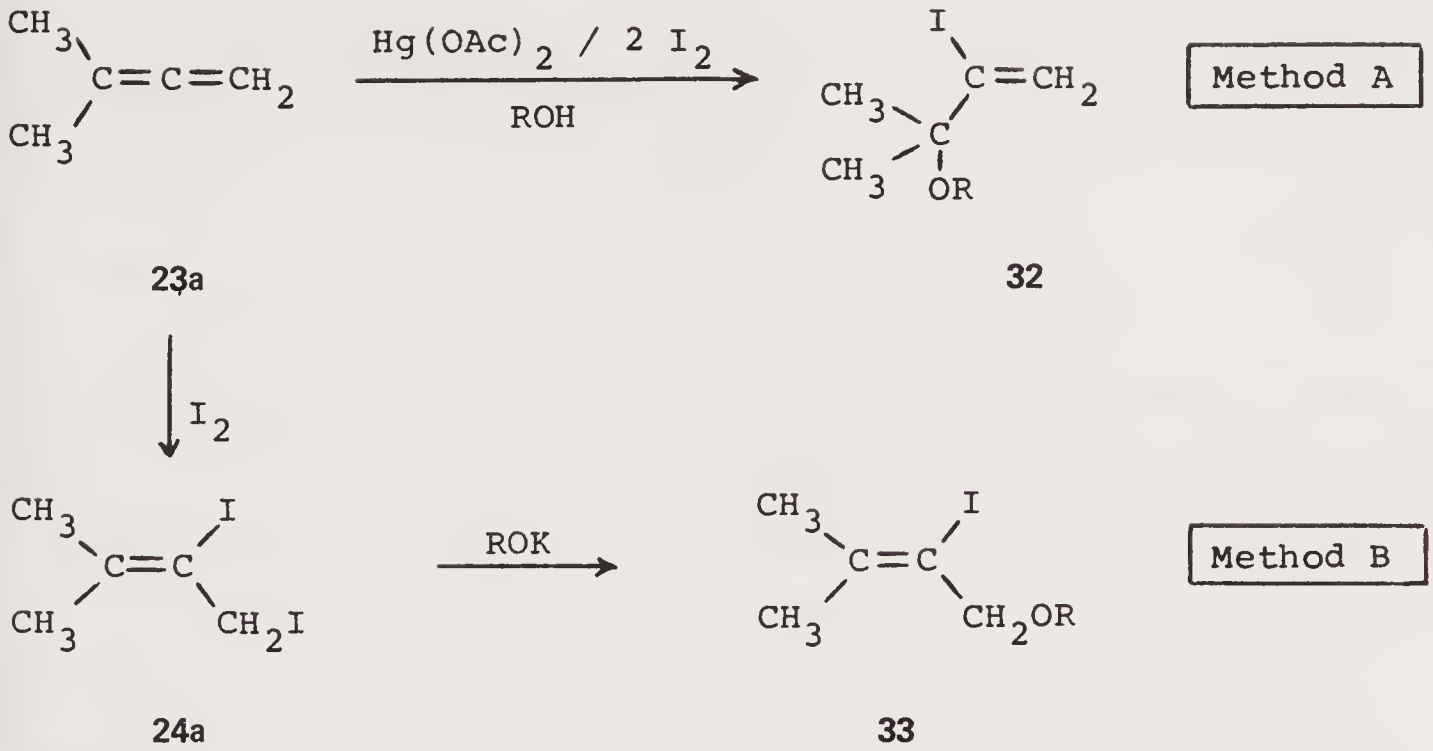


30 **31** (17)

Halogenation of allenes in protonic solvents (acetic acid[40] or methanol[44–46]) result in the displacement of the developing allyl halide by the solvent. In iodination reactions the regioselective formation of the ensuing iodoallylic ethers can be manipulated as illustrated in Scheme 4.[42] The diiodoalkene **24a**, whose preparation is illustrated in equation (16), is converted to the primary ether **33** by reaction with potassium alkoxide. Compounds **33** are produced with less than 3% contamination with isomeric **32**. Pretreatment of the allene **23a** with mercuric acetate prior to the iodination step affords 3-alkoxy-2-iodo-1-alkenes (**32**) as the major product, usually contaminated with 5–15% of **33**.

3.2.3. Oxymetallation Reactions

Symmetrically substituted allenes are particularly suited for oxymetallation reactions. These additions are regiospecific and afford an organometallic with the metal



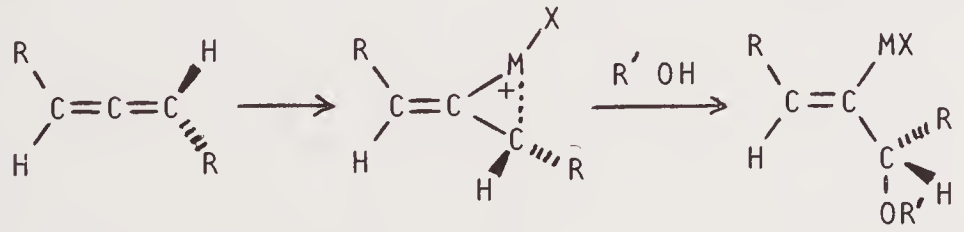
23a 32

24a 33

Scheme 4

R	Method	Yield (%)
CH_3	A	76
C_2H_5	A	84
i-C_3H_7	A	72
CH_3	B	90
C_2H_5	B	74
i-C_3H_7	B	90

bonded to the former central carbon of the allene and with nucleophilic attack of the oxygenating species at the terminal carbon.[49] In acyclic systems the stereoselectivity of the addition favors *trans*-adducts even though the nucleophile must approach from the sterically unfavorable side (see Figure 3). When chiral allenes are used, the optical activity is retained in the product, therefore suggesting the intermediacy of a π-complex **34**.[50,51]

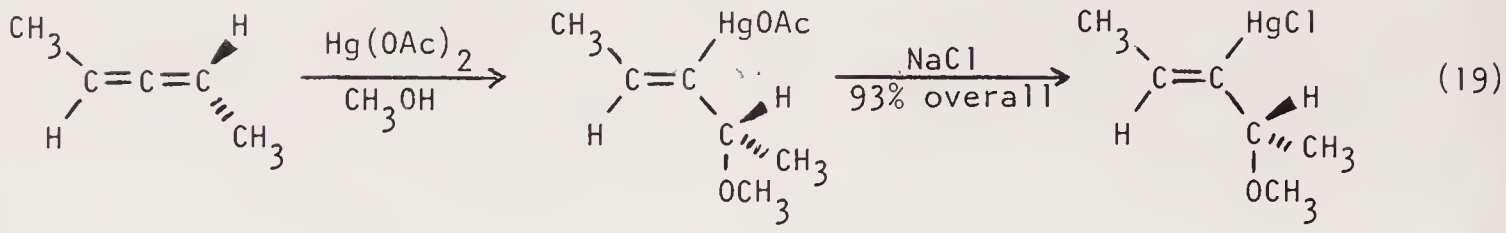


(18)

34

Methoxymercuration of (R)-(−)-2,3-pentadiene (**25**) with mercuric acetate in methanol gives a high yield of an 87 : 13 mixture of *trans*- and *cis*-3-acetoxymercuri-4-methoxy-2-pentenes (**35**) which can be converted to the 3-chloromercuri derivative **36** by treatment with aqueous sodium chloride.[46,50]

In cyclic systems the formation of *trans*-adducts would require an approach of the reagent from inside the ring. This geometric constraint consequently directs the addition of the electrophilic mercury to occur from the unencumbered face, thereby



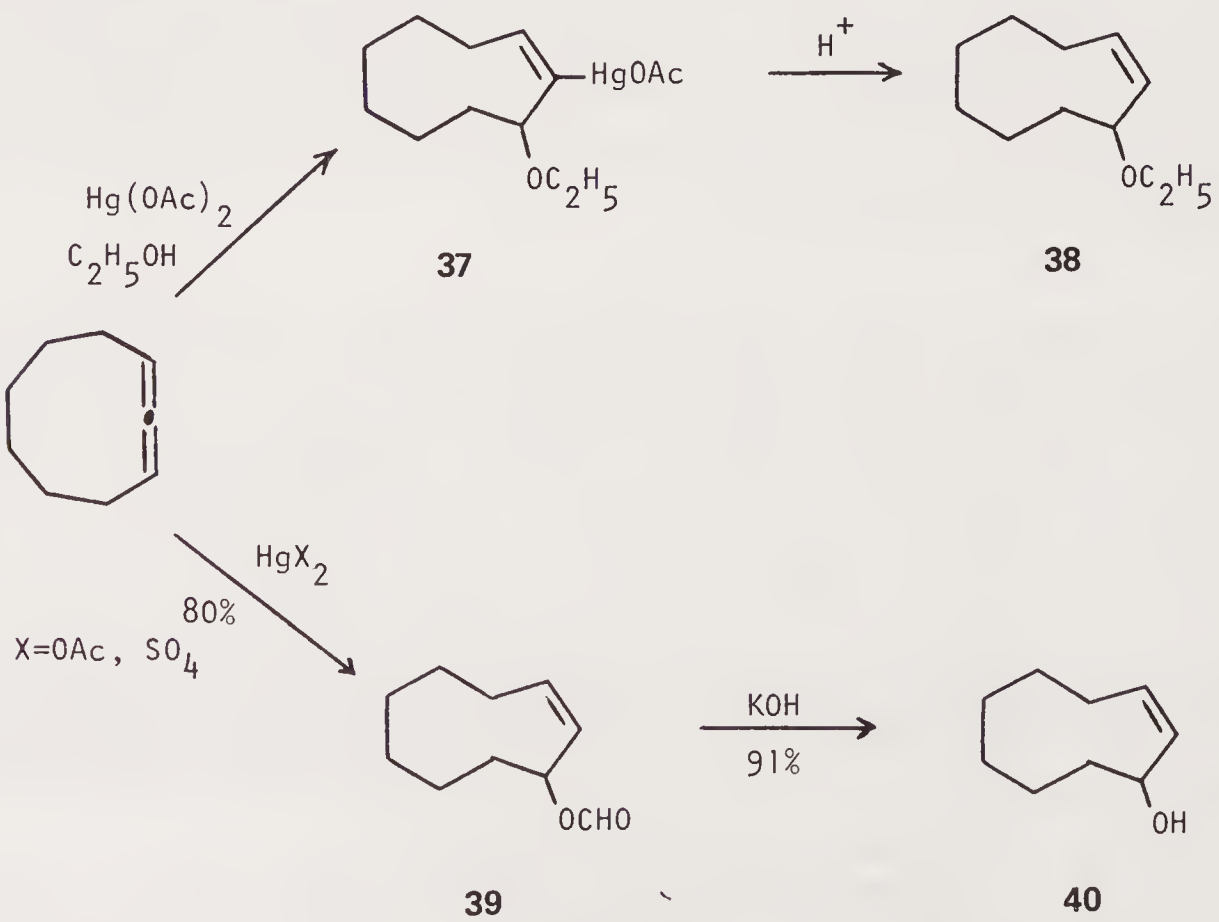
(19)

25 trans-**35** **36**

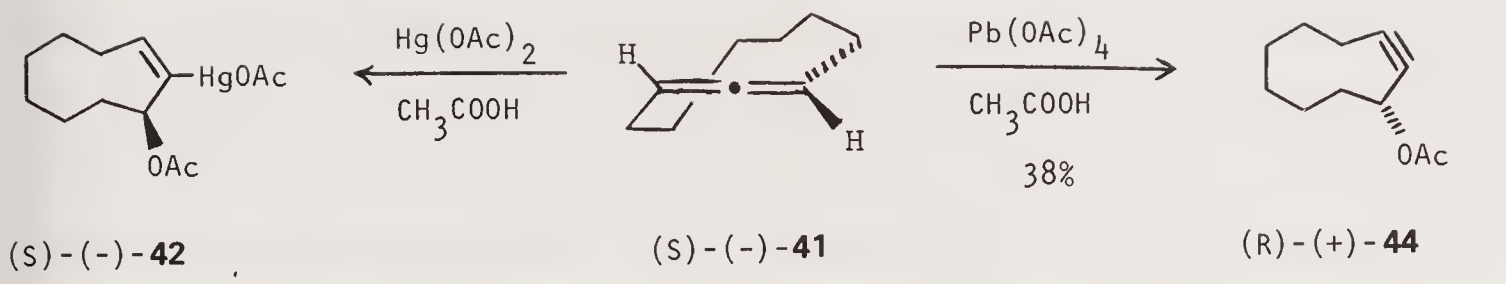
favoring *cis* products. However, as the size of the ring becomes progressively larger, the steric influence diminishes and the preferred *trans* mode of addition once again is observed. Addition of mercuric chloride to 1,2-cyclononadiene and 1,2-cyclodecadiene gives the respective *cis*-isomers, whereas analogous reactions with 1,2-cycloundecadiene and 1,2-cyclotridecadiene produces the *trans*-products.[52-54]

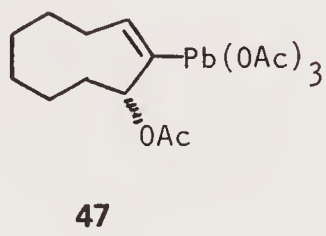
A variety of allylically oxygenated *cis*-cyclononenes are readily available from 1,2-cyclononadiene using the previously described oxymercuration procedures. The organomercuri function is sufficiently labile that its removal can be accomplished under mild conditions. When 1,2-cyclononadiene is treated with mercuric acetate in ethanol, *cis*-2-acetoxymercuri-3-ethoxycyclononene (**37**) is produced. When the reaction is performed in the presence of boron trifluoride etherate, the reaction medium is sufficiently acidic that cleavage of **37** occurs *in situ*, and *cis*-3-ethoxycyclononene (**38**) is isolated directly in high yield[55] (Scheme 5). By similar reasoning, reaction with either mercuric acetate[56] or mercuric sulfate[57,58] results in the direct isolation of *cis*-3-cyclononenyl formate (**39**). Hydrolysis with potassium hydroxide or barium hydroxide gives *cis*-3-hydroxycyclononene (**40**) in high yield.

Enantiomeric *cis*-3-acetoxycyclononenes **43** and **45** are selectively prepared from optically active 1,2-cyclononadiene (**41**) by taking advantage of alternate modes of addition to mercury, thallium, or lead π-complexes **34** [R,R = $(CH_2)_6$].



Scheme 5



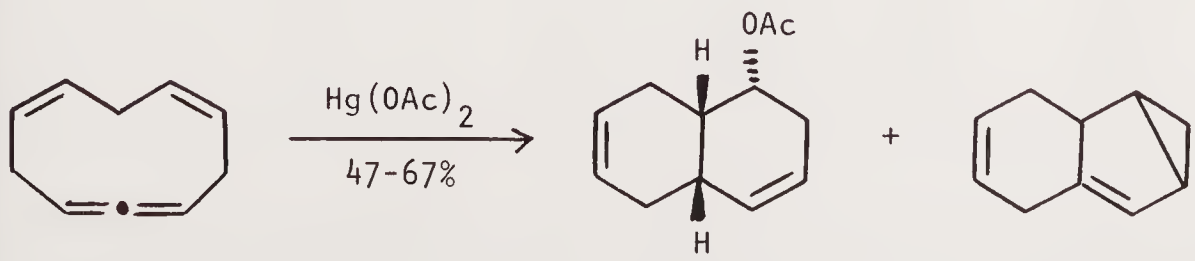


47

Scheme 6

Acetoxymercuration[59] or thallation[60] of the allene double bond occurs principally by antarafacial addition to give the respective organometallics **42** and **46** (Scheme 6). Reduction of either compound with sodium borohydride affords (S)-(+)-*cis*-3-acetoxycyclononene (**43**). Acetoxyplumbation with lead tetraacetate proceeds by suprafacial addition to give the organolead intermediate **47**. Under the reaction conditions the metal is lost by an *anti* elimination, and (R)-(+)-3-acetoxycyclononyne (**44**) is isolated. Hydrogenation in the presence of nickel boride catalyst produces (R)-(−)-3-acetoxycyclononene (**45**).[49]

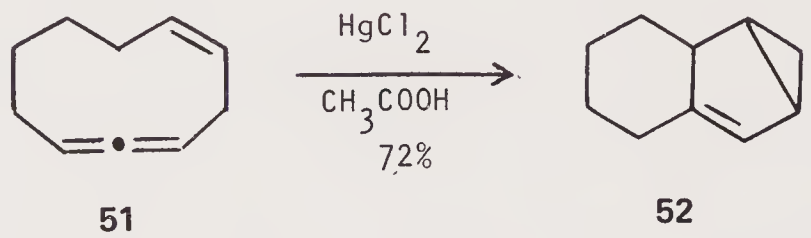
In contrast to most oxymercurations, the reaction of 1,2,5,8-cyclodecatetraene (**48**) and 1,2,5-cyclodecatriene (**51**) with mercury salts gives only rearranged prod-



(20)

48 49 50

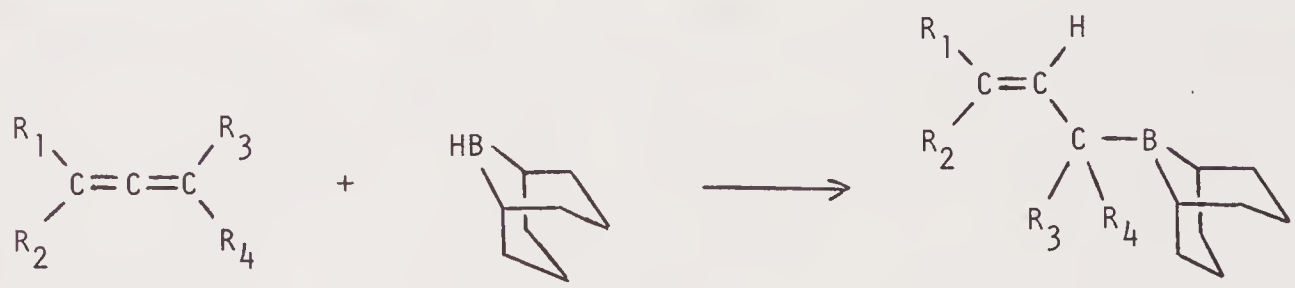
ucts.[61,62] The treatment of **48** with mercuric acetate (or mercuric sulfate) in acetic acid furnishes nearly a statistical mixture of *cis,syn*-decalin-2-yl acetate (**49**) and tricyclo[4.4.0.$0^{2,4}$]deca-5,8-diene (**50**) (equation 20). When the reaction is performed in 60% aqueous acetone, the ratio shifts dramatically in favor of **49** (88% of the product mixture). A similar reaction of **51** with mercuric chloride only gives tricyclo[4.4.0.$0^{2,4}$]dec-5-ene (**52**) in good yield (equation 21).



51 **52** (21)

3.2.4. Addition of Boron Electrophiles

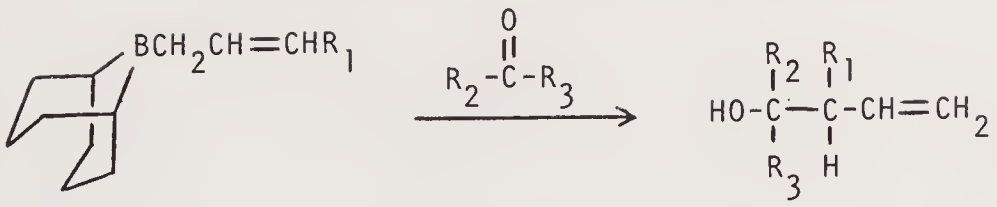
The hydroboration of allenes generally follows the regioselectivity obtained for that of oxymercuration reactions. Electrophilic attack of the boron on the terminal carbon of the allene is predominant when the terminal carbon atom is unsubstituted, whereas attack on the central carbon is preferred with internal allenes.[63] Although the steric or electronic nature of the allene can control the product distribution, the regiochemical outcome of the reaction can be manipulated by prudent selection of the hydroborating reagent. Disiamylborane or dicyclohexylborane exhibits preferential substitution on the central allene carbon to form vinylboranes. In contrast, 9-BBN exclusively forms allylboranes by way of attack at the terminus of the allene linkage[64] (equation 22).



(22)

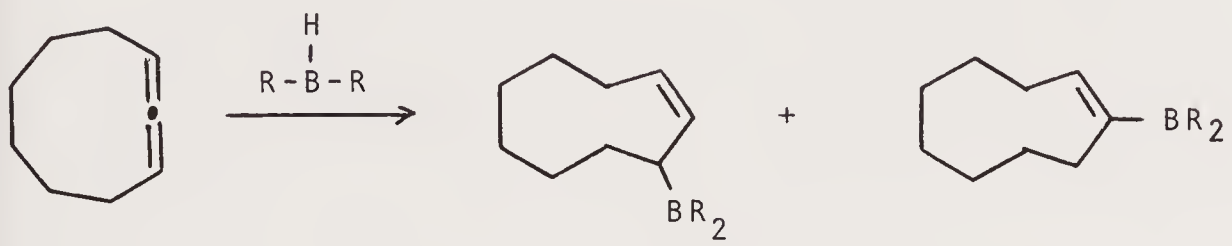
R_1	R_2	R_3	R_4	Yield (%)
CH_3	H	H	H	74
CH_3	CH_3	H	H	92
CH_3	H	CH_3	H	72
CH_3	CH_3	CH_3	CH_3	94

Allylboranes can be used for the addition of any allyl group to carbonyl-containing compounds. This useful synthesis of homoallylic alcohols serves as an interesting alternative to Grignard type allylations[64,65] (equation 23).



(23)

In reactions involving 9-BBN, the only instance in which the appearance of any vinylborane is observed is with 1,2-cyclononadiene (equation 24). In this case the reaction is not regiospecific, but the ratio remains overwhelmingly in favor of the allylborane **53**.

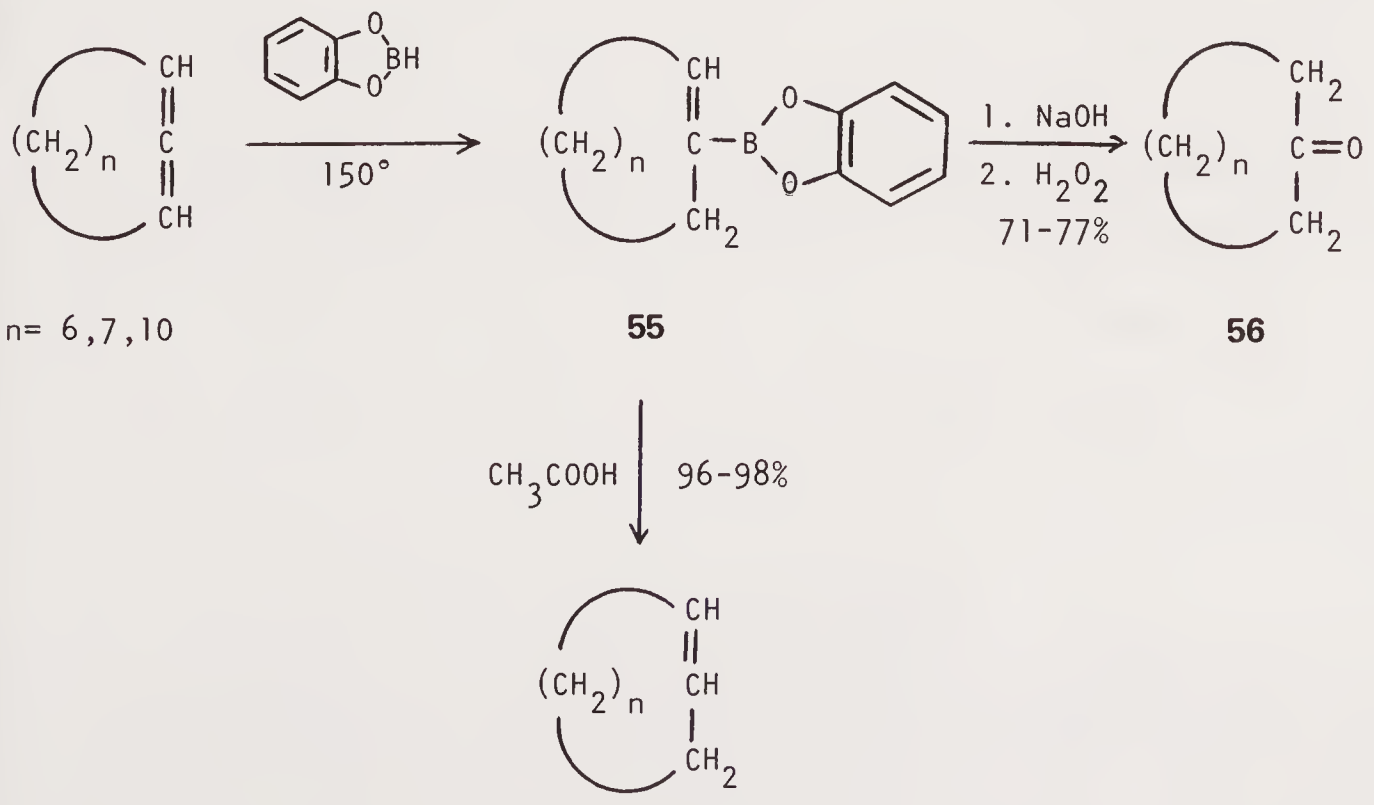


(24)

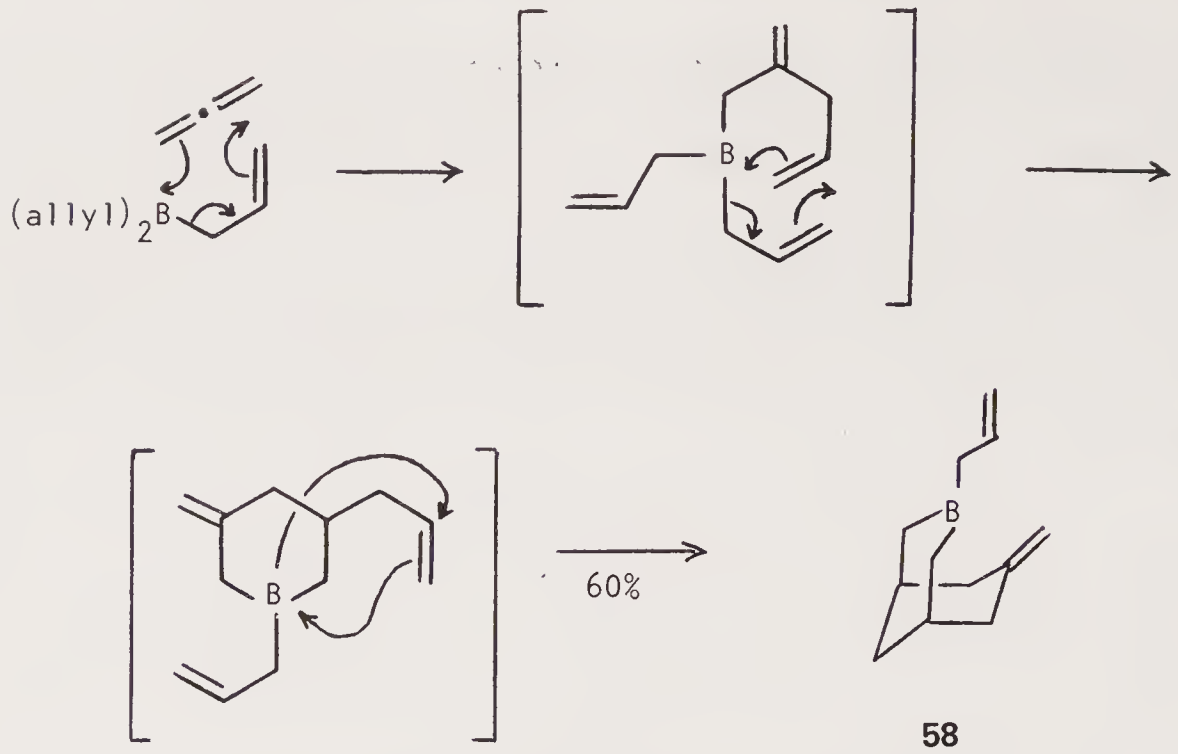
53 **54**

Borane Reagent	%**53**	%**54**	Reference
9-BBN	83	17	64
Disiamylborane	17	83	66
Catechol borane	0	100	67

The monohydroboration of cyclic allenes with catechol borane is characterized by the exclusive formation of cyclic vinylboranes **54** or **55** (equation 24 and Scheme 7).[67] The borane **55** can either be oxidized with hydrogen peroxide to give the cyclic ketones **56,** or protonated with acetic acid to produce the cycloolefins **57.** When



Scheme 7



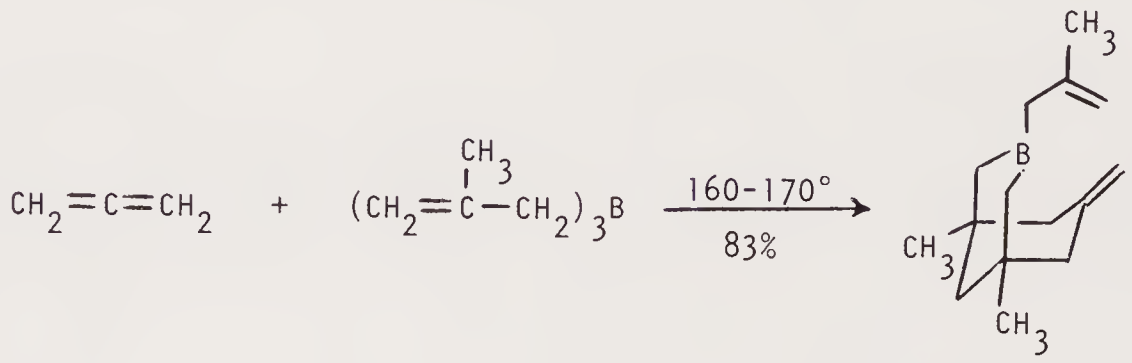
58

Scheme 8

n = 6 or 7 only the *cis* olefins are isolated, however in the case of 1, 2-cyclotridecadiene (n = 10) a 76:24 mixture of *cis*- and *trans*-cyclotridecene is produced.

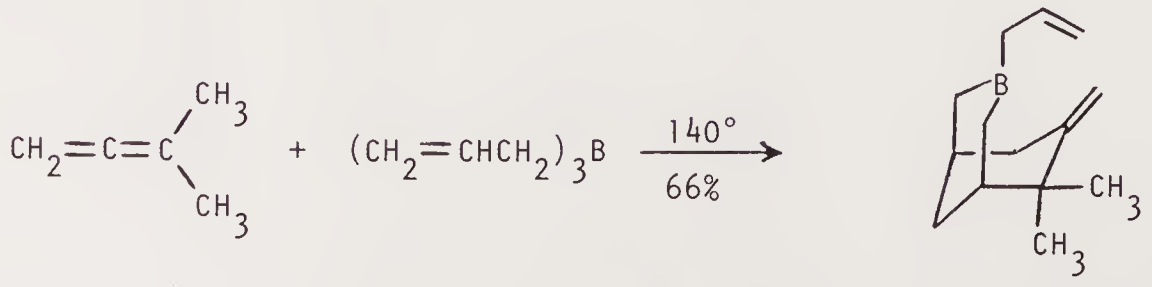
Allenes are susceptible to electrocyclic reactions with allylboranes to form boron heterocycles. When allene is heated with triallylborane at 150°, 3-allyl-7-methylene-3-borabicyclo[3.3.1]nonane (**58**) is obtained in 60% yield[68,69] by way of a series of intramolecular insertion reactions illustrated in Scheme 8.[70]

By modifying the allene or borane, substituted borabicyclononanes **59** and **60** are readily prepared[69] (equations 25 and 26).



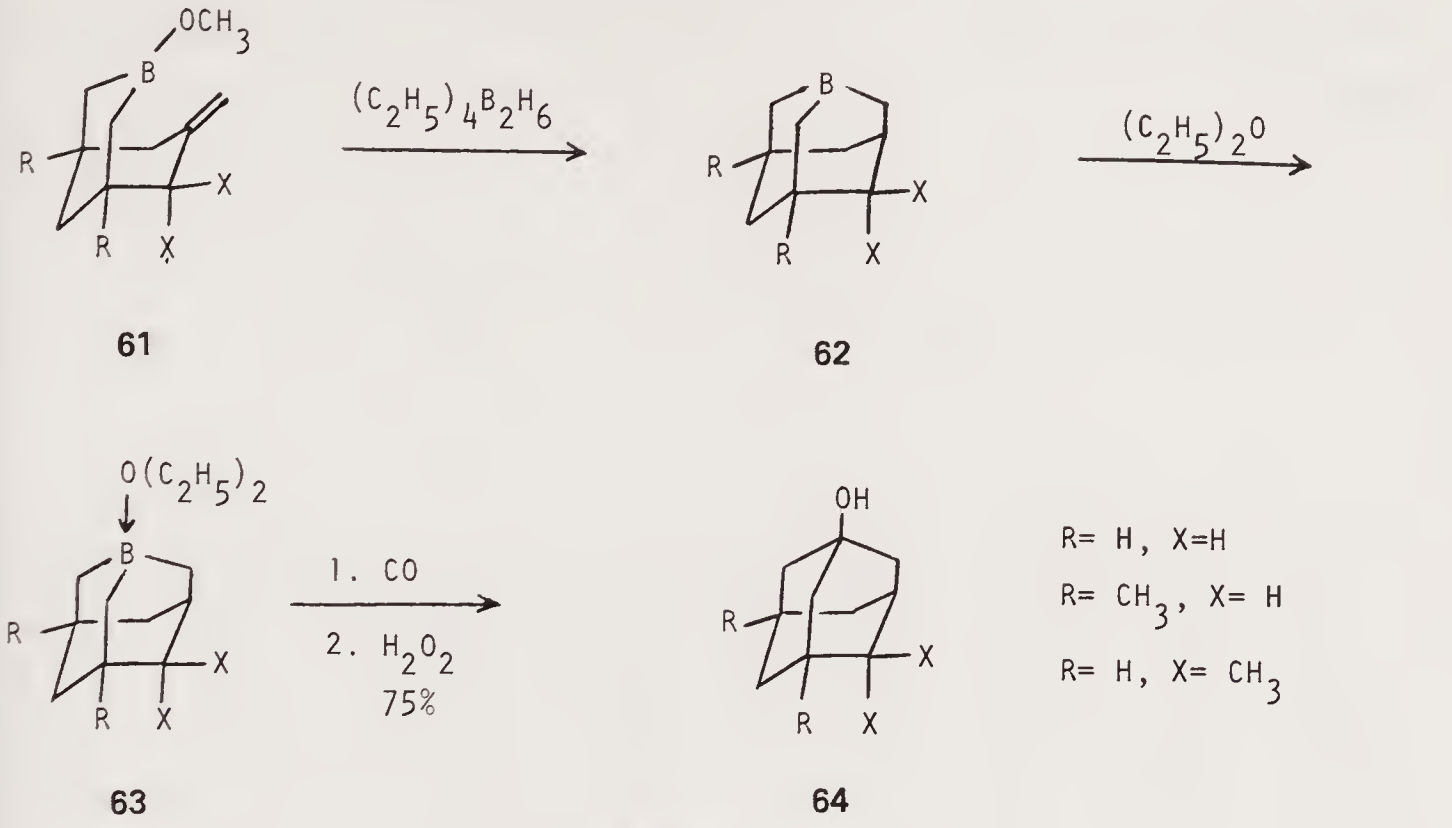
(25)

59



(26)

60

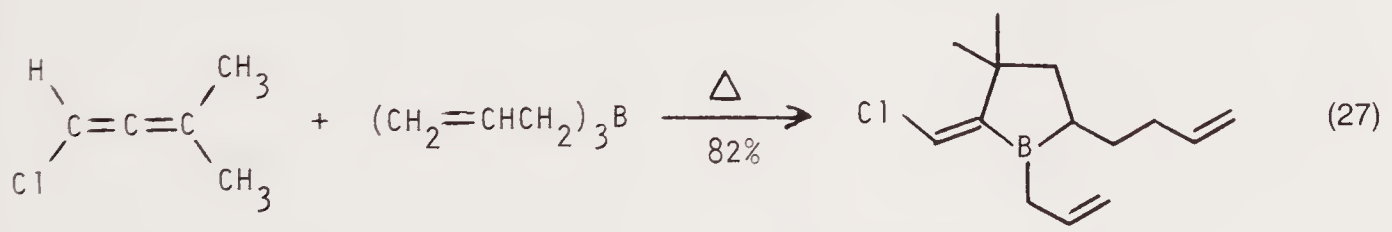


61 62 63 64

Scheme 9

Compound **58–60** can be additionally transformed into 1-boraadamantanes (**62**) by sequential treatment with methanol (to form the 3-methoxy derivatives **61**) then tetraethyldiborane (Scheme 9). Complexation with ether furnishes the 1-boraadamantane etherate **63** which, upon carbonylation followed by oxidation, results in the formation of 1-hydroxyadamantane derivatives **64**.[69,71] These unusually substituted carbocycles are not readily available by standard synthetic transformations.

In contrast to the reaction outlined in equation (26) the interaction of triallylborane with 1-chloro-3-methyl-1,2-butadiene (**65**) only produces 1-allyl-5-(3-buten-1-yl)-2-chloromethylene-3,3-dimethyl-1-boracyclopentane (**66**) in high yield (equation 27).[69,72]



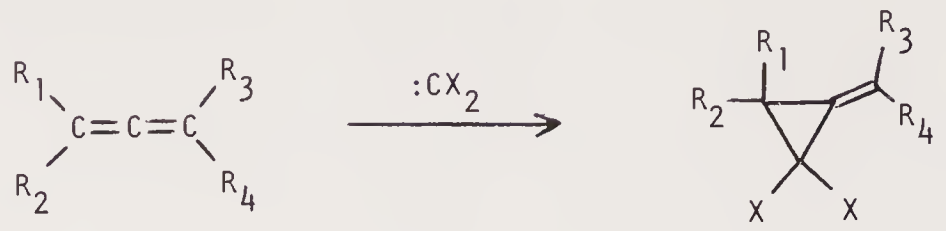
(27)

65 66

3.2.5. Addition of Carbenes

Carbenes, which are electrophilic in nature, readily add to the allene framework to give alkylidenecyclopropane derivatives **67** (equation 28). Singlet dihalocarbenes predominantly, if not exclusively, add to the double bond that contains the most electron-donating groups. With alkylallenes this represents the more substituted double bond. In contrast, triplet carbenes (e.g., methylcarboethoxycarbene) gives

cyclopropanes that appear to arise from addition to the less substituted double bond.[73,74]

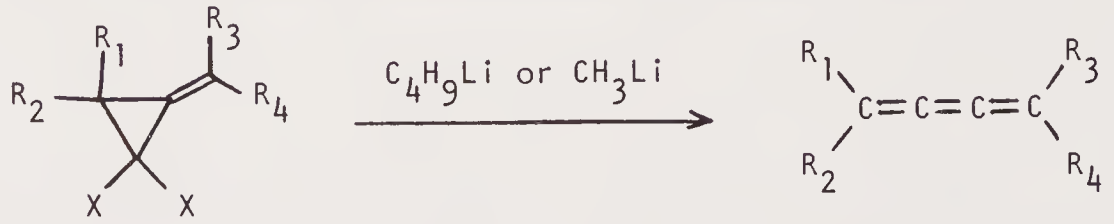


(28)

67

R_1	R_2	R_3	R_4	X	$:CX_2$ Source	Yield (%)	Reference
H	H	H	H	Cl	$C_6H_5HgCCl_2Br$	64	75
CH_3	H	CH_3	H	Br	$CHBr_3/t\text{-}C_4H_9OK$	87	76
CH_3	CH_3	H	H	Br	$CHBr_3/t\text{-}C_4H_9OK$	75	76–79
CH_3	CH_3	H	H	Cl	$CHCl_3/t\text{-}C_4H_9OK$	49	78, 79
CH_3	CH_3	H	H	Cl	$CHCl_3$/NaOH/BTA	88	80
CH_3	CH_3	CH_3	H	Br	$CHBr_3/t\text{-}C_4H_9OK$	78	76, 78, 79
CH_3	CH_3	CH_3	CH_3	Cl	$CHCl_3/t\text{-}C_4H_9OK$	73	81
H	$-(CH_2)_6-$		H	Br	$C_6H_5HgCBr_3$	100	82, 83
$-(CH_2)_3-$		$-(CH_2)_3-$		Br	$CHBr_3/t\text{-}C_4H_9OK$	89	84

Dihalocyclopropane derivatives **67** can be converted to cumulenes **68** by reaction with an organolithium base (equation 29). The oxygen sensitive 1,2,3-trienes are formed in good yield and are quite stable when stored as ether solutions under nitrogen.

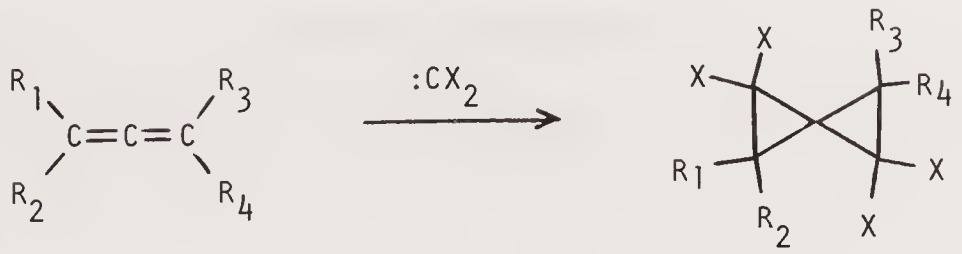


(29)

67 **68**

R_1	R_2	R_3	R_4	X	Yield (%)	Reference
CH_3	CH_3	H	H	Br	75	79
CH_3	C_2H_5	H	H	Br	75	79
CH_3	CH_3	CH_3	CH_3	Cl	100	81
H	$-(CH_2)_6-$		H	Br	93	82
$-(CH_2)_3-$		$-(CH_2)_3-$		Br	69	84

When allenes are treated with an excess of a dihalocarbene, reaction occurs at both double bonds and spiropentanes **69** are produced (equation 30). Dehalogenation of **69** with methyllithium affords cumulated tetraenes.[81,84]

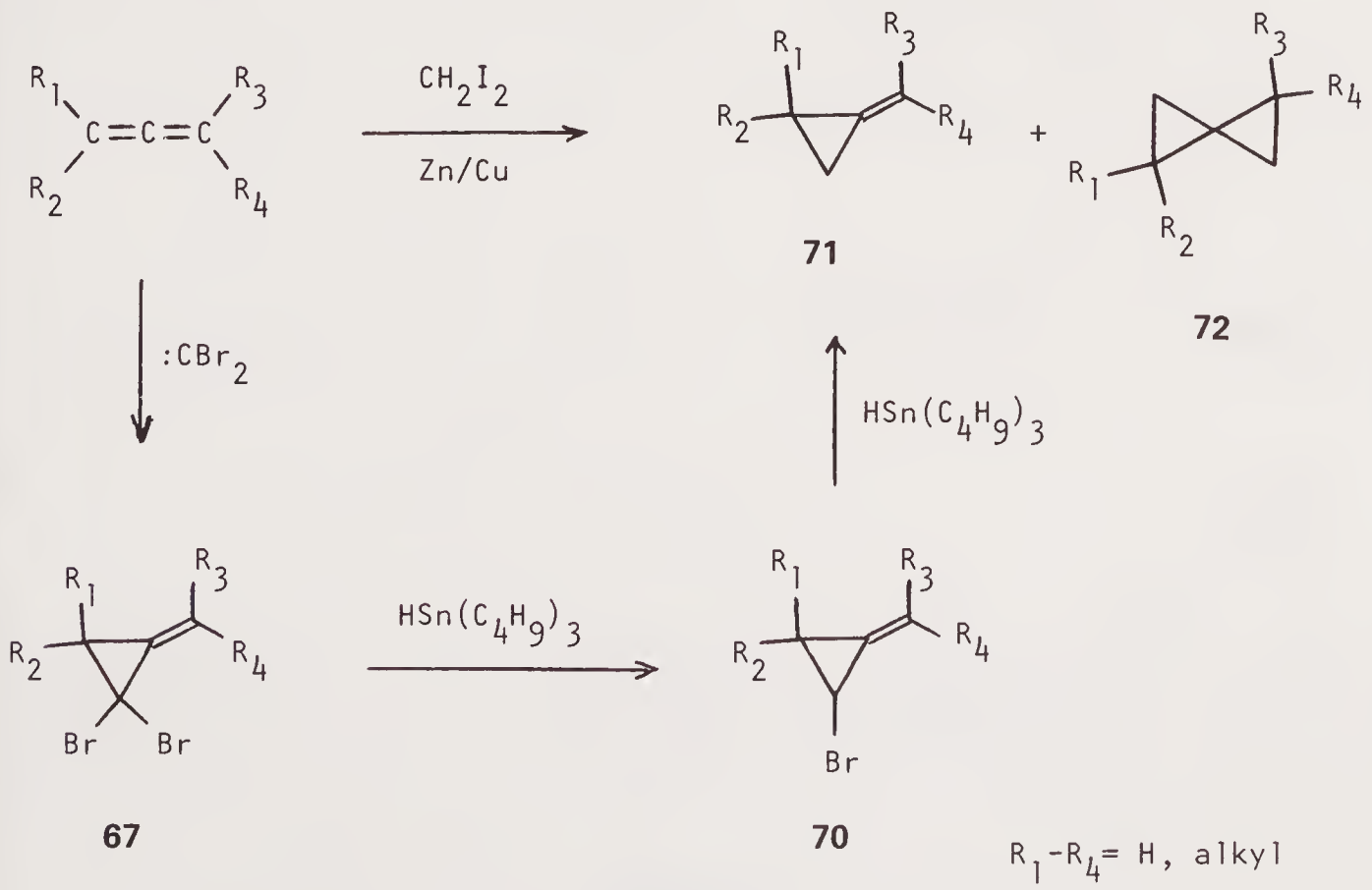


(30)

69

R_1	R_2	R_3	R_4	X	: CX_2 Source	Yield (%)	Reference
H	H	H	H	Cl	$CHCl_3$/NaOH/BTA	34	80
CH_3	CH_3	H	H	Cl	$CHCl_3$/NaOH/BTA	70	80
CH_3	CH_3	CH_3	CH_3	Cl	$CHCl_3$/NaOH/BTA	90	80
$-(CH_2)_3-$		$-(CH_2)_3-$		Br	$CHBr_3$/*t*-C_4H_9OK	21	84

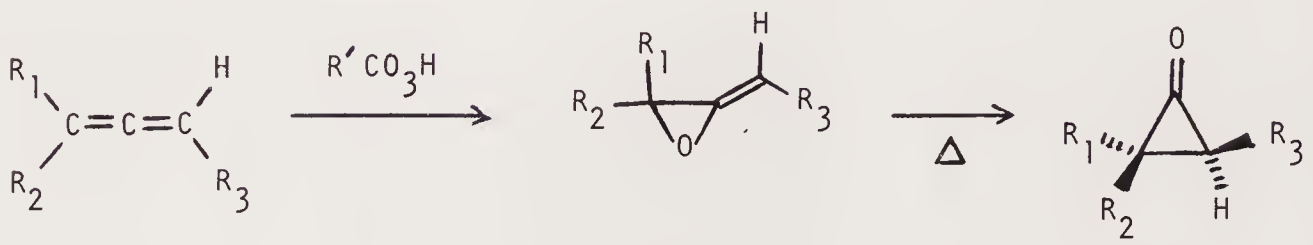
The use of Simmons–Smith reagent to effect the monocyclopropanation of allene hydrocarbons is of limited synthetic value. However, employing a 4–6 molar excess of the reagent results in dicyclopropanation to give spiropentanes **72** in moderate yield[85,86] (Scheme 10). If the alkylidenecyclopropanes **71** are desired, the most efficient route for their preparation involves reaction of the allene with dibromocarbene then debromination of **67** with tri-*n*-butyltin hydride. When one equivalent of the hydride reagent is used, the monobromocyclopropane **70** can be isolated in good yield.[76,87]



Scheme 10

3.2.6. Oxidation of Allenes

Allenes are susceptible to oxidation by peracids (equation 31). The resulting allene oxides are extremely reactive molecules and generally react further to give a complex mixture of products.[88] Isolable allene oxides such as **74**, however, can be generated if the allene bears bulky substituents. Thus 1,3-di-*t*-butylallene (**73a**),[89] 1,1-di-*t*-butylallene (**73b**),[90] and 1,1,3-tri-*t*-butylallene (**73c**),[91] when treated with either *m*-chloroperbenzoic acid (MCPBA) or *p*-nitroperbenzoic acid, afford allene oxides



(31)

73 **74** **75**

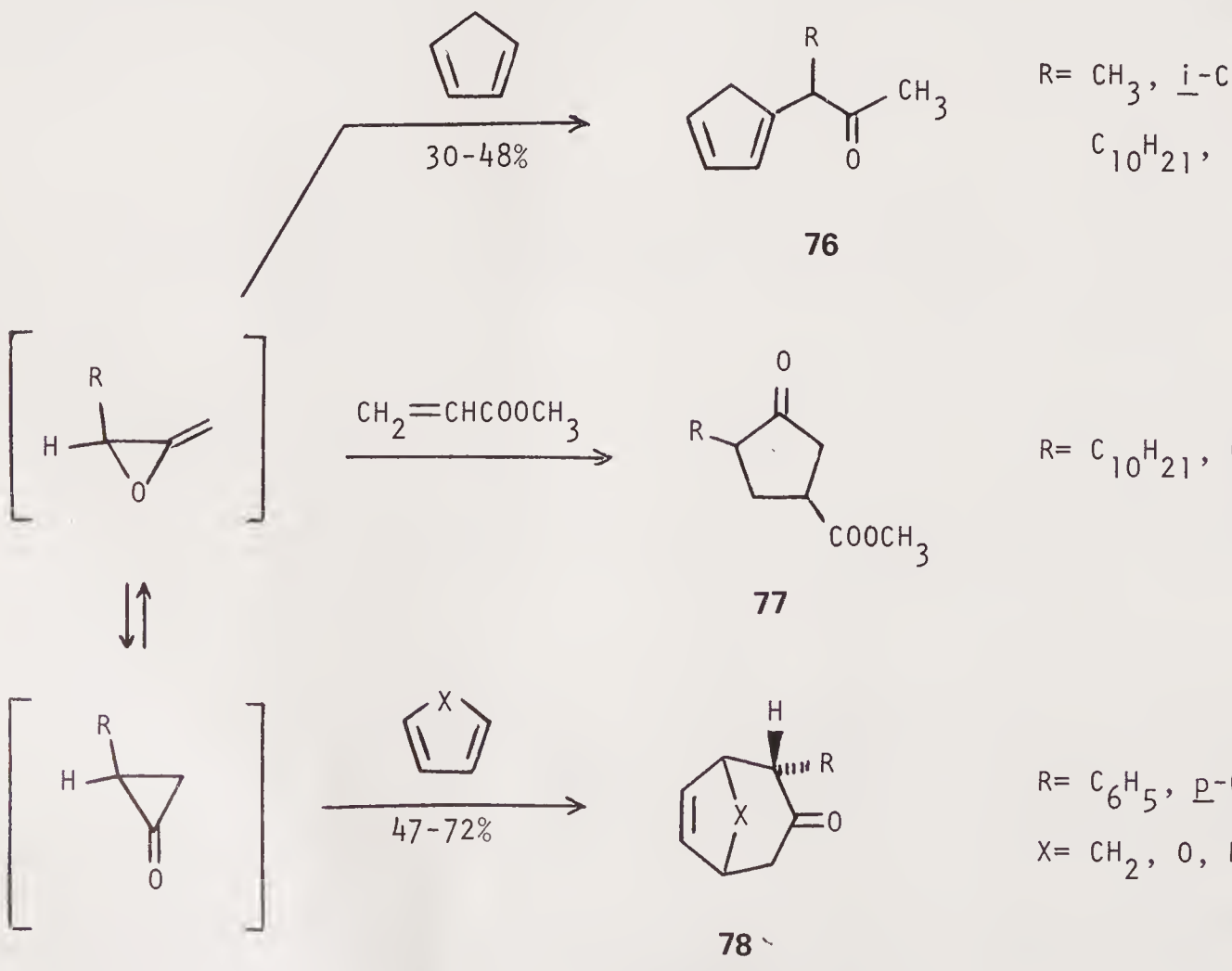
a, $R_1 = R_3 = t\text{-}C_4H_9$

b, $R_1 = R_2 = t\text{-}C_4H_9$

c, $R_1 = R_2 = R_3 = t\text{-}C_4H_9$

74a–74c. Upon heating, compounds **74a** and **74b** isomerize to cyclopropanones **75a** and **75b**.[89,90]

Allene oxides are valuable synthetic intermediates and have been the topic of a recent review.[7] When generated *in situ* in the presence of a trapping agent, a variety

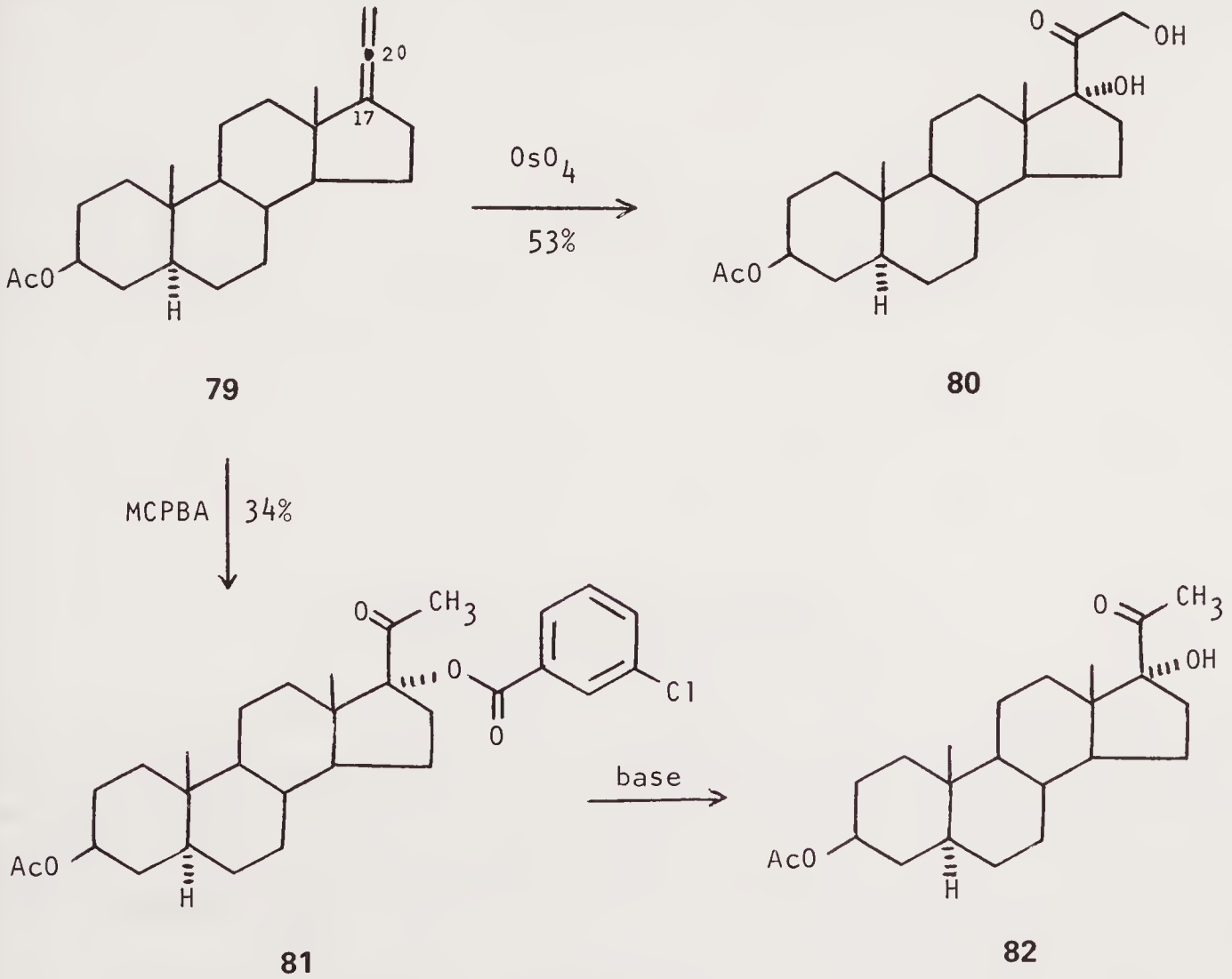


Scheme 11

of useful products are produced (Scheme 11).[92] Alkyl-substituted allene oxides react with cyclopentadiene to give the substitution products **76**. In contrast, generation of aryl-substituted allene oxides in the presence of a diene gives exclusively the cycloadducts **78**. The products arise from an initial rearrangement of the allene oxide to a cyclopropanone followed by cycloaddition with the diene. When generated in the presence of methyl acrylate, alkyl or aryl substituted allene oxides undergo regiospecific cycloaddition, affording in each case a 2,4-disubstituted cyclopentanone **77** in moderate yields.[93]

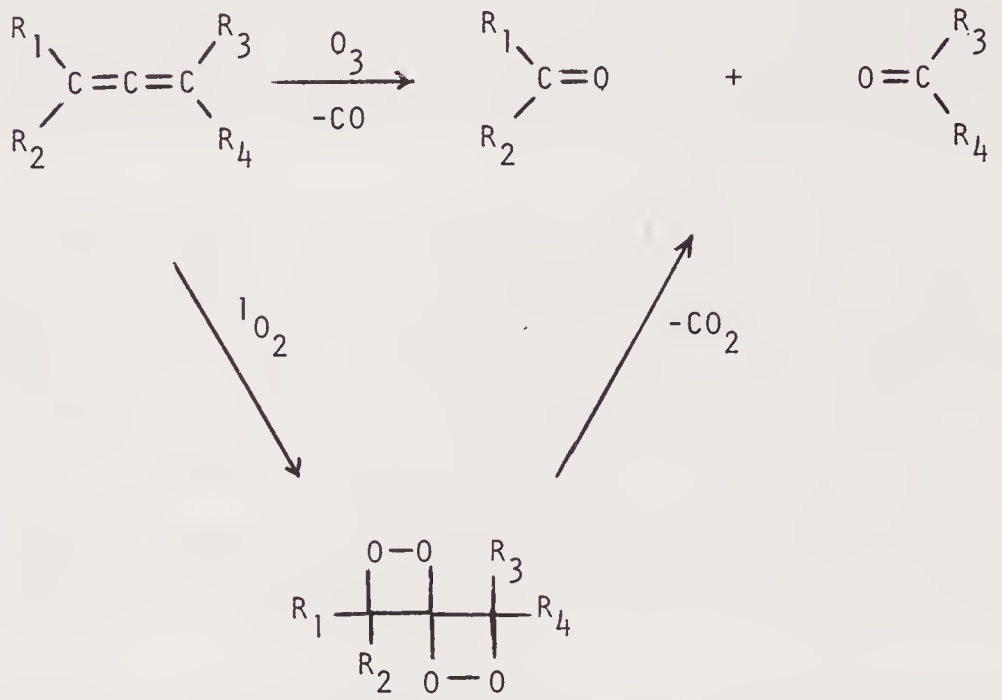
The introduction of either a corticoid or pregnane side-chain into a steroid can be accomplished by oxidative manipulations of an allene function attached to the steroidal skeleton (Scheme 12). When **79** is treated with osmium tetroxide-pyridine followed by cleavage of the osmate ester with sodium sulfite and potassium bicarbonate, the 17α, 21-dihydroxyketosteroid **80** is obtained in moderate yield. Alternately, when **79** is allowed to react with MCPBA buffered with disodium phosphate, only the pregnane derivative **81** is formed (presumably through a 17,20-allene oxide). Mild base hydrolysis of the 17α-chlorobenzoate **81** furnishes the diol **82**.[94]

The reaction of allenes with a stoichiometric quantity of ozone proceeds by an unknown mechanism to give two carbonyl fragments, derived from the terminal allene carbons, and carbon monoxide derived from the central atom[95] (equation 32). Ozone also functions as an oxygen transfer reagent with sterically hindered allenes to afford cyclopropanones by way of an initially formed allene oxide.[90,96] The



Scheme 12

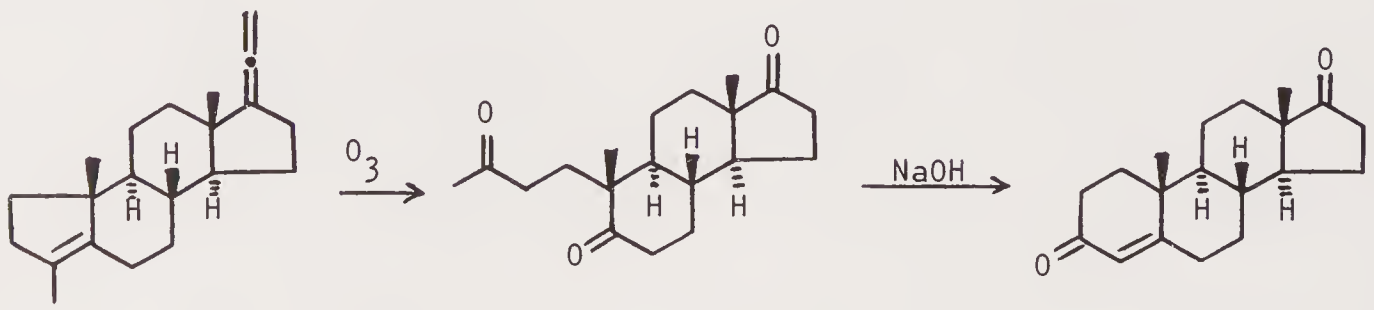
reaction shown in equation (32) can also be effected with singlet oxygen. The transformation is believed to proceed through an unstable tetraoxaspirocycloheptane intermediate **83**.[97]



(32)

83

An interesting application of allene ozonolysis is demonstrated in the two-step conversion of tetracyclic allene **84** to the steroidal enedione **85**. The overall sequence shown in equation (33) proceeds in 46% yield.[98]



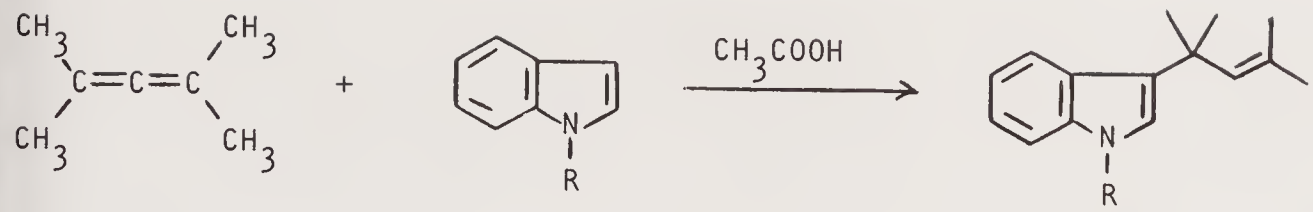
(33)

84 **85**

3.3. NUCLEOPHILIC ADDITIONS

Allene hydrocarbons are not susceptible to nucleophilic addition reactions unless the allene skeleton is activated with an electron-withdrawing group. One notable exception is the reaction of 2,4-dimethyl-2,3-pentadiene (**86**) with indole derivatives[99] (equation 34). The transformation is regiospecific giving high yields of the terminally substituted adducts **87**. The reaction, however, is not general and is limited only to the illustrated reactants.

The base-catalyzed cyclization of *o*-allenylphenol (**88**, R = H) affords 2-methylbenzofuran (**89**) by way of an intramolecular nucleophilic addition of phenoxide



(34)

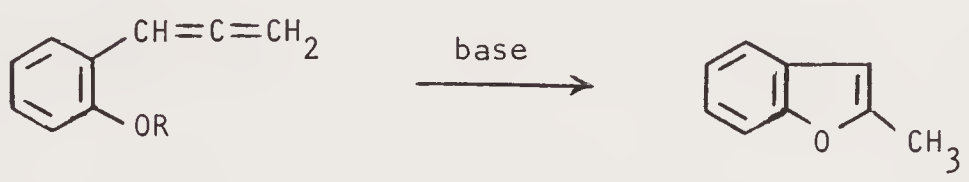
86

87

R= H, 96%

R= CH_3, 84%

to the central allene carbon[100] (equation 35). The reaction can be catalyzed with either aqueous alkali or triethylamine and furnishes the observed product in 60% yield. When the reaction is performed with *o*-allenylphenyl acetate (**88**, R = OAc) in the presence of sodium methoxide, **89** is isolated in 81% yield.



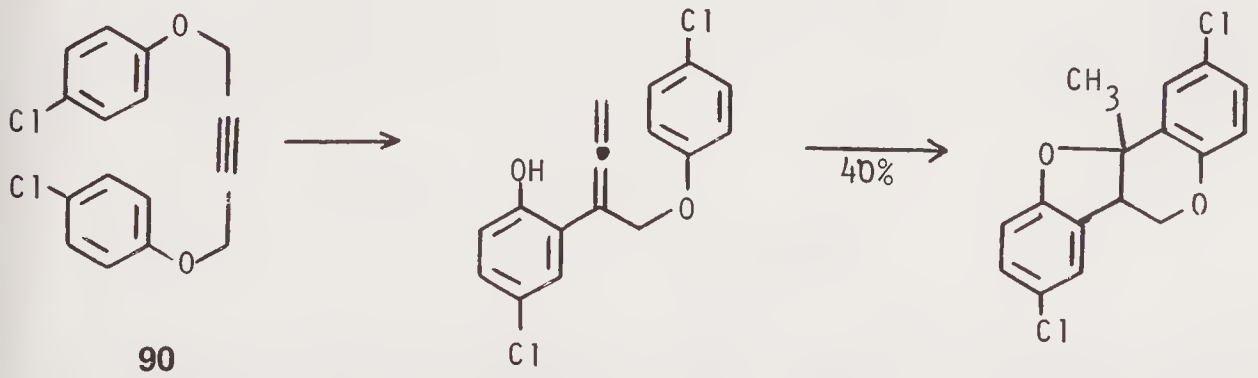
(35)

88

R= H, OAc

89

The generation of *o*-allenylphenols can also be accomplished by a Claisen rearrangement of a phenylpropargyl ether. Refluxing a solution of 1,4-bis-(*p*-chlorophenoxy)-2-butyne (**90**) in diethylaniline gives tetracycle **92**, which is postulated to arise from the intermediacy of **91**.[101]



(36)

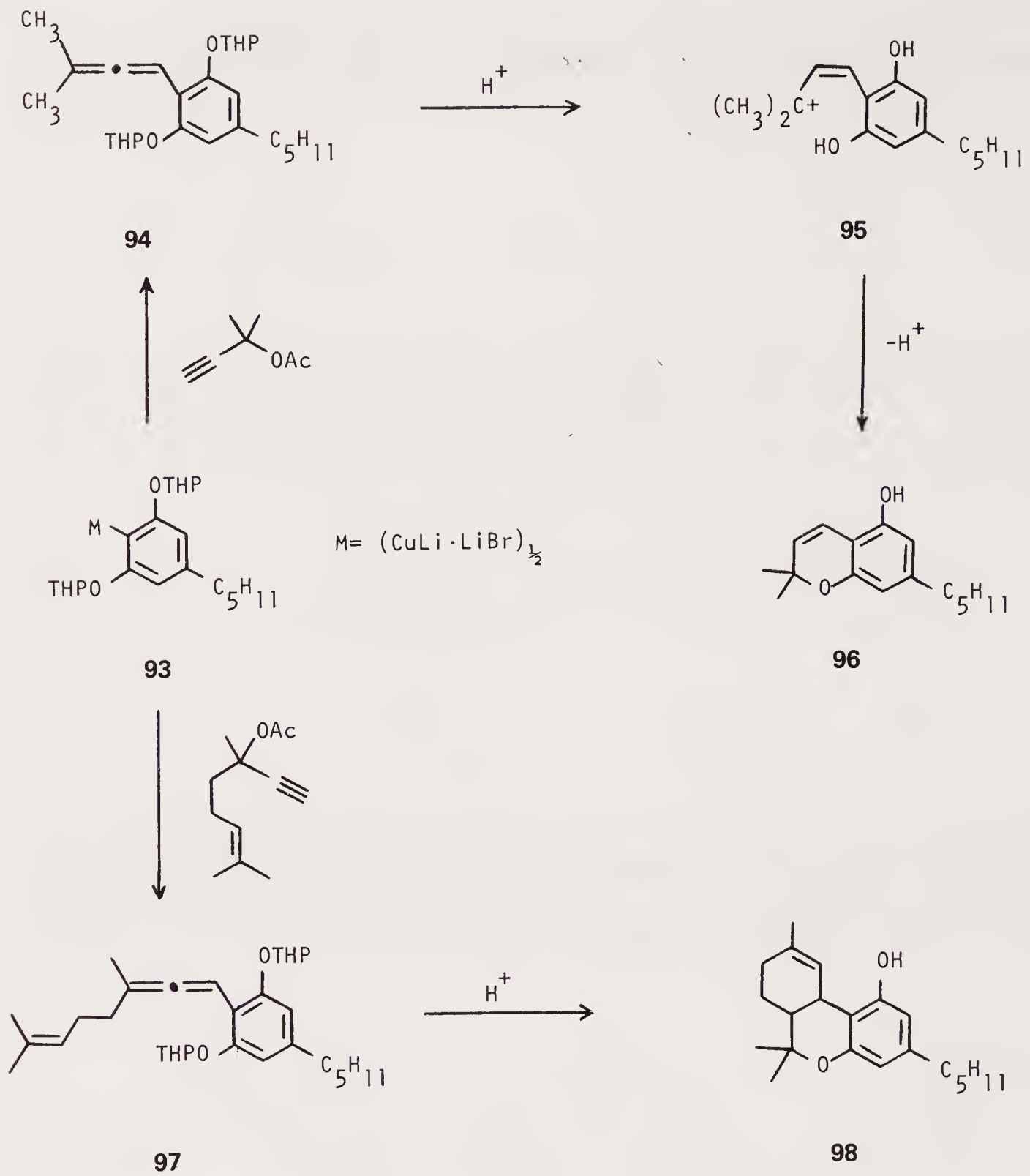
90

91

92

3.4. MISCELLANEOUS ADDITIONS

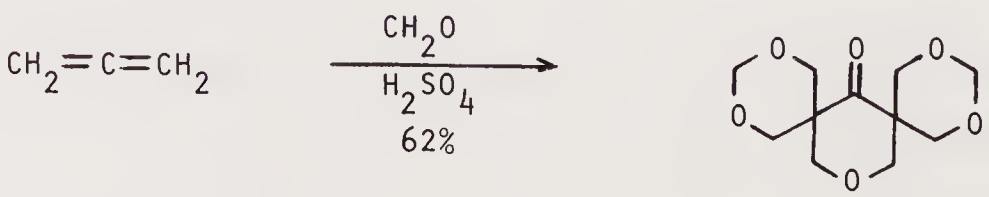
The acid-catalyzed cyclization of *o*-allenylphenols leads to the formation of chromene heterocycles. Reaction of homocuprate **93** with 3-acetoxy-3-methyl-1-butyne followed by acidic workup results in the formation of 5-hydroxy-2,2-dimethyl-7-pentylchromene (**96**) in 70–80% yield. The conversion is believed to proceed by way of initial formation of the allene **94**, then subsequent ring closure of the allylic cation **95** (Scheme 13).[102] This methodology can be conveniently applied to the synthesis of *cis*-cannabinoids. Thus when **93** is allowed to react with dehydrolinaloöl



Scheme 13

acetate, 3,4-*cis*-$\Delta^{1,2}$-tetrahydrocannabinol (**98**) is obtained in 20% overall yield. This procedure is particularly useful since no other isomeric tetrahydrocannabinols are formed.

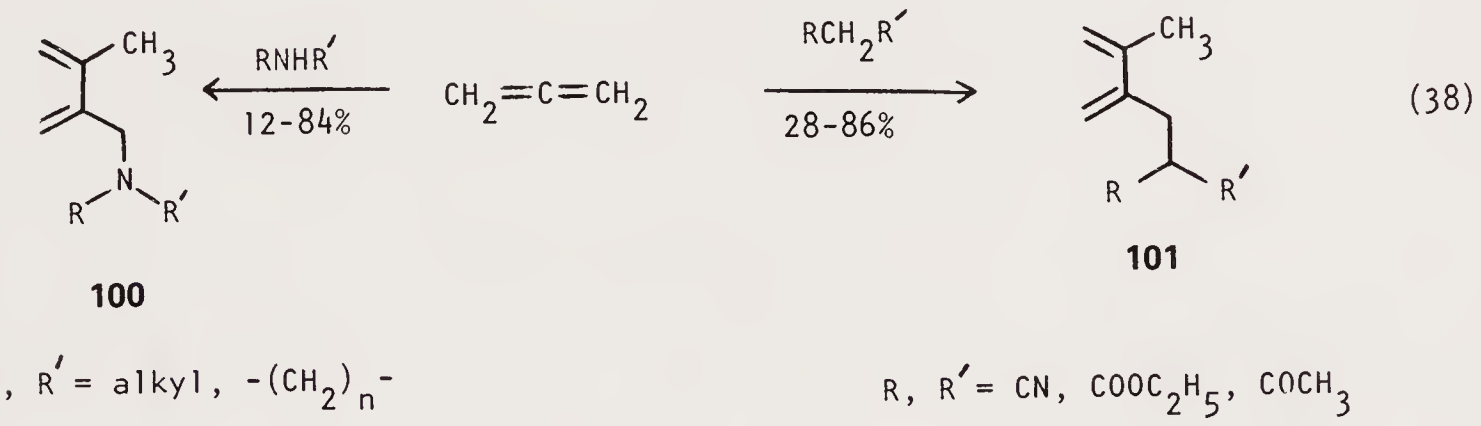
The addition of formaldehyde to allene in the presence of aqueous sulfuric acid results in the formation of 2,4,10,12,15-pentaoxadispiro[5.1.5.3]hexadecan-7-one (**99**) by way of a Prins reaction.[103]



(37)

99

Allene can also be induced to undergo reactions with amines or active methylene derivatives when catalyzed with transition metals (equation 38). The resulting 1,3-dienes **100** or **101**, formed from a condensation of two molecules of allene with one of reactant, are usually isolated in high yields.[104] In these reactions the Pd(0) complex bis(triphenylphosphine)–(maleic anhydride)palladium is used most frequently because of its high solubility and stability in air.

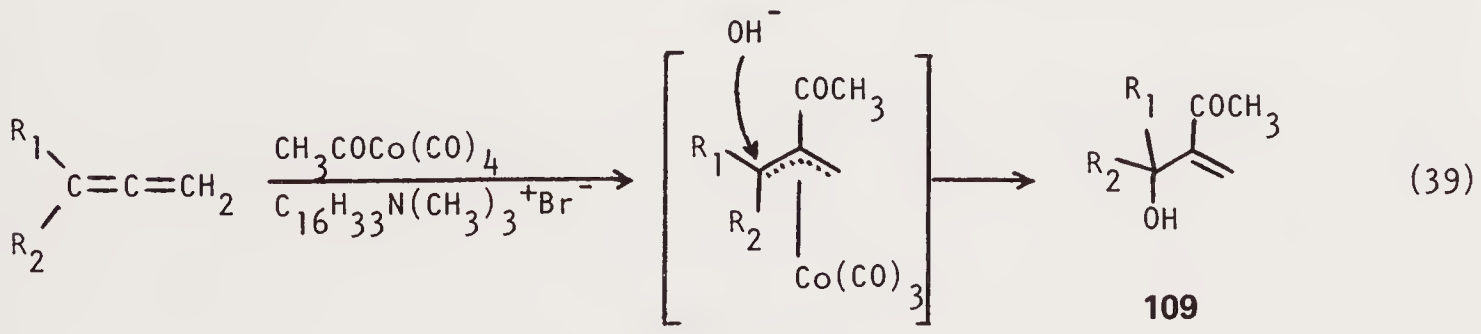


100 **101**

R, R′ = alkyl, $-(CH_2)_n-$ R, R′ = CN, $COOC_2H_5$, $COCH_3$ (38)

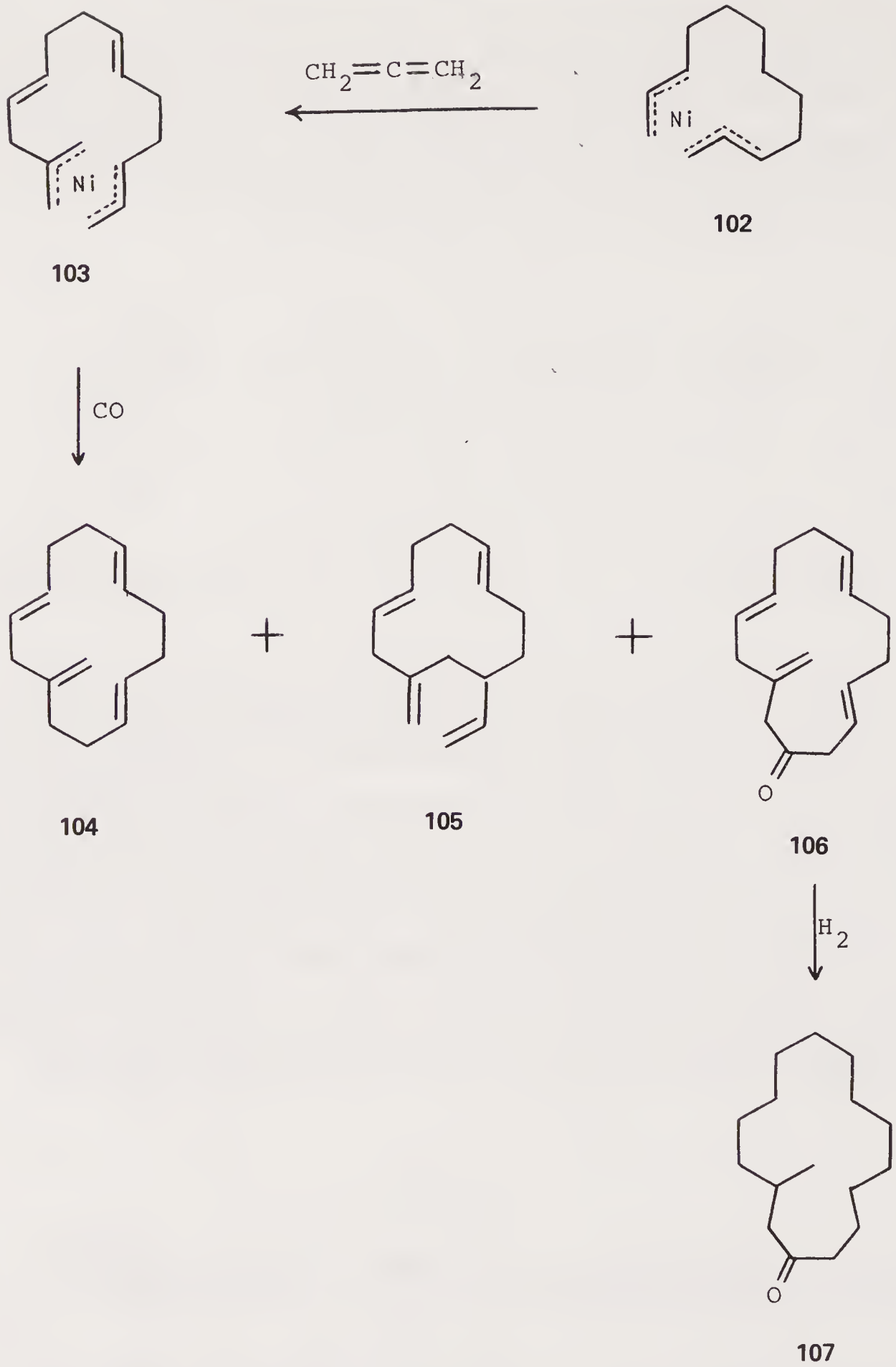
The dodecatrienylnickel complex **102** absorbs one equivalent of allene to give the bis-π-allyl intermediate **103**. Carbonylation of **103** with carbon monoxide furnishes a mixture of three products **104–106** (Scheme 14). Compound **106**, which represents only 4–5% of the total reaction mixture, is readily hydrogenated to (±)-muscone (**107**).[105] Although the sequence gives a low overall yield of the natural product, it is worth mentioning because of its exceedingly simple synthesis.

Phase transfer catalyzed reactions of allenes with acetylcobalt tetracarbonyl afford unsaturated hydroxy ketones **109** in moderate yields[106] (equation 39). The initial step of the reaction is the generation of the 2-acetyl-π-allylcobalt tricarbonyl complex **108.** Regiospecific attack by hydroxide at the more substituted terminal carbon on the complex, after decomplexation, gives the observed products **109**.



108 **109** (39)

R_1	R_2	Yield (%)
C_8H_{17}	H	43
CH_3	CH_3	23
$-(CH_2)_5-$		40
$-(CH_2)_6-$		38

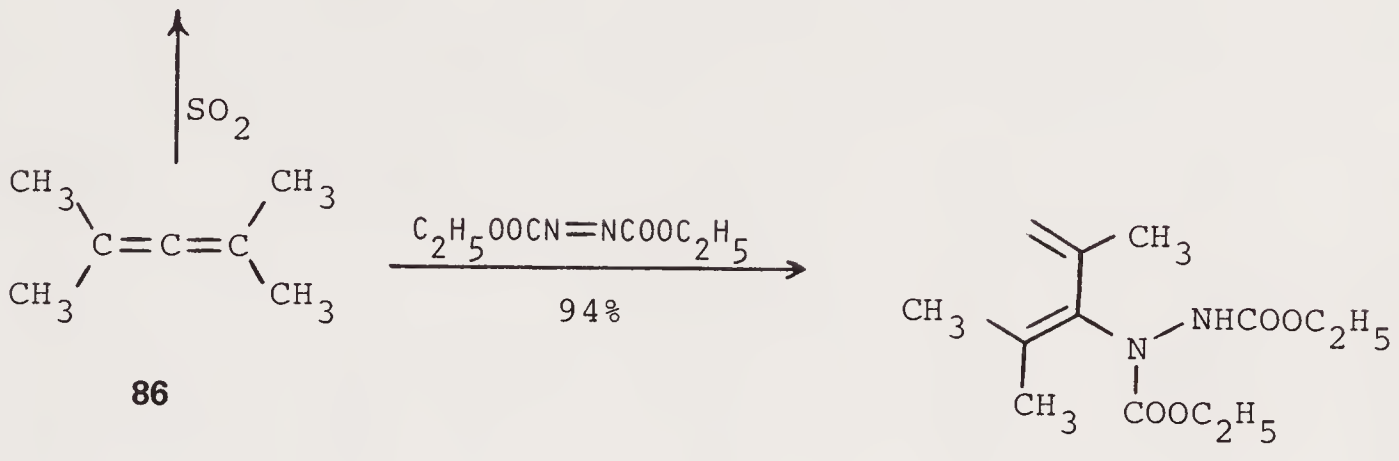


102 **103** **104** **105** **106** **107**

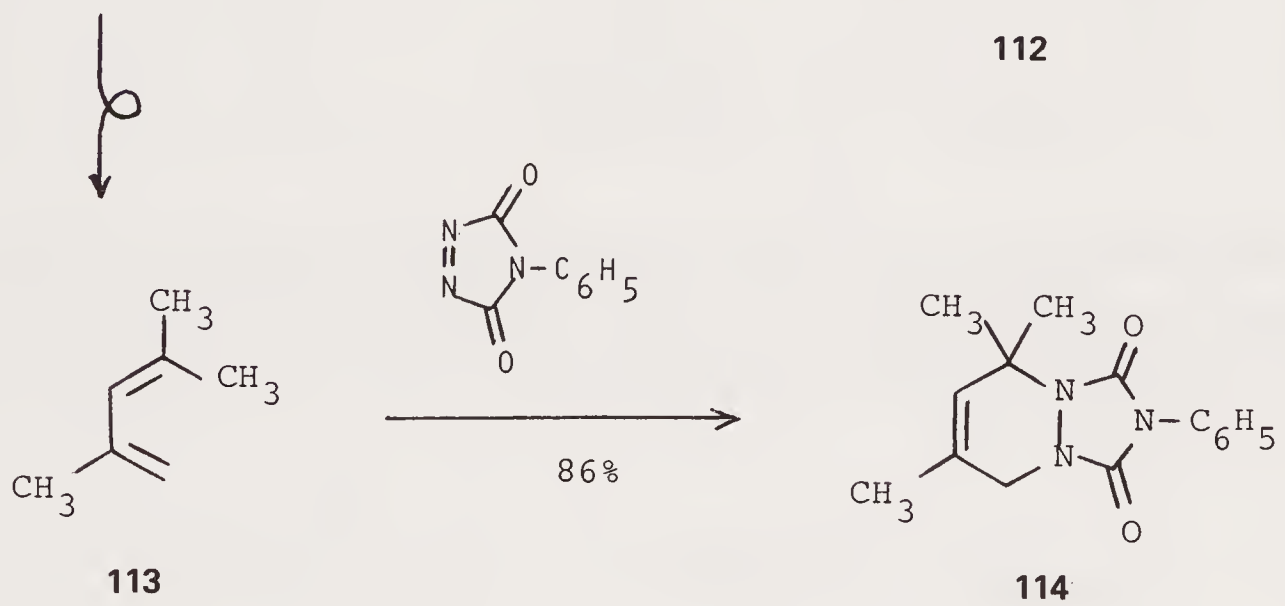
Scheme 14

In the presence of suitable enophiles, alkylallenes are highly reactive substrates in Alder ene reactions by virtue of the energetically favorable bond reorganization that such reactions entail[107] (e.g., **110** in Scheme 14). In liquid sulfur dioxide, 2,4-dimethyl-2,3-pentadiene (**86**) undergoes an ene addition with the solvent to give 3-(2,4-dimethyl-1,3-pentadienyl)sulfinic acid (**111**).[108] Diethyl azodicarboxylate analogously reacts with **86** to give **112** in high yield. However, with the powerfully enophilic 4-phenyltriazolinedione, **86** rearranges to 2,4-dimethyl-1,3-

110 111



86 112



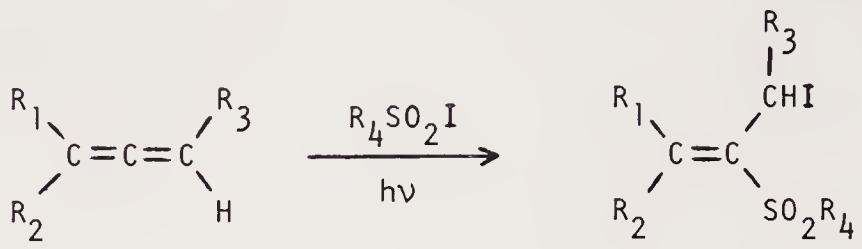
113 114

pentadiene (**113**) prior to capture by the enophile, and only the Diels–Alder adduct **114** is obtained.[107]

In the scope of synthetic applications, the addition of radicals to allenes generally does not represent a useful process. The product distribution is highly dependent on the substituents attached to the allene, the nature of the attacking radical, and the reaction conditions.[5] Under kinetic control, fluorine, bromine, trimethyltin, and benzenethiyl radicals are relatively nondiscriminating and give mixtures of products derived from both central and terminal carbon attack (central attack becomes more favored with increasing methyl substitution on the allene). In contrast, CX_3 radicals regiospecifically attack the terminus of the allene framework regardless of the nature of X (F, Cl, or H).[109]

Sulfonyl radicals, on the other hand, exclusively give products derived from central attack on allenes bearing one or more alkyl or aryl substituents.[109–111] Photolysis of a mixture of an aryl or alkylsulfonyl iodide in the presence of a twofold molar excess of an allenic hydrocarbon rapidly (15–20 minutes) produces the sulfonyl-substituted allyl iodides **115** in high yields (equation 40). It is interesting to

note that addition of tosyl iodide to allenes capable of producing *cis*- or *trans*-allylic iodides occurs in a stereospecific fashion and gives only a single isomer.

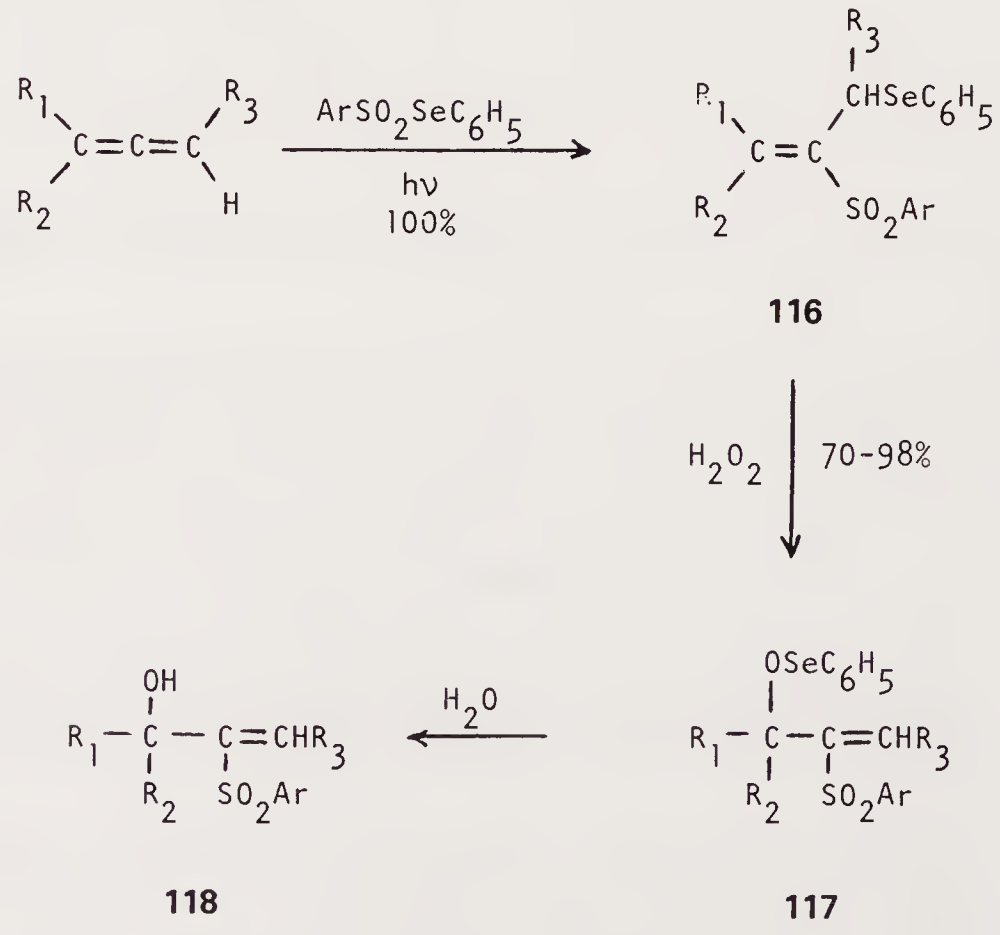


(40)

115

R_1	R_2	R_3	R_4	Yield (%)	Reference
CH_3	H	H	*p*-$CH_3C_6H_4$	73	109
CH_3	CH_3	H	*p*-$CH_3C_6H_4$	97	111
CH_3	CH_3	H	CH_3	100	111
C_6H_5	H	H	C_6H_5	94	111
C_6H_5	H	H	C_2H_5	92	111
CH_3	H	CH_3	*p*-$CH_3C_6H_4$	82	109
H	-$(CH_2)_6$-		*p*-$CH_3C_6H_4$	80	109

Areneselenosulfonates also readily undergo free-radical addition to allenes in a regiospecific manner (equation 41). The arylsulfonyl group adds to the central carbon of the allene, and the phenylseleno group becomes attached to the less highly



116

118 **117**

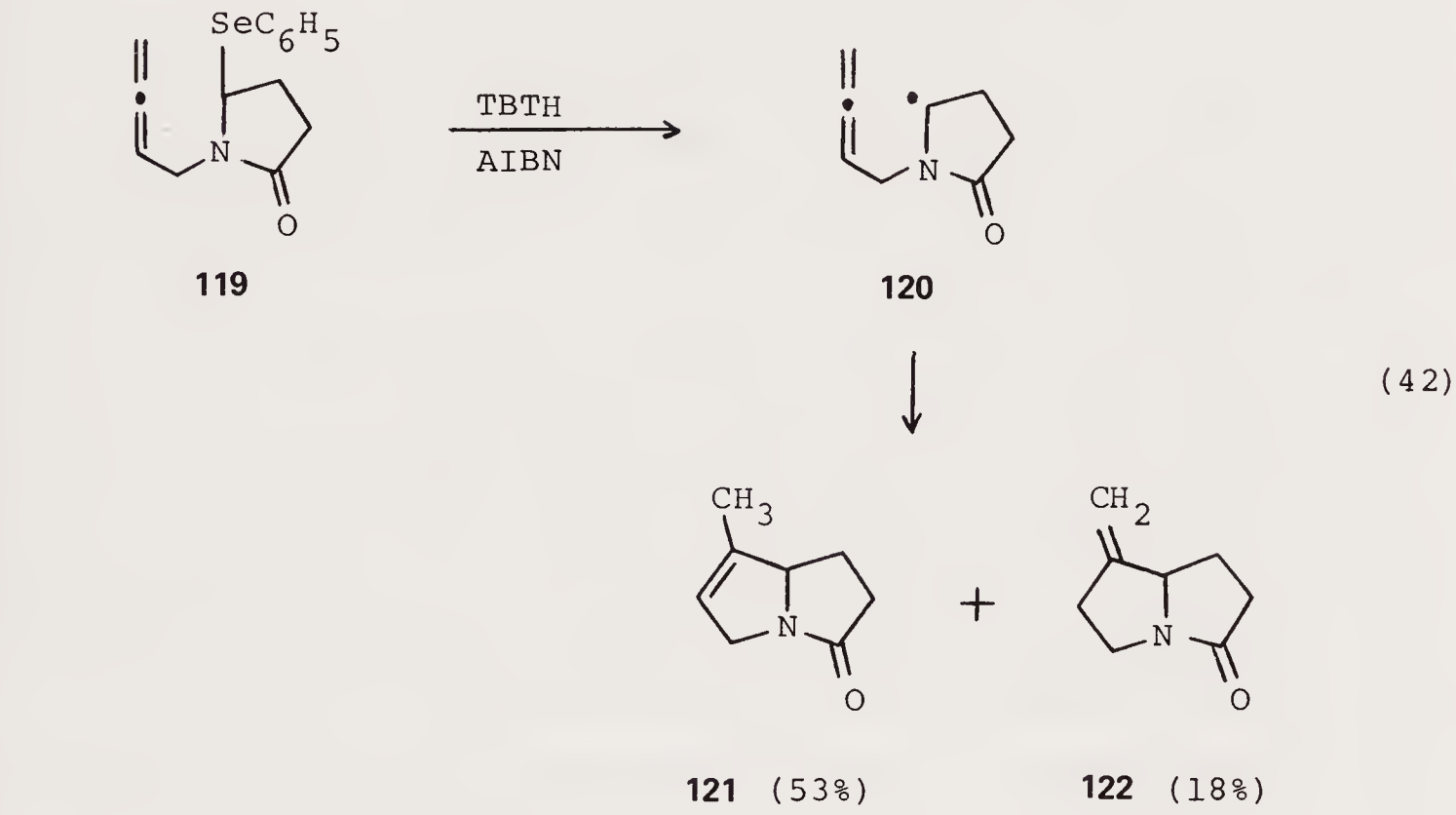
(41)

R_1, R_2, R_3= H, alkyl, C_6H_5

Ar= p-tolyl

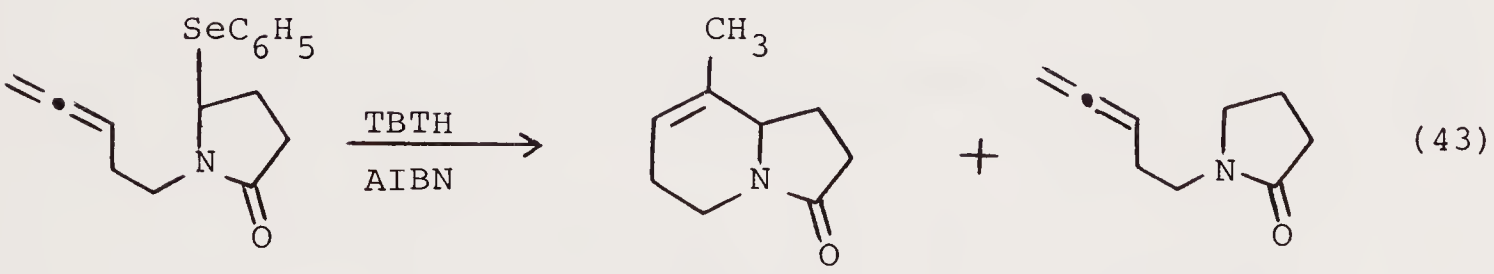
substituted of the two terminal carbons.[112] Oxidation of the phenylseleno group in **116** with hydrogen peroxide results in a [2,3] sigmatropic rearrangement to selenate **117** which, upon hydrolysis, furnishes β-arylsulfonyl allylic alcohols **118**.

In an interesting study, Hart[113] has investigated the intramolecular addition of radicals to allenes. The addition of **119** to a refluxing solution of tri-*n*-butyltin hydride and AIBN in benzene (over a period of 7 hours) results in the generation of radical **120**. Internal capture of the radical by the allene gives a separable mixture of 1-azabicyclo[3.3.0]octan-2-ones **121** and **122** (equation 42). Increasing the distance of the allene from the pyrrolidone by one methylene unit (**123**) gives 6-methyl-1-azabicyclo[4.3.0]non-6-en-2-one (**124**) as the only cyclization product along with deselenated starting material **125** (equation 43).



119 **120** (42)

121 (53%) **122** (18%)



123 **124** (60%) **125** (26%) (43)

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CHAPTER FOUR

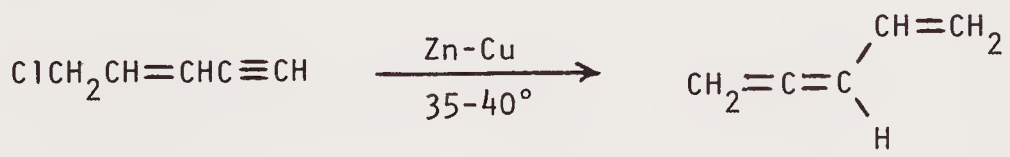
ALLENES CONTAINING UNSATURATED SUBSTITUENTS

Allenes which contain either alkenyl, alkynyl or allenyl substituents are accessible by a variety of synthetic methods. Because these substituents interact with the allene portion of the molecule to affect its chemical reactivity, these derivatives lend themselves to very interesting and useful synthetic transformations. It is the purpose of this chapter to introduce these synthetic approaches and to describe the applicability of these allenes to the synthesis of complex molecules and natural products.

4.1. VINYL ALLENES (1,2,4-TRIENES)

4.1.1. Synthesis

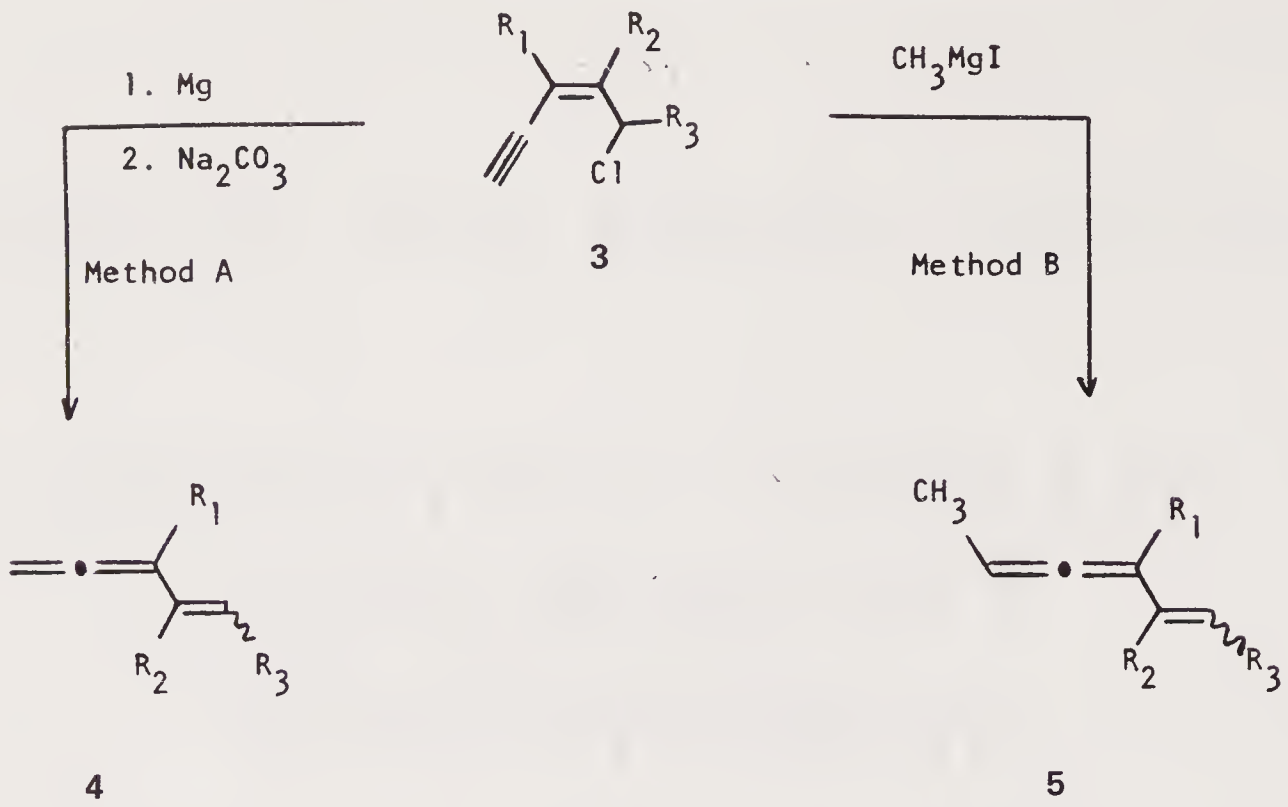
1,2,4-Pentatriene (**2**), the smallest molecule that contains a cumulenic and conjugated vinyl functionality, was first prepared in 70% yield by treating *trans*-5-chloro-3-penten-1-yne (**1**) with zinc–copper couple in butanol[3] (equation 1). This ene–allene is distillable but decomposes slowly at room temperature. It can, however, be stored at −40°C for several months.



(1)

1 **2**

A more general approach for the preparation of substituted vinylic allene hydrocarbons is illustrated in Scheme 1. Two methods are shown, each proceeding from a common starting material (**3**).[4,5,6] When chloropentenynes **3** are allowed to react with magnesium in ether at 0°C, the corresponding terminal ene–allenes **4** are



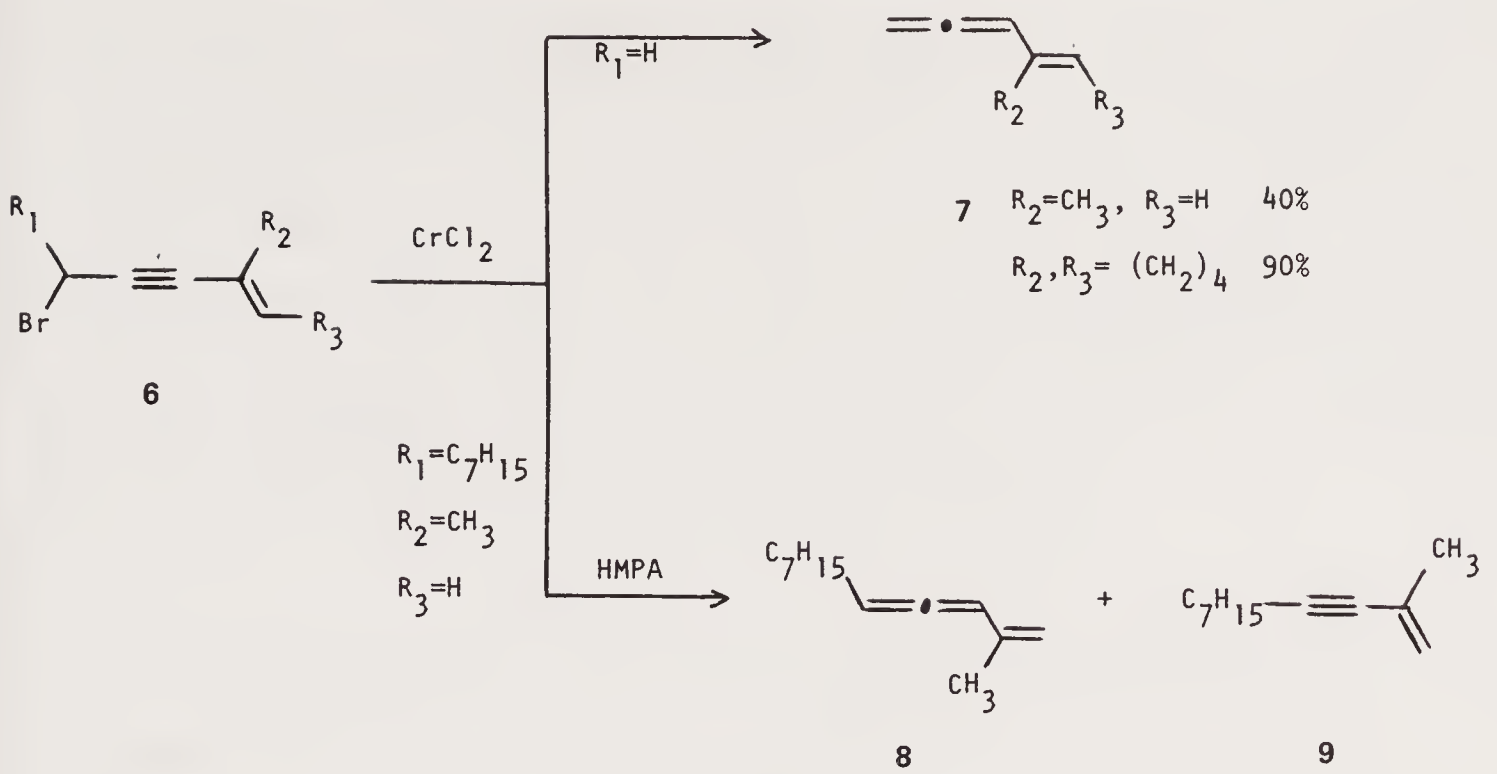
Scheme 1

obtained in moderate yields (Table 4.1). Internal vinylallenes **5** can be generated by the treatment of **3** with methylmagnesium iodide in refluxing ether. This conversion requires 3–4 hours for completion and gives 2,3,5-trienes **5** uncontaminated with enynes. This reaction, however, lacks generality with respect to the organomagnesium halide. Grignard reagents other than methylmagnesium iodide do not produce conjugated ene–allenes.

Bromoenynes of type **6** are readily converted to allenes **7** or **8** (Scheme 2) by treatment with two equivalents of Hiyama's reagent [prepared *in situ* from the reduction of chromium(III) chloride with lithium aluminum hydride]. Primary bromides only produce allenes **7**, whereas secondary bromides provide allene **8** and its isomeric acetylene **9**. The addition of HMPA to the reaction significantly increases the overall yield as well as the ratio of allene formed[7] (see tabular list accompanying Scheme 2).

Table 4.1. Preparation of Allenes 4 or 5 (Scheme 1)[4,5,6]

R_1	R_2	R_3	Allene Type	Method	Yield (%)
H	H	H	4	A	31
H	H	CH_3	4	A	40
CH_3	H	H	4	A	47
CH_3	CH_3	H	4	A	55
H	H	H	5	B	22
H	H	CH_3	5	B	50
CH_3	H	H	5	B	52
CH_3	CH_3	H	5	B	75
CH_3	CH_3	CH_3	5	B	78
$-(CH_2)_4-$		CH_3	5	B	48
CH_3	$-(CH_2)_4-$		5	B	55



Scheme 2

HMPA (ml)[a]	% **8**	% **9**	Overall Yield (%)
0	76	24	85
0.5	80	20	95
1.0	90	10	95
2.0	>95	<5	97

[a]1 ml HMPA = 6.0×10^{-3} mole (reaction at 10^{-3} mole)

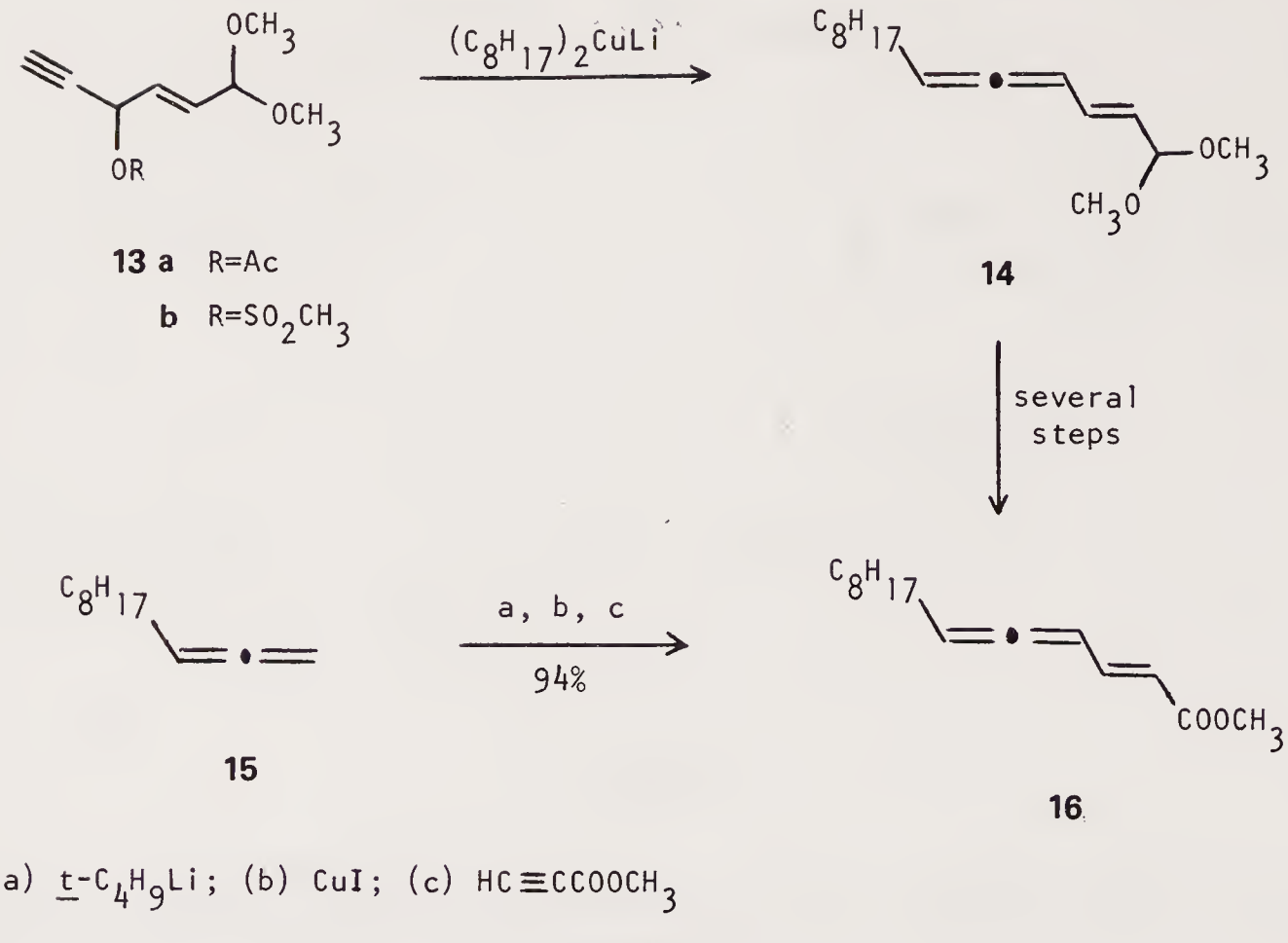
Vinyl allenes are also accessible from an S_N2' reaction of organocuprates with suitably functionalized propargyl derivatives. Treatment of 3-acetyl-1-penten-4-yne (**10**) with a lithium dialkylcuprate in ether affords a mixture of ene–allene **11** and conjugated eneyne **12** in moderate yield[10] (equation 2).

(2)

10 **11** **12**

R	% **11**	% **12**	Overall Yield (%)
CH_3	94	6	42
C_4H_9	80	20	60
C_8H_{17}	90	10	52

This methodology has been used successfully in the synthesis of methyl (E)-2,4,5-tetradecatrienoate (**16**), the sex pheromone produced by the male dried bean beetle, *Acanthoselides obtectus*. The key intermediate **14** (Scheme 3) is obtained in 25% yield from the reaction of acetal **13a** with lithium dioctylcuprate.[10] Alternately, the



13 a R=Ac
b R=SO_2CH_3

14

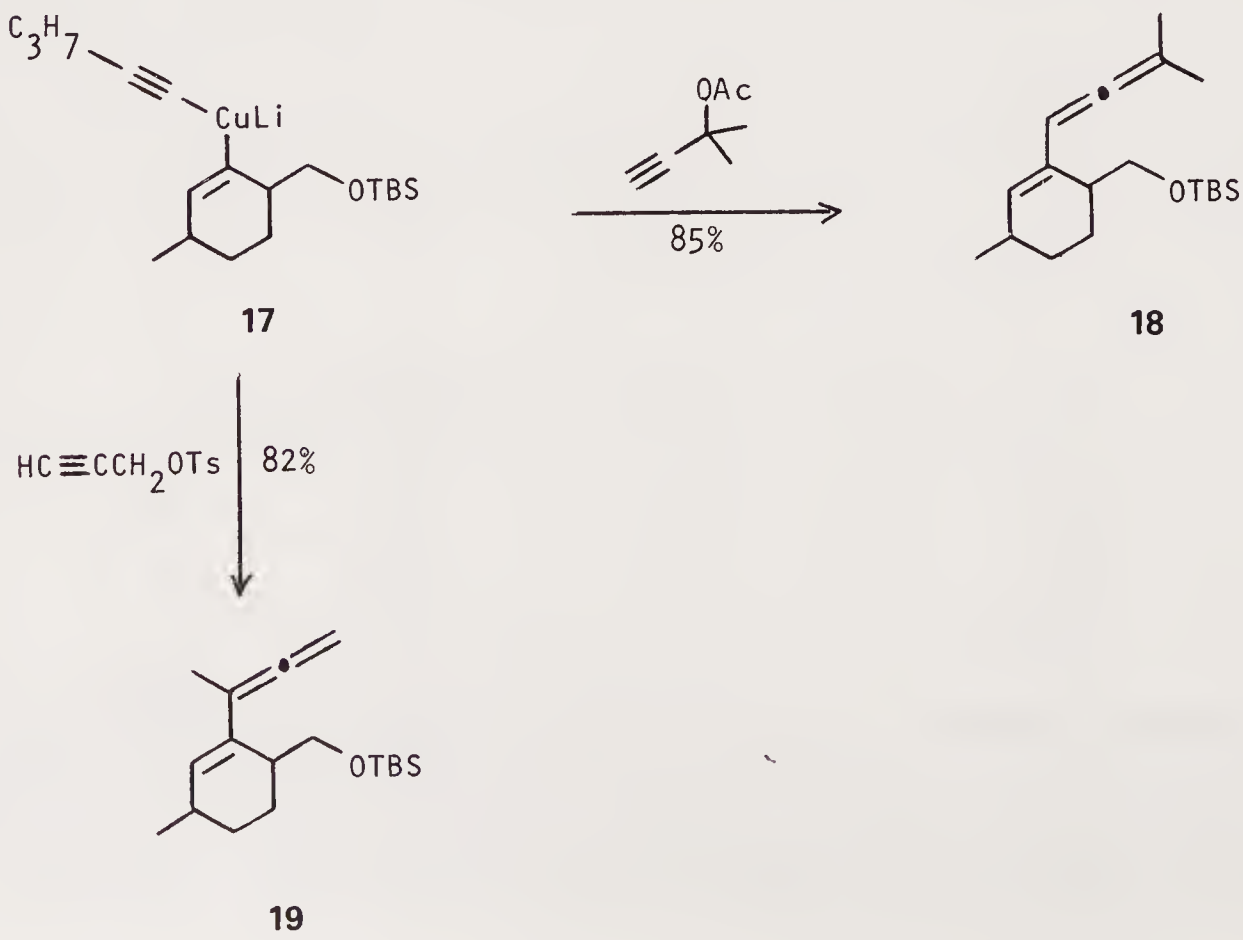
15

16

Scheme 3

reaction of methanesulfonate **13b** with the heterocuprate $[C_8H_{17}CuBr]MgBr \cdot LiBr$ gives **14** in 90% yield (contaminated to the extent of 10% with its isomeric acetylene).[11] The acetal group of **14** can then be elaborated to the methyl ester **16** by hydrolysis followed by oxidation of the resulting aldehyde with manganese dioxide.

A particularly elegant approach to **16** has been devised by Michelot and Linstrumelle.[12] 1,2-Undecadiene (**15**), when treated with *t*-butyllithium, is regioselectively lithiated at the terminal position. Subsequent addition of cuprous iodide results



17

18

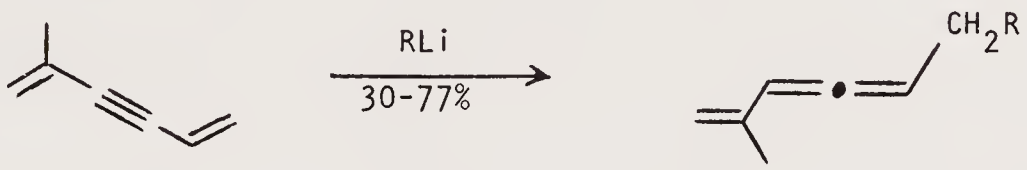
19

(3)

in the formation of a lithium diallenylcuprate, which then undergoes addition with methyl propiolate to produce **16** in excellent yield.

Mixed vinyl cuprates such as **17** react with tertiary acetates or primary and secondary tosylates to give vinyl allenes **18** or **19** in excellent yields[13] (equation 3). Primary acetates fail to react under these conditions. With hindered cuprates, the only product is the β-enyne arising from direct substitution of the tosyl group.[13]

Organolithium reagents (with the exception of methyllithium) add in a 1,4 fashion to conjugated dienynes **20** to give vinyl allenes **21**[14,15] (equation 4). The addition occurs only at the unsubstituted vinyl group and always at its terminus. Aromatic and heterocyclic organolithium reagents behave similarly.[16]

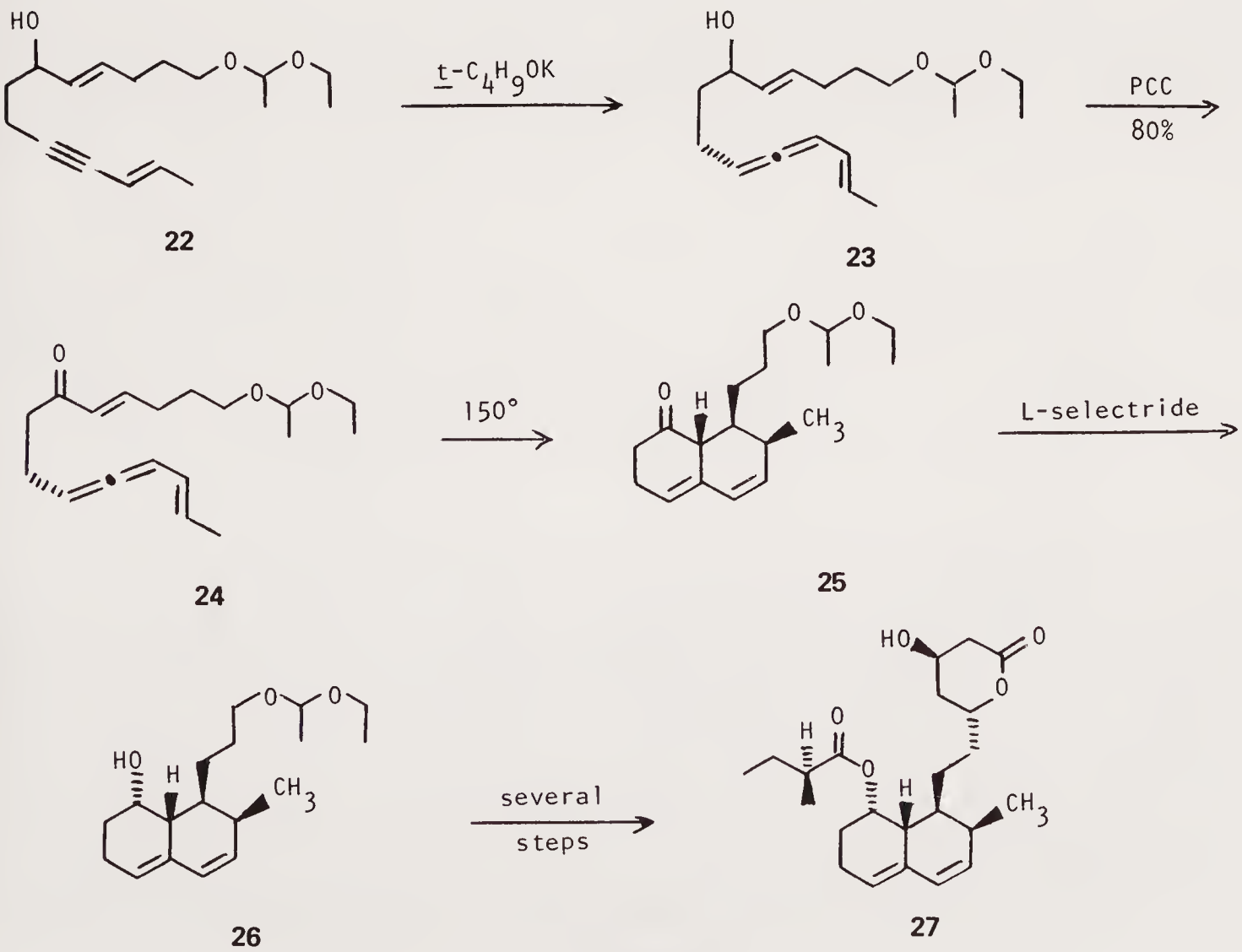


(4)

20 **21**

R= alkyl, aryl, naphthyl, 2-pyridyl

The base-catalyzed prototropic rearrangement of 4-alken-1-ynes provides a useful entrance into the vinyl allene skeleton.[17] Deutsch and Snider[18] ingeniously use this concept to prepare a key intermediate for the preparation of the hexalin portion of compactin (**27**), a fungal metabolite isolated from strains of *Penicillium brevicompactum*[19] and *Penicillium citrinum*[20] (Scheme 4). When **22** is treated with



22 **23** **24** **25** **26** **27**

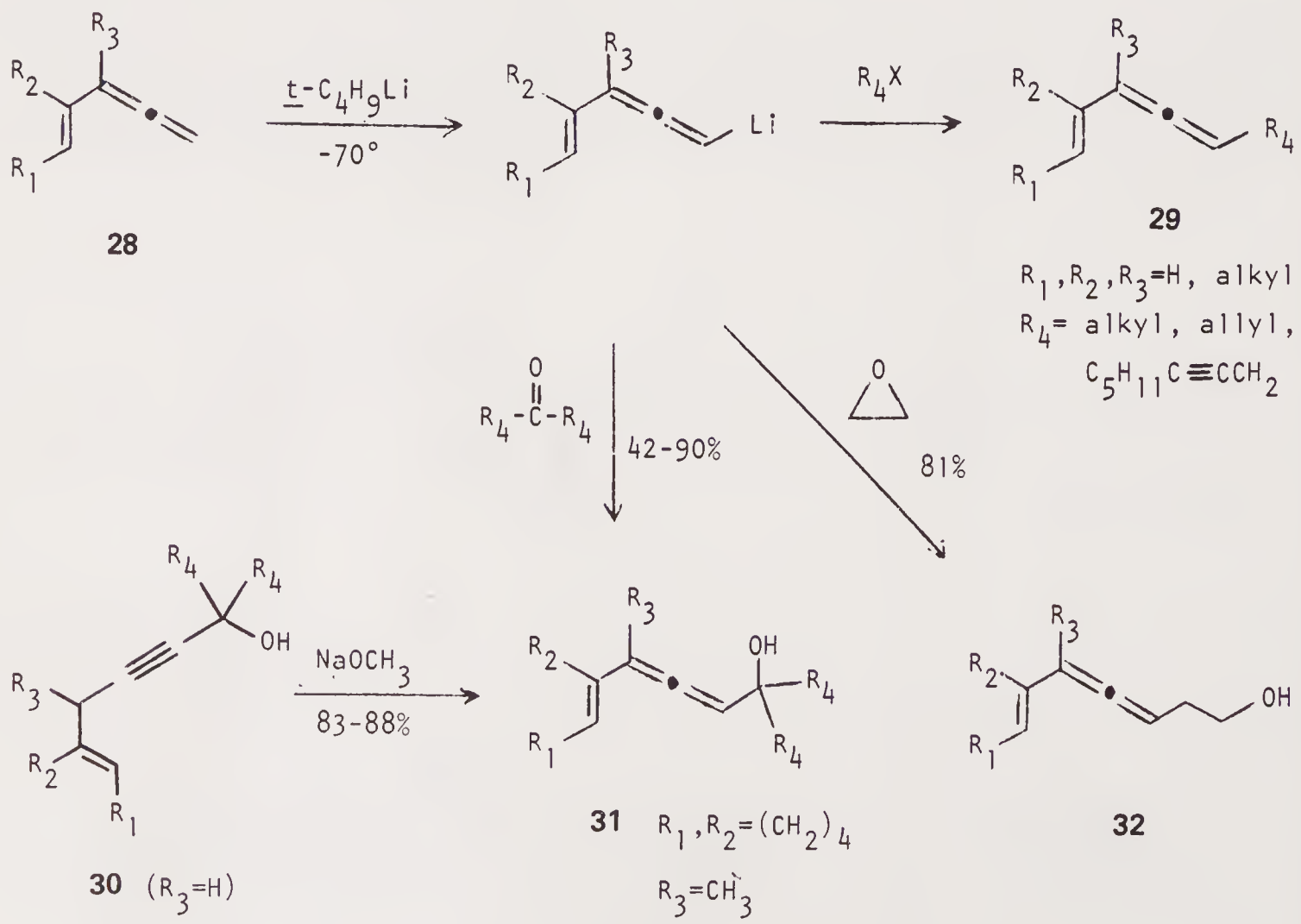
Scheme 4

potassium *t*-butoxide at 40°C for 12 hours, a mixture containing 50% of the desired ene-allene **23** plus conjugated enynes and unreacted starting material is obtained. Oxidation to the enone **24** is effected with pyridinium chlorochromate. An intramolecular Diels–Alder reaction produces the *exo* adduct **25** which contains three of the four contiguous stereocenters present in the natural product. Reduction of the ketone to the alcohol **26** with L-selectride introduces the fourth center.

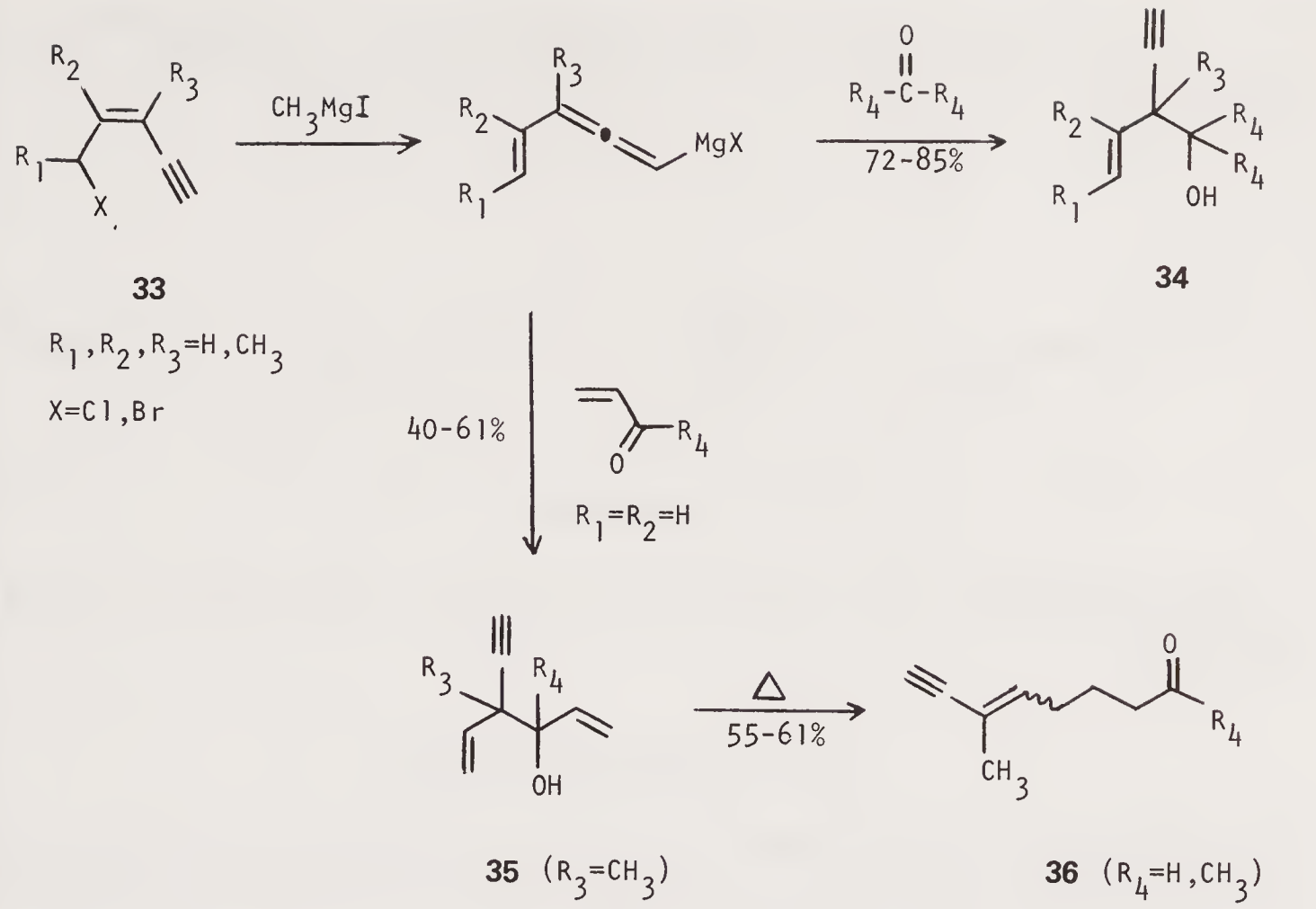
Terminal vinyl allenes **28** can be regioselectively lithiated at the terminal allenic carbon with *t*-butyllithium. Alkylation on the same carbon with alkyl iodides, allyl bromides, or propargyl bromides furnishes internal vinyl allenes **29** generally in 50–80% yield[21] (Scheme 5). Optimum yields are realized utilizing a 1:1 mixture of ether/THF in the presence of an equimolar quantity of HMPA. Lithio vinyl allenes also react with electrophiles such as aldehydes, ketones, or epoxides to give allenic alcohols **31** and **32** in good yields.[22] Alcohols **31** are also accessible from the base-catalyzed isomerization of propargyl alcohols **30**.[23]

Magnesium derivatives of vinyl allenes, prepared from 5-halo-3-en-1-ynes **33**,[5] behave differently in reactions with carbonyl-containing compounds (Scheme 6). Aliphatic aldehydes and ketones produce β-acetylene-β-ethylenic alcohols **34** in good yields.[24] Reactions with α,β-unsaturated carbonyls initially gives alcohols **35**. Refluxing these alcohols in diglyme for 2 hours gives the interesting enyne carbonyls **36** by way of a Cope rearrangement.[25]

As shown in Scheme 5, internal α-hydroxy vinyl allenes are readily accessible by two routes. The hydroxyl functionality, however, can also be incorporated in the vinyl portion of the molecule or on the other terminal carbon of the allene unit.

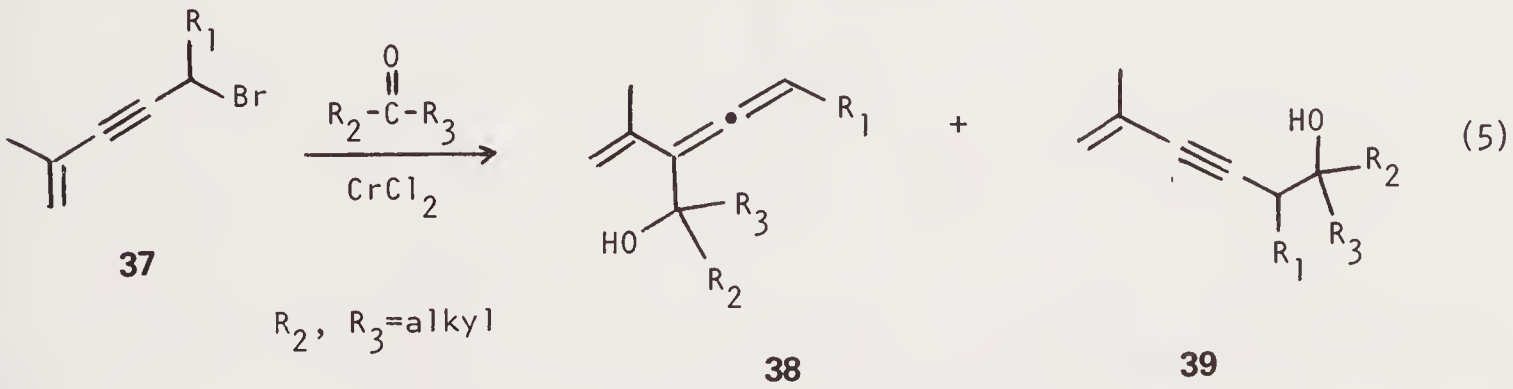


Scheme 5



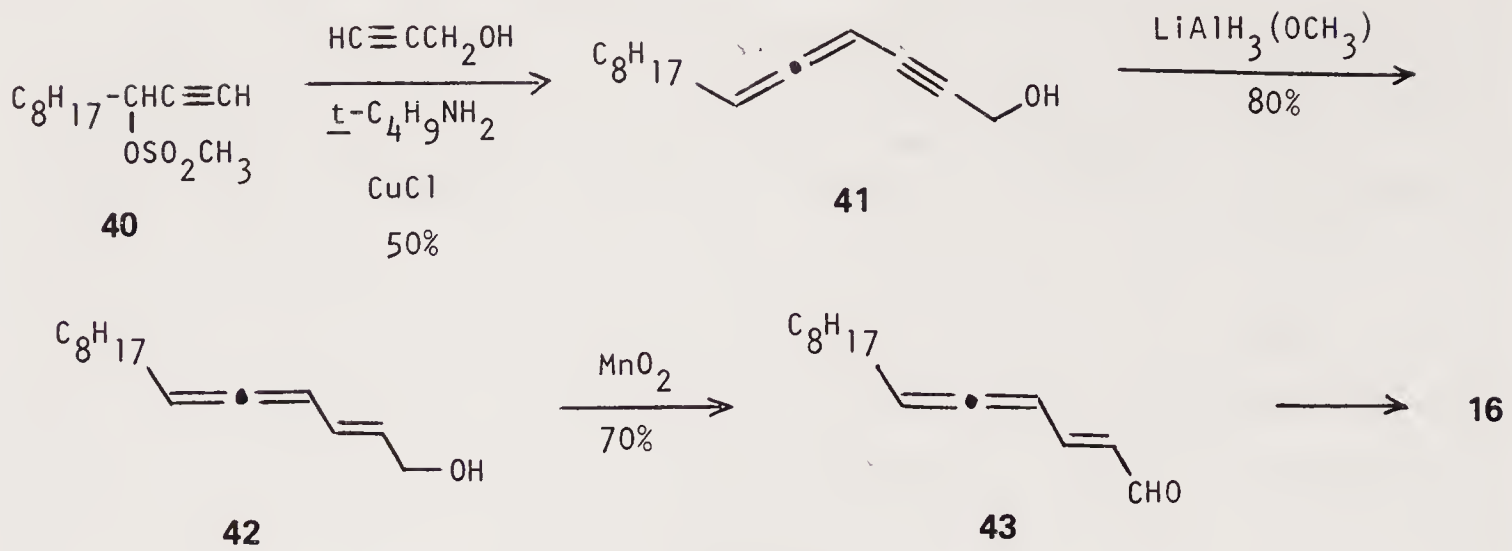
Scheme 6

Primary propargyl bromides **37** (R_1 = H), when condensed with aldehydes or ketones in the presence of Hiyama's reagent, produce only terminal α-hydroxy vinyl allenes **38** in 50–75% yield.[7] Secondary propargyl bromides **37** (R = C_7H_{15}) give mixtures of **38** and **39** (equation 5). The addition of HMPA to the reaction mixture favors the formation of the allene, but the effect is not as pronounced as that for vinyl allene hydrocarbons (see Scheme 2).



(5)

Ene–allenes with an alcohol substituent situated α to the vinyl moiety are easily prepared by the reduction of allenyl propargylic alcohols or acetates with lithium aluminum hydride.[26] The method has been incorporated in a relatively short synthesis of methyl (E)-2,4,5-tetradecatrienoate (**16**) (Scheme 7).[27] The key step in the sequence is the stereospecific reduction of yne–allene **41** with lithium methoxyaluminum hydride to give exclusively the *trans*-alcohol **42**. Manganese dioxide oxidation of **42** furnishes aldehyde **43**, which is the same intermediate produced from the hydrolysis of acetal **14** (Scheme 3). The conversion of **43** to **16** follows Corey's method[28] for the stereospecific oxidation of allylic alcohols to allylic esters.



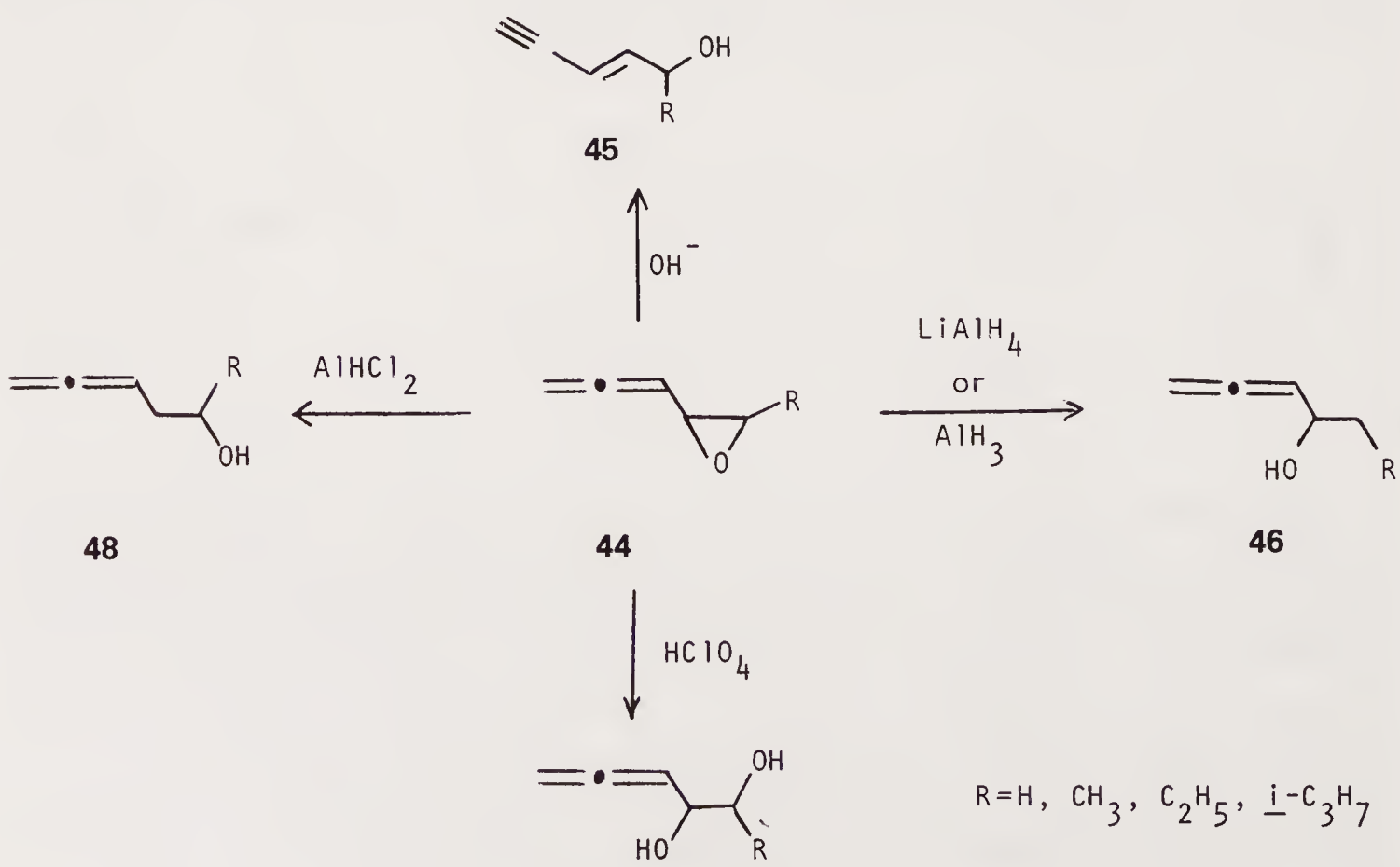
Scheme 7

Other approaches to the synthesis of vinyl allenic hydrocarbons are listed in Table 4.2.

4.1.2. Chemical Reactivity

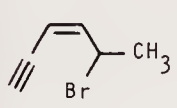
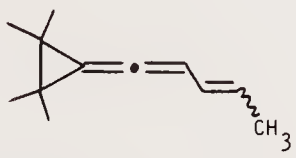
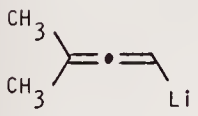
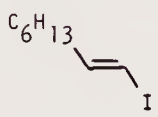
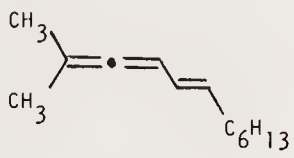
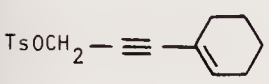
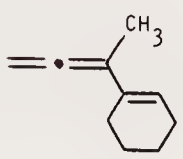
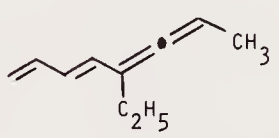
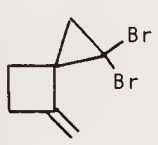
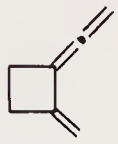
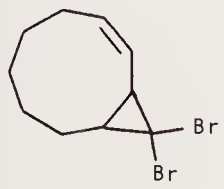
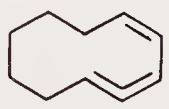
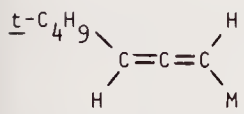
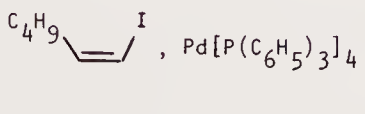
Vinyl allenes can be regiospecifically epoxidized with peracids on the vinyl portion of the molecule (equation 6). The ratio of *cis* and *trans*-epoxides corresponds to the isomer ratio of the corresponding vinyl allene.[36] As shown in Scheme 8, α-allenic epoxides **44** can be readily converted to α- and β-allenic alcohols, **46** and **48**, vicinal allenic diols **47**, and enynols **45**.[37]

(6)



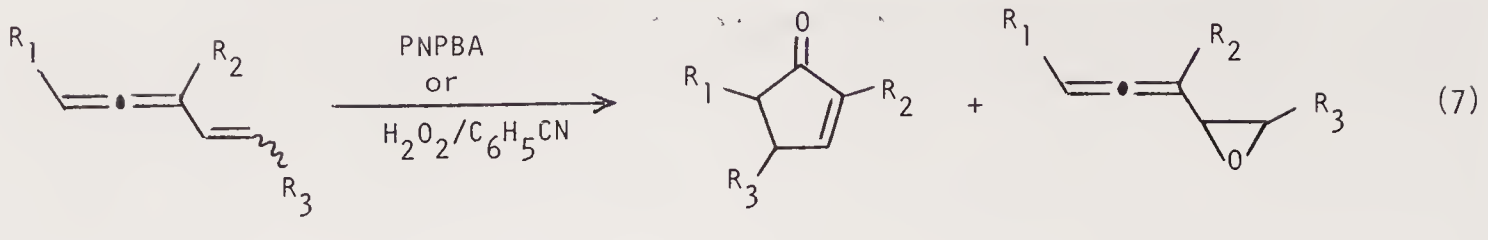
Scheme 8

Table 4.2. Alternate Methods for Preparing Vinyl Allenic Hydrocarbons[a]

Substrate	Reagent (conditions)	Product	Yield,%	reference
$CH_2{=}CHCH_2C{\equiv}CH$	NaOH, CH_3OH (reflux)	$CH_2{=}C{=}CH{-}CH{=}CH_2$	80	29
	 , $\underline{t}$-C_4H_9OK		43	30
	 , $Pd[P(C_6H_5)_3]_4$		80	31
$(C_6H_{13}CH{=}CH)_2CuLi$	$HC{\equiv}CCH_2Br$ (-30°, 2hr)		10	32
	CH_3MgCl, CuBr (-30°)		80	8
	C_2H_5MgBr, CuBr (ether, THF)		73	9
	CH_3Li		-	33
	CH_3Li		94	34
 M= MgCl, Cu, ZnCl			98	35

[a]Only one example for each method is given. Additional examples are provided in the references cited.

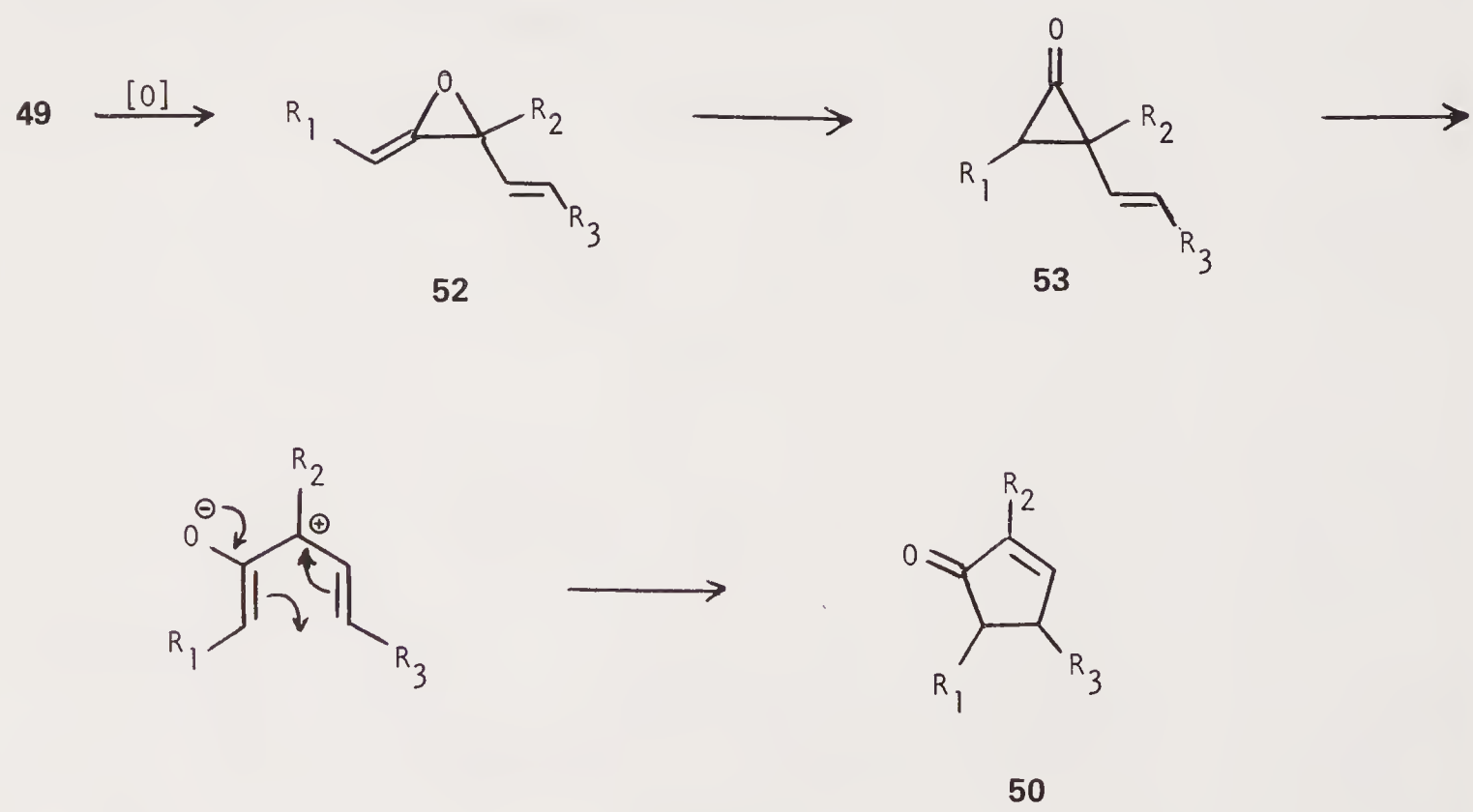
If the allene portion of the vinyl allene bears an alkyl substituent on either terminal carbon, peracid oxidation leads to the preferential formation of conjugated cyclopentenones **50** (equation 7).[38–41] If an optically active allene is used, the chirality is transferred to the resulting cyclopentenone presumably by means of a $({}_{\pi}2_s + {}_{\sigma}2_a + {}_{\pi}2_a)$ process.[42]



49 50 51 (7)

R_1	R_2	R_3	% **50**	% **51**	Overall Yield (%)	Reference
H	H	CH_3	100	0	60	38
H	H	C_3H_7	100	0	60	38
C_3H_7	H	H	95	5	55	38
$(CH_3)_3Si$	CH_3	H	100	0	60	41

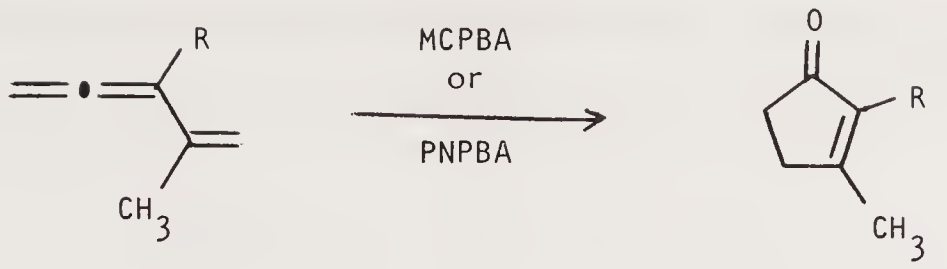
Mechanistically, the formation of cyclopentenones can be explained by the initial formation of an allene oxide **52** which subsequently isomerizes to a vinyl cyclopropanone **53**. The illustrated electrocyclic transformation then leads to **50** Scheme 9).[38]



Scheme 9

Compounds in the jasmone series are particularly suited for synthesis using this vinyl allene → cyclopentenone methodology. Dihydrojasmone (**55a**) and dehydrojasmone (**55b**) are prepared in good yields by such a transformation.

Bicyclic enones **58** and **60**, key intermediates for the synthesis of macrocyclic ketones such as exaltone and muscone, are readily obtained by oxidation of ene–allenes **57** and **59** with *m*-chloroperbenzoic acid[44] (Scheme 10).



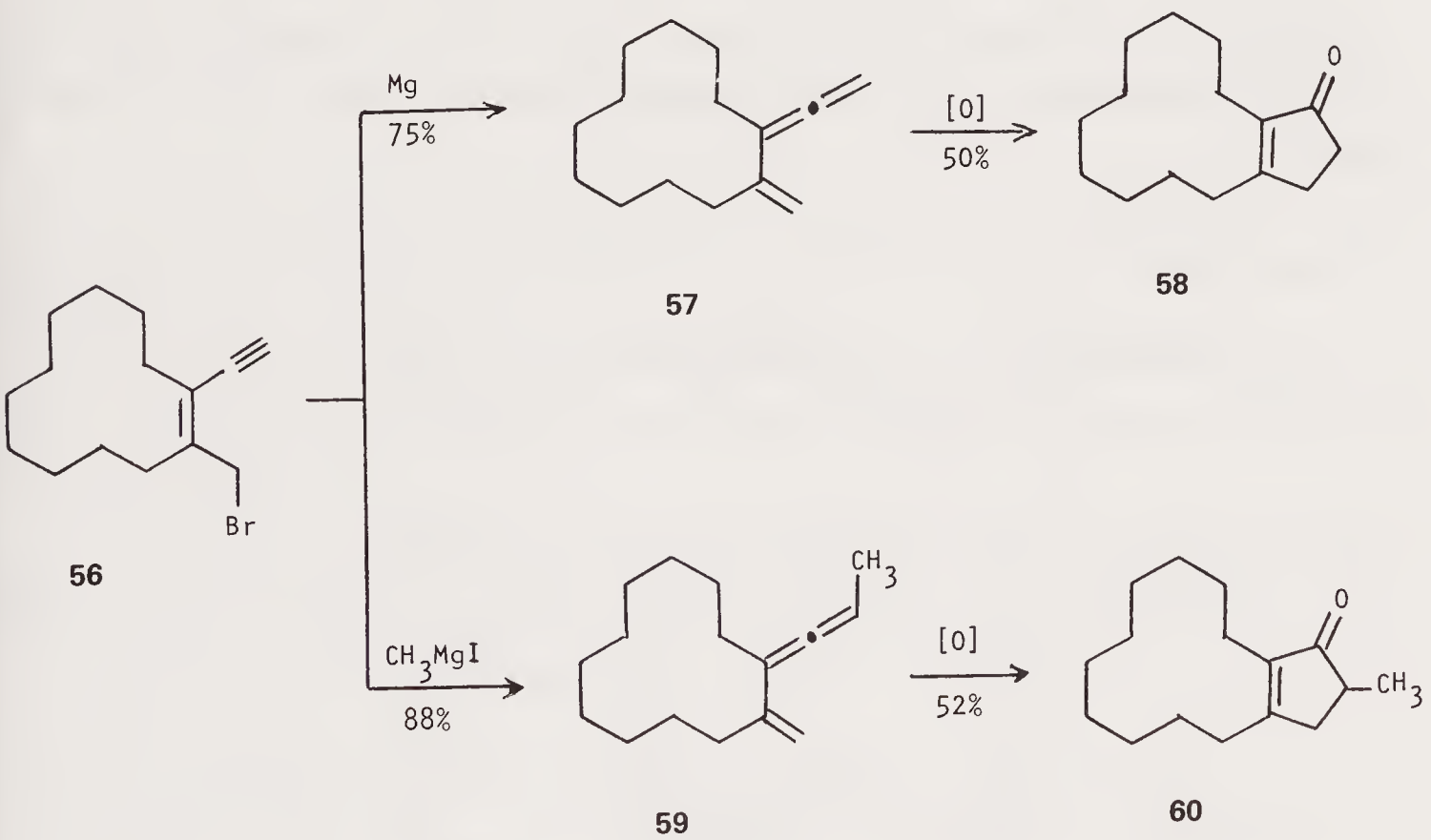
(8)

54

55a R= $CH_2CH{=}CHC_2H_5$ (65%)

55b R= $CH_2C{\equiv}CC_2H_5$

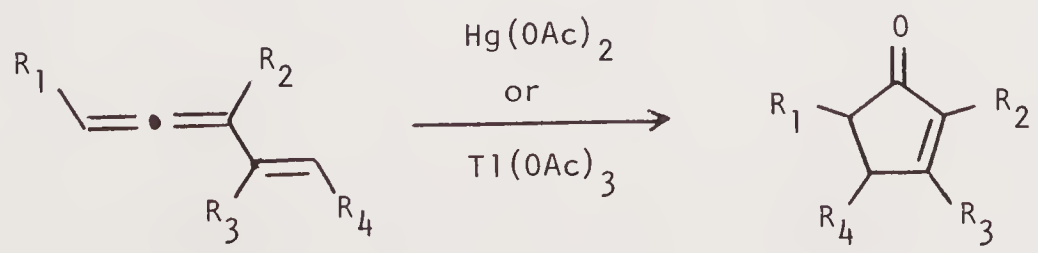
An interesting alternative for the preparation of cyclopentenones is the acetoxymercuration[45] or acetoxythallation,[8,41] of vinyl allenes (equation 9). These reactions proceed rapidly and afford products that are easily purified. The demetallation step is particularly favorable and is spontaneous in acetic acid. Table 4.3 illustrates the generality of this reaction in the synthesis of jasmone analogs. Note that the third entry is dihydrojasmone (yield, 54%).



56 **57** **58** **59** **60**

Scheme 10

A third method for transforming vinyl allenes into cyclopentenones involves photoepoxidation with molecular oxygen in the presence of a sensitizer (biacetyl).[45] The reaction generally produces cyclopentenones in approximately 50% yield (dihydrojasmone, 35%); however, the reaction fails with α-vinyl allenic alcohols or ethers.



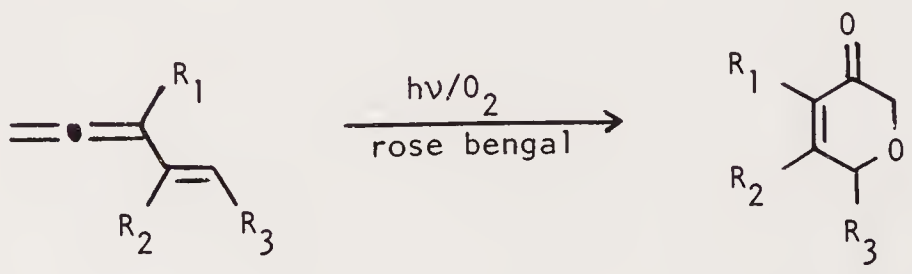
(9)

Table 4.3. Cyclopentenones by Way of Acetoxymercuration or Acetoxythallation of Vinyl Allenes[a] (Equation 9)

				Yield (%)	
R_1	R_2	R_3	R_4	$Hg(OAc)_2$	$Tl(OAc)_3$
H	C_5H_{11}	H	H	70	60
CH_3	C_5H_{11}	H	H	50	68
H	C_5H_{11}	CH_3	H	54	45
H	C_5H_{11}	H	CH_3	78	—
CH_3	C_5H_{11}	CH_3	H	79	61
H	H	$-(CH_2)_4-$		—	36
H	CH_3	$-(CH_2)_4-$		75	60
CH_3	CH_3	$-(CH_2)_4-$		49	44

[a]Source: Ref. 8.

Reactions of vinyl allenes with singlet oxygen take a different course. Dye-sensitized photooxidation leads to Δ-4-tetrahydropyran-3-ones (**61**) in moderate yields.[46]

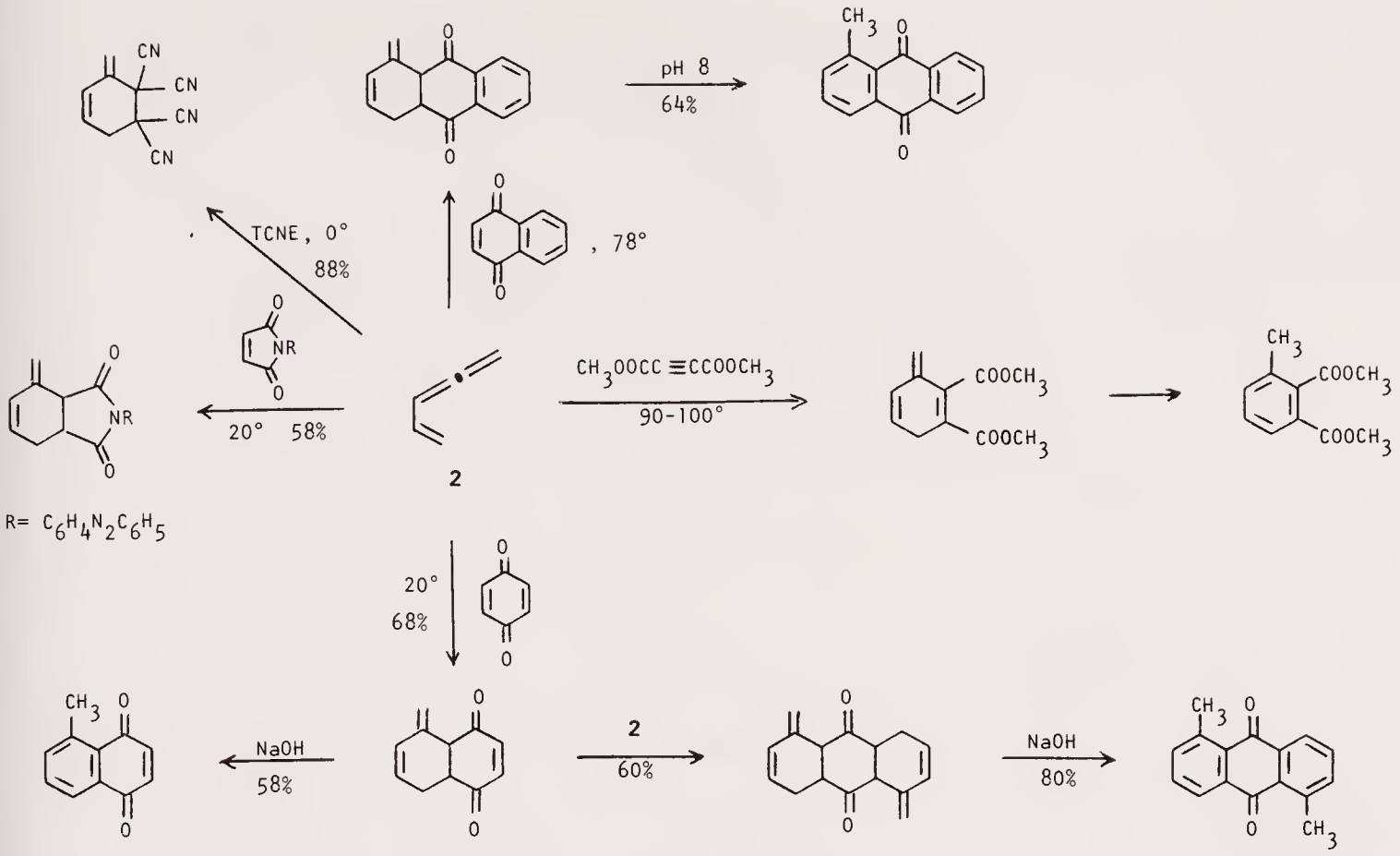


(10)

61

R_1	R_2	R_3	Yield (%)
C_4H_9	H	H	55
C_5H_{11}	CH_3	H	48
C_2H_5	$-(CH_2)_4-$		65

An interesting property of vinyl allenes is their ability to participate in Diels–Alder type [4 + 2] cycloadditions as the diene component of the reaction. The mechanism of the reaction requires that the allene must adopt a *cisoid* conformation prior to the interaction with the dienophile.[47] Moreover, if the R substituent is not

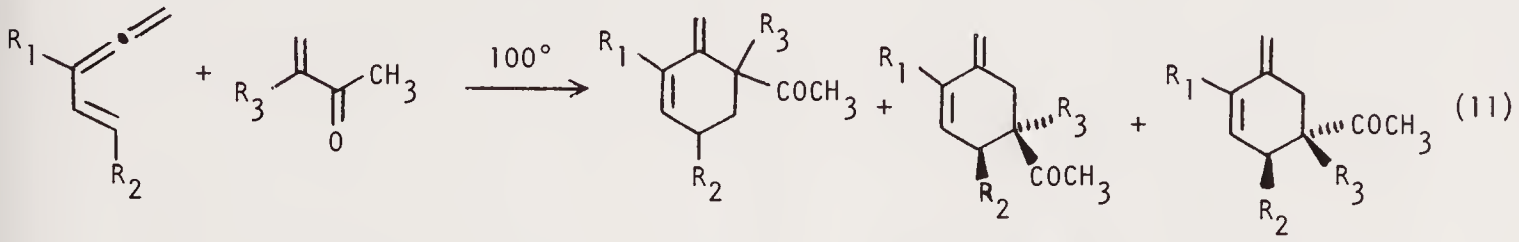


Scheme 11

hydrogen, the vinyl geometry must be *trans* to alleviate steric compression in the *cisoid* conformation. The stereochemistry associated with the products suggests a concerted process.

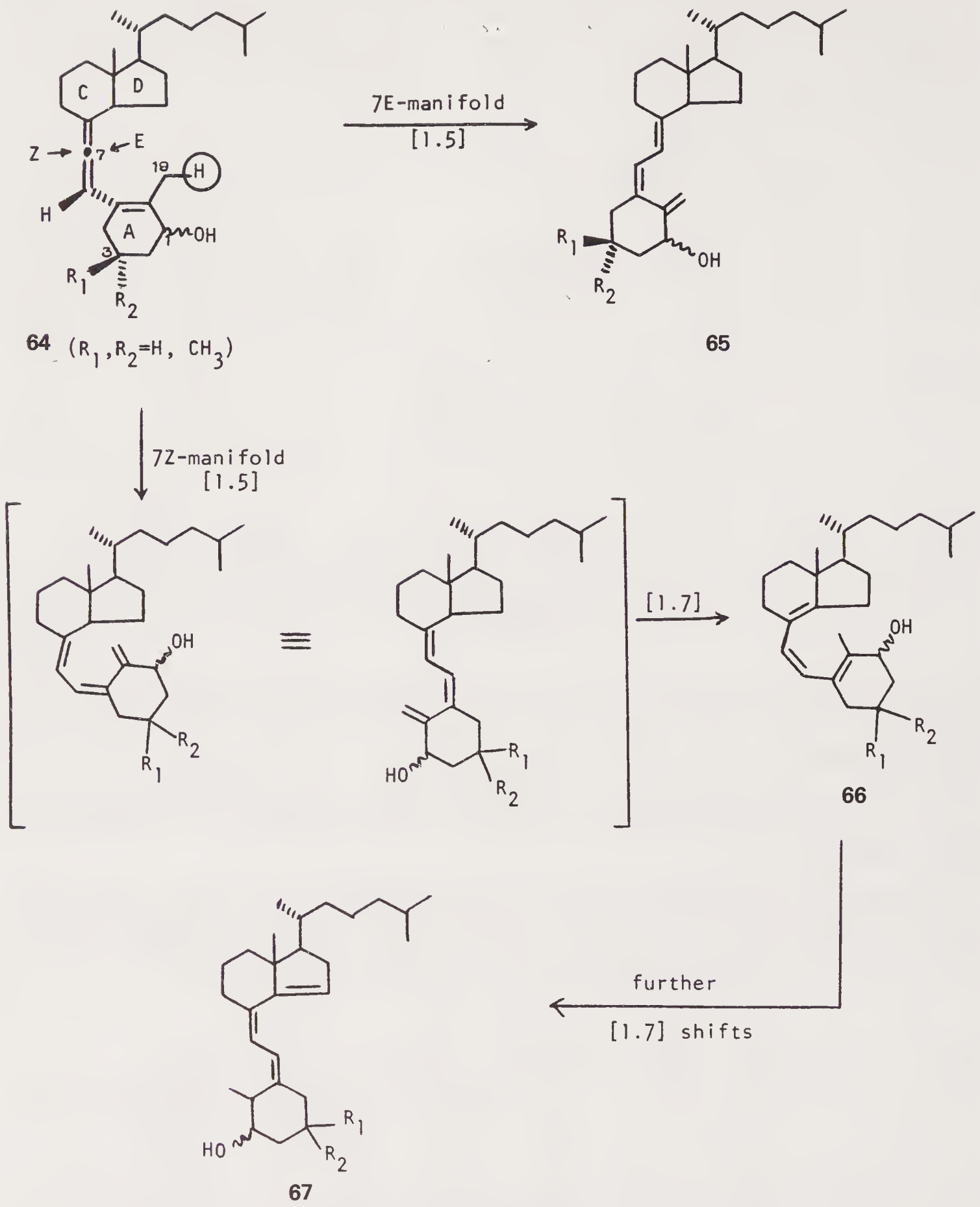
When the parent compound **2** is allowed to react with various dienophiles, a variety of methylene cyclohexenes are obtained (Scheme 11), some of which are readily aromatized.[3]

Nonsymmetrical dienophiles such as α,β-unsaturated ketones react with vinyl allenes to produce mixtures of regio- and stereoisomeric adducts, the ratio of which depends on the substitution pattern on the ene–allene (equation 11).[47,48]



(11)

R_1	R_2	R_3	Total Yield (%)	% **62**	% **63**	% **63a**	% **63b**
H	H	H	60	28	72	—	—
H	CH_3	H	75	20	80	—	—
H	H	CH_3	40	21	79	—	—
CH_3	H	H	50	0	100	75	25
CH_3	CH_3	H	75	0	100	80	20
CH_3	H	CH_3	35	0	100	100	0

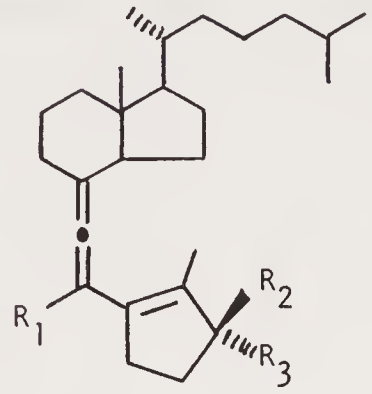


Scheme 12

Vinyl allenes are also capable of undergoing thermal [1.5]sigmatropic hydrogen shifts to 1,3,5-triene systems.[49] This is elegantly applied to the efficient construction of the 1,3,5-hexatriene moiety of the 1-hydroxy vitamin D system **65**.[50–56] The thermal rearrangement of vinyl allene **64** involves a suprafacial [1.5]sigmatropic hydrogen shift from C19 → C7 by way of either of two competing pathways (Scheme 12).[53,54] One path leads to the desired 7E manifold **65**, whereas the other path leads to the 7Z manifold in which the primary [1.5] product is not observed because of subsequent antarafacial [1.7]sigmatropic shifts.[54] The major influence in migration

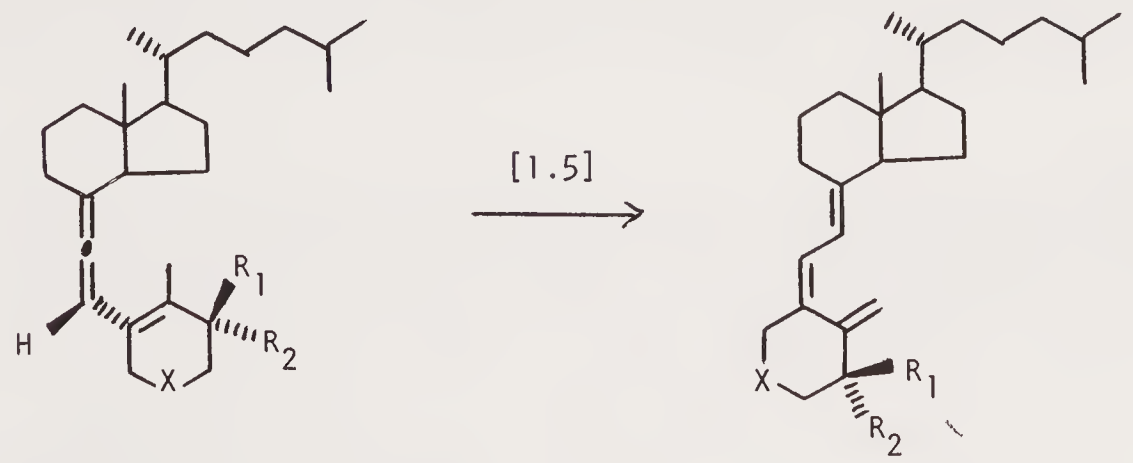
preference is attributed to the relative orientation of the C1 hydroxyl group in the A-ring and the trajectory of the migrating C19 hydrogen.[51,54] Substitution at C3 of the A-ring by a methyl[55] or *gem*-dimethyl[52] has no significant effect on this migration.

Changing the distance between migrating hydrogen termini, C19 and C7, for the [1.5]sigmatropic shift as in the A-nor analog **68**, results in a failure to arrange under the optimal conditions defined for the six-membered cases.[55]



68

Replacing the C3 carbon of the A-ring with a sulfur atom results in a significant change in the [1.5]sigmatropic migration. Normally the β-hydroxy allene **69a** leads to the 7E vitamin **70a**, but in the case of the thia analog **69b**, it is the epimeric 1α-hydroxy allene that leads to 7E product **70b** (equation 12). This presumably is due to the additional π-system perturbation by the allylic sulfur.[56]



69a X=CH_2 (R_1=H, R_2=OH)

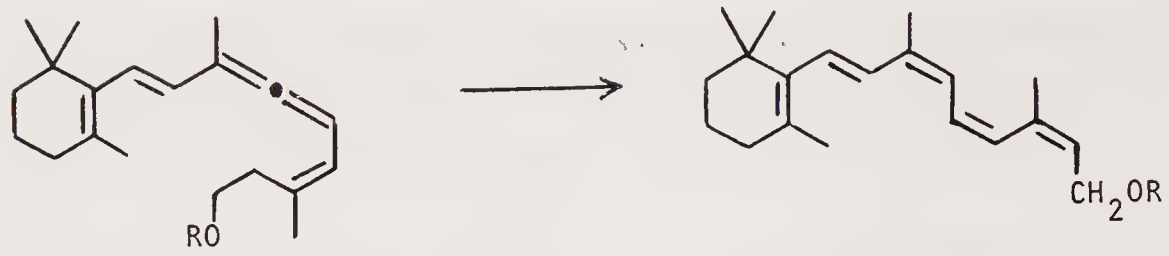
69b X=S (R_1=OH, R_2=H)

70a X=CH_2 (R_1=H, R_2=OH)

70b X=S (R_1=OH, R_2=H)

(12)

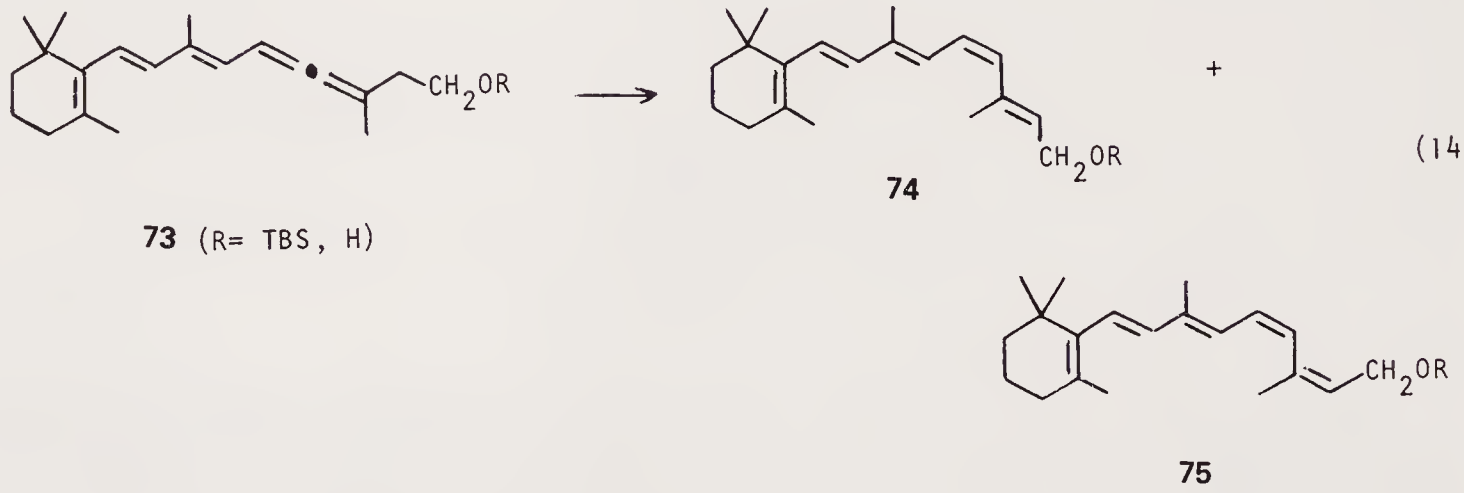
Introduction of the allene moiety into higher-order polyenes as found in the vitamin A series provides further application of the [1.5]sigmatropic rearrangement of vinyl allenes to the preparation of retinoids whose stereochemistry is difficult to obtain by standard synthetic reactions. Thus thermal isomerization of **71** results in a low yield of the highly hindered 9-*cis* , 11-*cis* , 13-*cis*-retinol **72**[57] (equation 13). Similarly, **73** rearranges to a mixture of 11-*cis*-retinol **74** and 11,13-*dicis*-retinol **75** along with products derived from the competitive Z-manifold migration[58] (equation 14). Although yields are generally low and the products are thermally unstable,



(13)

71 (R= TBS, H) **72**

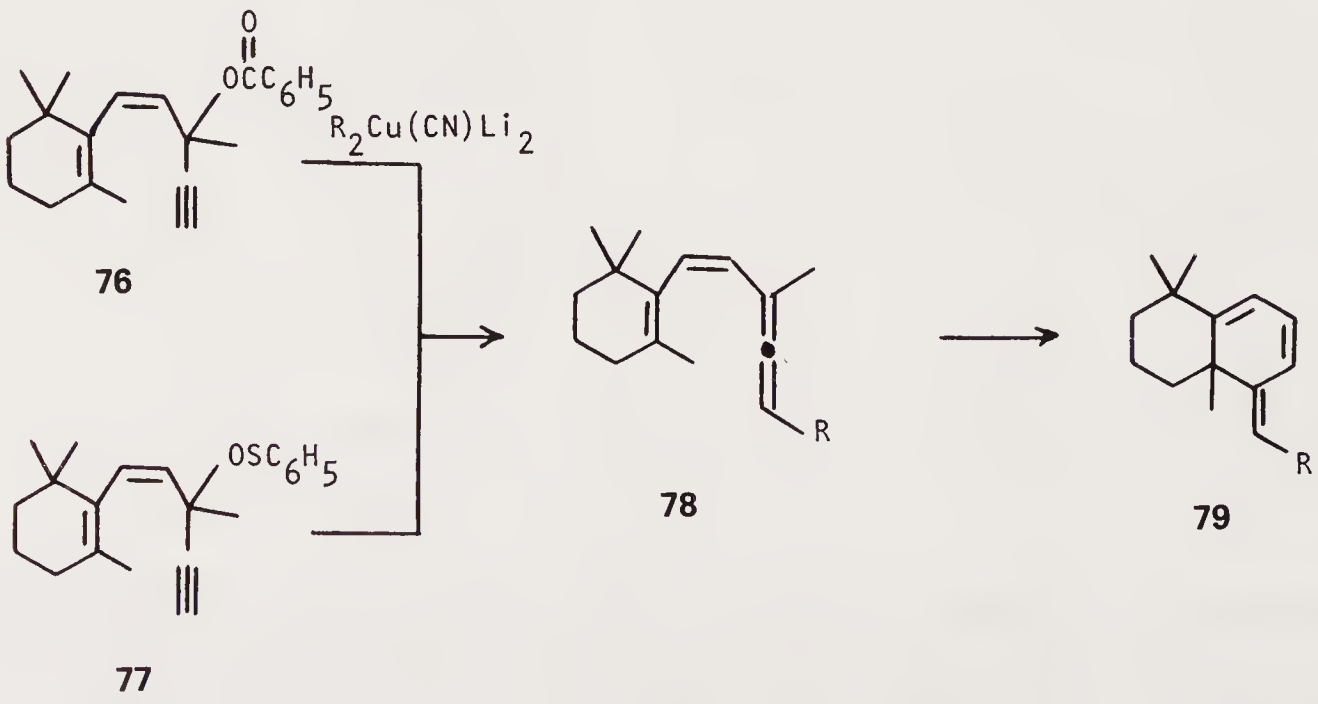
this method still allows rapid access to certain hindered 11-*cis*-retinoids in sufficient quantity for further studies.[59]



(14)

73 (R= TBS, H) **74** **75**

The isomeric *cis*-diene-allene **78** does not undergo the anticipated antarafacial [1.7]sigmatropic shift. In fact, **78** is nonisolable and undergoes spontaneous six-electron electrocyclization to the drimatriene **79.** The conversion from the propargyloxy derivatives **76** and **77** is extremely efficient and affords **79** in good yield.[60]



(15)

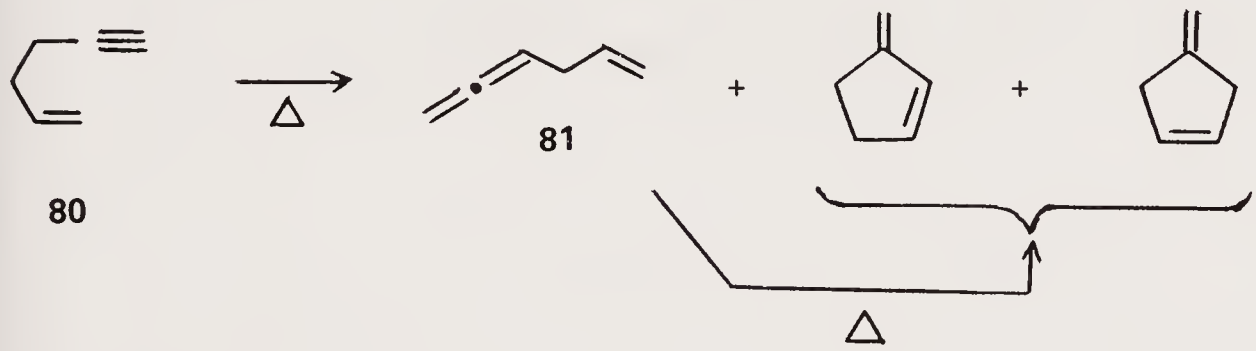
76 **77** **78** **79**

R	Yield (%)
C_4H_9	77
t-C_4H_9	79
C_6H_5	60
SOC_6H_5	80

4.2. HIGHER VINYLOGOUS ALLENES: ALLYLIC ALLENES (1,2,5-TRIENES)

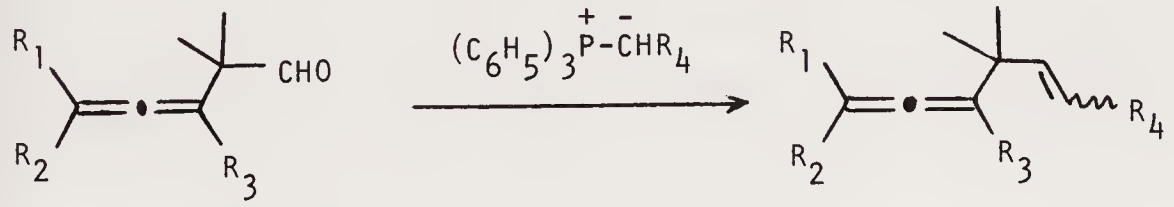
4.2.1. Hydrocarbons

The inherent reactivity of this class of ene–allenes affects their syntheses, diversity, and reactivity. The condensation of allenyl magnesium bromide with allylic halides gives a mixture from which 1,2,5-trienes can be chemically separated.[61–63] However, this reaction has not been extended to more general cases. The thermal Cope-type rearrangement of 1-alken-5-yne **80** affords 1,2,5-hexatriene (**81**) which, under the reaction conditions, cyclize further to 3- and 4-methylene cyclopentenes.[64]



(16)

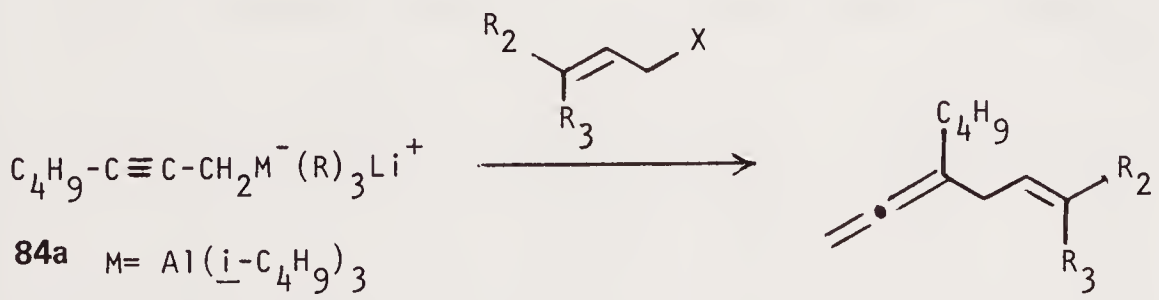
The Wittig reaction of β-allenic aldehydes **82** (equation 17) provides one of the best ways to synthesize a variety of 1,2,5-trienes in approximately 50% yield.[65,66]



82 **83**

(17)

Triorganoalanates **84a** or triorganoborates **84b** exhibit enhanced reactivity toward electrophiles and can be used to synthesize allylic allenes **85** in good yields contaminated with only a very minor amount of acetylene side products[67] (equation 18).



84a M= Al(i-C_4H_9)$_3$

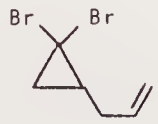
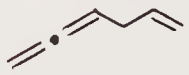
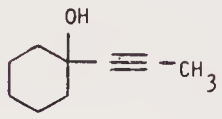
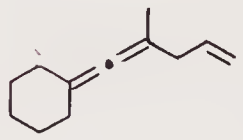
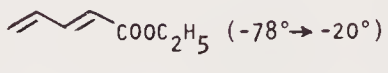
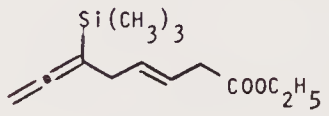
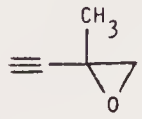
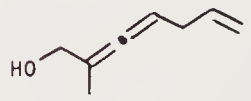
84b M= B(s-C_4H_9)$_3$

85

(18)

M	R_2	R_3	X	Yield (%)
Al	H	H	Br	78
B	H	H	Br	74
Al	CH_3	CH_3	Br	84
B	CH_3	CH_3	Br	84
Al	C_4H_9	H	Cl	76

Table 4.4. Alternate Preparations of Allylic Allenes

Substrate	Reagent (conditions)	Product	Yield,%	reference
	CH_3Li (-78°)		46	68
	$CH_2{=}CHCH_2MgBr$ (110°)		80	69
$(CH_3)_3Si\text{-}C{\equiv}C\text{-}CH_2Cu$	 (-78°→ -20°)		80	70
	$CH_2{=}CHCH_2MgBr/CuBr$		80	82

Additional examples of allylic allene preparations are found in Table 4.4.

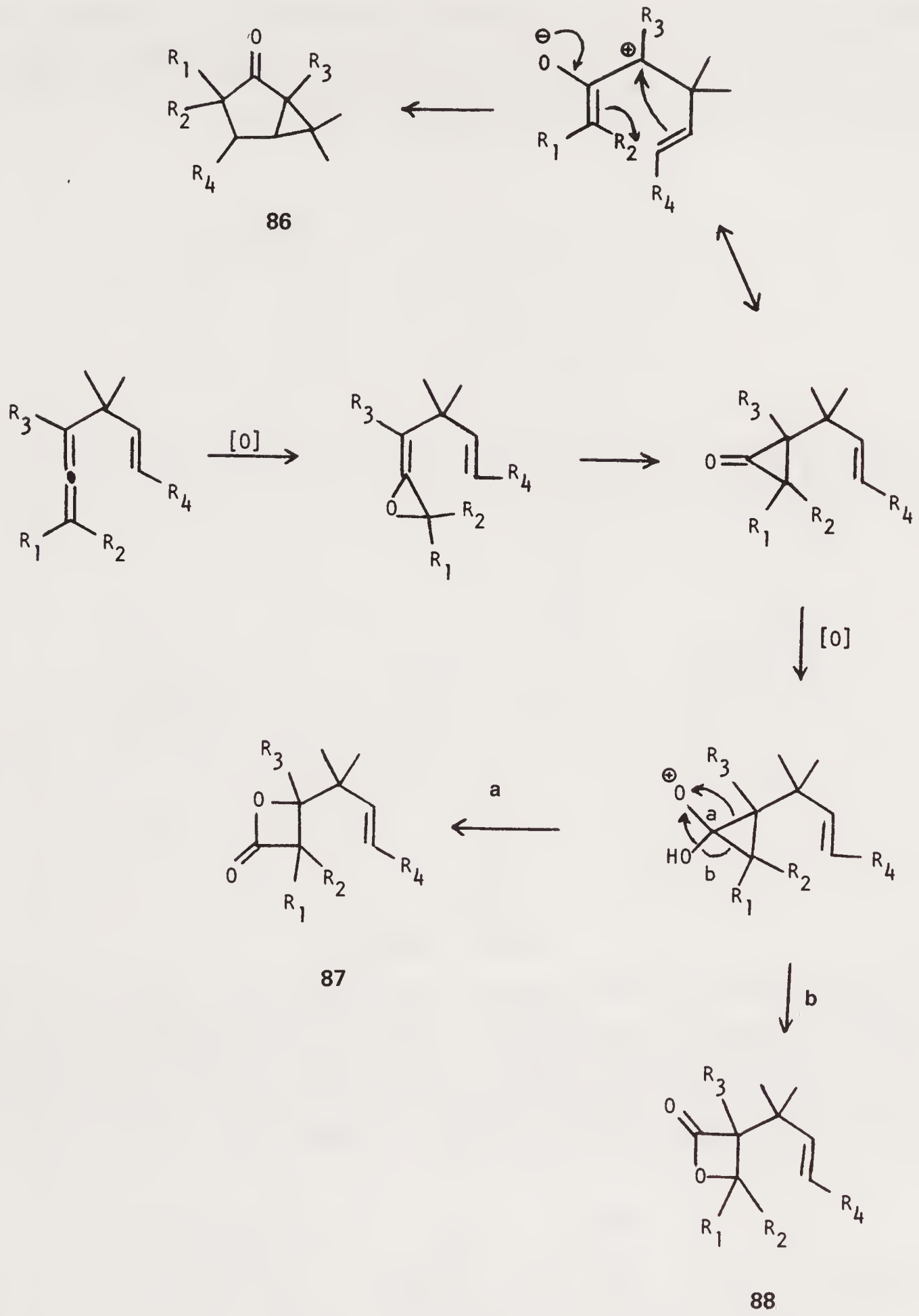
Allylic allenes, when oxidized with *p*-nitroperbenzoic acid, produce bicyclo[3.1.0]hexane-2-ones (**86**) or propiolactones **87** (Scheme 13), the ratio of which depends on the substitution of the ene–allene and the solvent used (Table 4.5).[71–73] Methylene chloride tends to favor **87**, whereas methanol gives almost exclusively **86**.

The initial step in the transformation is the formation of an allene oxide which then rearranges to the isomeric cyclopropanone. Subsequent cyclization by way of an electrocyclic process, as illustrated in Scheme 13, provides the observed bicyclohexanones **86**. If the cyclopropanone is further oxidized by a Baeyer–Villiger

Table 4.5. Distribution of Cyclic Products for the Peracid Oxidation of Allylic Allenes (Scheme 13)[a]

R_1	R_2	R_3	R_4	Solvent	% **86**	% **87**	% **88**
CH_3	H	H	H	CH_2Cl_2	0	35	0
C_3H_7	H	H	H	CH_2Cl_2	0	80	0
CH_3	CH_3	H	H	CH_2Cl_2	0	80	0
CH_3	CH_3	H	H	CH_3OH	100	0	0
CH_3	C_2H_5	H	H	CH_2Cl_2	50	50	0
CH_3	C_2H_5	H	H	CH_3OH	90	10	0
CH_3	C_2H_5	H	CH_3	CH_2Cl_2	35	60	0
—$(CH_2)_5$—		H	H	CH_2Cl_2	25	40	0
CH_3	H	C_2H_5	H	CH_2Cl_2	0	0	50

[a]Source: Refs. 71–73.

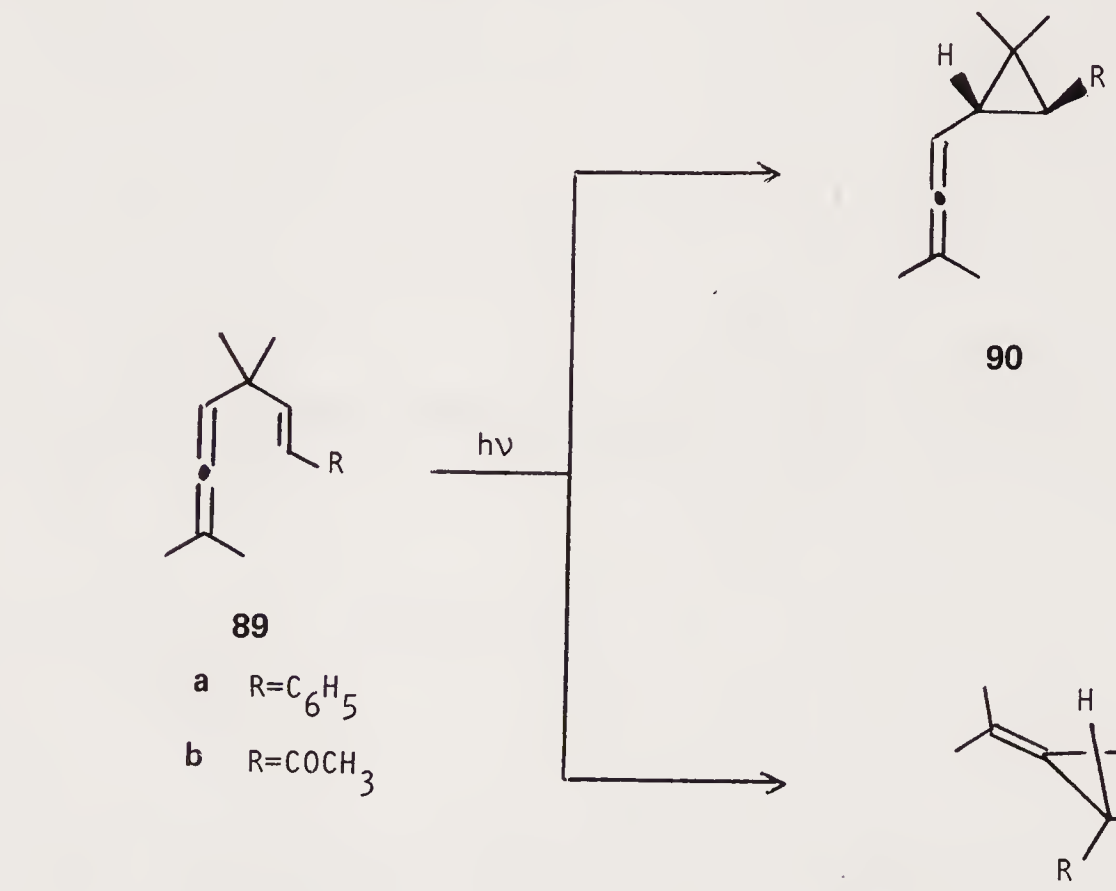


Scheme 13

type process, either **87** or **88** can be formed depending on which of the cyclopropane bonds migrates to the oxygen. When R_3 = H, the *a* bond migrates to give lactones of type **87**, whereas when R_3 = alkyl, the *b* bond migrates to give the isomeric **88**.

Substituted propenyl allenes **89** are interesting intermediates in photochemical reactions. Upon irradiation, these allenes can lead to **90** by way of a di-π-methane

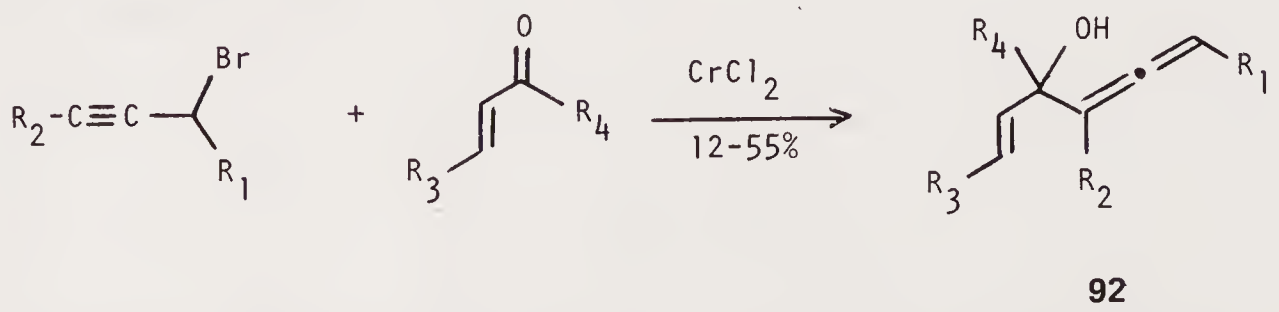
rearrangement, or to bicyclo[2.1.0]pentanes (housanes) **91** by a symmetry allowed [2 + 2] intramolecular cycloaddition. In practice, the di-π-methane route is suppressed and housanes are overwhelmingly formed.[74,75] In the case of **89b**, the conversion is extremely facile and proceeds in 70% yield.[76]



(19)

4.2.2. Alcohols

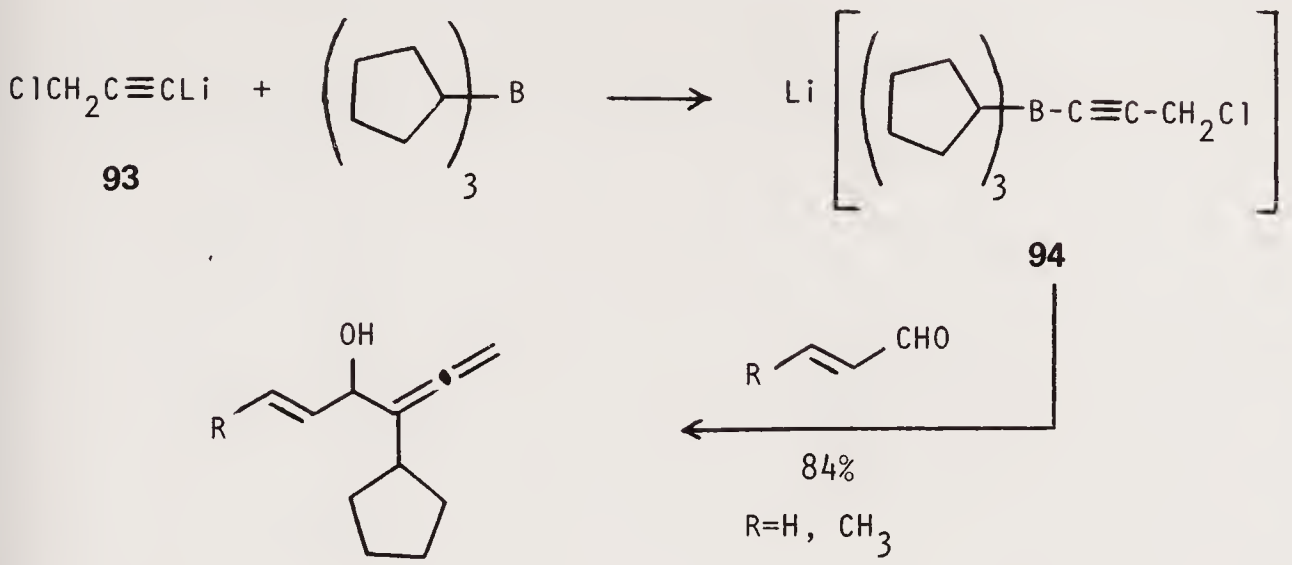
Considerable effort has been directed to the synthesis of a variety of ene–allenic alcohols. Propargylic bromides condense with α,β-unsaturated aldehydes or ketones in the presence of Hiyama's reagent to give α-allenic alcohols **92** (equation 20). The selectivity of this reaction depends on the substitution of the bromide, the structure of the carbonyl, and the presence of HMPA in the reaction mixture.[77]



(20)

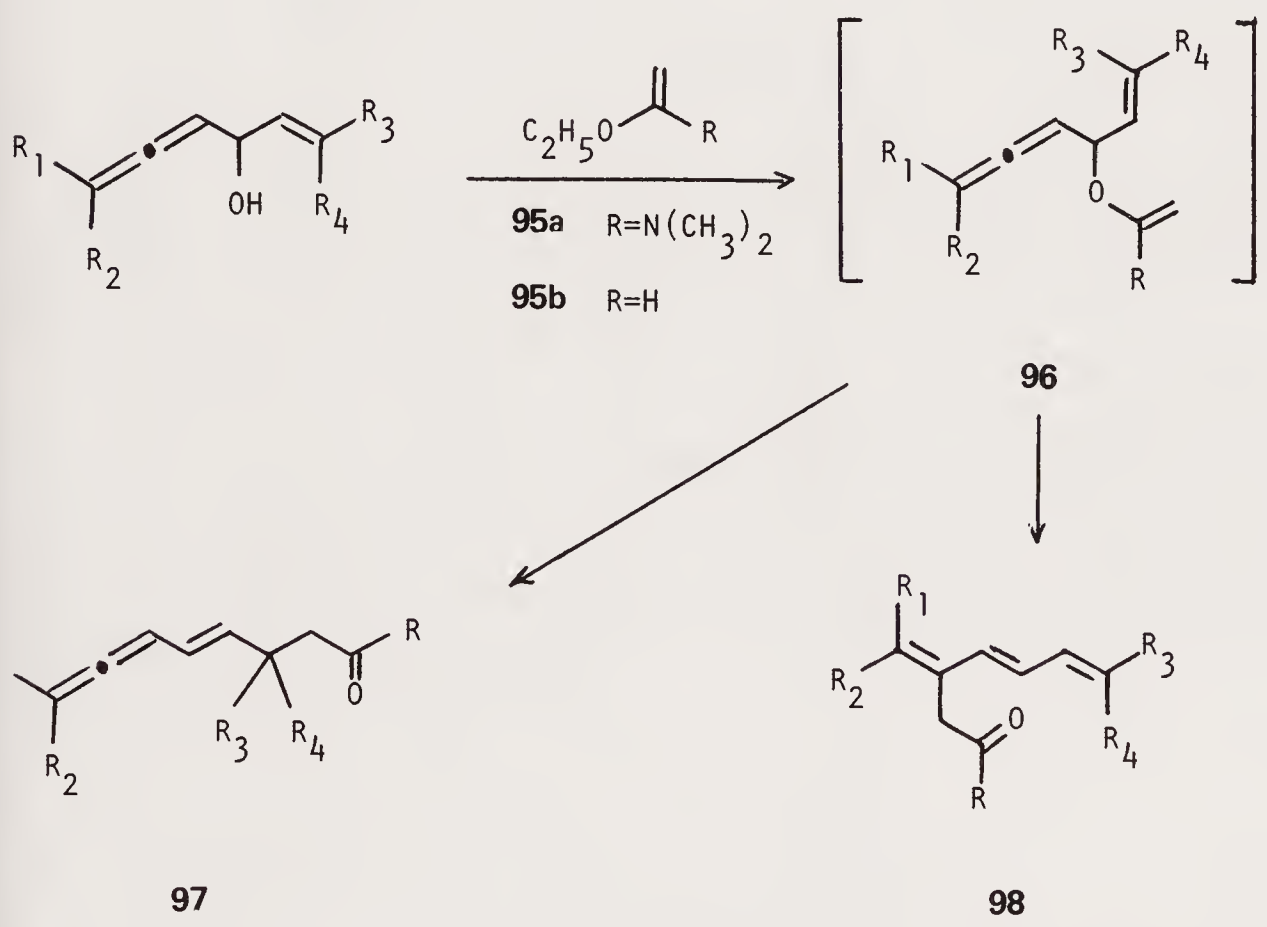
These alcohols have also been prepared by the reaction of trialkylboranes with lithium chloropropargylide (**93**) followed by treatment of the intermediate **94** with aldehydes at room temperature.[78] This reaction, however, lacks generality.[67]

Alcohols of this type can react with either dimethylamino-1-ethoxy-1-ethylene (**95a**)[79,80] or 1-ethoxyethylene (**95b**)[81] to produce the corresponding vinyl ethers **96**,



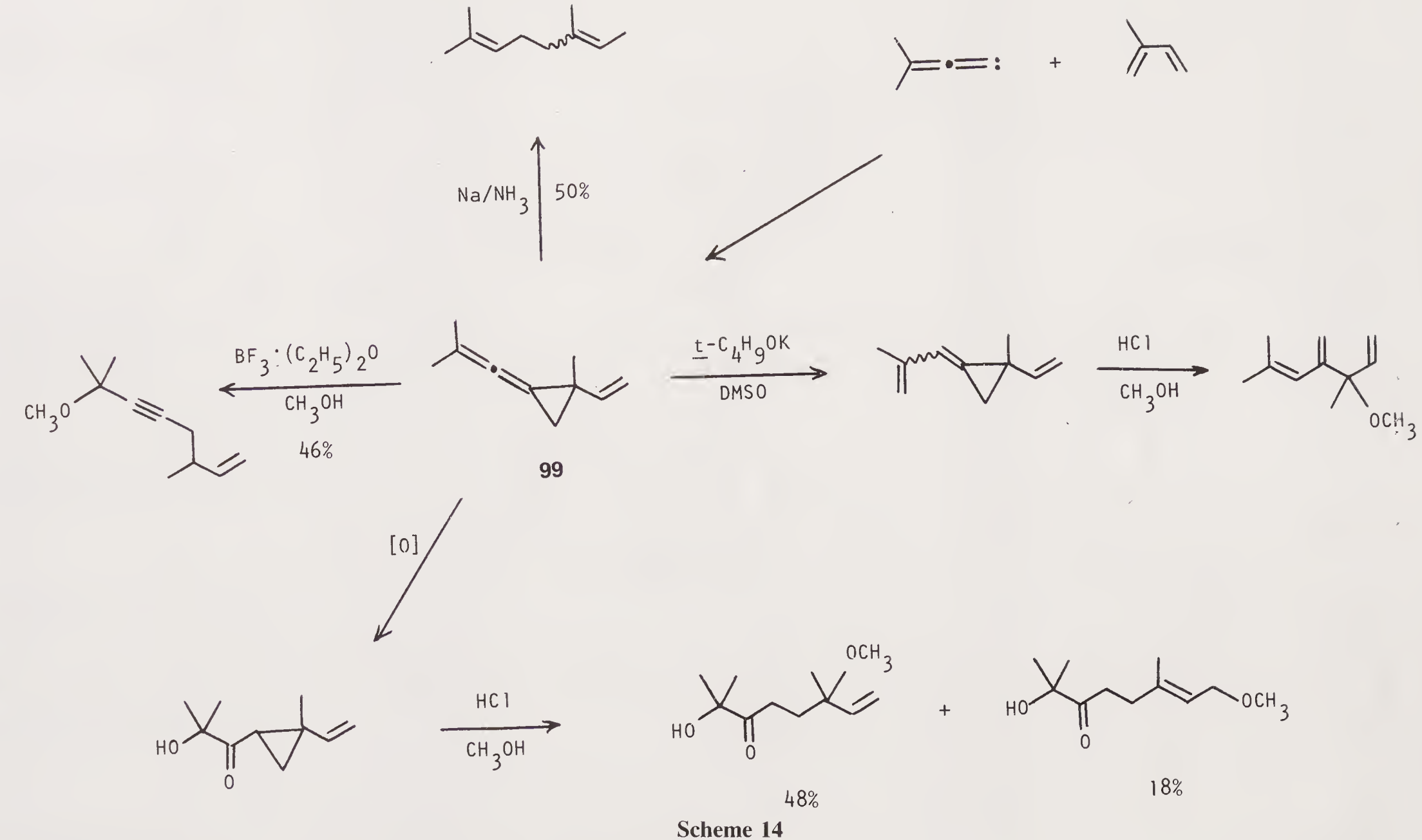
(21)

which undergo a thermal [3.3]sigmatropic rearrangement to give a mixture of vinyl allenes **97** and conjugated trienes **98** (equation 22), the ratio depending on the nature of the allene substitution.

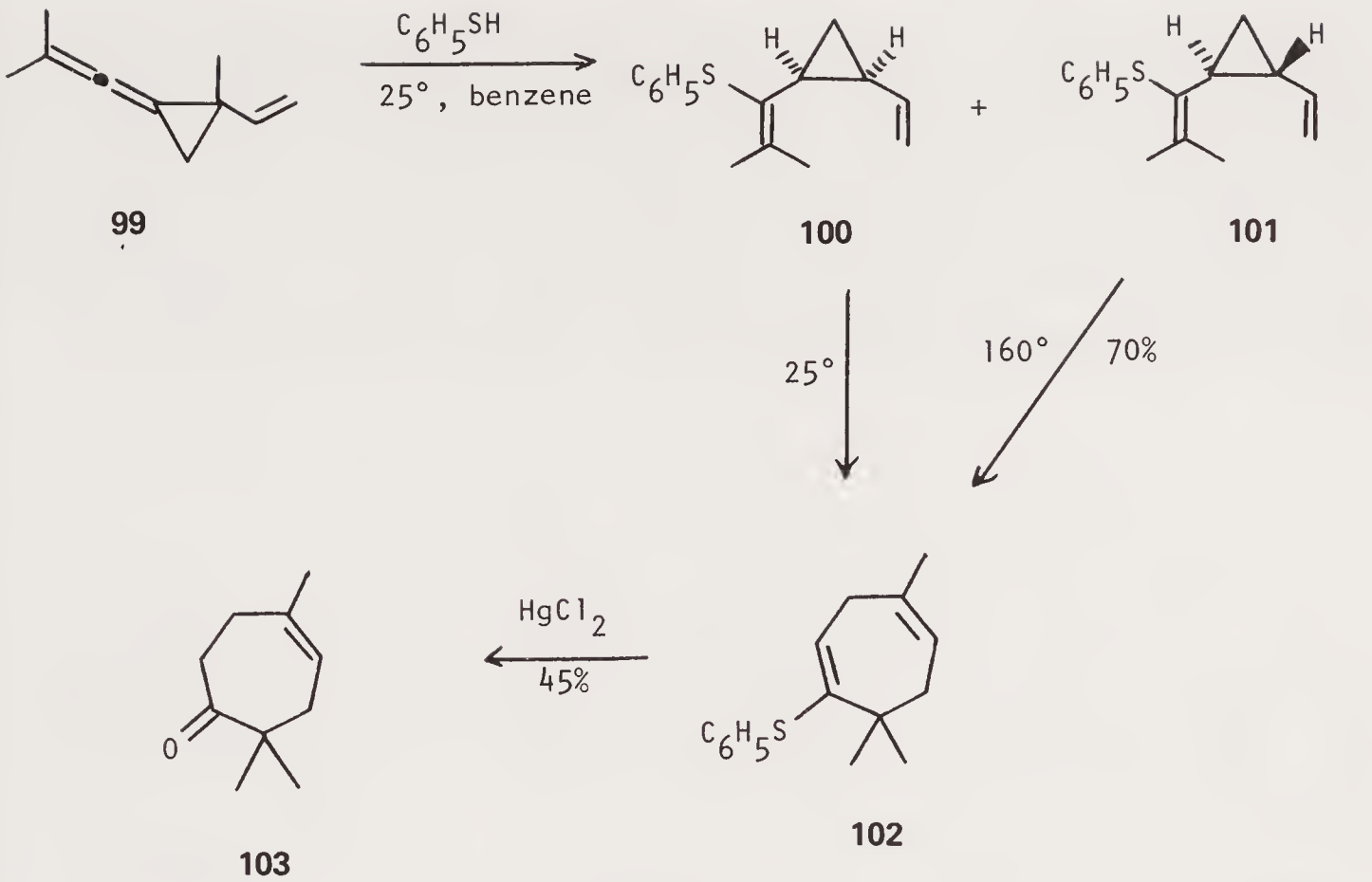


(22)

R_1	R_2	R_3	R_4	R	% **97**	% **98**
H	H	H	H	$N(CH_3)_2$	61	39
CH_3	CH_3	H	H	$N(CH_3)_2$	87	13
C_2H_5	CH_3	H	H	$N(CH_3)_2$	100	—
H	H	CH_3	CH_3	$N(CH_3)_2$	13	87
H	H	C_2H_5	C_2H_5	$N(CH_3)_2$	24	76
H	H	H	H	H	77	23
H	H	CH_3	H	H	59	41
CH_3	H	H	H	H	81	19


Na/NH3
50%
+
BF3·(C2H5)2O
CH3OH
46%
CH3O
99
t-C4H9OK
DMSO
HCl
CH3OH
OCH3
[O]
HO
O
HCl
CH3OH
HO
O
OCH3
48%
+
HO
O
OCH3
18%

Scheme 14



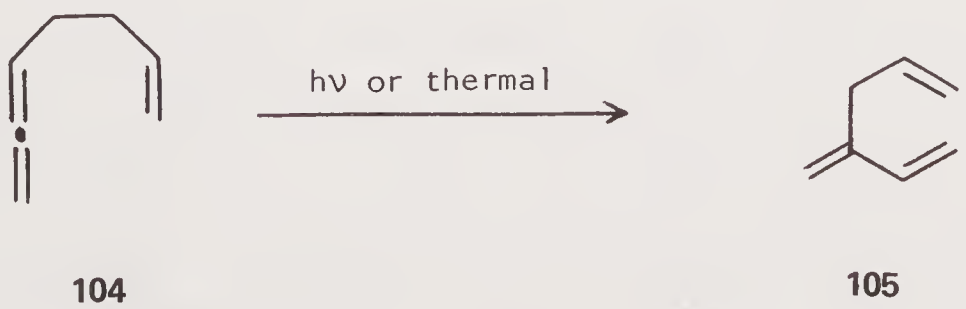
Scheme 15

The acid- or base-catalyzed rearrangement of the allene cyclopropane **99**, prepared by the addition of dimethyl allene carbene to isoprene, leads to a variety of products possessing a terpenoid carbon skeleton (Scheme 14).[83]

The addition of thiophenol to **99** occurs in a regioselective manner to produce a 2:1 mixture of *cis*- and *trans*-divinyl cyclopropanes **100** and **101**.[84] The *cis*-isomer **100** spontaneously undergoes a Cope rearrangement *in situ* at 25°C to give the 1,4-cycloheptadiene **102** while the *trans*-isomer **101** requires heating at 160° for 3 hours to effect the conversion (Scheme 15). Subsequent hydrolysis of **102** leads to karahanaenone (**103**), the odoriferous constituent of Japanese hop and Cypress oil *Cupressus sempervirens*.[85,86]

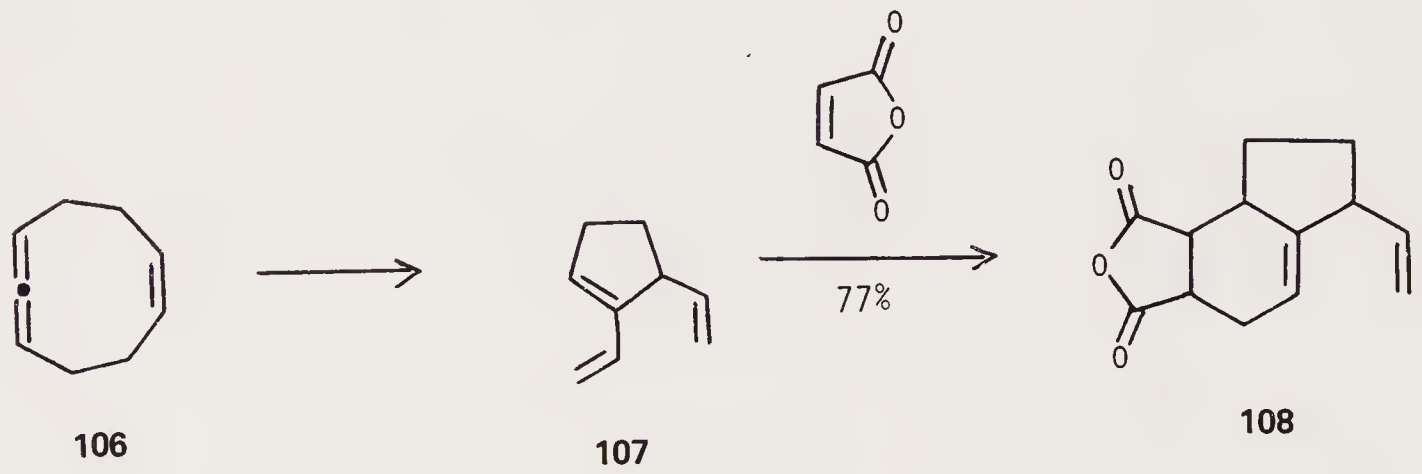
4.3. 1,2,6-TRIENES

The 1,2,6-triene system is ideally set up to undergo a Cope rearrangement. The simplest member of this family, 1,2,6-heptatriene (**104**), can be rearranged to 3-methylene-1,5-hexadiene (**105**) by thermal[87] as well as photosensitized[88] processes.



104 105 (23)

When incorporated into a cyclic system [e.g., 1,2,6-cyclononatriene (**106**)], the isomerization, whether thermal[89] or photochemical,[88] proceeds analogously and affords 2,3-divinylcyclopentene (**107**).[90,91] This intermediate can be trapped as its Diels–Alder adduct when allowed to react with dienophiles such as maleic anhydride or dimethyl acetylene dicarboxylate (Scheme 16). Compound **109** spontaneously aromatizes to **110** when allowed to stand overnight.[89] Such an approach may be useful for the synthesis of indanes not easily available by standard methods.

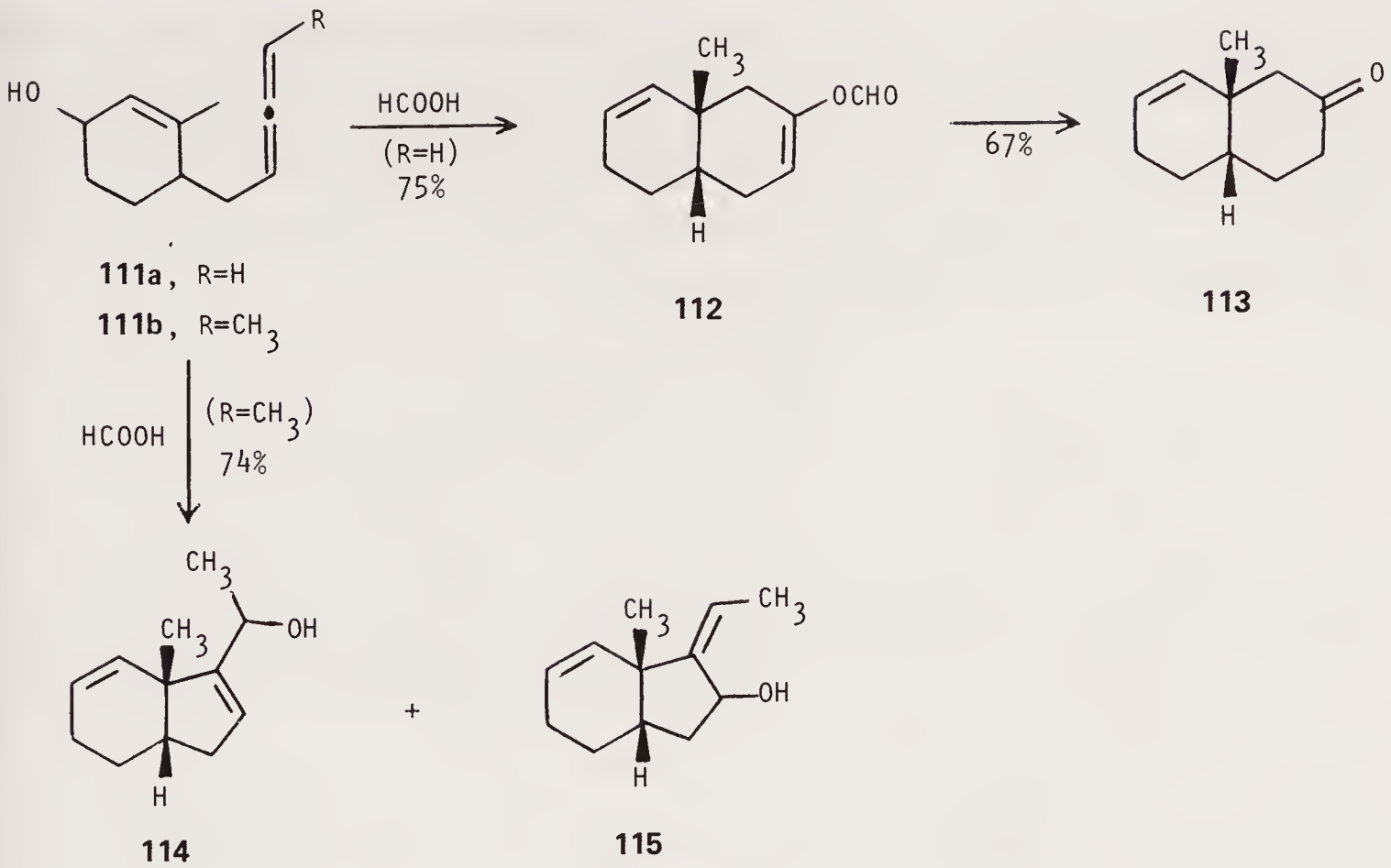


106 **107** **108**

109 **110**

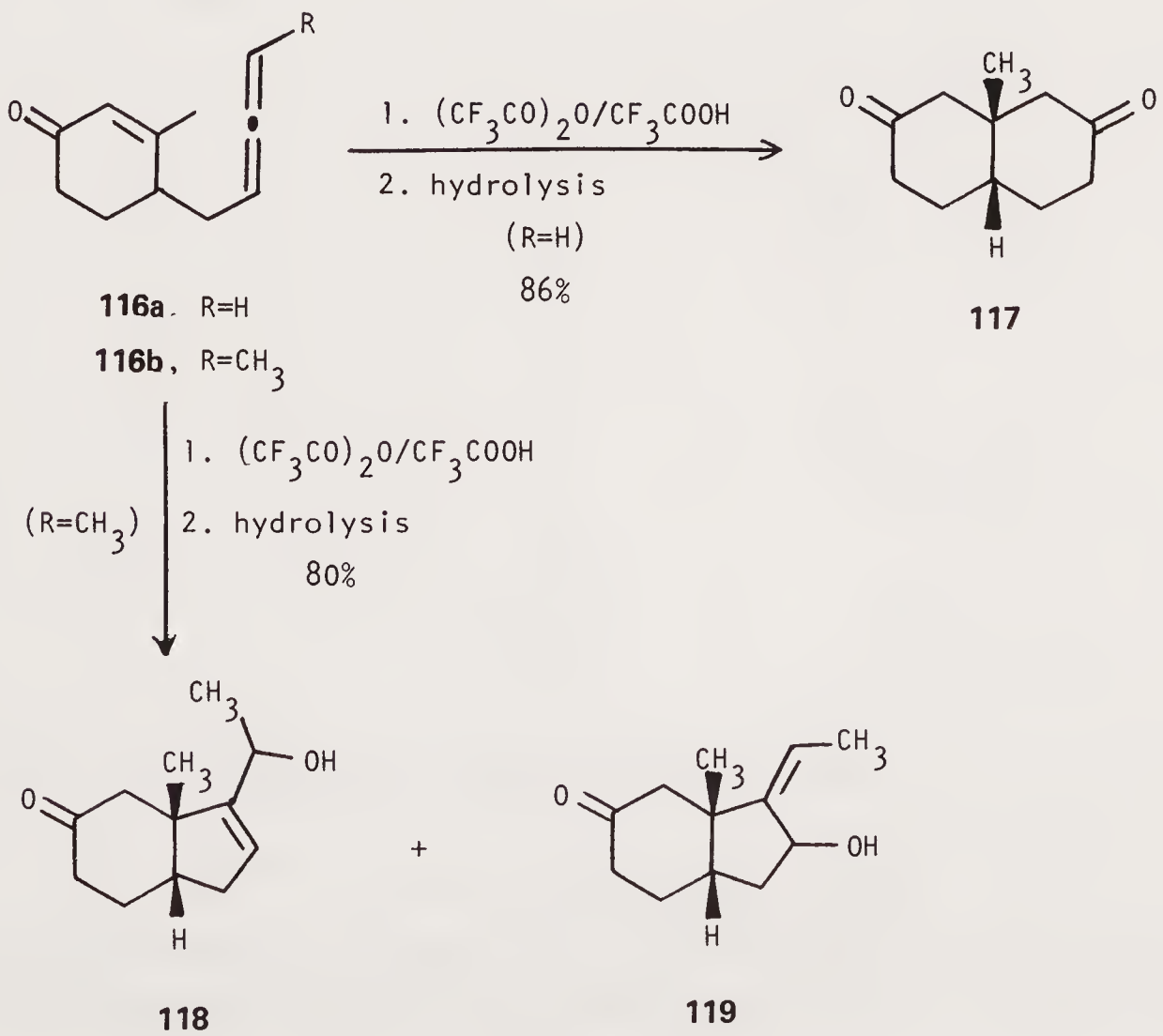
Scheme 16

One of the more synthetically applicable transformations involving 1,2,6-trienes is their participation in cationic π-cyclizations to produce carbocyclic ring systems[92] (Scheme 17). The regiochemical outcome of the reaction is dictated by the substitution of the terminal allenic carbon. Unsubstituted allenes undergo electrophilic cyclization exclusively at the terminal carbon, whereas terminally methylated allenes undergo attack at the central carbon. In all cases, the *cis*-fusion is observed. Thus when **111a** is treated with anhydrous formic acid, the cyclic formate **112** is produced, which can be subsequently hydrolyzed to *cis*-9-methyl-Δ^7-2-octalone (**113**). Analogous treatment of **111b** results in the formation of the five-membered ring products **114** and **115** (ratio 2:1).



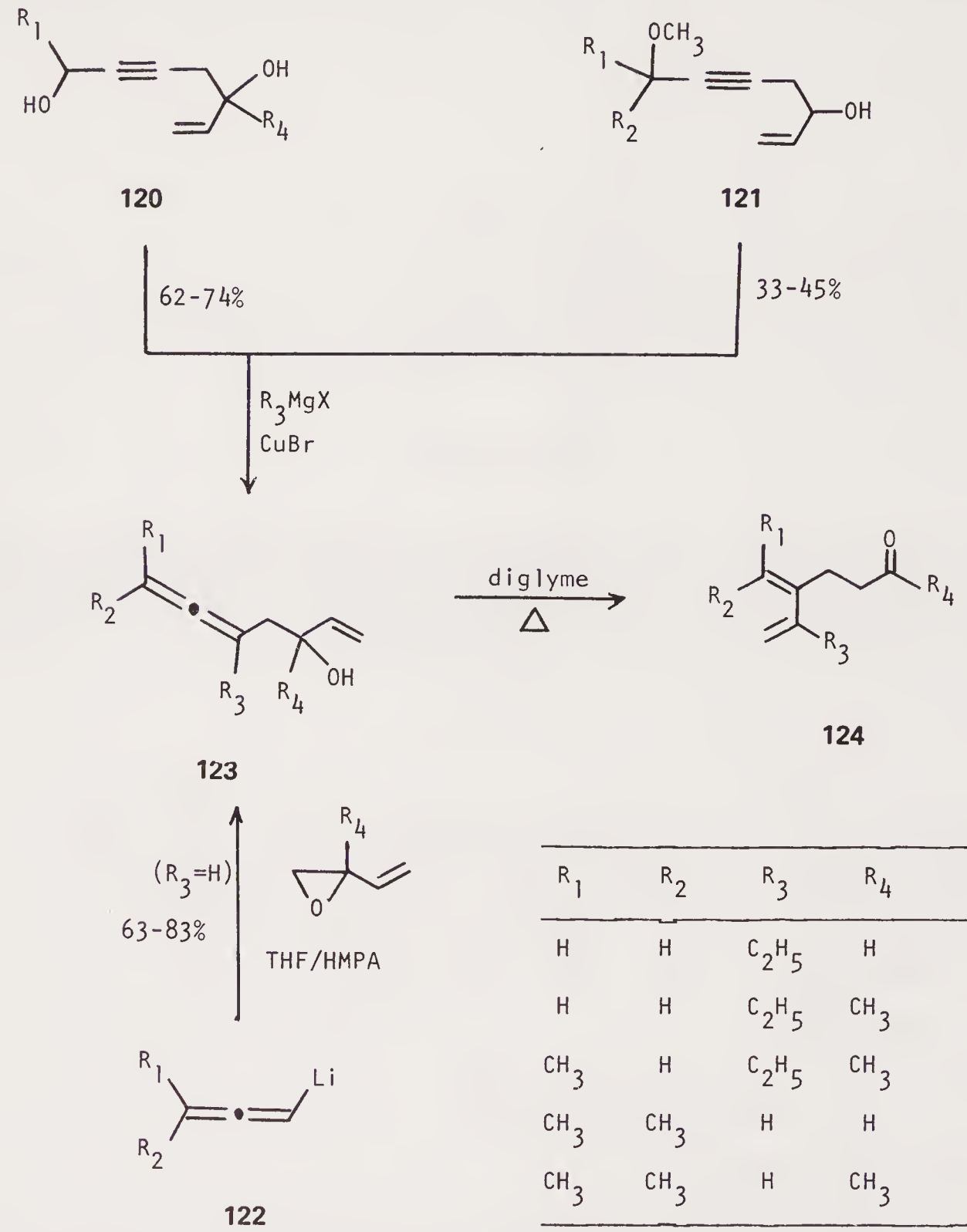
Scheme 17

A similar transformation can be performed on the enone **116**. However, better yields are obtained with the use of trifluoroacetic anhydride in trifluoroacetic acid rather than formic acid. In the case of **116b**, the reaction produces a 4:1 mixture of **118** and **119**.



Scheme 18

α-Ethylenic-β′-allenic alcohols (**123**) are readily accessible by three separate routes. Two of the three involve the addition of an organocopper reagent[93,94] to a β-hydroxy-γ-ethylenic alcohol **120** or **121**; the third is an attack of an allenyl lithium **122** on a vinyl epoxide.[95] Heating the alcohols **123** in diglyme causes them to undergo a [3.3]sigmatropic rearrangement that leads to γ-dienic aldehydes and ketones **124** in moderate yields[94] (Scheme 19).



R_1	R_2	R_3	R_4	Yield,%
H	H	C_2H_5	H	52
H	H	C_2H_5	CH_3	70
CH_3	H	C_2H_5	CH_3	58
CH_3	CH_3	H	H	40
CH_3	CH_3	H	CH_3	30

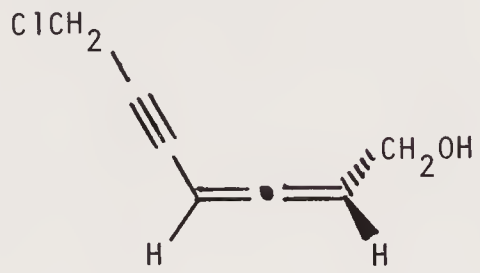
Scheme 19

4.4. ACETYLENIC ALLENES

4.4.1. Conjugated (C=C=C—C≡C)

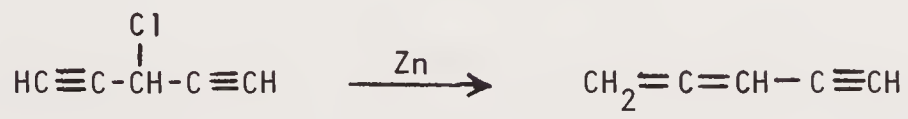
A number of natural allenes contain, as an important structural feature, the conjugated alleneyne linkage. The structure of the biologically active metabolite, Sco-

rodonin (**125**), isolated from the mushroom *Marasmius scorodonius,* exhibits such a system.[96]



125

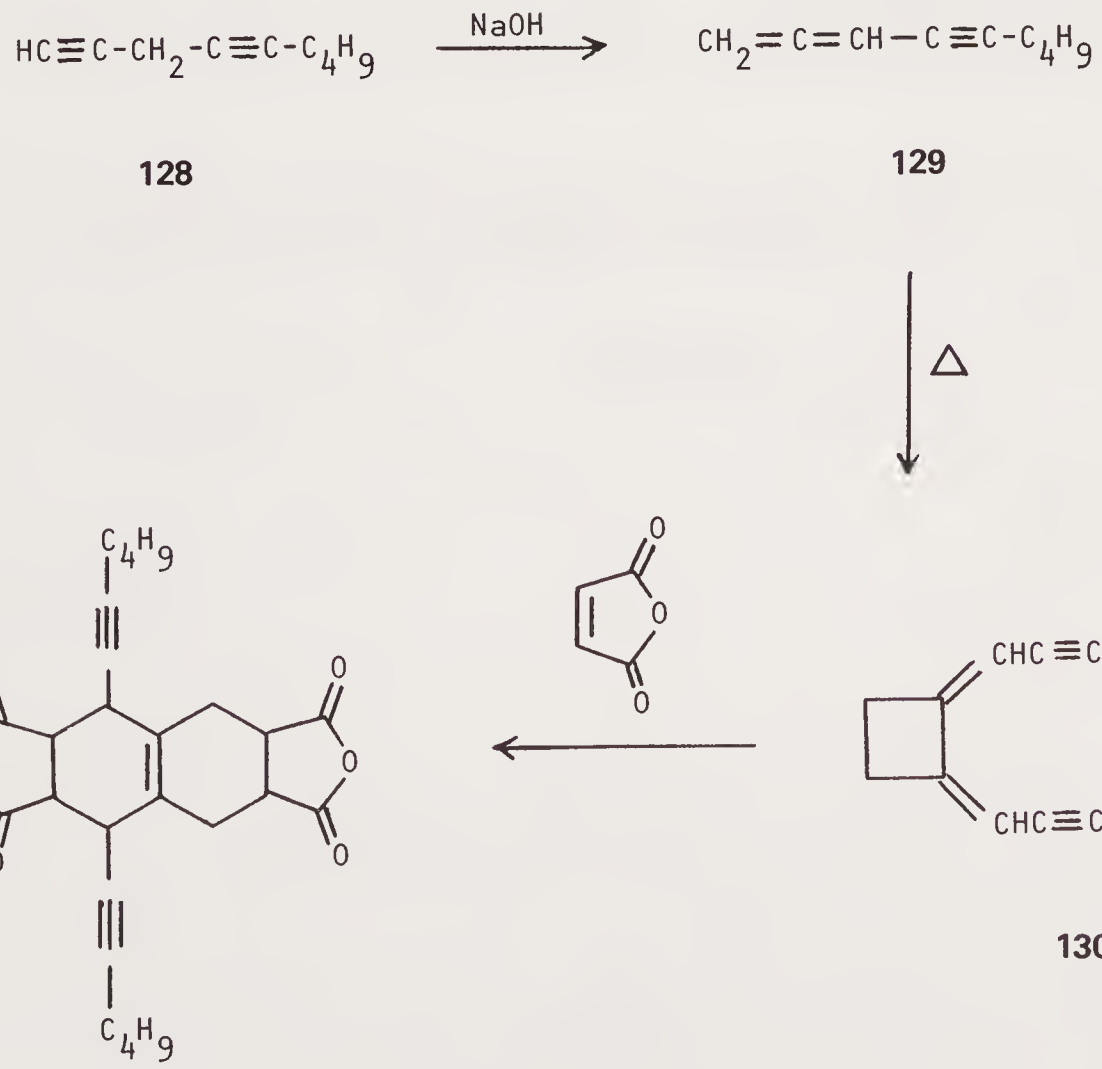
The simplest representative in this class of compounds, 1,2-pentadiene-4-yne (**127**), is prepared in 60% yield by the reductive elimination of 3-chloro-1,4-pentadiyne (**126**) with activated zinc in *n*-butanol.[3]



(24)

126 **127**

In the presence of aqueous sodium hydroxide, 1,4-nonadiyne (**128**) readily isomerizes to 1,2-nonadiene-4-yne (**129**).[97] At temperatures exceeding 100°C, the allene undergoes a thermal [2 + 2] cycloaddition to a short-lived dimer **130** which is easily trapped with maleic anhydride.



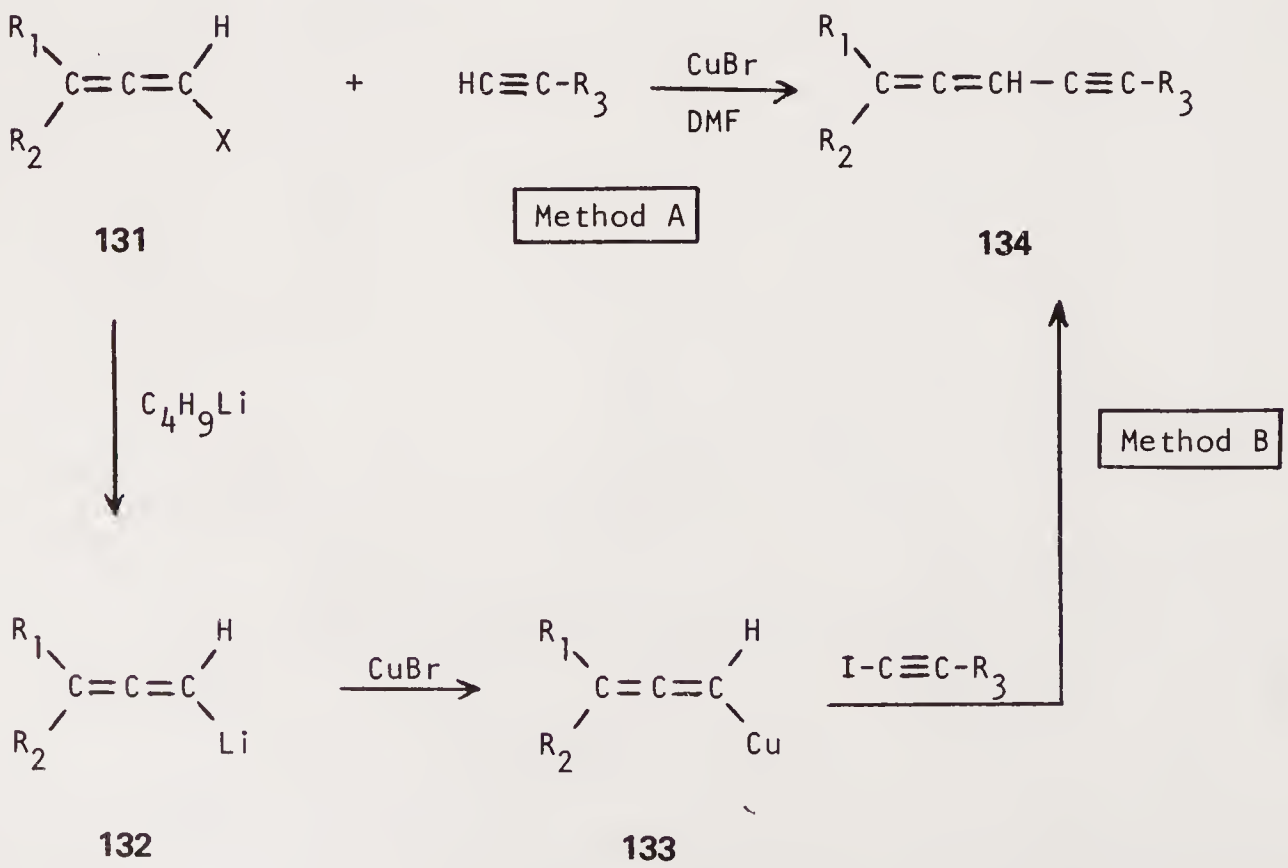
(25)

128 **129** **130**

Table 4.6. Allenynes 134 from Coupling Reactions of Allenes with Acetylenic Derivatives (Scheme 20)

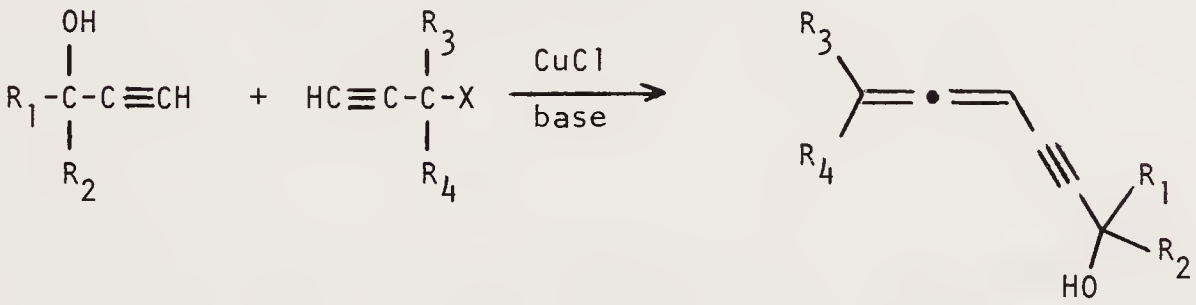
R_1	R_2	R_3	X	Method	Yield (%)
H	H	CH_2OH	I	A	45
C_3H_7	H	CH_2OH	Br	A	51
CH_3	CH_3	CH_2OH	Br	A	33
t-C_4H_9	CH_3	CH_2OH	Br	A	62
t-C_4H_9	CH_3	C_4H_9	Br	A	82
C_2H_5	CH_3	—C≡CH	Br	A	25
H	H	C_6H_5	H	B	89
CH_3	CH_3	C_6H_5	H	B	90
t-C_4H_9	H	$Si(CH_3)_3$	H	B	77
t-C_4H_9	H	—C≡C—CH_3	H	B	75

A more general route to allenynes consists of coupling allenes with an appropriate ethynyl compound (Scheme 20). Two methods produce consistently good results. Method A involves the reaction of allenic halides **131** with acetylenes (usually alcohols) in the presence of cuprous bromide and an organic base (either aqueous ethylamine or t-butylamine).[98,99] The larger the substituent R on the haloallene, the higher the yield of product (see Table 4.6). An alternate approach (Method B) is a cross-coupling reaction of monoallenylcopper(I) derivatives **133** with 1-iodo-1-alkynes.[100] The reaction is highly regioselective and produces allenynes **134** in 74–90% yields. An interesting feature of both methods is that no prototropic rearrangement to diynes is observed.



Scheme 20

Allenynes containing a hydroxy group α to the acetylene function are easily prepared by the condensation of a propargyl alcohol with a propargyl halide in the presence of a catalytic amount of cuprous chloride and a suitable base[101,102] (equation 26). The reaction occurs by initial formation of a copper acetylide which then adds to the propargyl halide in an S_N2' fashion. The base (ammonium hydroxide, hydroxylamine, or *t*-butylamine) is necessary to neutralize the liberated hydrochloric acid as well as to aid in the formation of the copper complex. The reactivity of the complex depends upon its solubility. With alkynes bearing α-hydrophilic groups, aqueous or alcoholic solvents are favored, whereas for hydrocarbon substituents, DMF or DMSO is required. The halide reactivity follows the order Cl > Br ≫ I with tosylates being almost as effective as chlorides.



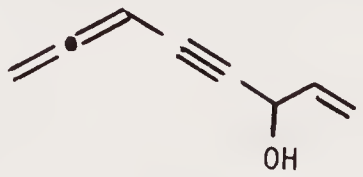
(26)

135

R_1	R_2	R_3	R_4	Base	Yield (%)
H	H	H	H	NH_4OH	60
H	H	CH_3	H	t-$C_4H_9NH_2$	50
CH_3	H	CH_3	H	NH_4OH	50
CH_3	CH_3	CH_3	CH_3	t-$C_4H_9NH_2$	70

The more complex alcohols represented by skeletal systems **136**, **137**, and **138** are also easily prepared in 50–90% yields by this method.[103]

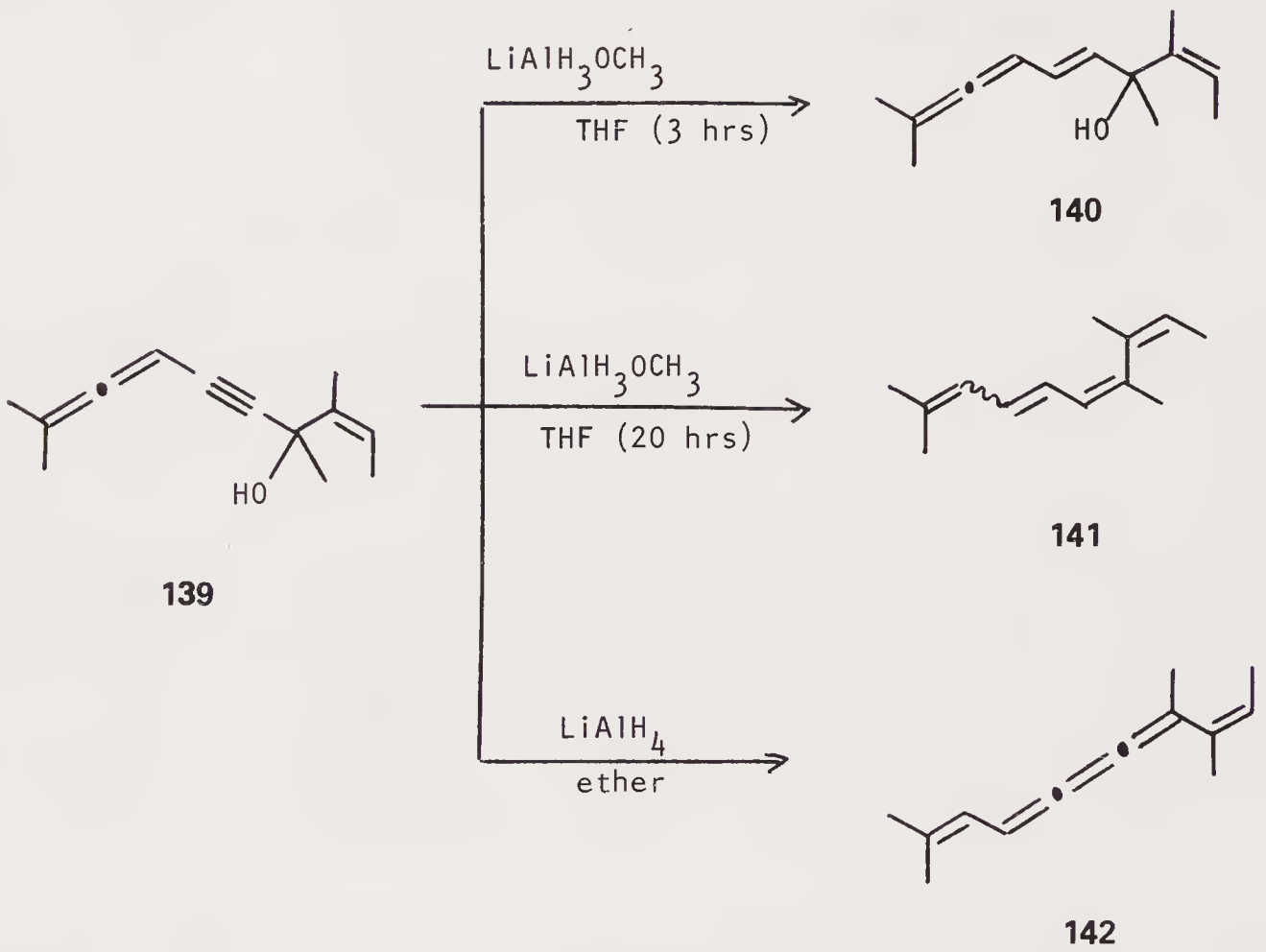
136



137

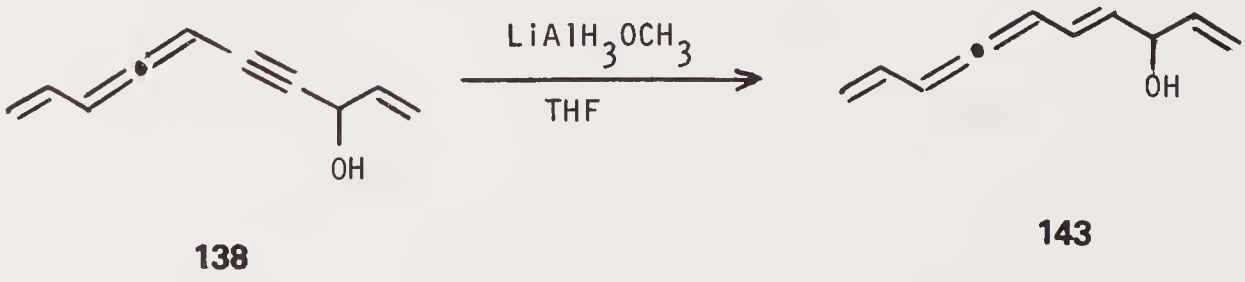
138

An interesting transformation involving the skeletal system **137** is its behavior toward various hydride-reducing reagents. The product obtained from the reduction of these derivatives depends on the type of hydride used, the solvent employed, and the length of the reaction time.[104,105] The treatment of the methylated derivative **139** with lithium methoxyaluminum hydride in THF at 70°C for less than 3 hours results in the formation of *trans*-vinyl allene **140**. Prolonged reaction time allows a second addition of hydride to occur to give the conjugated tetraene **141**. When lithium aluminum hydride is used in ether at 55° for 20–30 hours, the divinyl cumulene **142** is obtained in 64% yield[104] (Scheme 21).



Scheme 21

A similar reduction of **138** with lithium methoxyaluminum hydride in THF for 2 hours results in the formation of divinyl allenols **143** in 55–72% yield.[104]

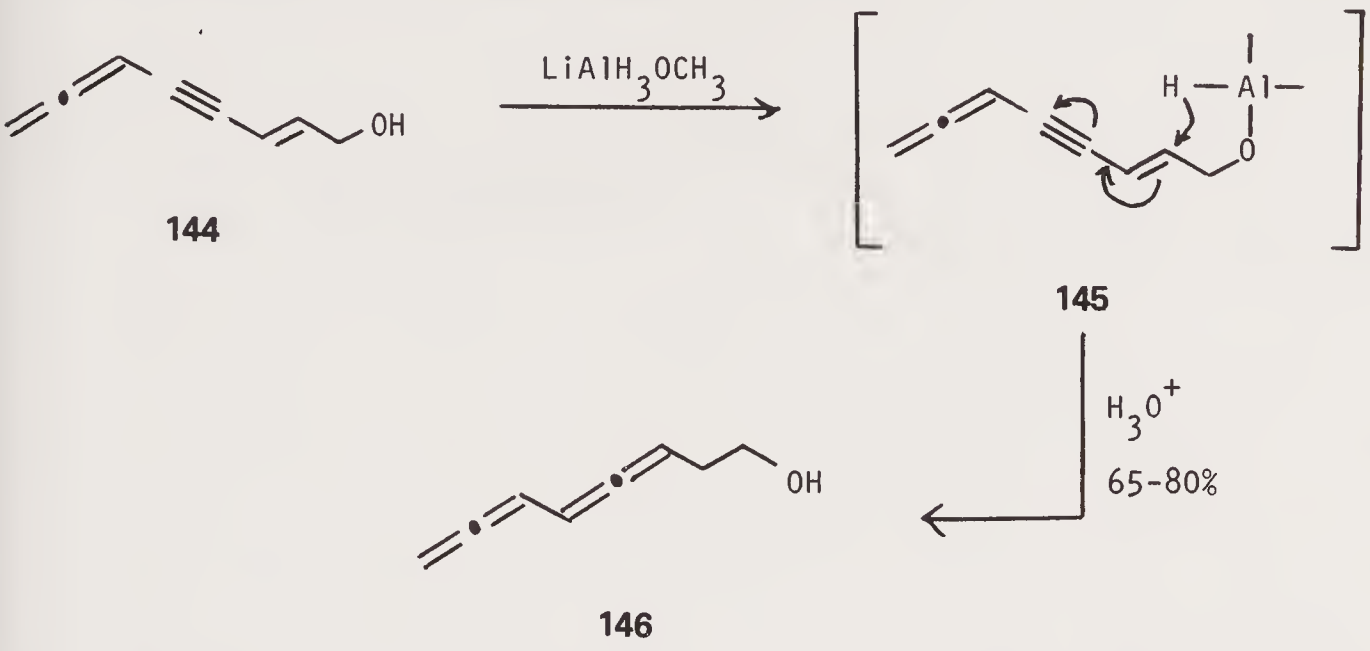


138 143 (27)

4.4.2. C=C=C—C≡C—C=C

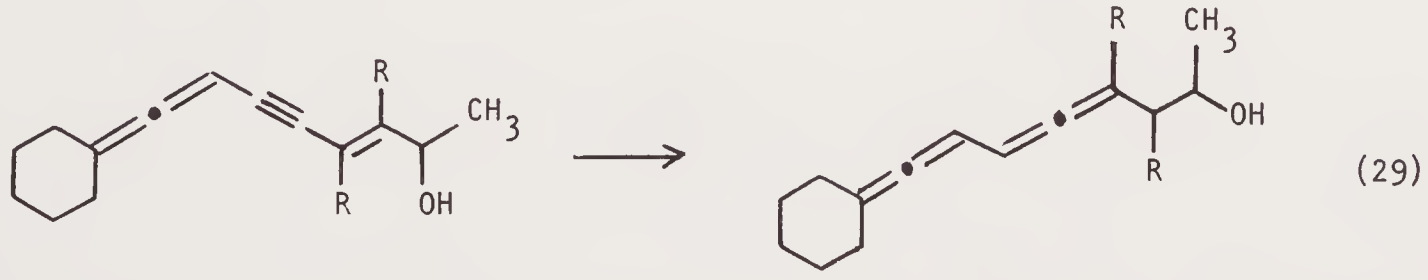
Skeletal systems containing an allenic unit in which the conjugation is extended through both the triple bond of the acetylene and the double bond of the ethylene function are readily accessible by the coupling process described in equation (26).[103]

The reduction of **144** with lithium methoxyaluminum hydride in THF at 80°C provides the β-diallenol **146** by means of nucleophilic addition of hydride to the ethylene bond, as shown in **145** (equation 28).[105–107]



144 **145** **146** (28)

In those cases where the olefin is substituted (e.g., **147**, R═CH_3) the results are affected by the choice of reducing agent as well as the time of the reaction (equation 29).[105]



147 **148** (29)

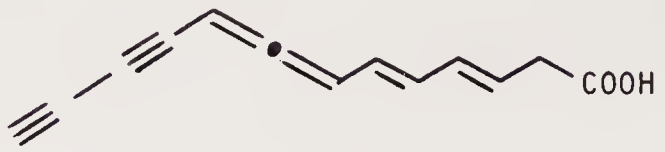
R	Hydride Source	Time (hr)	Yield (%)
H	$LiAlH_4$	10	76
H	$LiAlH_3OCH_3$	2	55
CH_3	$LiAlH_4$	10	22
CH_3	$LiAlH_3OCH_3$	2	68

It should be kept in mind that structures **138–146** represent only the basic skeletons and that a wide variety of substitution patterns are available for each one. These can be found in the references cited.

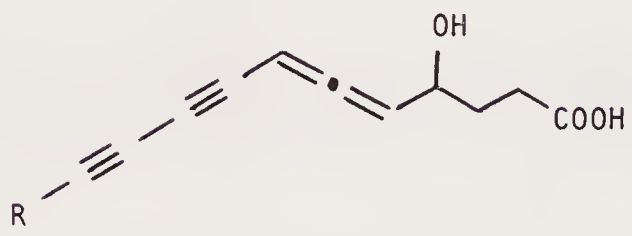
4.4.3. C═C═C—C≡C—C≡C

Allene diynes are a unique class of compounds. Their complexity suggests that structures like this would represent chemical curiosities posing a synthetic challenge to the organic chemist as well as an interesting system of conjugation for study by

the physical chemist. Amazingly enough, this functional grouping occurs in nature and is an important structural feature of fungal metabolites such as mycomycin (**149**),[108,109] nemotinic acid (**150a**) and nemotin (**151a**),[110] odyssic acid (**150b**) and odyssin (**151b**), and others,[111] many of which possess antibiotic activity.



149



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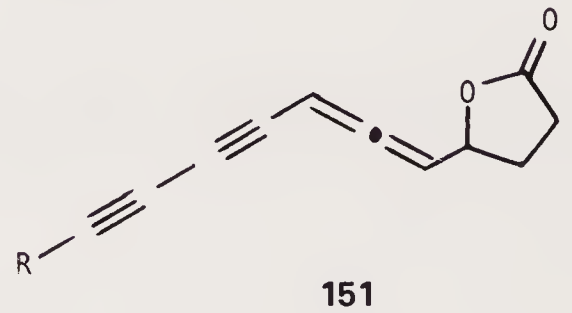
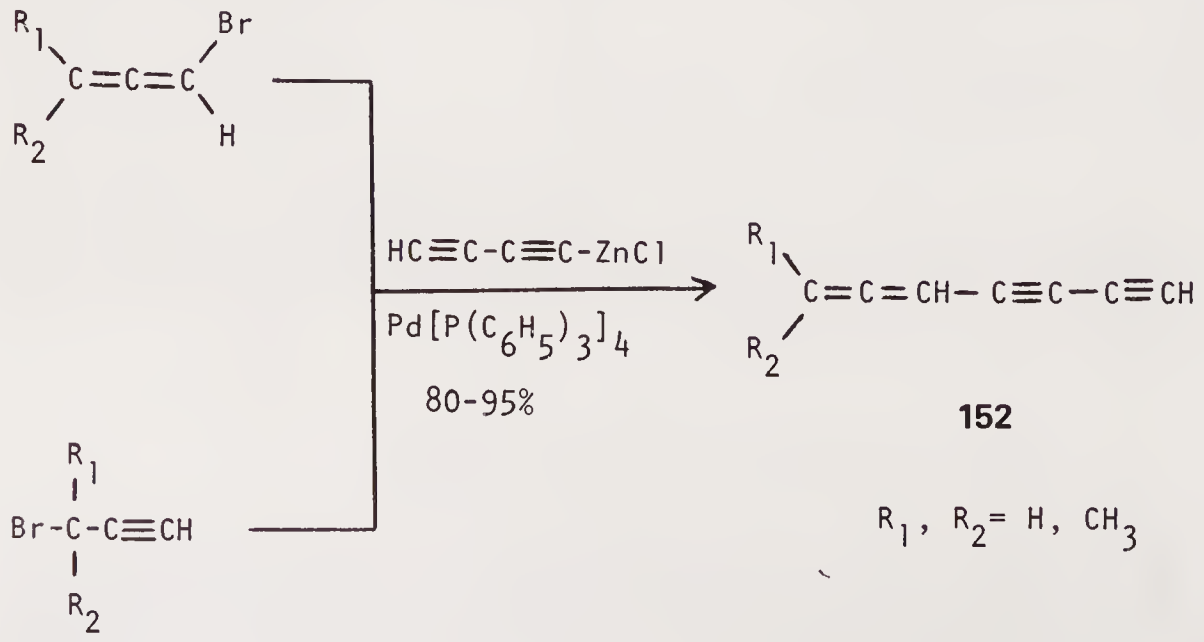


151

a, R=H

b, R=CH_3

Synthetically, the allenediyne system can be constructed by two basic coupling procedures: the first involves the reaction of allenic or propargylic bromides with 1-butadiynylzinc chloride in the presence of 0.5–2.0 mole % of tetrakis(triphenylphosphine)palladium (equation 30).[112,113]

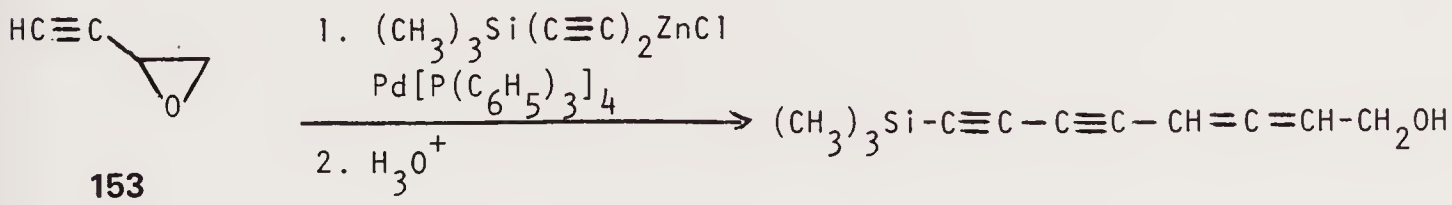


152

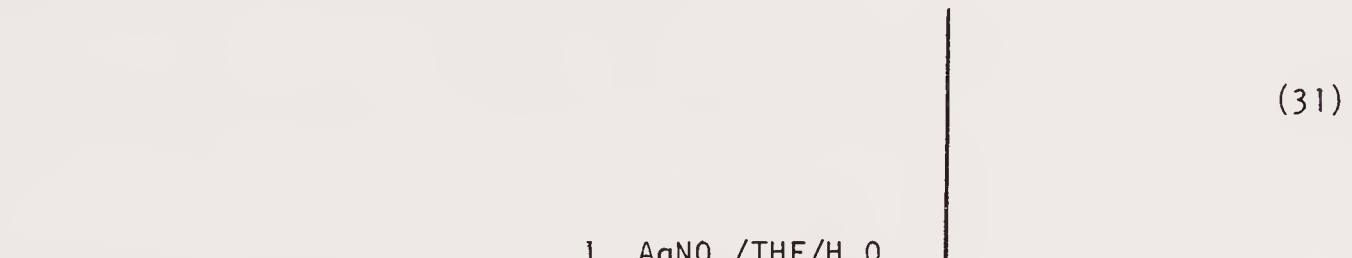
R_1, R_2= H, CH_3

(30)

When the 1-butadiynylzinc chloride is reacted with α-acetylene epoxide **153** under palladium(0) catalysis, followed by several standard chemical conversion steps, the fungal metabolite (±)-2,3-octadiene-5,7-diyne-1-ol (**154**) is obtained in a 30% overall yield.[114]



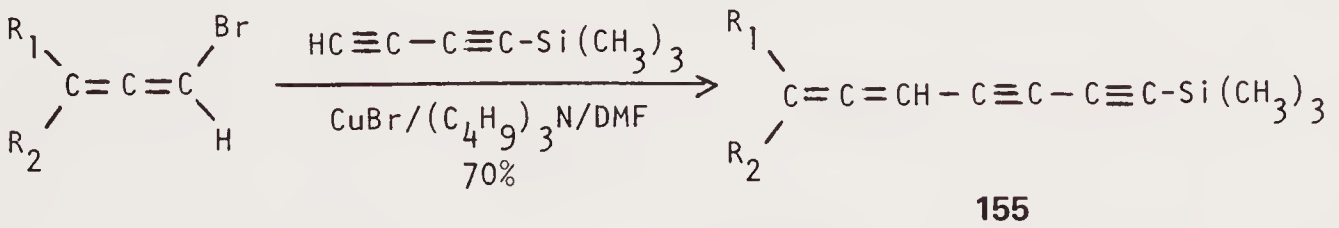
153



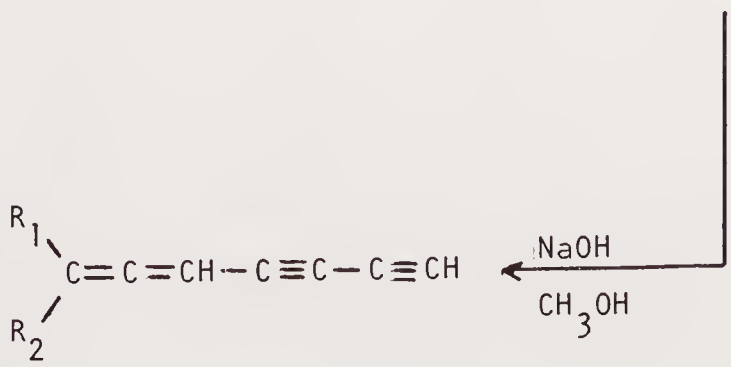
154

(31)

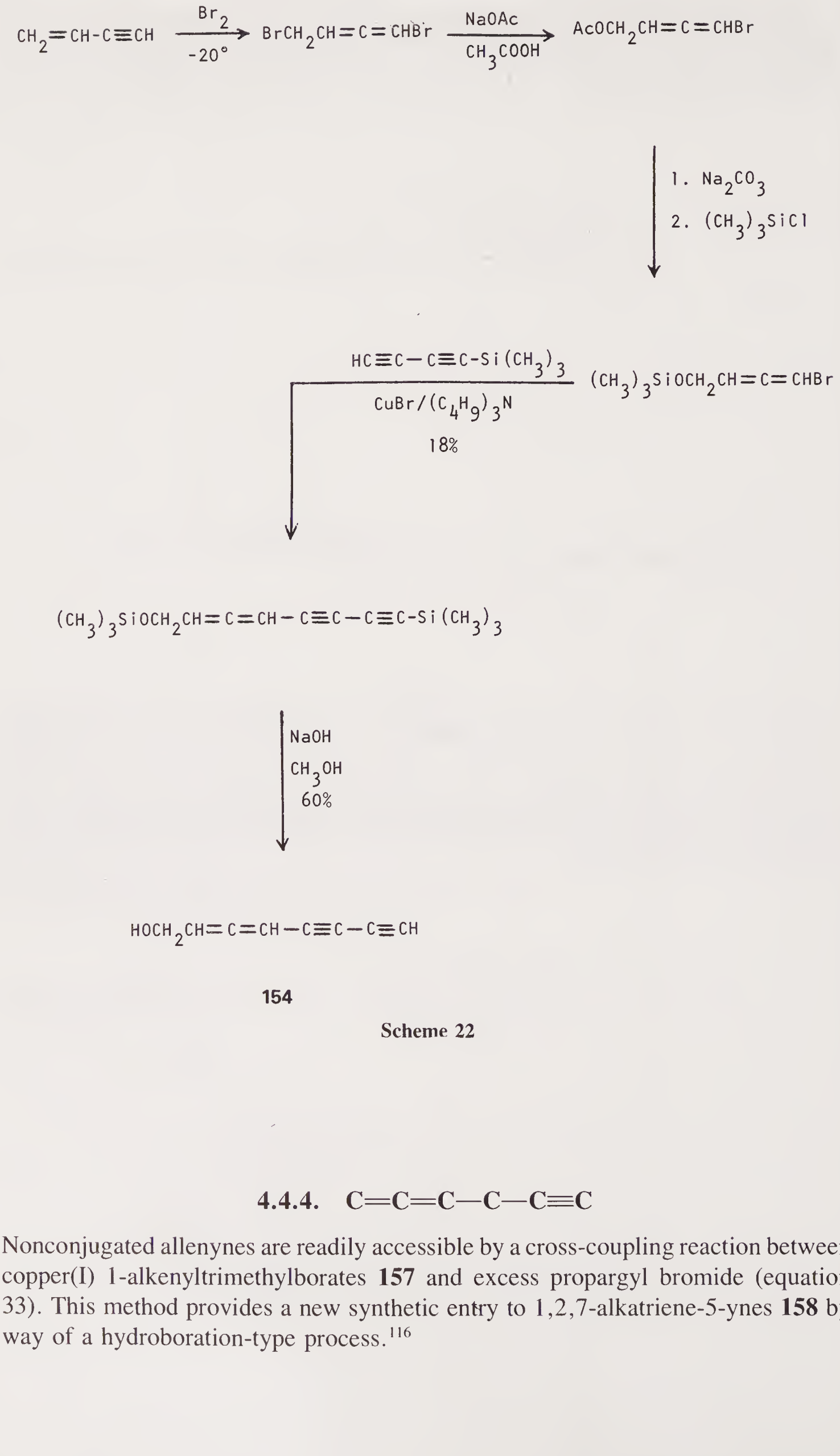
The second procedure is an extension of the coupling reaction illustrated in Scheme 20. An allenic bromide is reacted with 1-trimethylsilylbutadiyne in which the terminal acetylene of the resulting allenediyne **155** is protected by a stabilizing trimethylsilyl group (equation 32).[115] Landor[115] has applied this method to the synthesis of **154** and (±)-5,6-undecadiene-8,10-diyne-1-ol (**156**) (Scheme 22 and Scheme 23, respectively).



155



(32)

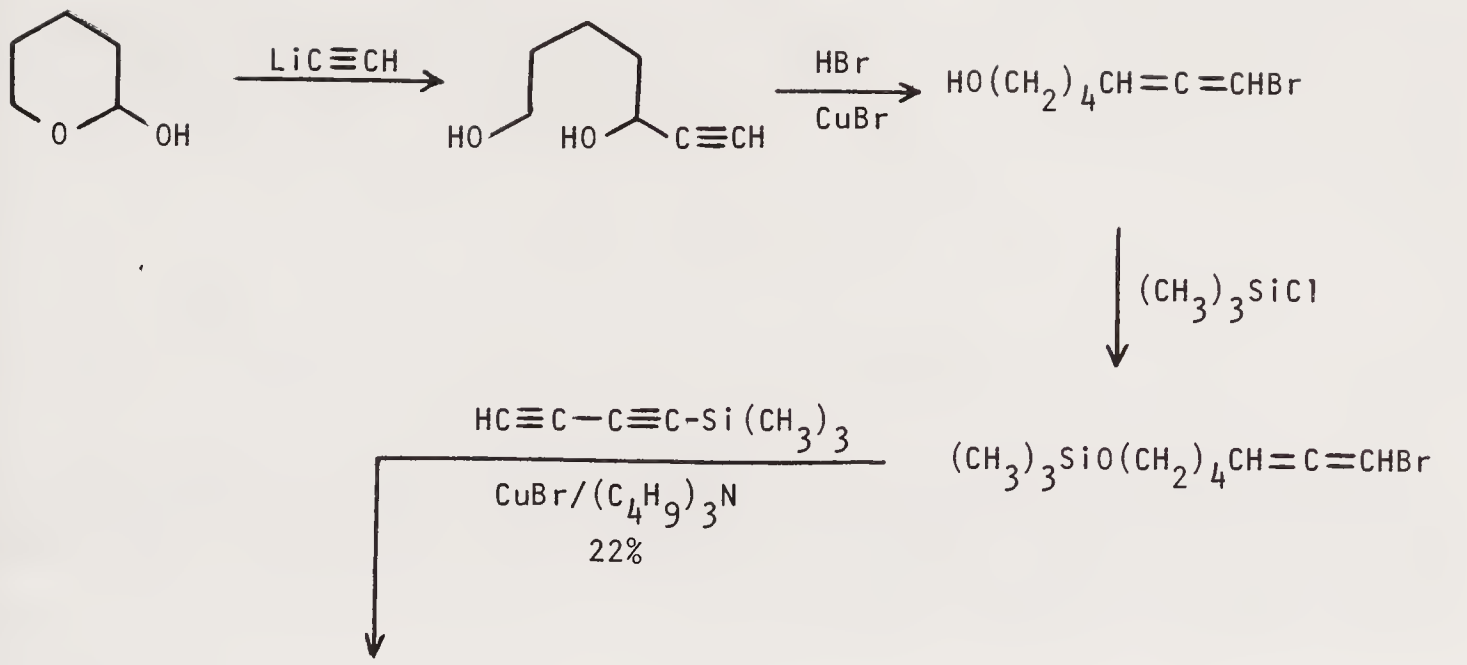


154

Scheme 22

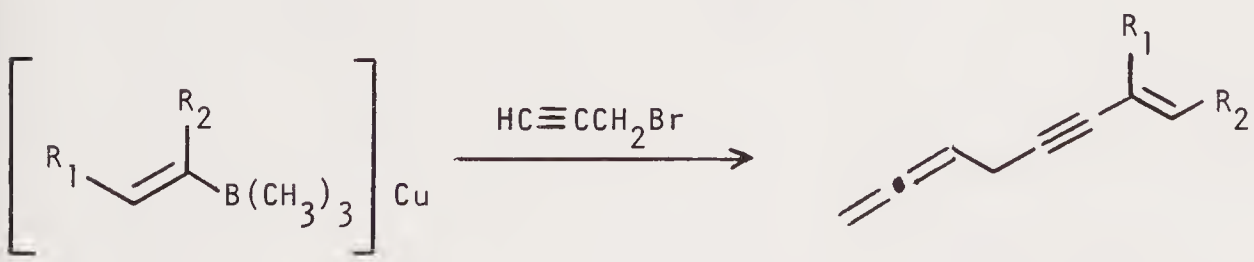
4.4.4. C=C=C—C—C≡C

Nonconjugated allenynes are readily accessible by a cross-coupling reaction between copper(I) 1-alkenyltrimethylborates **157** and excess propargyl bromide (equation 33). This method provides a new synthetic entry to 1,2,7-alkatriene-5-ynes **158** by way of a hydroboration-type process.[116]



156

Scheme 23

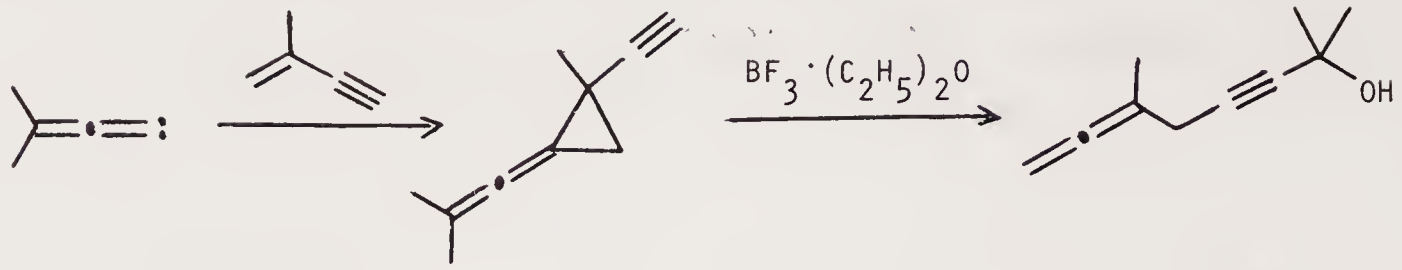


(33)

157 **158**

R_1	R_2	Yield (%)
C_4H_9	H	54
C_5H_{11}	H	55
C_6H_{13}	H	40
C_2H_5	C_2H_5	71

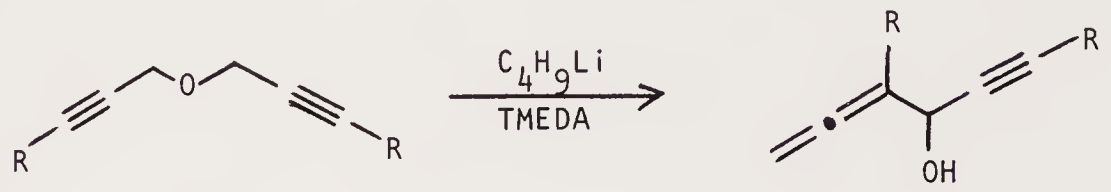
Acetylene alkenylidene cyclopropane **159**, when treated with boron trifluoride etherate in methanol, leads directly to the head-to-tail terpenoid allene–acetylene **160** in 50% yield.[83]



(34)

159 160

Propargylic allenes containing an α-hydroxy function are readily obtained by an anionic [2.3]sigmatropic rearrangement of β,β′-alkynyl ethers **161** with *n*-butyl lithium/TMEDA in DMSO (equation 35).[117]

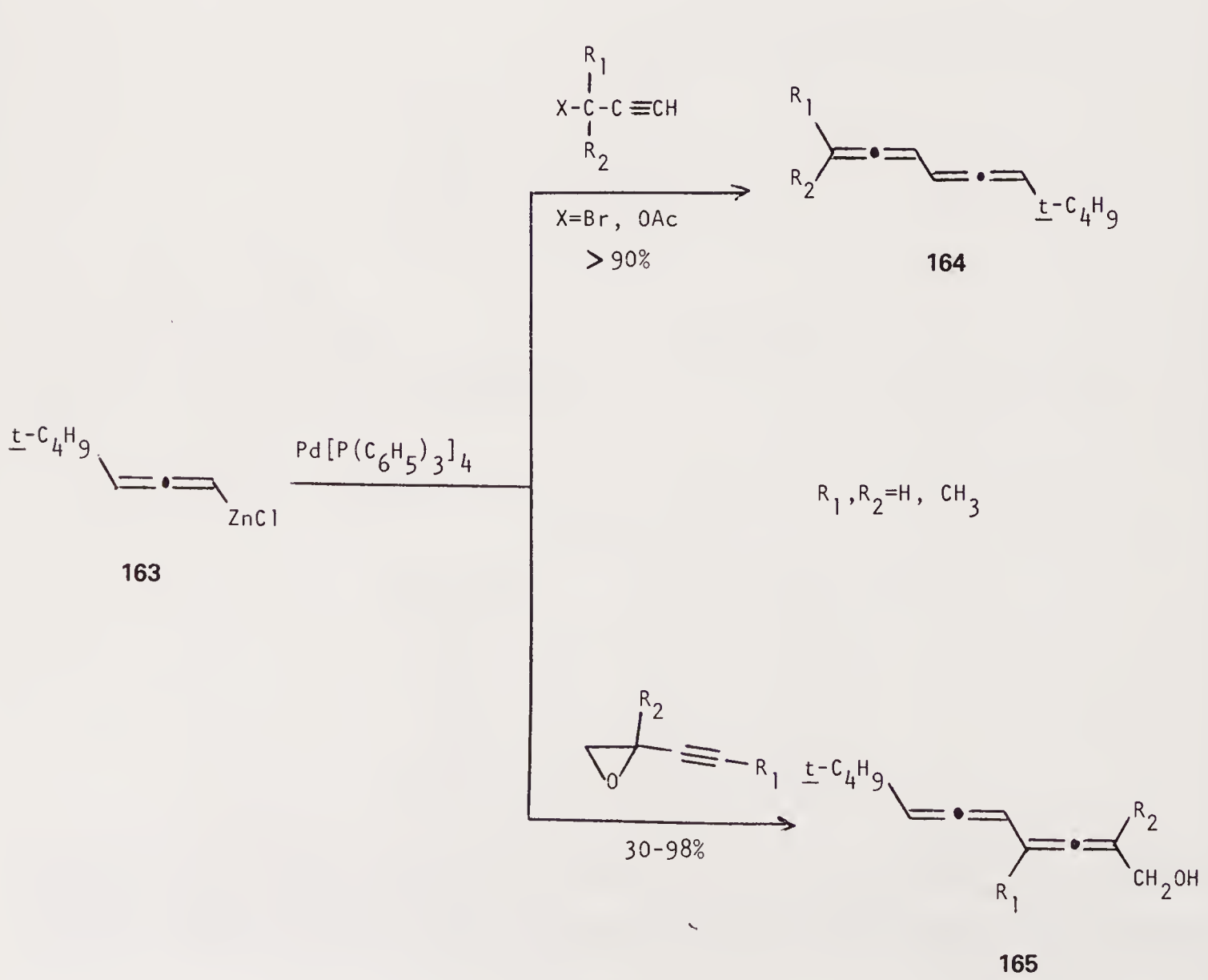


(35)

161 162

R=CH3 64%

R=(CH3)3Si 52%



164 163 165

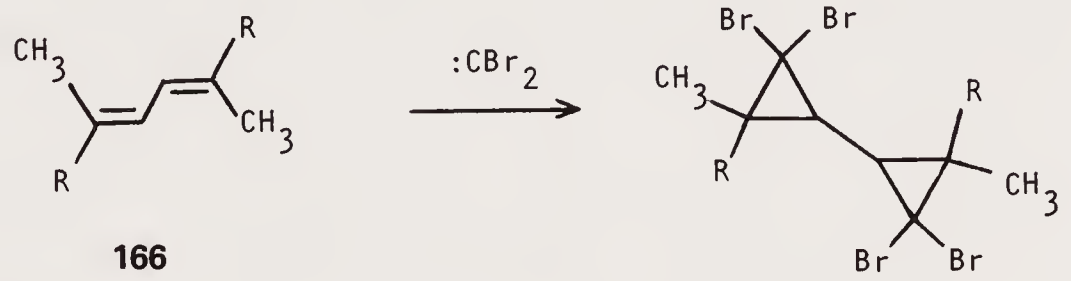
Scheme 24

To date no synthetic utility has been associated with such systems, although they present some interesting possibilities.

4.5. DIALLENES

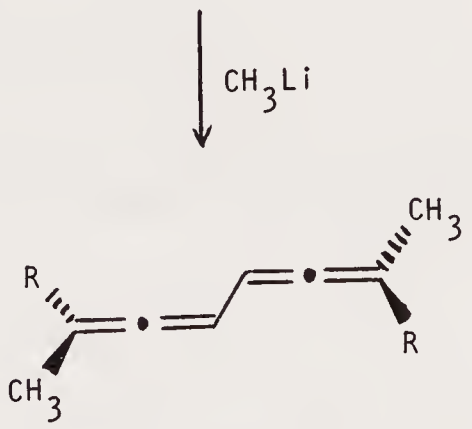
Attempts to prepare diallenes by various coupling reactions[118,121] have usually led to a mixture of isomers, generally in moderate yields, except in certain phenyl-substituted cases.[119,121] However, the coupling reaction of propargylic bromides or acetates with an allenylzinc chloride **163** in the presence of 0.5–2.0 mole % of $Pd[P(C_6H_5)_3]_4$ leads to conjugated diallenes **164** in high yields.[112,113] A similar reaction with acetylenic epoxides provides β-diallenols **165** also in high yields[114] (Scheme 24).

In a somewhat general synthetic method, conjugated *meso*-diallenes **168** are prepared from *trans*-dienes **166** by dibromocarbene addition followed by a stereospecific ring opening of **167** with methyl lithium.[122]



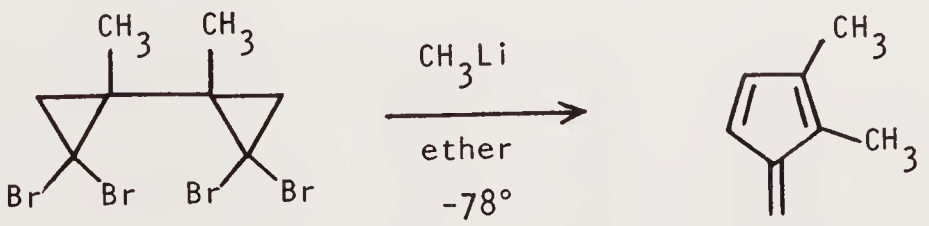
166 **167**

R	Yield **168**, %
CH_3	93
C_2H_5	82
C_6H_5	90
$\underline{t}\text{-}C_4H_9$	91



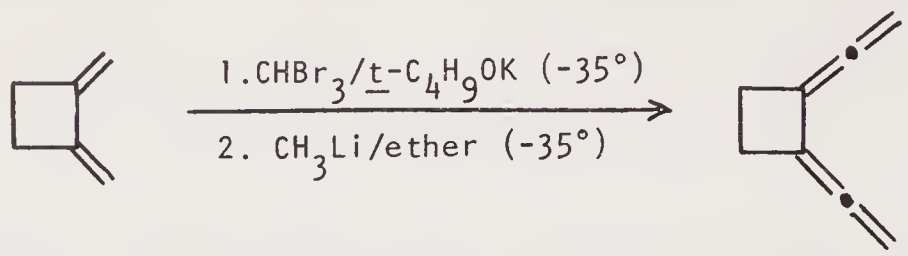
168 (36)

The manner of substitution is important in determining the products obtained. With 1,1′-dimethyl-2,2,2′,2′-tetrabromocyclopropyl cyclopropane (**169**), the only product observed is 1,2-dimethylfulvene (**170**).[123]



169 **170** (37)

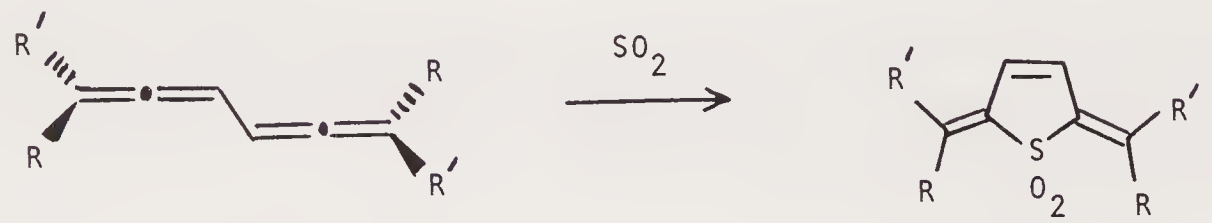
Exocyclic diallenes such as **172** can also be prepared by this method.[124]



(38)

171 **172**

The reaction of sulfur dioxide with conjugated diallenes takes place at room temperature with the formation of methylene sulpholenes (**173**) in good yields[125,126] (equation 39).

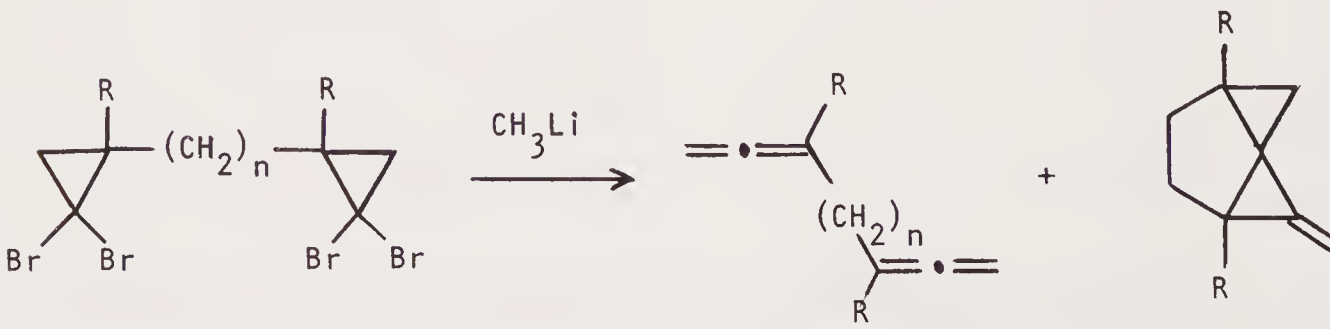


(39)

173

R	R′	Yield (%)
CH_3	CH_3	85
CH_3	t-C_4H_9	74
CH_3	C_6H_5	78
C_6H_5	C_6H_5	73

α,ω-Diallenes (**175**) are prepared from α,ω-bis(2,2-dibromocyclopropyl) alkanes (**174**) by reduction with methyl lithium[127] (equation 40).



(40)

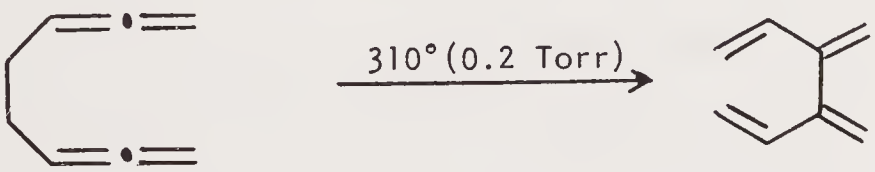
174 **175** **176**

R	n	% **175**	% **176**
H	2	68	28
CH_3	2	50	50
H	3	83	—
H	4	86	—

The length of the bridging chain is a factor in the outcome of the reaction. When $n = 2$, the proximity of the intermediate carbenoid species **177** is such that competitive formation of tricyclo[4.1.0.$0^{4,6}$]heptane (**176**) (by insertion of the carbene into the more substituted allene double bond) is observed. 1,2,5,6-Heptatetraene (diallenylmethane, **175** R = H, $n = 1$) cannot be prepared by this method.[128]

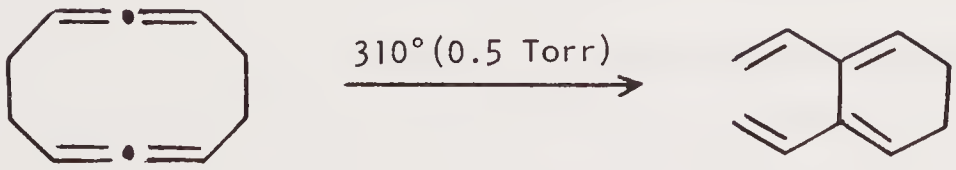
177

Some of these α,ω-diallenes undergo a thermal Cope rearrangement by means of a diradical mechanism. Thus heating 1,2,6,7-octatetraene (**178**) at 310°C under 0.2 torr pressure results in the formation of 3,4-dimethyl-1,5-hexadiene **179**.[129–131] The cyclic bisallene **180** rearranges to **181** under similar conditions.[132]



(41)

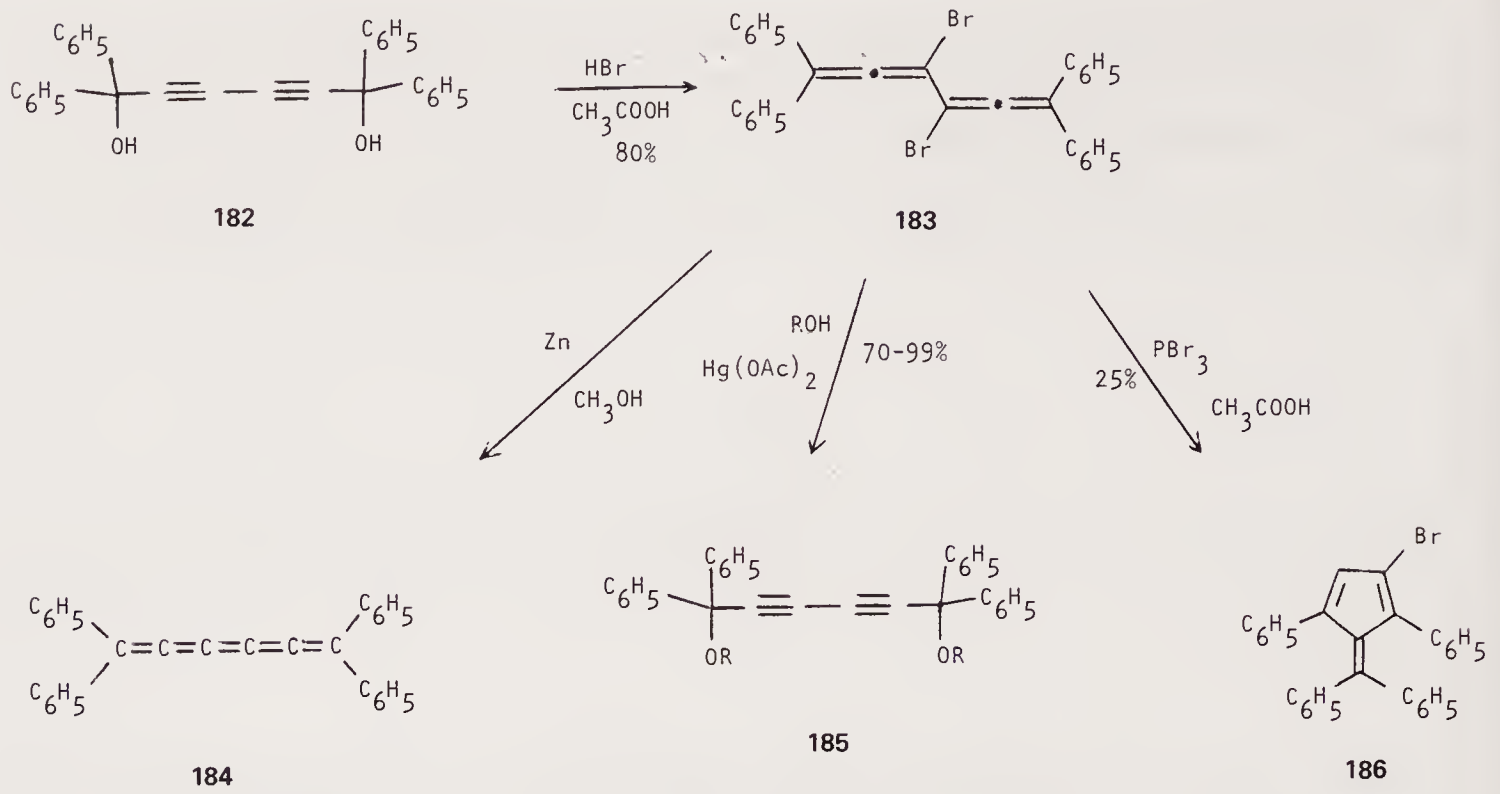
178 **179**



(42)

180 **181**

Halogen-substituted diallenes have also been prepared in good yields. When the diol **182** is treated with concentrated hydrobromic acid in acetic acid for 30 minutes, 1,1,6,6-tetraphenyl-3,4-dibromo-1,2,4,5-hexatetraene (**183**) is produced in 80% yield as colorless plates.[133] When this is heated with zinc dust in methanol, 1,1,6,6-tetraphenyl hexapentaene (**184**) is obtained, whereas heating for 30 minutes with mercuric acetate in various alcoholic solvents affords the diynes **185** in good yields. Treatment with phosphorus tribromide in acetic acid yields 1,4,6,6-tetraphenyl-3-bromofulvene (**186**) (Scheme 25).



Scheme 25

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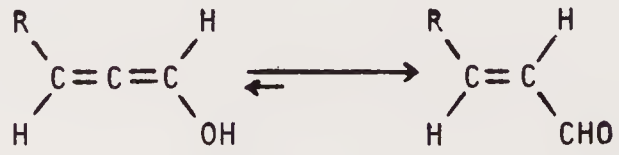
CHAPTER FIVE

HYDROXY AND OXO-SUBSTITUTED ALLENES

Allenic hydrocarbons can be functionalized with oxygen substituents in virtually any position. Nuclear hydroxy allenes are nothing more than the enol tautomer of acrolein derivatives. The equilibrium, however, lies so far to the right that the allene structure is not present in any significant quantity. When the tautomerism is frozen in the allenic form by substitution on the oxygen, stable allenic ethers result, and these are discussed in Chapter 7.

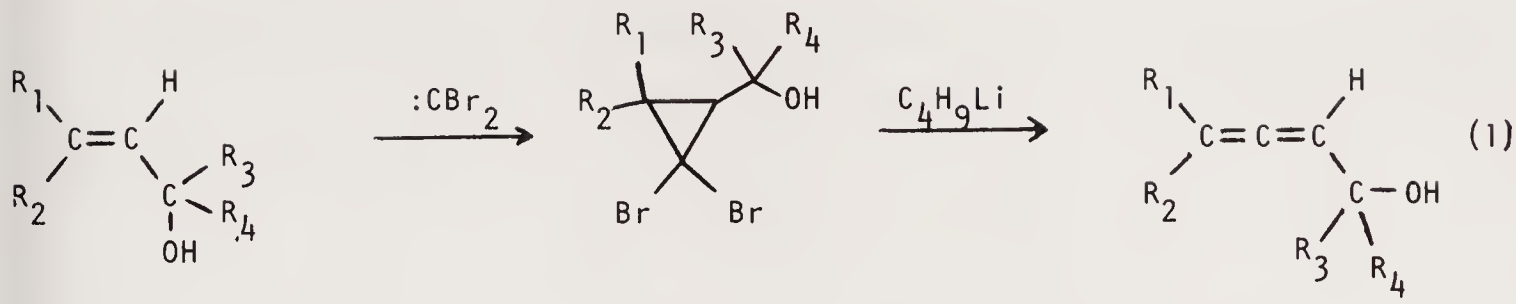


Moving the hydroxy substituent away from the nucleus to the α-position and beyond results in allenic alcohols that are stable and isolable. Since allenic alcohols and aldehydes (or ketones) are interconvertible by oxidative or reductive methods, they are both presented in this chapter.

5.1. ALCOHOLS

5.1.1. α-Allenic Alcohols

Allenic alcohols are readily synthesized using the same general reaction types employed for the preparation of alkylallenes. Allylic alcohols **1** are converted to *gem*-dibromocyclopropylcarbinols **2** by treatment with dibromocarbene. Reduction with *n*-butyllithium gives allenic alcohols **3** in moderate yields.

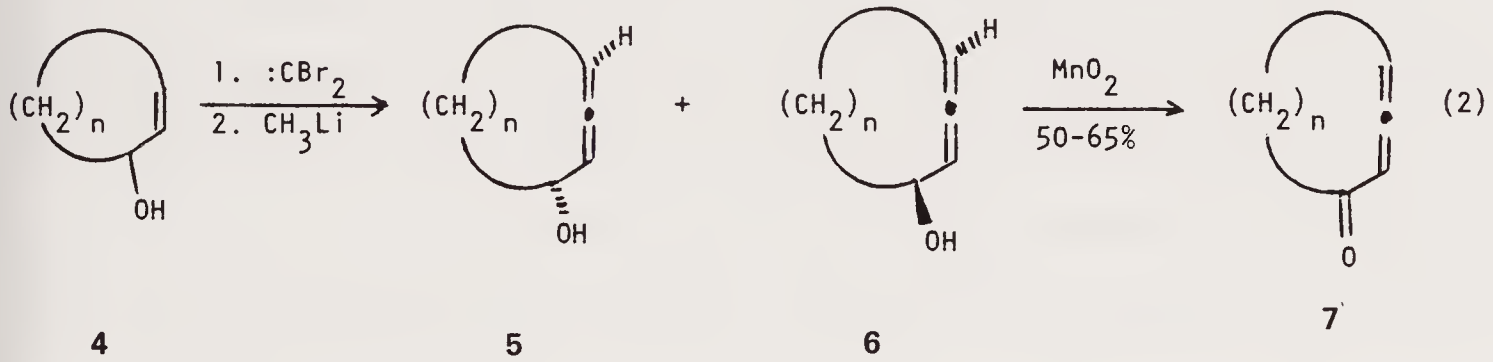


(1)

1 **2** **3**

R_1	R_2	R_3	R_4	Yield (%)	Reference
CH_3	CH_3	H	H	43	3, 4, 5
CH_3	CH_3	CH_3	H	44	3, 4, 5
CH_3	CH_3	CH_3	CH_3	65	3, 4, 5
H	$—(CH_2)_6—$		H	58	3, 6

Cyclic allylic alcohols **4** can be resolved as their camphanate esters. Sequential treatment with dibromocarbene followed by methyllithium gives a mixture of the diastereomeric allenic alcohols **5** and **6** which are readily separable by chromatographic techniques (equation 2). It is interesting to note that **6** is easily oxidized to the cycloallenone **7** with manganese dioxide, whereas **5** remains unchanged.[7]

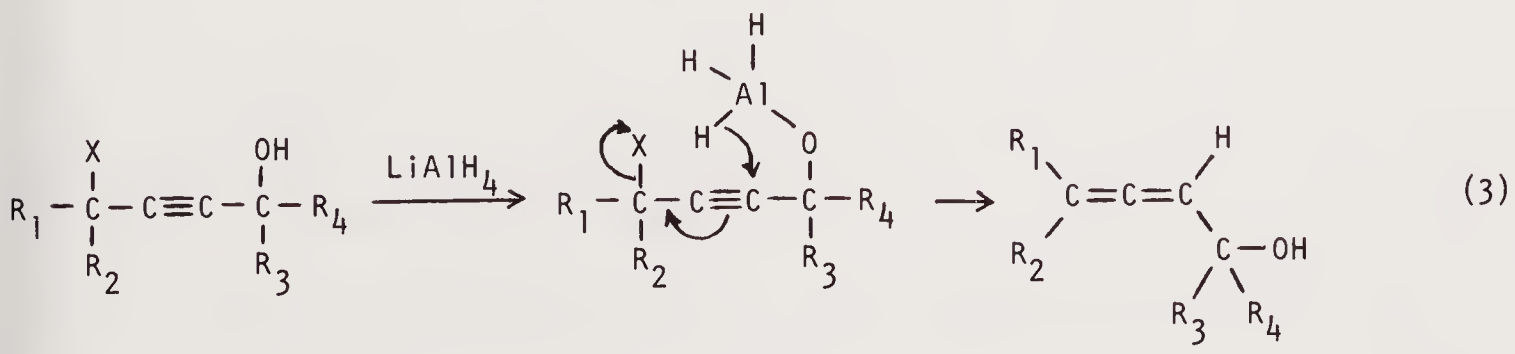


(2)

4 **5** **6** **7**

n=5,7,9

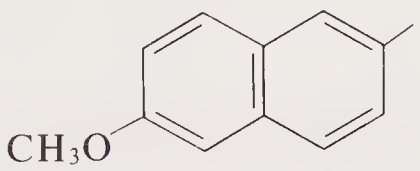
One of the most versatile and widely used methods for allenic alcohol synthesis is the S_N2' addition of hydride (from lithium aluminum hydride) to propargylic alcohols **8** (equation 3). One particular advantage of this reaction is the variety of functionalities capable of behaving as a suitable leaving group (X). The most commonly used X groups are chlorine,[8,9] alkyl ether derivatives,[10–12] THP-oxy,[11,13–17] nitro,[18] and quaternary ammonium salts[19–21] (see Table 5.1)



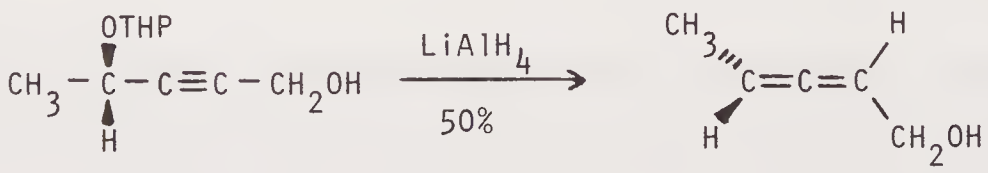
(3)

8 **9** **3**

TABLE 5.1. α-Allenic Alcohols Prepared from Hydride Addition to Propargylic Alcohols (Equation 3)

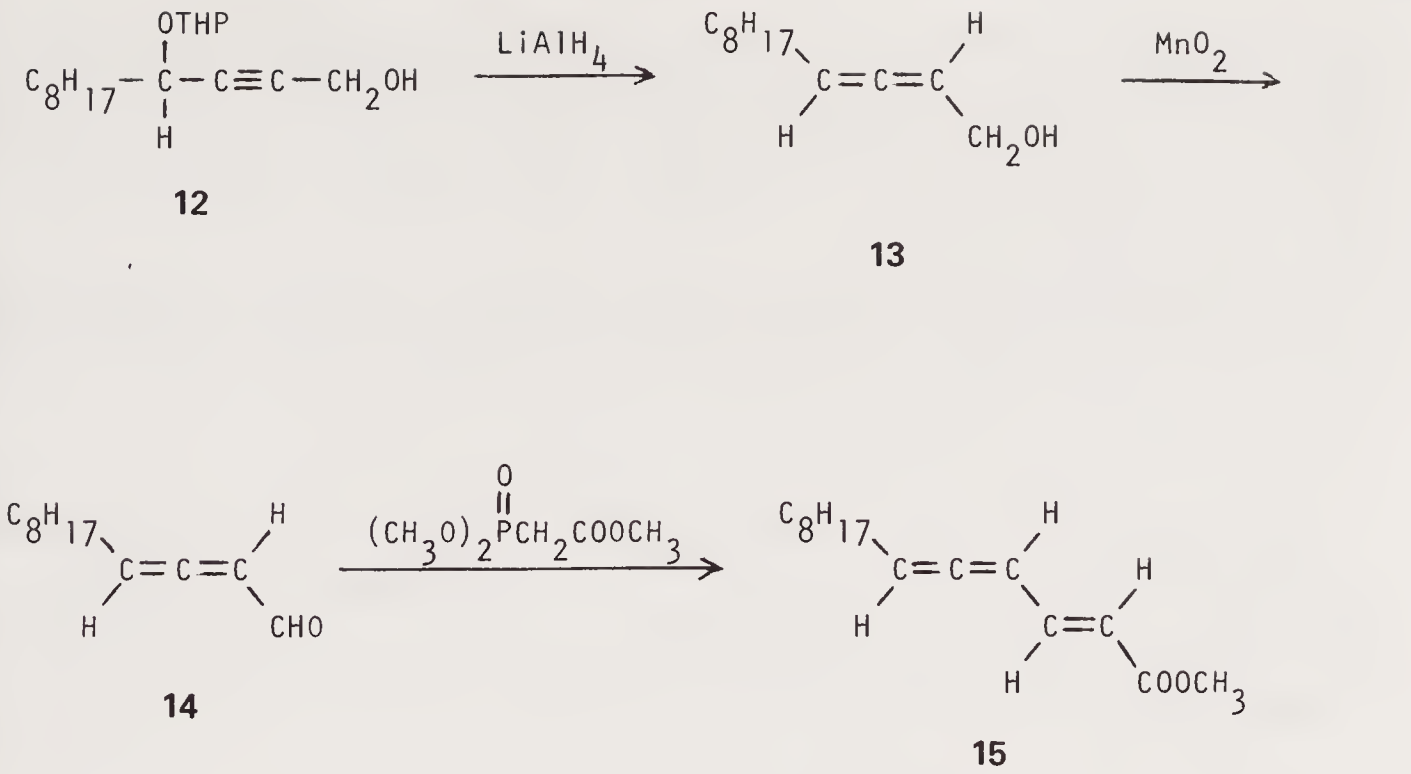
R_1	R_2	R_3	R_4	X	Yield (%)	Reference
H	H	H	H	Cl	68	8
CH_3	H	H	H	Cl	72	9
H	H		CH_3	$\overset{+}{N}(CH_3)_3$	84	19
C_6H_5	H	H	H	OCH_3	70	10
—$(CH_2)_5$—		H	H	OCH_3	97	10
CH_3	C_2H_5	H	H	OCH_3	98	10
CH_3	CH_3	H	H	NO_2	93	18
C_3H_7	H	H	H	OTHP	95	15
CH_3	C_2H_5	H	H	OTHP	73	15
H	H	C_4H_9	H	OTHP	82	13
H	H	—$(CH_2)_5$—		OTHP	72	11, 13

Mechanistically, the transformation proceeds by initial formation of an O-aluminum species **9** which then internally delivers hydride, followed by an *anti*-selective 1,2-elimination of X. For THP-oxy derivatives this *anti* elimination is nearly exclusive (>95%).[22] When an asymmetric propargyl derivative such as **10** is employed, the chirality is almost completely transferred to the alcohol **11** (>90% ee). Chiral allenic alcohols are additionally prepared from racemic propargyl alcohols containing an optically active quaternary ammonium derivative as the leaving group, however, the asymmetric induction is substantially lower.[20,23]



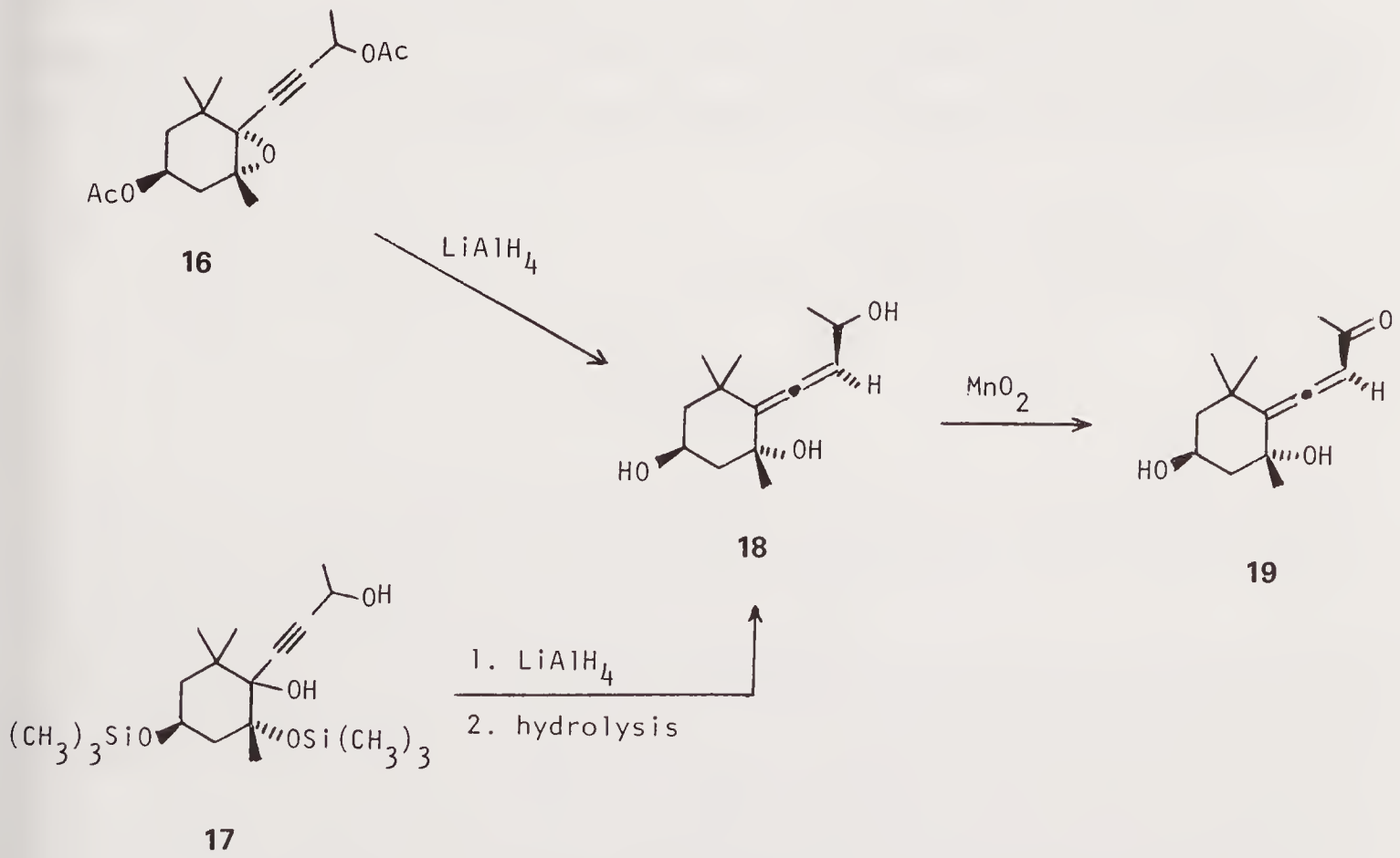
(S)-(-)-**10** (R)-(-)-**11** (4)

Several naturally occurring compounds are readily accessible by using the propargyl alcohol → α-allenic alcohol conversion as a key step in their syntheses. (−)-Methyl (E)-2,4,5-tetradecatrienoate (**15**) is an allenic sex attractant produced by the male Dried Bean Beetle (*Acanthoscelides obtectus*). Its synthesis in racemic form is outlined in Scheme 1.[24] The aldehyde **14** is relatively unstable, and spectral monitoring of the reaction mixture in the oxidation step is essential for optimum yield. An interesting alternate synthesis of **13** has recently been reported in one step from 1-undecyne by reaction with formaldehyde/dimethylaluminum chloride complex.[25]



Scheme 1

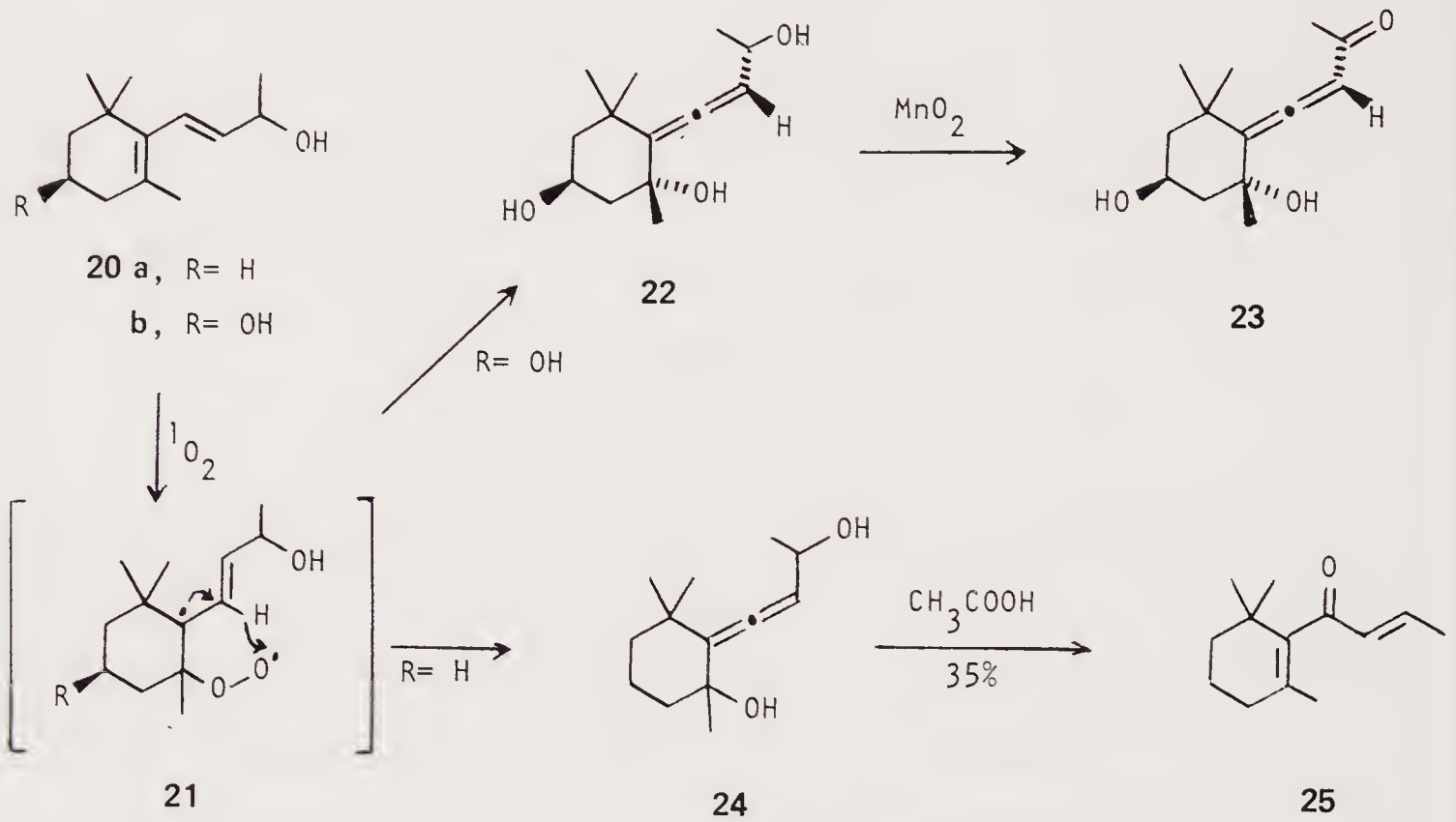
The defense mechanism of the large, flightless grasshopper, *Romalea microptera,* responds by secreting a froth from respiratory openings on its thorax.[26] A major component of the secretion is a conjugated allenic ketone called ''grasshopper ketone'' (**19**). Its synthesis has been accomplished in both racemic[27–29] and optically active[30] form. The penultimate step in the sequence (Scheme 2) involves the formation of allenic triol **18** from either epoxide **16** or diol **17**. Selective oxidation of the α-allenic alcohol with manganese dioxide furnishes the natural product.



Scheme 2

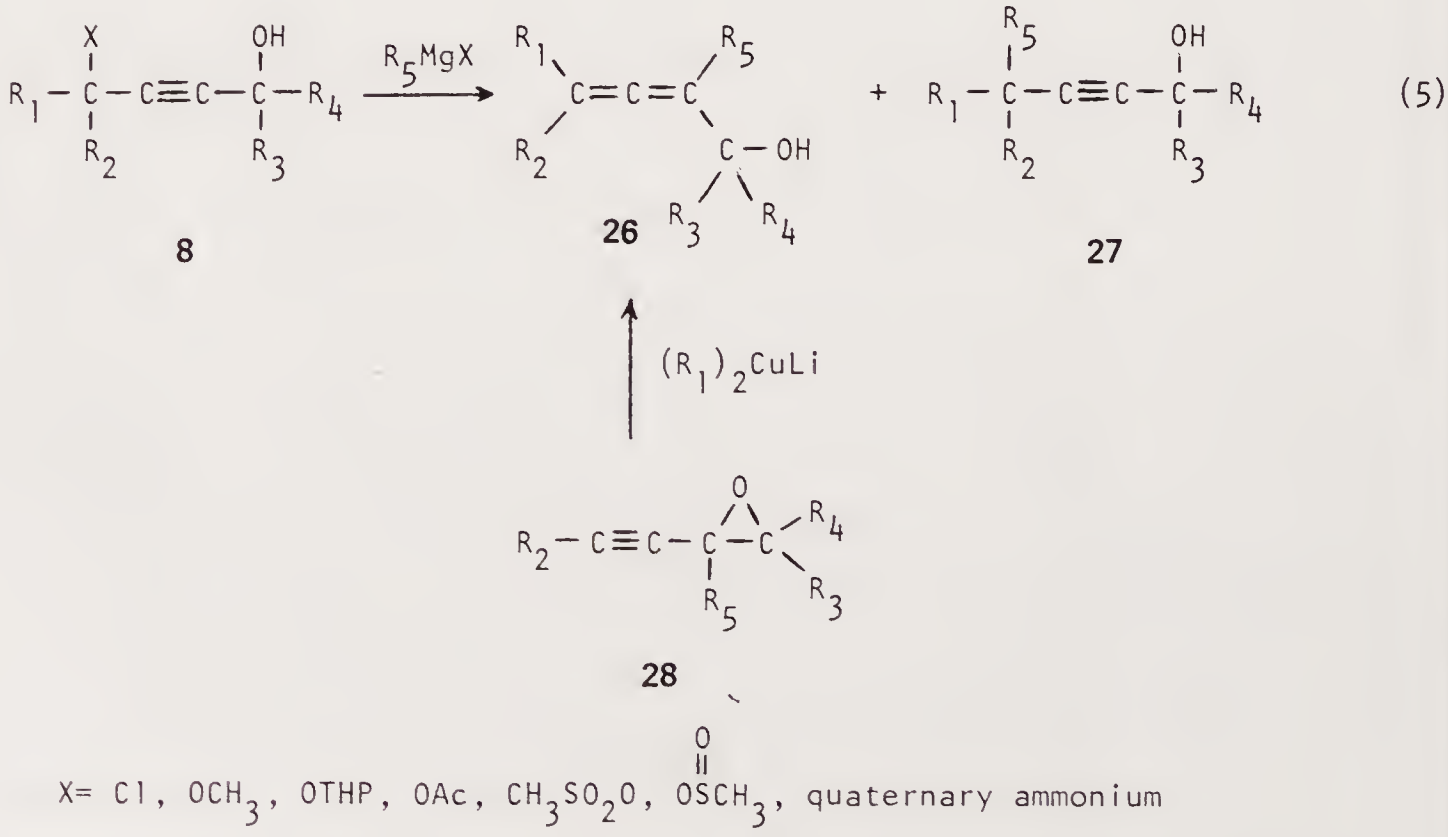
The unnatural isomer of grasshopper ketone, **23**, is available from a biogenetic-type synthesis starting from 7-*trans*-3-hydroxy-β-ionol (**20b**; Scheme 3). In the presence of singlet oxygen, **20b** produces allenic triol **22** by way of an hydroperoxide-type intermediate **21b**.[31] Evidently, attack of singlet oxygen occurs *trans* to the hydroxy group at C-3.[29]

In an analogous transformation β-ionol (**20a**) is oxidized by singlet oxygen to the diol **24**.[32] Subsequent treatment with acetic acid furnishes β-damascone (**25**).[33]



Scheme 3

The addition of organometallics to propargyl alcohol derivatives (**8**) result in the formation of allenic alcohols of type **26** (equation 5). The competitive formation of allene **26** versus its isomeric acetylene **27** can be biased to favor, if not exclusively

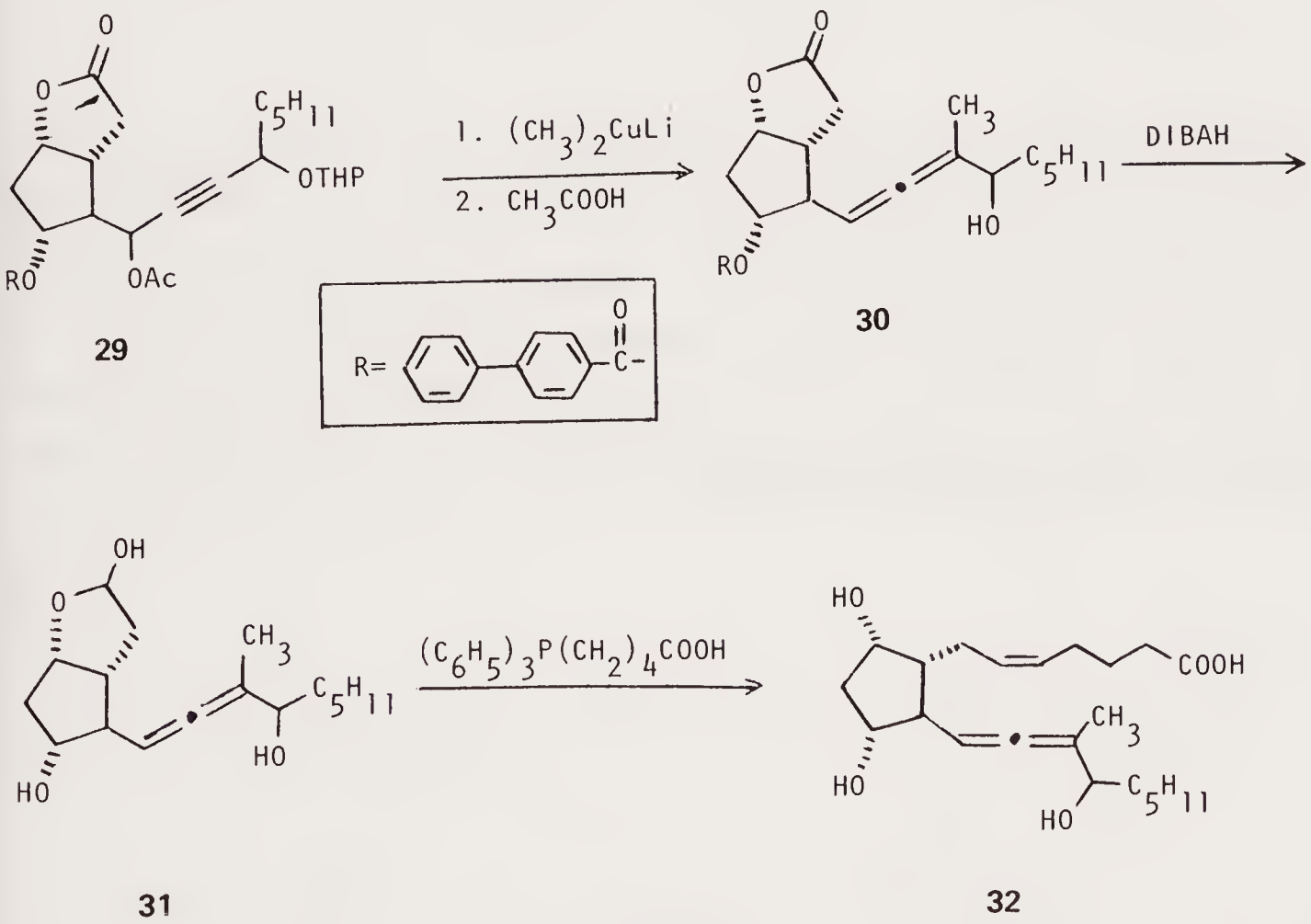


(5)

produce, the allene by varying the organometallic reagent in conjunction with prudent selection of reaction conditions. When Grignard reagents are used, the temperature, quantity of reagents, and order of addition strongly influence the proportion of the allene formed[34,35] (up to 90% of **26** can be obtained).

The nature of the leaving group X also has an effect on the **26**:**27** ratio. Substitution reactions of **8** (X = OCH_3,OTHP) with alkyl Grignard reagents in the presence of cuprous iodide afford mixtures of **26** and **27** where, in some cases, the acetylene represents the major component.[36] The use of acetate or methanesulfinate as the leaving group with lithium dimethylcuprate[37] or $[R_5CuBr]MgX \cdot LiBr$[38] as the organometallic reagent furnishes excellent yields of the allenic alcohol with no contamination with the acetylene.

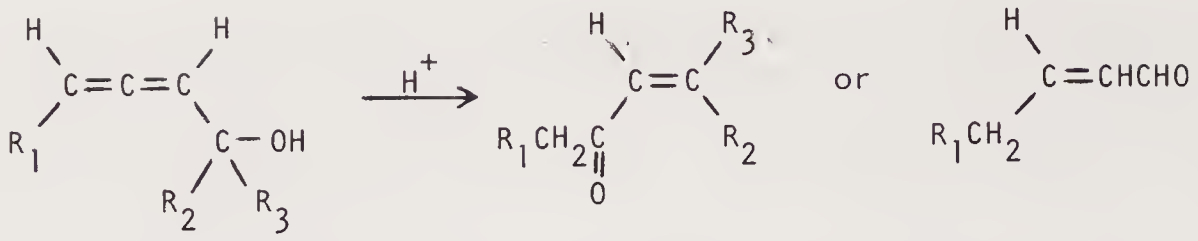
An interesting application of this type reaction is the synthesis of a lower-chain allenic prostaglandin (**32**). The preparative sequence **29** → **32** is illustrated in Scheme 4.[39]



Scheme 4

Allenes **26** can alternately be obtained by the addition of organocopper reagents to α-acetylenic epoxides **28**.[40,41] When lithium dialkylcuprates are used, acetylene-free allenic alcohols are produced in 30–75% yield.

The ability of allenic alcohols to enter into reactions in an inter- or intramolecular fashion makes them valuable intermediates for the preparation of synthetically useful substances. In the presence of aqueous acid, secondary and tertiary α-allenic alcohols isomerize to give α,β-unsaturated ketones (**33**) in good yields (equation 6). Primary alcohols give mixtures containing both **33** and α,β-unsaturated aldehydes **34**.[42,43] The use of sulfuric acid results in the enhancement of the ketone portion of the mixture, whereas phosphoric acid favors the aldehyde.

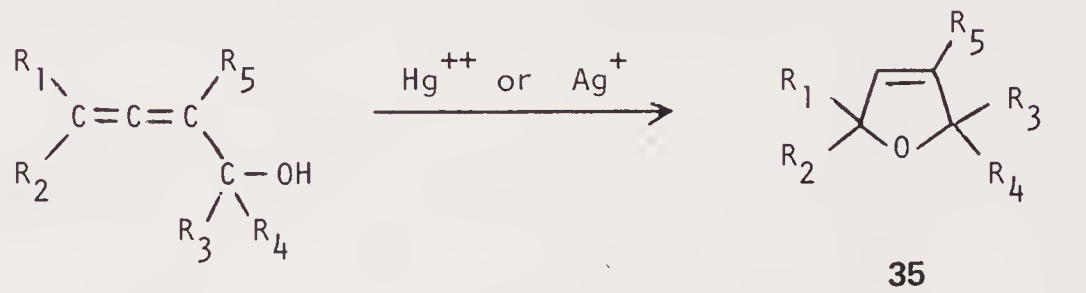


33 **34** (6)

acids: H_2SO_4, CH_3COOH, H_3PO_4

R_1	R_2	R_3	Yield, **33** (%)	Reference
H	H	C_2H_5	75	44
H	CH_3	CH_3	95	45
H	—$(CH_2)_5$—		80	45
—$(CH_2)_6$—		H	81	6

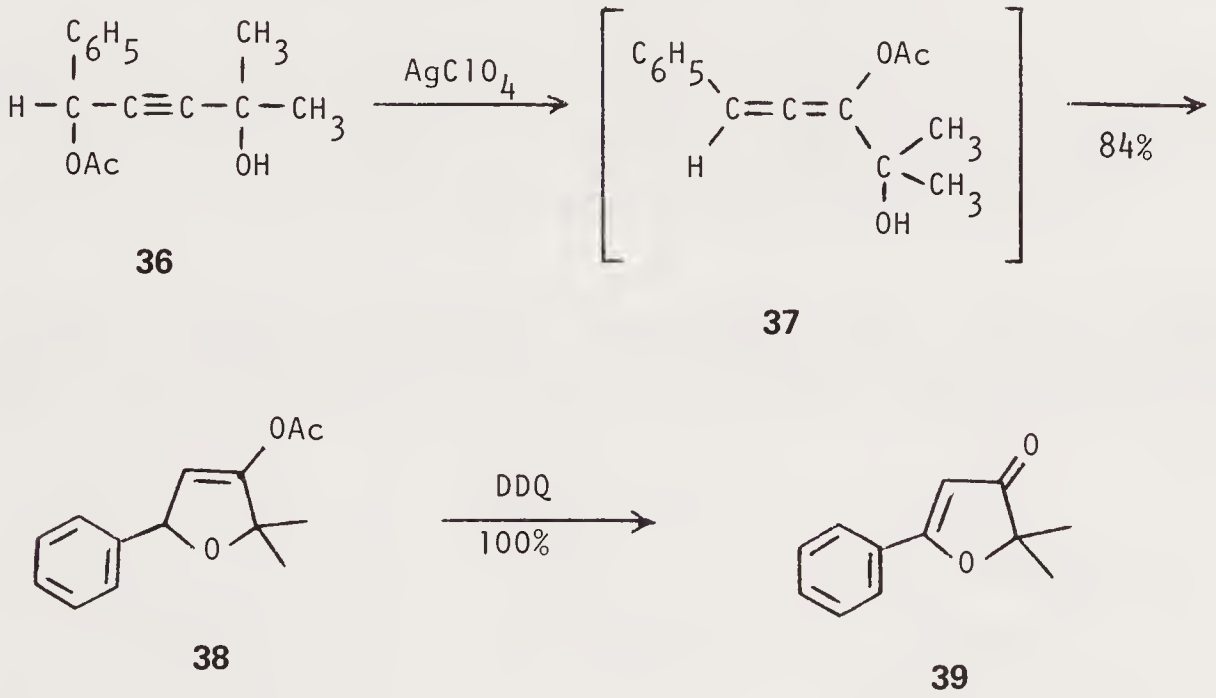
In the presence of mercury(II) or silver(I) ions, α-allenic alcohols **26** cyclize to produce 2,5-dihydrofurans **35** in moderate yields (equation 7). In mercury-assisted cyclizations, only primary alcohols ($R_3 = R_4 = H$) are converted to furans.[42,46] Secondary or tertiary alcohols give only α,β-unsaturated ketones similar to **33**. This limitation can be easily circumvented by employing silver(I) salts.[47] Silver tetrafluoroborate is the catalyst of choice when **26** is functionalized in the δ position. However, when the δ position is unoccupied ($R_1 = R_2 = H$), silver nitrate is required to obtain complete cyclization.



26 **35** (7)

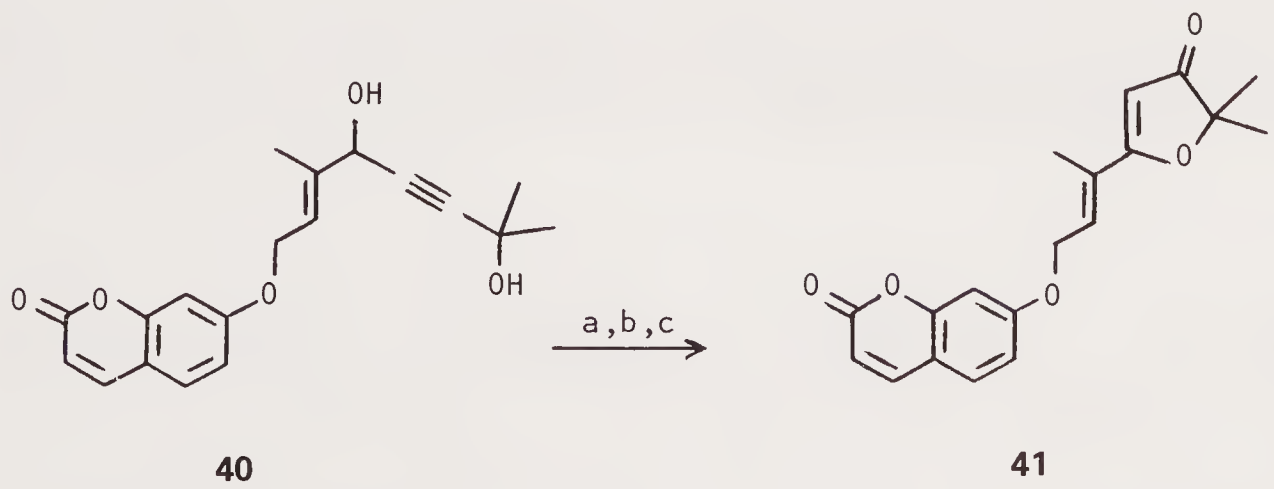
R_1	R_2	R_3	R_4	R_5	Metal Salt	Yield (%)	Reference
H	H	H	H	CH_3	$HgSO_4$	47	42, 46
CH_3	CH_3	H	H	H	$Hg(OAc)_2$	49	46
CH_3	CH_3	*i*-C_3H_7	H	H	$AgBF_4$	61	47
H	H	*i*-C_3H_7	CH_3	H	$AgNO_3$	57	47
H	H	—$(CH_2)_5$—		H	$AgNO_3$	60	47

Unsymmetrically substituted 2-butyne-1,4-diols can be monoacetylated at the less hindered hydroxyl group with acetic anhydride in pyridine. When acetate **36** (prepared in this fashion) is treated with silver perchlorate, the dihydro-3(2H)-furanone enol acetate **38** is obtained in excellent yield. The transformation can be explained by initial silver(I)-catalyzed isomerization of **36** to allenyl acetate **37** followed by a silver(I)-assisted cyclization.[48] Oxidation of **38** with DDQ affords a quantitative yield of bullatenone (**39**).



Scheme 5

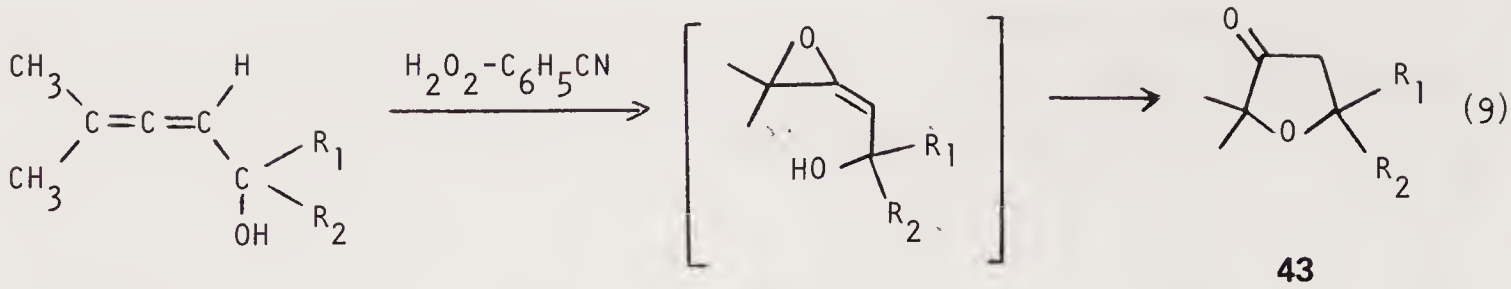
By a similar sequence of reactions (equation 8), geiparvarin (**41**), a furanone possessing antitumor activity, is prepared from **40** in 61% yield.[48]



(8)

(a) Ac_2O, (b) $AgClO_4$, (c) DDQ

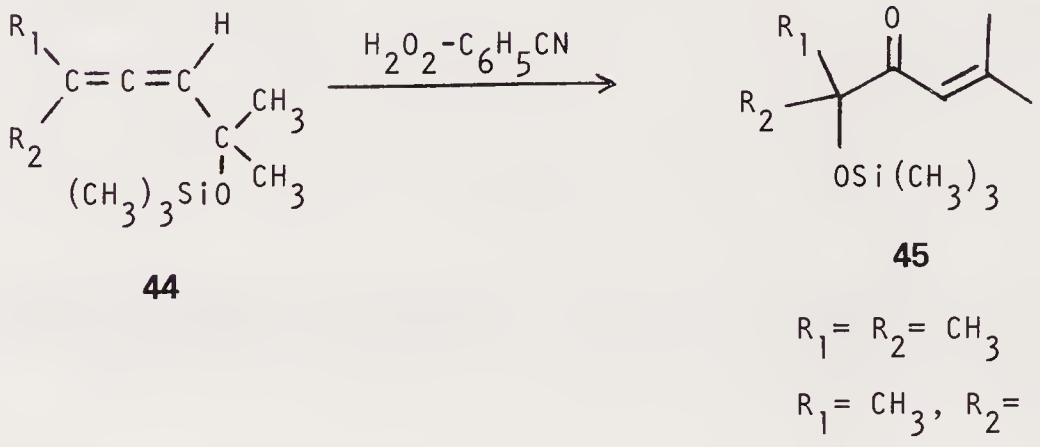
The oxidation of α-allenic alcohols with peroxybenzimidic acid results in the direct formation of 3-furanones (**43**) by way of an intermediate allene oxide[49] (equation 9). The efficiency of the reaction depends on the degree of functionalization of the α-carbon. Primary alcohols afford a negligible amount of product, whereas tertiary alcohols give quantitative conversions.



42 43 (9)

R_1	R_2	Yield (%)
H	H	10
CH_3	H	60
CH_3	CH_3	100

Protected alcohols, when subjected to analogous conditions, react by a 1,4-migration of the oxygen function to give α,β-unsaturated ketones[50] (equations 10 and 11).

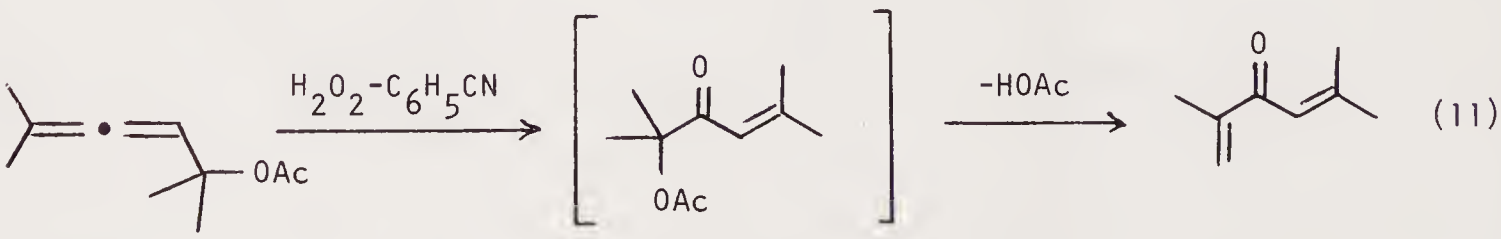


44 45 (10)

$R_1 = R_2 = CH_3$ 62%

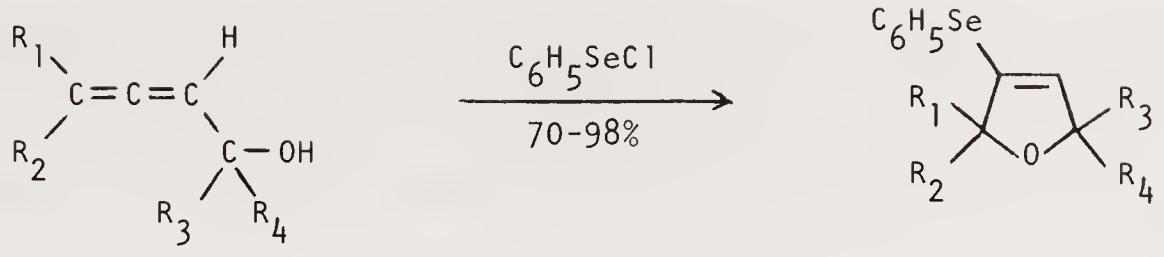
$R_1 = CH_3$, $R_2 = C_2H_5$ 75%

In the case of allenic acetate **46**, the intermediate **47** eliminates acetic acid to give dienone **48** in 72% yield.



46 47 48 (11)

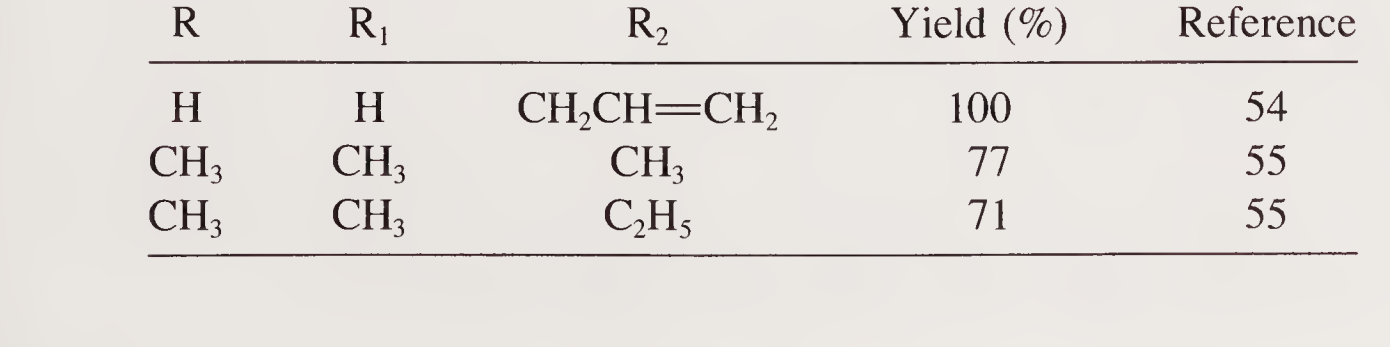
The electrophilically induced cyclization of α-allenic alcohols with phenylselenyl chloride produces derivatives of 3-phenylseleno-2,5-dihydrofuran (**49**) in high yields[51] (equation 12). Reactions involving terminal allenes proceed at a much slower rate than with internal allenes, however, the rate (and yield) can be increased by the addition of triethylamine to absorb any HCl that is generated.



3 **49** (12)

R_1, R_2, R_3, R_4= H, CH_3, C_2H_5, i-C_3H_7, t-C_4H_9

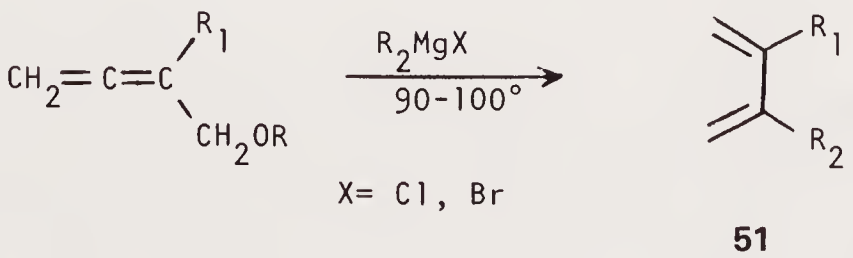
Conjugated dienes **50** are readily accessible from **3** by the S_N2' addition of hydride[52,53] (equation 13). The reaction is usually performed in refluxing THF to sustain a reasonable rate for the complete consumption of **3** (3 hours).



3 **50** (13)

R_1	R_2	R_3	R_4	Yield (%)
H	H	—$(CH_2)_5$—		75
CH_3	CH_3	C_2H_5	C_2H_5	70

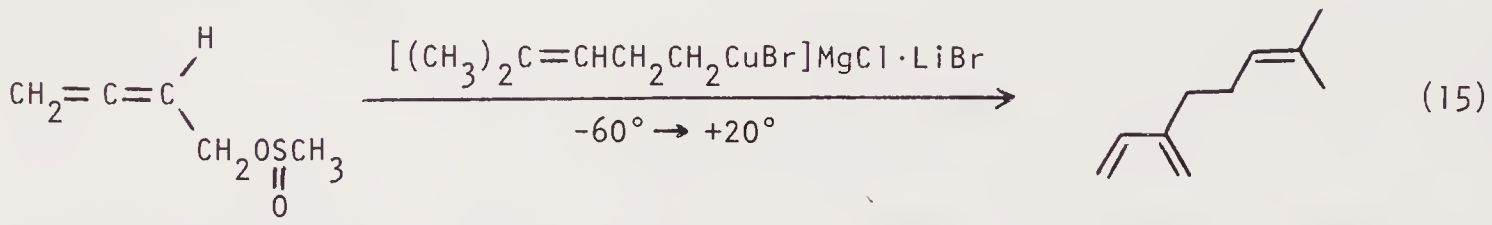
Mono- or disubstituted 1,3-dienes (**51**) can be obtained by the addition of Grignard reagents to either α-allenic alcohols or ethers (equation 14). In reactions involving allenyl ethers, high temperatures and long reaction times (40 hours) are required for complete conversion.



51 (14)

R	R_1	R_2	Yield (%)	Reference
H	H	$CH_2CH{=}CH_2$	100	54
CH_3	CH_3	CH_3	77	55
CH_3	CH_3	C_2H_5	71	55

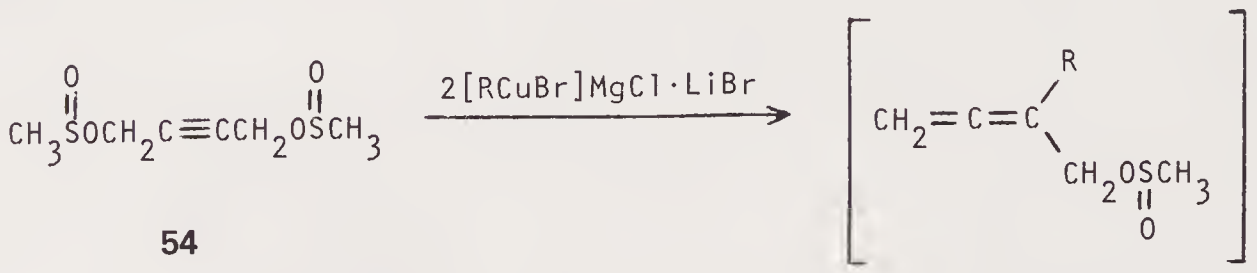
A much milder and more efficient process for the preparation of conjugated dienes is the reaction of an α-allenyl sulfinate with an organocopper(I) reagent (equation 15). The transformation is usually complete within 30 minutes at a temperature below 25°C. In this manner the natural product myrcene (**53**) is obtained from **52** in 90% yield.[56]



(15)

52 **53**

Symmetrically 2,3-disubstituted-1,3-dienes can be formed directly from propargyl disulfinate **54** without the isolation of the initially generated allene **55** (equation 16).

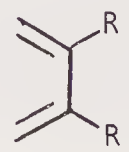


54 **55**

R= C_4H_9, i-C_3H_7, t-C_4H_9

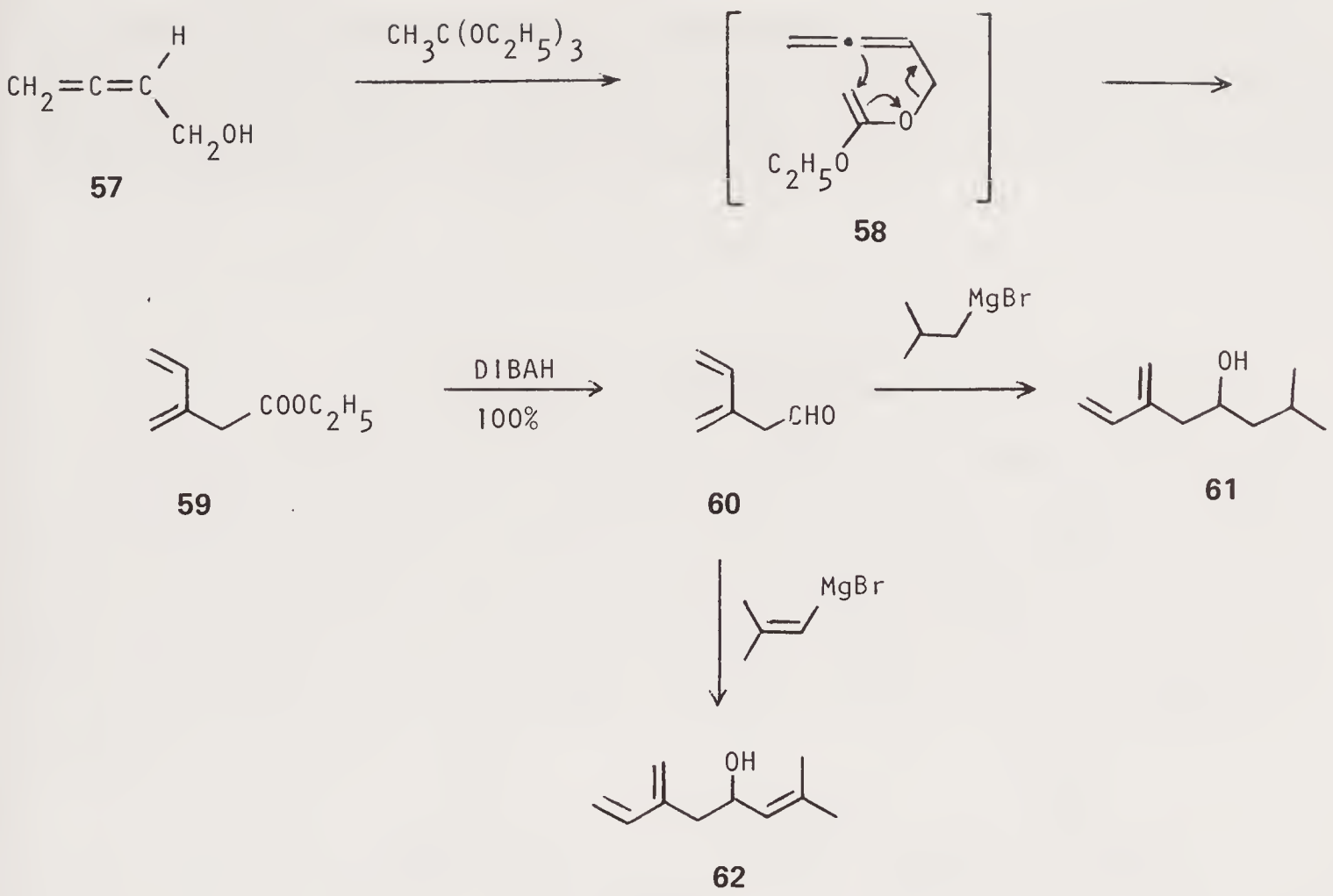
80-95%

(16)



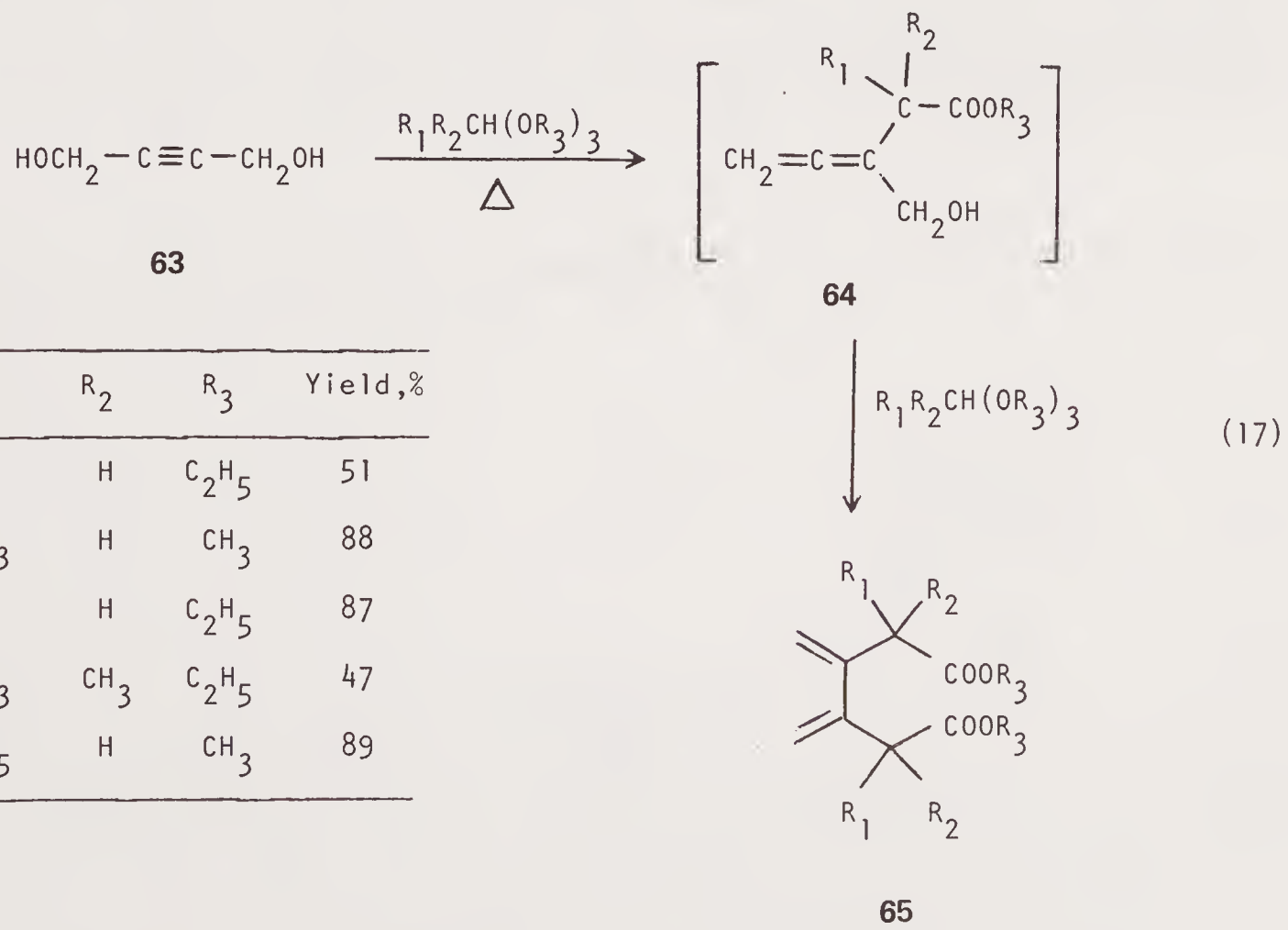
56

1-Hydroxy-2,3-butadiene (**57**), when allowed to react with triethyl orthoacetate at elevated temperatures, undergoes a Claisen orthoester rearrangement by way of **58** to produce dienyl ester **59** in high yield (Scheme 6). Amide analogs of **59** are also available from α-allenic alcohols by reaction with either N,N-diethylaminopropyne[57] or 1-dimethylamino-1-ethoxyethylene.[58] Ester **59** serves as a vital intermediate in the synthesis of two closely related natural products. Ipsenol (**61**) and ipsdienol (**62**), the principal components of the aggregation pheromone of *Ips confusus* (a bark beetle in ponderosa pine),[59,60] are readily synthesized in two steps from **59**. Conversion of the ester function to an aldehyde is achieved quantitatively by reduction with DIBAH. Treatment of this common intermediate (**60**) with either isobutylmagnesium bromide or 2-methylpropenylmagnesium bromide affords the desired sex attractants, each in 60% yield[61] (Scheme 6).



Scheme 6

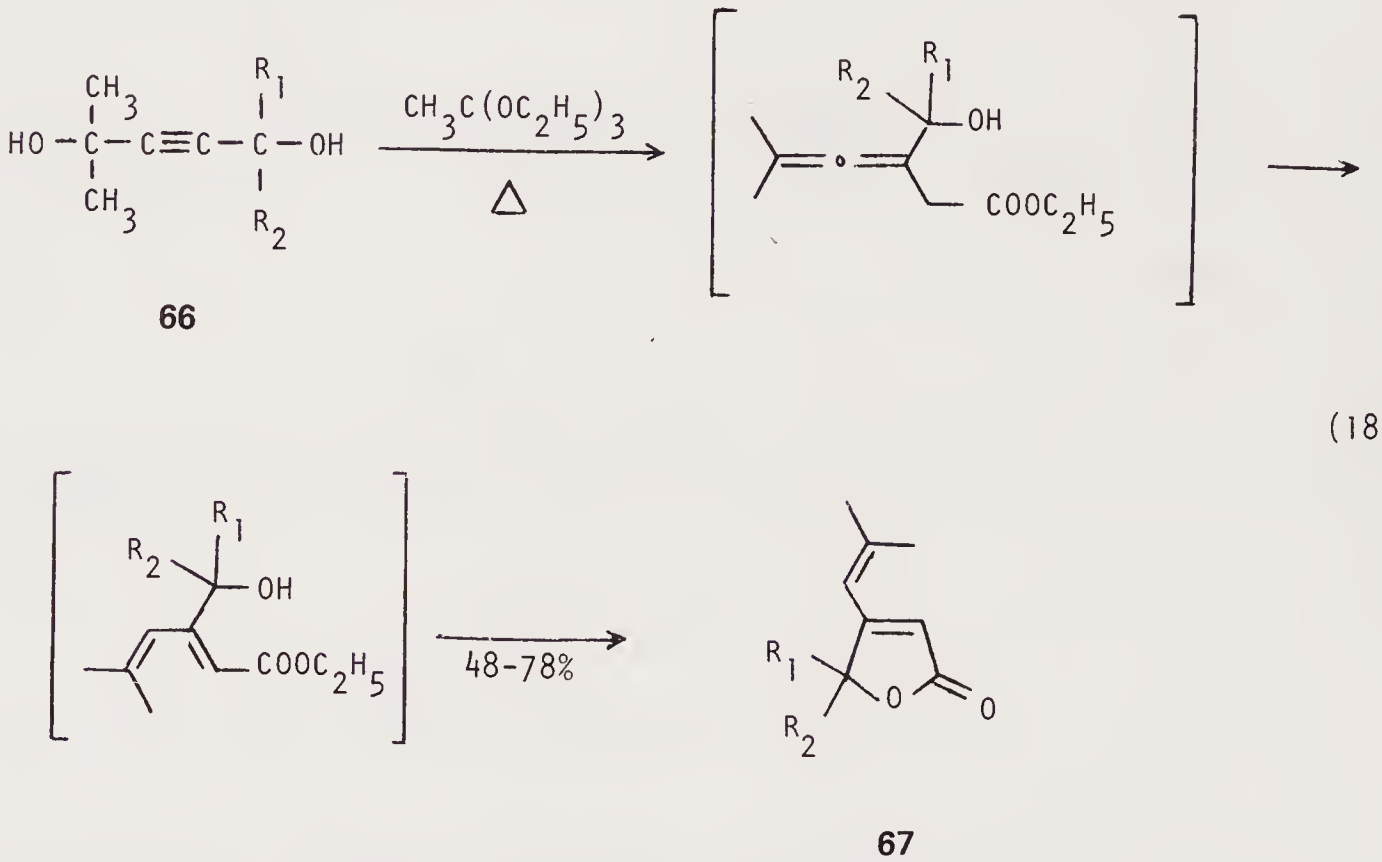
A convenient synthesis of 3,4-bis[methylene]hexanedioic esters (**65**) from 2-butynediol (**63**) makes use of a double Claisen orthoester rearrangement (equation 17) in which one of the mechanistic intermediates is allenic alcohol **64**. These unusually substituted dienes are obtained in good yield by heating **63** with an excess of an orthoester at 110°C in the presence of a catalytic quantity of propanoic acid.[62]



R_1	R_2	R_3	Yield,%
H	H	C_2H_5	51
CH_3	H	CH_3	88
Cl	H	C_2H_5	87
CH_3	CH_3	C_2H_5	47
C_6H_5	H	CH_3	89

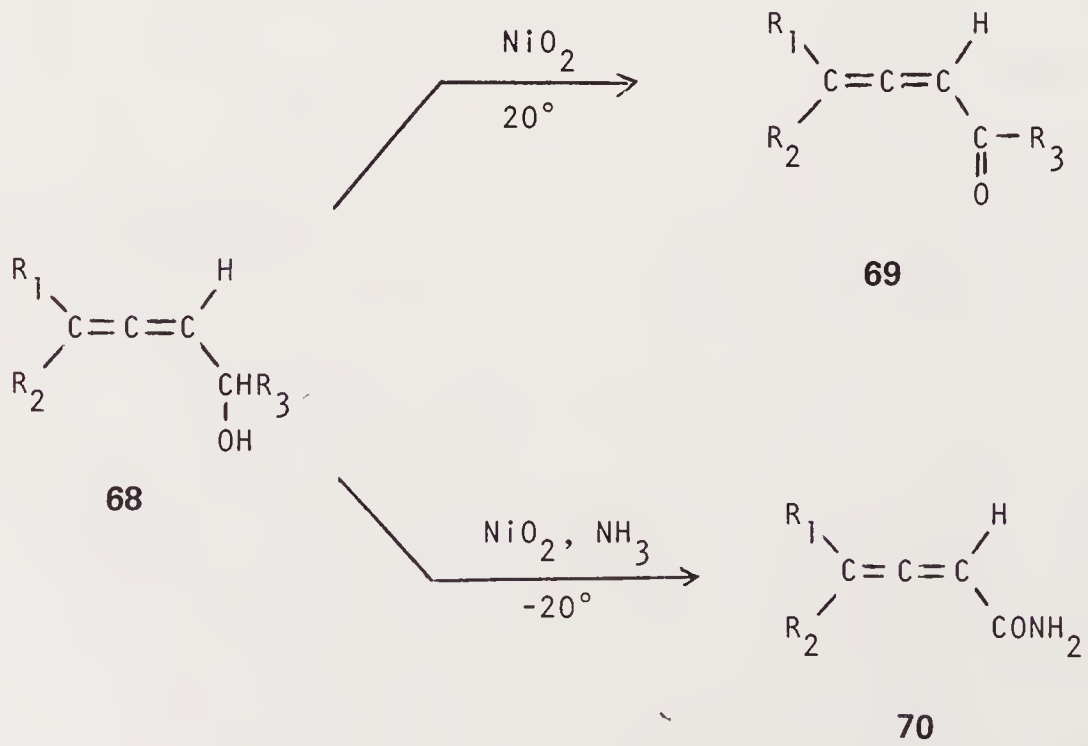
(17)

Tetrasubstituted 2-alkyne-1,4-diols (**66**), when heated at 140–150°C in the presence of a catalytic amount of pivalic acid, regioselectively produce butenolides **67**.[63] Under the reaction conditions, the initially formed allenic alcohol presumably rearranges to a 1,3-diene where subsequent lactonization gives the observed product.



(18)

Nickel peroxide selectively oxidizes disubstituted allenic alcohols **68** to the corresponding α-carbonyl derivatives **69**. The oxidation is usually performed in ether at room temperature utilizing 2.5–3 equivalents of the reagent. This method appears to be superior to manganese dioxide oxidations, where up to 30 equivalents of the reagent are required for complete conversion.[64,65] When the reaction is performed in the presence of ammonia, primary allenic amides **70** are directly obtained.[66]

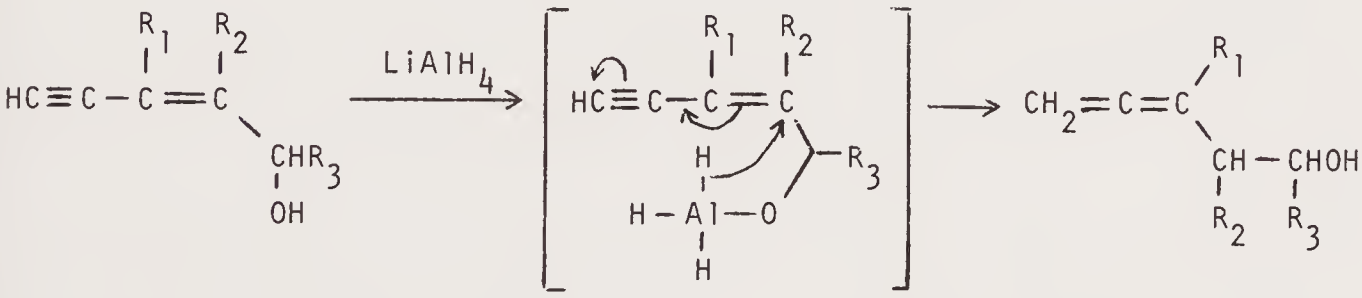


(19)

R_1	R_2	R_3	Yield, **69** (%)	Yield, **70** (%)
CH_3	CH_3	H	90	60
—$(CH_2)_5$—		H	75	55
CH_3	CH_3	CH_3	89	—
—$(CH_2)_5$—		CH_3	74	—

5.1.2. β-Allenic Alcohols

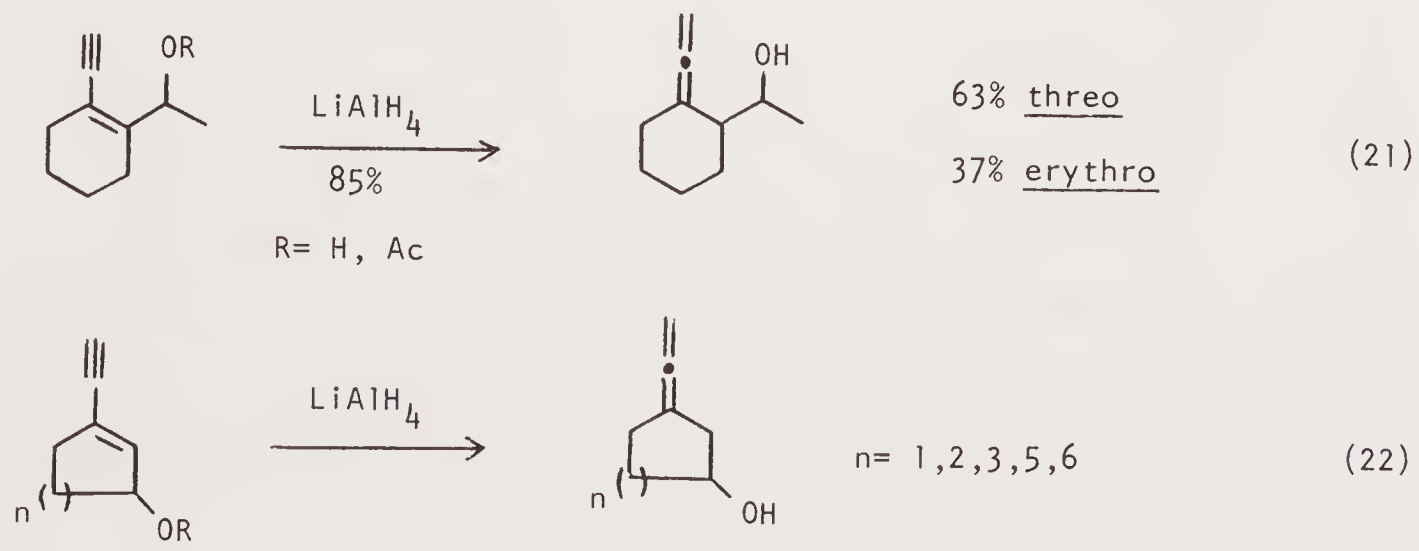
A generally reliable method for the preparation of β-allenic alcohols is the addition of hydride (lithium aluminum hydride) to hydroxy enynes as shown in equation (20). When the reduction is performed with chiral reducing agents such as lithium bismenthyloxyaluminum hydride[67,68] or lithium aluminum hydride-3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose complex,[69] optically active products are obtained. The former gives (+)-β-allenic alcohols, whereas the latter produces (−)-alcohols.



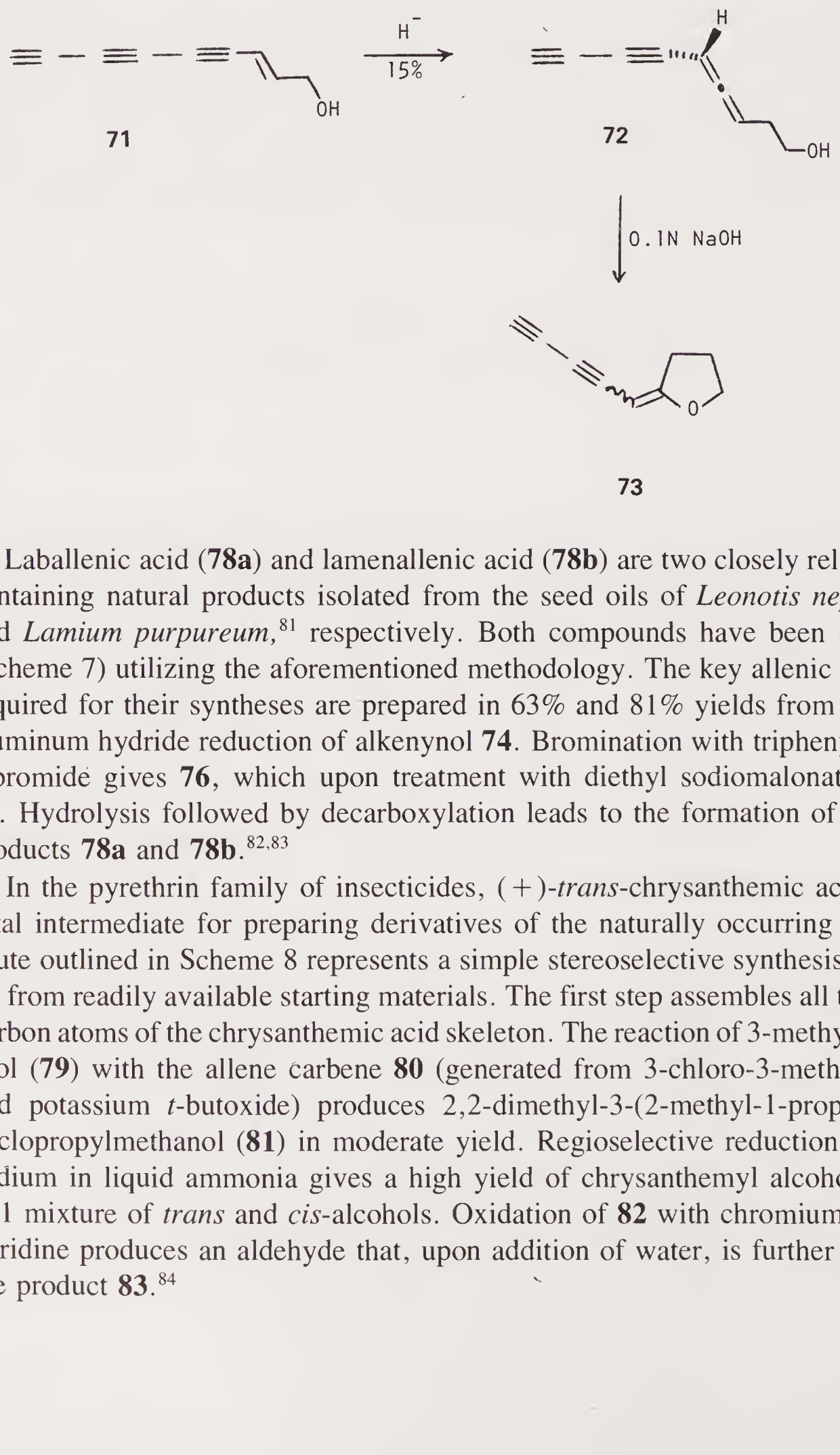
(20)

R_1	R_2	R_3	Yield (%)	Reference
H	H	H	83	70, 71
CH_3	H	H	60	72
H	H	CH_3	68	70
CH_3	CH_3	H	60	72
CH_3	CH_3	CH_3	60	72

Equations (21)[73,74] and (22)[6,72,75–77] illustrate the method's applicability for the preparation of exocyclic allenic alcohols.



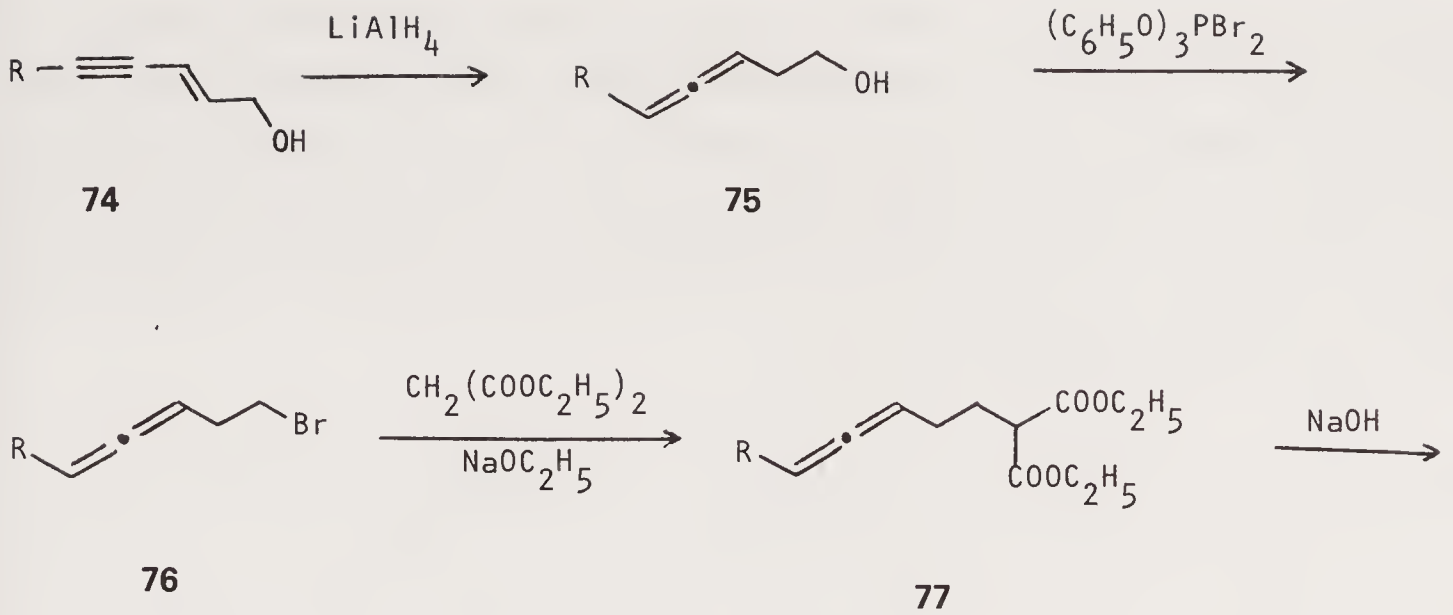
(+)-Marasin (**72**), an antibiotic isolated from the culture medium of *Aleurodiscus roseus,*[78] contains a β-hydroxy allene as part of its skeletal arrangement. Its synthesis is readily accomplished by the asymmetric reduction of 2-nonene-4,6,8-triyn-1-ol (**71**) with a fourfold excess of lithium bismenthyloxyaluminum hydride[68] (equation 23). The enantiomeric (−)-marasin can also be obtained from **71** by reduction with lithium aluminum hydride-3-O-benzyl-1,2-O-cyclohexylidene-α-D-glucofuranose complex.[69] Marasin is unstable toward aqueous alkali and cyclizes to isomarasin (**73**).[79]



71 **72** **73** (23)

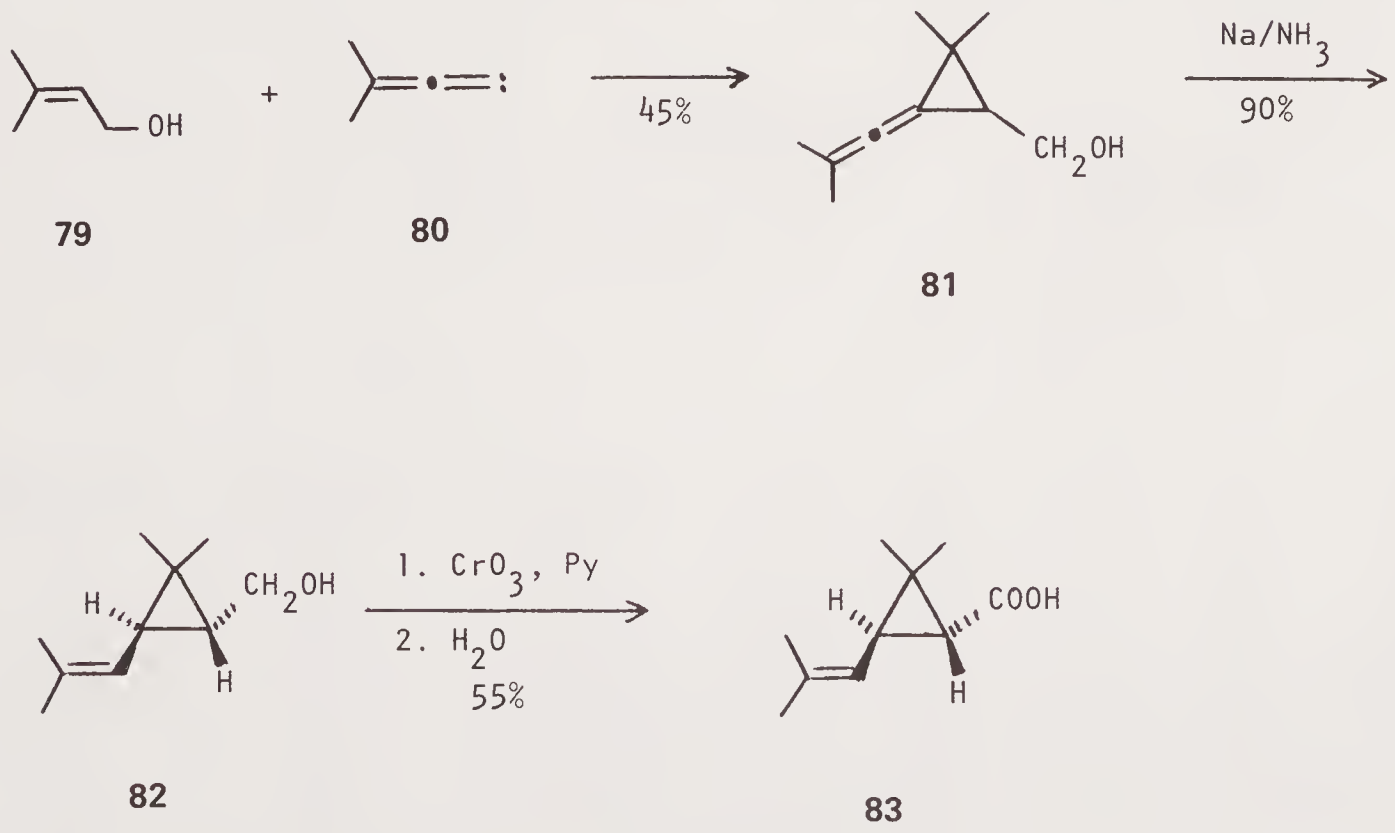
Laballenic acid (**78a**) and lamenallenic acid (**78b**) are two closely related allene-containing natural products isolated from the seed oils of *Leonotis nepetaefolia*[80] and *Lamium purpureum,*[81] respectively. Both compounds have been synthesized (Scheme 7) utilizing the aforementioned methodology. The key allenic alcohols **75** required for their syntheses are prepared in 63% and 81% yields from the lithium aluminum hydride reduction of alkenynol **74**. Bromination with triphenylphosphite dibromide gives **76**, which upon treatment with diethyl sodiomalonate furnishes **77**. Hydrolysis followed by decarboxylation leads to the formation of the natural products **78a** and **78b**.[82,83]

In the pyrethrin family of insecticides, (+)-*trans*-chrysanthemic acid (**83**) is a vital intermediate for preparing derivatives of the naturally occurring esters. The route outlined in Scheme 8 represents a simple stereoselective synthesis of racemic **83** from readily available starting materials. The first step assembles all the required carbon atoms of the chrysanthemic acid skeleton. The reaction of 3-methyl-2-butene-1-ol (**79**) with the allene carbene **80** (generated from 3-chloro-3-methyl-1-butyne and potassium *t*-butoxide) produces 2,2-dimethyl-3-(2-methyl-1-propenylidene)-cyclopropylmethanol (**81**) in moderate yield. Regioselective reduction of **81** with sodium in liquid ammonia gives a high yield of chrysanthemyl alcohol (**82**) as a 3:1 mixture of *trans* and *cis*-alcohols. Oxidation of **82** with chromium trioxide in pyridine produces an aldehyde that, upon addition of water, is further oxidized to the product **83**.[84]



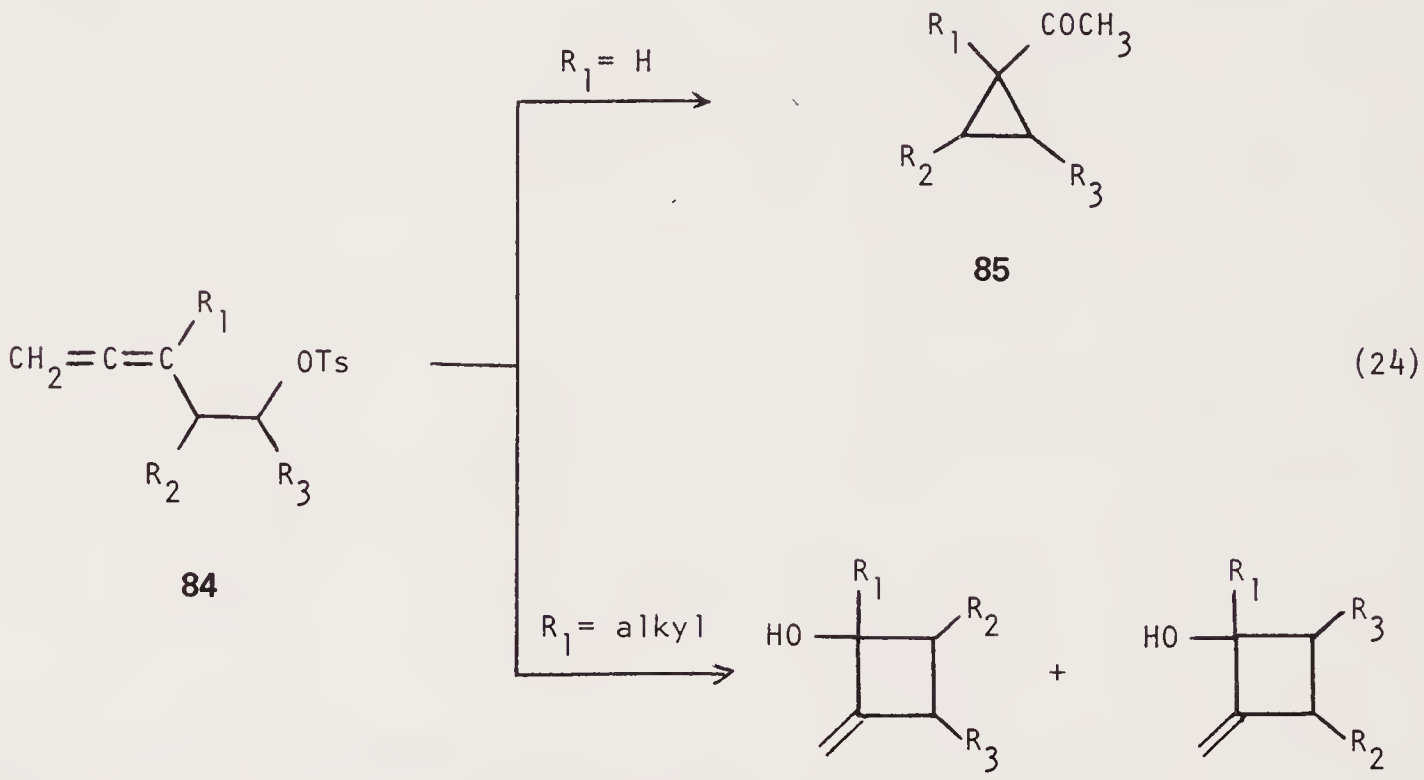
Scheme 7

Solvolysis reactions of allenic tosylates generally produce mixtures containing four or more products and therefore are not normally suitable as useful synthetic transformations. However, solvolytic cyclizations of selected acyclic β-allenic tosylates do give respectable yields of products with potential synthetic utility (equation 24). The course of the reaction depends upon the R_1 substituent of the allene



Scheme 8

84. The treatment of **84** (R_1 = H) with water/calcium carbonate[85,86] or acetic acid/sodium acetate[87,88] furnishes cyclopropylketones **85** in 70–80% yield. When R_2 or R_3 are alkyl, mixtures of *cis* and *trans* isomers are obtained. Under analogous conditions, alkyl-substituted allenes **84** (e.g., R_1 = CH_3) produce methylenecyclobutanols **86** in 70–75% yield.[86,87,89,90] Whenever R_2 and R_3 are different, an apparent exchange of positions between them occurs during the cyclization, and both isomers **86a** and **86b** are obtained.



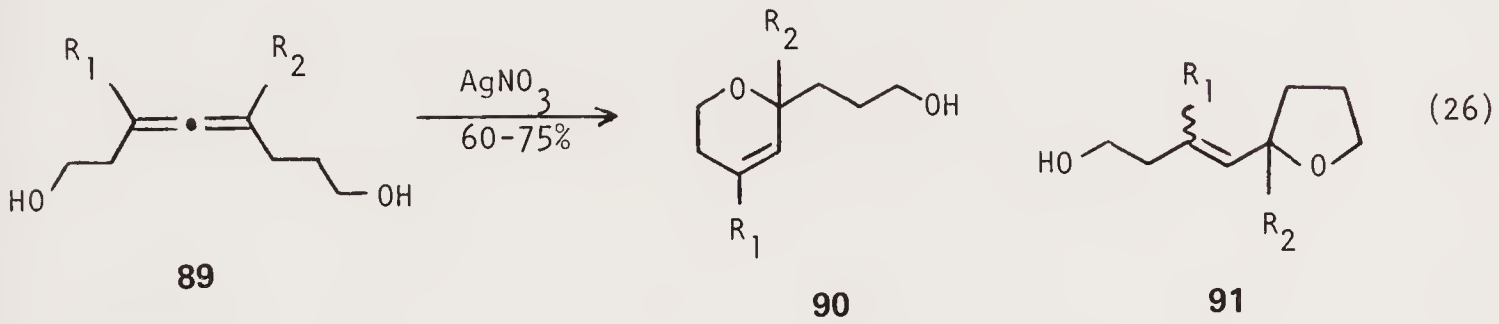
(24)

β-allenic alcohols **87** are readily cyclized to 5,6-dihydro-2H-pyrans (**88**) under the influence of silver(I) salts or boron trifluoride (equation 25). These reactions are extremely clean, with less than 5% of other products being formed.

(25)

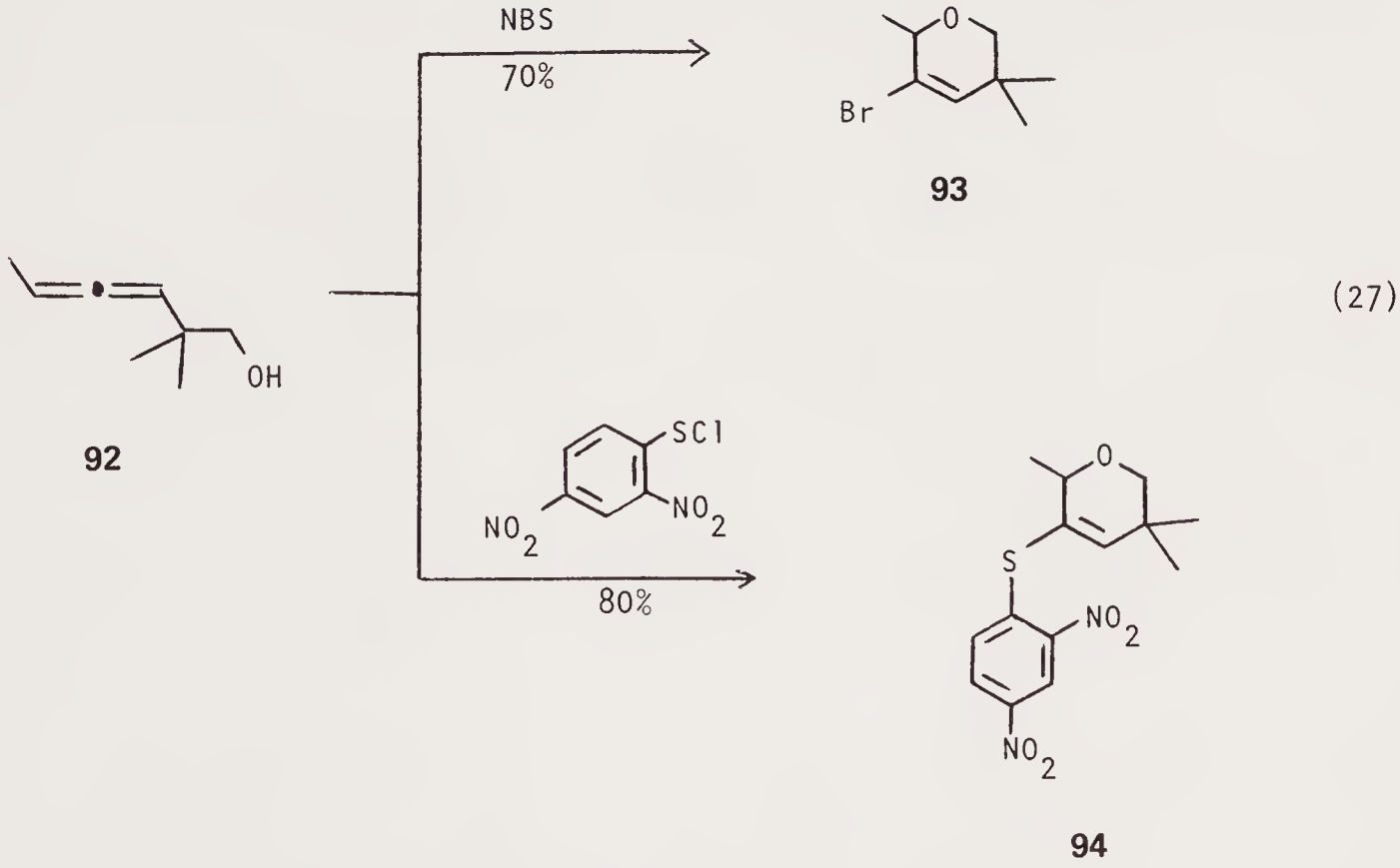
R_1	R_2	R_3	R_4	R_5	Catalyst	Yield (%)	Reference
CH_3	CH_3	H	H	H	$AgBF_4$	85	47
CH_3	C_2H_5	H	H	CH_3	$AgNO_3$	63	47
C_3H_7	H	H	H	H	$AgNO_3$	69	47
CH_3	CH_3	CH_3	CH_3	H	$BF_3,2H_2O$	60	91
—$(CH_2)_5$—		CH_3	CH_3	H	$BF_3,2H_2O$	60	91
CH_3	CH_3	CH_3	CH_3	CH_3	$BF_3,2H_2O$	60	91

Silver nitrate assisted cyclization of allene diols **89** produces either dihydropyrans **90** or tetrahydrofurans **91** (equation 26). The product distribution depends on the substitution pattern of the allene. When R_1 is alkyl, only dihydropyrans **90** are produced, whereas when R_1 is hydrogen, competitive cyclization of both the β- and γ-alcohol chains gives a statistical mixture of **90** and **91**.[92]



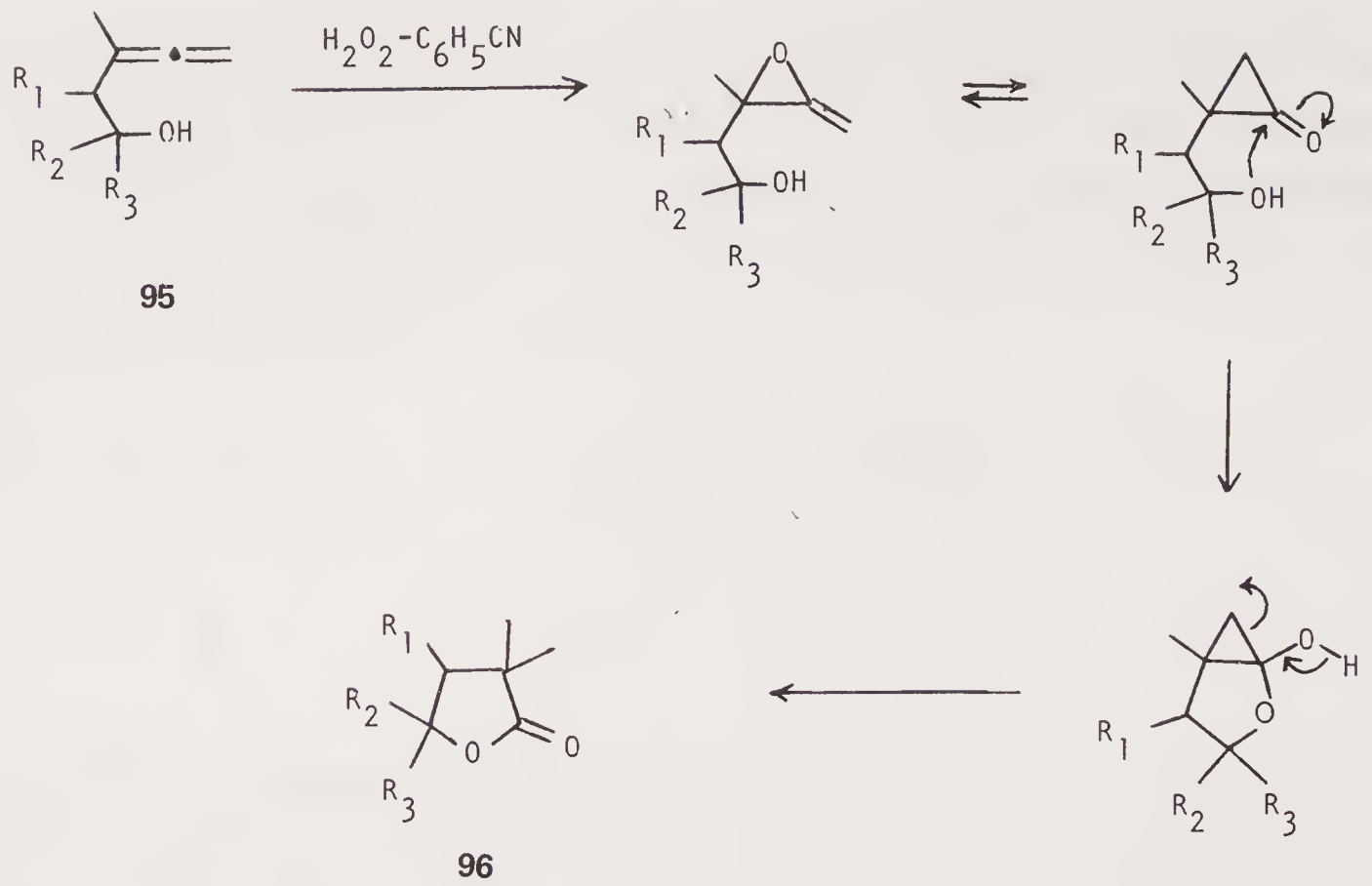
89 **90** **91** (26)

The addition of bromine or NBS to 2,2-dimethyl-3,4-hexadien-1-ol (**92**) results in the formation of the 3-bromodihydropyran **93** (equation 27). Bromine gives **93** in 48% yield; NBS increases the yield to 70%. Addition of 2,4-dinitrobenzenesulfenyl chloride to **92** gives the 3-thiodihydropyran derivative **94** in good yield.[93] When optically active **92** is employed, the chirality is transferred to the product **94**, therefore suggesting an episulfonium ion intermediate.



93 **92** **94** (27)

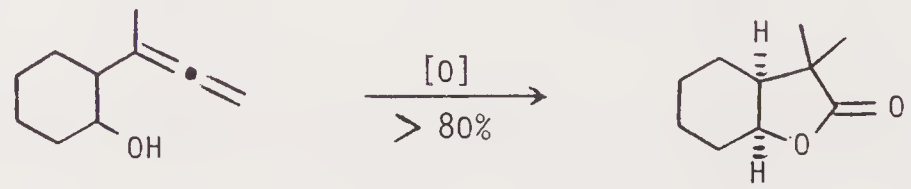
The selective oxidation of β-allenic alcohols with peroxybenzimidic acid furnishes either γ- or δ-lactones depending on the substitution pattern on the allene skeleton. When the allene is methylated in the 3 position (**95**), butyrolactone derivatives **96** are produced in greater than 80% yield by way of the mechanistic pathway outline in Scheme 9.[94]



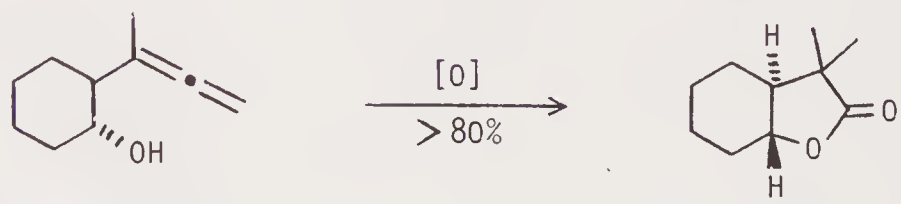
95 **96**

Scheme 9

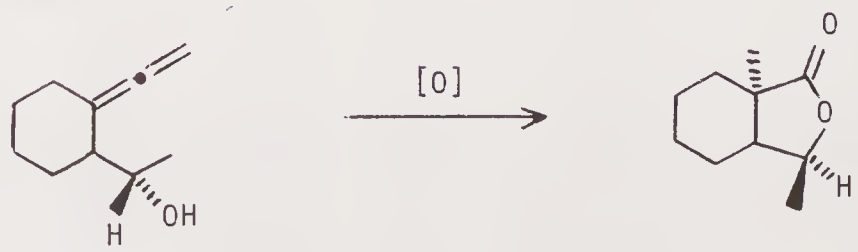
Analogous reactions with cyclohexyl analogs **97**, **99**, and **101** afford fused γ-lactones **98**, **100**, and **102**, also in excellent yields[94,95] (equations 28, 29, 30).



97 **98** (28)

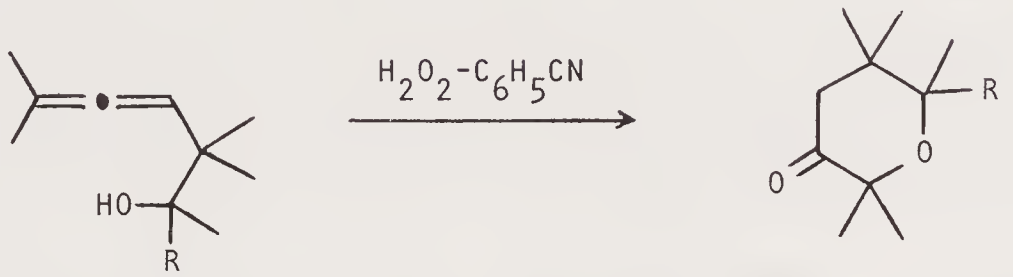


99 **100** (29)



101 **102** (30)

Allenes with no substituents in the 3 position (e.g., **103**), when subjected to the same oxidation conditions, cyclize by a concerted mechanism (see Scheme 10) to give tetrahydropyranones **104**.[49] Tertiary alcohols are favored for highest yields (equation 31).

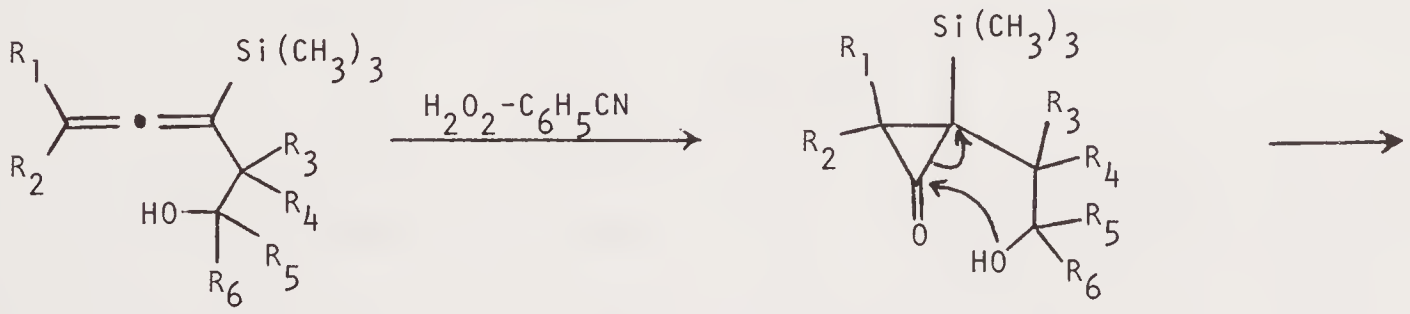


103

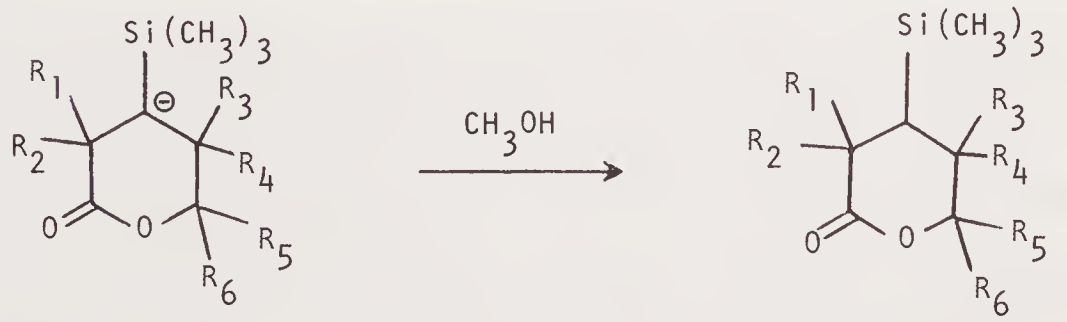
104 R=H, 60%
R=CH_3, 100%

(31)

The introduction of a trimethylsilyl function into the 3 position of the allene (**105**) enhances both the epoxidation and lactonization steps owing to the localization of the negative charge on the carbon bearing the silicon atom. After the initial allene oxide → cyclopropanone isomerization, cyclization (as outlined in Scheme 10) gives rise to silyl δ-lactones **106** in quantitative yield.[96] When the alcohol **105** is chiral, the optical activity is transferred to the product, therefore indicating a concerted mechanism.



105



106

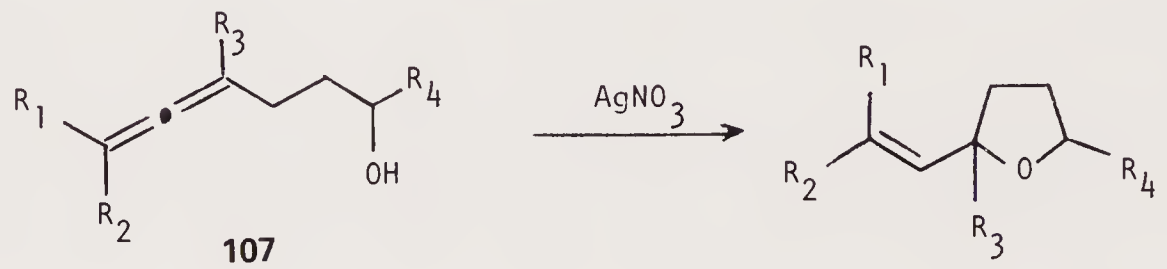
R_1-R_6= H, alkyl

Scheme 10

5.1.3. γ-Allenic Alcohols

Allenes having a hydroxyl substituent three carbons removed from the propadiene unit are easily prepared using techniques previously discussed in this chapter. Two general methods that give consistently good results are organocuprate-induced S_N2' displacement of THP-oxy-protected propargyl mesylates,[97] and the alkylation of an appropriately substituted allenyl lithium with the THP ether of 3-bromo-1-propanol.[97,98] Acidic hydrolysis of the γ-THP-oxy allenes then furnishes the desired alcohols **107**. Introduction of R_4 into the system can be accomplished by oxidation of the alcohol to the γ-aldehyde with either pyridinium dichromate[97] or Collins reagent,[72,97] followed by reaction of the aldehyde function with an organomagnesium halide.

In the presence of aqueous silver nitrate, alcohols **107** are converted to 2-vinyltetrahydrofuran derivatives **108** in very good yields[97] (equation 32). In cases where R_1 and R_2 are not equal the stereochemistry around the vinyl group of the product has the E configuration. Cyclization of secondary alcohols (**107**, $R_4 \neq H$) produces mixtures of diastereomers.

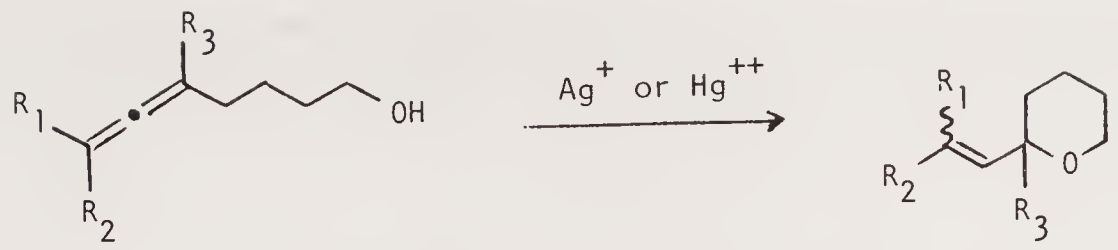


107 **108** (32)

R_1	R_2	R_3	R_4	Yield (%)
H	H	CH_3	H	75
H	H	CH_3	CH_3	95
CH_3	CH_3	H	H	95
CH_3	CH_3	H	CH_3	40
H	C_3H_7	H	H	68

5.1.4. δ-Allenic Alcohols

2-Alkenyl tetrahydropyrans are valuable components found in perfumes. They can be easily synthesized by the silver- or mercury-assisted intramolecular cyclization of δ-allenic alcohols (equation 33). The facility of the reaction is affected by the nature of the substitution on the allene. Terminal or monosubstituted allenes cyclize readily in the presence of silver nitrate, however, when both R_1 and R_2 are alkyl, the use of silver nitrate gives only poor yields of **109** (35–40%). In these cases, the yields can be increased with mercuric trifluoroacetate catalysis. Where $R_1 = R_3 = H$ and $R_2 = C_2H_5$, the cyclization exhibits a high degree of stereoselectivity and produces almost exclusively (96%) the E-isomer.[99]



(33)

109

R_1	R_2	R_3	Metal Salt	Yield (%)
H	H	H	$AgNO_3$	95
H	C_2H_5	H	$AgNO_3$	90
C_2H_5	C_4H_9	H	$Hg(OCOCF_3)_2$	80
CH_3	C_4H_9	CH_3	$Hg(OCOCF_3)_2$	70

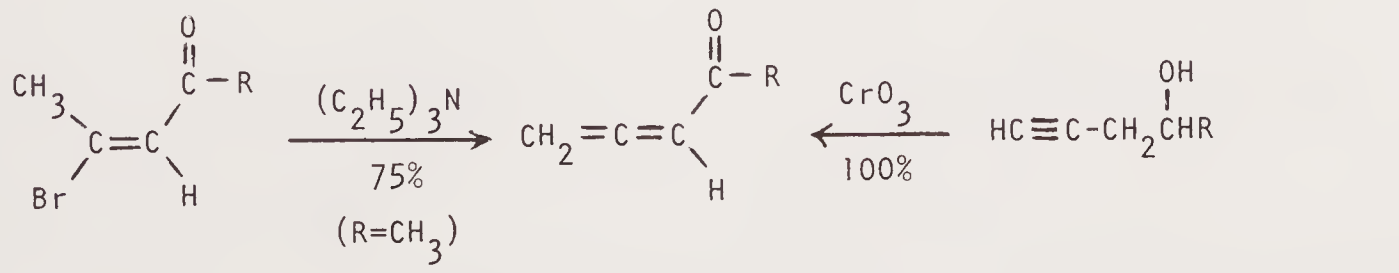
Other approaches to the synthesis of allenic alcohols are listed in Table 5.2.

5.2. ALLENIC ALDEHYDES AND KETONES

The substitution of the allene linkage with a carbonyl function confers upon the system properties different from those of allene hydrocarbons. The electron-withdrawing nature of the carbonyl group activates the propadiene unit therefore making it susceptible to nucleophilic attack at the central carbon atom. In addition, the proximity of the carbonyl substituent renders the system capable of cyclization subsequent to the reaction of the allene nucleus.

5.2.1. α-Oxo-Allenes

According to classical synthesis, the formation of α-oxo-allenes should be attainable by the dehydrohalogenation of β-haloenones. Recently a high-yielding approach to acetylallene (**111**, R = CH_3) using this strategy was reported[113] and entails the dehydrobromination of (E)-2-bromo-4-oxo-2-pentene (**110**) with triethylamine (equation 34). Analogous reactions starting with β-chloroacrolein derivatives produce α-allenic aldehydes.[114]



(34)

110 **111** **112** (R= C_2H_5, C_3H_7)

An alternate approach to simple allenic ketones is the oxidation of homopropargylic alcohols **112** with chromium trioxide in sulfuric acid.[115,116] As long as the

Table 5.2. Alternate Methods for Preparing Allenic Alcohols[a]

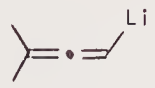
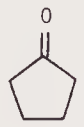
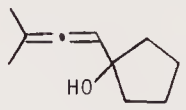
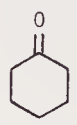
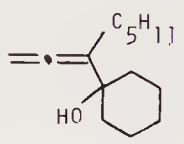
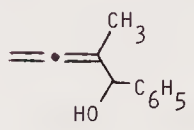
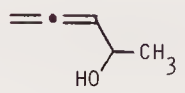
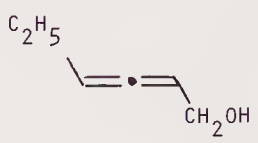
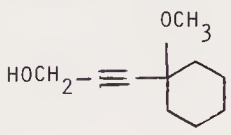
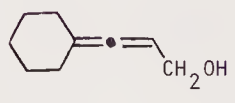
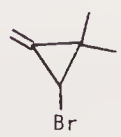
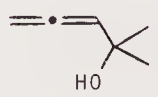
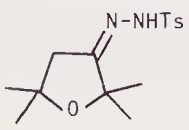
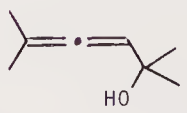
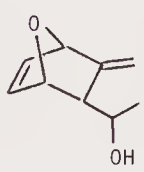
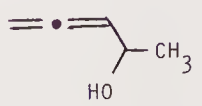
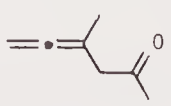
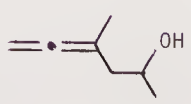
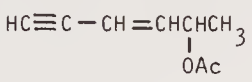
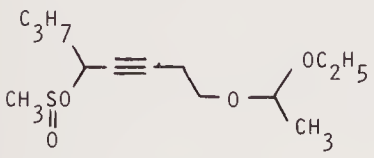
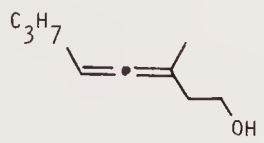
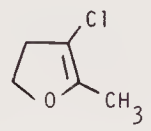
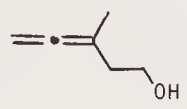
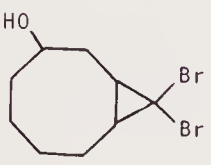
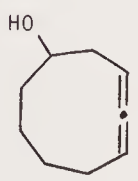
Substrate	Reagent, conditions	Product	Yield,%	Reference
α-Allenic Alcohols				
	 , -78°		95	100
$BrCH_2C{\equiv}CC_5H_{11}$	 , $CrCl_2$, 25°		78	101
$CH_3C{\equiv}CCH_2I$	C_6H_5CHO , $SnCl_2$, 0°		79	102
$HC{\equiv}CCH_2Si(CH_3)_3$	CH_3CHO , $(C_4H_9)_4N^+F^-$		65	103
	1. $(C_2H_5)_3B$ / O_2 2. H_2O		53	104
	1. $LiAlH_4$ 2. I_2 (solid)		97	105
	$CaCO_3$ / dioxane / H_2O 80°		61	106, 107
	C_4H_9Li , 25°		58	108
	480°		86	109
β- Allenic Alcohols				
	$LiAlH_4$		100	110

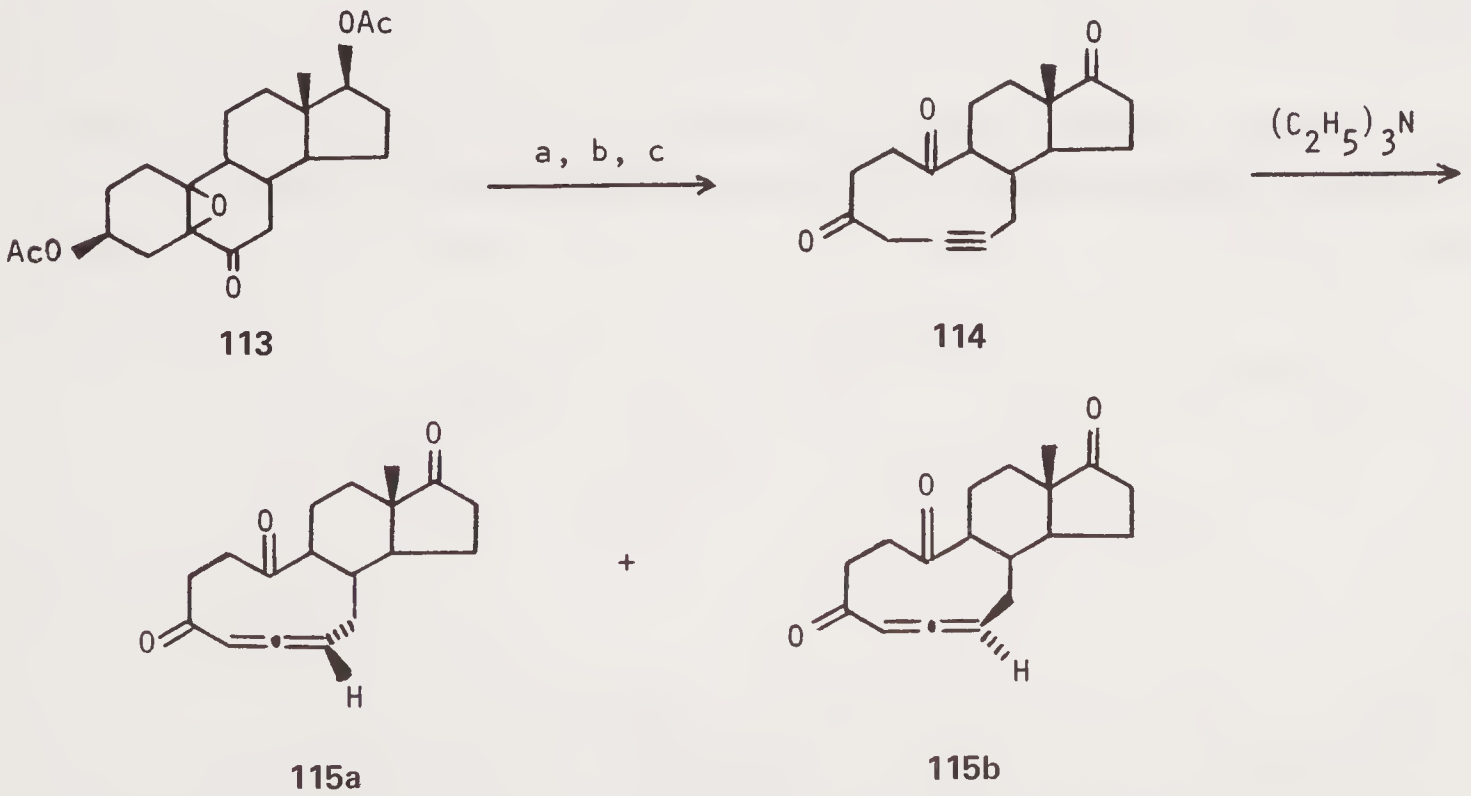
Table 5.2. (*Continued*)

Substrate	Reagent, conditions	Product	Yield,%	Reference
	$LiAlH_4$, ether, reflux		85	111
	1. $[CH_3CuBr]MgCl \cdot LiBr$ 2. PTSA		77	38
	2 CH_3Li		38	112
	C_4H_9Li		74	75, 77

[a]Only one example is shown for each method. In most cases each literature reference provides several derivatives.

starting acetylene is not substituted with a phenyl group, the conversion is almost quantitative, with only traces of the isomeric β-acetylenic ketones being formed. The oxidation of 4-hydroxy-1-phenyl-1-heptyne forms an equilibrium mixture of α-allenic and β-acetylenic ketones. When the mixture is treated with triethylamine at room temperature, the acetylene portion completely isomerizes to the allenic ketone.[115]

Conjugated allenic 3-oxo-5,10-secosteroids **115** are irreversible inhibitors of the enzyme Δ^5-3-ketosteroid isomerase of *Pseudomonas testosteroni*. The framework



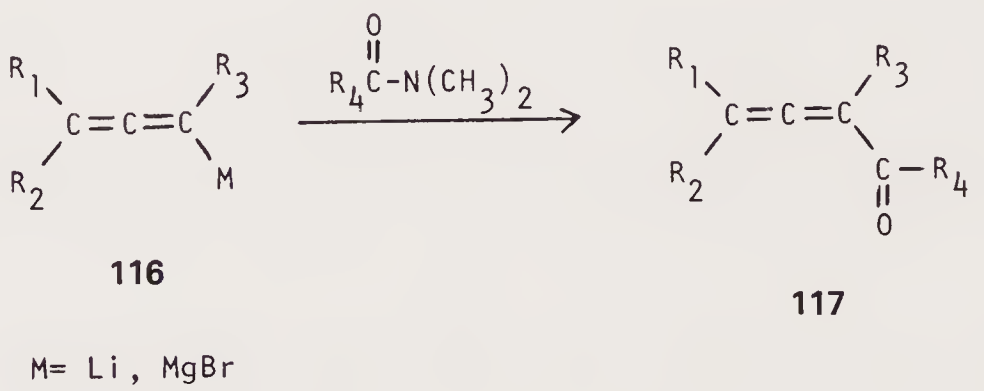
113 **114** **115a** **115b**

(a) PTSH / CH_3COOH (90%); (b) KOH (96%); (c) Jones [O] (53%)

Scheme 11

for these compounds is generated by a Tanabe–Eschenmoser fragmentation of 3β,17β-diacetoxy-5β,10β-oxidoestran-6-one (**113**)[117] (Scheme 11). After hydrolytic deprotection and oxidation, the resulting 5,10-secoestr-5-yne-3,10,17-trione (**114**) is readily isomerized with triethylamine (25°C, 30 minutes) to give a 7:3 mixture of (4R)-5,10-secoestra-4,5-diene-3,10,17-trione (**115a**) and its (4S)-isomer **115b**.[118,119]

The interaction of allenyl lithium or allenyl Grignard reagents with N,N-dimethylamides affords oxo-allenes in good yields (equation 35). The lithium derivatives of **116** are preferred because no isomeric acetylenes are formed. These lithiated allenes **116** are prepared either by regioselective metallation of allene hydrocarbons with *n*-butyllithium or LDA, or by metal–halogen exchange of haloallenes with *n* or *t*-butyllithium.[120]



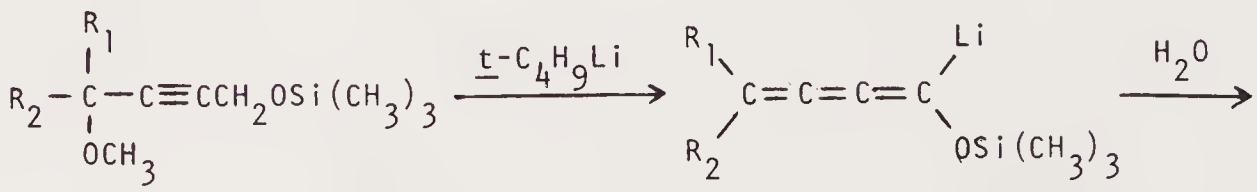
116 **117**

M= Li, MgBr

(35)

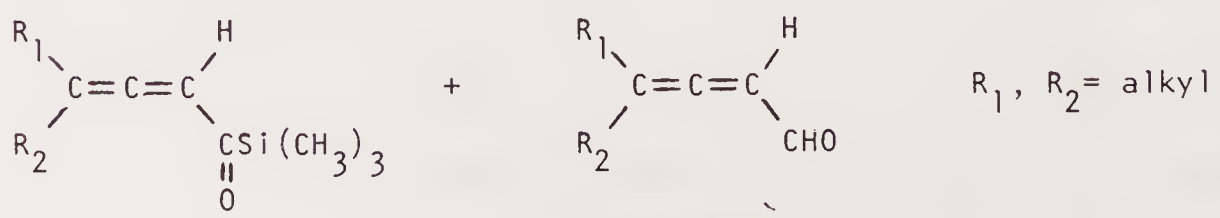
R_1	R_2	R_3	R_4	Metal	Yield (%)	Reference
CH_3	CH_3	H	H	Li	78	120
CH_3	CH_3	H	CH_3	Li	75	120
C_8H_{17}	H	H	CH_3	Li	62	120
CH_3	CH_3	C_4H_9	H	Li	86	120
CH_3	CH_3	C_4H_9	CH_3	Li	83	120
CH_3	H	CH_3	C_6H_5	MgBr	40	121, 122

A variety of additional synthetic strategies have been applied to the preparation of conjugated allenic ketones, and they are briefly outlined in Scheme 12.

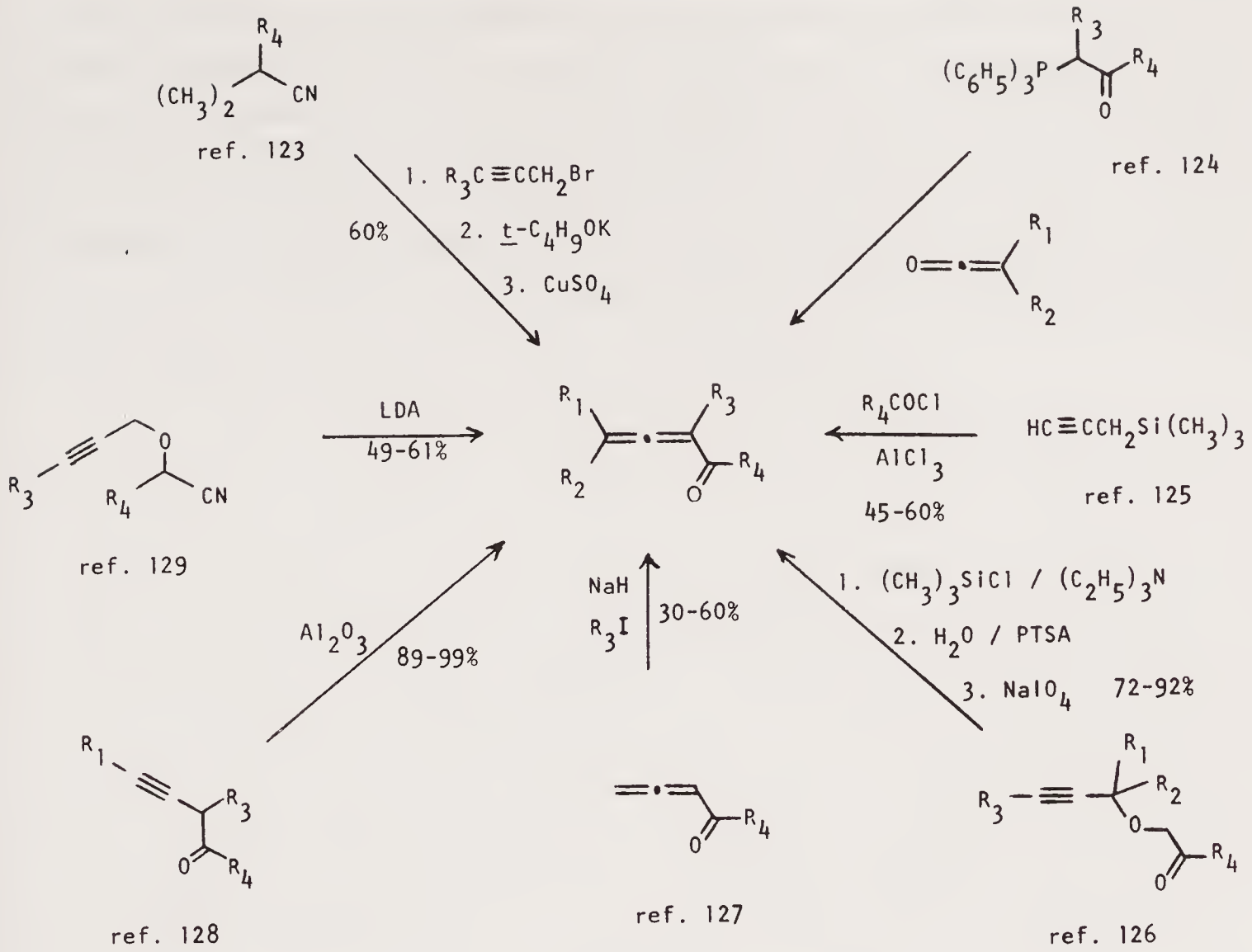


118 **119**

(36)



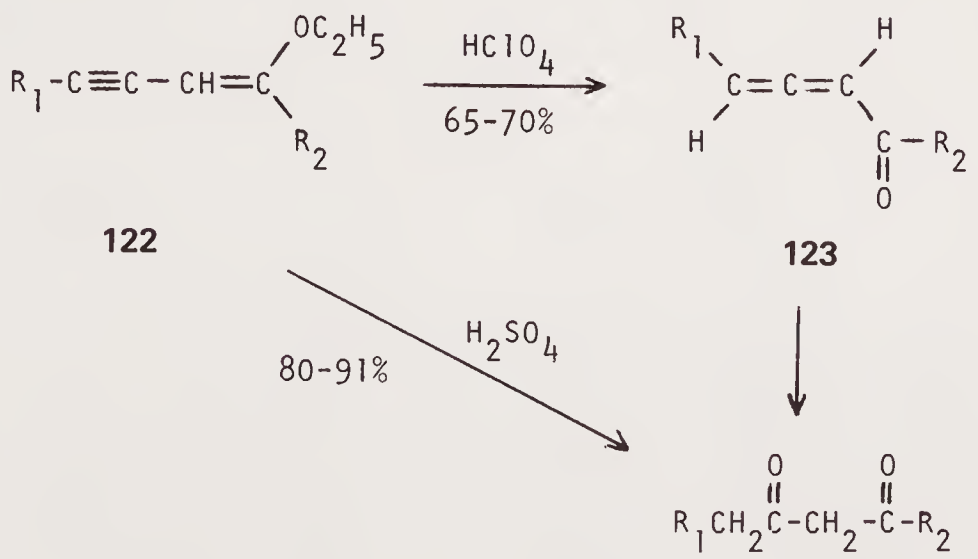
120 **121**



Scheme 12

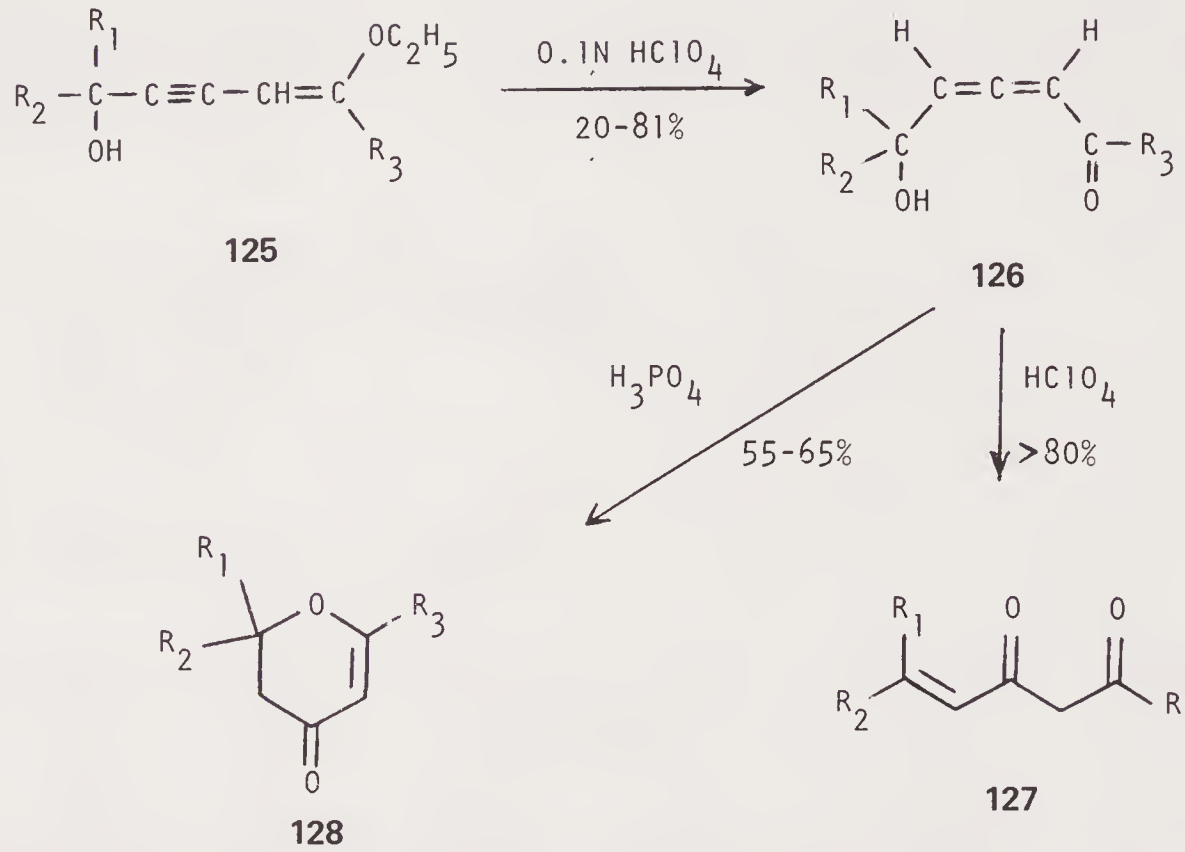
α-Lithiated (trimethylsiloxy)butatrienes (**119**) are generated by 1,4-elimination of methanol from siloxyalkynes **118**. Upon aqueous hydrolysis, mixtures of allenic aldehydes **121** and trimethylsilyl ketones **120** (separable by distillation) are formed. The ratio of **120**:**121** is solvent dependent. If the reaction is performed in ether/pentane, ketones **120** are isolated in 40–60% yield, whereas in THF/pentane, aldehydes **121** can be isolated in 25–70% yield.[130]

Mild acid hydrolysis of conjugated ethoxyenynes **122** provides an efficient route for the preparation of β-diketones (equation 37). The reaction proceeds through an α-allenic ketone intermediate **123**, and in cases where $R_1 = H$ these intermediates are isolable.[131]



(37)

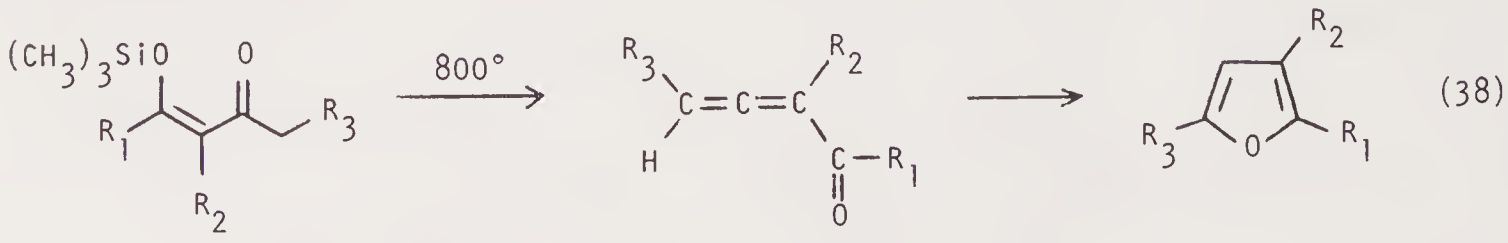
Treatment of ethoxyenynols **125** with cold dilute perchloric acid furnishes hydroxy allenones **126** in good yield[132] (Scheme 13). When compounds **126** are hydrolyzed with 1N perchloric acid at room temperature, β-diketones of type **127** are obtained. The progress of the reaction is followed with infrared spectrometry, and the reaction is terminated upon the disappearance of the allene band. Under more forcing conditions, allenones **126** are converted directly to 5,6-dihydro-4-pyranones **128** by treatment with 20% phosphoric acid at 80°C.[133]



125 **126** **128** **127**

Scheme 13

Flash vacuum thermolysis of β-keto-trimethylsilyl enol ethers **129** afford either α-allenic ketones **130** or furan derivatives **131**, depending on the contact time in the reactor. When the reaction is performed in 10^{-3} seconds at 800°C, good yields of **130** are obtained in the pyrolyzate. Longer contact times only produce furans **131** resulting from an intramolecular rearrangement of **130**.[134]

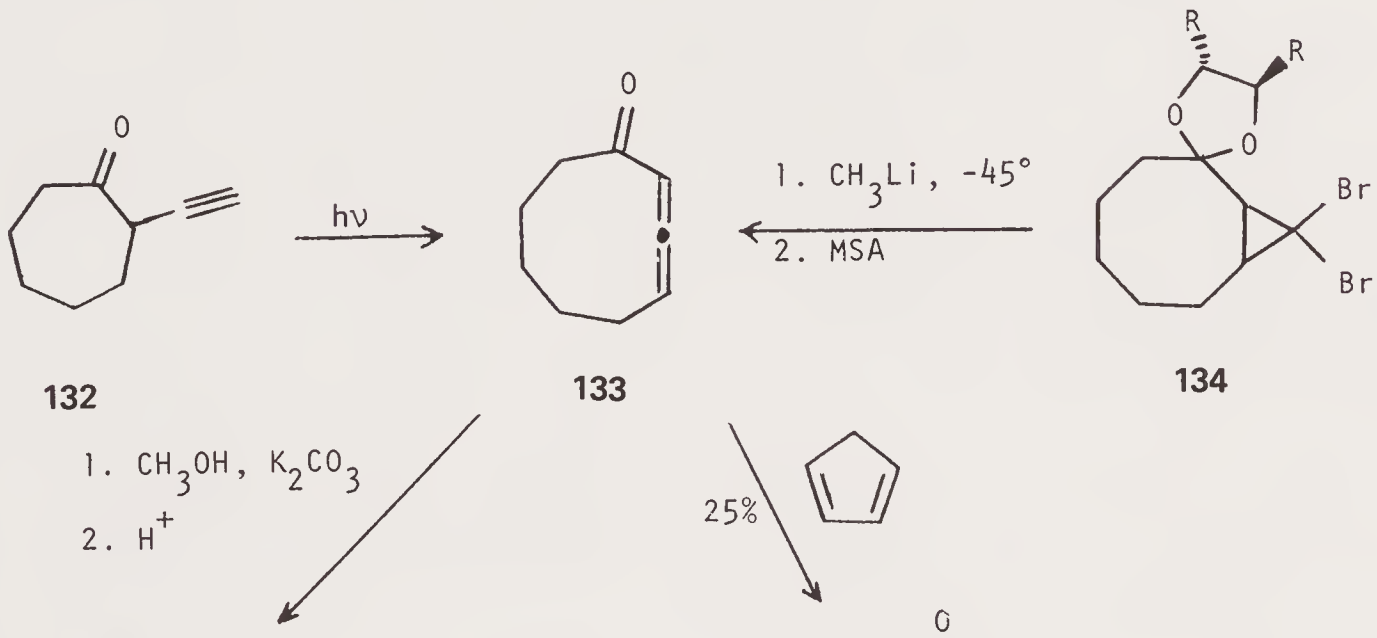


(38)

129 **130** **131**

R_1	R_2	R_3	Yield **131** (%)
CH_3	CH_3	H	40
CF_3	H	H	50
C_6H_5	H	H	36
—$(CH_2)_4$—		H	48
—$(CH_2)_4$—		CH_3	50

The unstable cyclic allenic ketone 2,3-cyclononadienone (**133**), can be prepared by two methods (Scheme 14). Irradiation of 2-ethynylcycloheptanone (**132**) gives **133** as the major product.[135] Alternately, treatment of **134** (R = H) with methyllithium at −45°C followed by hydrolysis of the ketal group with MSA gives **133**, although in a somewhat lower yield.[136] A similar reaction of **134** (R = CH_3) at −90° provides approximately 8% optical induction to give (+)− **133**. Compound **133** is readily converted to 1,3-cyclononanedione (**135**) by addition of methanol followed by hydrolysis of the intermediate enol ether. It can also be trapped as the Diels–Alder adduct **136** by treatment with cyclopentadiene.[135]

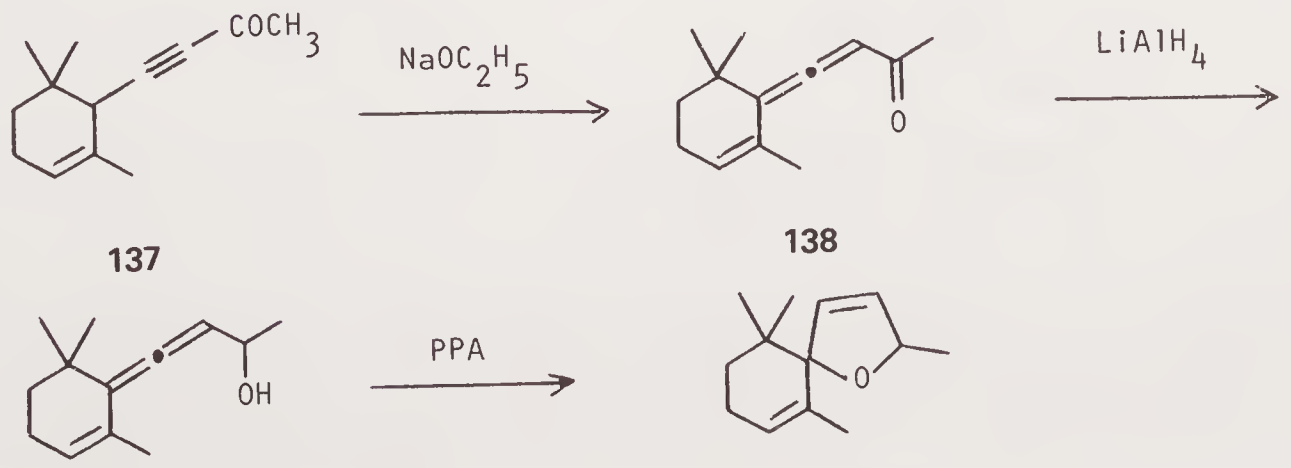


132 **133** **134**

135 **136**

Scheme 14

Scheme 15 outlines an efficient route for the synthesis of 2,6,10,10-tetramethyl-1-oxaspiro[4.5]deca-3,5-diene (**140**), a key intermediate in the synthesis of theaspiranes and vetispiranes.[137] Base-catalyzed isomerization of acetylene **137** furnishes 6,7-dehydro-α-ionone (**138**) which upon reduction with lithium aluminum hydride gives 6,7-dehydro-α-ionol (**139**). Intramolecular electrophilic cyclization then produces the desired product.

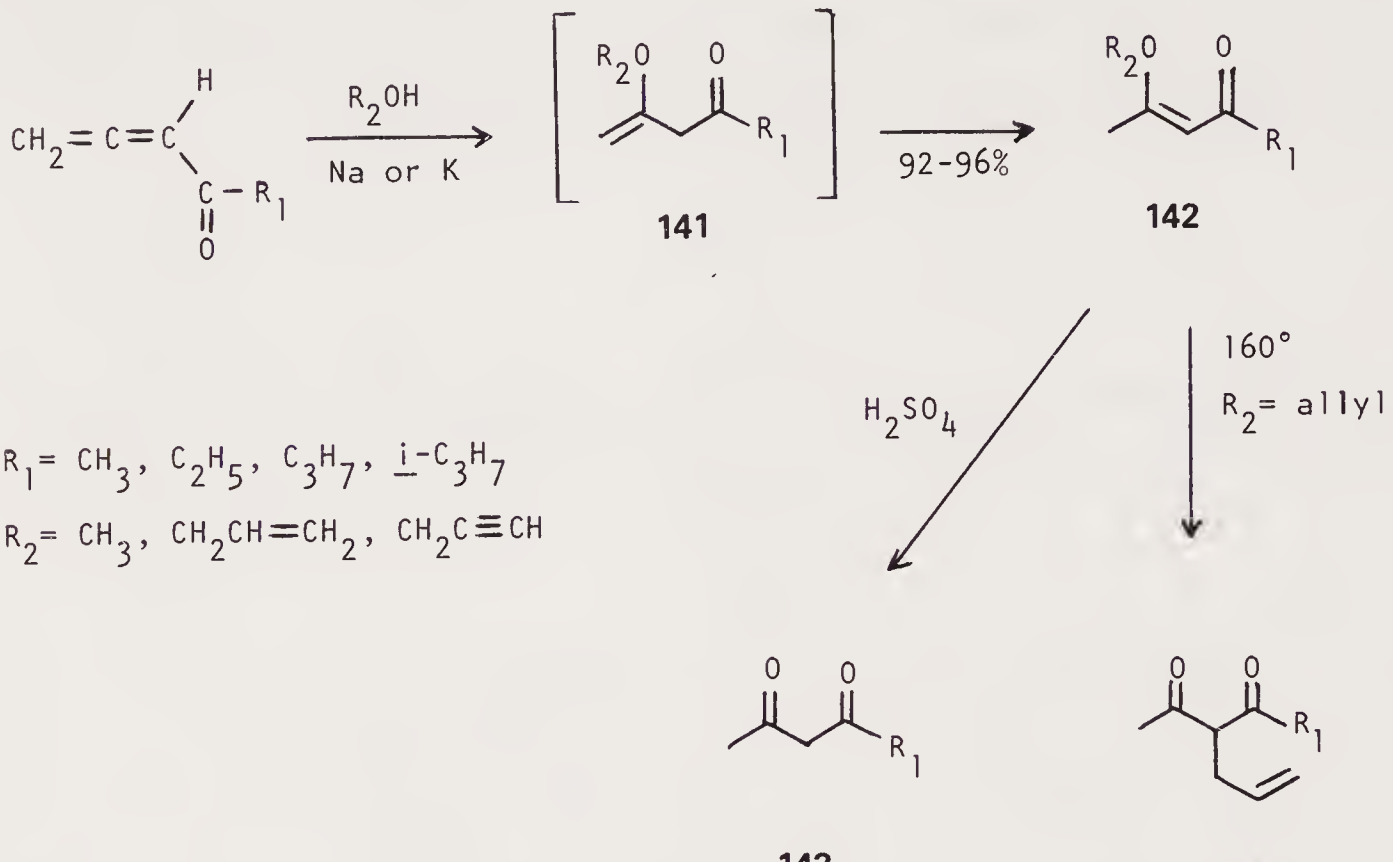


137 **138**

139 **140**

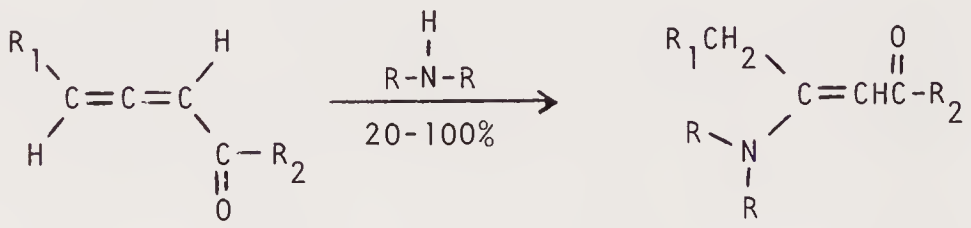
Scheme 15

Under base catalysis, alcohols add nucleophilically to the central carbon atom of allenic ketones to give β,γ-alkoxyvinyl ketones **141**, which then spontaneously isomerize to the α,β-enones **142**[138,139] (Scheme 16). Acid hydrolysis of **142** furnishes β-diketones **143**. Thermolysis of the corresponding allyl enol ethers results in the migration of the allyl group to give C-allyl-β-diketones **144** in 98% yield.



Scheme 16

Aliphatic and aromatic primary or secondary amines react vigorously with α-allenic ketones to produce aminovinyl ketones **145** in moderate yield[115,140] (equation 39).



(39)

145

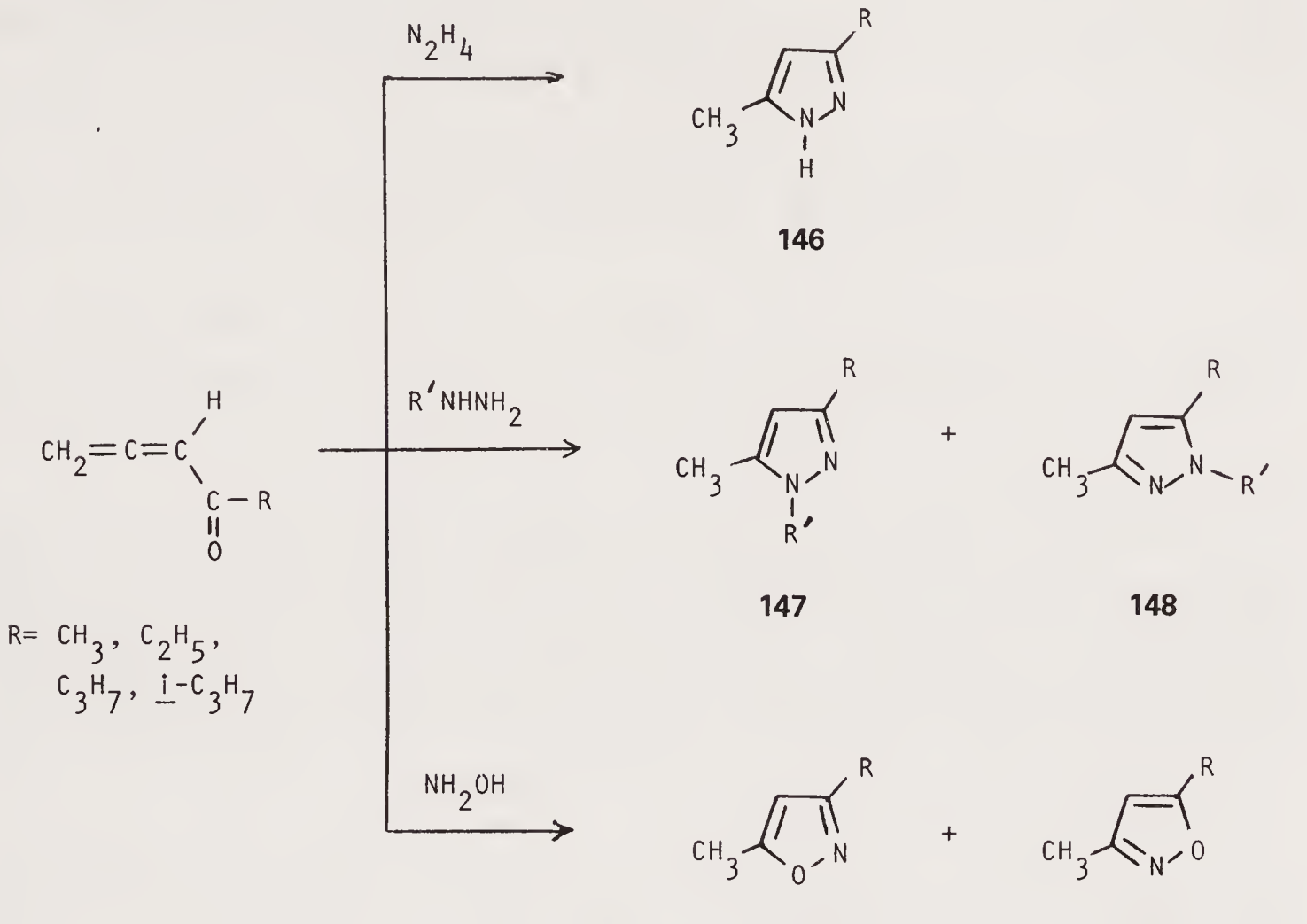
R_1= H, alkyl, C_6H_5

R_2= alkyl, C_6H_5

R= H, alkyl, C_6H_5,

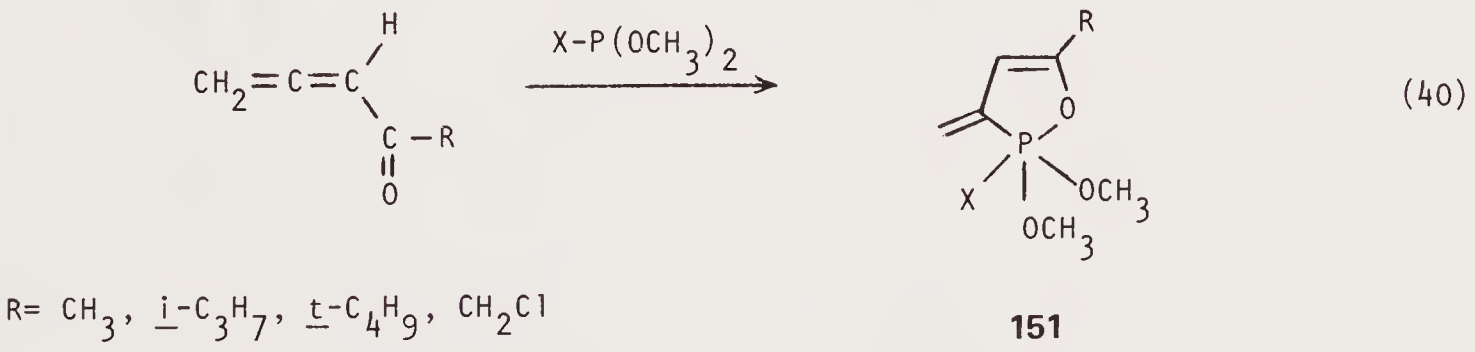
The action of hydrazine on allenic ketones results in the formation of 3,5-disubstituted pyrazoles (**146**) by means of cyclization with the carbonyl group.[141] Monosubstituted hydrazines give mixtures of pyrazoles **147** and **148** the ratio of which depends on the nature of the R′ substituent (Scheme 17). Methylhydrazine

produces a 91:9 ratio of **147** and **148**, whereas phenylhydrazine gives a 55:45 mixture.[140] Hydroxylamine analogously forms mixtures of isoxazoles **149** and **150**.[142]



Scheme 17

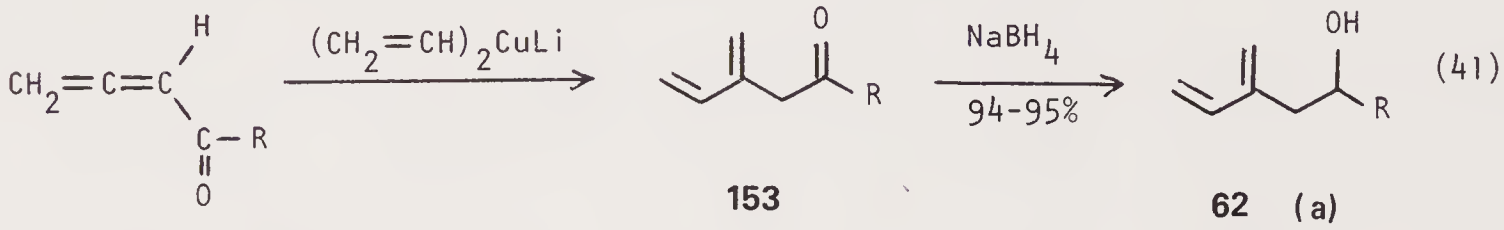
The addition of trivalent phosphorus reagents to allenic ketones allows entry into the exomethylene 1,2-oxaphospholene ring system **151**[143,144] (equation 40). The reaction can accept a wide variety of substituents on the phosphorus with X being OCH_3, OC_6H_5, SCH_3, $N(CH_3)_2$, CH_3, C_6H_5, CN, or $CH{=}CH_2$.



(40)

The behavior of allenic ketones is similar to α,β-unsaturated ketones in their reactivity towards organometallics. Organomagnesium halides and organolithium reagents add in a 1,2-fashion to produce α-allenic alcohols.[145,146] Organocopper reagents react as expected by a conjugate mode of addition to give β,γ-unsaturated ketones as the major product.[147,148] The mild reaction conditions are conducive for the isolation of the β,γ-isomer contaminated with only minor amounts of the isomerized α,β-unsaturated ketones.

A useful application of this methodology is the simple, high-yielding synthesis of ipsenol (**62**) and ipsdienol (**63**) (equation 41). The addition of lithium divinylcuprate to allenones **152a** and **152b** furnishes ketones **153a** (95%) and **153b** (85%), respectively. Reduction of the carbonyl group with sodium borohydride in aqueous methanol at 0°C gives the desired products in high yield.[120]



152 a R= $CH_2CH(CH_3)_2$

b $CH{=}C(CH_3)_2$

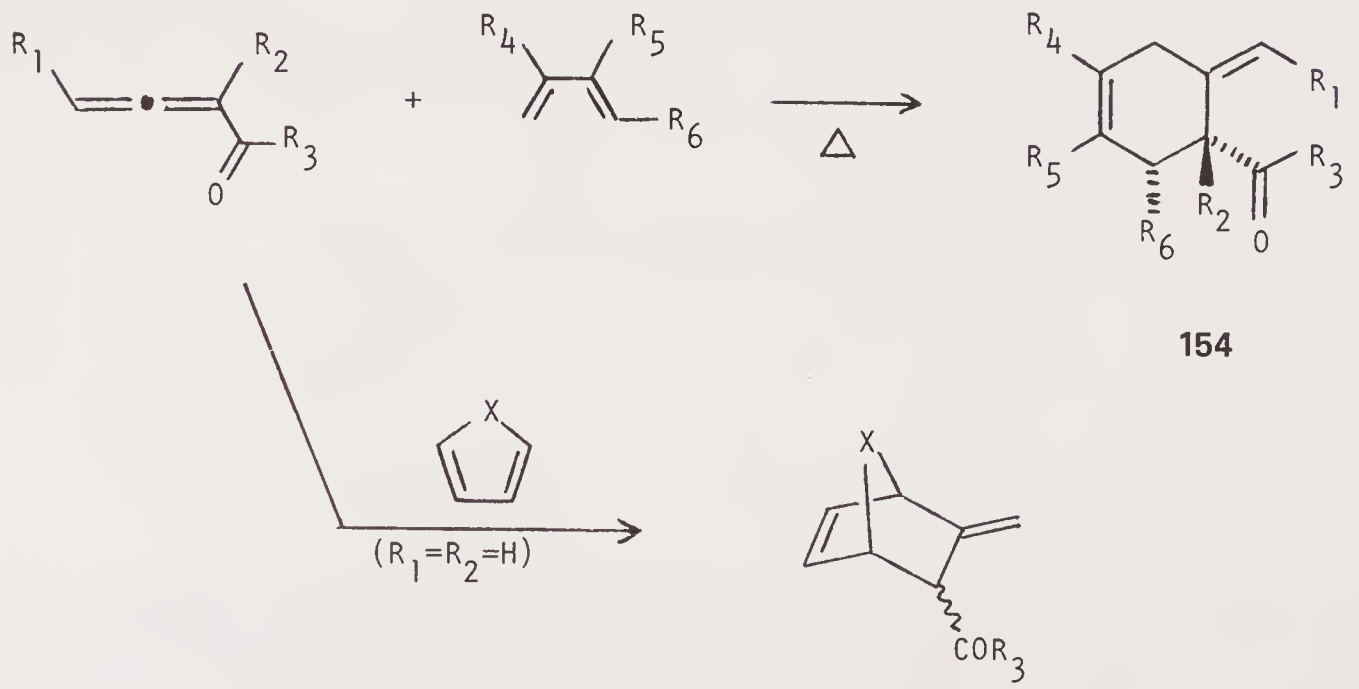
153

62 (a)

63 (b)

α-Allenic ketones behave as excellent dienophiles in Diels–Alder reactions. The orthogonal geometry of the substituents of the keto allene induce high regio- and stereoselectivities in reactions with unsymmetrical dienes. The out-of-plane substituent R_1 on the allene (see Figure 4) directs the approach of the conjugated diene from the less hindered side, which therefore produces a Z stereorelationship at the exocyclic double bond of the product **154**[149] (Scheme 18).

These reactions exhibit a high degree of *endo*-selectivity. With piperylene ($R_4 = R_5 = H$, $R_6 = CH_3$), only one adduct having the relative *cis*-configuration (**154**) is formed. In reactions involving isoprene ($R_4 = CH_3$, $R_5 = R_6 = H$), the addition leads to a mixture of geometrical isomers in which the 1,4-disubstituted cyclohexene always predominates. This ratio can be further enhanced to favor the 1,4-isomer by the use of a Lewis acid (zinc chloride).



154

155 (R_3= C_2H_5, C_3H_7, i-C_3H_7)

X= CH_2, >94%

X= O, 60-65%

Scheme 18

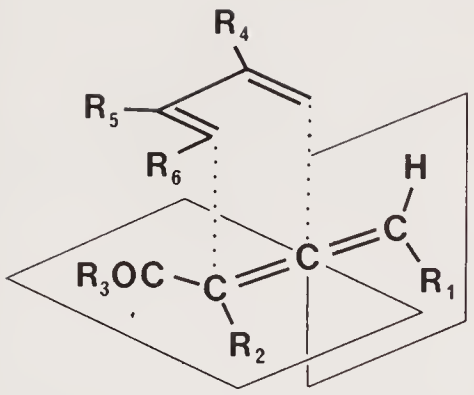
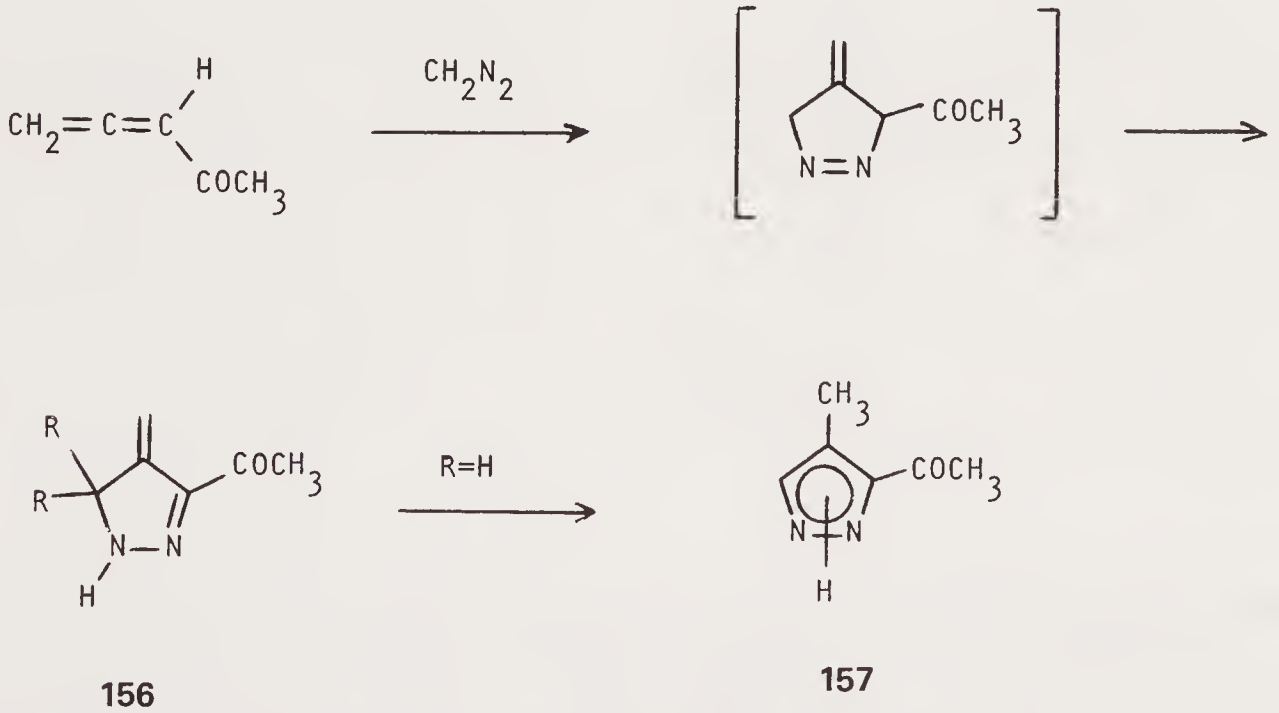


Figure 4. Approach of reactants leading to regio- and stereoselective orientation of adducts in Diels–Alder reactions.

Reactions with cyclopentadiene are rapid even at room temperature and give norbornene derivatives **155** (X = CH_2) in excellent yield. Furan, however, requires 4 hours at 80–90°C to complete the conversion.[109,150,151]

The cycloaddition of diazomethane with acetylallene (**111**) gives pyrazole derivatives **157** that arise from a series of isomerizations shown in Scheme 19.[152] If the reaction is carried out at 0°C with one equivalent of diazomethane, a mixture of **156** (R = H) and **157** is formed. With an excess of reagent at room temperature only **157** is isolated. When disubstituted diazoalkanes are used, only pyrazoles of type **156** are produced because the geminal disubstitution in the ring precludes further isomerization.

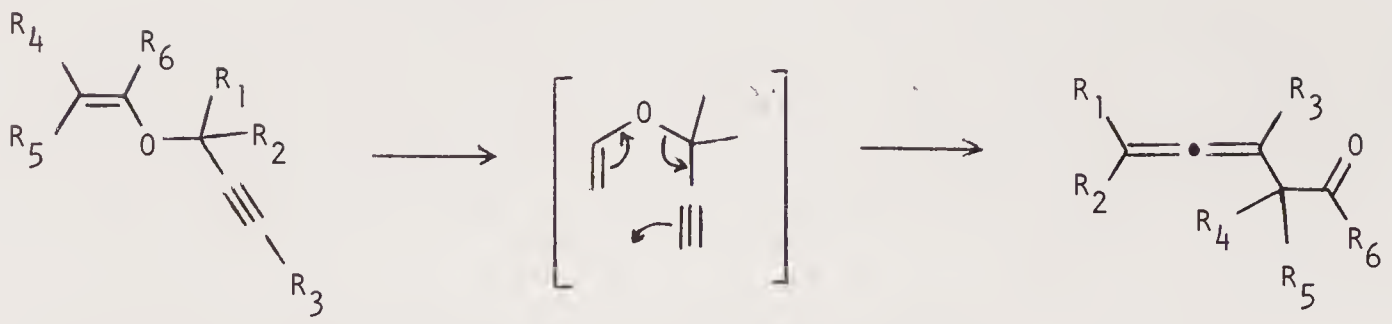


156 **157**

Scheme 19

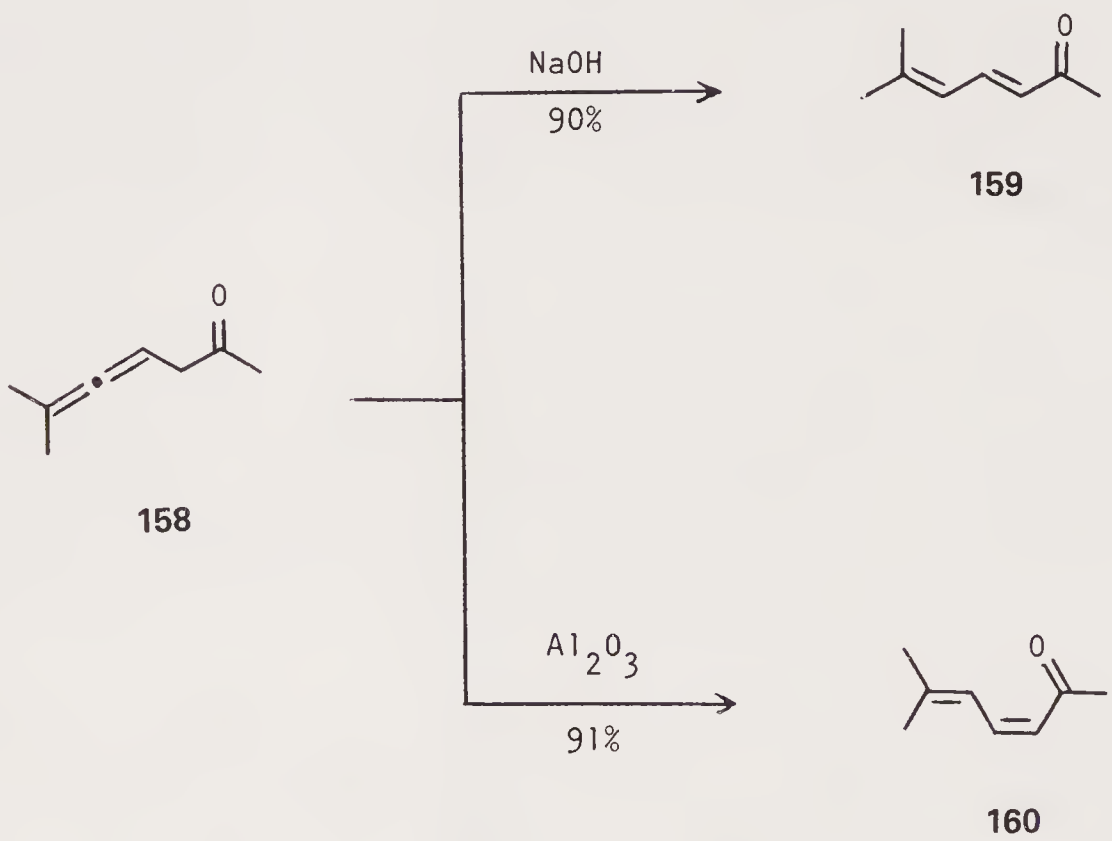
5.2.2. β-Oxo-Allenes

A wide variety of β-allenic aldehydes and ketones are available in good yield from a Claisen rearrangement of propargyl vinyl ethers (equation 42).[68,153–156] Highest conversions are usually obtained by generating the propargyl vinyl ether *in situ* and then performing the rearrangement at 80–150°C. The method is applicable for the preparation of a variety of allenyl ketosteroids.[157–159]



(42)

β-Ketoallenes are particularly sensitive to base and undergo facile isomerization to conjugated dienones. The nature of the base dictates the stereochemistry of the product. For example, when 6-methyl-4,5-heptadiene-2-one (**158**) is treated with aqueous alkali, an 86:14 mixture of *trans* and *cis*-dienones **159** and **160** is formed[160] (equation 43). Similar transformations are also effected with sodium methoxide.[161] However, when heated in ethanol in the presence of aluminum oxide, **159** isomerizes predominantly to the *cis*-dienone **160** (91.6:8.4 ratio).[162]

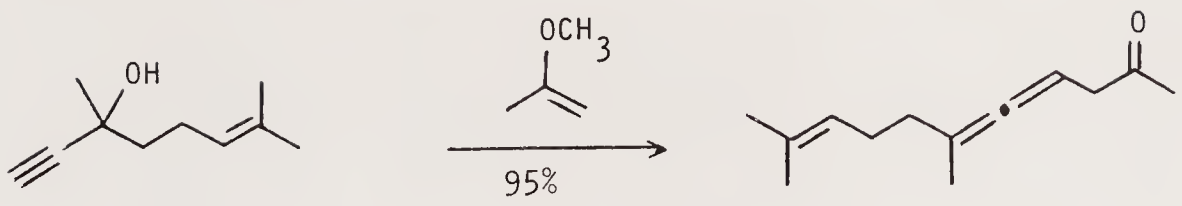


158 **159** **160**

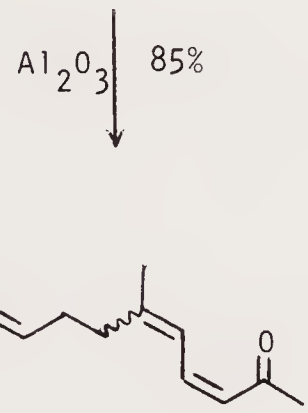
(43)

Pseudoionone (**163**), a key intermediate for the commercial production of vitamin A, is particularly suited for synthesis using the aluminum oxide isomerization technique. The requisite allenyl ketone **162** is readily prepared by heating dehydrolinalool with isopropenyl methylether. Treatment with aluminum oxide furnishes *cis*-isomers **163** with 93% purity.[162,163]

Furfuryl phenyl selenides (**164**), when treated with *n*-butyllithium or metallic lithium, experience a facile ring-opening reaction of the furan ring to give a mixture of allenyl ketone **166** and conjugated dienone **167**[164] (Scheme 20). The initial driving force of the reaction is a lithium–selenium exchange to generate a furfuryllithium, which then opens to the enolate of the allenyl ketone. A second equivalent of base is required for completion of the reaction owing to the highly acidic nature of the allenic hydrogen. Quenching the resulting dianion **165** with water produces a



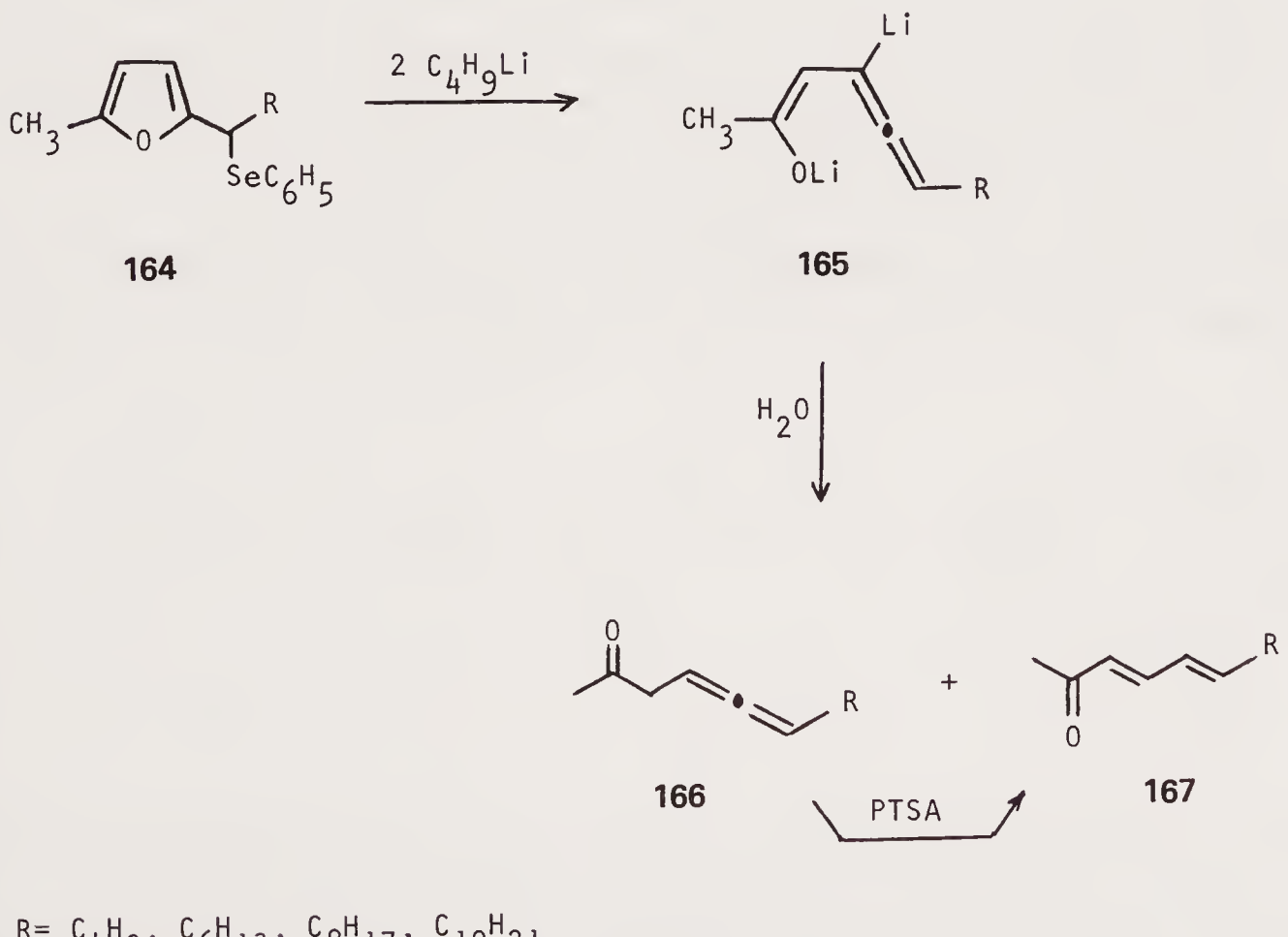
161 162



(44)

163

mixture of **166** and **167** that, upon treatment with *p*-toluenesulfonic acid, is converted in high yield (75–95%) to **167**.

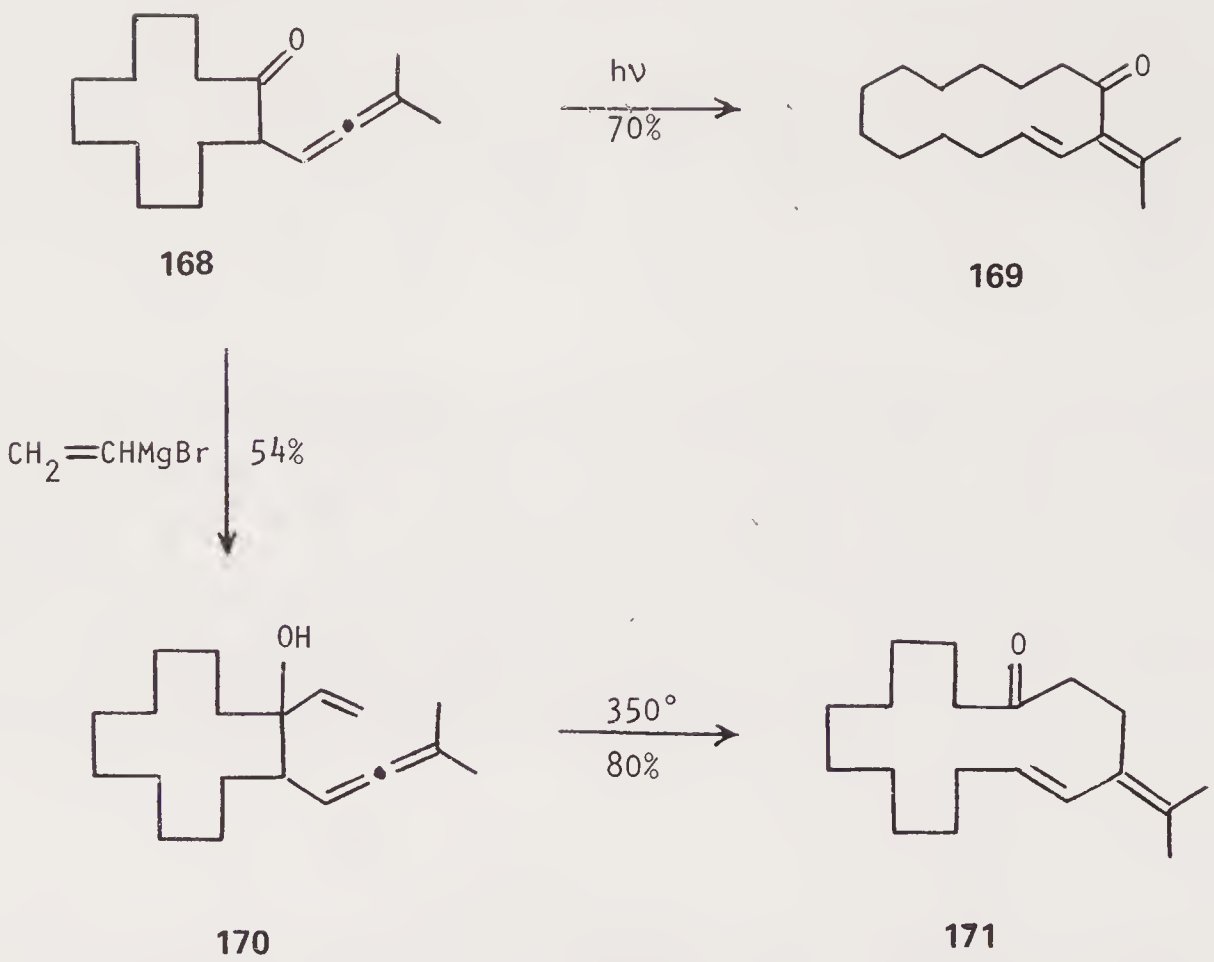


164 165

R= C_4H_9, C_6H_{13}, C_8H_{17}, $C_{10}H_{21}$

Scheme 20

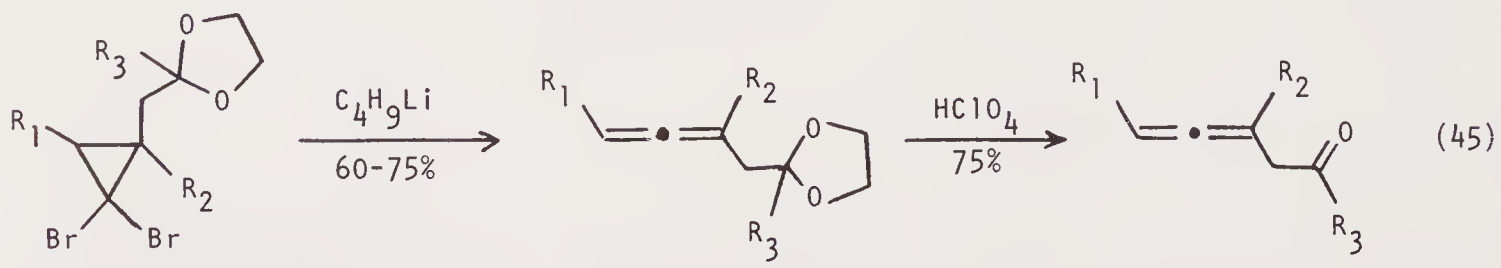
Macrocyclic ketones are useful intermediates in the synthesis of 15- to 17-membered ring musk ketones and lactones. Allenyl-substituted cyclododecanone **168** can be ring expanded by two or four carbon atoms according to the reactions



Scheme 21

illustrated in Scheme 21.[156] Irradiation of **168** for five days results in the formation of ketodiene **169** by way of a 1,3-acyl migration. Reaction of **168** with vinylmagnesium bromide affords **170**, which upon thermolysis undergoes a Cope rearrangement to give the 16-membered dienone **171** in good yield.

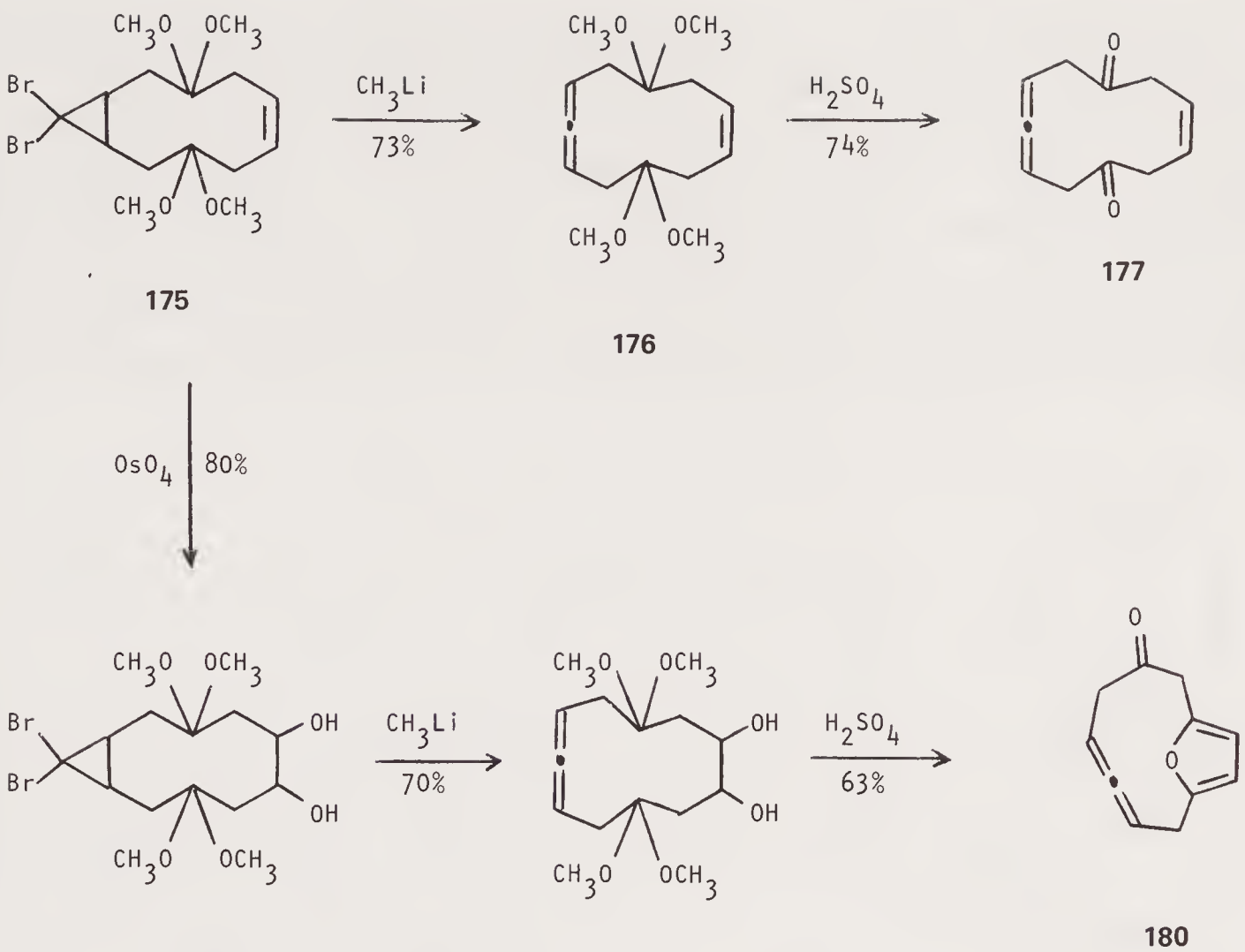
The treatment of dibromocyclopropane **172** with *n*-butyllithium results in the formation of β-allenic ethylene ketals **173**[165,166] (equation 45). Deprotection with perchloric acid in dioxane gives the corresponding ketones **174** in good yield.[110]



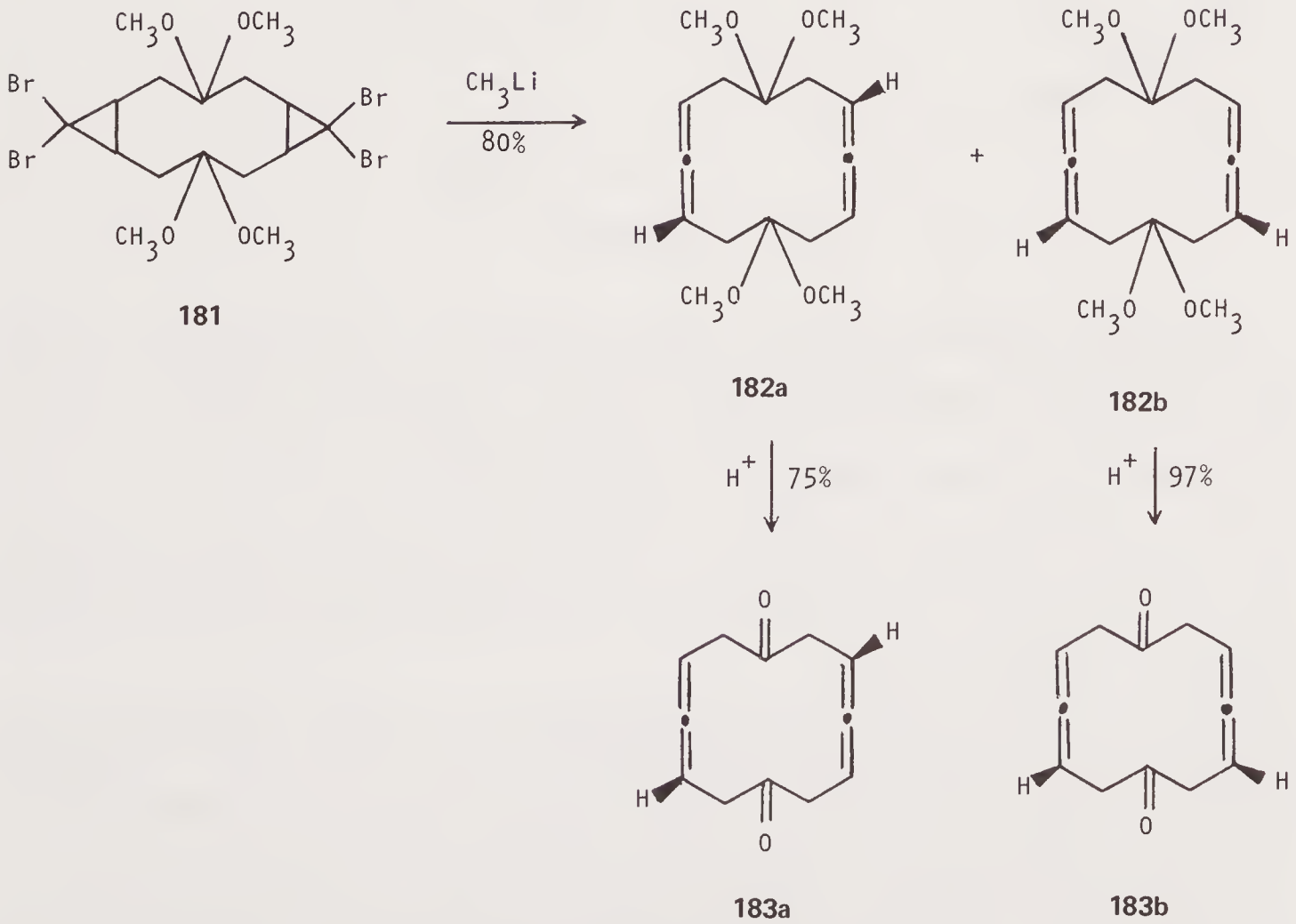
172 173 174 (45)

The interesting monocyclic allenic diketone, 3,8,9-cycloundecatriene-1,6-dione (**177**), can be prepared by the treatment of **175** with methyllithium at −10°C followed by hydrolysis with dilute sulfuric acid[167] (Scheme 22). Under similar conditions diol **178** is converted to **179**, however, when hydrolyzed with 80% sulfuric acid in ether, only the furanophane **180** is obtained.

In exploring the limits of these types of reactions, Garratt[168,169] has successfully converted the tetrabromide **181** to a diastereomeric mixture (1:2) of racemic **182a** and *meso* **182b** (Scheme 23) that could be separated by chromatography. The hydrolysis of either **182a** or **182b** furnishes the respective diones **183**.

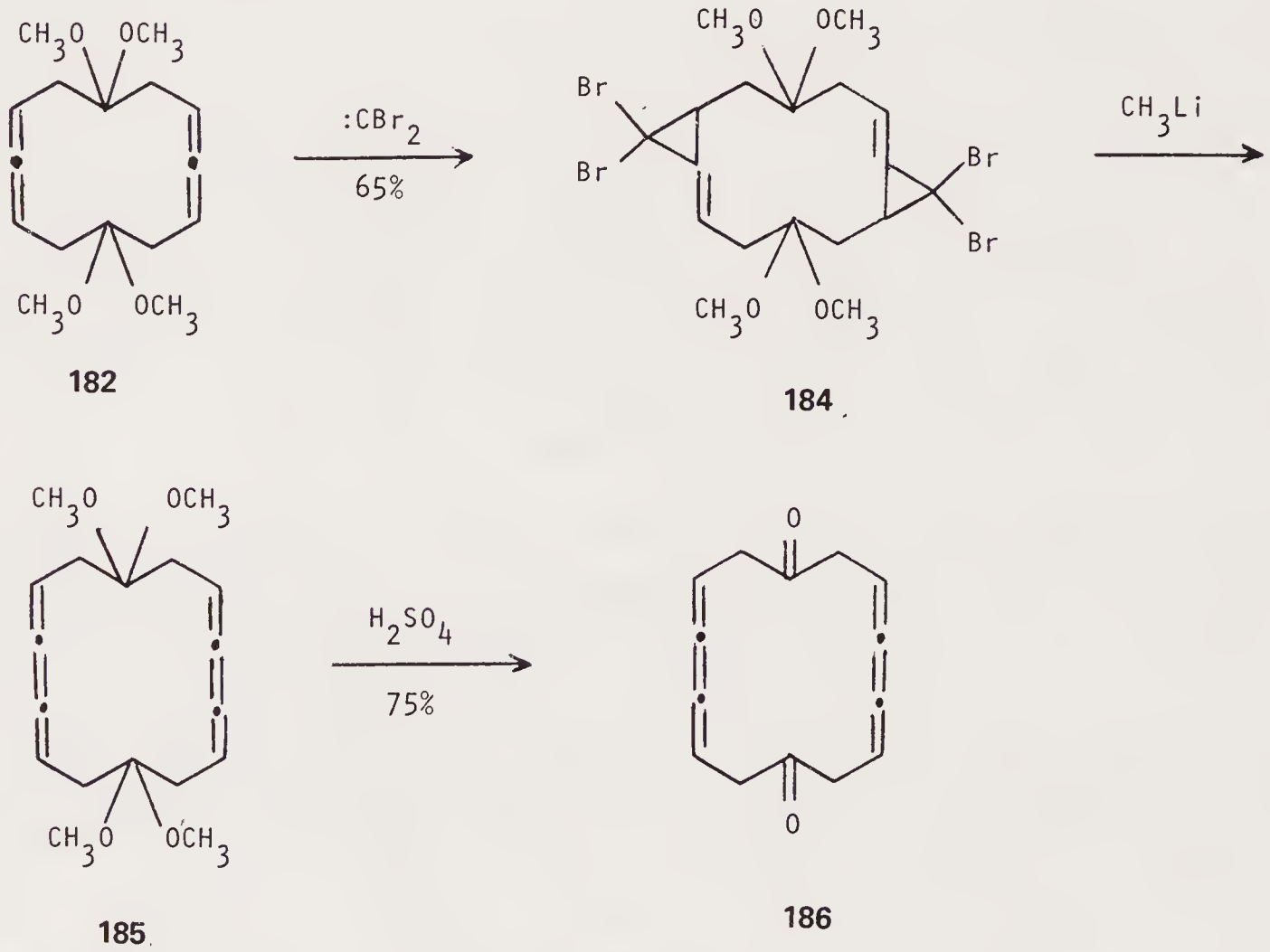


Scheme 22



Scheme 23

Allenic diketals **182** can be ring expanded to produce the novel monocyclic dicumulenedione **186** according to the series of reactions outlined in Scheme 24.[170,171] When a mixture of racemic **182a** and *meso* **182b** is allowed to react with dibromocarbene, a mixture of four bis adducts (only one is shown as **184**) is produced. Treating this mixture with methyllithium at $-10°C$ gives a solution of **185** which remains stable for several days under these conditions. Hydrolysis of diketal **185** with concentrated sulfuric acid at 0°C for one minute gives the crystalline dione **186** which is stable at room temperature either in solution or in the crystalline state.



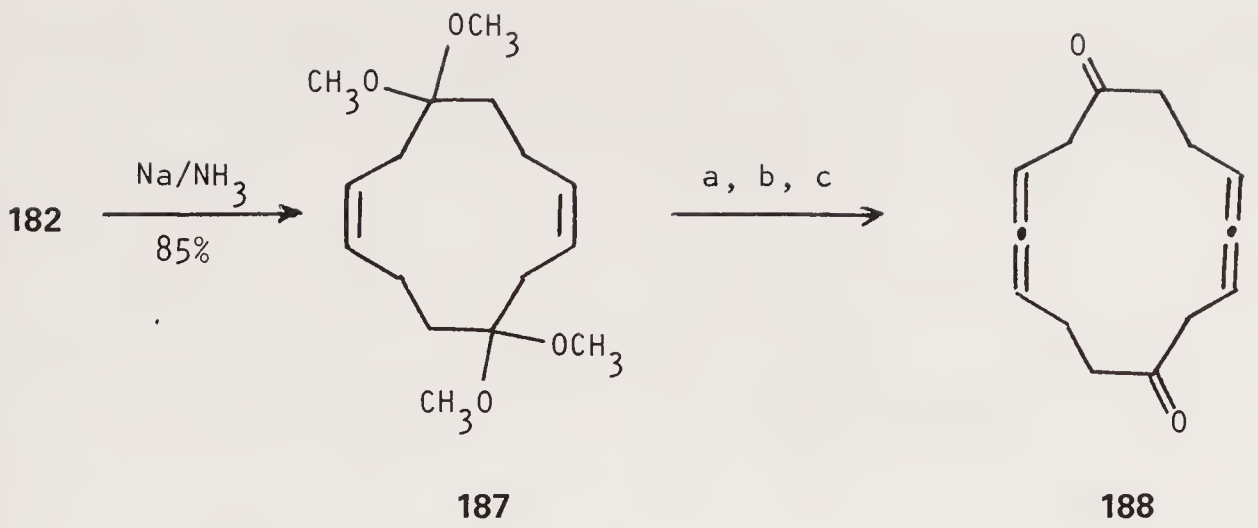
Scheme 24

Reduction of **182** with sodium in liquid ammonia at $-78°C$ gives the crystalline diketal **187** plus three additional minor isomers. Conversion of **187** to 3,4,10,11-cyclotetradecatetraene-1,8-dione (**188**) (mixture of racemic and *meso*) is effected by the three-step sequence shown in equation (46).[169]

When treated with methyllithium in refluxing ether, **182** is converted to tricycle **190** in moderate yield[169] (equation 47). The rearrangement presumably proceeds by way of initial formation of an allenic anion which then undergoes an intramolecular cyclization as shown in **189**.

In protic solvents propynylammonium salts **191** and **193** rearrange under base catalysis to give α-amino-β-ketoallenes **192** and **194** in good yields[172,173] (equations 48 and 49). Bases such as sodium carbonate, sodium methoxide, sodium hydroxide, and sodium hydride are most frequently used and produce consistent results.

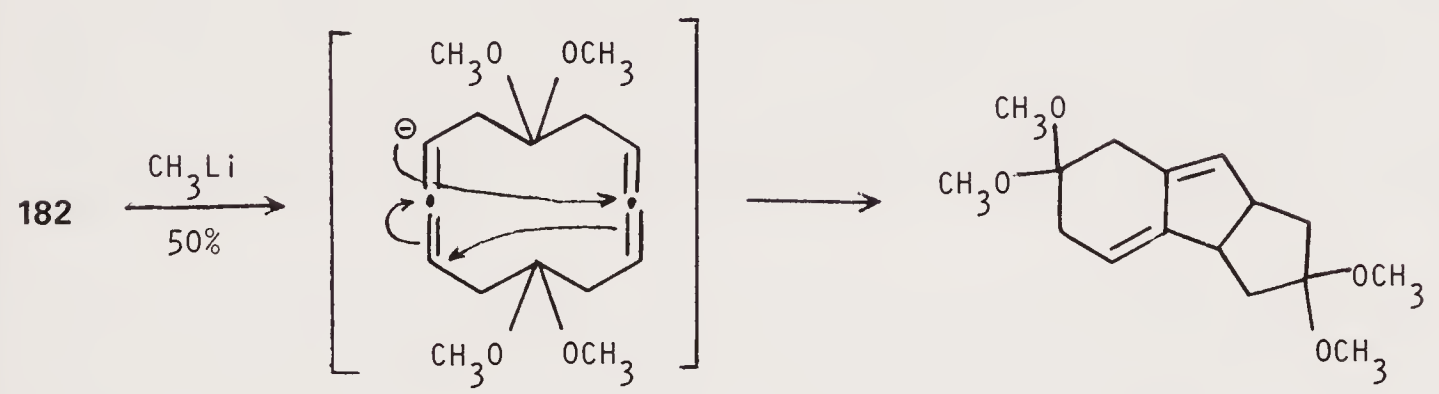
Heating allene **192** ($R = C_6H_5$) at 55°C for 9 hours results in the formation of furan **195** by way of an intramolecular nucleophilic addition of the enol tautomer



(46)

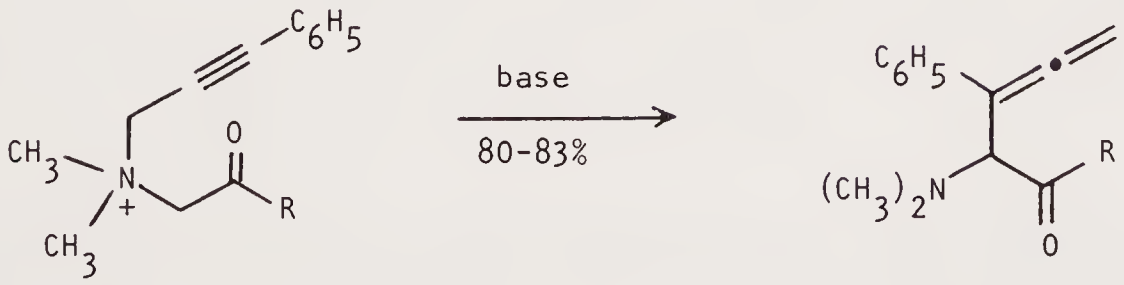
187 **188**

(a) $:CBr_2$ (44%); (b) CH_3Li (90%); (c) H^+ (83%)



(47)

189 **190**

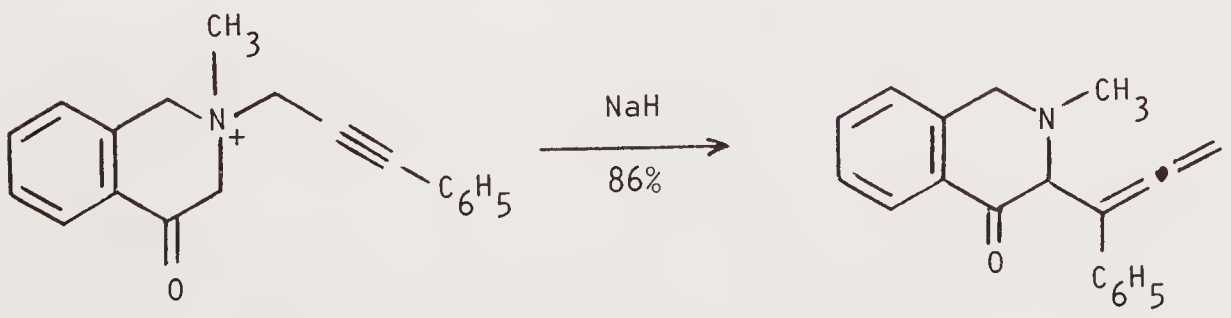


(48)

191

R= CH_3, C_6H_5

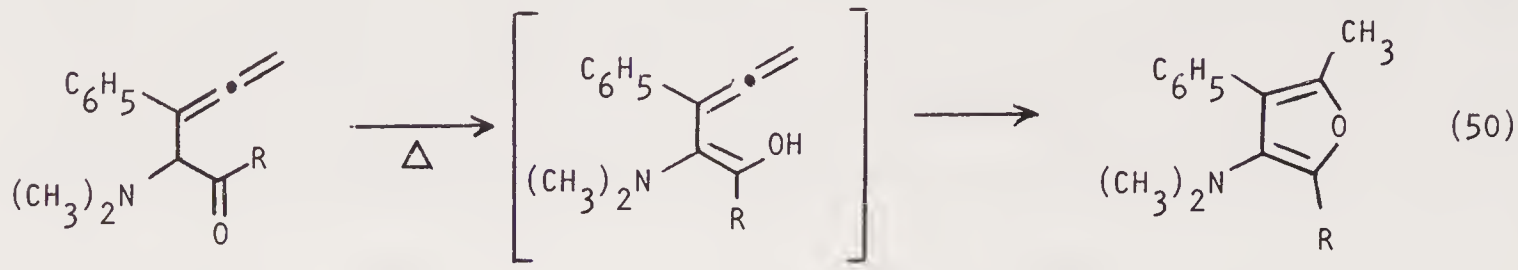
192



(49)

193 **194**

to the central carbon of the allene (equation 50). In the case where R = CH_3 the formation of the furan requires a reaction temperature of 138°C. Furans **195** are rather unstable and decompose on exposure to light and air.



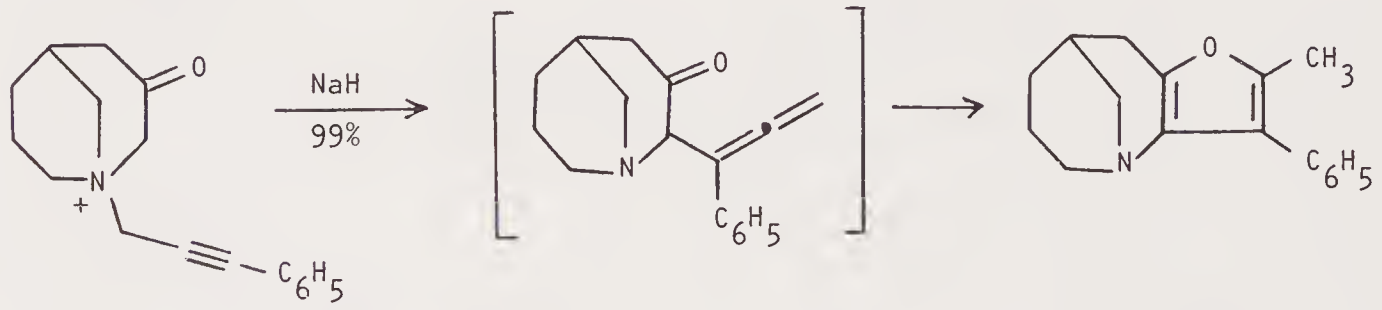
192

R= CH_3, C_6H_5

195

(50)

Azabicyclo[3.3.1]nonane derivative **196**, when treated with sodium hydride in DMSO, rearranges in nearly quantitative yield to **198**. Under these reaction conditions, the intermediate allene **197** is not isolable and proceeds directly to **198**. However, **197** can be obtained in low yield by reaction of **196** with aqueous sodium hydroxide. Analogous treatment of **197** with sodium hydride in DMSO furnishes **198**.



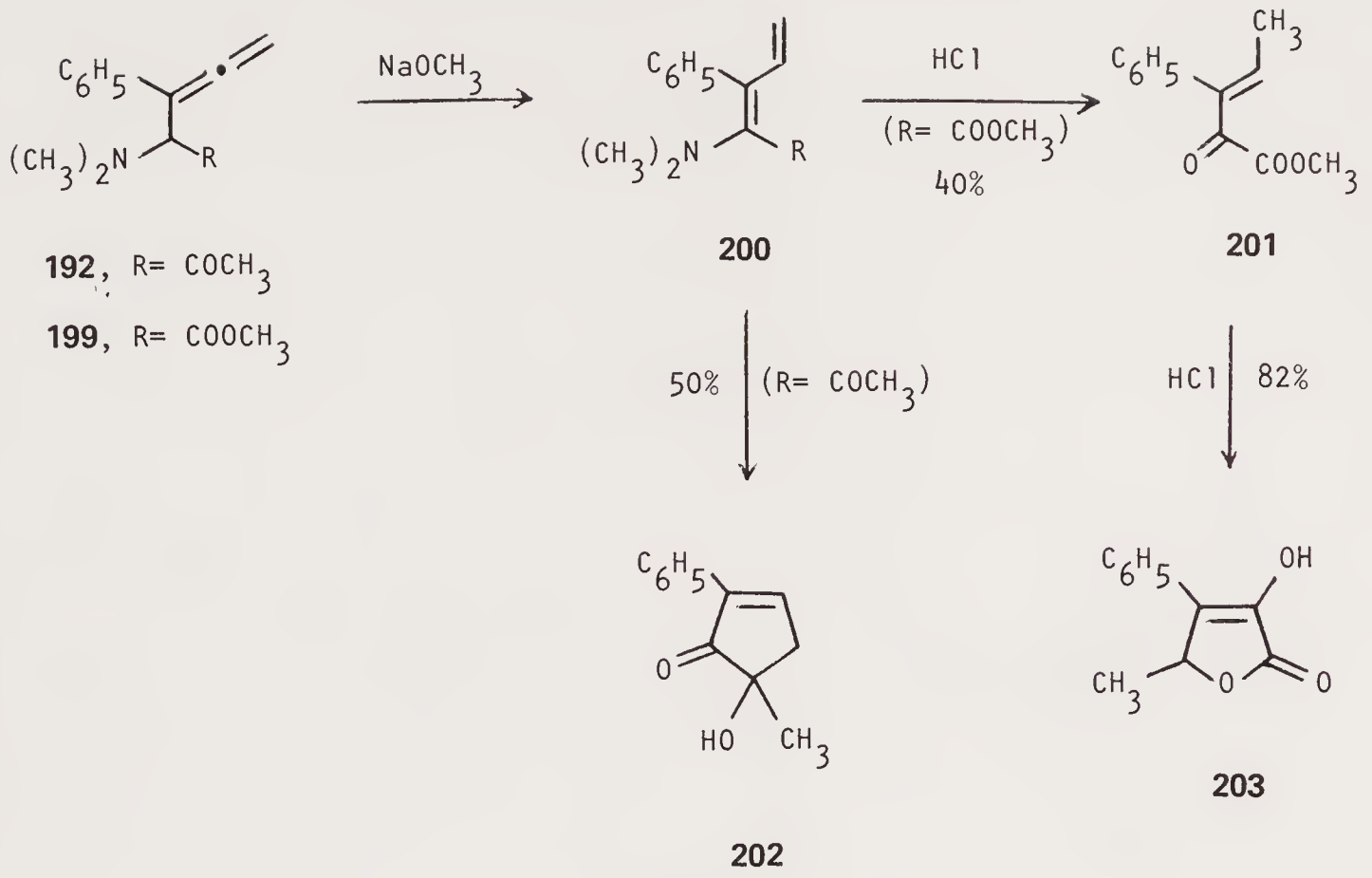
196 **197** **198**

(51)

Allenes **192** and **199** undergo various reactions and are summarized in Scheme 25. Both **192** and **199** rearrange to their respective conjugated dienes **200** when treated with sodium methoxide in DMSO. The diene **200** (R = $COCH_3$) is unstable under the reaction conditions, and only the hydroxycyclopentenone **202** is obtained. On the other hand, **200** (R = $COOCH_3$) is stable to the reaction medium and is isolable. Subsequent treatment with hydrochloric acid hydrolyzes the enamine and produces the α-ketoester **201**. Prolonged exposure to concentrated hydrochloric acid results in the formation of lactone **203**.

β-Allenic aldehydes **204** react with primary amines to form allenyl Schiff bases **205**. When reduced *in situ* with potassium borohydride, allenic amines **206** are obtained generally in 50–80% overall yield.[174]

2-Amino-4,5-hexadienoic acid (**209**, $R_1 = R_2 = R_3 = H$) is an unusual naturally occurring amino acid isolated from the mushroom *Amanita solitaria*.[175] Its synthesis, as well as several of its derivatives, has been accomplished by Landor[176] according to the three-step procedure outlined in Scheme 26. Substrates with a



192, R= $COCH_3$

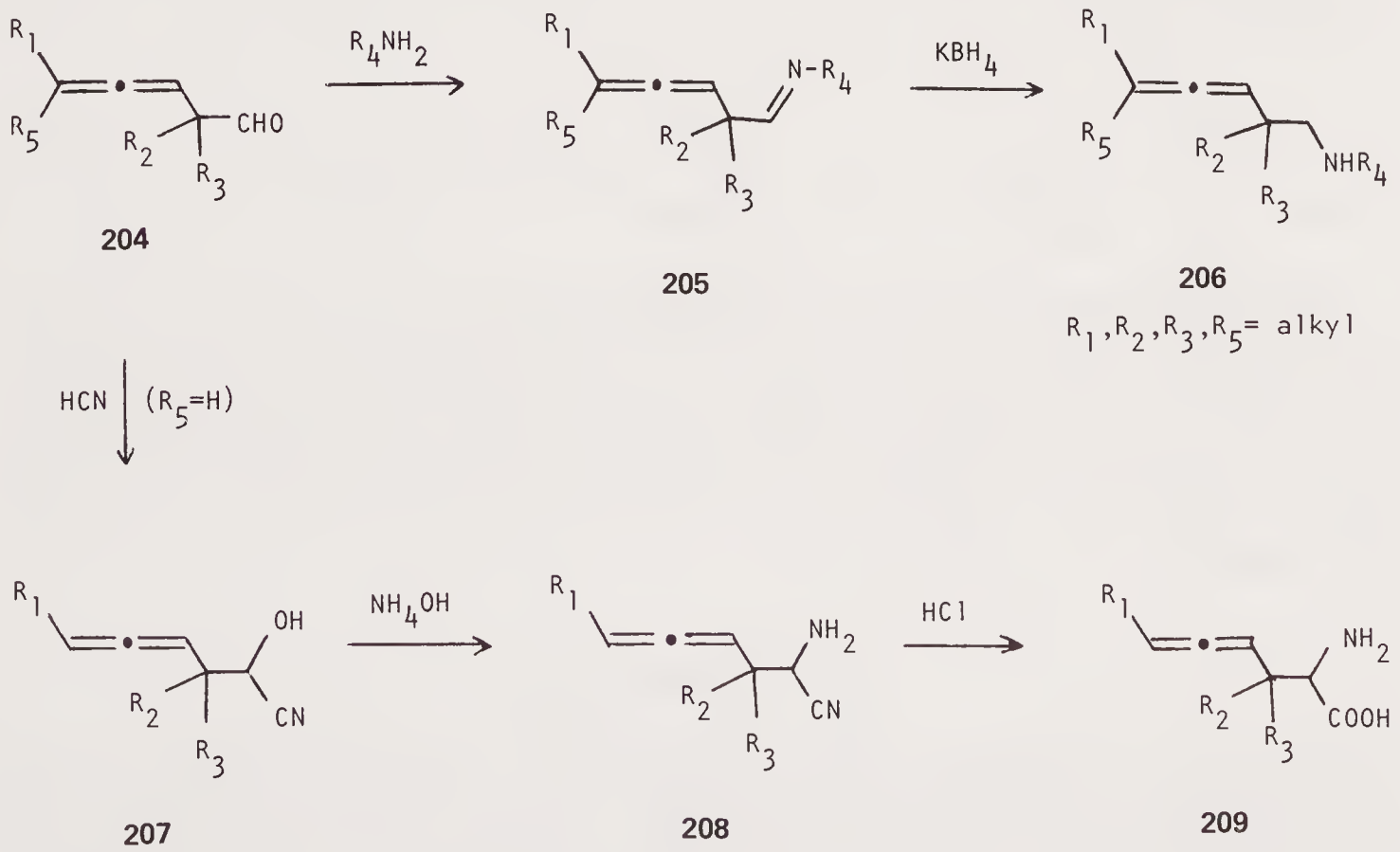
199, R= $COOCH_3$

200 **201**

202 **203**

Scheme 25

proton α to the allene function ($R_2 = R_3 = H$) are not suitable for preparative scale reactions because 3,4-dienals rearrange to 2,4-dienals in the presence of base. However, when the α position is disubstituted ($R_2 = R_3 = CH_3$), the isomerization process is blocked and the conversion proceeds in good yield.



204 **205** **206**

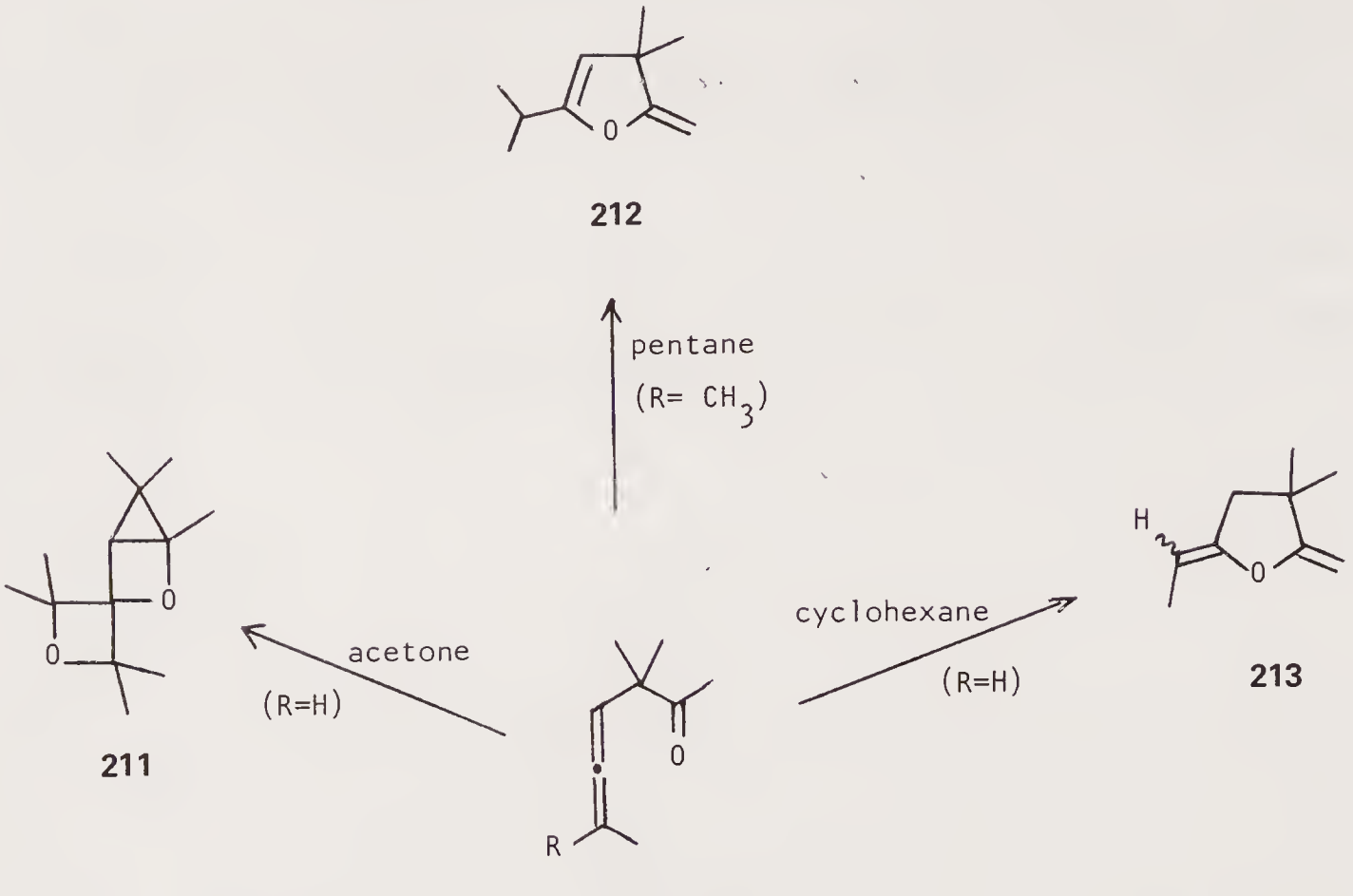
R_1, R_2, R_3, R_5= alkyl

207 **208** **209**

R_1= H, CH_3, C_3H_7

R_2=R_3= H or CH_3

Scheme 26



212 **211** **213** **210** **215** **214** R′ = C_2H_5, i-C_3H_7

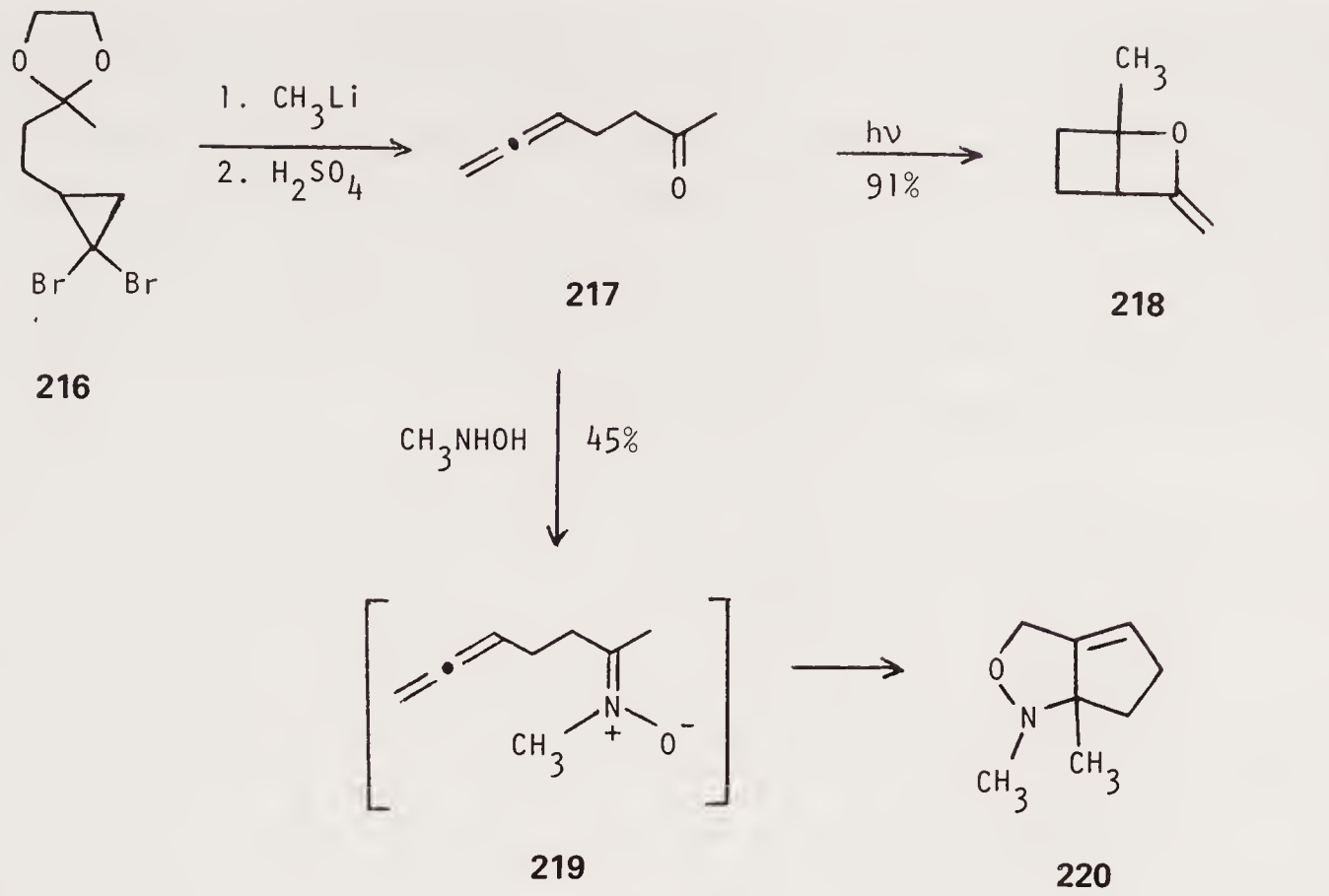
Scheme 27

Photoirradiation of β-allenic ketones **210** (Scheme 27) gives a variety of products, the distribution of which depends on the solvent employed (only the major products are shown).[177] In hydrocarbon solvents, enol ethers **212**, **213**, and **215** are produced by way of cyclization followed by a 1,5-hydride shift. On T-sensitization in acetone, spirodioxetane **211** is formed in high yield, and in alcoholic solvents acetals **214** are produced.

5.2.3. γ-Oxo-Allenes

5,6-Heptadien-2-one (**217**), synthesized from **216** by standard procedures, contains an isolated carbonyl and allene group suitably located to undergo an intramolecular Paterno–Büchi reaction. When photolyzed in petroleum ether, **217** is converted to 1-methyl-3-methylene-2-oxabicyclo[2.2.0]hexane (**218**) by way of an intramolecular [2 + 2] cycloaddition between the ketone and the internal double bond of the allene.[178]

When **217** is allowed to react with N-methylhydroxylamine, the bicyclic isox-



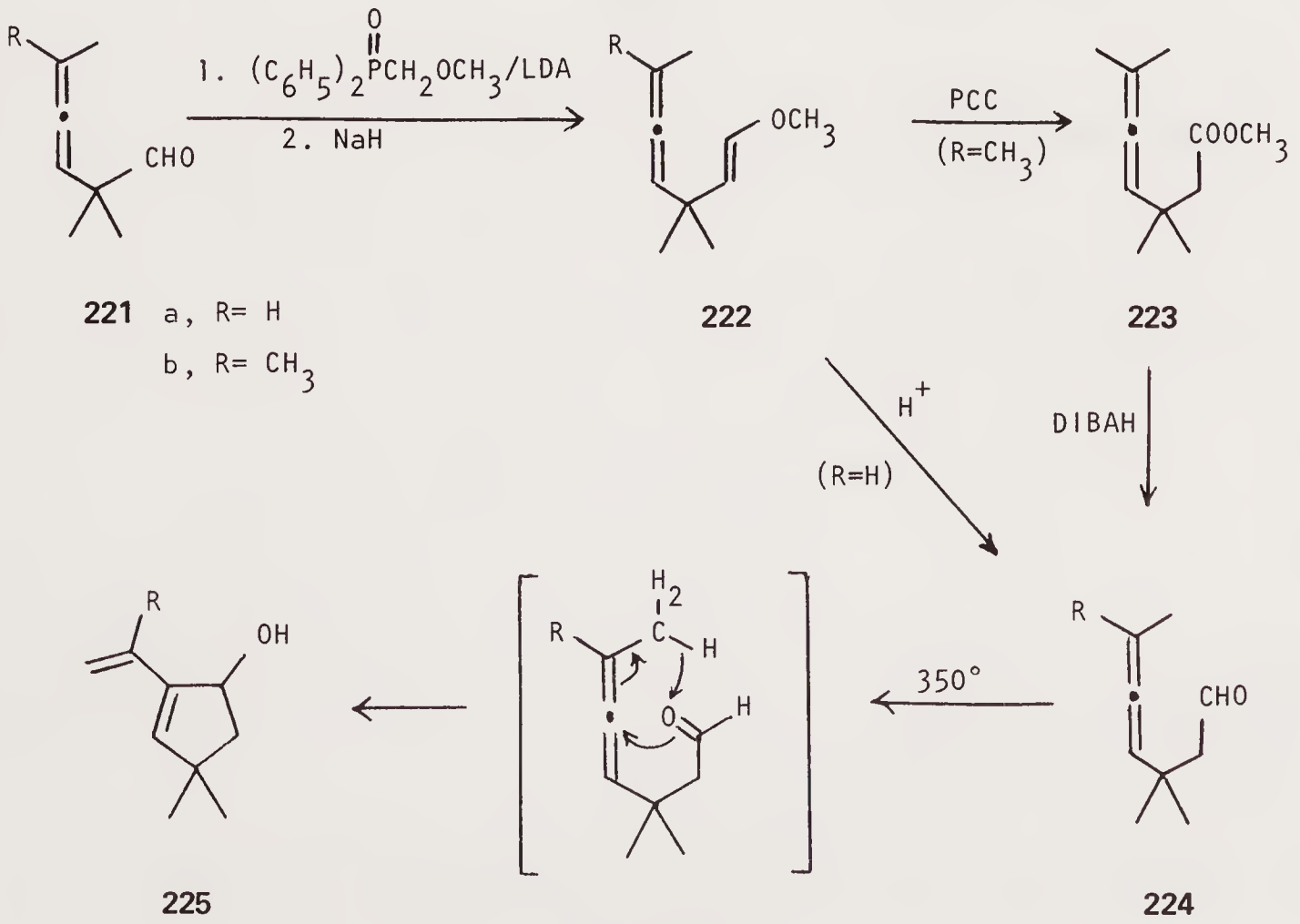
216 **217** **218**

219 **220**

Scheme 28

azolidine **220** is formed.[179] Undoubtedly the initial step in the reaction is the formation of nitrone **219**, which then undergoes an intramolecular 1,3-dipolar cycloaddition with the terminal double bond of the allene to produce the observed product.

γ-Allenic aldehydes **224** are readily accessible from β-aldehydes **221** by homologation using a Horner–Wittig reaction. Acid hydrolysis of **222a** gives **224a** in



221 a, R= H
b, R= CH_3

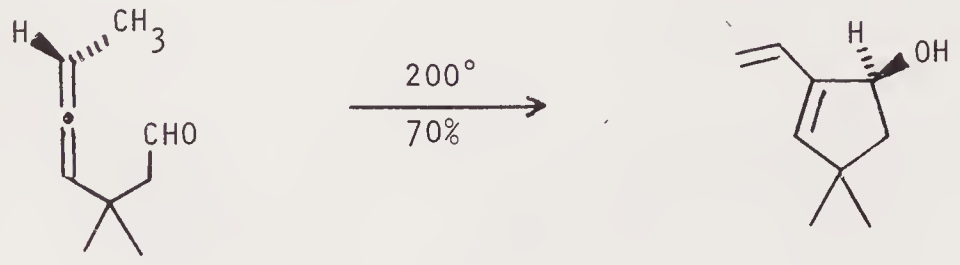
222 **223**

225 **224**

Scheme 29

85% overall yield from **221a**. Analogous treatment of **222b** gives a mixture of products. This can be circumvented by the oxidation of **222b** with PCC followed by reduction of the ester **223** with DIBAH to give **224b** in 76% overall yield from **221b** (Scheme 29). Thermolysis of aldehydes **224** affords cyclopentenols **225** as a result of an intramolecular hetero–ene cyclization. The conversion **224b** → **225b** can also be accomplished quantitatively by the chromatography of **224b** on silica gel.[180]

When the hetero–ene synthesis is performed with optically active aldehyde **226**, the chirality is transferred to the product **227**.[181]



(S)-(+)-**226** (S)-(-)-**227** (52)

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CHAPTER SIX

ALLENIC ACIDS AND THEIR DERIVATIVES

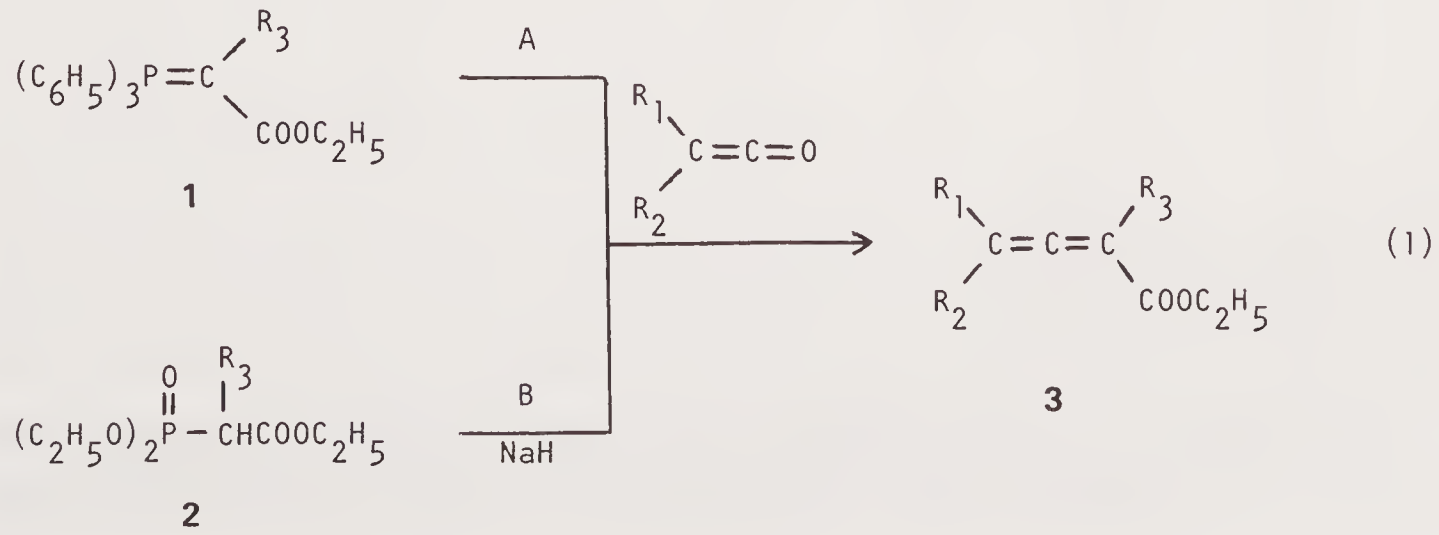
Allenes that are functionalized by carbon-containing electron-withdrawing groups such as carboxylic acid derivatives or nitriles exhibit enhanced reactivity toward nucleophiles. This property makes them excellent candidates as precursors in synthetic manipulations. The functional group attached to the allene also serves as a convenient handle for further elaboration or cyclization to produce a variety of complex acyclic, carbocyclic, or heterocyclic molecules.

6.1. ALLENIC ACIDS AND ESTERS

6.1.1. Allene Carboxylic Acid Derivatives

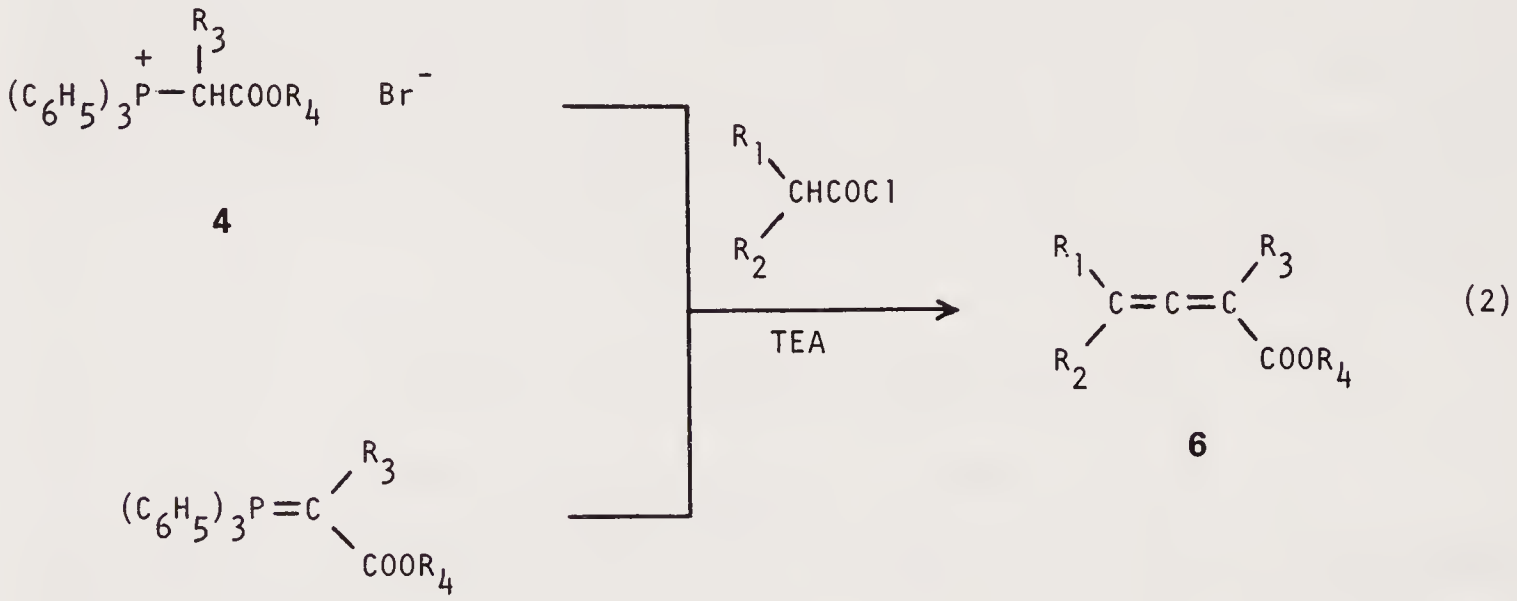
The syntheses of allenic acids and esters of this type are numerous, and the literature is replete with various preparations. We discuss only those methods that present the widest range of generality. The remainder are listed in Table 6.1 at the end of this section.

A simple synthesis of allene carboxylates (**3**) is shown in equation (1). Ketenes undergo a Wittig reaction with either phosphoranes **1** or phosphonates **2** at room temperature or below to produce esters **3** in good yields. An advantage of this procedure over some of those listed in Table 6.1 is that no isomeric acetylenes are formed.

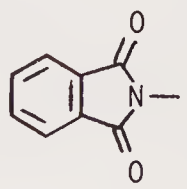


allene	R_1	R_2	R_3	route	yield, %	reference
3a	H	H	H	A	64	1
3b	H	H	CH_3	A	71	1,2
3c	$Si(CH_3)_3$	H	H	A	85	3
3d	C_6H_5	CH_3	CH_3	B	67	4,5
3e	CH_3	C_2H_5	C_6H_5	B	74	4
3f	$COOC_2H_5$	$COOC_2H_5$	CH_3	A	62	6

The ketene need not be synthesized prior to the reaction but can be generated *in situ* by the action of triethylamine on an acid chloride. Consequently, when either the phosphonium salts **4** or the phosphoranes **5** are allowed to react with an acid chloride in the presence of triethylamine at room temperature, allenic esters **6** are obtained in moderate yields. The list of compounds in equations (1) and (2) represents only selected examples from many reported in each literature reference.



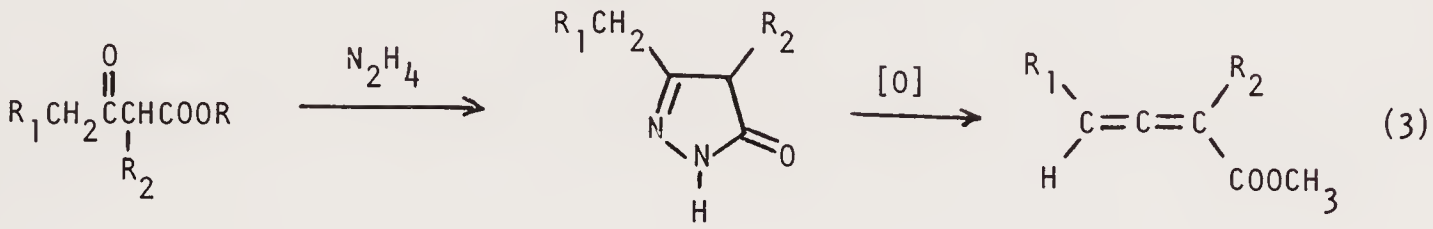
allene	R_1	R_2	R_3	R_4	yield, %	reference
6a	H	H	H	CH_3	40	7
6b	CH_3	H	H	CH_3	58	7
6c	H	H	CH_3	C_2H_5	59	2,8
6d	CH_3	H	CH_3	C_2H_5	66	9
6e	CH_3	CH_3	CH_3	C_2H_5	42	2
6f	H	H	$—(CH_2)_2—$		37	10
6g	Pht	H	CH_3	C_2H_5	42	11

Pht = 

The oxidation of 3,4-disubstituted-5-pyrazolones (**8**) provides another general route to 2,3-alkadienoic esters. The transformation can be effected with oxidizing

agents such as thallium(III) nitrate[12–14] (48–70% yields) or lead(IV) acetate[15] (60–76% yields). The only limitation of the reaction is that R_2 cannot be a proton. If R_2 = H, then the isomeric 2-alkynoic esters are produced.

The pyrazolones **8** can be generated *in situ* by the addition of hydrazine to a methanol solution of the β-ketoester **7**, then the allene is produced by subsequent addition of the oxidizing agent. This one-pot procedure (equation 3) formally represents a dehydration of the β-ketoester **7**.



(3)

7 **8**

R_1, R_2= alkyl, $(CH_2)_n$ (n=6-9)

Nucleophiles add to allenic esters at their central carbon atom. Sodium ethanethiolate reacts smoothly with ethyl 2,3-butadienoate (**3a**) to give the nonconjugated ester **9** in high yield[16] (equation 4).

(4)

3a **9**

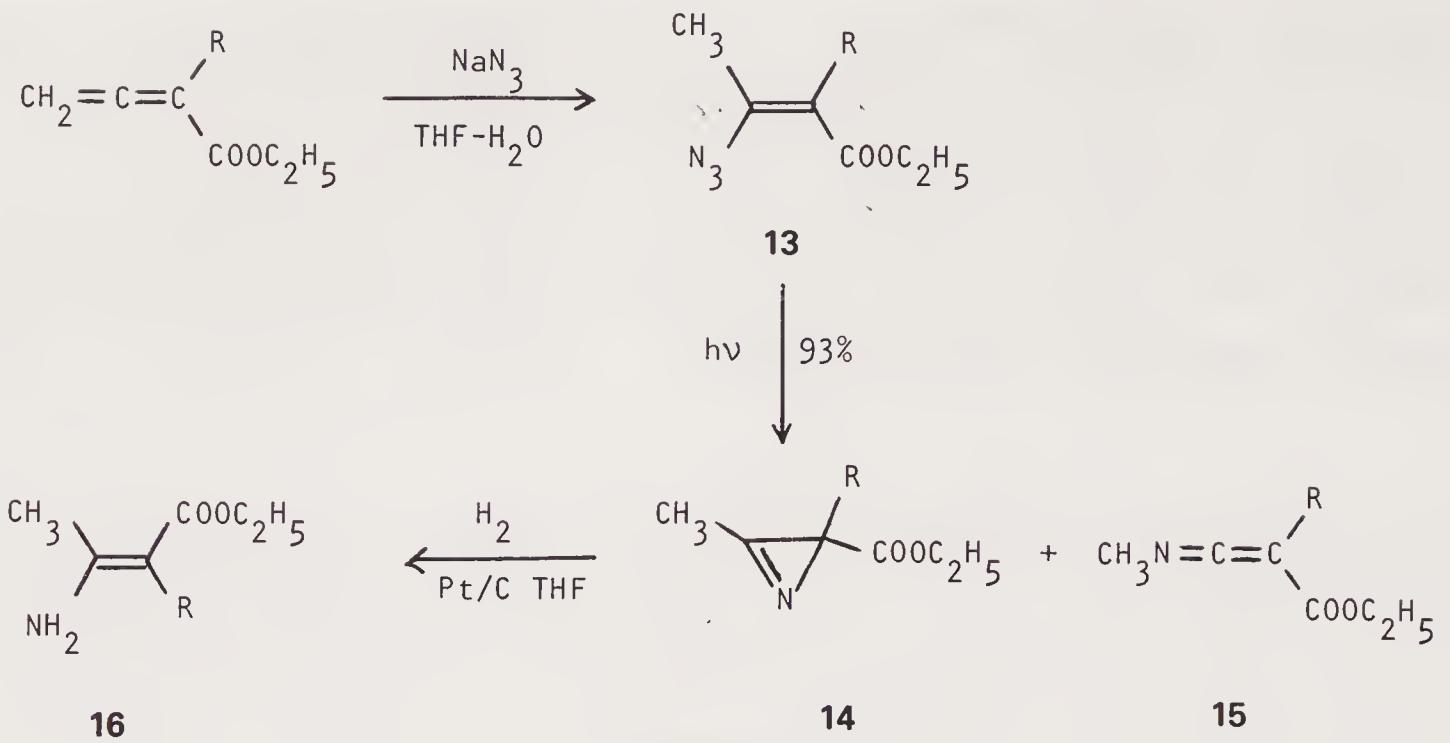
Allene carboxylates can be easily converted to β-ketoesters by the two-step procedure shown in equation (5).[17] Piperidine adds readily to allenes **10** to form enamines **11** which, upon acidic hydrolysis, furnish the β-ketoesters **12** in 69–94% overall yields.

(5)

10 **11** **12**

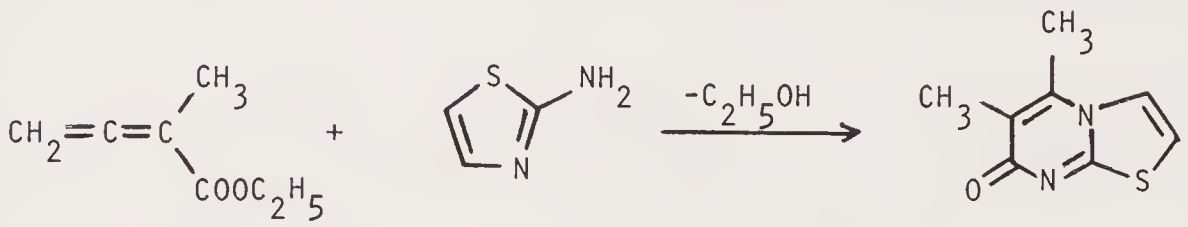
R_1, R_2= alkyl

The addition of azide ion to allenic esters results in the formation of β-azidocrotonates **13**. Photolysis of **13** in benzene, leads to a 4:1 mixture of azirene **14** and ketenimine **15** (Scheme 1) which are separable by chromatographic techniques. Azirenes **14** are remarkably stable and can be stored under nitrogen at room temperature for several months. These azirenes rapidly absorb one equivalent of hydrogen at atmospheric pressure to give β-aminocrotonates (**16**).[18]



Scheme 1

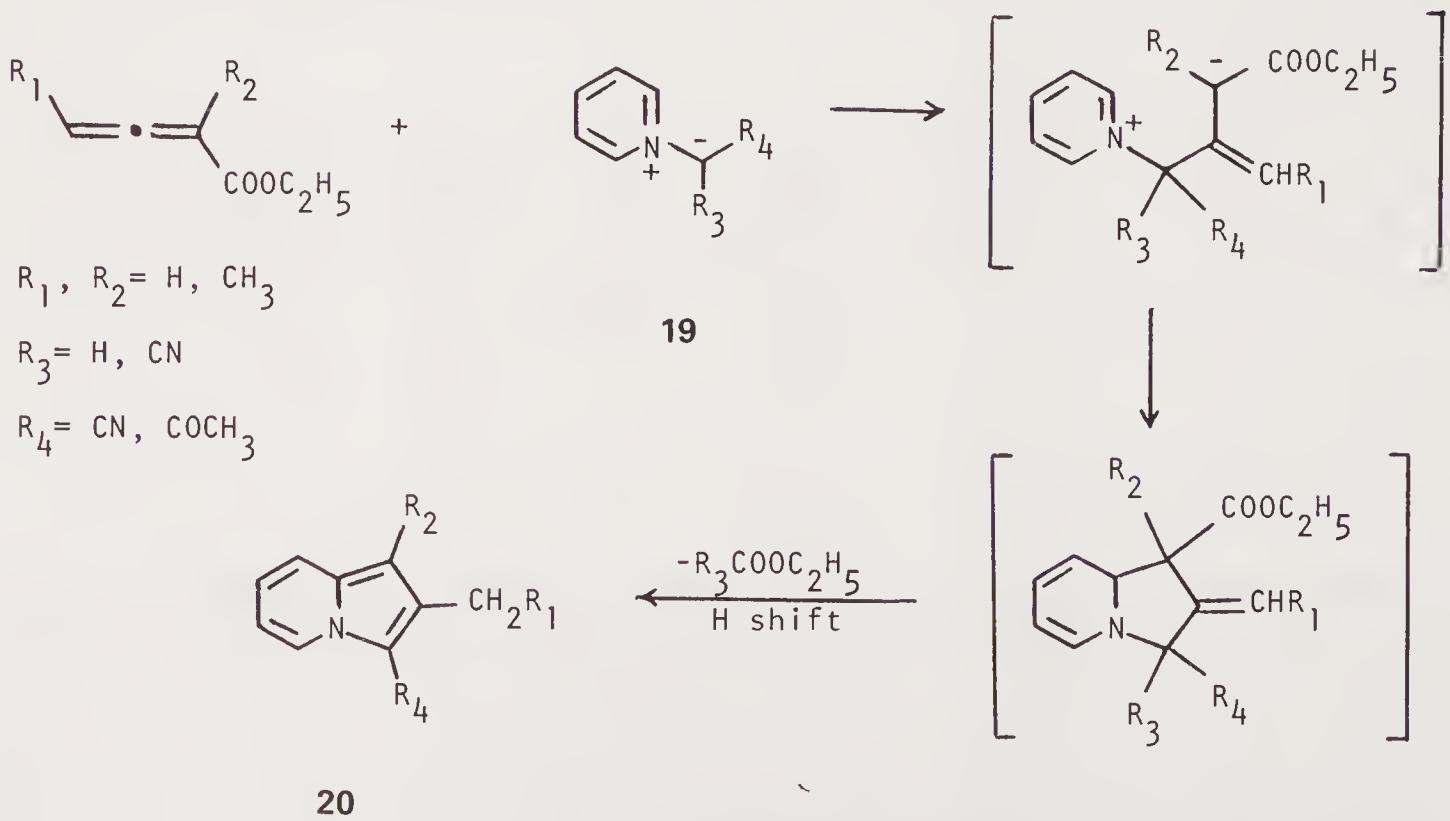
Ethyl 2-methyl-2,3-butadienoate (**3b**) reacts with 2-aminothiazole (**17**) at the heterocyclic nitrogen atom to produce 5,6-dimethylthiazolo[3,2-a]pyrimidin-7-one (**18**) in 53% yield[19] (equation 6).



(6)

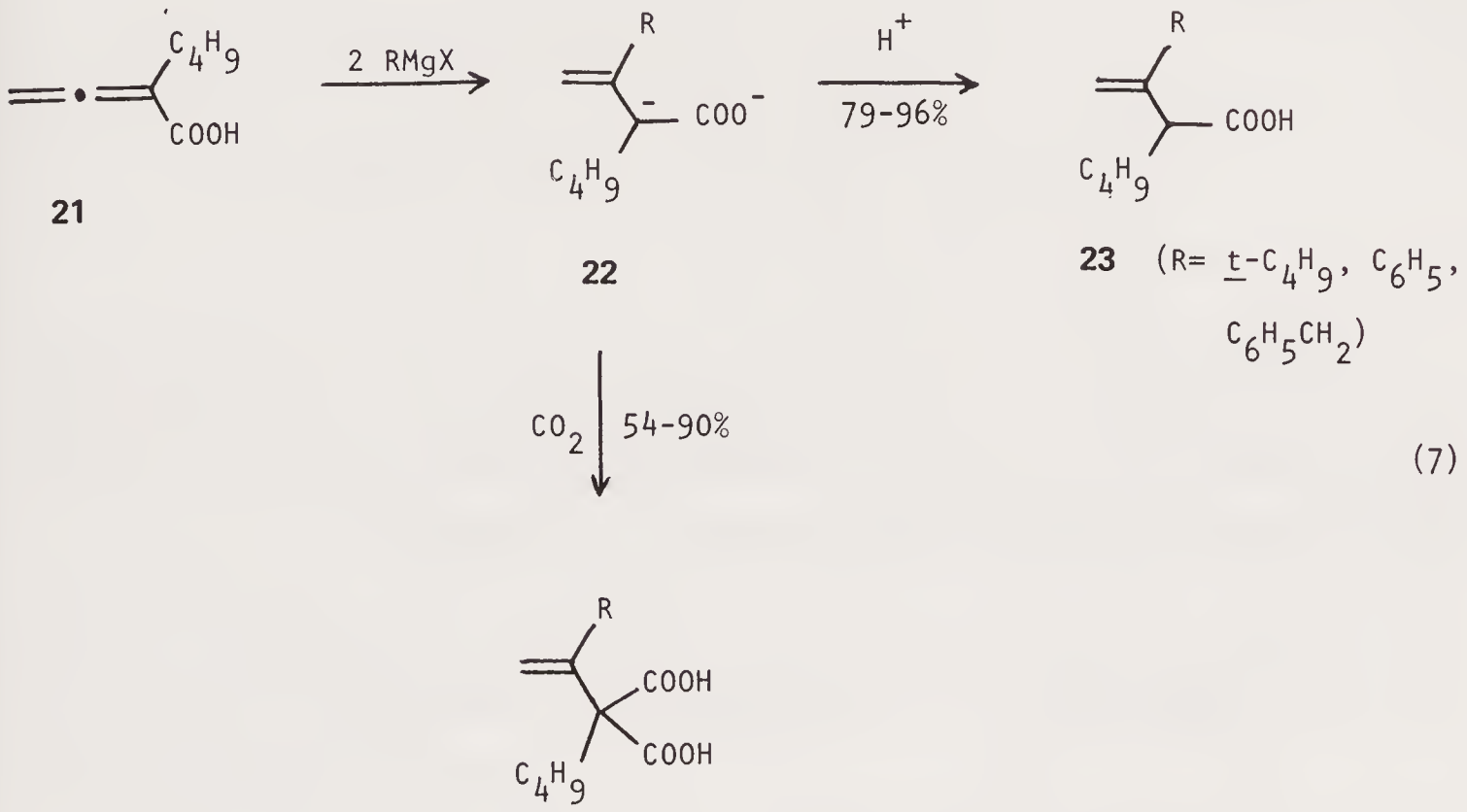
3b **17** **18**

Pyridinium methylides (**19**) combine with allenic esters to give indolizines **20** according to the mechanism outline in Scheme 2.



Scheme 2

Grignard reagents added at room temperature to 1,2-heptadiene-3-carboxylic acid (**21**) to generate the dianionic species **22**. Protonation with dilute HCl furnishes the β,γ-unsaturated acids **23**, whereas carbonation affords malonic acid derivatives **24** (equation 7).[20,21]



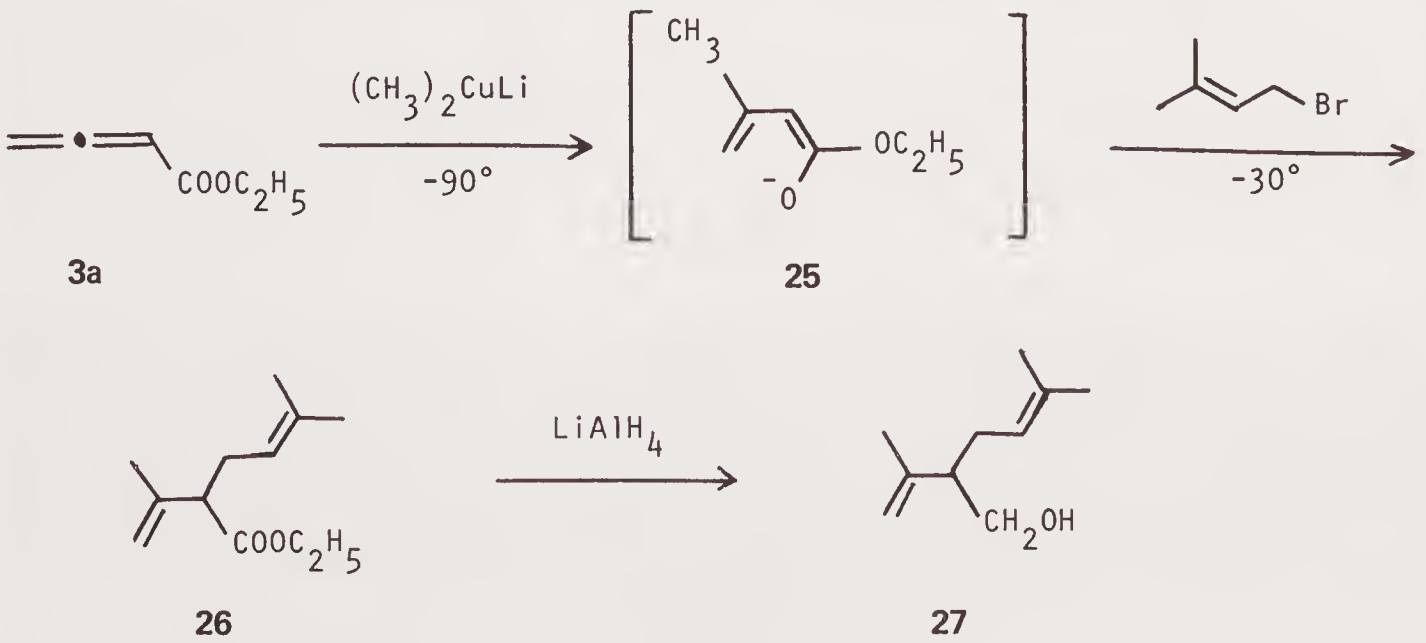
21 **22** **23** (R= t-C_4H_9, C_6H_5, $C_6H_5CH_2$)

24 (R= C_2H_5, i-C_3H_7, t-C_4H_9, $C_6H_5CH_2$)

(7)

An extension of this type of reaction involves the use of an organocuprate in place of the Grignard reagent. These additions proceed very rapidly at −90°C and are stereospecific. An interesting application of this concept is the synthesis of lavandulol (**27**) (Scheme 3), a naturally occurring monoterpene found in lavender.

The addition of lithium dimethylcuprate to **3a** occurs almost instantaneously to generate the ester enolate **25**. Alkylation of **25** with prenyl bromide gives **26** which, upon reduction with lithium aluminum hydride, furnishes the product in approximately 50% yield from **3a**.[22]

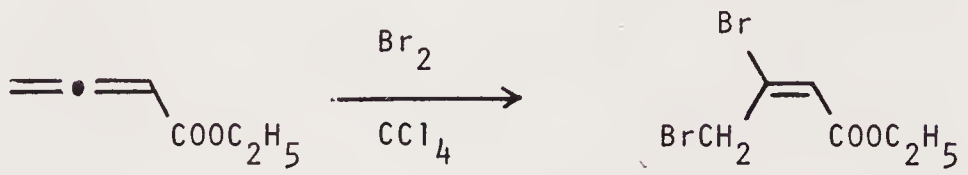


3a **25**

26 **27**

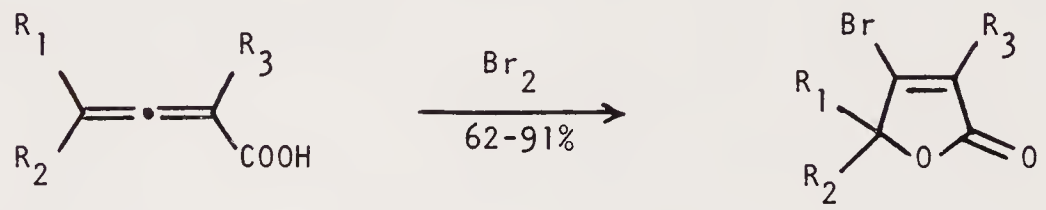
Scheme 3

The addition of electrophiles to 2,3-alkadienoic esters occurs at the double bond in the 3,4-position to yield crotonate derivatives. Thus, when bromine is allowed to react with **3a** at room temperature, ethyl 3,4-dibromocrotonate (**28**) is obtained (equation 8). The product consists of a mixture of stereoisomers with the E isomer predominating.[23,24]

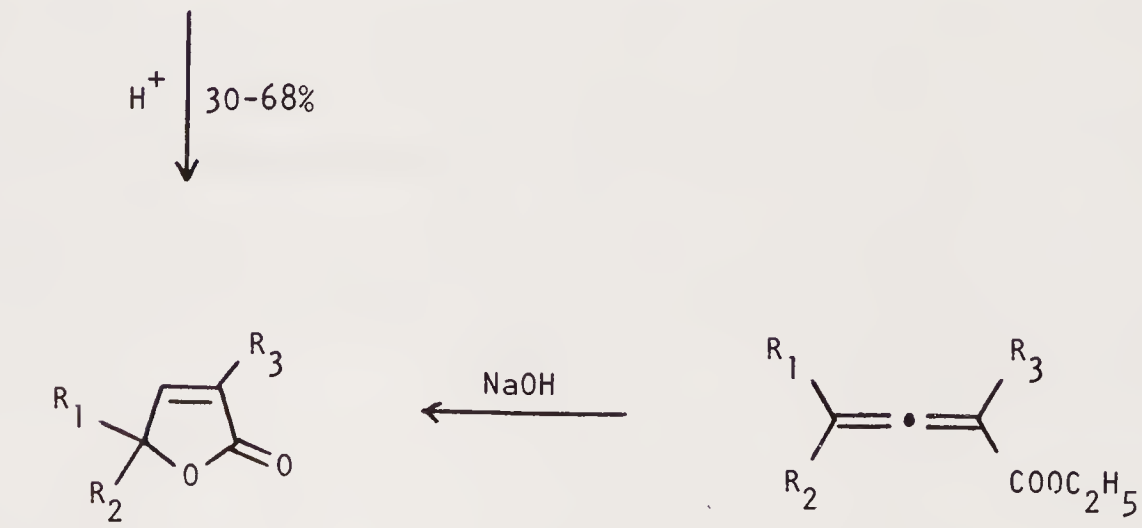


3a **28** (8)

An analogous addition of bromine to allenic acids produces bromobutenolides **29** as the consequence of a bromolactonization reaction.[25–27] The bromine-free butenolides **30** can be prepared by either the acid-catalyzed cyclization of allenic acids or the base hydrolysis of allenic esters[4,26,28,29] (Scheme 4).



29

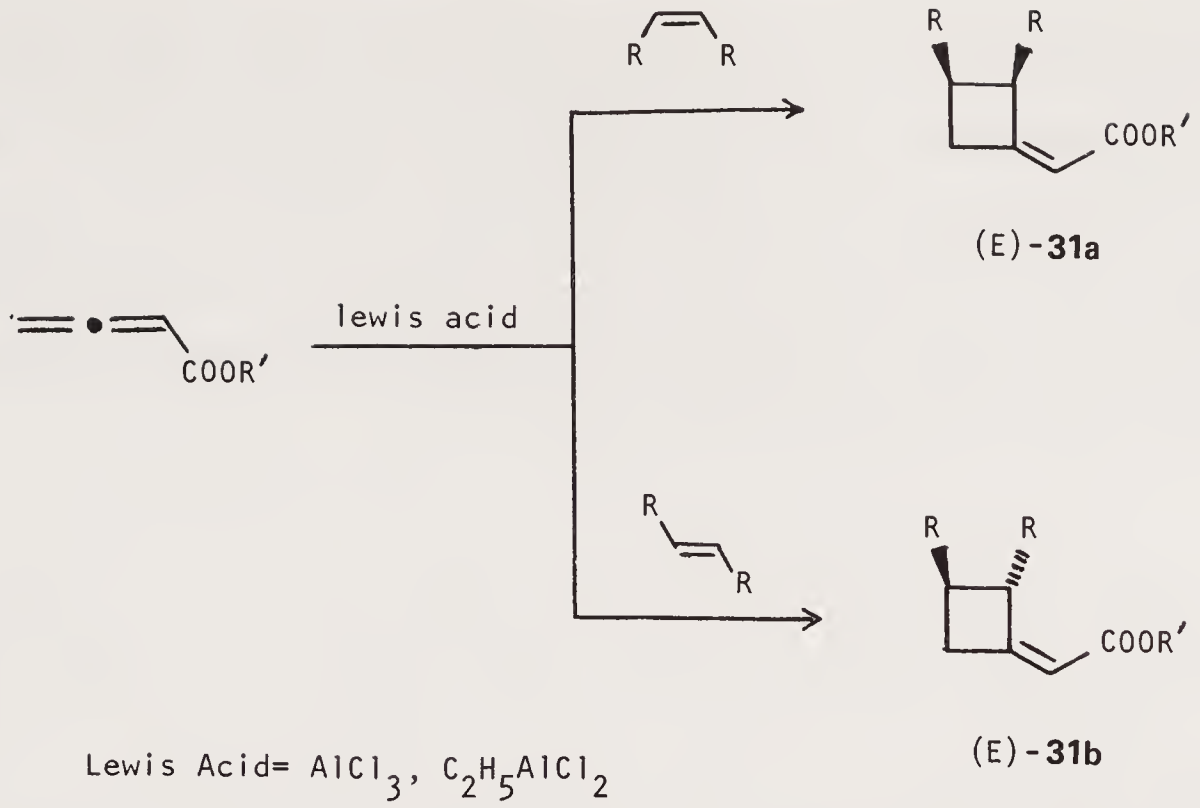


30

R_1-R_3= H, alkyl, C_6H_5

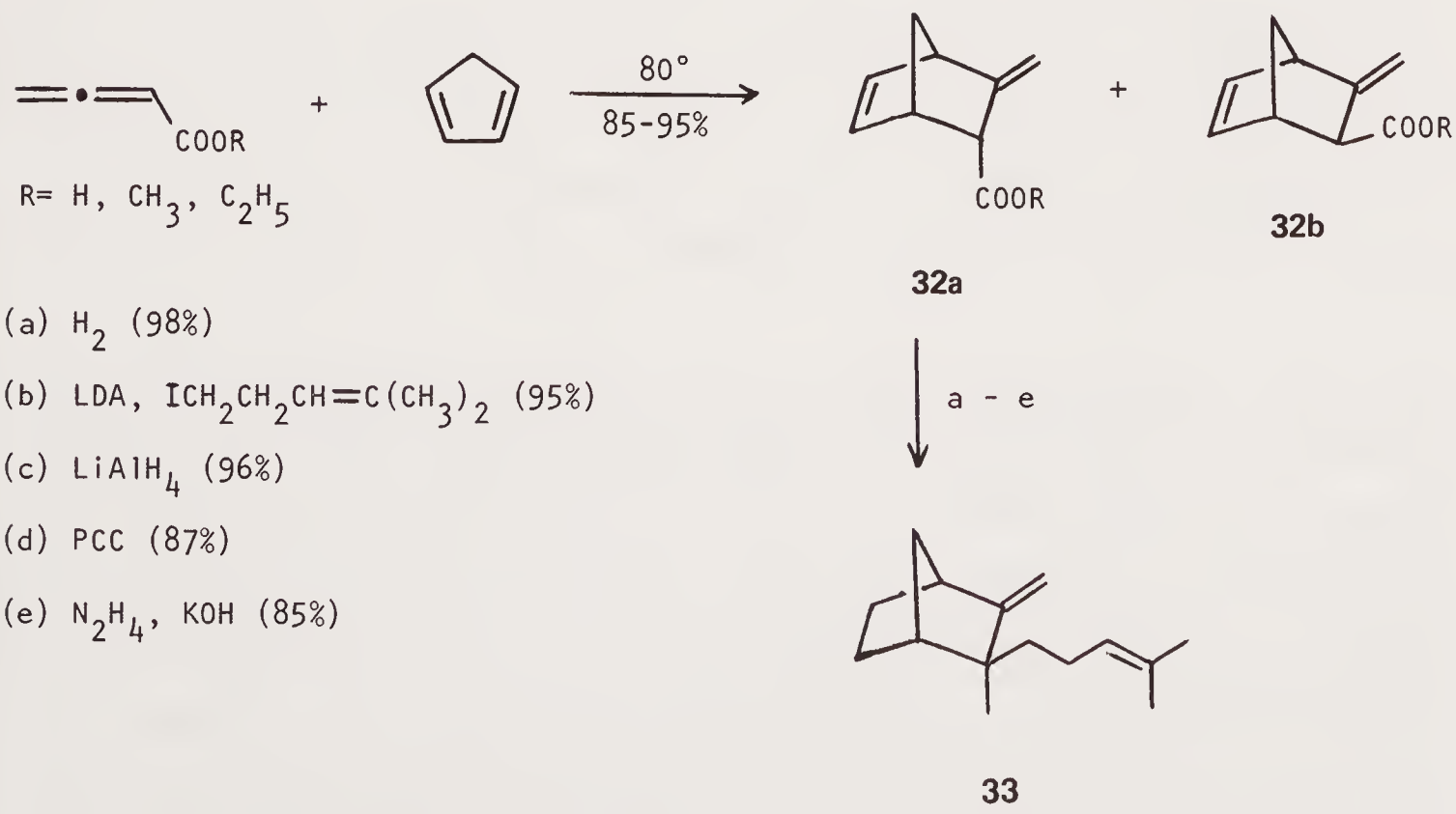
Scheme 4

Under Lewis-acid catalysts, 2,3-butadienoic esters undergo [2 + 2] cycloaddition reactions with olefins at the terminal allene double bond to give cyclobutylideneacetate derivatives **31**.[30,31] The transformation is stereospecific with respect to the alkene (equation 9) but produces a mixture of isomers about the exocyclic double bond. The E isomer always predominates, and the ratio can reach as high as 93:7.



The activating influence that a carboxylate function exerts upon the allene framework makes these compounds excellent candidates as dienophiles in Diels–Alder reactions. The specific site of activation by the electron-withdrawing group is the 2,3-double bond of the allene, and it is this portion of the molecule that enters into reactions with 1,3-dienes.

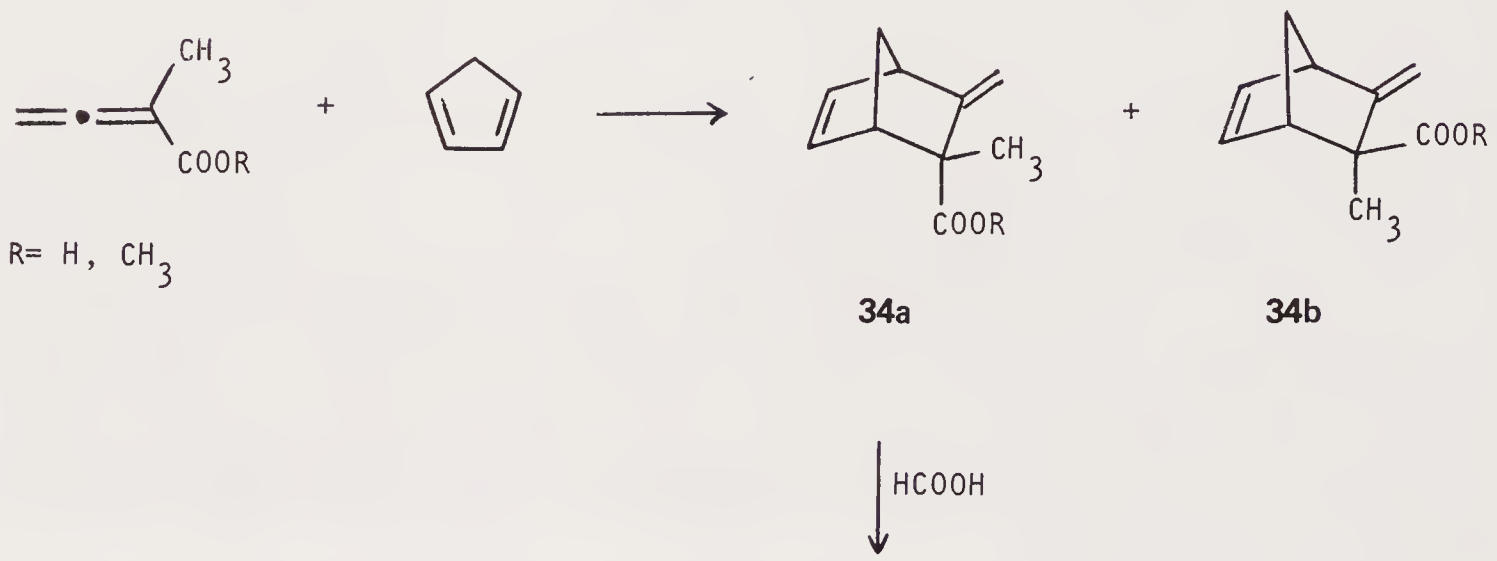
With cyclopentadiene, allenic acids and esters undergo a thermal [4 + 2] cycloaddition to afford norbornene derivatives **32** as a mixture of *endo* (**32a**) and *exo* (**32b**) products (64:36).[14,32] The addition of a Lewis-acid catalyst allows the reaction to be performed at lower temperatures while increasing the yield and *endo* selectivity (86:14). The methyl esters of **32** have been used successfully in the synthesis of (±)-β-santalene (**33**)[33] (Scheme 5).



Scheme 5

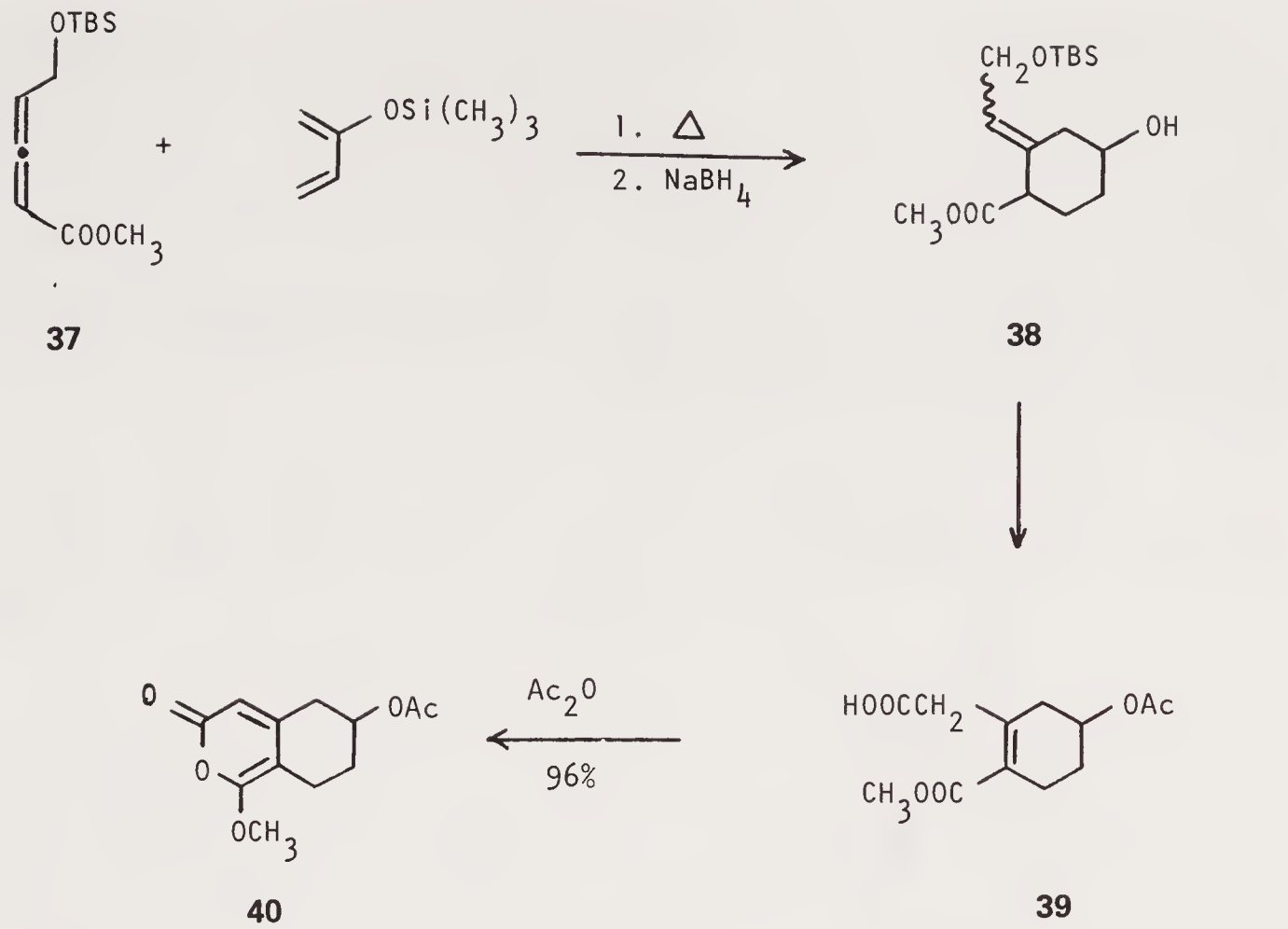
Analogous thermal Diels–Alder reactions of 2-alkyl allenic acids or esters such as **6a** violate the Alder *endo* rule and produce the *exo* adduct **34b** as the major product (ratio **34a/34b** = 40:60).[34] In the presence of aluminum chloride, the *endo* selectivity is enhanced and the *endo*/*exo* ratio increases to 76:24.[14]

The *endo* acid **34a**, upon treatment with formic acid at 90°C, undergoes an interesting acid-catalyzed lactonization to give the tetracyclic lactone **35**. This lactone is a useful synthon for sesquiterpenes related to tricyclene and has been used in a total synthesis of teresantalol (**36**)[35] (Scheme 6).



Scheme 6

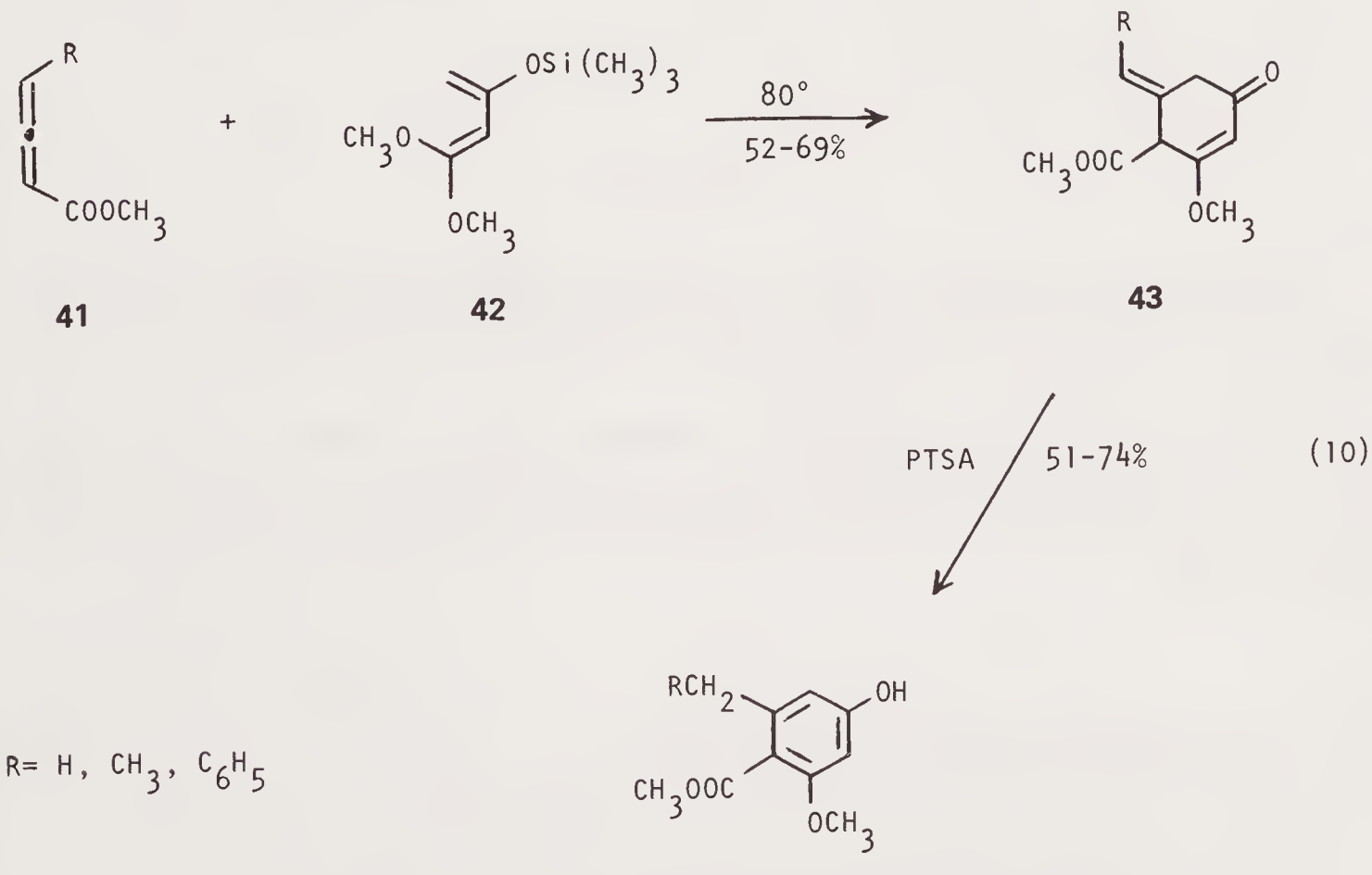
6-Alkoxy-2-pyrones (e.g., **40**) are key molecules for the preparation of tetracyclic intermediates in the synthesis of 11-deoxyanthracyclines. They can be regiospecifically synthesized (Scheme 7) by a Diels–Alder reaction of allenic ester **37** with 2-trimethylsiloxybutadiene. The initially formed product **38** is converted to the glutaconic half-ester (**39**) by the following series of reactions: (1) acetylation of the hydroxy group with acetic anhydride; (2) oxidation of the TBS ether to the acid with Jones reagent; and (3) treatment with triethylamine to move the double bond into the ring. Cyclization of **39** with refluxing acetic anhydride then gives the pyrone **40** in nearly quantitative yield.[36] Reaction of **40** with juglone produces the anthracycline tetracycles.



37 38 39 40

Scheme 7

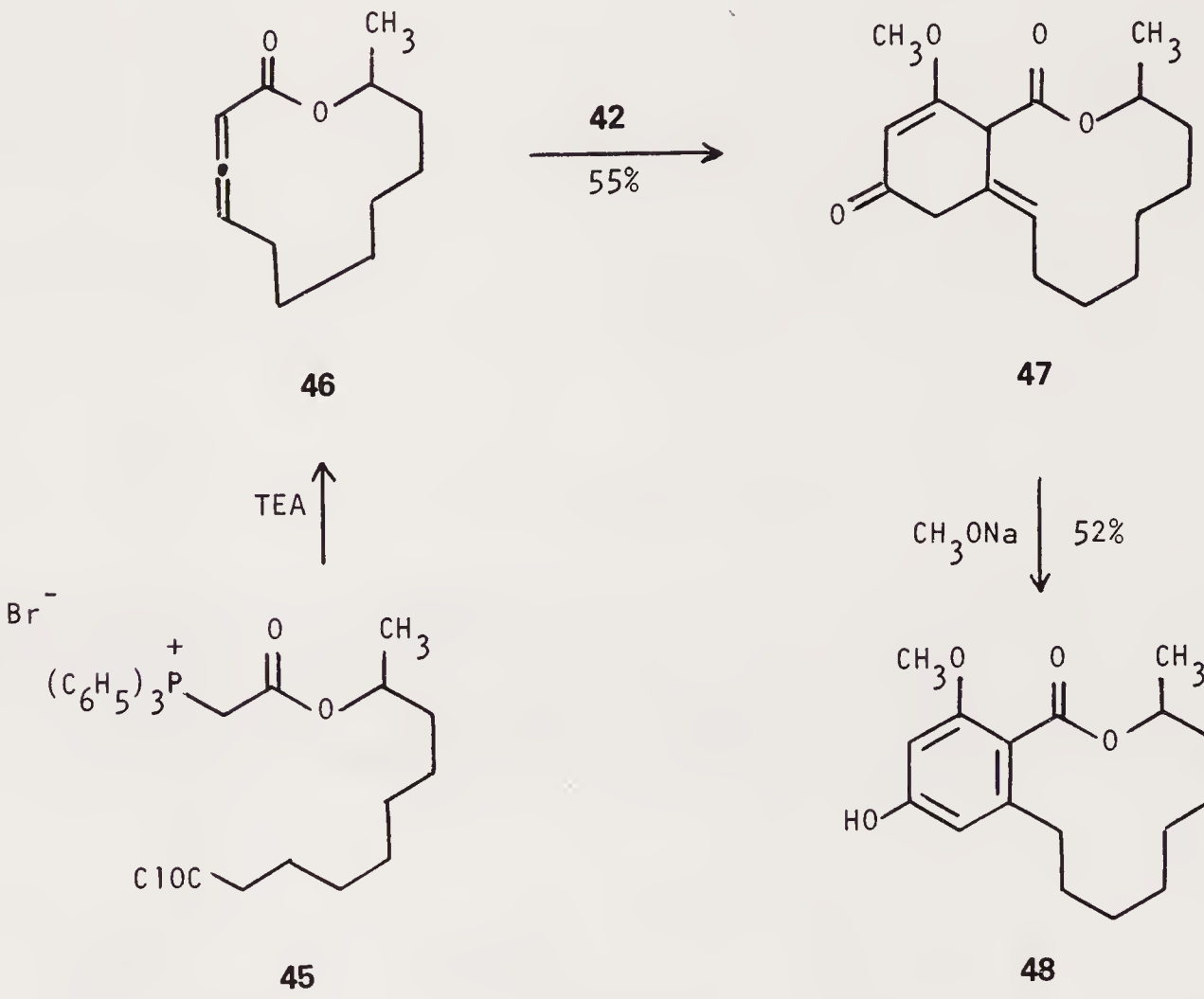
Methyl 2,3-alkadienoates **41** react with 1,1-dimethoxy-3-trimethylsiloxy-1,3-butadiene (**42**) in refluxing benzene to give adduct **43** in good yield. These adducts rearrange under the influence of *p*-toluenesulfonic acid or sodium methoxide to give 6-substituted-4-hydroxy-2-methoxybenzoates **44**[37] (equation 10).



41 42 43 44

(10)

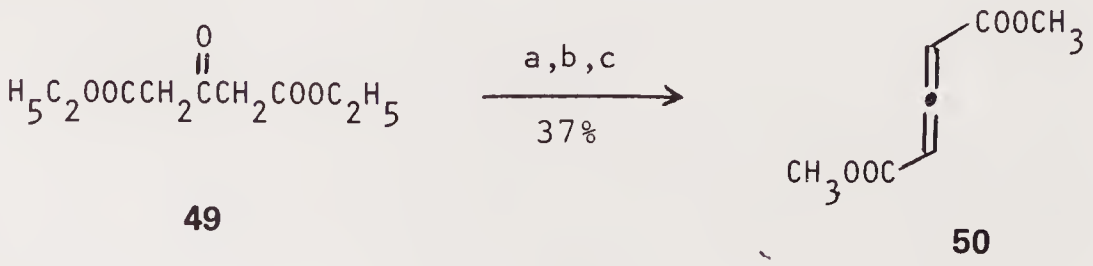
An elegant application of this methodology is demonstrated in the synthesis of lasiodiplodin (**48**), a plant-growth inhibitor and antileukemic agent isolated from either *Lasiodiplodia theobromae*[38] or *Euphorbia splendens*.[39] The intramolecular Wittig condensation of **45** generates the interesting cyclic allene, dodeca-2,3-dien-11-olide (**46**), in 42% yield. Heating **46** with **42** at 80°C for 4 hours produces the Diels–Alder adduct **47** which, when isomerized with sodium methoxide, furnishes racemic **48** (Scheme 8). A parallel sequence starting from (R)-**45** gives the naturally occurring (+)-(R)-**48** in complete yields.[37]



Scheme 8

Although the propadiene unit can be functionalized by as many as four ester groups,[6] symmetrical allenic diesters possess the greatest potential in intermolecular reactions.

Dimethyl 2,3-pentadienoate (**50**), "glutinic ester," is readily prepared from diethyl acetone-1,3-dicarboxylate in three steps as outlined in equation (11).[40] Diethyl phosphorchloridate may be substituted for the phosphorus pentachloride in the first step.[41]

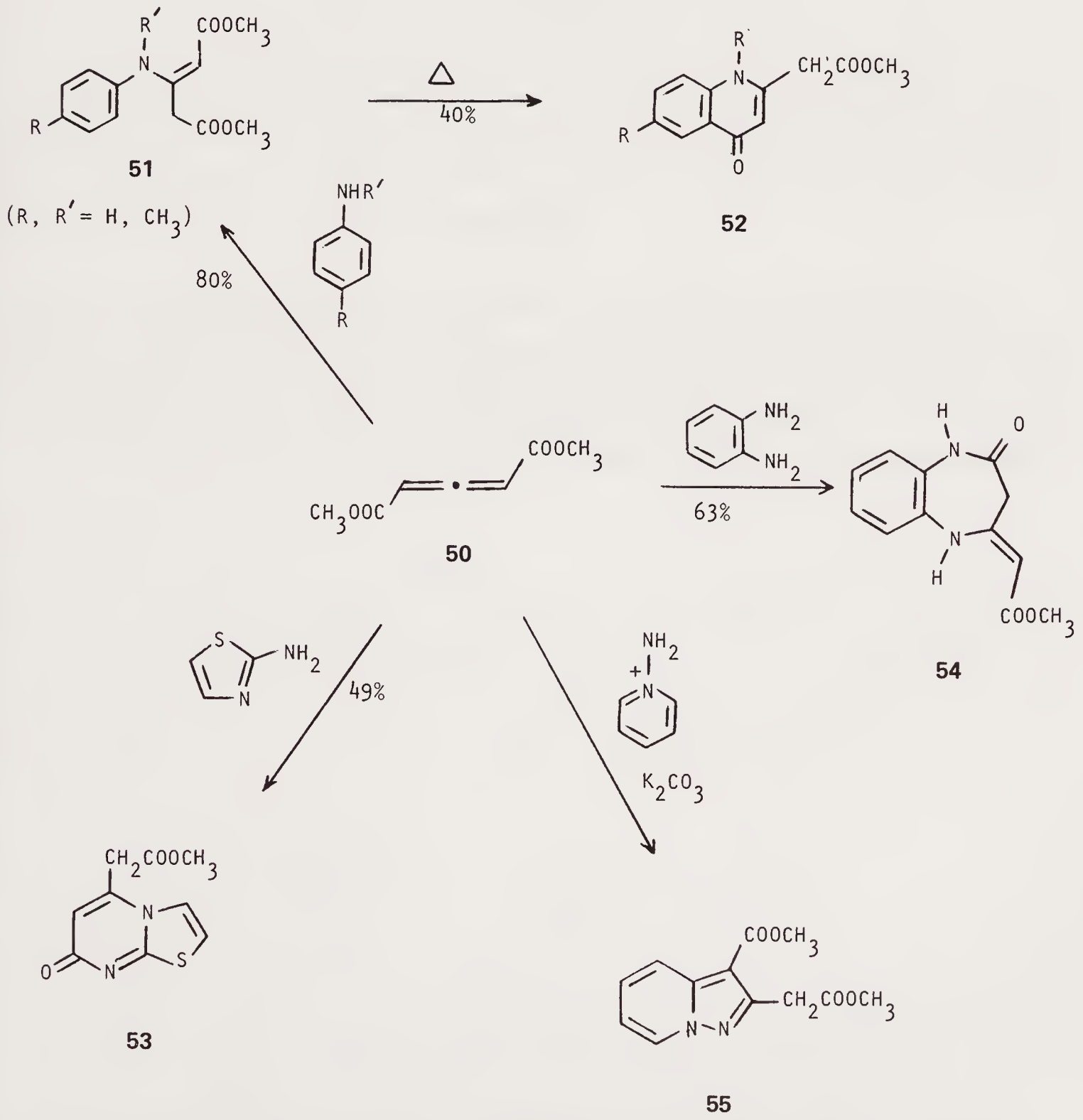


49 **50** (11)

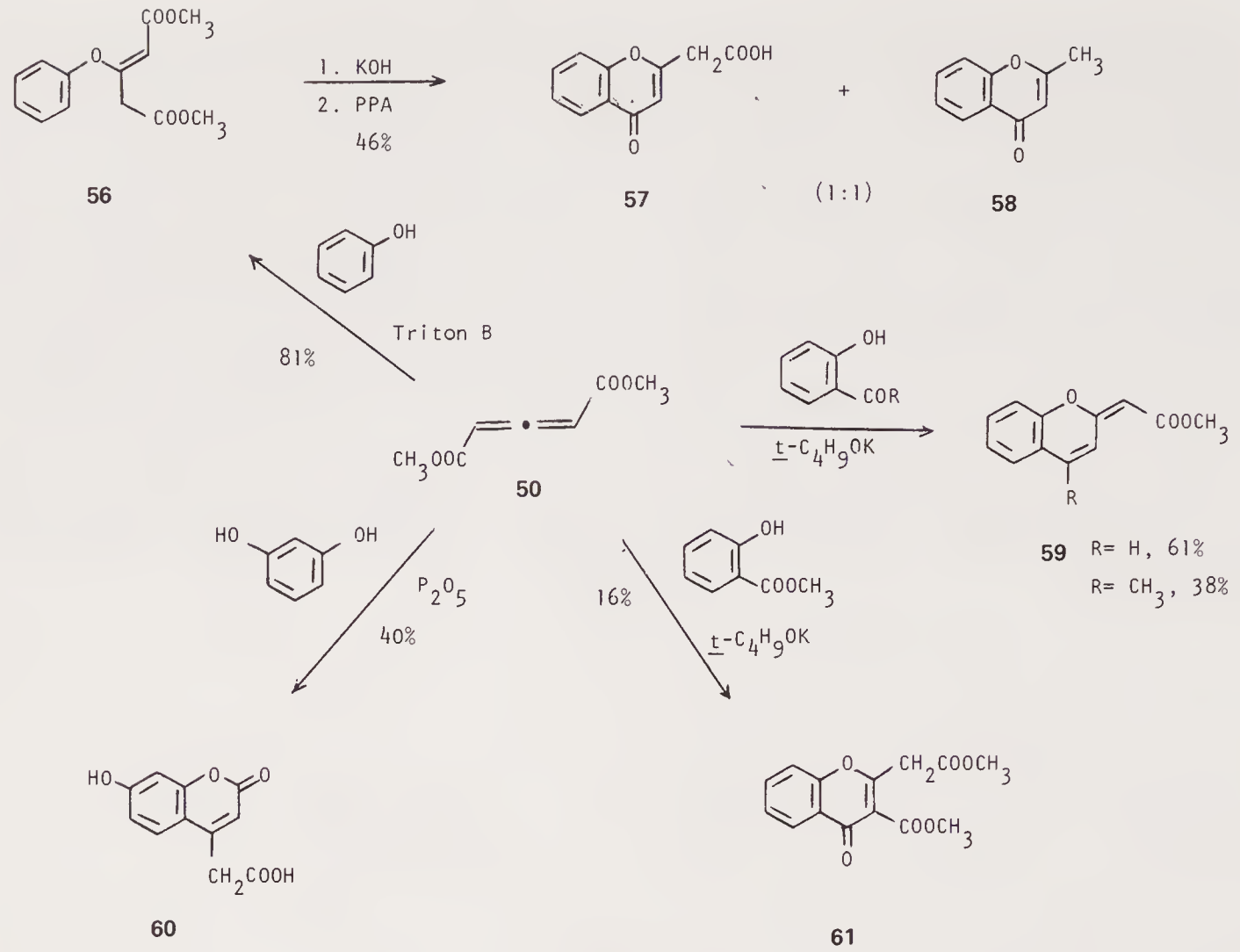
(a) PCl_5; (b) H_2SO_4, CH_3OH; (c) TEA

By virtue of the double activation of the allene nucleus by the two ester groups, nucleophiles add to the central carbon atom with great ease (Schemes 9 and 10). Anilines react with **50** in boiling methanol to give enamine **51**.[42,43] Cyclization in *o*-dichlorobenzene (180°C) furnishes the quinolone **52**. The enamine **51** (R′ = CH_3) derived from N-methylaniline requires polyphosphoric acid at 100° to effect the cyclization to **52** (R = H, R′ = CH_3, 71% yield). *o*-Phenylenediamine reacts with **50** at room temperature to give the 1H-1,5-benzodiazepinone **54** directly.[42,44] 2-Aminothiazole attacks **50** with the heterocyclic nitrogen atom to produce the thiazolo[3,2-a]pyrimidin-7-one (**53**) after ring closure. Pyrazolopyridine **55** is obtained in low yield from **50** and the ylid derived from 1-aminopyridinium iodide.[19]

Methyl 2,3-pentadienoate (**50**) also reacts with phenols to afford a variety of chromene (**59**), chromone (**57, 58, 61**), and coumarin (**60**) derivatives[43] (Scheme 10).

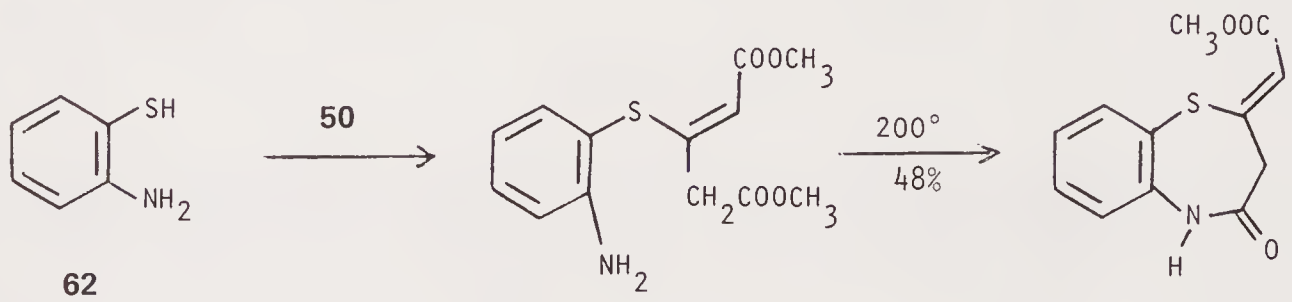


Scheme 9



Scheme 10

In reactions of **50** with molecules containing both sulfur and nitrogen nucleophiles, the sulfur atom adds in preference to the nitrogen. *o*-Aminothiophenol (**62**) gives thioenol ether **63** which cyclizes at 200°C to the 1,5-benzothiazepinone **64** (equation 12). Thiourea also reacts with **50** on the sulfur, and the resulting intermediate then cyclizes with the nitrogen to form thiazinone **65**[42] (equation 13).



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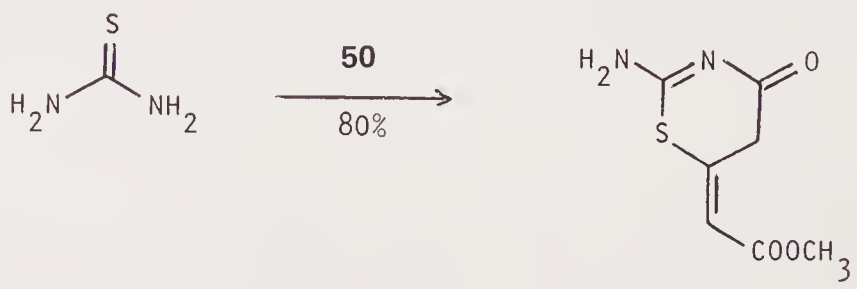
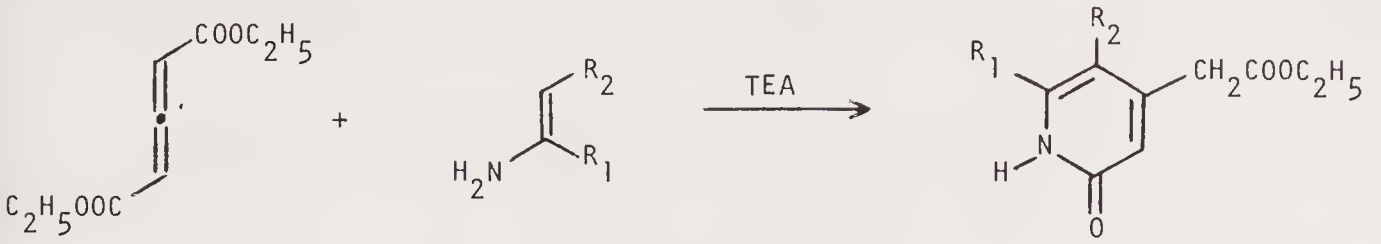


(13)

Allene 1,3-dicarboxylates are such potent receptors toward Michael additions that even enamines add to them under the influence of an organic base. Diethyl

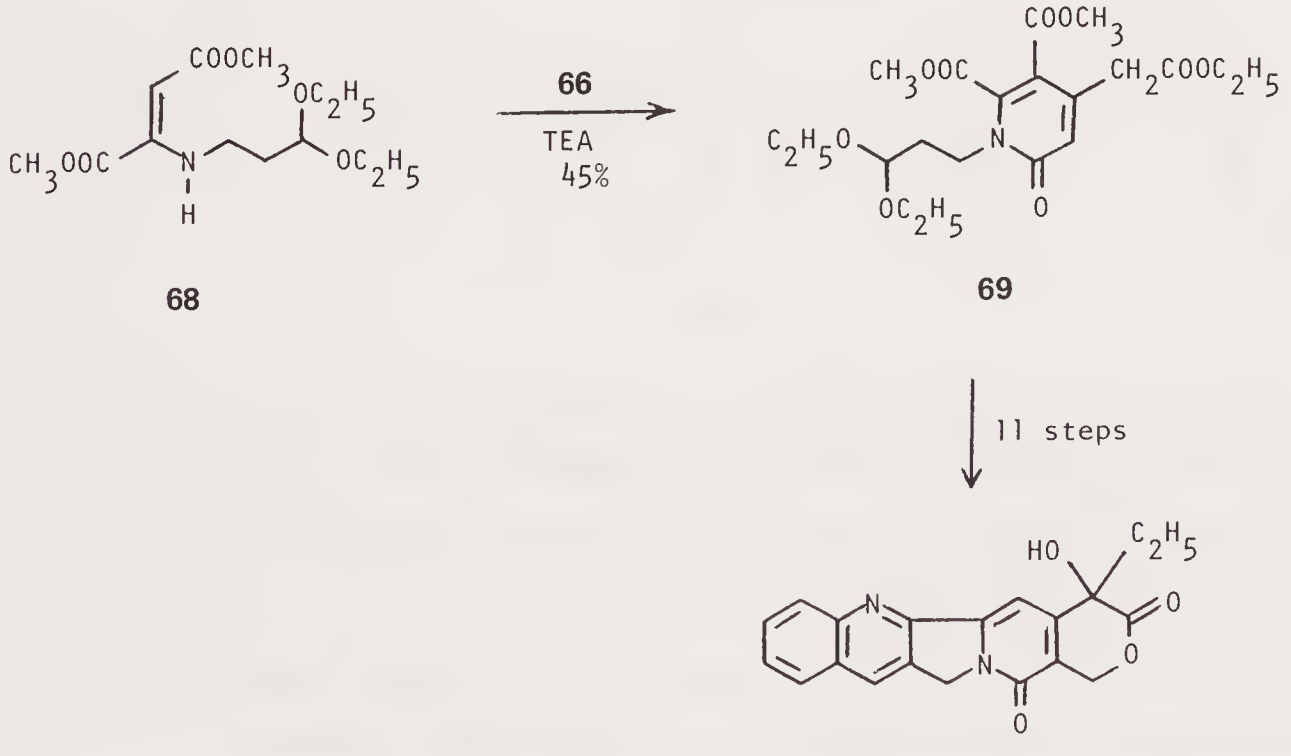
2,3-pentadienoate (**66**) reacts with *trans*-β-aminocrotonate derivatives or monoenamines of β-diketones in the presence of one equivalent of triethylamine to give α-pyridones **67** in moderate yields[45] (equation 14).



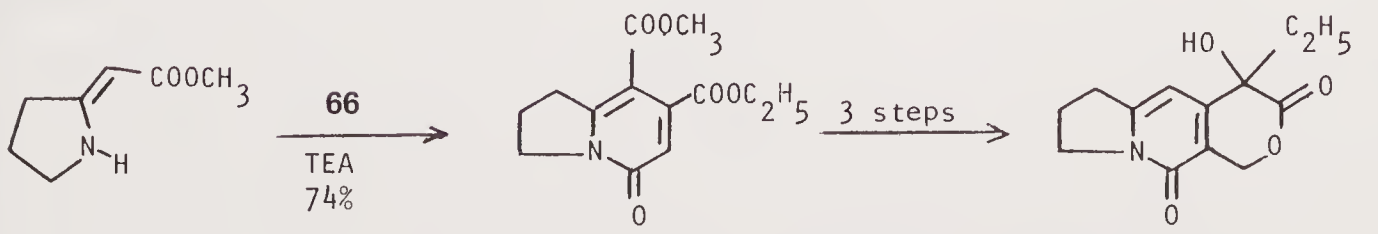
66 **67** (14)

R_1	R_2	Yield, %
CH_3	$COOC_2H_5$	70
$CCH_3(OC_2H_5)_2$	$COOCH_3$	36
CH_3	$COCH_3$	48

Condensing enamino diester **68** with **66** at room temperature gives the pyridone triester **69** which is an important intermediate in the synthesis of the antitumor alkaloid campthothecin (**70**)[46] (equation 15). De-A,B-campthothecin (**73**) can be prepared from **71** as shown in equation (16).[47]

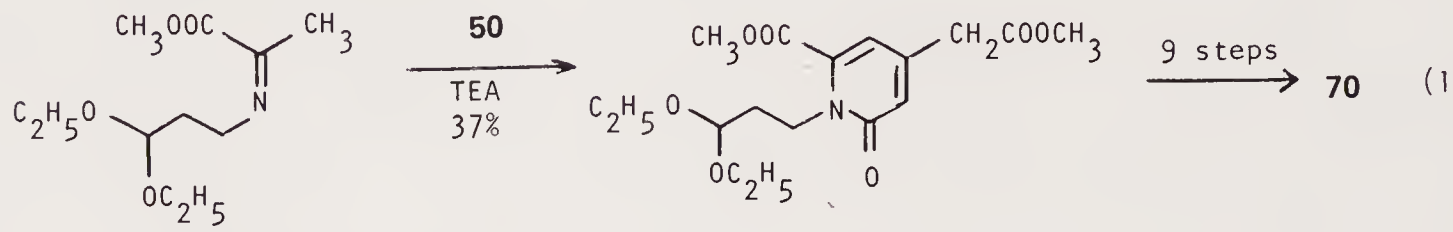


68 **69** (15) **70**



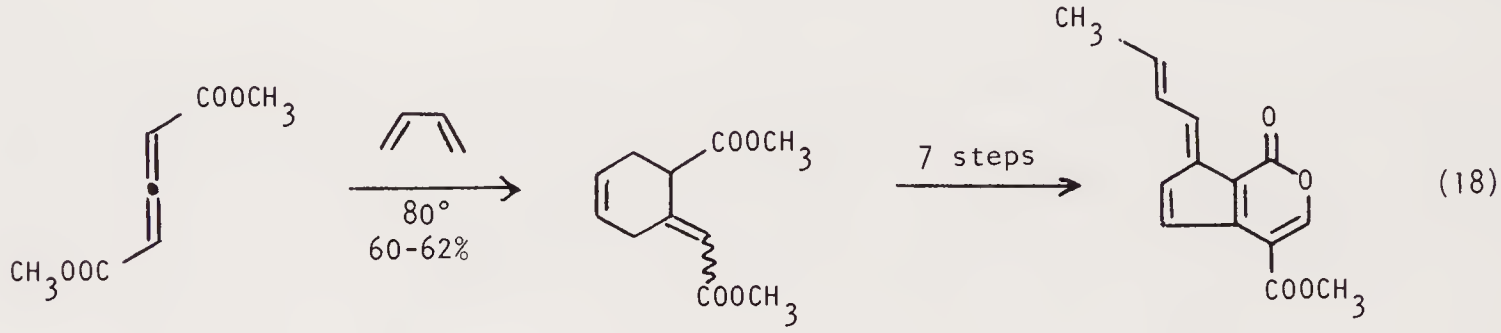
71 **72** **73** (16)

An alternate approach to campthothecin utilizes imine **74** as one of the primary reactants[48] (equation 17). The transformation **74** → **75** probably proceeds by reaction of **50** with small amounts of the enamine tautomer of **74**. This route offers the advantage of directly furnishing the desired 5-unsubstituted pyridone, which in equations (15 and 16) requires a vigorous pyrolytic decarboxylation to achieve.



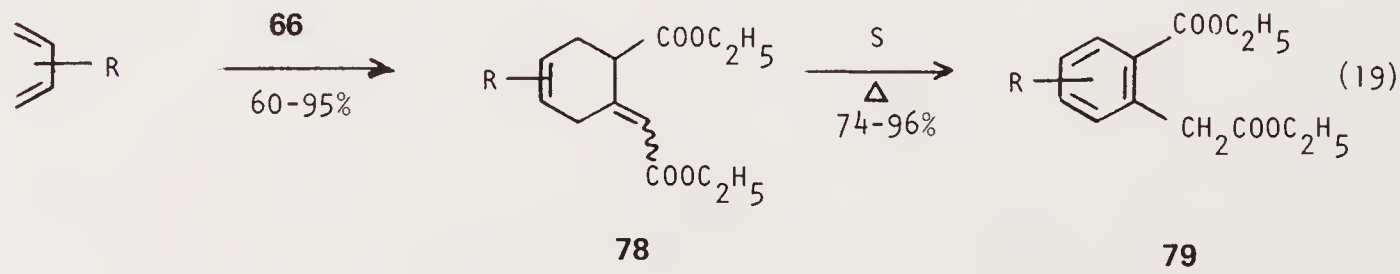
74 **75**

Allenic diesters readily undergo [4 + 2] Diels–Alder cycloadditions with conjugated dienes and have been employed in several natural product syntheses. The initial step in the synthesis of fulvoplumierin (**77**), an antibacterial orange pigment isolated from the bark of *Plumiera acutifolia* and *Plumiera rubra* var. alba,[49] involves the condensation of **50** with butadiene. The resulting adduct **76** was then transformed to the desired product by a sequence of seven synthetic manipulations[50,51] (equation 18).



50 **76** **77**

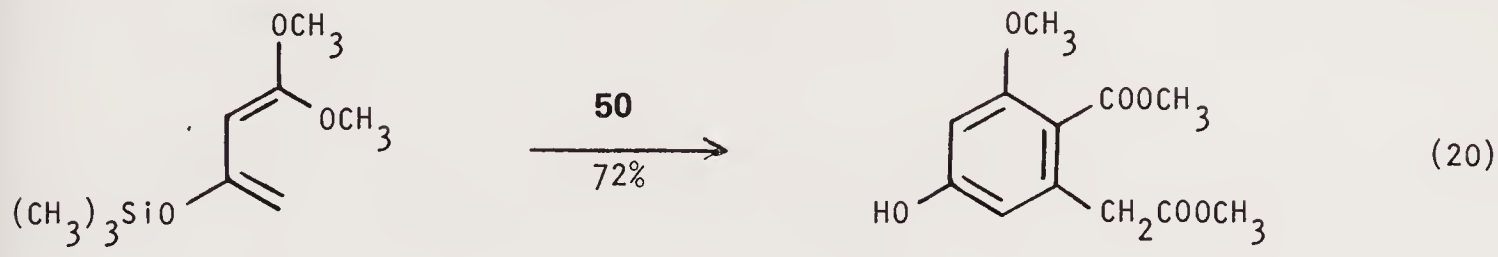
Adducts such as **78**, obtained from the reaction of **66** with substituted 1,3-dienes, can be efficiently dehydrogenated with sublimed sulfur in boiling decalin to give diethyl homophthalates **79** (equation 19). Dienes that contain functional groups that do not exhibit strong electronic effects produce mixtures of regioisomeric homophthalates after dehydrogenation.[52] However, if the reaction is performed at room temperature in the presence of a Lewis acid (aluminum chloride), predominantly one regioisomer can be obtained (e.g., reaction with isoprene).



78 **79**

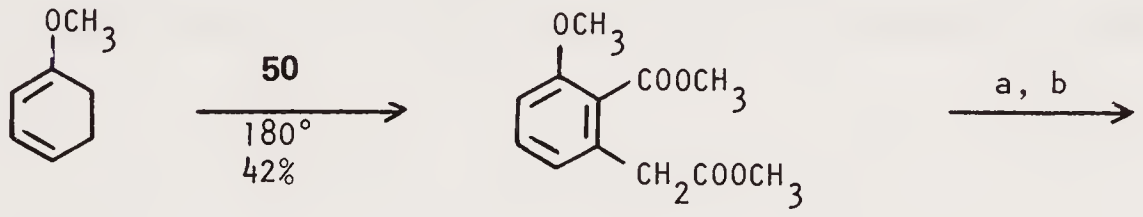
R= H, CH_3, $OSi(CH_3)_3$, $COOC_2H_5$

Homophthalate derivative **80** can be obtained directly from the Diels–Alder reaction of **50** with siloxydiene **42** (benzene, reflux, 1 hour).[53]

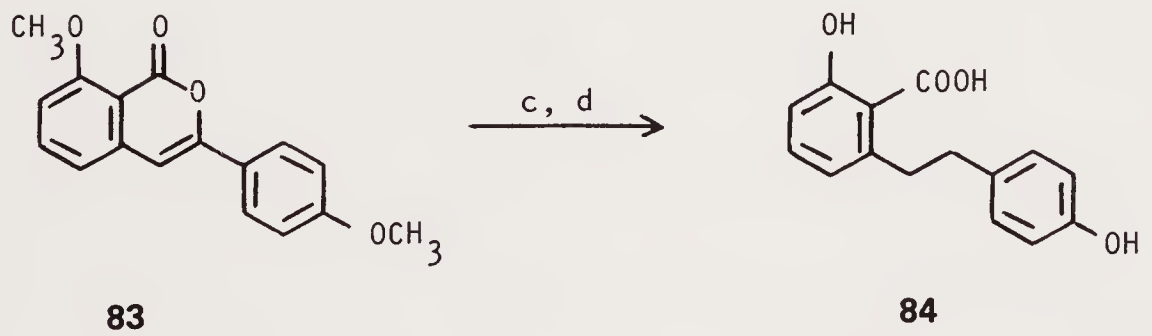


42 **80** (20)

The plant-growth inhibitor lunularic acid (**84**), which appears to occur in all liverworts and fresh water and marine algae, has been conveniently synthesized (Scheme 11) by way of a [4 + 2] cylcoaddition reaction of 1-methoxy-1,3-cyclohexadiene (**81**) with **50**.[54] Dimethyl 3-methoxyhomophthalate (**82**) is directly produced from the reaction and is easily converted to the natural product in four steps.



81 **82**

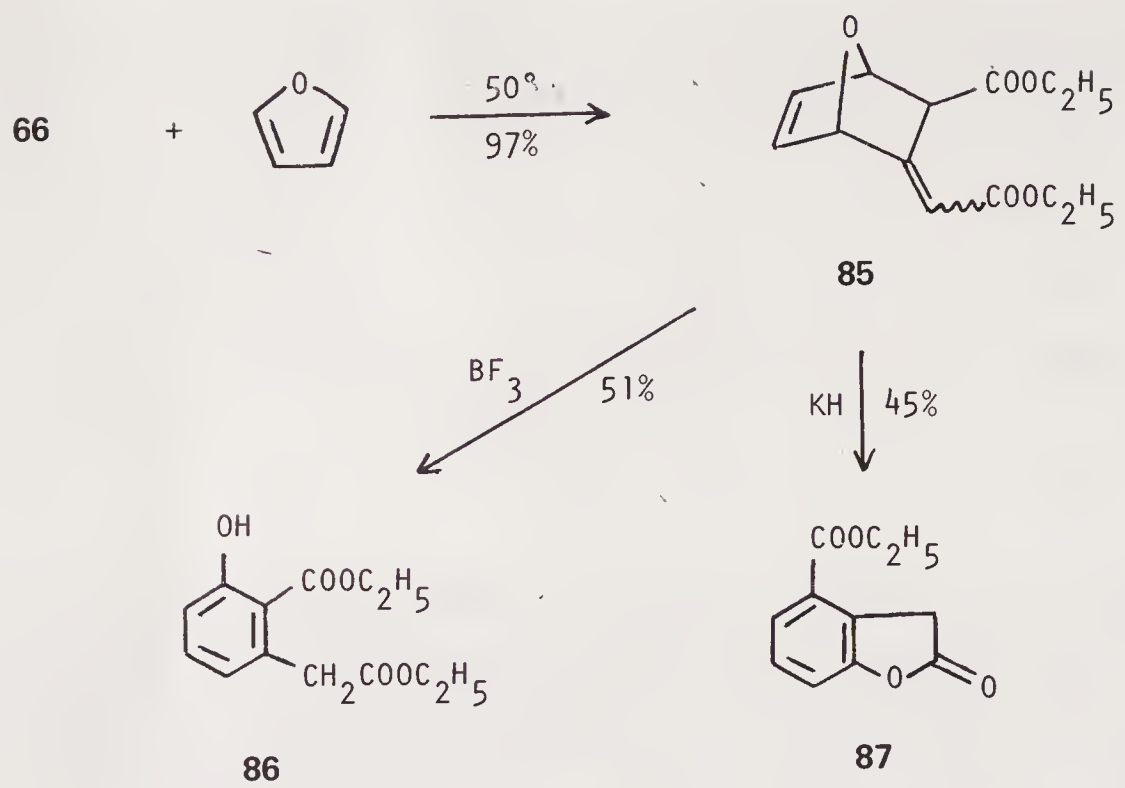


83 **84**

(a) NaOH; (b) anisole, PPA (81% yield); (c) H_2/Pd/C (100%); (d) BBr_3 (63%)

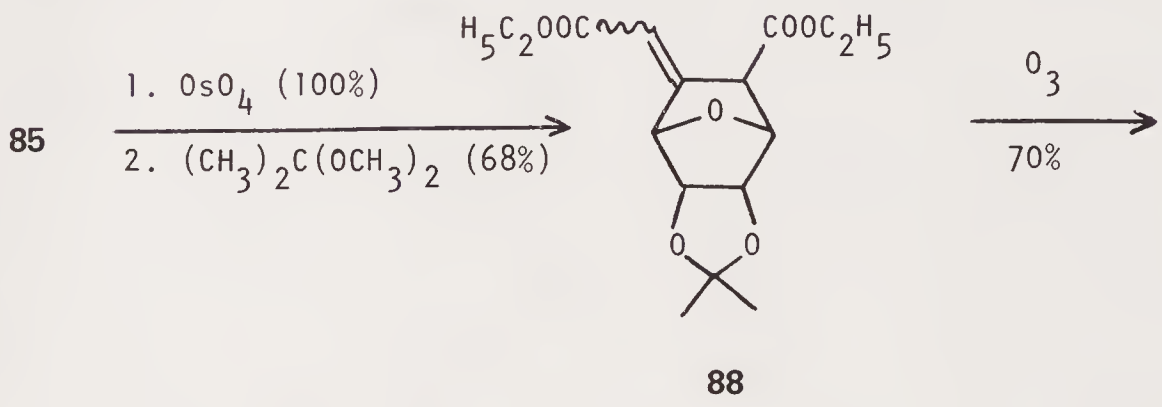
Scheme 11

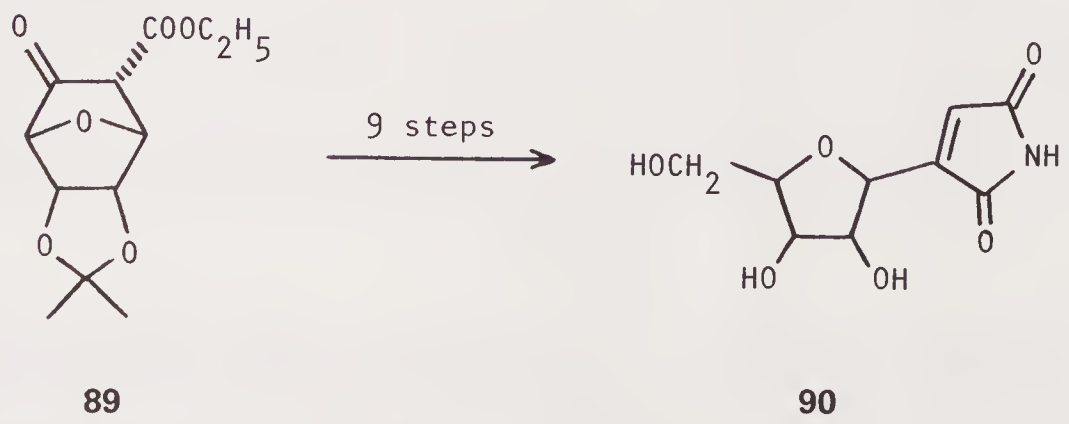
Heterocyclic dienes also form [4 + 2] cycloadducts when condensed with allenic diesters. If furan is allowed to react with **66** (either at 50°C for 62 hours or at room temperature for 1 hour with $AlCl_3$ catalysis), high yields of oxabicycloheptene **85** are obtained.[55,56] Exposure of **85** to boron trifluoride in methylene chloride affords diethyl 3-hydroxyhomophthalate (**86**) in 51% yield. In the presence of excess potassium hydride, the heteroatom bridge of adduct **85** can be induced to undergo β-elimination to produce the benzofuranone **87** in moderate yield[57] (Scheme 12).



Scheme 12

Adduct **85** has also been used as a key intermediate in the synthesis of showdomycin (**90**), a C-nucleoside possessing antibiotic and antitumor activity (Scheme 13).[56]

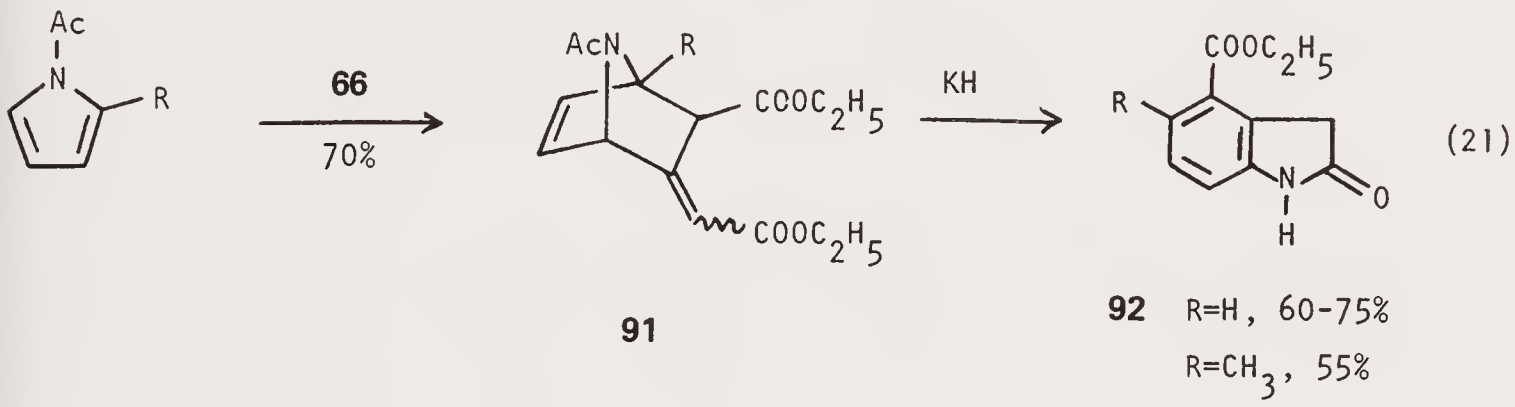




Scheme 13

The ease of ozonolysis of **88** to the β-ketoester **89** establishes that allenic diesters such as **50** or **66** can function as a carboalkoxyketene equivalent in the Diels–Alder reaction.

4-Carboethoxyoxindoles (**92**) are valuable precursors for the synthesis of ergot alkaloids. These intermediates are readily prepared in two steps as shown in equation (21).[57] The azabicyclo[2.2.1]heptene **91**, which is available from a Diels–Alder reaction of an *N*-acetylpyrrole with **66**, experiences β-elimination of the heteroatom bridge (analogous to **85** → **87**) when treated with 4–5 equivalents of potassium hydride.



91

92 R=H, 60-75%
R=CH_3, 55%

(21)

Table 6.1. Alternate Syntheses of Allenic Acids and Esters

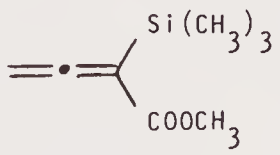
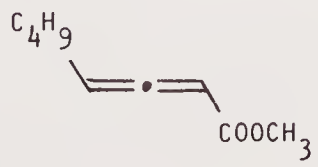
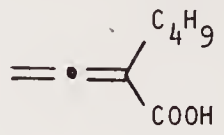
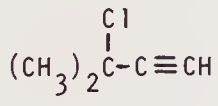
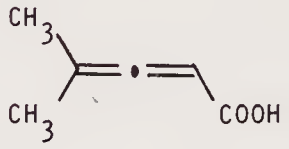
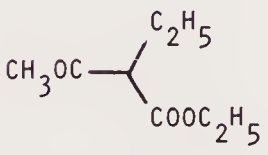
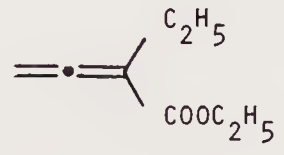
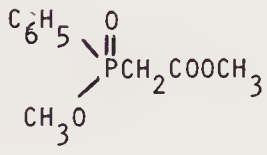
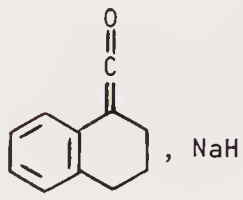
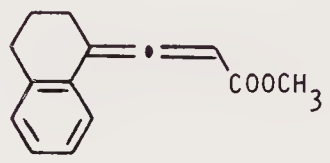
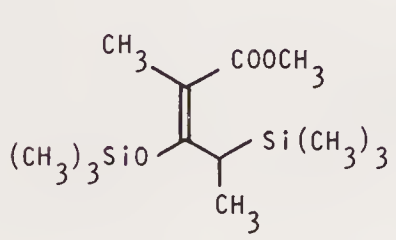
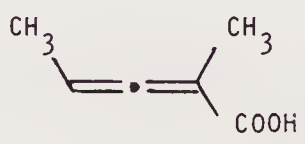
Substrate	Reagent (conditions)	Product	Yield, %	Reference
$HC\equiv C-CH_2COOC_2H_5$	K_2CO_3	$CH_2=C=CHCOOC_2H_5$	92	58
$CH_2=C=CHLi$	1. CO_2 (-78°) 2. K_2CO_3	$CH_2=C=CHCOOH$	62	59
$CH_3C\equiv C-COOCH_3$	1. LiICA 2. H_3O^+	$CH_2=C=CHCOOCH_3$	60	60
$CH_3C\equiv CCOOCH_3$	1. LDA 2. $ClSi(CH_3)_3$		40	61
$C_6H_{13}C\equiv CCOOH$	$NaNH_2$		100	62
$C_5H_{11}C\equiv CCOOCH_3$	1. MnL_3 2. Al_2O_3 3. $(NH_4)_2Ce(NO_2)_6$		71	63

Table 6.1. (*Continued*)

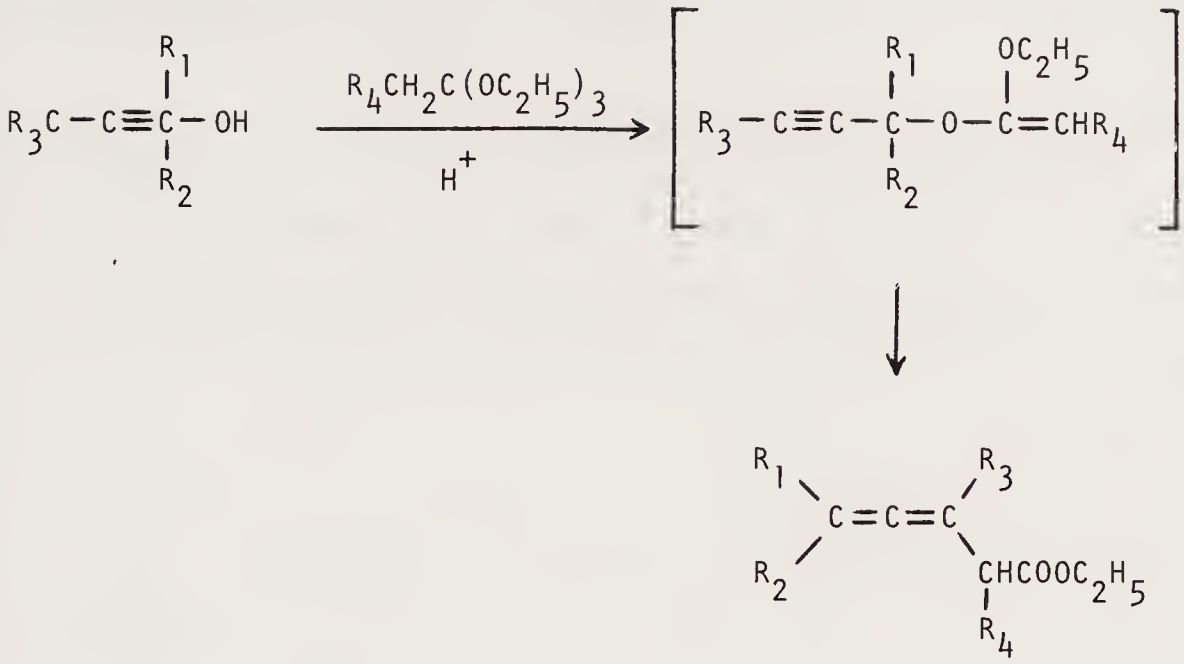
Substrate	Reagent (conditions)	Product	Yield, %	Reference
$C_4H_9C{\equiv}CCH_2B^-(s\text{-}C_4H_9)_3Li^+$	1. CO_2 2. $NaOH/H_2O_2$		76	64
	$Ni(CO)_4$		34	65
	$(C_6H_5)_3PBr_2$/TEA		53	66
	 , NaH		40	67
	1. 680° 2. H_3O^+		43	68

6.1.2 Allene Acetic Acids and Esters

Three general methods are available for the preparation of allenyl acetic acids or esters, and each has been incorporated into a natural product synthesis.

Propargyl alcohols undergo a Claisen-type rearrangement when heated with 4–7 equivalents of an orthoester in the presence of a catalytic amount of propionic acid. The resulting allenic esters **93** are distilled directly from the reaction mixture and are isolated in moderate yield.[69–73] This method provides a full range of substitution at any position on the molecule (equation 22).

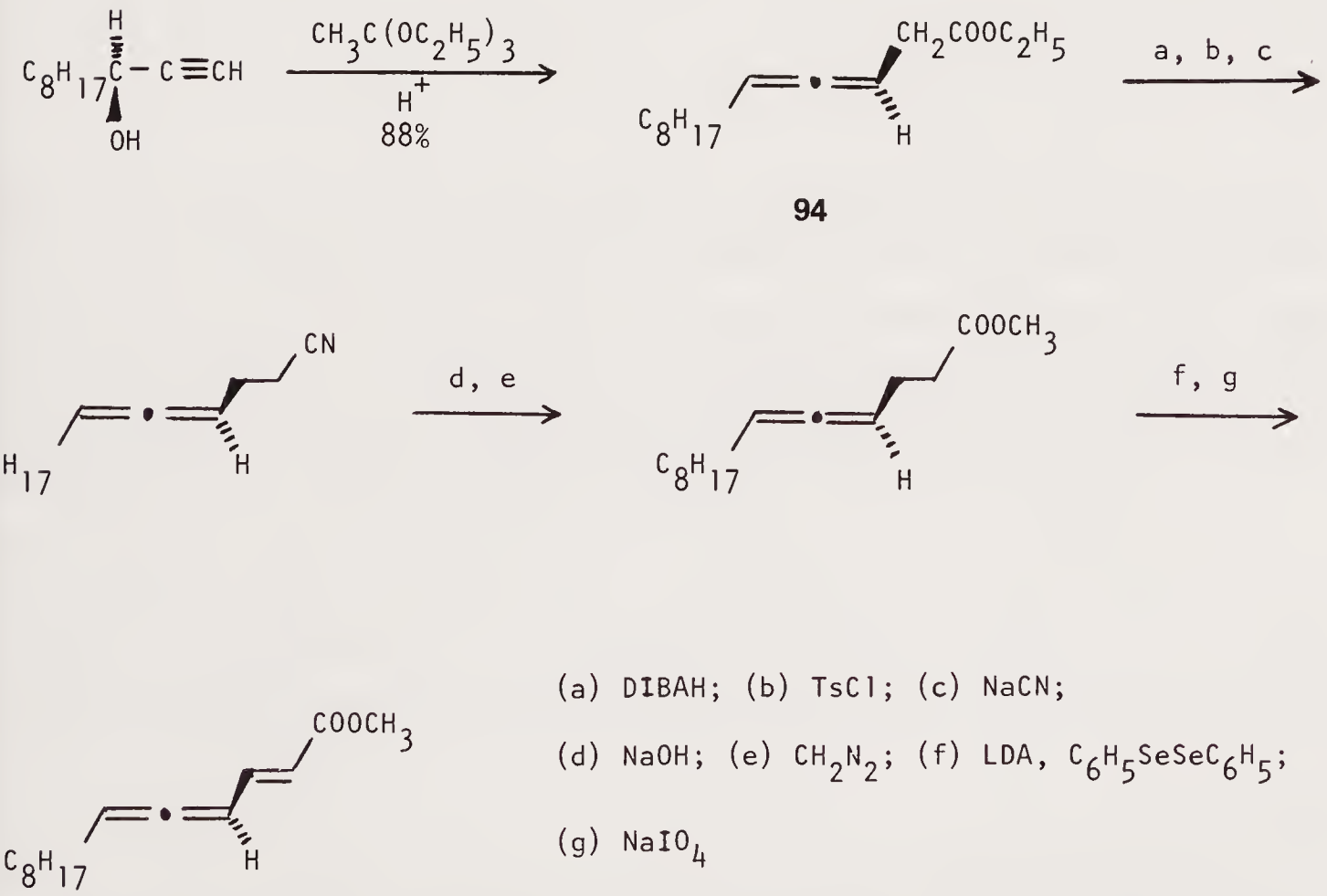
Methyl (E)-(-)-2,4,5-tetradecatrienoate (**95**), the sex pheromone produced by the male dried bean beetle, has been synthesized in racemic[74] and optically active form.[75] The key intermediate in each route is ethyl 3,4-tridecadienoate (**94**) which is readily obtained in high yield using the method in equation (22). The required one-carbon chain elongation and introduction of the α,β-unsaturation is shown in Scheme 14 for the preparation of the naturally occurring enantiomer. It is interesting to note



(22)

93

R_1	R_2	R_3	R_4	yield, %
H	H	H	H	34
CH_3	CH_3	H	H	63
CH_3	CH_3	CH_3	H	61
CH_3	CH_3	H	CH_3	59



(a) DIBAH; (b) TsCl; (c) NaCN;

(d) NaOH; (e) CH_2N_2; (f) LDA, $C_6H_5SeSeC_6H_5$;

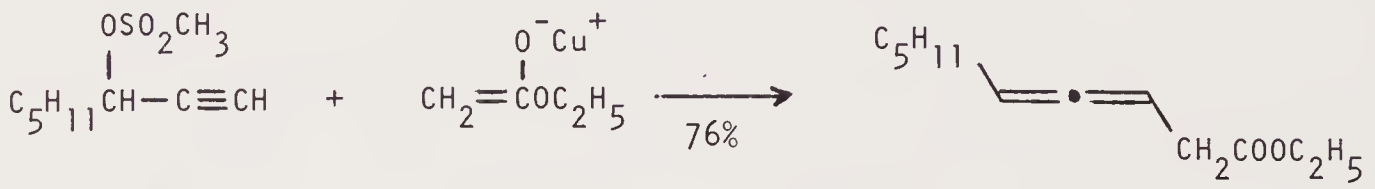
(g) $NaIO_4$

(R)-**95**

Scheme 14

that the rotatory power of the synthetic material exceeds (125–127%) that of the natural product.

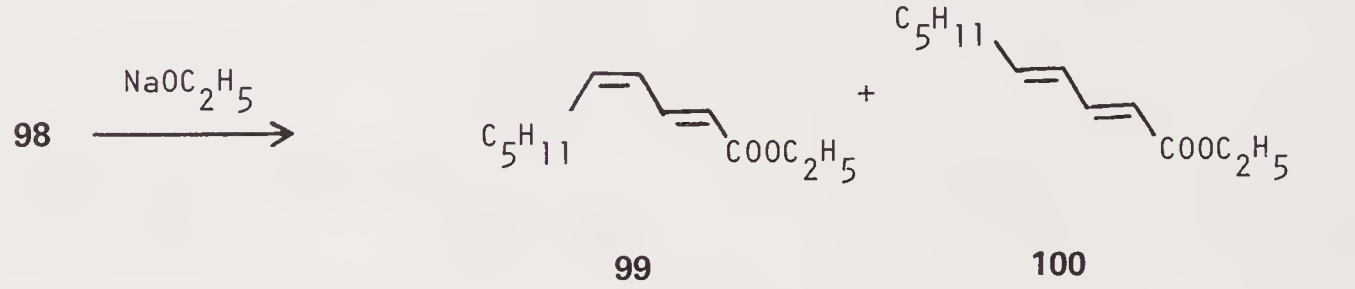
The copper enolate species **97**, derived from the treatment of the corresponding lithium enolate of ethyl acetate with cuprous iodide, reacts cleanly in an S_N2' fashion with methanesulfonate **96** at $-78°C$ to give ethyl 3,4-decadienoate (**98**) (equation 23). No isomeric acetylene (from an S_N2 pathway) is formed. The reaction is catalytic in copper and proceeds at a comparable rate with only 0.2 equivalents of cuprous iodide.



(23)

96 **97** **98**

Ethyl (2E,4Z)-decadienoate (**99**), a component of the odoriferous principle of the Bartlett pear,[76] can be obtained from **98** by a kinetically controlled base-catalyzed reconjugation (equation 24). The predominant geometry of the newly generated α,β double bond is the E configuration, while the γ,δ double bond consists of a mixture of 4Z (**99**) and 4E (**100**) isomers (ratio 2:1).



(24)

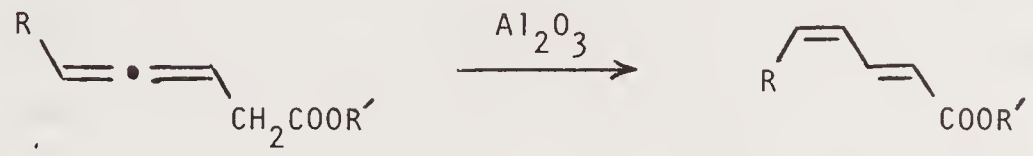
99 **100**

Such a result can be rationalized by visualizing the enolate (Figure 5) presumed to be the intermediate in the reconjugation. Approach of the proton to the central allene carbon would be expected to occur from the less hindered side (*cis*) opposite the bulky R group, thereby affording the Z geometry at the γ,δ bond. The configuration of the α,β double bond is determined by the more stable rotamer of the α,β bond in the extended enolate. The conformation having the bulky groups in an *s-trans* configuration is more stable and affords the observed E geometry.[77]

A superior method for the generation of the 2E,4Z geometry in dienoic esters is the thermal treatment of β-allenic esters with alumina catalyst (equation 25). Consequently, when esters **101** are heated with 4–7 equivalents of alumina in refluxing benzene (2–5 hours), the desired reconjugated esters **102** are produced

Figure 5. Trajectory of protonation leading to either 4Z or 4E dienoic esters. (Reprinted from ref. 77 with permission from the authors. Copyright 1978 American Chemical Society.)

with 91–100% stereoselectivity.[78] Note that entry 4 is the same natural product synthesized in equation (24).



101 **102** (25)

Allene	R	R′	Yield (%)	2E,4Z Geometry (%)
102a	CH_3	CH_3	57	100
102b	C_2H_5	CH_3	82	96
102c	C_3H_7	CH_3	80	96
99	C_5H_{11}	C_2H_5	82	100
102d	C_8H_{17}	CH_3	87	91

A plausible first step in the reaction may be the coordination of the carbonyl oxygen of **101** to the alumina surface followed by a proton shift to produce an enolate intermediate. A subsequent pseudointramolecular approach of the proton to the central allene carbon from the less hindered side generates the 4Z geometry (Figure 6). Elimination of the enolate from the alumina surface (curved arrows) produces the thermodynamically more stable 2E geometry.[79]

The *trans,cis*-butadiene geometry appears in a host of naturally occurring substances, and 2E,4Z-dienoates **102** provide an easy entry to these products (Scheme 15).[79] The reduction of methyl (2E,4Z)-heptadienoate (**102b**) with lithium aluminum hydride gives (2E,4Z)-heptadienol (**103**, R = C_2H_5) in 84% yield. Oxidation of **103** with manganese dioxide affords (2E,4Z)-heptadienal (**104a**, 81% yield), a flavor component of tomatoes.[80] A similar sequence of reactions starting from **99** produces (2E,4Z)-decadienal (**104b**, 57% overall yield), a flavor component of groundnuts and carrot root.[81] The acetate of **103** (R = C_2H_5) can be converted, in four steps, to (7E,9Z)-dodecadienyl acetate (**105**), the sex pheromone of the European grapevine moth *Lobesia botrana*.[82] An analogous coupling with an eight-carbon Grignard reagent furnishes bombykol (**106**), the sex attractant of *Bombyx mori*.[83,84]

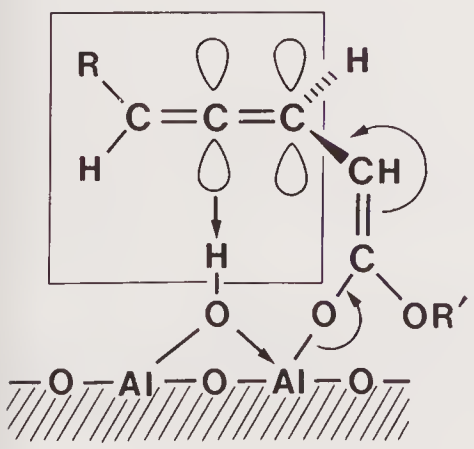
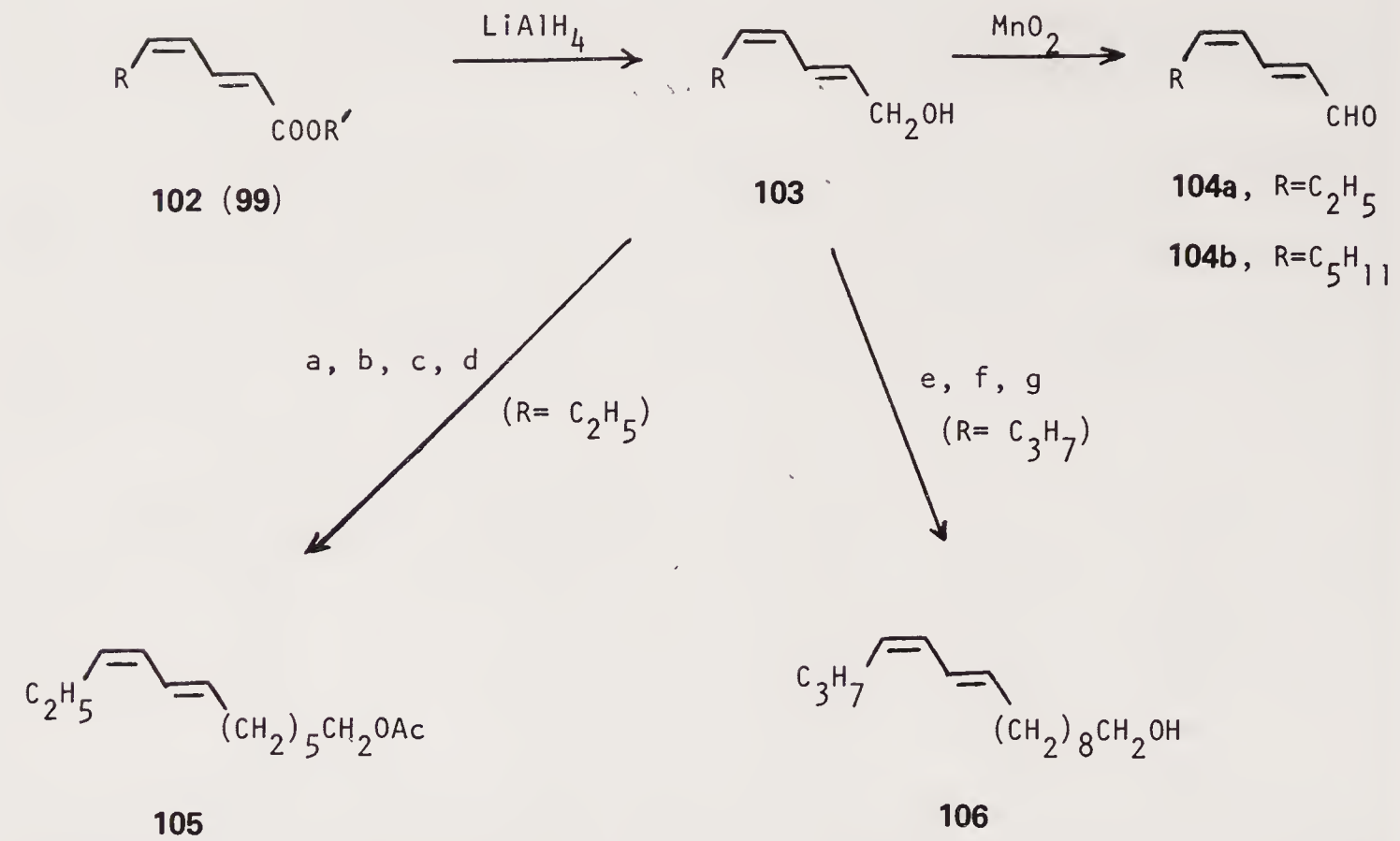


Figure 6. 2E,4Z-Dienoic esters **102** from alumina-catalyzed rearrangement of β-allenic esters. (Reprinted with permission from ref. 79. Copyright 1982 American Chemical Society.)



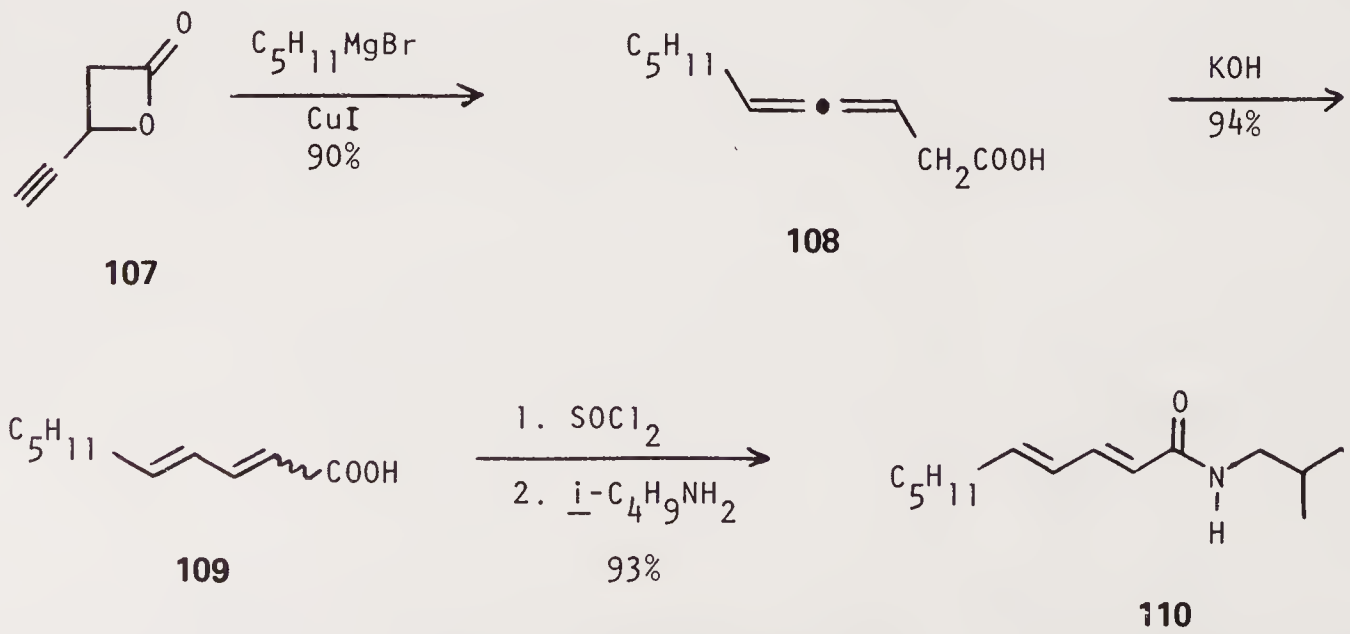
(a) CH_3COCl, Py; (b) $THPO(C_5H_{11})MgCl$, Li_2CuCl_4; (c) CH_3COOH; (d) CH_3COCl; (e) CH_3COCl, HMPA; (f) $C_2H_5OCH(C_8H_{17})MgBr$, CuI; (g) H_3O^+

$$C_2H_5O\underset{\displaystyle CH_3}{\underset{|}{C}}H(C_8H_{17})MgBr$$

Scheme 15

An interesting five-carbon homologation leading to 3,4-alkadienoic acids employs an S_N2' reaction of β-ethynyl-β-propiolactone (**107**) with Grignard reagents in the presence of cuprous iodide catalyst.[85] The reaction appears to be general, and good yields are obtained with primary, secondary, and tertiary Grignard reagents as well as aromatic, vinylic, and allylic reagents.

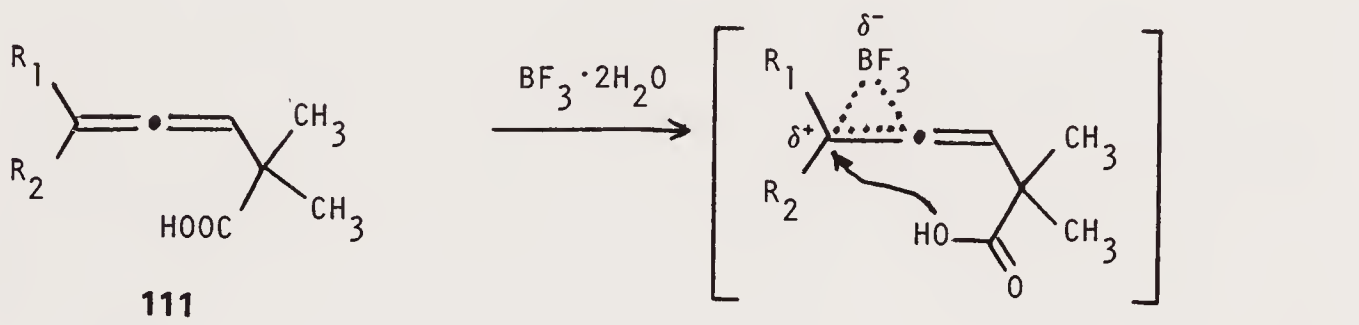
This regioselective reaction is useful in assembling the carbon skeleton of pellitorine (**110**), an insecticide isolated from *Anacyckus pyrethrum* roots. The action of *n*-amylmagnesium bromide on **107** produces 3,4-decadienoic acid (**108**) in high



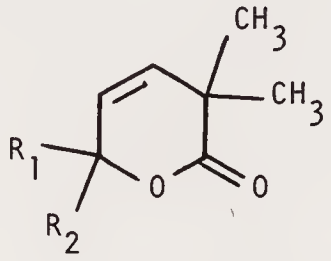
Scheme 16

yield. Isomerization of **108** to 2,4-decadienoic acid (**109**) is effected with aqueous potassium hydroxide (E,Z:E,E = 41:59). The desired E,E isomer can be produced in preponderance (22:78) by equilibrating the **109** mixture with thiophenol and AIBN. The treatment of (2E,4E)-**109** with thionyl chloride followed by isobutylamine gives the natural product **110** (Scheme 16).

α-Dimethyl-β-allenic acids (**111**), when treated with boron trifluoride, form δ-lactones **112** in essentially quantitative yield[86] (equation 26). The Lewis acid polarizes the 4,5-double bond of the allene making it susceptible to nucleophilic attack by the oxygen of the acid. Alkyl groups are favorable for R_1 and R_2 because they stabilize the incipient positive charge at the terminal carbon atom of the allene.



R_1, R_2= CH_3, C_2H_5, $(CH_2)_5$

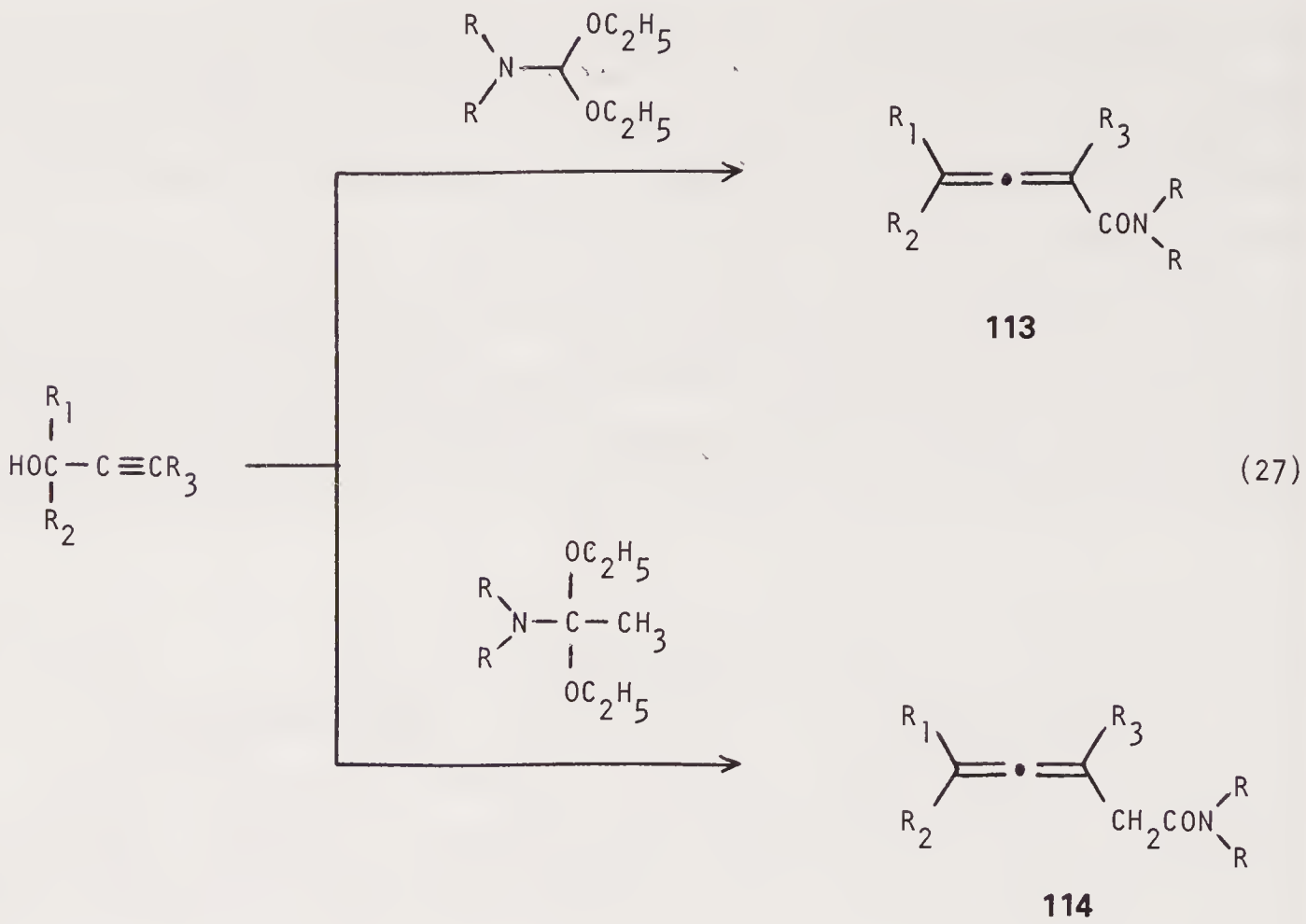


112

6.2. ALLENIC AMIDES

Tertiary allenic amides are most easily prepared by the reaction of propargyl alcohols with amide acetals in refluxing hydrocarbon solvents (equation 27). When formamide acetals are employed, allenic carboxamides **113** are produced in good yields.[87,88] The reaction appears to be highly sensitive to steric bulk around the nitrogen with diethylformamide acetals (R = C_2H_5) producing more consistent results than their dimethyl counterparts (R = CH_3). Substituents are preferred at R_3 but are not essential.

When analogous reactions are performed with dimethylacetamide acetals, only allenyl acetamides **114** are produced as a result of a Claisen rearrangement involving the carbon–carbon triple bond of the initially formed intermediate.[89,90]



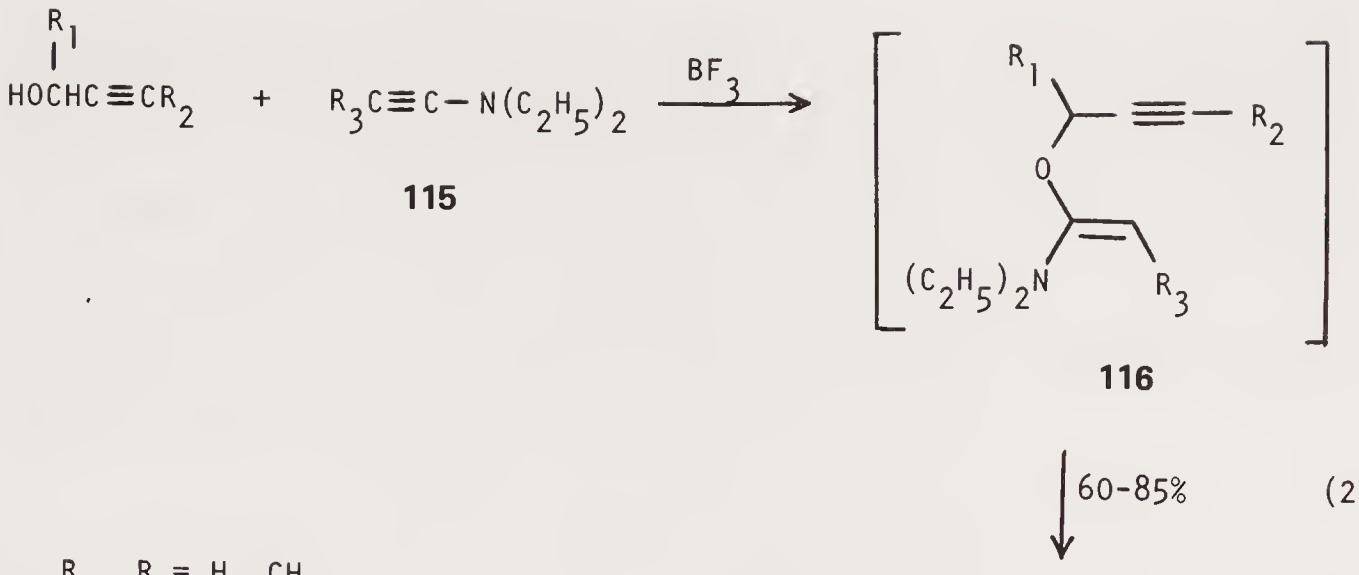
(27)

R	R_1	R_2	R_3	Yield **113** (%)	Yield **114** (%)
C_2H_5	—$(CH_2)_5$—		H	50	—
C_2H_5	—$(CH_2)_5$—		CH_3	92	—
CH_3	—$(CH_2)_5$—		CH_3	72	—
C_2H_5	CH_3	CH_3	C_6H_5	84	—
C_2H_5	C_8H_{17}	H	CH_3	93	—
CH_3	CH_3	CH_3	C_3H_7	—	81
CH_3	H	H	$Si(CH_3)_3$	—	80
CH_3	CH_3	H	$Si(CH_3)_3$	—	86
CH_3	CH_3	CH_3	$Si(CH_3)_3$	—	59

An alternate route for the preparation of allenyl acetamides is the condensation of propargyl alcohols with ynamines (**115**; equation 28).[91] The reaction is accelerated in the presence of a catalytic amount of boron trifluoride, and the products **117** are produced by means of a Claisen-type rearrangement involving an intermediate such as **116**.

Allenic amide **118** is readily converted to butenolide **119** upon treatment with aqueous formic acid. In the presence of iodine in aqueous THF, **118** undergoes hydrolytic iodolactonization to produce iodobutenolide **120**.[90]

2,4-Dimethyl-2,3-pentadienoic acid *bis*-N,N-diethylamide (**122**) is prepared in nearly quantitative yield by an unusual cycloaddition of diethylaminopropyne (**121**) with carbon dioxide.[92] The reaction is extremely rapid and is complete within one



115

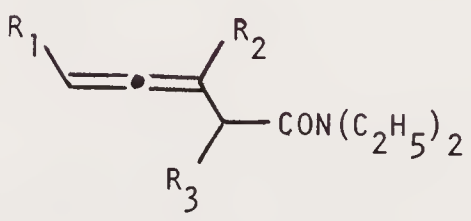
116

60-85%

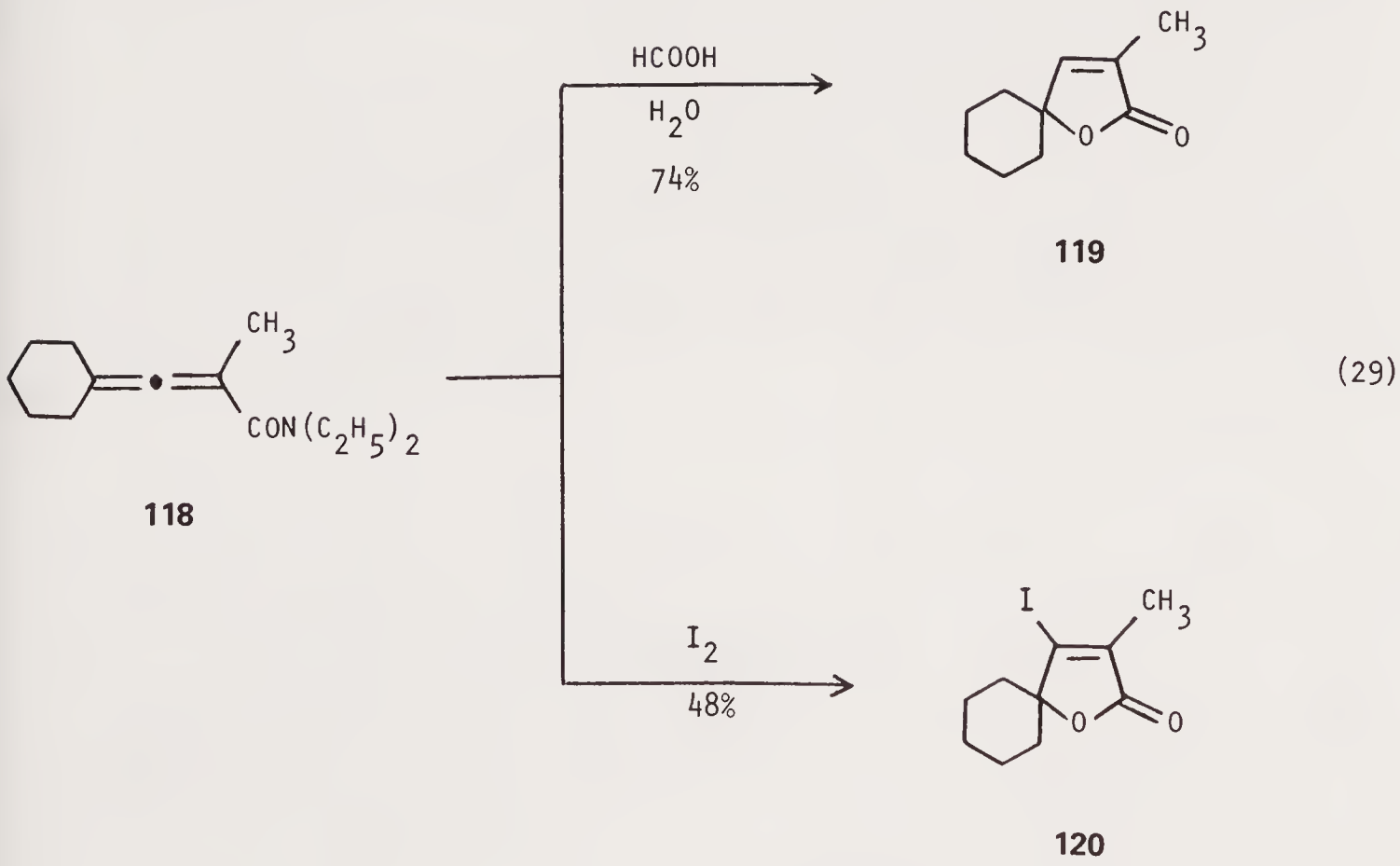
(28)

R_1, R_2= H, CH_3

R_3= CH_3, C_6H_5



117



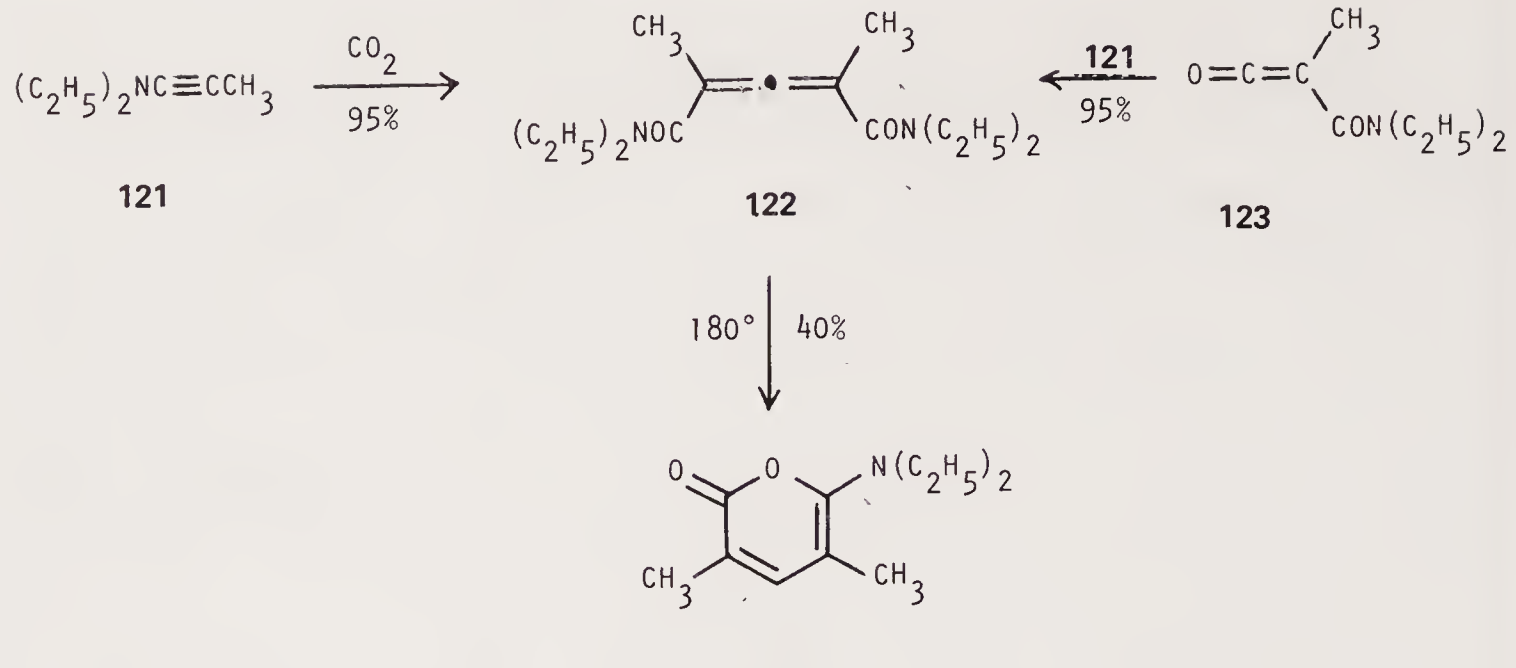
118

119

120

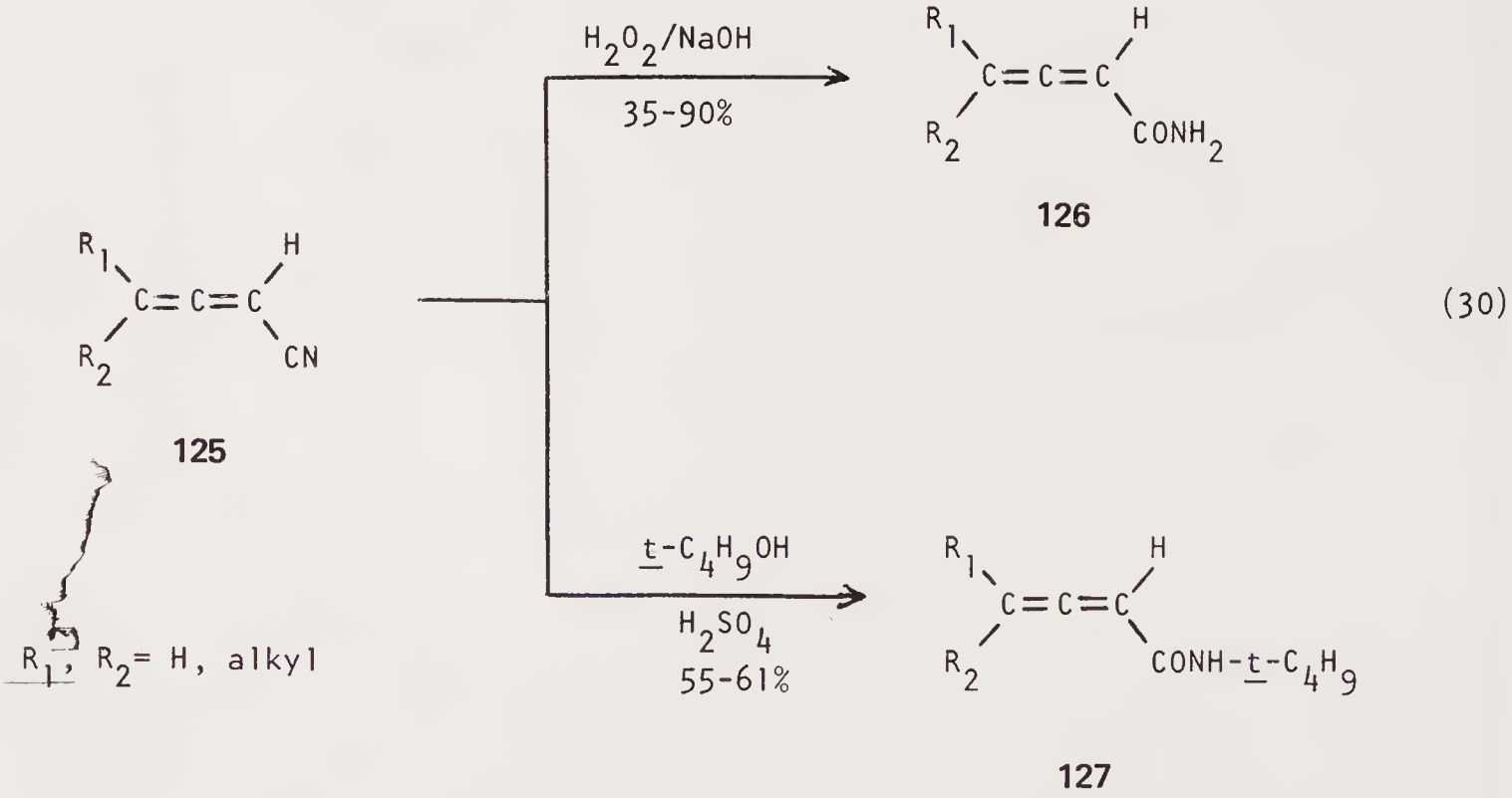
(29)

hour at −60°C or 15 minutes at room temperature. Mechanistically, the initially formed four-membered [2 + 2] cycloadduct rearranges to the ketene **123** which then reacts with another molecule of **121** to give the product. The suggested mechanism was confirmed by independently synthesizing ketene **123** and reacting it with **121**.[93] Thermolysis of **122** under vacuum produces the novel 6-amino-α-pyrone **124**.



Scheme 17

Secondary and primary allenic amides are quite rare. The sensitivity of the activated allene nucleus reduces the variety of amide-forming reactions that the system will tolerate. Both types of amides, however, can be prepared from allenic nitriles **125** (equation 30). Alkaline hydrogen peroxide reacts with **125** exothermically to give primary amides **126** within a few minutes. Similarly, a Ritter reaction of **125** gives rise to allenic *t*-butylamides **127**.[94,95]



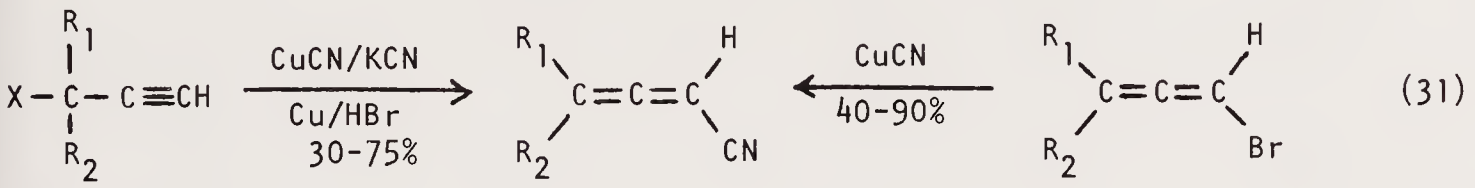
(30)

6.3. ALLENIC NITRILES

Cyanoallenes (**130**) are readily prepared from propargyl alcohols (**128a**) or allenic bromides (**129**) as shown in equation (31). Tertiary acetylenic alcohols are converted to **130** by treatment with 1.5 equivalents of cuprous cyanide, one equivalent of potassium cyanide, and 2.5 equivalents of 48% hydrobromic acid in the presence

of a catalytic quantity of copper. Under similar conditions, secondary acetylenic alcohols do not react. The transformation can be explained by the initial formation of an acetylenic bromide (**128b**) followed by an S_N2' displacement by cyanide ion. When the reaction is performed with tertiary propargyl halides **128b** as the starting material, more by-products are produced at the expense of **130**.

Sterically hindered and polysubstituted allenic nitriles cannot be obtained by the foregoing method but are easily obtained from bromoallenes (**129**) by treatment with anhydrous cuprous cyanide at 100–120°C.[96,97]



(31)

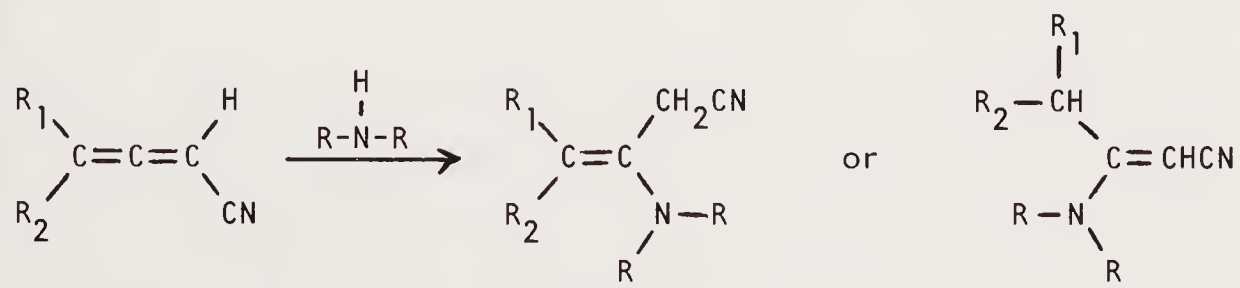
128a, X= OH
b, X= Br
(R_1, R_2= alkyl)

130

129 (R_1, R_2= H, alkyl)

Allenic nitriles, like other activated allenes, are susceptible to nucleophilic attack at the central carbon atom by such nucleophiles as alkoxides,[98] thiolates,[16] xanthates,[98] and amines.[99,100]

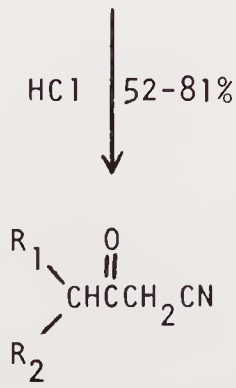
With amines, unconjugated (**131**) or conjugated (**132**) enamino nitriles can be obtained quantitatively by regulating the reaction conditions. When stoichiometric quantities of cyanoallenes and primary or secondary amines are allowed to react at temperatures between −33 and 0°C, only the nonconjugated nitriles **131** are produced. These nitriles can be converted to the conjugated form **132** by briefly heating the reaction mixture at 150–200°C. Either **131** or **132** is easily hydrolyzed with dilute acid to the β-ketonitrile **133**.



(R_1, R_2= H, alkyl)

131

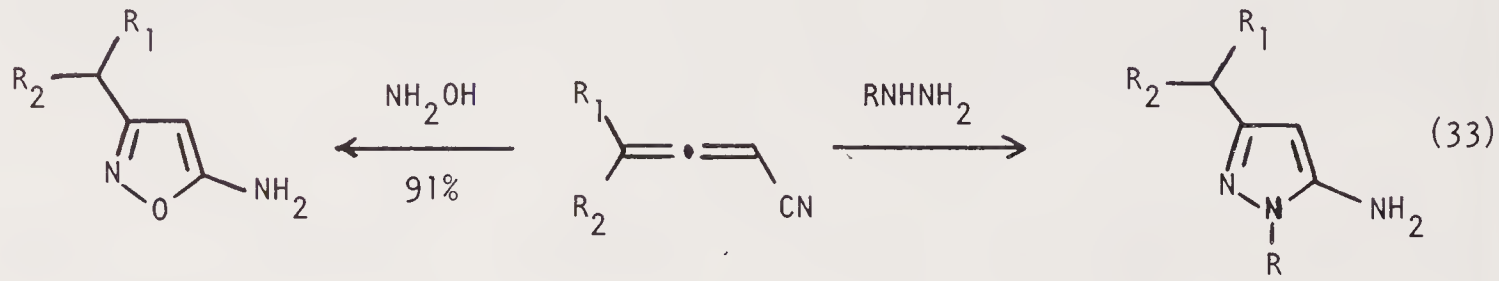
132



(32)

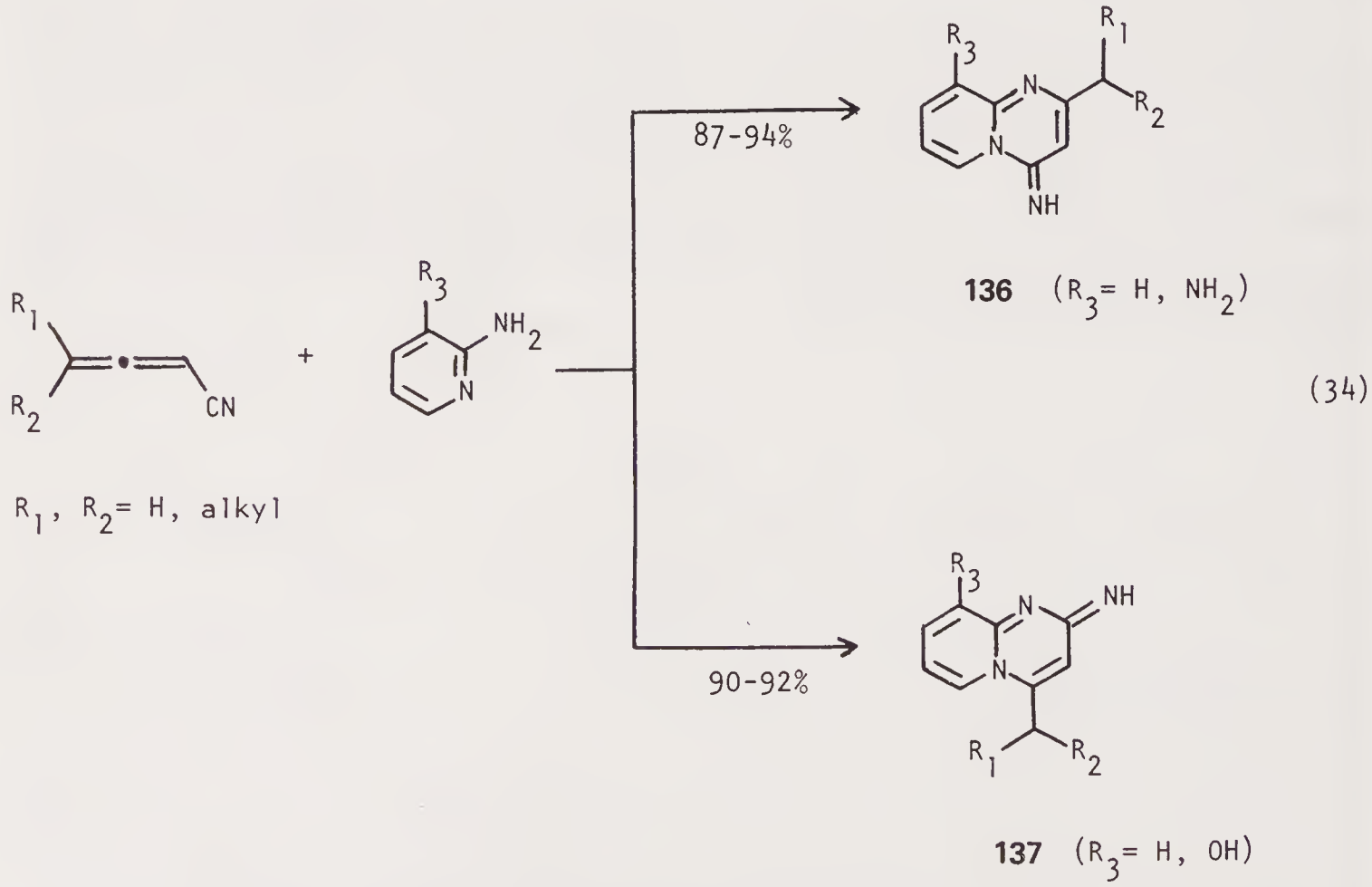
133

Bifunctional amines such as hydroxylamine or hydrazine react with cyanoallenes as in equation (32) and then spontaneously cyclize with the nitrile to directly produce either 5-aminoisoxazoles **134**[98] or 5-aminopyrazoles **135**[101,102] in essentially quantitative yield (equation 33). The intermediate enaminonitriles cannot be isolated except in the case of phenylhydrazine.[103]



134 **135**

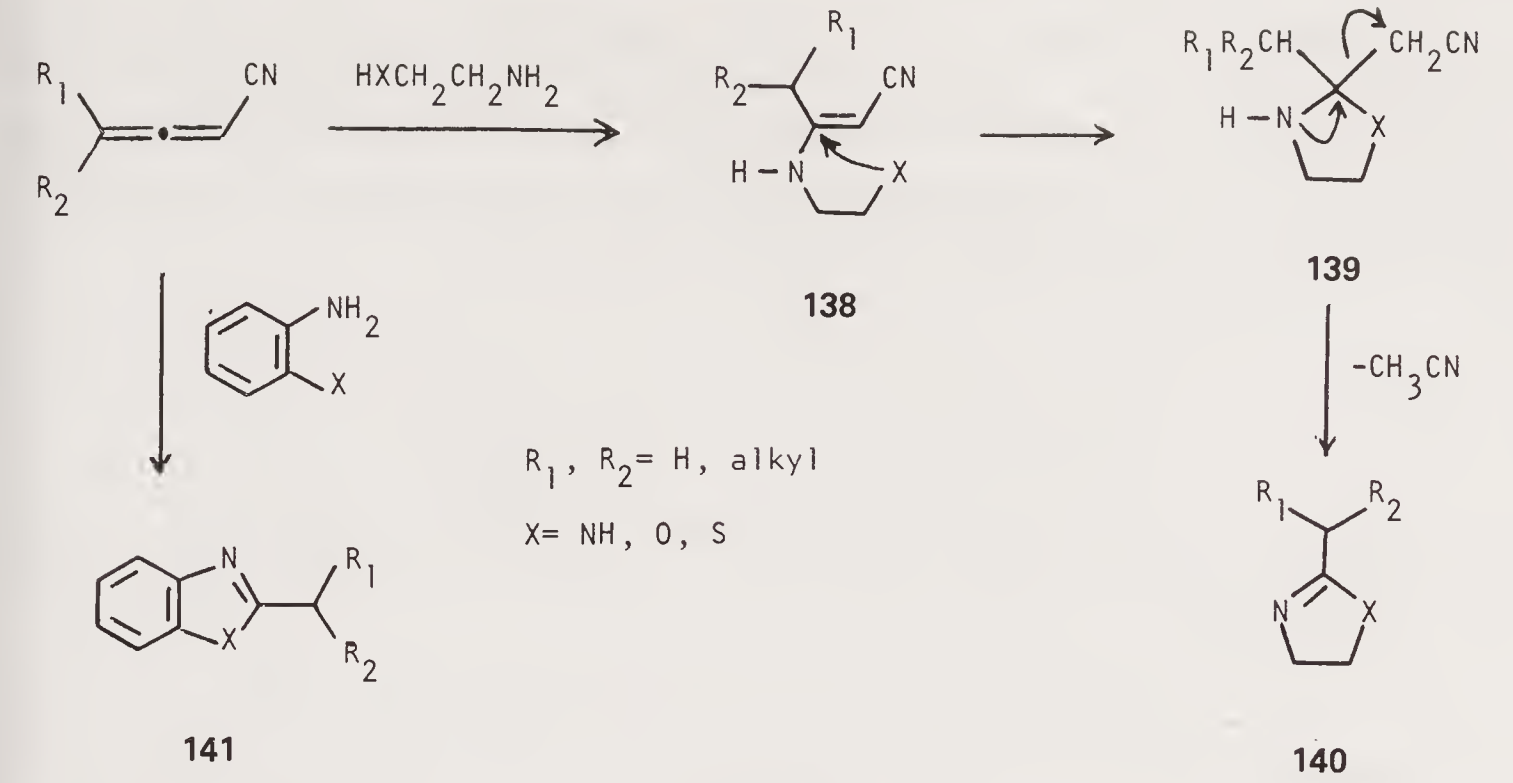
When 4,4-dialkylallenyl nitriles are heated with 2-aminopyridine or 2,3-diaminopyridine, 4-iminopyrido[1,2-a]pyrimidines (**136**) are isolated as their monohydrates. However, when 4-monoalkylallenyl nitriles are allowed to react with 2-aminopyridine in a similar fashion, only anhydrous 2-iminopyrido[1,2-a]pyrimidines (**137**) are formed (equation 34). 3-Hydroxy-2-aminopyridine gives 2-imino derivatives **137** with either mono or dialkylallenyl nitriles.[104]



136 (R_3= H, NH_2)

137 (R_3= H, OH)

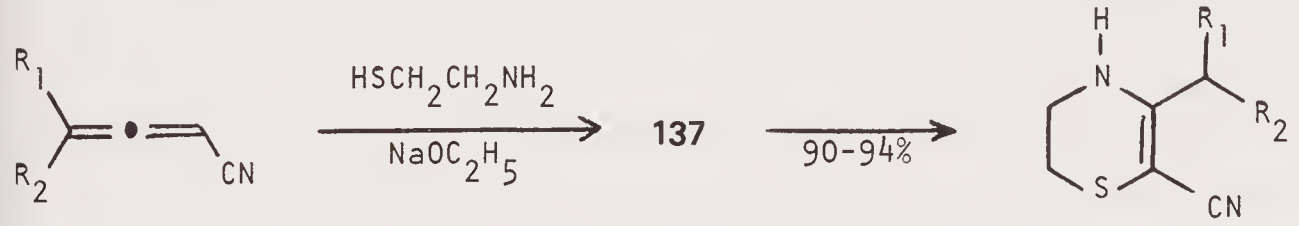
In such additions where the amine reagent possesses another nucleophilic site removed by two carbon atoms (e.g., ethylenediamine, 2-aminoethanethiol, ethanolamine, and *o*-aminophenol), the reaction with cyanoallenes follows another course (Scheme 18). After initial addition to the allene to give **138**, a second Michael addition to the enamine takes place (in preference to reaction with the nitrile) to form an unstable imidazolidine **139**. At this point, the molecule eliminates aceto-



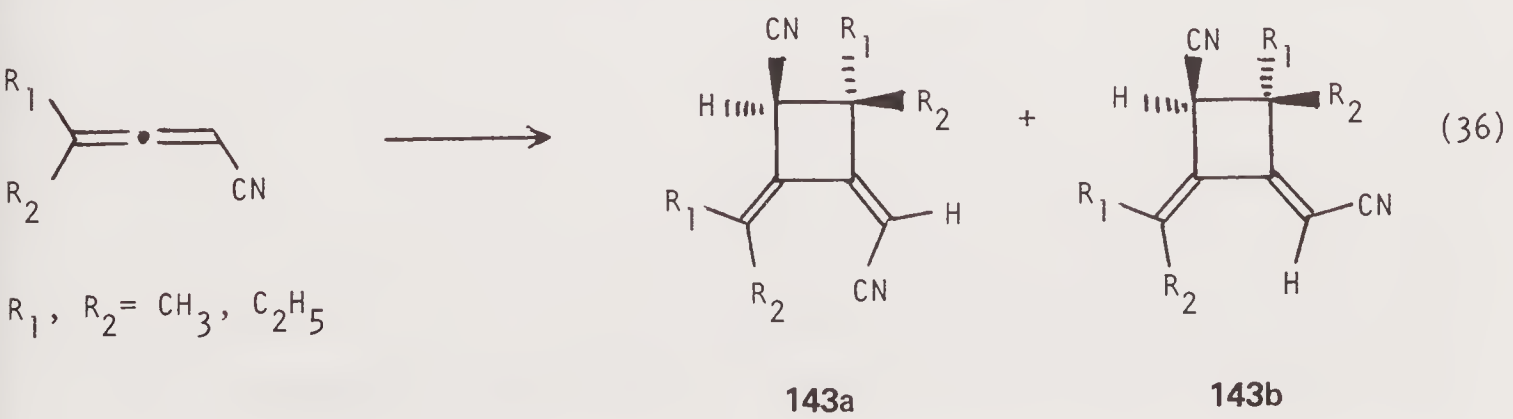
Scheme 18

nitrile to generate imidazolines, oxazolines, or thiazolines (**140**), usually in excess of 80% yield.[101,102,105,106] If aromatic bifunctional amines are used, the corresponding benzo derivatives **141** are produced.

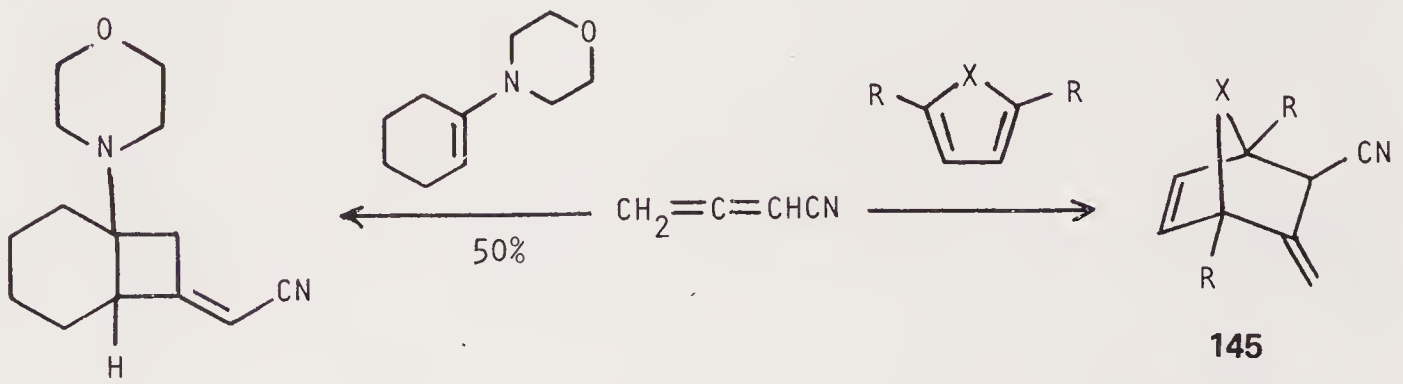
If reactions with 2-aminoethanethiol are performed in the presence of two equivalents of sodium ethoxide, the elimination of acetonitrile from **139** is suppressed and only thiazine derivative **142** is formed (equation 35).[107]



Allenic nitriles are inherently unstable and slowly dimerize to cyclobutanes **143** when kept at room temperature for extended periods of time. They can be distilled *in vacuo* at temperatures less than 100°C with little or no dimerization, however, if retained between 100–130°C (2–4 hours), quantitative conversion to **143** takes place. At room temperature the *syn*-isomer **143a** predominates whereas elevated temperatures produce an excess of the *anti*-isomer **143b**[108,109] (equation 36).



Cyanoallene undergoes a [2 + 2] cycloaddition with 1-(N-morpholino)cyclohexene to give 1-(N-morpholino)-(E)-7-cyanomethylene-*cis*-bicyclo[4.2.0]octane (**144**).[110,111] It is also such a potent dienophile that it enters into Diels–Alder reactions exothermically with either cyclopentadiene or 2,5-dimethylfuran to afford adducts **145** in high yield[98] (equation 37).



144

145

R=H; X=CH_2, 82%

R=CH_3; X=O, 87%

(37)

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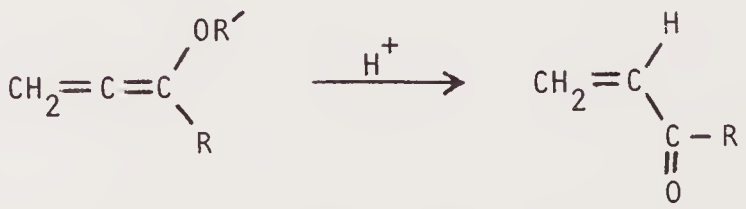
CHAPTER SEVEN

HETERO-SUBSTITUTED ALLENES

Allenes bearing hetero substituents are extremely useful substrates in organic synthesis. The direct substitution of a hetero atom on the allene framework confers upon the system an electronic bias that allows the molecule to react in a regioselective manner. The latent functionality represented by these systems can be easily transformed into their respective functional groups by simple manipulations with standard reagents, under fairly mild conditions.

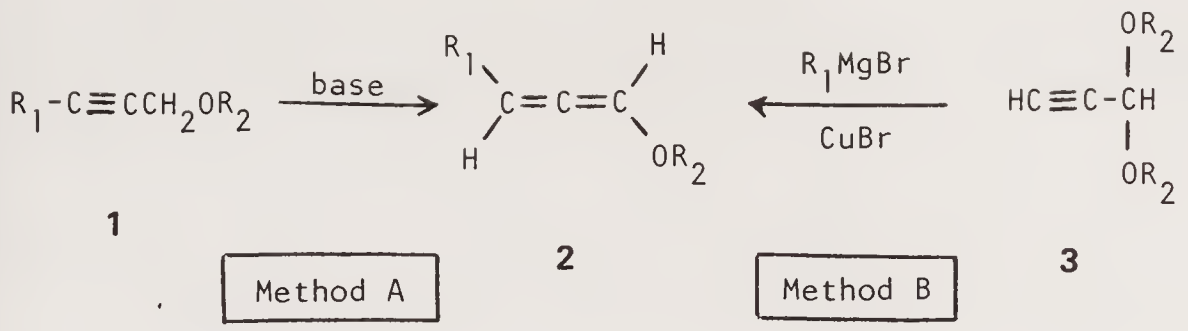
7.1. OXYGEN

Oxygenated allenes are the most versatile of the heteroallene family. They are susceptible to both nucleophilic and electrophilic substitution and are readily hydrolyzed under acidic conditions to give carbonyl-containing compounds. Therefore these allenes serve as excellent masked aldehydes or ketones.



(1)

Alkoxyallenes are easily prepared by the two basic methods shown in equation (2). Propargyl ethers (**1**) can be isomerized to their corresponding allenic ethers in 70–95% yield by treatment with either potassium *t*-butoxide[2,3] at 70°C or with sodamide in liquid ammonia.[4] Alternately, allenes **2** are produced by an S_N2' addition of an organocuprate to propargyl acetal **3**.[5]



1 2 3 (2)

Allene	R_1	R_2	Method	Yield (%)	Reference
a	H	CH_3	A	82	2
b	H	C_2H_5	A	85	2
c	H	C_4H_9	A	91	2
d	H	*t*-C_4H_9	A	66	6
e	C_4H_9	C_2H_5	B	78	5
f	*t*-C_4H_9	C_2H_5	A	96	4

7.1.1. Addition Reactions

Under acid catalysis, methoxyallene (**2a**) adds alcohols at the oxygenated (α) carbon to give acetals **4**.[7]

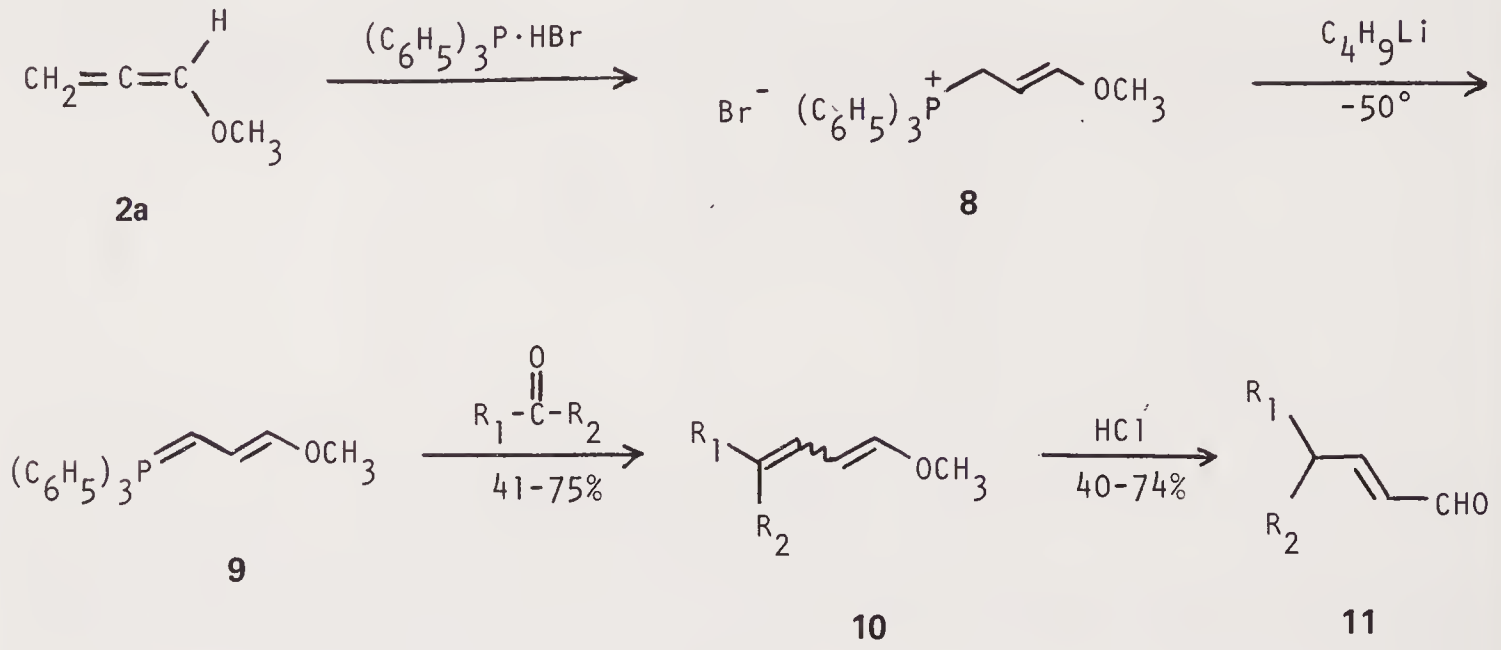
2a **4** R= CH_3, 73%; R= C_2H_5, 80% (3)

Thiophenol, on the other hand, adds to **2a** at the terminal carbon in a highly exothermic reaction to give the E-adduct **5** almost exclusively.[8] Compound **5** can then be converted to the (E)-γ-methoxyallylboronate **6** which, when reacted with aldehydes, is an excellent diastereoselective reagent for the preparation of methoxy homoallylic alcohols **7** (Scheme 1).

2a **5** **6** **7**

Scheme 1

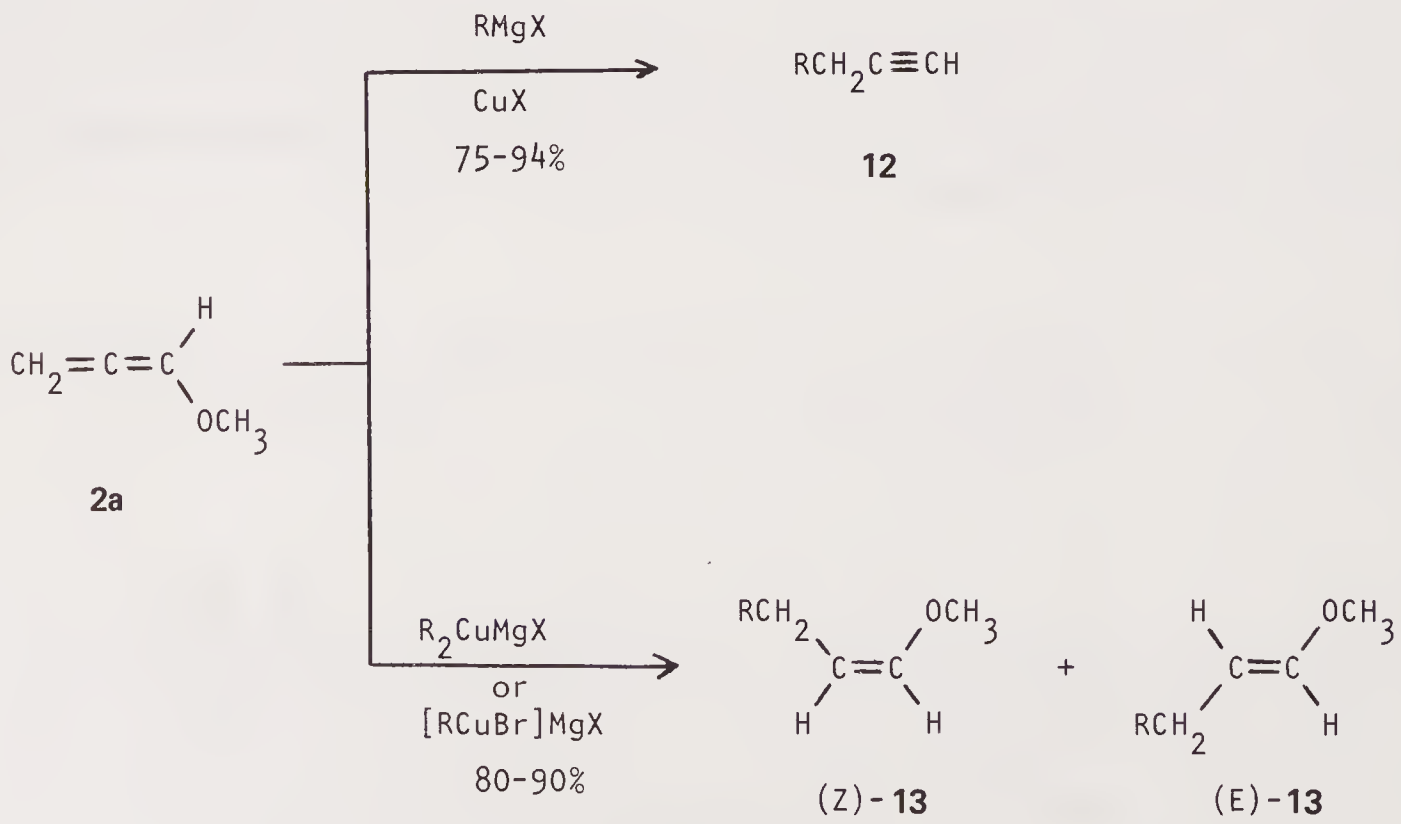
Triphenylphosphonium bromide also adds to **2a** at the terminal carbon to give **8** in 68% yield. Treatment of **8** with *n*-butyllithium produces ylid **9**, which reacts with simple carbonyl compounds in a normal Wittig fashion to give methoxybutadienes **10**. These may be isolated as such or can be hydrolyzed *in situ* with aqueous acid to give the (E)-α,β-unsaturated aldehydes **11**.[9] This facile one-pot procedure is an extremely useful three-carbon homologation technique.



2a **8** **9** **10** **11**

Scheme 2

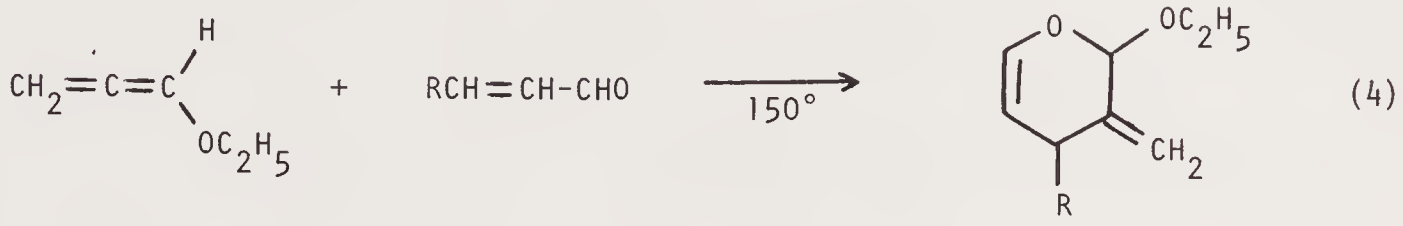
Under the influence of catalytic amounts of copper(I) halides, Grignard reagents add to **2a** in a 1,3 fashion to give 1-alkynes in high yields[10] (Scheme 3). When similar reactions are performed with a twofold excess of preformed homocuprates or heterocuprates, a mixture of isomeric adducts **13** is obtained, the Z-isomer always predominating.[11]



2a **12** (Z)-**13** (E)-**13**

Scheme 3

Ethoxyallene (**2b**) can participate as a dienophile in a hetero Diels–Alder reaction with acrolein derivatives to produce exomethylene-2,3-dihydropyrans (**14**) in moderate yield[7] (equation 4).



2b

14 R=H, 41%
R=CH_3, 19%

(4)

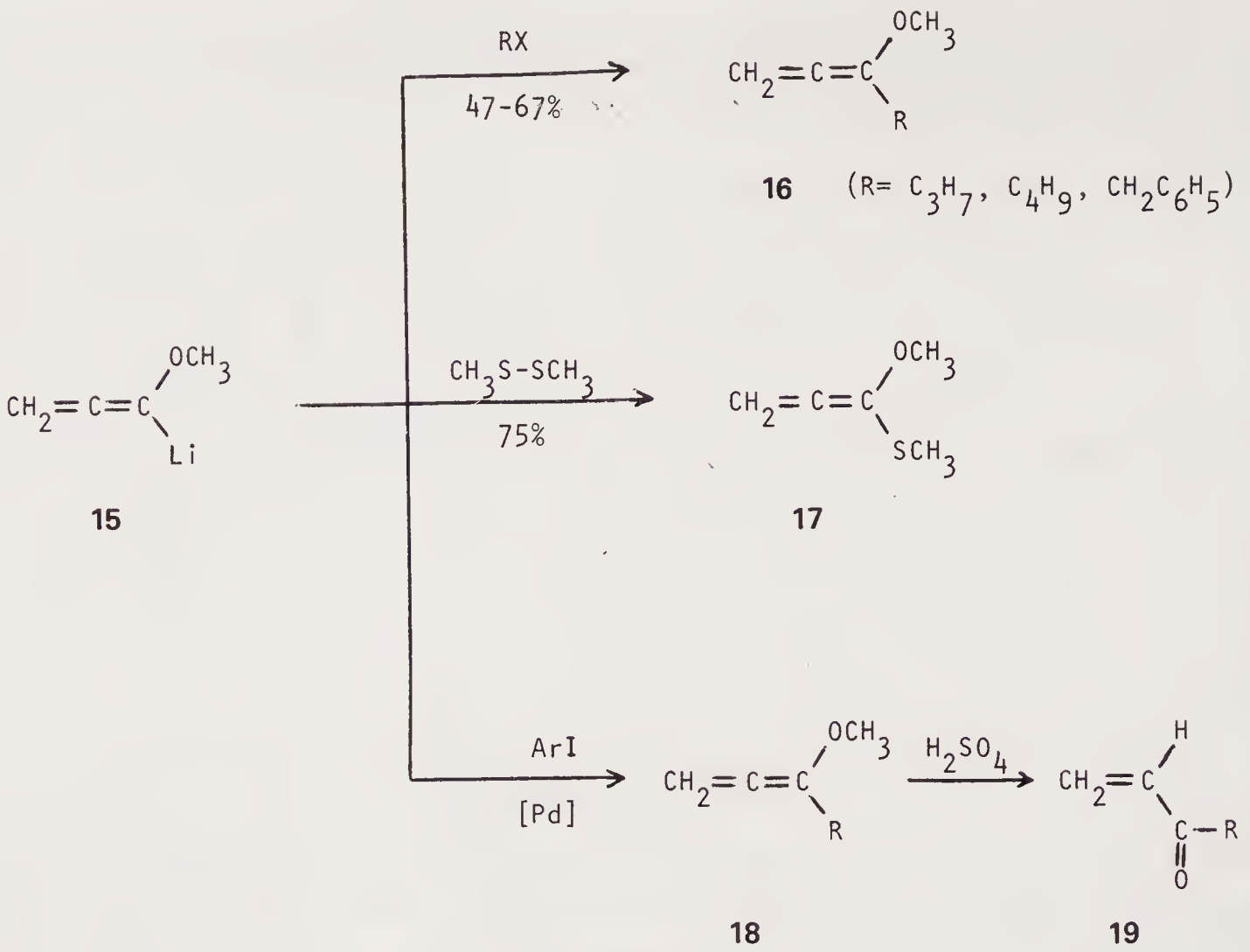
7.1.2. α-Lithiation

One of the more interesting properties of alkoxyallenes is their ability to be regioselectively metallated at either the α or γ positions. These anions exhibit a high degree of nucleophilic character and react with a wide variety of electrophiles. The α-lithiation of methoxyallene (**2a**) is easily accomplished with *n*-butyllithium at −30°C. The latent carbonyl functionality that is transferred to the product makes this lithiated species an excellent acyl anion equivalent.

15

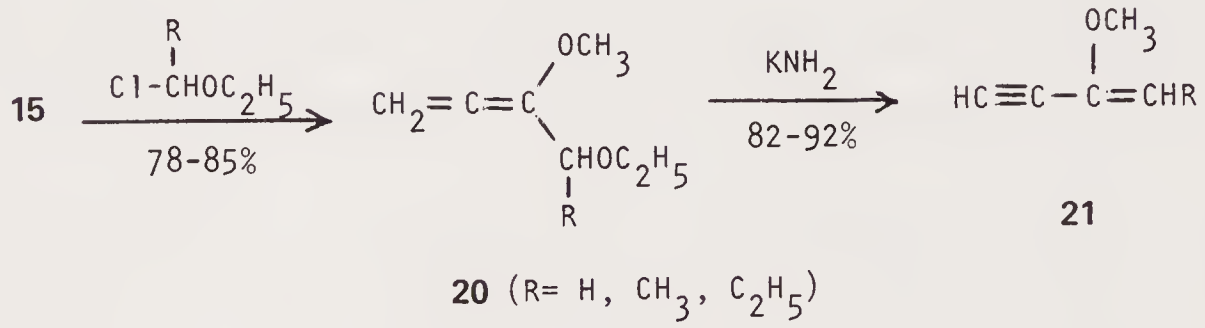
Ethereal solutions of **15** react smoothly with alkyl bromides or iodides to give **16**, provided that a sufficient quantity of THF is added.[2] Dimethyl disulfide reacts with **15** at a much faster rate and affords **17** in good yield.[7] In the presence of tetrakis[triphenylphosphine]palladium, **15** can be arylated with iodobenzene to produce **18** (R = C_6H_5). Subsequent acidic hydrolysis furnishes phenyl vinyl ketone (**19**, R = C_6H_5) in 42% overall yield.[12] Transmetallation of **15** to zinc (with zinc chloride) followed by reaction with aryl or alkenyl halides in the presence of Pd[0] catalyst provides a general route to α-aryl or alkenyl allenic ethers **18** (R = aryl, $CH_2CH{=}CH_2$).[13] Hydrolysis then gives the corresponding vinyl ketone derivative **19** in 27–84% yields (from **15**).

α-Chloroethers react exothermically with **15** to produce 4-ethoxy-3-methoxy-1,2-alkadienes (**20**) in high yields (equation 5). The treatment of **20** with 2 equiv-



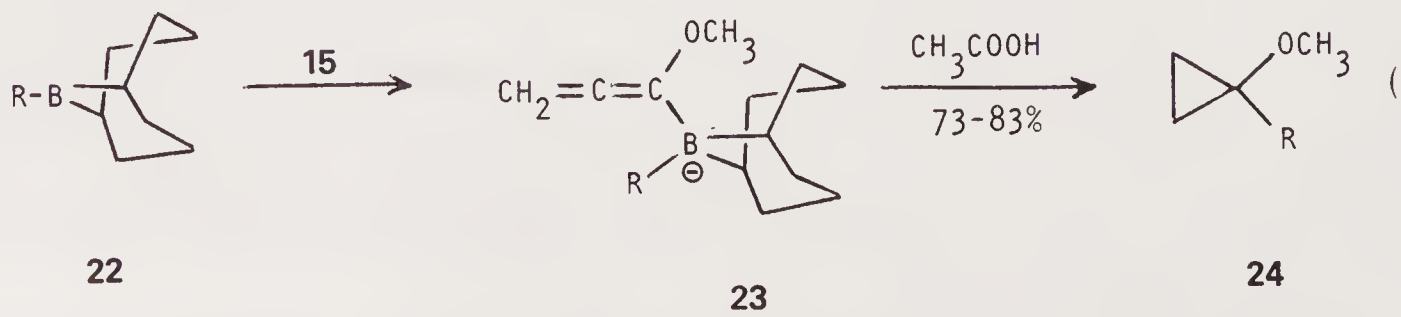
Scheme 4

alents of potassium amide in liquid ammonia results in a 1,4-elimination of ethanol to give 3-methoxy-3-alken-1-ynes (**21**) in excellent yields.[14]



(5)

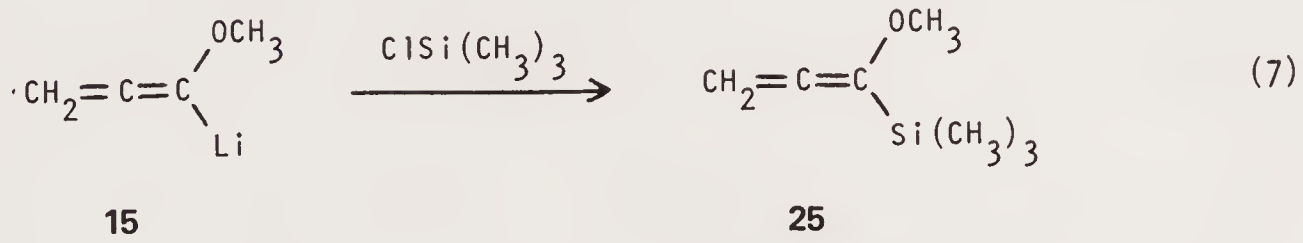
B-alkyl-9-borabicyclo[3.3.1]nonanes (**22**) form ate complexes (**23**) when allowed to react with **15** (equation 6). The addition of acetic acid to these complexes results in the formation of 1-alkyl-1-methoxycyclopropanones **24**.[15]



(6)

R = alkyl, *exo*-norbornyl, *trans*-2-methylcyclohexyl

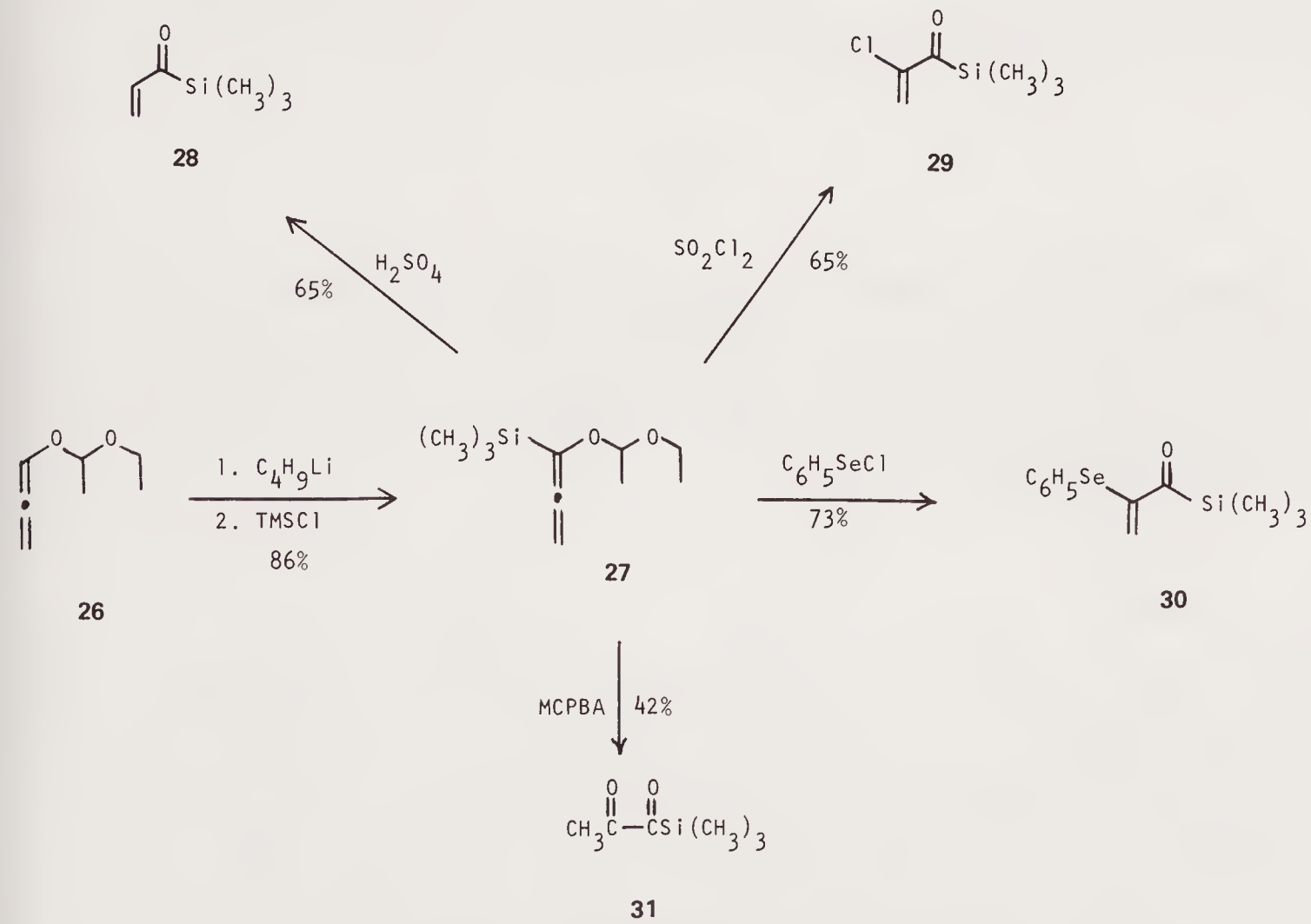
When **15** is treated with trimethylchlorosilane, 1-trimethylsilyl-1-methoxyallene (**25**) is produced in 81% yield[16,17] (equation 7).



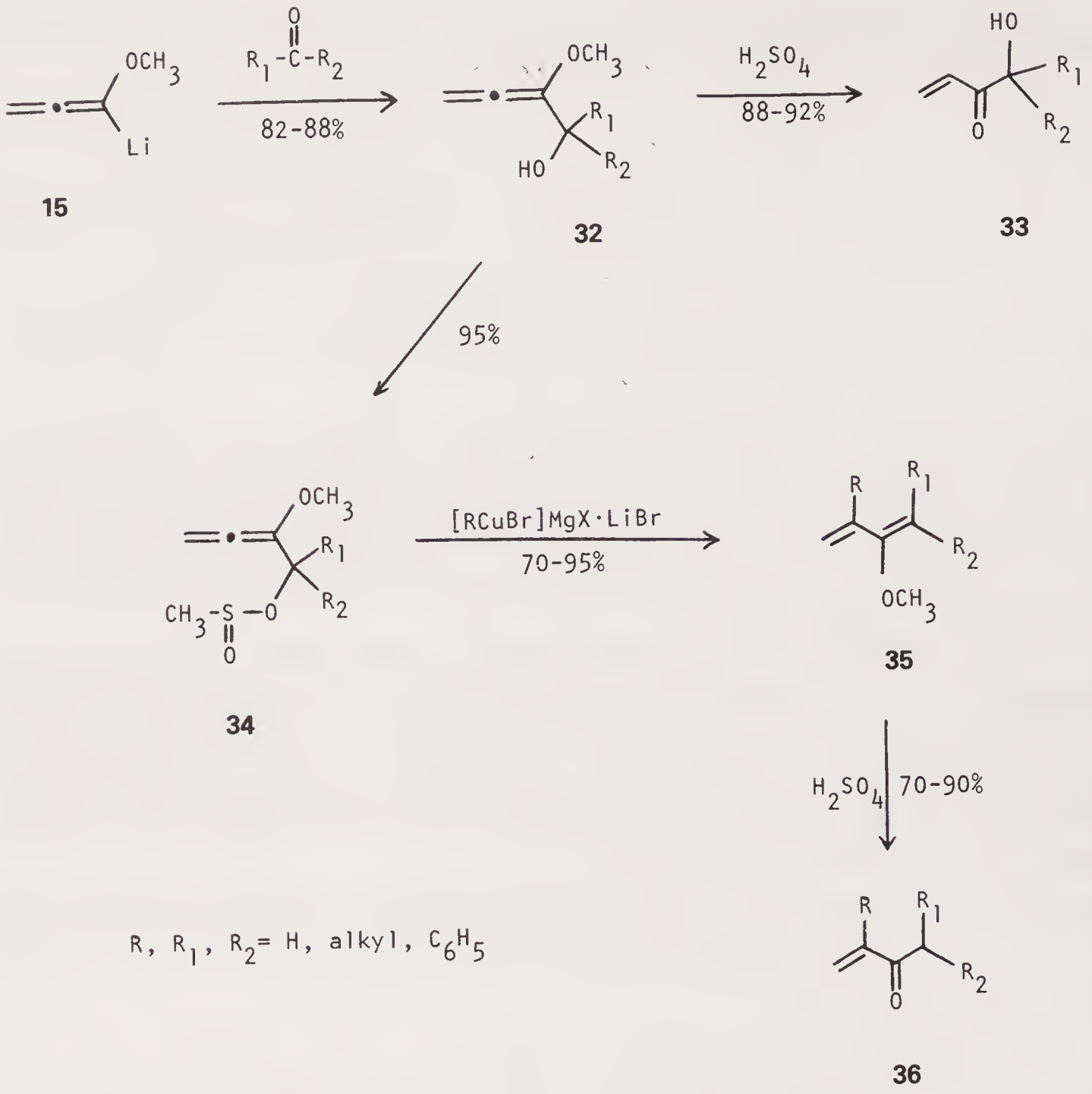
15 **25** (7)

By an analogous procedure, alkoxyallene **26** is converted to the silyl derivative **27** which is a key intermediate for the preparation of a whole family of interesting silyl ketones **28–31** (Scheme 5).[18] In certain instances when the trimethylsilyl group in **27** is replaced by *t*-butyldimethylsilyl, the conversion to silyl ketones proceeds in dramatically higher yields.

Solutions of **15** are sufficiently nucleophilic to react with carbonyl-containing compounds to give carbinols **32** in high yields. Acid-catalyzed hydrolysis of these intermediates furnishes the unsaturated ketols **33** (Scheme 6).[7] If the hydroxyl group in **32** is converted to a methanesulfinic ester (**34**), reactions with organoheterocuprates lead to the formation of 3-methoxy-1,3-dienes (**35**). These can be hydrolyzed to α,β-unsaturated ketones **36**.[19]

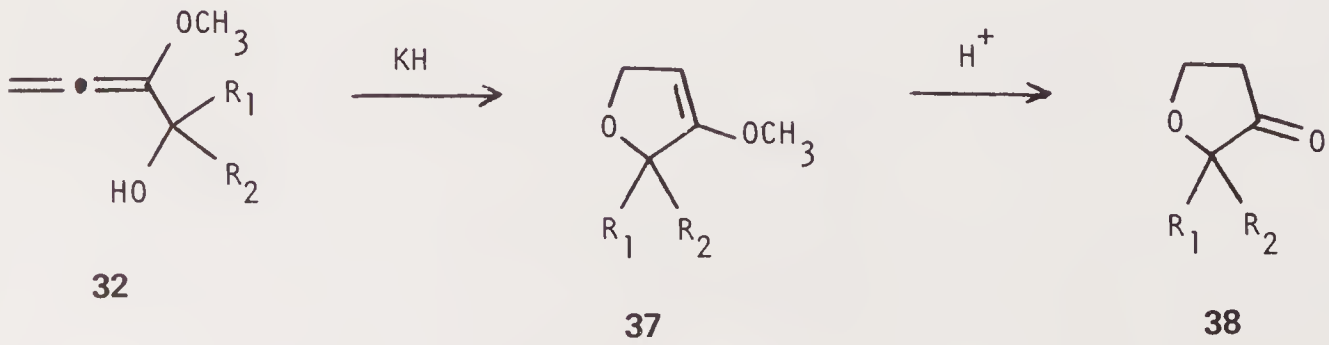


Scheme 5



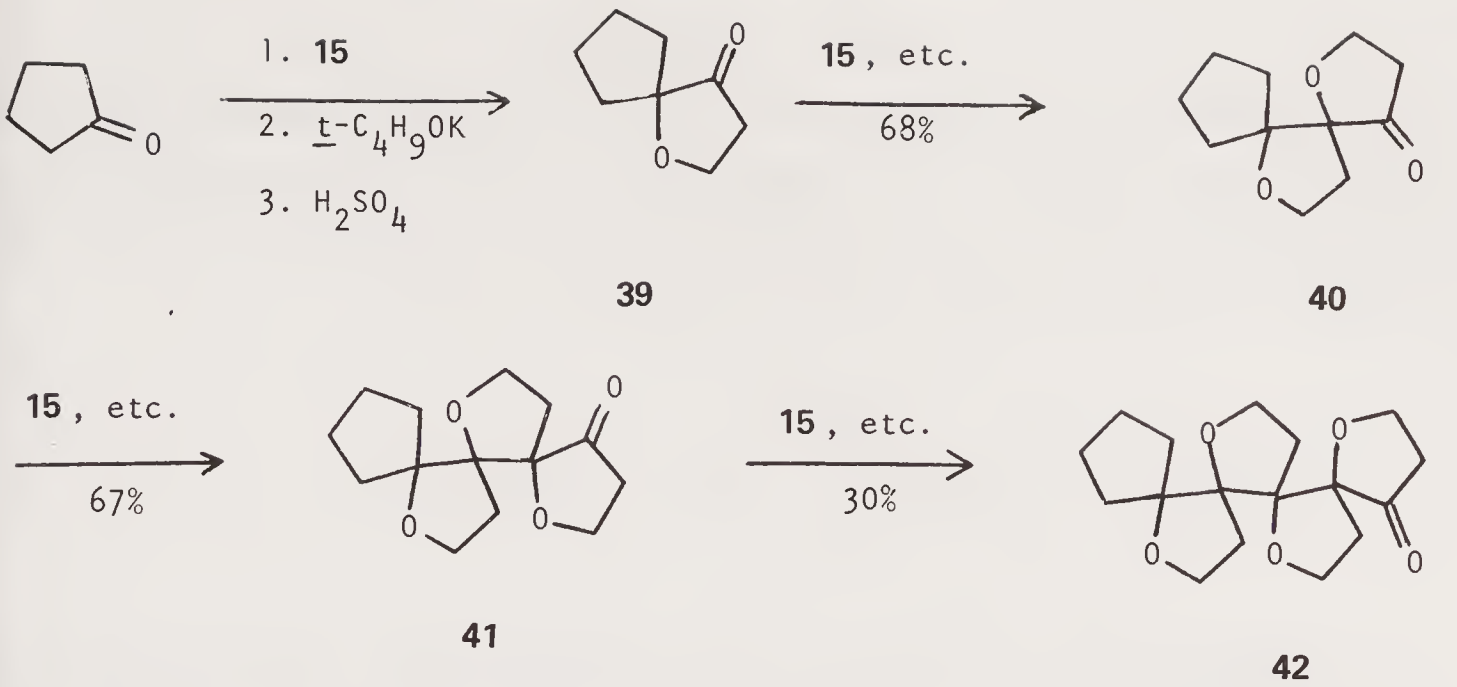
Scheme 6

Carbinols **32**, when treated with potassium hydride in the presence of dicyclohexyl-18-crown-6[20] or potassium *t*-butoxide in DMSO,[21] undergo an unusual cyclization to produce methoxydihydrofurans **37** (equation 8). Mild acid hydrolysis then furnishes dihydrofuran-3(2H)-ones (**38**), a relatively rare class of compounds, in 42–94% overall yield.



(8)

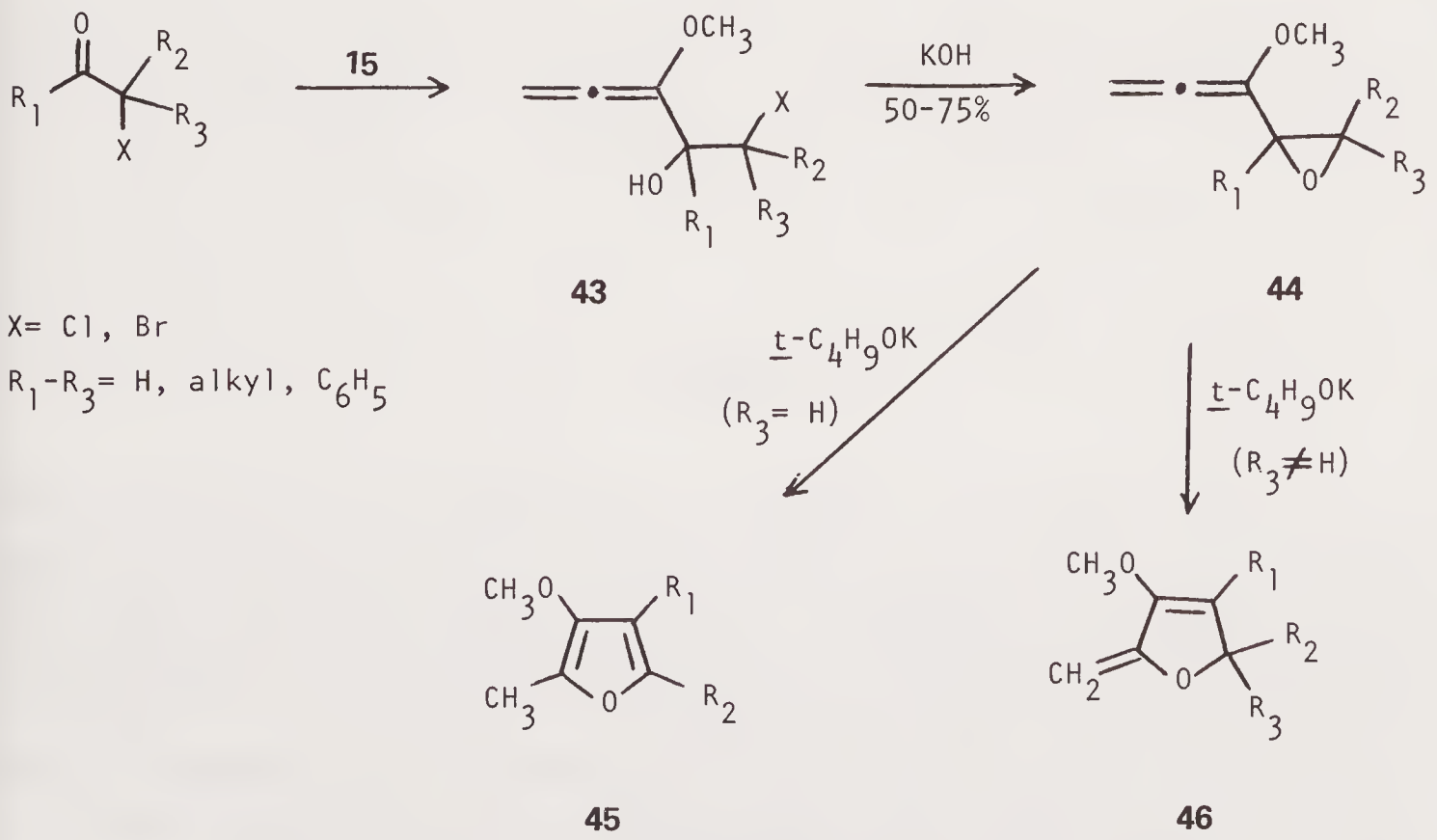
R_1, R_2= H, alkyl, cycloalkyl, cycloalkenyl, steroidal



Scheme 7

This methodology has been successfully applied to the synthesis of primary helical molecules based upon the tetrahydrofuran ring system.[22] The treatment of cyclopentanone with **15**, followed by cyclization with potassium *t*-butoxide (18-crown-6), then hydrolysis, gives the spirodihydrofuranone **39** in 82% overall yield. Repetition of the spiroannulation procedure on **39** affords **40**, which can be sequentially converted to cyclopentyl[4] helixane (**42**) as shown in Scheme 7.

α-Haloketones react with **15** to produce allenehalohydrins **43**. When these intermediates are treated *in situ* with potassium hydroxide, allenic epoxides **44** are formed in moderate yields. Further treatment of **44** with potassium *t*-butoxide in DMSO results in the formation of either furan derivatives **45** or dihydrofurans **46** depending on the substitution at R_3 (Scheme 8). Yields generally vary from 35 to 87%.[23]

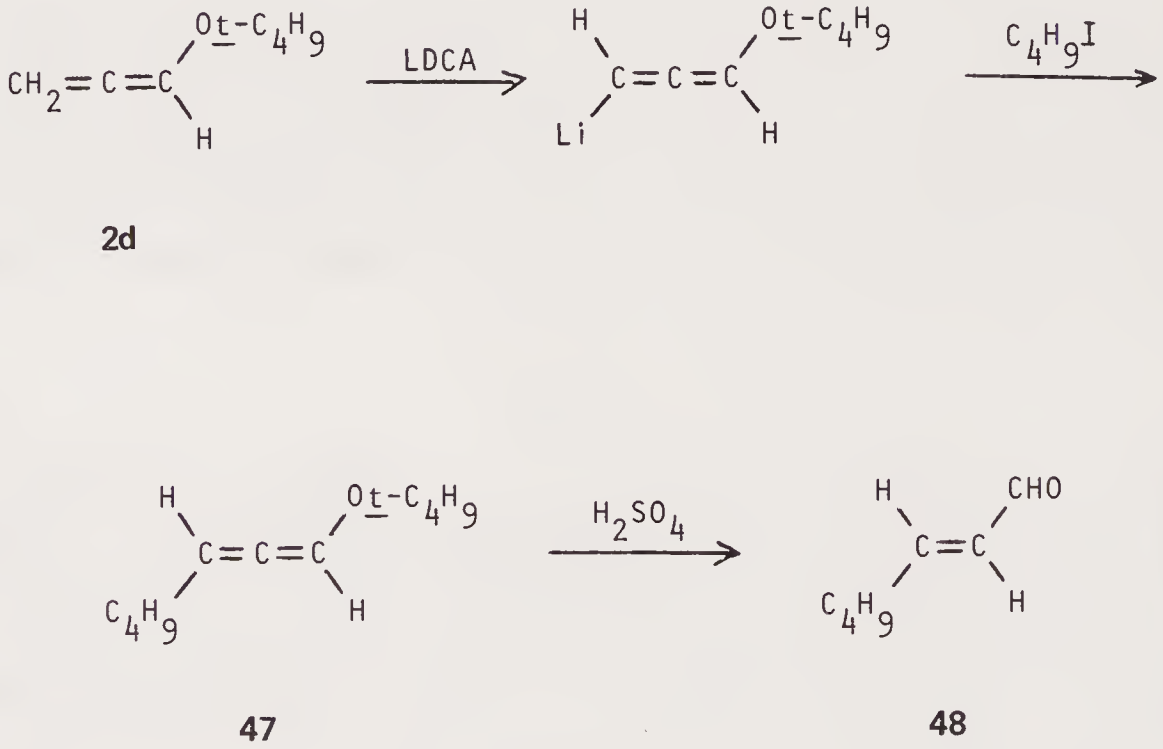


Scheme 8

7.1.3. γ-Lithiation

In the preceding section, the remarkable ease of α-lithiation of alkoxyallenes made these carbanions desirable intermediates of great synthetic utility. If alkoxyallenes can be similarly lithiated in the γ-position, they can be employed as a homoenolate equivalent, a highly desirable synthon in organic synthesis.

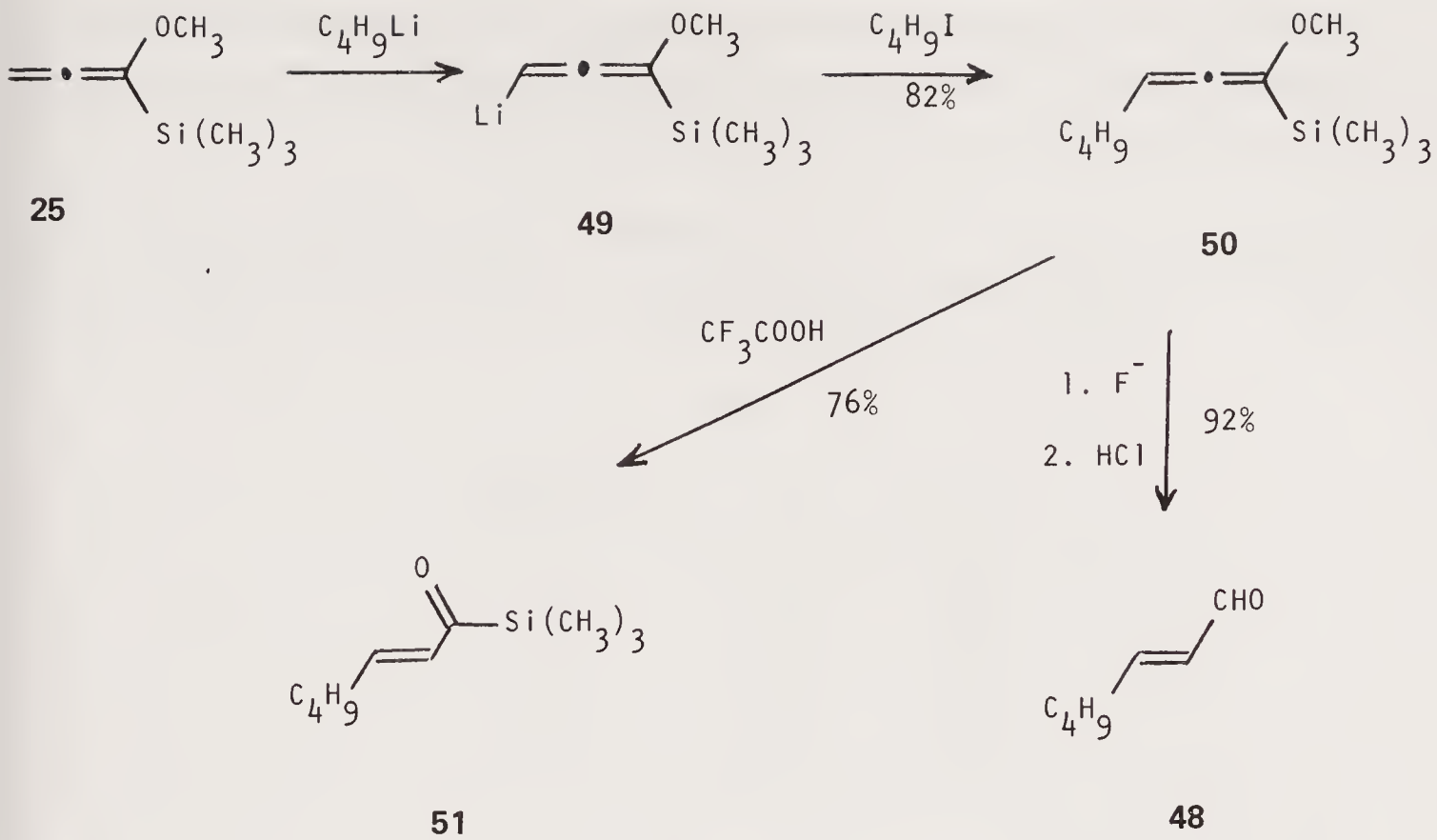
The regioselectivity in lithiation of alkoxyallenes can be changed to favor the γ-position by increasing the steric bulk of the alkoxy group in conjunction with increasing the size of the lithiating reagent. Consequently, when *t*-butoxyallene (**2d**) is treated with lithium dicyclohexylamide in THF at −55°C, the allene is terminally lithiated to an extent of 90–95%. Alkylation with *n*-butyl iodide gives **47** which, when hydrolyzed with sulfuric acid, furnishes (E)-2-heptenal (**48**) in 80% overall yield.[24]



2d **47** **48**

Scheme 9

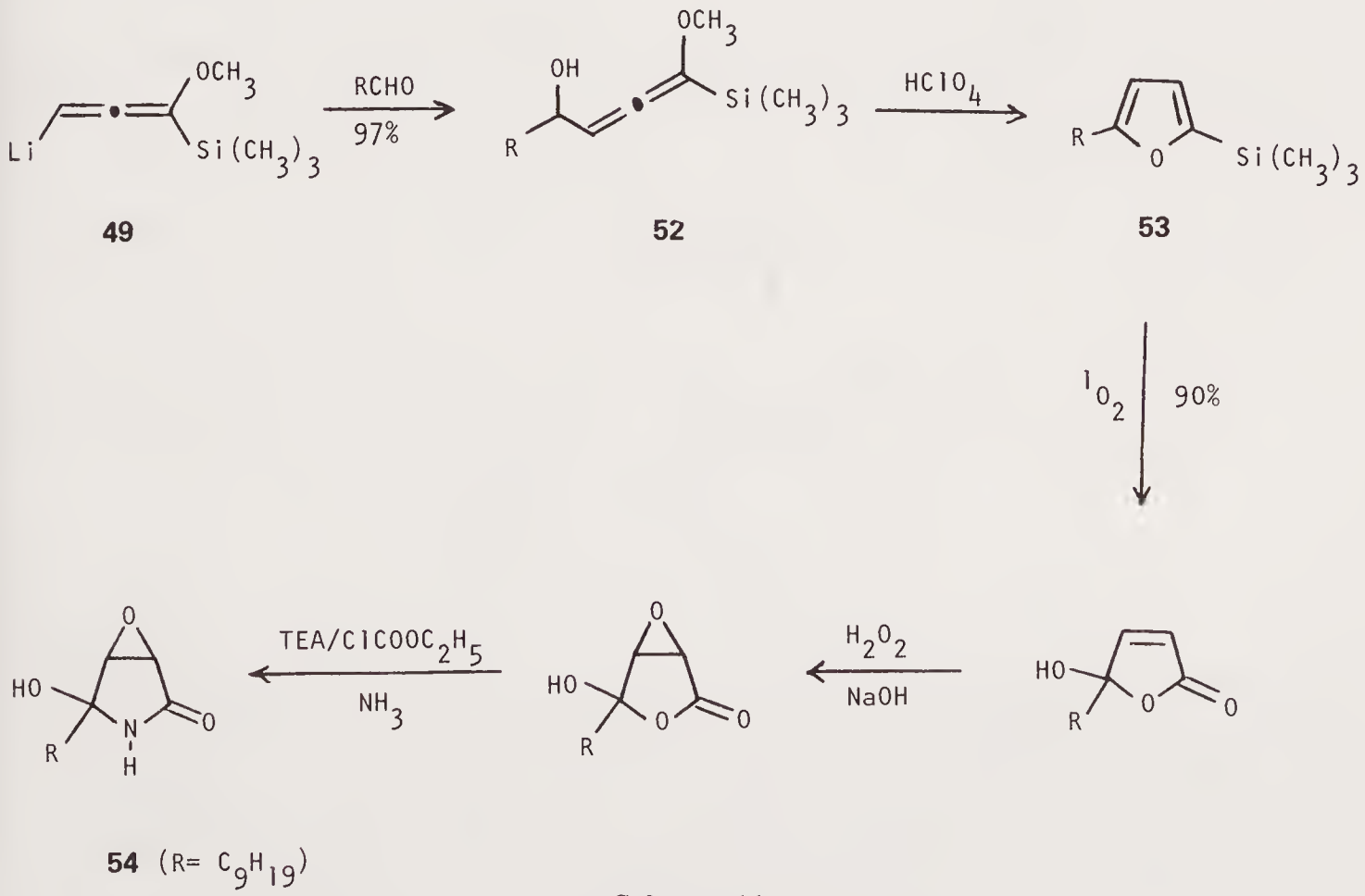
An alternate method for γ-lithiation of alkoxyallenes is to functionalize the α-position so as to preclude any lithiation at that site. An extremely useful allene for this purpose is 1-trimethylsilyl-1-methoxyallene (**25**). When **25** is treated with *n*-butyllithium[17] or *t*-butyllithium,[16] it is smoothly metallated to give the lithio species **49**. Alkylation with *n*-butyl iodide produces **50** which can suffer two modes of hydrolysis. Desilation of **50** with tetrabutylammonium fluoride followed by mild acid hydrolysis gives **48** in high yield. Alternately, the trimethylsilyl ketone **51** is obtained when **50** is treated with trifluoroacetic acid[17] (Scheme 10).



25 49 50 51 48

Scheme 10

Exposure of **49** to *n*-decanal gives the alcohol **52** which, when subjected to mild acid hydrolysis, furnishes the 2-trimethylsilyl furan **53** in 25% overall yield. The furan **53** can then be transformed to tetrahydrocerulenin (**54**) according to the series of reactions outlined in Scheme 11.[16]

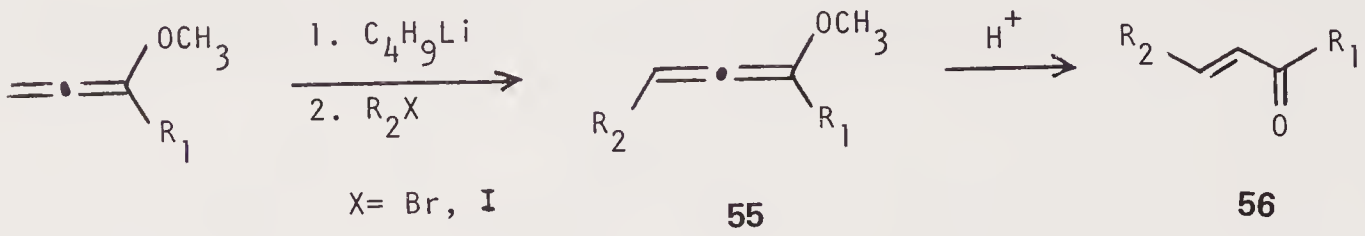


49 52 53

54 (R= C_9H_{19})

Scheme 11

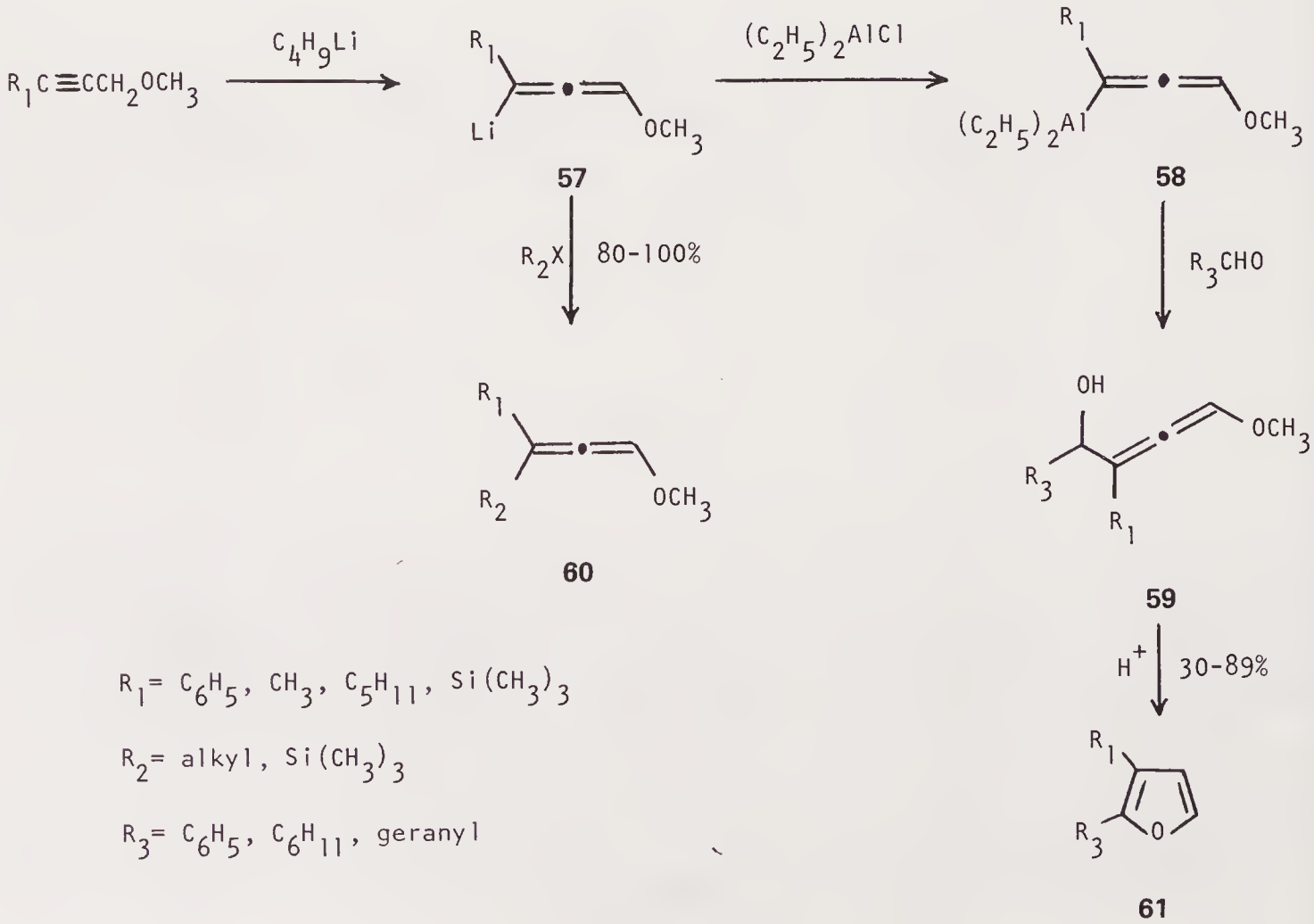
Alkoxyallenes bearing an alkyl substituent in the α-position can also be γ-lithiated and alkylated to produce internal alkoxyallenes **55**. Acid hydrolysis generates pure (E)-α,β-unsaturated ketones in good yields (equation 9).[12,24]



(9)

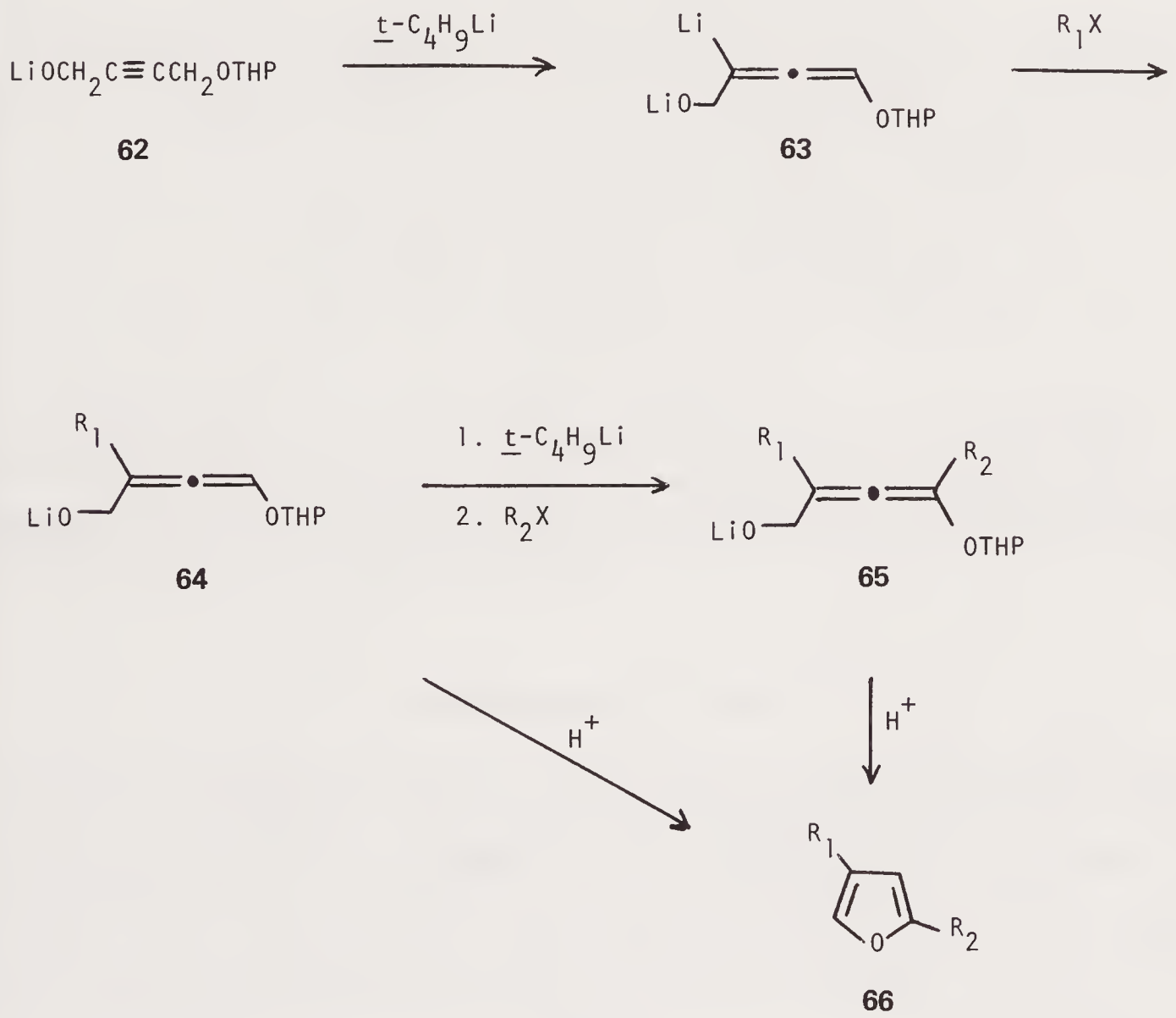
R_1	R_2	Yield (%)
CH_3	C_4H_9	89
C_2H_5	C_5H_{11}	66
C_4H_9	CH_3	86
C_4H_9	C_6H_5	78

Various propargyl esters, when metallated with either *n*-butyllithium[25–27] or *t*-butyllithium[28] produce the γ-lithiated species **57**. Exposure of **57** to a variety of alkylating agents gives the terminally disubstituted allenic ethers **60** in good yields. Treatment of **57** with aluminum reagents such as diethylaluminum chloride or triisobutylaluminum results in the formation of the aluminum allene **58**, which reacts rapidly at −78°C with aldehydes to produce the allenic alcohols **59**. Acid hydrolysis then furnishes 2,3-disubstituted furans **61**[28] (Scheme 12).



Scheme 12

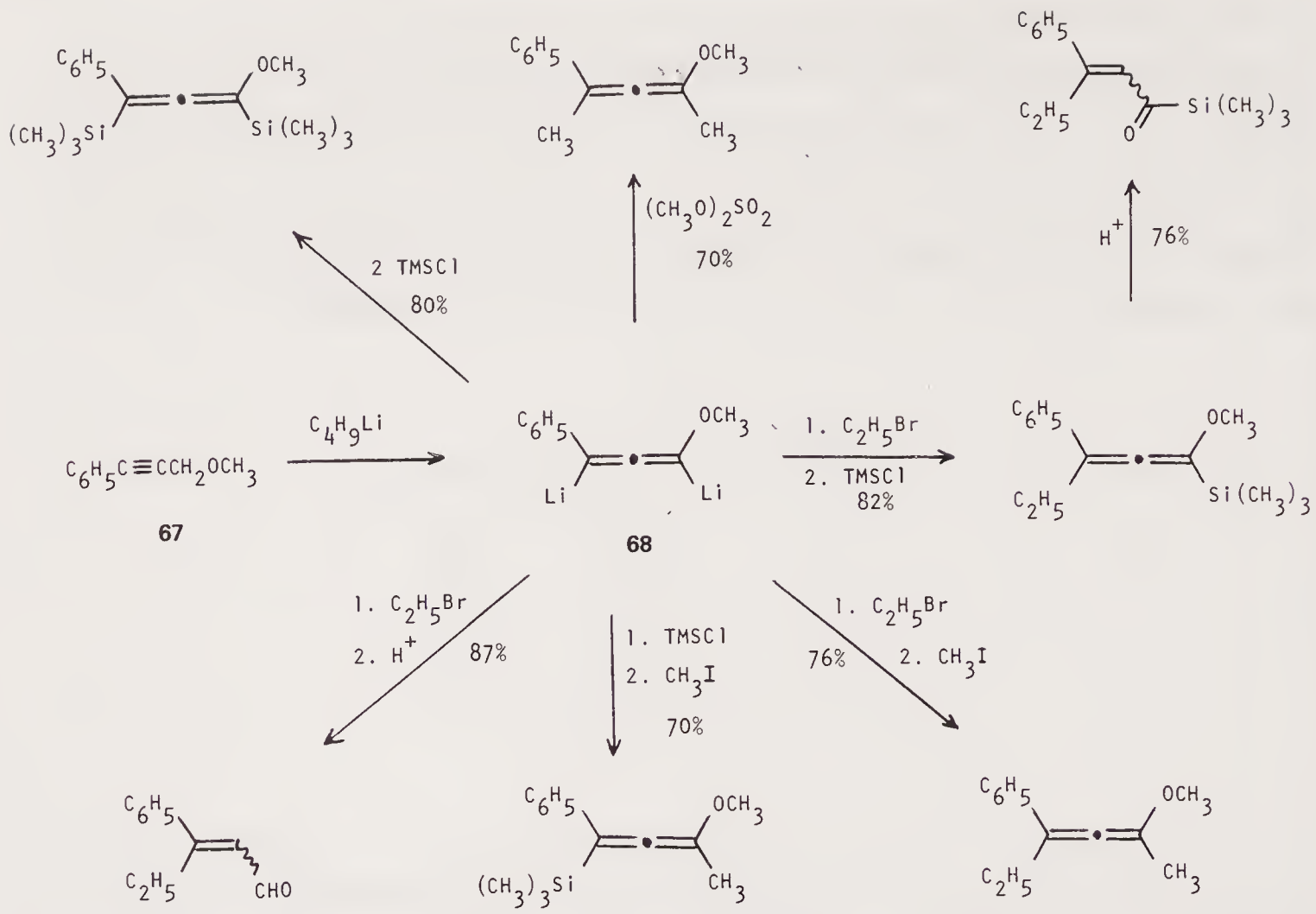
In a similar transformation, lithium 4-(2-tetrahydropyranyloxy)-2-butynolate (**62**) is quantitatively metallated with *t*-butyllithium to give **63**. Methanol protonates the allenyl anion to afford **64** (R = H), while reaction with alkyl halides yields the corresponding alkylated derivatives. Further treatment of **64** with *t*-butyllithium generates an α-lithiated species that can also be alkylated to give **65**. Acid hydrolysis of either **64** or **65** furnishes 3- or 3,5-disubstituted furans **66** (Scheme 13). The entire multistep reaction sequence can be performed in one flask.[29]



Scheme 13

R_1	R_2	Yield, %
C_6H_{13}	H	67
$CH_2C_6H_5$	H	39
C_6H_{13}	CH_3	55

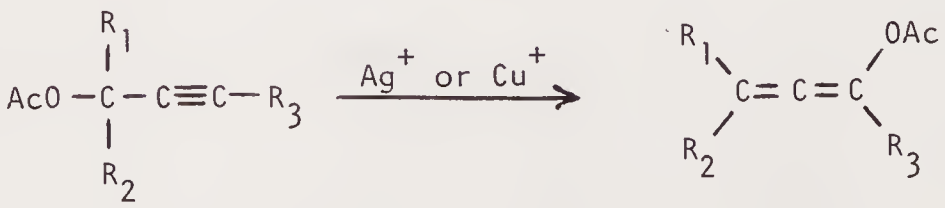
Allenic dianions are not easily generated except in special cases.[25,30,31] For example, the treatment of the phenylpropargylic ether **67** with 2 equivalents of *n*-butyllithium at −75°C leads to the formation of the dilithiated allene **68**. Dianion **68**, which is stable up to −50°, can be monoalkylated on the γ-carbon, bisalkylated at the γ- and α-positions, or selectively monoalkylated in the γ-position followed by a second monoalkylation in the α-position (Scheme 14).



Scheme 14. Reprinted from ref. 30, with permission from the authors and Pergamon Press, Copyright 1971.

7.1.4. Acetoxyallenes

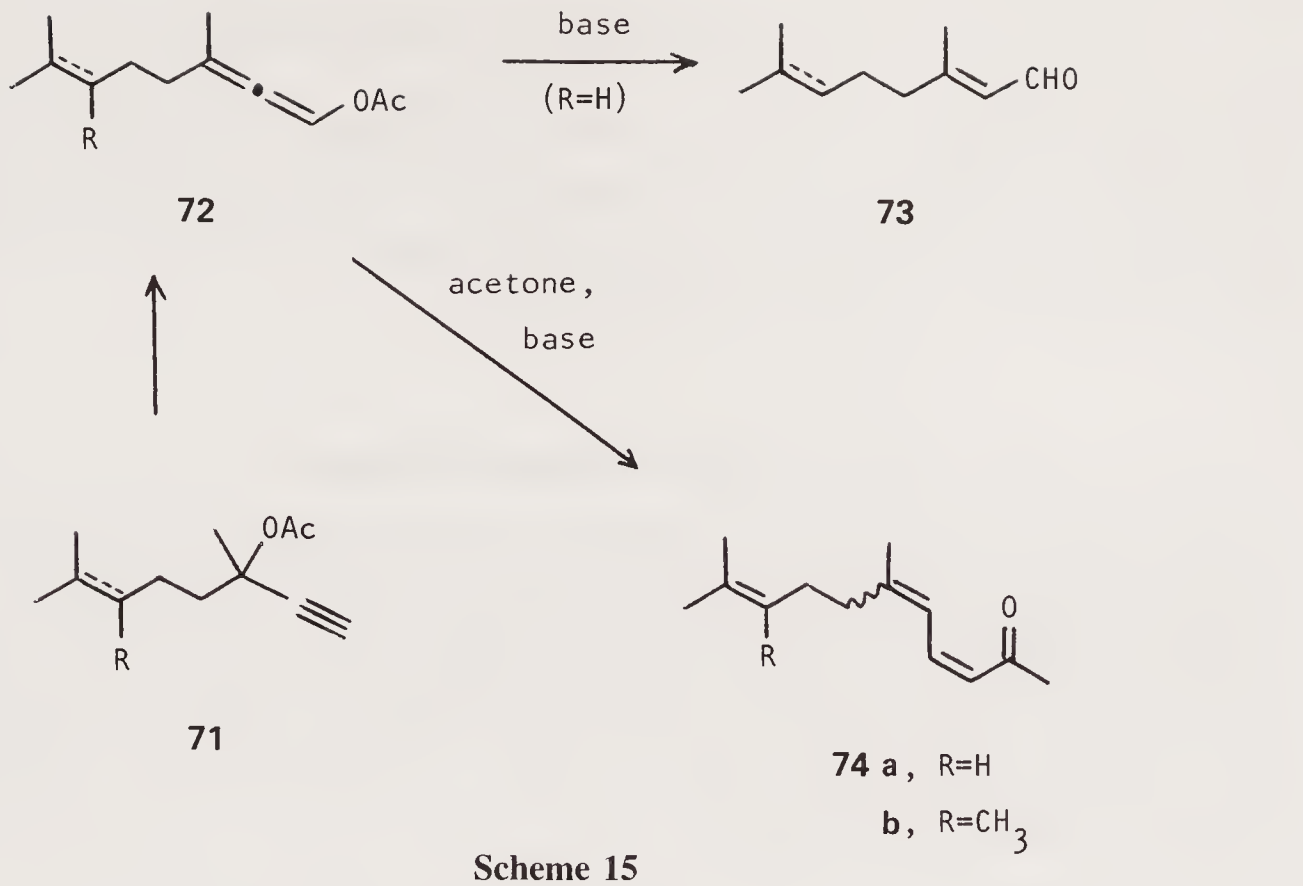
Acetoxyallenes (**70**) represent another variety of oxygenated propadienes possessing synthetic utility. They are readily prepared by a silver[32–34] or copper ion [35] catalyzed S_Ni' rearrangement of propargyl acetates **69** (equation 10). The use of silver perchlorate or silver tetrafluoroborate in methylene chloride results in the formation of **70** in yields ranging from 46 to 70%. In the cases where $R_1 = R_2 = CH_3$ and $R_3 = H$, cuprous chloride in benzene furnishes the corresponding allenyl acetate in quantitative yield.



69 **70**

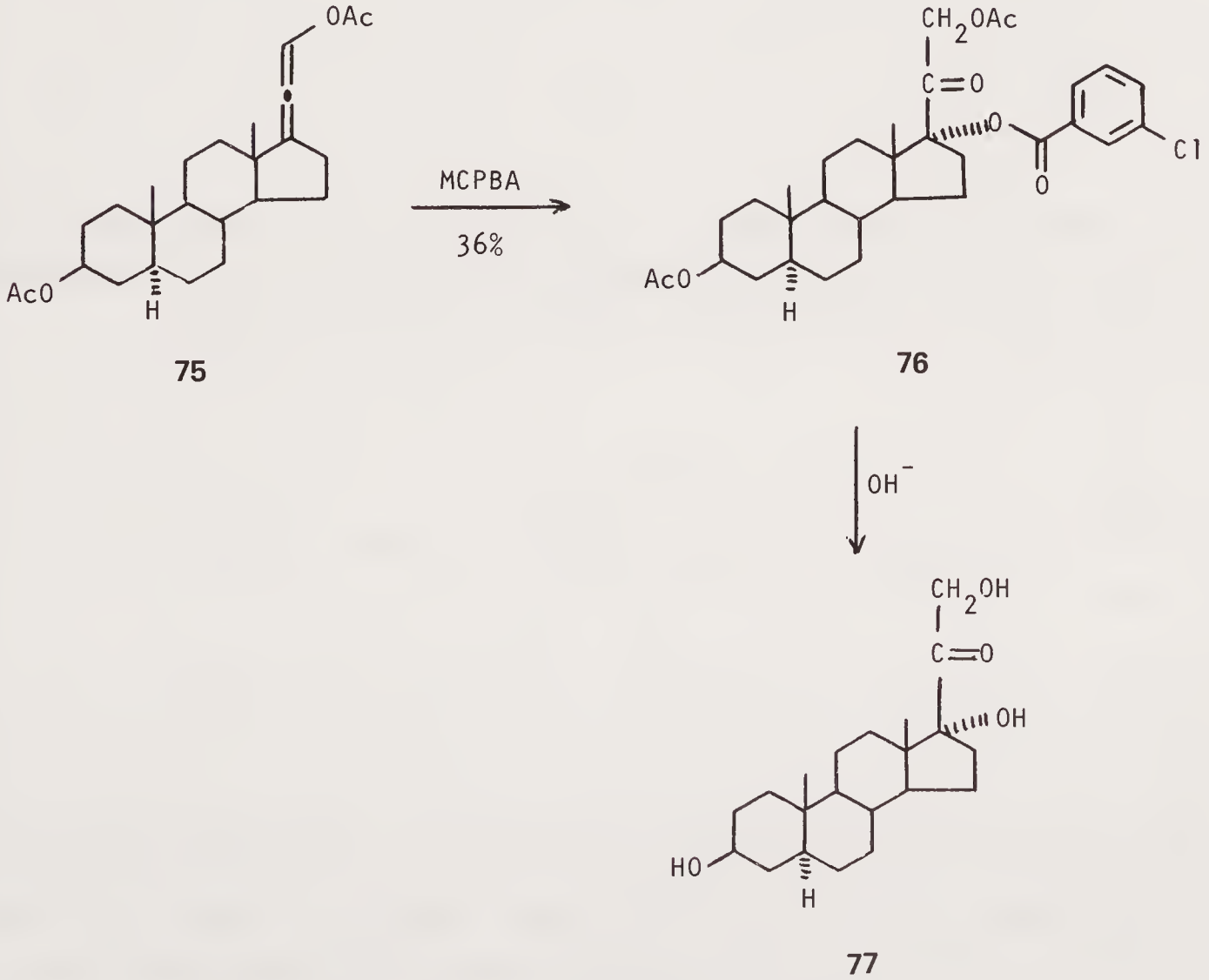
R_1-R_3 = H, alkyl (10)

Under alkaline hydrolysis conditions, acetoxyallenes are converted to α,β-unsaturated carbonyl derivatives. This transformation has been successfully applied to the synthesis of citral and dihydrocitral[36] (Scheme 15). When the hydrolysis is performed in acetone, α,β,γ,δ-unsaturated ketones are produced (e.g., pseudoionone **74a** and pseudoirone **74b**).



Scheme 15

The allene portion of the steroidal acetoxyallene **75** can be transformed into a corticoid chain (β-configuration) by peracid oxidation in the presence of disodium hydrogen phosphate.[37] The intermediate 17α-chlorobenzoate **76** is then converted to the triol **77** by mild alkaline hydrolysis.



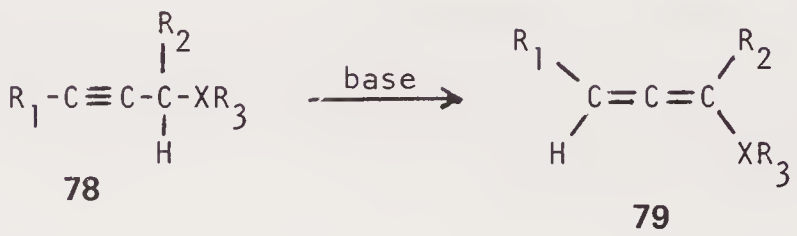
Scheme 16

7.2. SULFUR (AND SELENIUM)

In addition to oxygen, the other members of the group VI elements that have been successfully attached to an allene framework are sulfur, selenium, and tellurium. Of these three, sulfur is the most versatile owing to the variety of oxidation states the sulfur atom is capable of attaining.

7.2.1. Allenic Sulfides

Allenic sulfides, selenides, or tellurides are prepared by the base-catalyzed prototropic rearrangement of their propargyl derivatives **78**[38,39] (equation 11). Generally, catalytic amounts of either potassium or sodium alkoxides are used to promote the isomerization. The efficiency of the reaction depends on the base and follows the order $t\text{-}C_4H_9O^- \gg i\text{-}C_3H_7O^- > C_2H_5O^- \gg CH_3O^-$ with the potassium counterion being superior to sodium and lithium.[40]

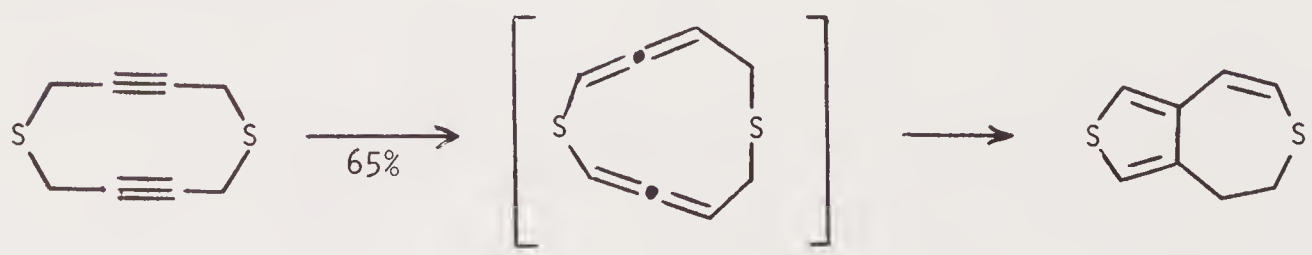


78 79 (11)

$R_1\text{-}R_3$ = H, alkyl, C_6H_5

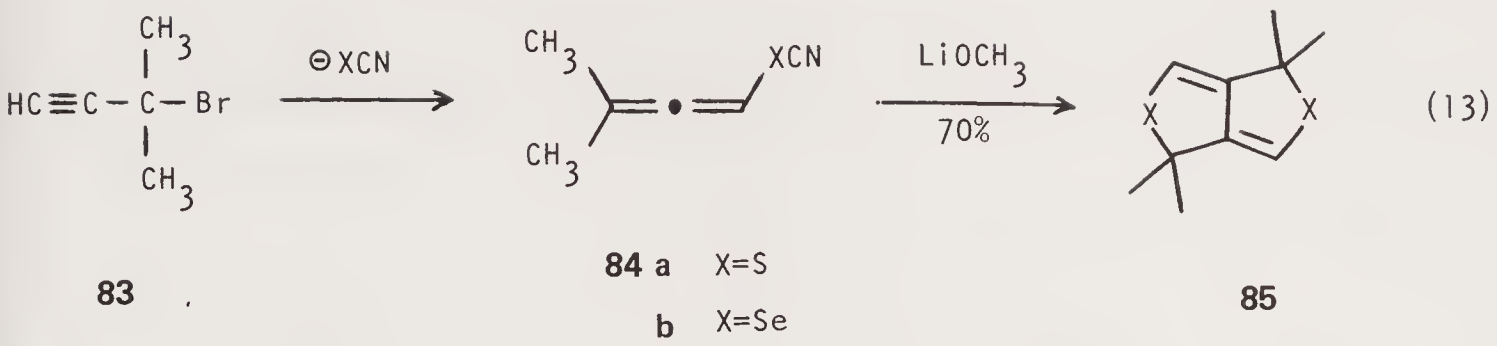
X = S, Se, Te

In a similar type transformation, 1,6-dithiacyclodeca-3,8-diyne (**80**), when treated with potassium *t*-butoxide, rapidly rearranges to the bicyclic thiophene **82** (equation 12). The conversion presumably proceeds through the diallene **81**.[41]



80 81 82 (12)

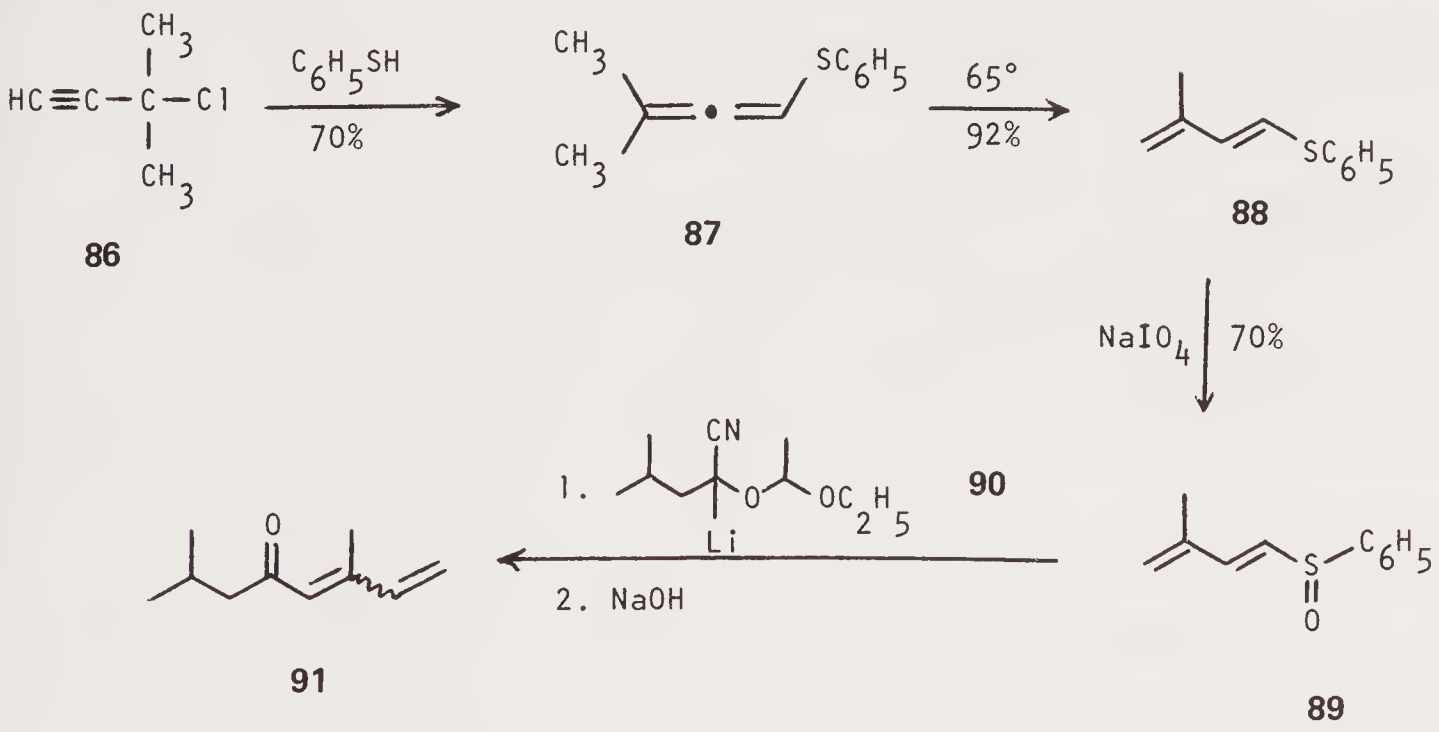
The S_N2' displacement reaction by thiocyanate or selenocyanate anion on 3-bromo-3-methyl-1-butyne (**83**) results in the formation of 3-methyl-1,2-butadienyl thiocyanate (**84a**) or its selenium analog **84b**. When **84** is exposed to lithium methoxide in THF (8 hours), 1,1,4,4-tetramethyl-1H,4H-thieno[3,4-c]thiophene (**85a**) or its diselenium derivative **85b** is obtained[42] (equation 13).



(13)

83 **84** a X=S b X=Se **85**

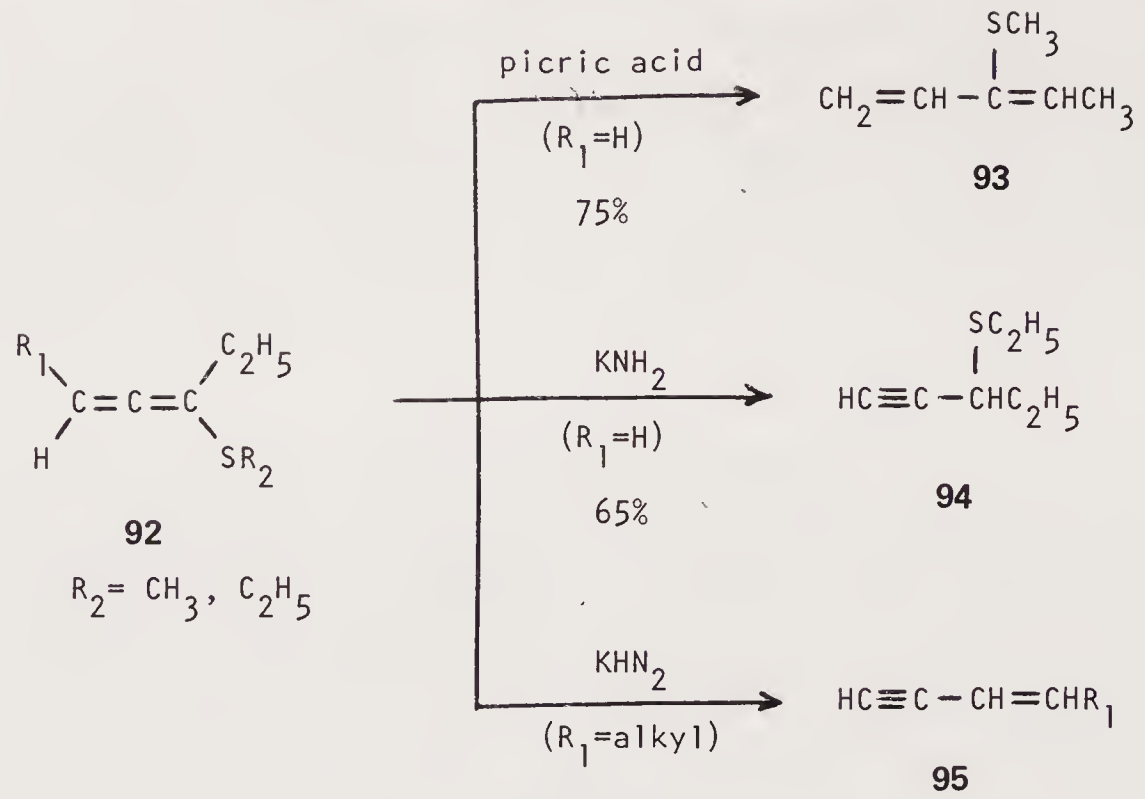
In certain reactions 3-methyl-1,3-butadienyl phenyl sulfoxide (**89**) can be considered as an isoprenic carbonium ion equivalent. This synthetically useful intermediate is available in three steps from the reaction of 3-chloro-3-methyl-1-butyne (**86**) with either thiophenol (under phase transfer conditions)[43,44] or phenylthiocopper trimethylphosphite complex in TMEDA.[45] The resulting allenic sulfide **87** can be cleanly isomerized to **88** when heated for 2 hours in *sym*-tetrachloroethane. Subsequent oxidation with a peracid or sodium metaperiodate then gives **89**. The reaction of **89** with **90** followed by deprotection and hydrolysis, furnishes a mixture of the (E)- and (Z)-tagetones **91** (ratio 55:45) in 50% overall yield from **89**[43] (Scheme 17).



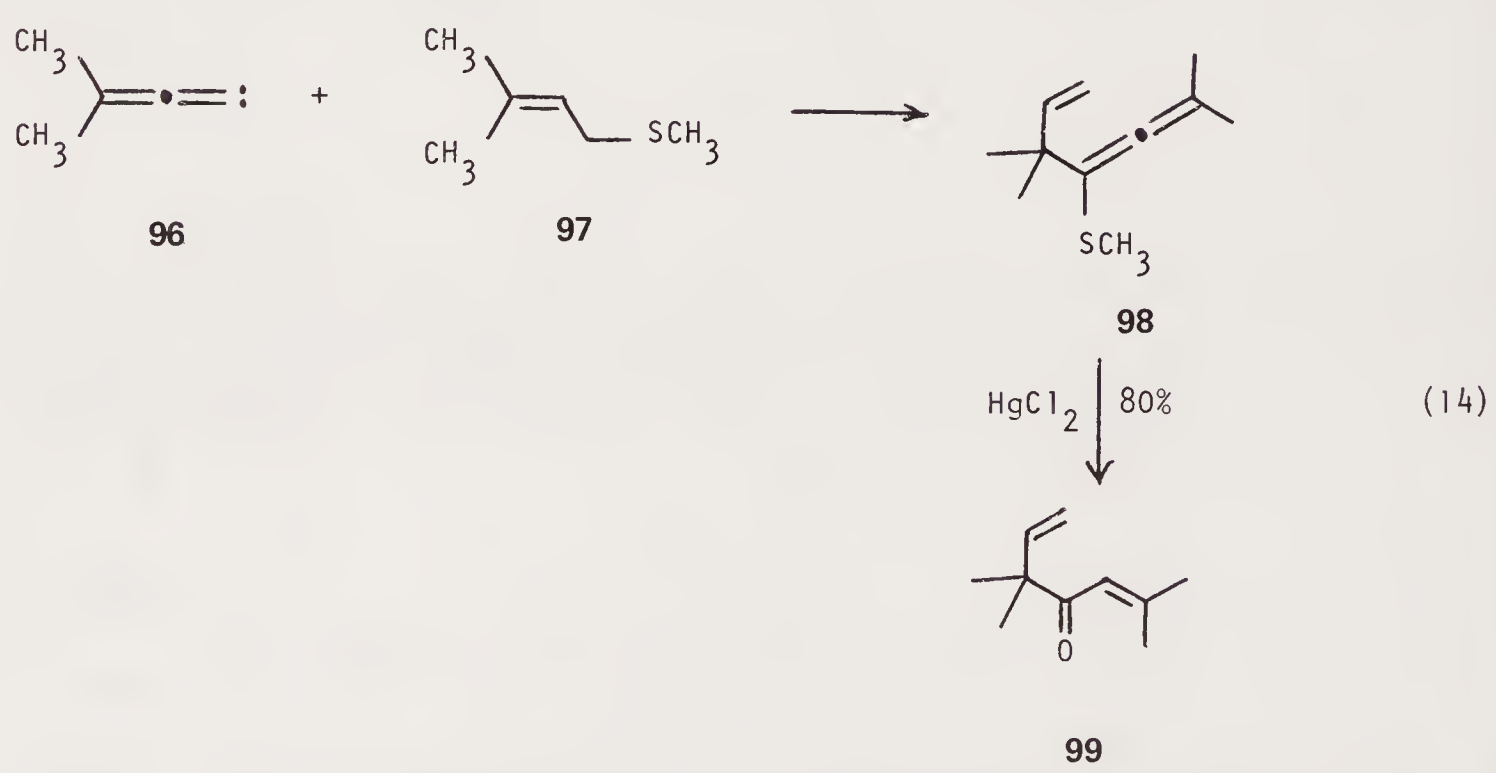
86 **87** **88** **89** **91**

Scheme 17

Allenic sulfides are not only prone to isomerization under thermal conditions (as shown by the **87** → **88** conversion), but also under acid or base catalysis as shown in Scheme 18. The addition of 100 mg of picric acid to 0.4 mole of **92** at room temperature exothermically produces the 1,3-diene **93**.[46] Terminal allenic sulfides rearrange to 2-alkynyl thioethers (e.g., **94**) in the presence of 1 equivalent of potassium amide,[47] however, when the corresponding internal allenes **92** (R_1 = alkyl) are treated with 2 equivalents of potassium amide, 1,3-enynes **95** are produced in excellent yields.[48]

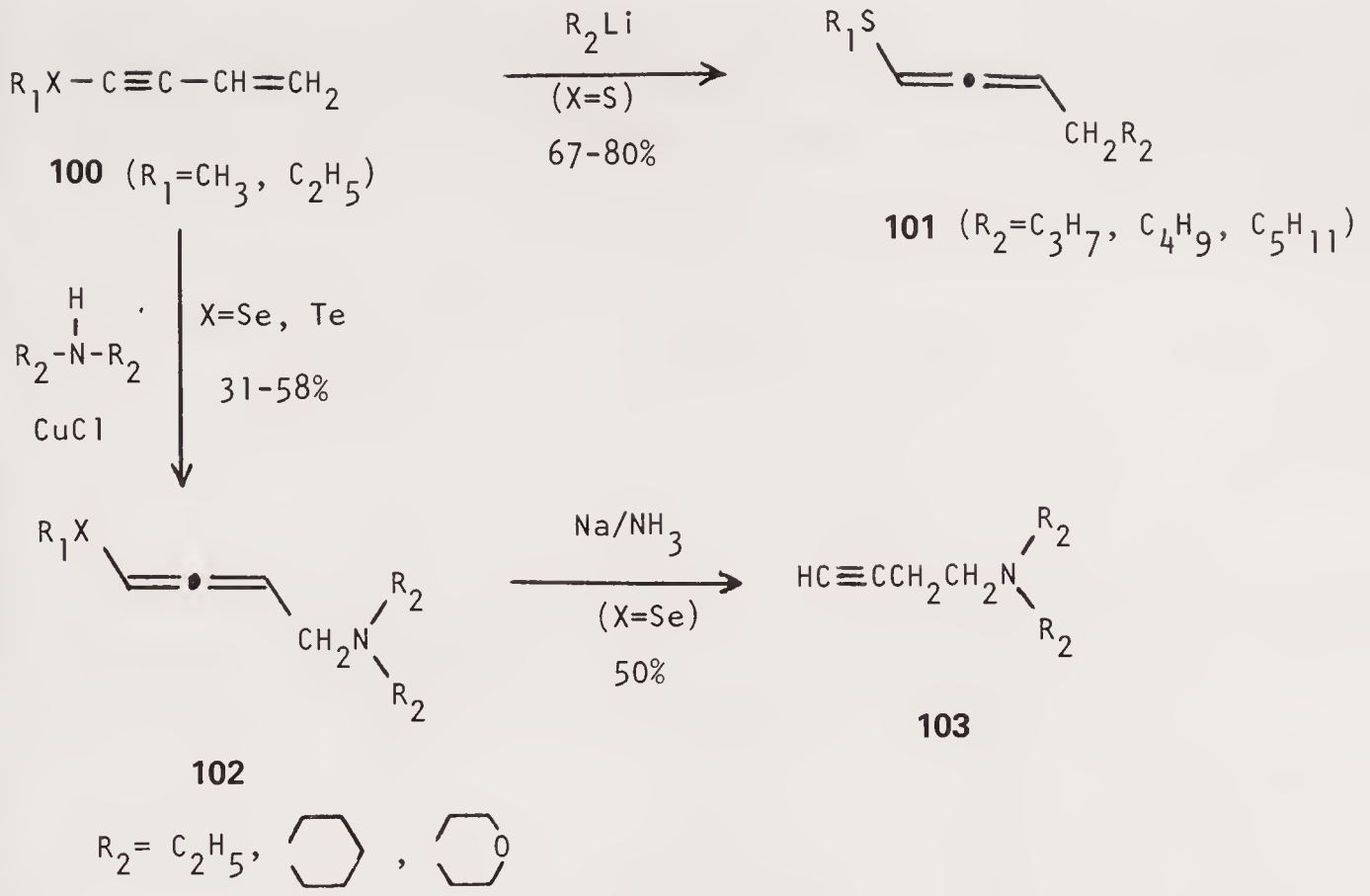


Scheme 18



Artemisia ketone (**99**), a naturally occurring monoterpene, is easily synthesized by way of an allenic sulfide intermediate (equation 14). The requisite allene **98** is formed from the reaction of dimethylallene carbene **96** with methyl 3-methyl-2-butenyl sulfide (**97**). Hydrolysis of **98** with mercuric chloride in aqueous acetonitrile furnishes the natural product in good yield.[49]

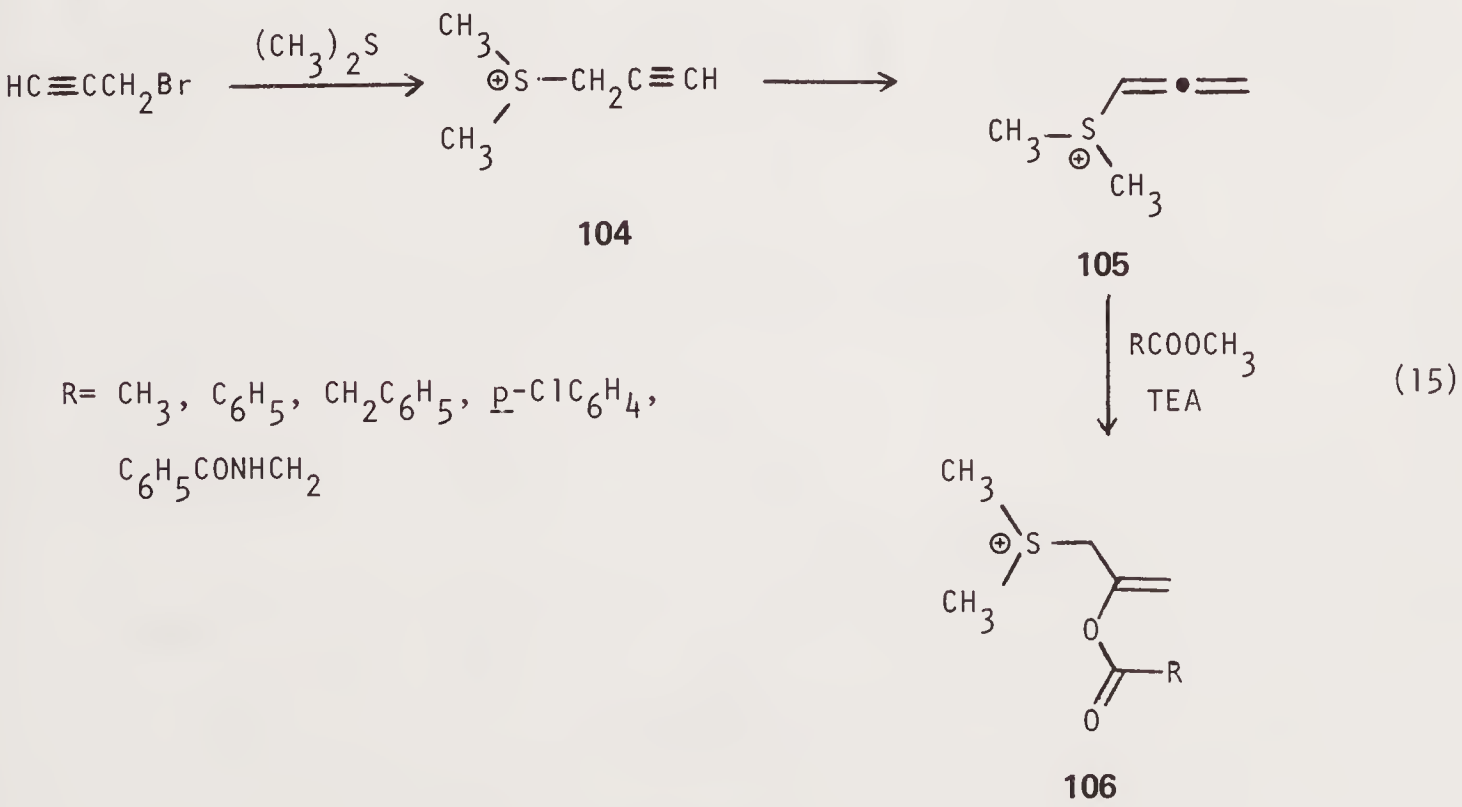
The ability of vinylacetylenes to undergo 1,4-addition of nucleophiles makes them attractive candidates for the preparation of group VI substituted allenes. Lithium alkyls add to the terminus of alkylthiovinylacetylenes **100** to give internal allenic thioethers **101**.[50] The analogous alkylselenovinylacetylenes (**100**, X = Se) suffer attack at the selenium atom. Secondary amines react with vinylacetylenic selenides and tellurides in the presence of catalytic amounts of cuprous chloride to form derivatives **102** in moderate yields. The 1-alkylseleno-4-dialkylamino-1,2-butadienes (**102**, X = Se) are readily cleaved by sodium in liquid ammonia at the



Scheme 19

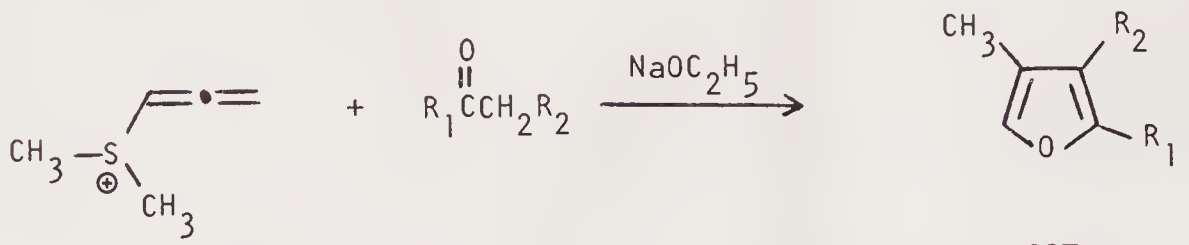
carbon–selenium bond to give 4-dialkylamino-1-butynes **103** by way of a Favorskii rearrangement[51] (Scheme 19).

Allenic sulfonium salts are susceptible to the addition of nucleophiles and are useful intermediates in organic synthesis. Dimethylpropadienylsulfonium bromide (**105**) is conveniently prepared by the treatment of propargyl bromide with dimethyl sulfide. The initially formed dimethyl-2-propynylsulfonium bromide (**104**) readily isomerizes to **105** under neutral conditions (5 hours) or in the presence of an equimolar amount of triethylamine (5 minutes).[52] Compound **105** adds acids at the central carbon to give the vinyl esters **106** that are useful as acylating agents for amines and alcohols. The entire acylation procedure can be carried out in one flask starting from propargyl bromide.



(15)

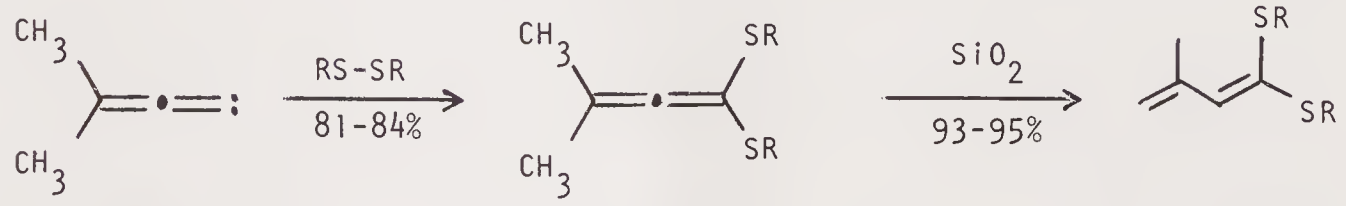
Sulfonium salt **105** also reacts with β-ketoesters, β-ketosulfones, or β-diketones in the presence of 1 equivalent of sodium ethoxide to give furan derivatives **107** in good yields (equation 16). Again, the entire sequence can be performed as a one-pot procedure.[53]



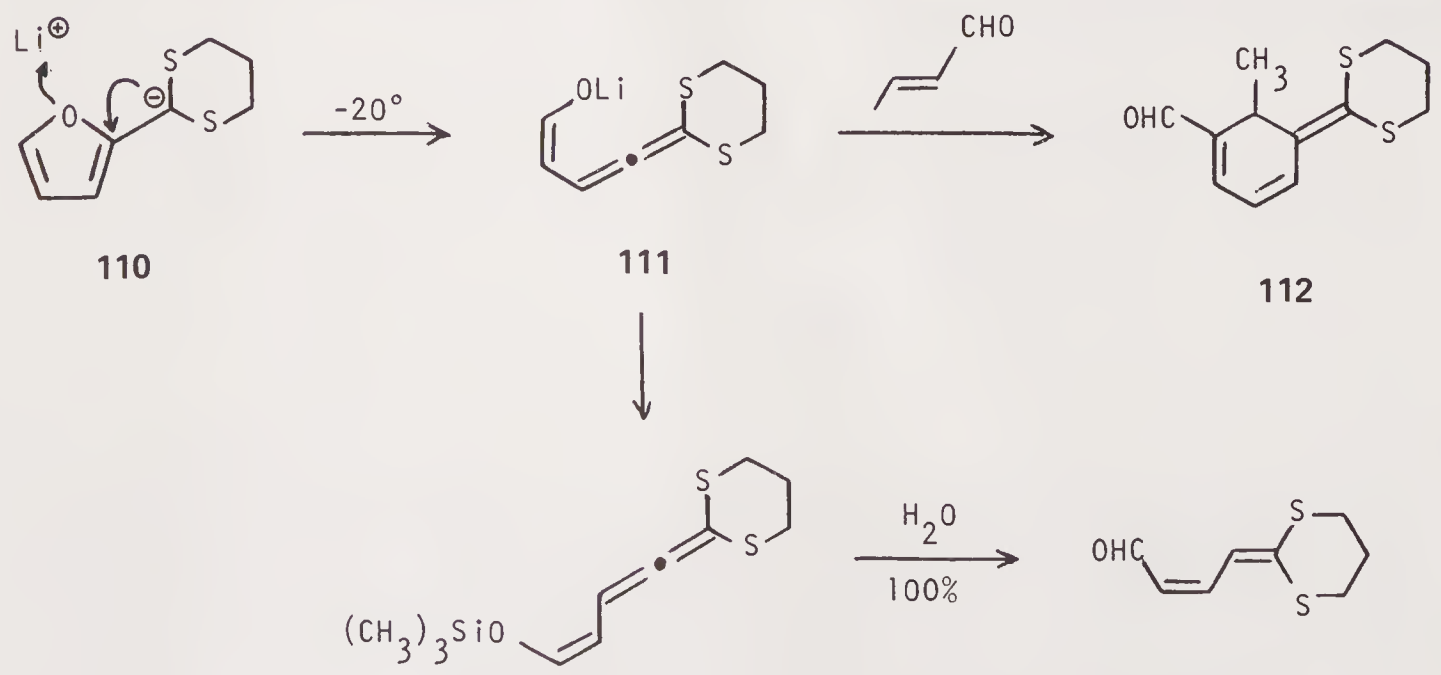
(16)

R_1	R_2	Yield (%)
CH_3	$COOC_2H_5$	86
CH_3	$COCH_3$	89
C_6H_5	COC_6H_5	72
CH_3	$SO_2C_6H_4CH_3$	78

Dimethylallene carbene (**96**) reacts with disulfides to give allenic dithioacetals **108** (equation 17). When solutions of **108** are filtered through silica gel, they efficiently isomerize to conjugated ketene dithioacetals **109**.[44,54]



(17)

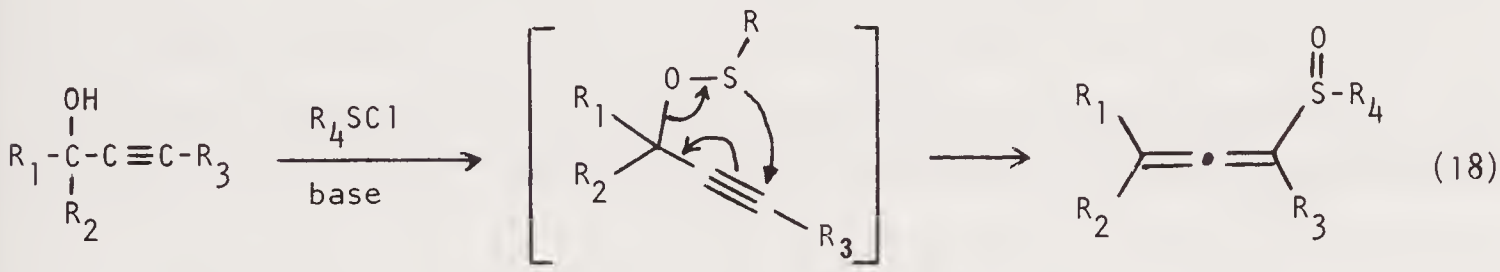


Scheme 20

2-(2-Furyl)-2-lithio-1,3-dithiane (**110**), while stable at −78°C, rearranges at −20°C to form the interesting allene dithioacetal **111** (Scheme 20). Quenching the anion **111** with trimethylchlorosilane followed by aqueous workup produces the *cis*-unsaturated aldehyde **114** in quantitative yield. The addition of crotonaldehyde to **111** results in the formation of **112**, apparently by means of a Diels–Alder reaction followed by elimination of water.[55]

7.2.2. Allenic Sulfoxides

Allenic sulfoxides (**117**) are readily prepared by a [2,3]sigmatropic rearrangement of sulfenic esters (**116**) of propargyl alcohols **115** (equation 18).[56–58] The esters **116** are rarely isolable and spontaneously isomerize to give the allene.

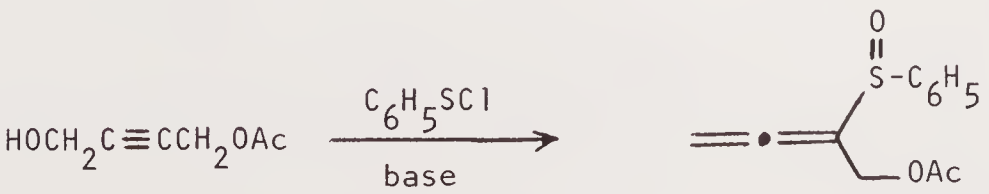


115 **116** **117** (18)

base: triethylamine, pyridine

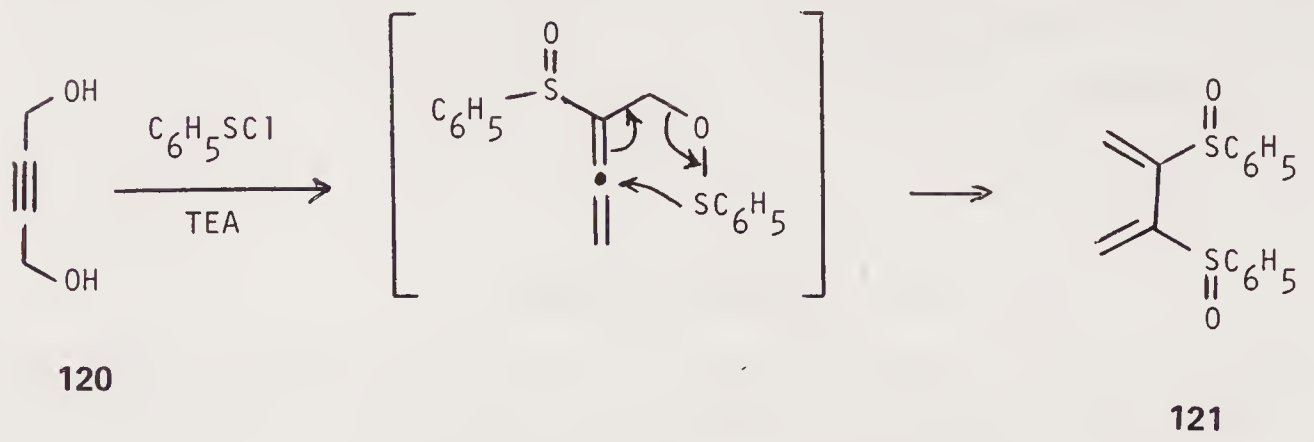
R_1	R_2	R_3	R_4	Yield (%)	Reference
H	H	H	*o*-$NO_2C_6H_4$	96	56
CH_3	H	H	*p*-$CH_3C_6H_4$	75	56
C_6H_5	H	H	CCl_3	90	56, 59
CH_3	CH_3	H	C_6H_5	48	57
—$(CH_2)_5$—		H	*p*-$CH_3C_6H_4$	84	56, 57
H	H	CH_3	*p*-$CH_3C_6H_4$	82	56

In an analogous transformation, 4-acetoxy-2-butyne-1-ol (**118**), when treated with benzenesulfenyl chloride in the presence of diisopropylethylamine, gives **119** in 70% yield[60] (equation 19).



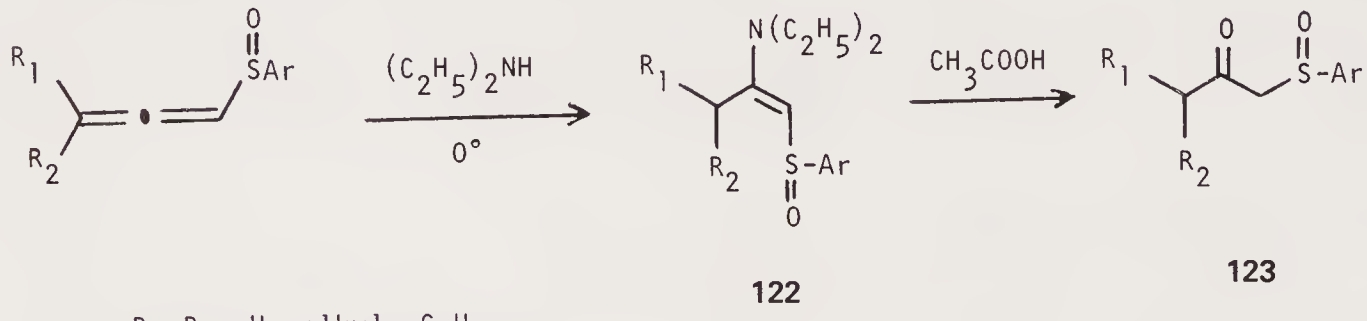
118 **119** (19)

When the scope of the reaction is extended to include 2-butyne-1,4-diol (**120**), a double [2,3]sigmatropic rearrangement occurs to produce 2,3-di(phenylsulfinyl)-1,3-butadiene (**121**) directly in 76% yield[61] (equation 20).



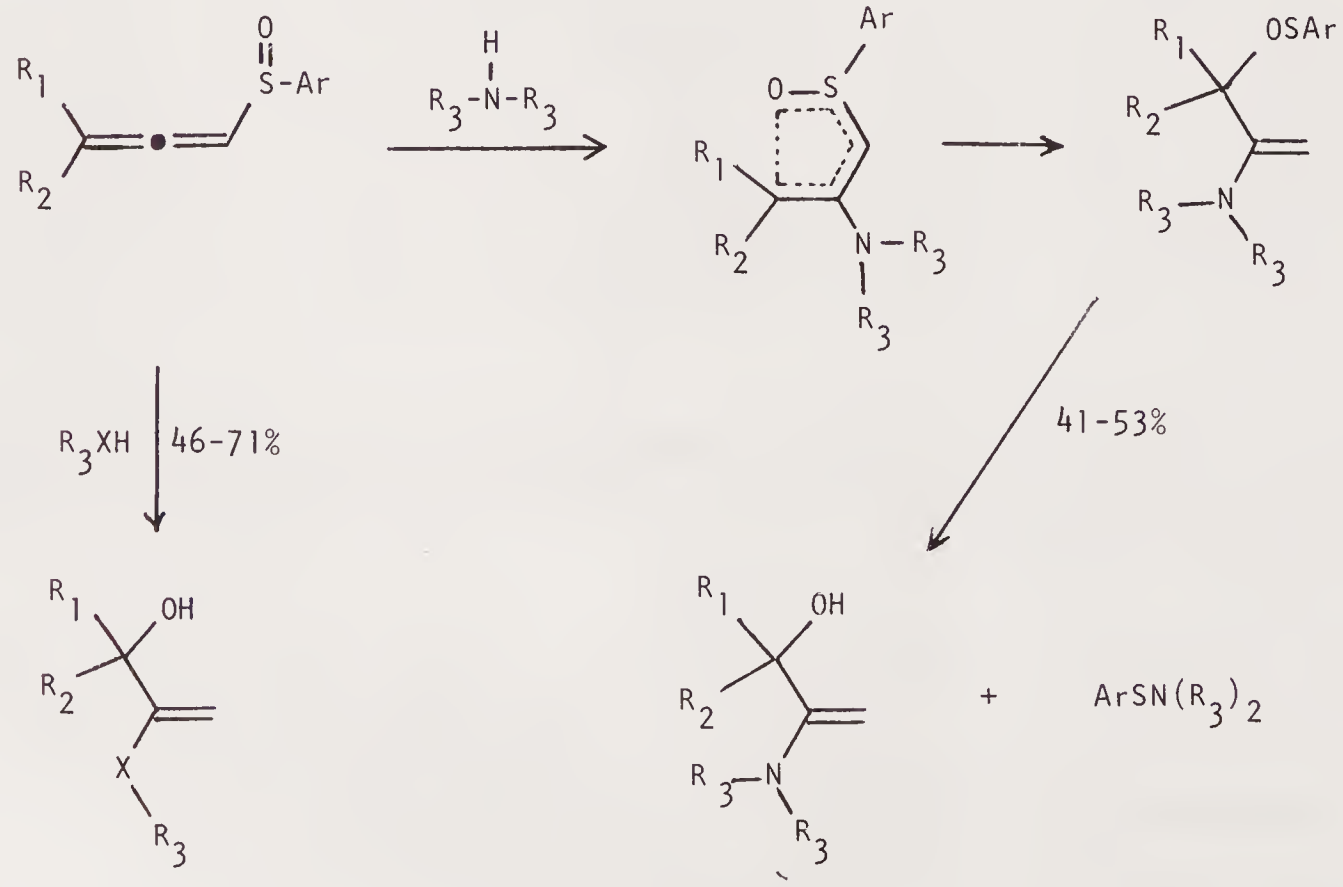
120 **121** (20)

Owing to the activating influence of the sulfoxide group, the allene skeleton becomes susceptible to nucleophilic attack at its central carbon atom. The addition of equimolar amounts of diethylamine[56] or piperidine[62] to allenic sulfoxides results in the formation of enamines **122** that can be easily converted to β-keto sulfoxides **123** upon acid hydrolysis (equation 21). Overall yields range from 50 to 86%.



122 **123**

R_1, R_2 = H, alkyl, C_6H_5

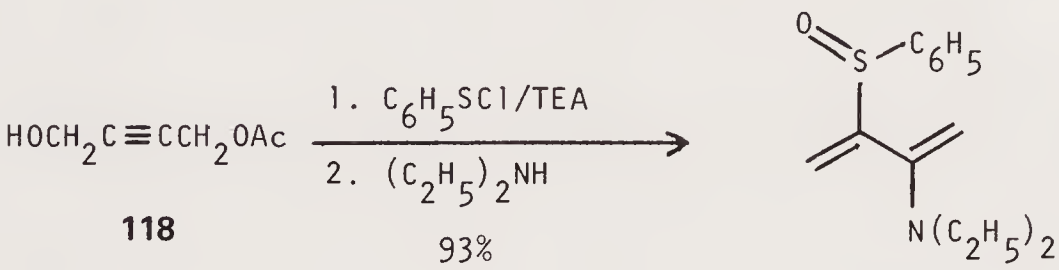


125 (X= O, S) **124**

Scheme 21

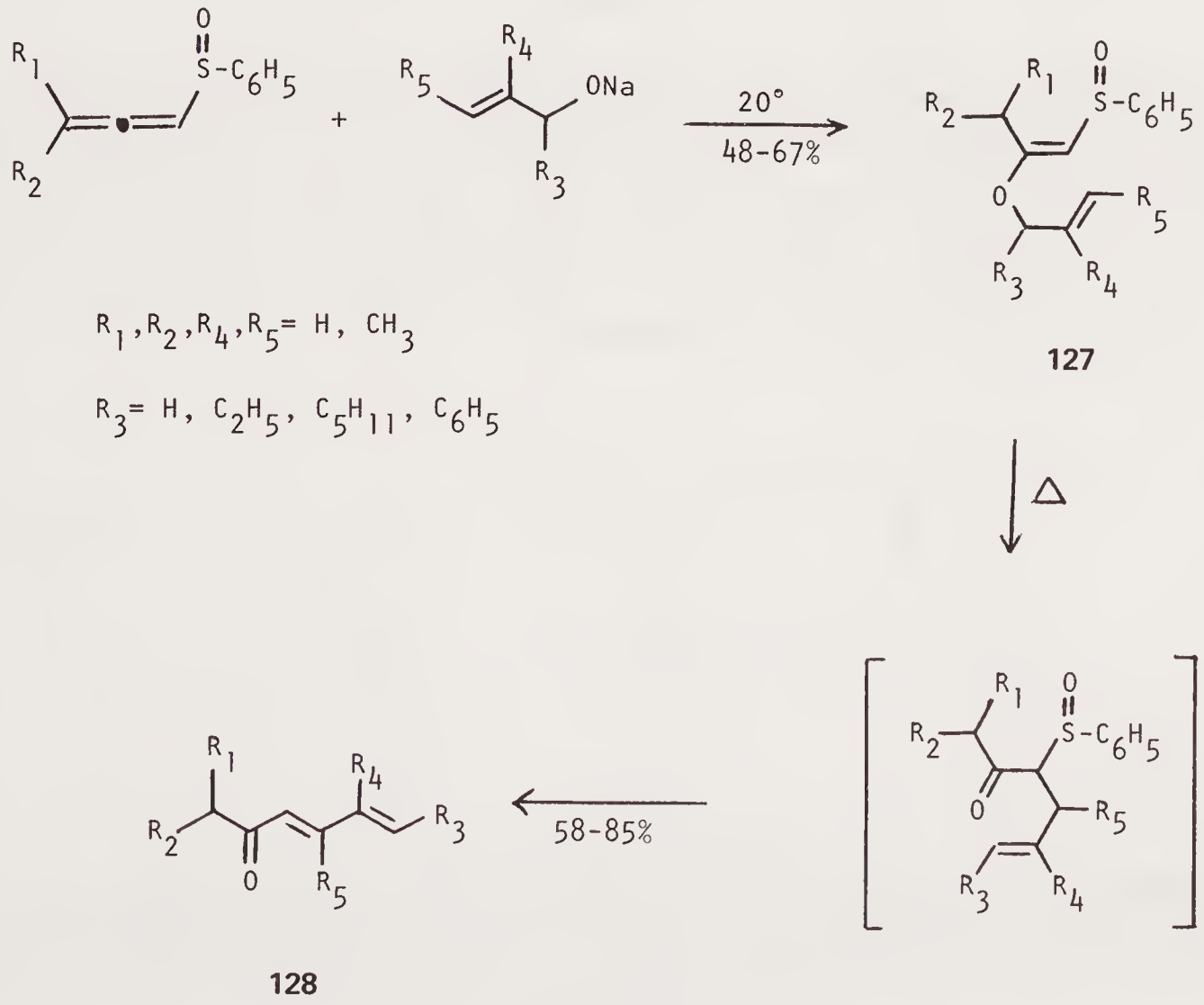
When the amine is used as the solvent, the reaction proceeds further and produces enamines **124**, as shown in Scheme 21.[57] Addition of alkoxides or thiolates to allenic sulfoxides in alcoholic solvents at elevated temperatures affords vinyl ethers or thioethers **125** by the same mechanistic pathway.

The interestingly substituted butadiene derivative **126** can be prepared in a one-pot procedure by the sequential treatment of **118** with triethylamine, benzenesulfenyl chloride, and two equivalents of diethylamine[60] (equation 22).



118 **126** (22)

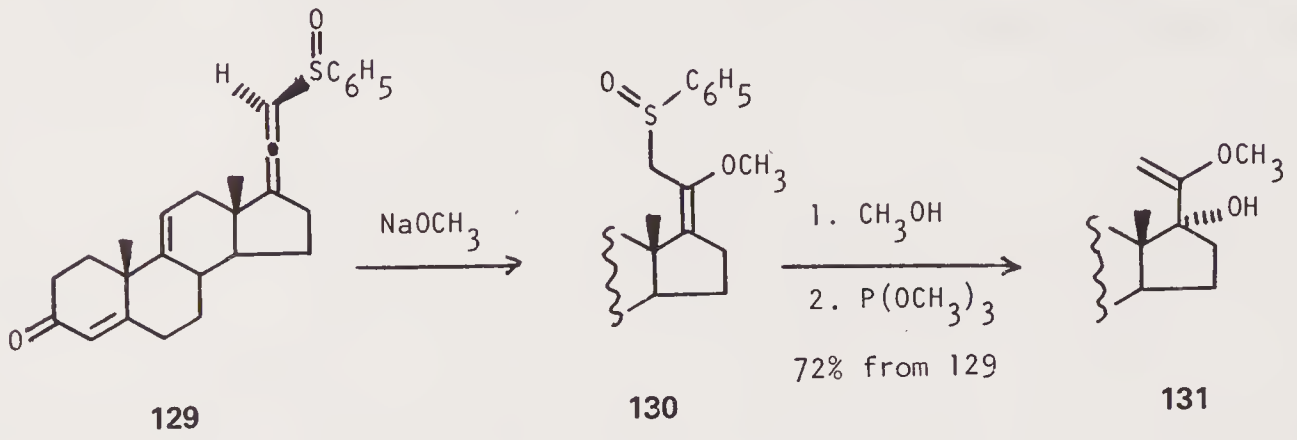
In contrast to the formation of vinyl ethers **125**, sodium alkoxides (one molar equivalent) add to allenic sulfoxides at room temperature to give α,β-unsaturated sulfinyl enol ethers. Under these stoichiometric proportions, primary and secondary allyl alcohols add to allenyl phenyl sulfoxides to form adducts **127** (Scheme 22). Distillation of **127** from zinc carbonate induces Claisen rearrangement and elimination of benzenesulfenic acid to produce dienones **128**.[63]



127 **128**

Scheme 22

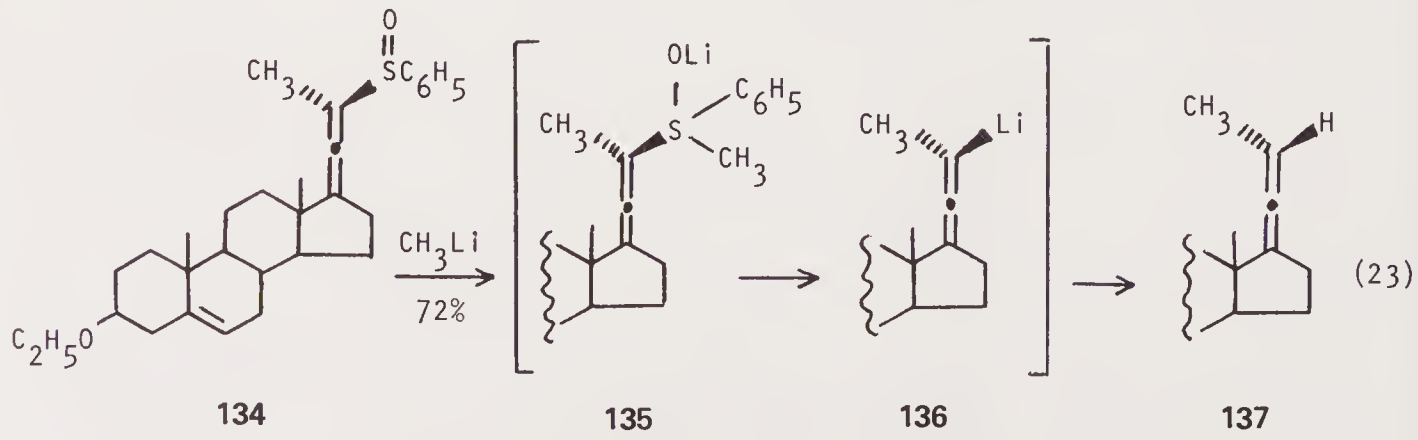
Corticosteroids, an important class of antiinflammatory agents, possess a dihydroxyacetone side chain at C-17. An efficient synthesis of hydrocortisone acetate (**133**) makes use of the conjugate addition of sodium methoxide to the steroidal allenic sulfoxide **129**. The resulting enol ether **130** is then elaborated to the desired product according to the route shown in Scheme 23.[64]



129 **130** **131** **132** **133**

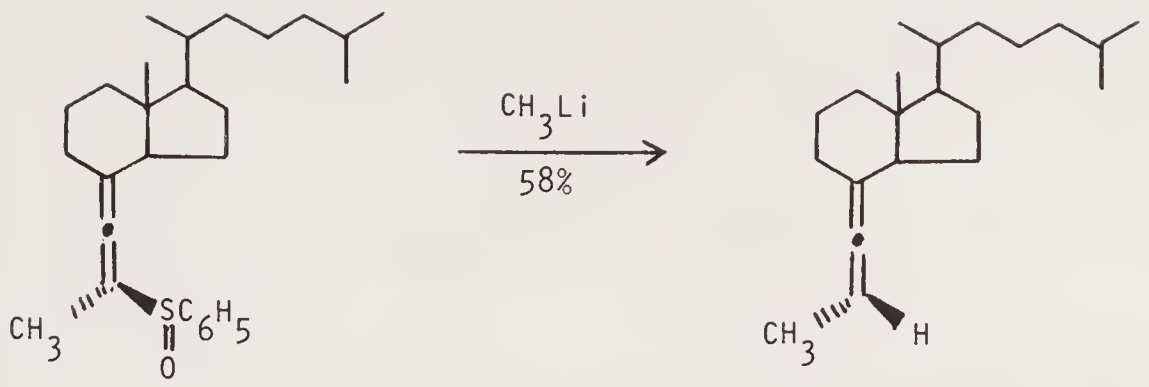
Scheme 23

Methyllithium nucleophilically attacks the sulfur atom of allenic sulfoxides and affords a stereospecific route to sulfur-free allenes. The steroidal allene **134** is rapidly converted to **137** upon treatment with 4 equivalents of methyllithium at −78°C for 10 minutes[65] (equation 23). The driving force for such a reaction is that, in the initial intermediate **135**, the lithioallene **136** is a much better leaving group than is either methyl or phenyllithium.



134 **135** **136** **137**

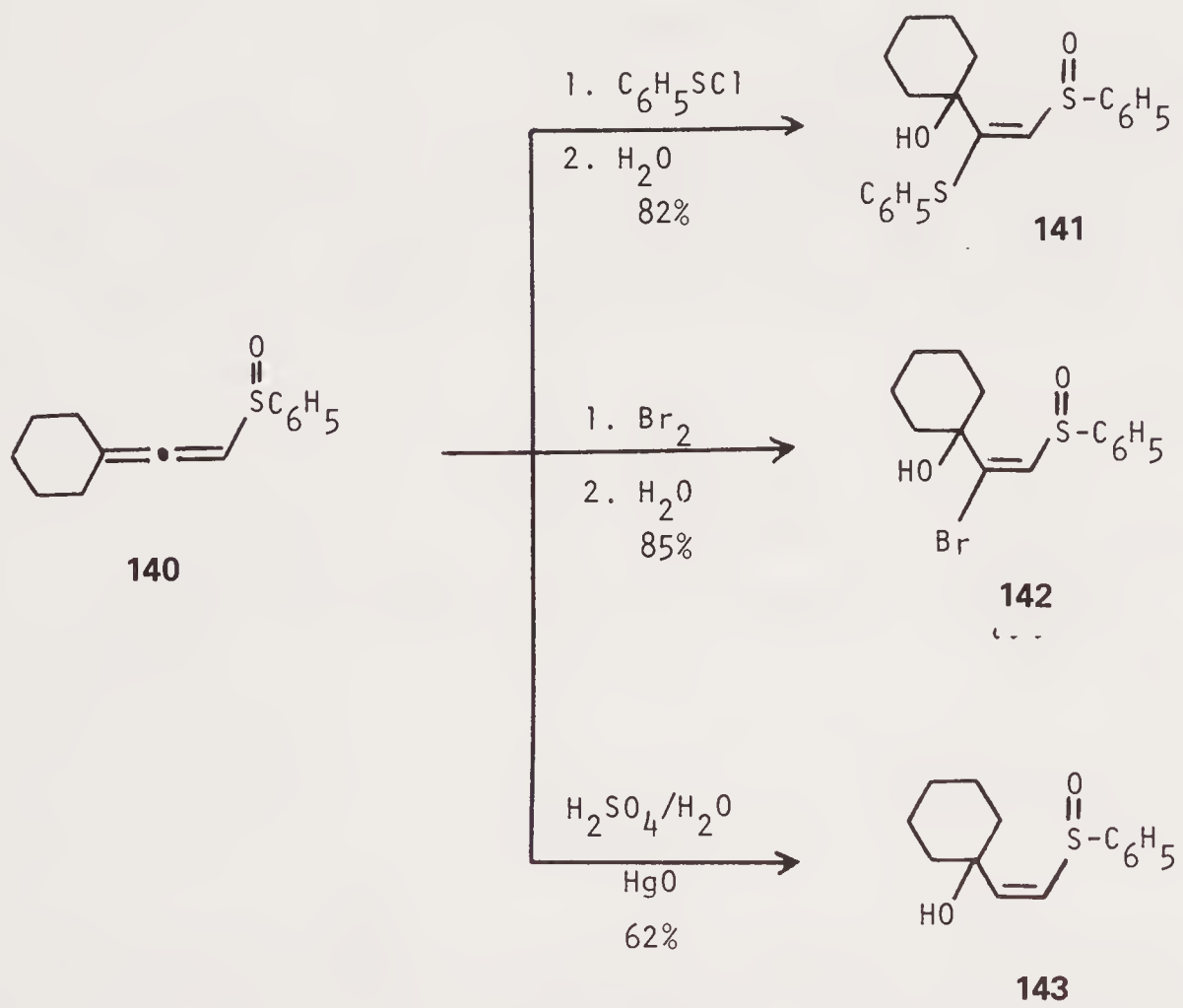
Analogously, the transformation, when performed on the steroidal C/D ring fragment **138**, gives rise to the formation of only the (6R)-allene **139**[66] (equation 24).



(24)

138 **139**

Allene sulfoxides are also susceptible to attack by electrophilic reagents (Scheme 24). The cyclohexylallene **140** adds electrophiles such as benzenesulfenyl chloride or bromine to the allene double bond furthest from the hetero atom. The resulting alkoxysulfonium halides are then hydrolyzed to the ethylene derivatives **141** or **142**, which possess an intramolecular hydrogen bond. In the presence of mercuric oxide, **140** adds water to the $\Delta^{2,3}$-bond to give **143**.[57]

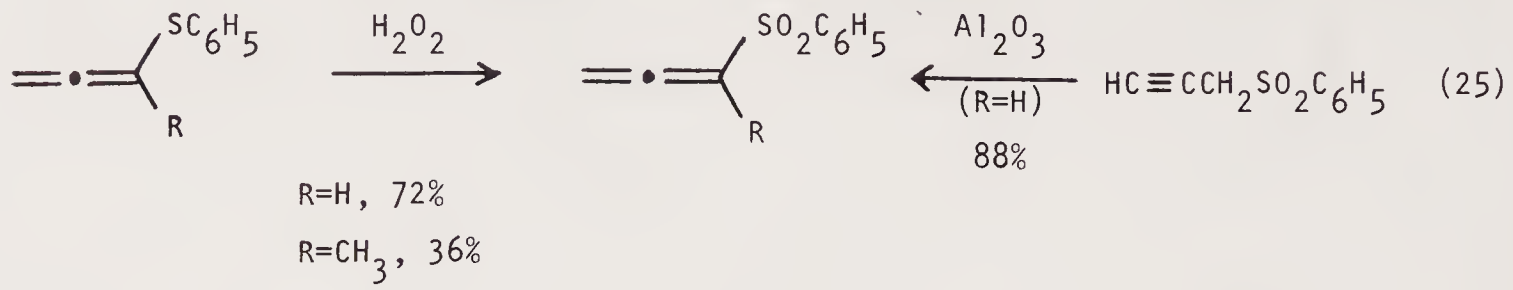


Scheme 24

7.2.3. Allenic Sulfones

Proceeding to the next oxidation state, allenic sulfones exhibit properties similar to those of the previously discussed sulfoxide derivatives. Obvious methods for

their preparation are the oxidation of an allenic sulfide[67] or sulfoxide,[62] or the base-catalyzed isomerization of a propargyl sulfone[68] (equation 25).



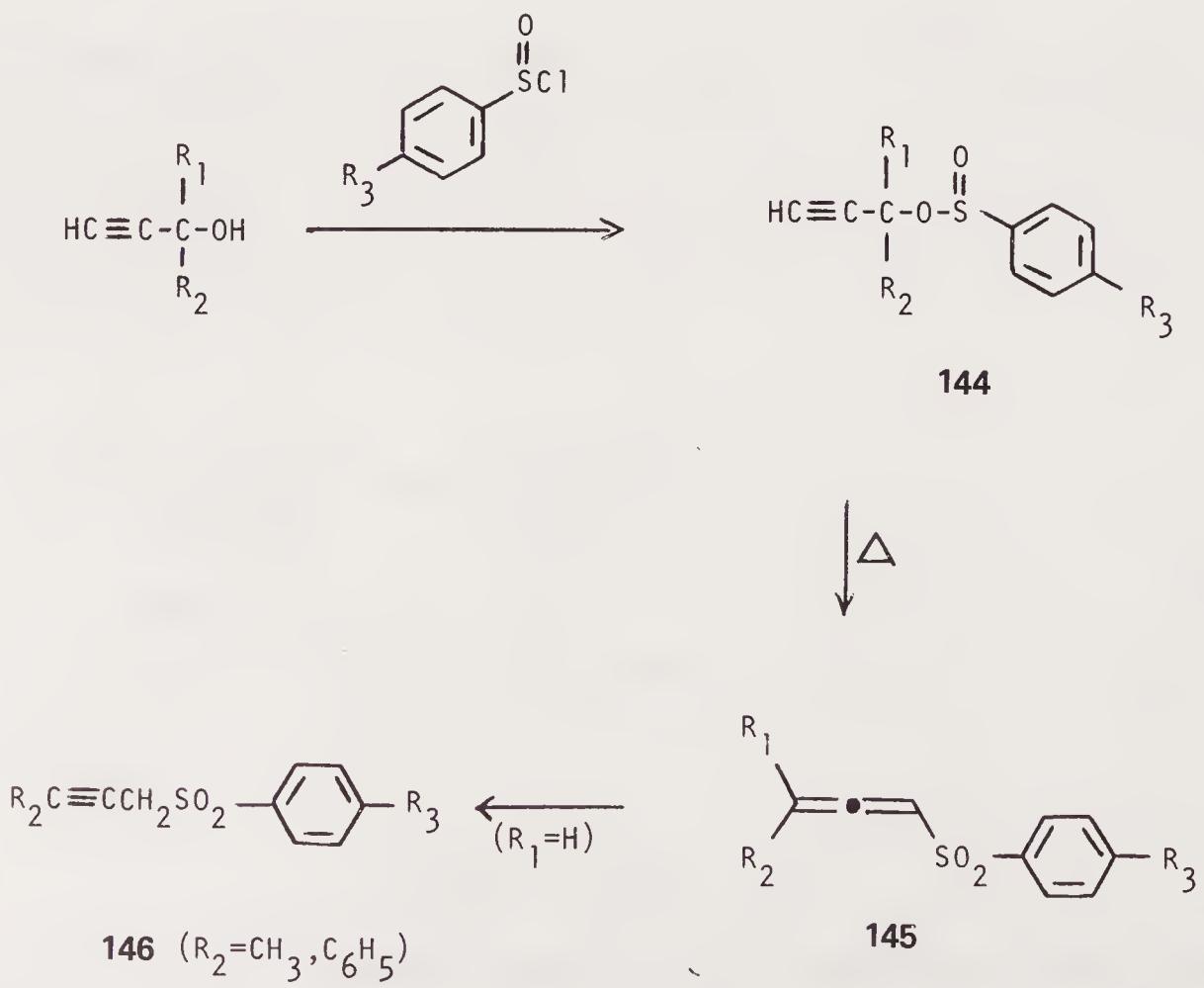
(25)

However, a shorter and more direct route involves a thermal [2,3]sigmatropic rearrangement of a propargyl arenesulfinate **144** (Scheme 25). The driving force for the sulfinate → sulfone isomerization is the formation of the strong sulfur–oxygen bond in the developing sulfonyl group.[69]

The reaction can be performed either under neutral conditions by heating **144** in chlorobenzene at 130°C,[70,71] or in the presence of 2,6-lutidine in refluxing ethanol.[69,72] A potential drawback to the base-catalyzed method occurs when α-monosubstituted propargyl esters (**144**, R_1 = H) are used; further [1,3]prototropic shift can occur to give propargyl sulfones **146**. In fact, when internal allene **145** (R_1 = H,R_2 = R_3 = CH_3) is chromatographed on a column of alumina, complete isomerization to **146** occurs.[71]

This isomerization is interesting because of its direct contrast to the alumina-promoted conversion of propargyl sulfone to allene in equation (25). It appears that in this series the thermodynamic stability follows the order

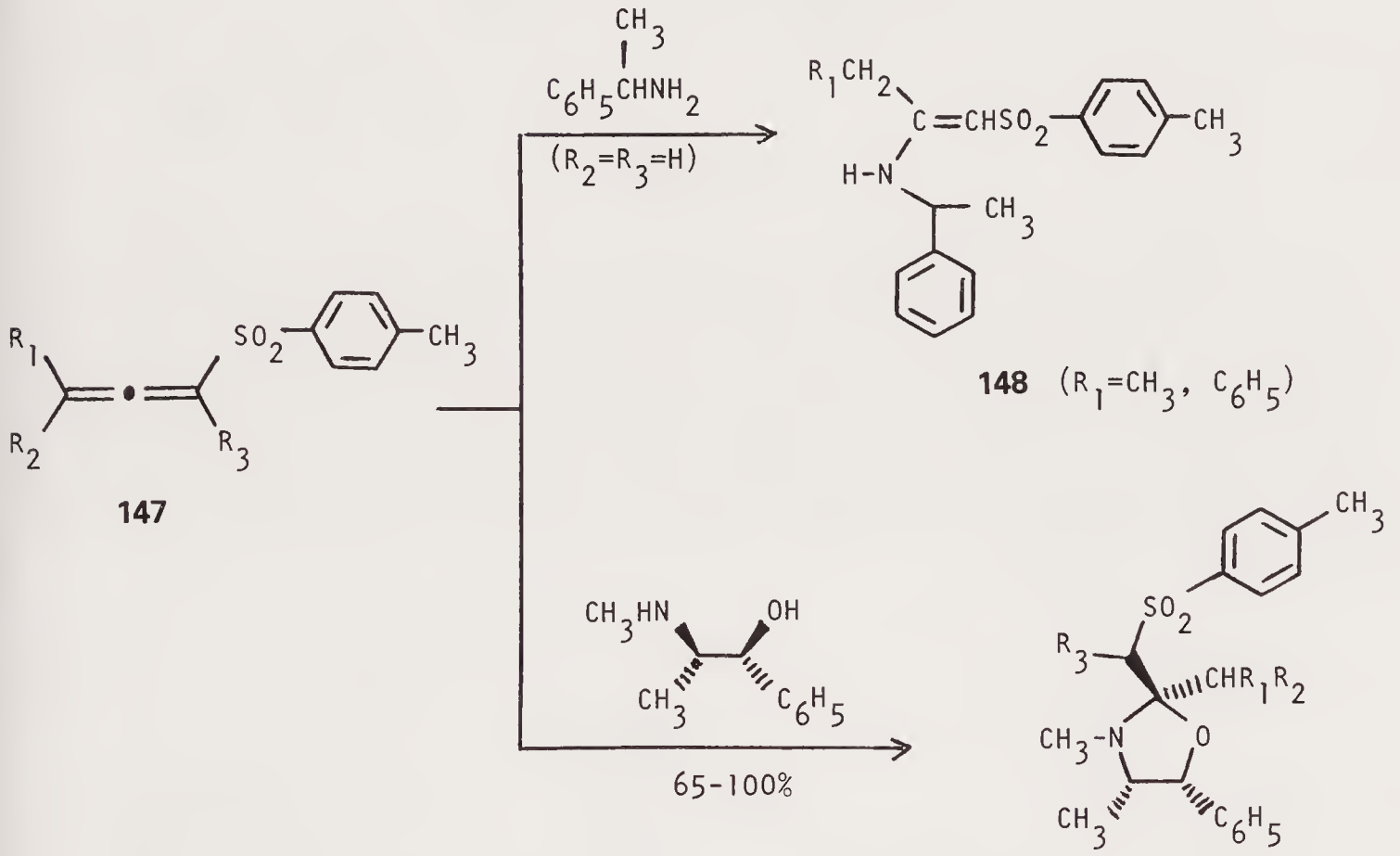
$$R{-}C{\equiv}C{-}CH_2SO_2R > RCH{=}C{=}CHSO_2R > HC{\equiv}C{-}CH_2SO_2R.$$



Scheme 25

R_1	R_2	R_3	Yield **145** (%)	Reference
H	H	CH_3	80	70
CH_3	CH_3	H	99	69
H	CH_3	CH_3	46	71

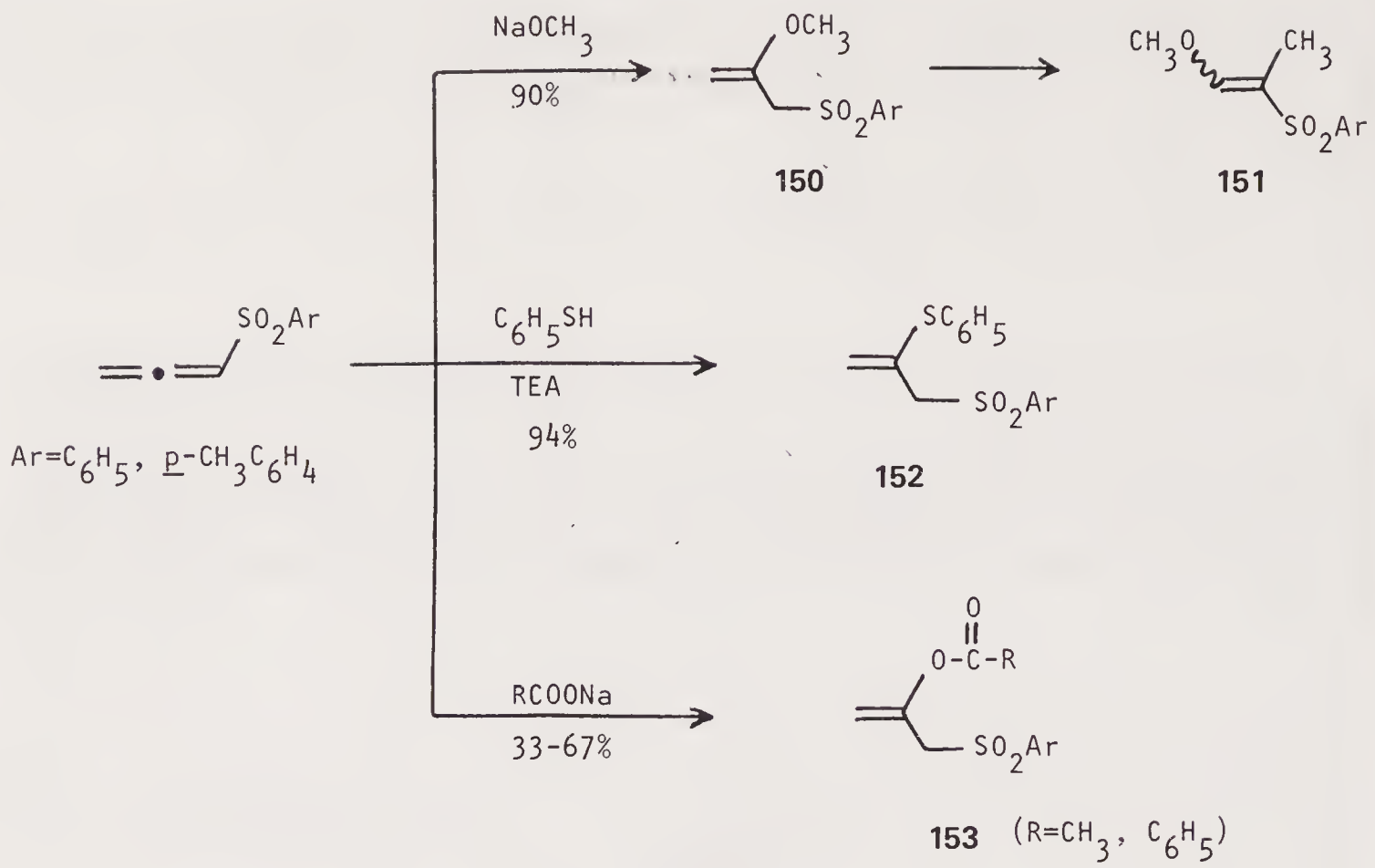
By taking advantage of the strong activation of the allene system by the sulfonyl group toward nucleophilic addition, racemic sulfonyl allenes can be partially resolved by reaction with a deficiency of an optically active amine.[73] The treatment of **147** with (+)-α-methylbenzylamine (2:1 ratio) results in the formation of enamine **148** with the recovered **147** being enriched in the (R)-enantiomer to the extent of 70%.



Scheme 26

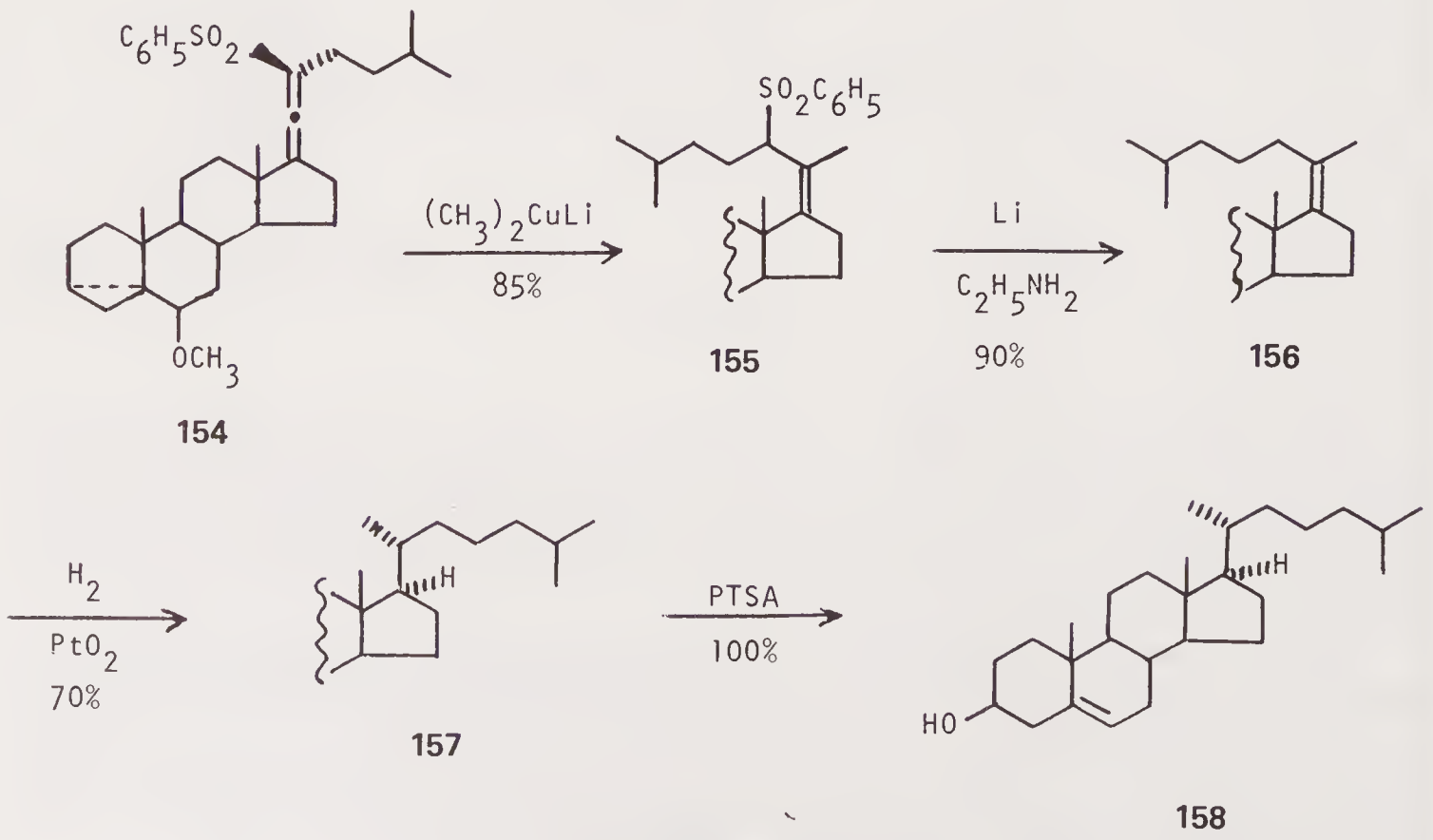
Allenes **147** also react with (−)-ephedrine to produce 1,3-oxazolidines **149** in high yield.[74] The reaction occurs in a stereospecific fashion and proceeds by way of initial formation of a conjugated enamine followed by cyclization (on the same carbon) with the hydroxyl group.

Further examples of additions of simple nucleophiles to sulfonyl allenes are summarized in Scheme 27.[68,75,76] In reactions with sodium methoxide, the isolated product is dependent on the concentration of the base. When 0.01N methanolic sodium methoxide is used, 2-methoxy-3-phenylsulfonylpropene (**150**) only is produced, whereas at higher concentrations **150** slowly isomerizes to **151**.



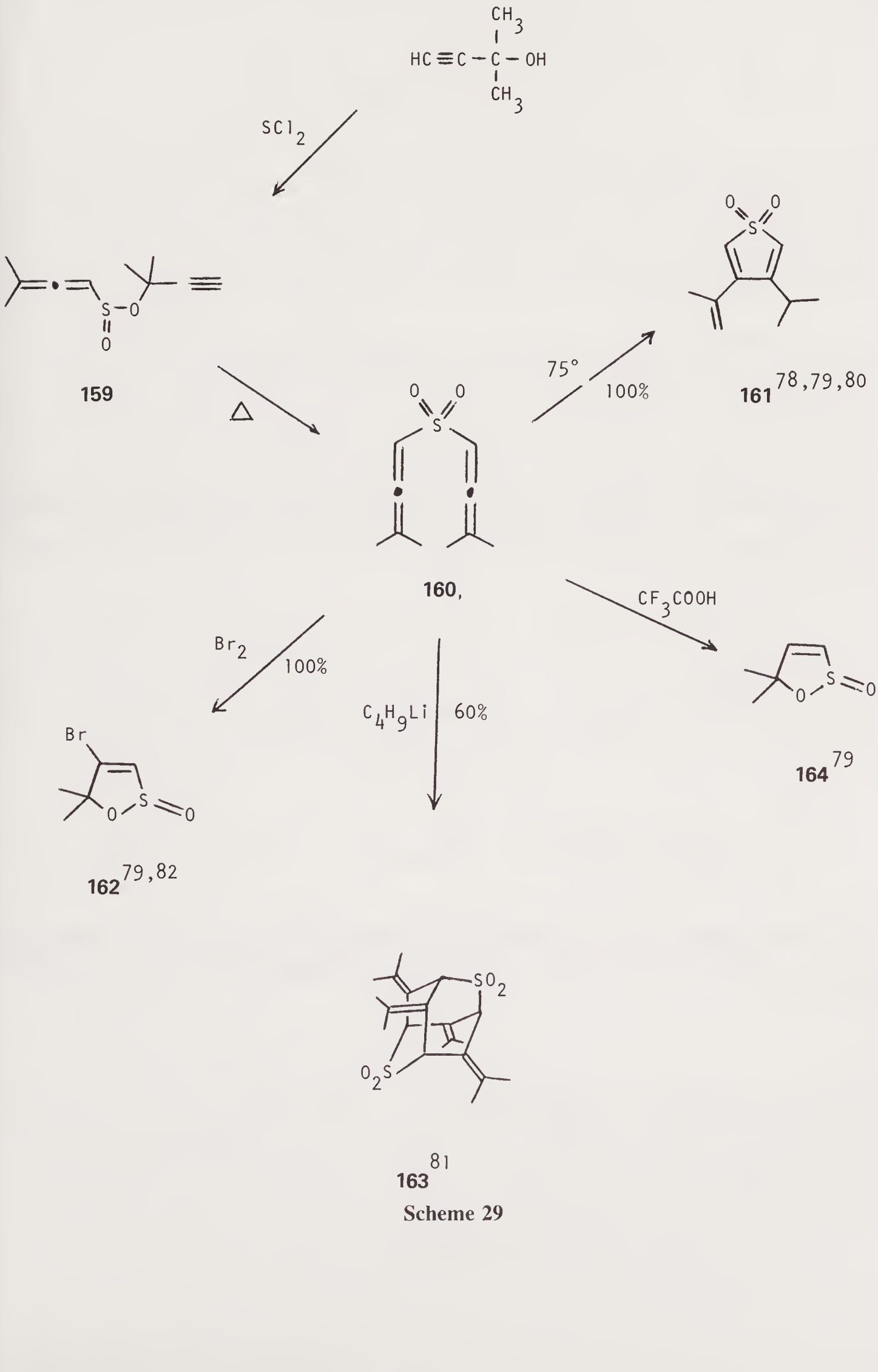
Scheme 27

Organocuprates add stereospecifically to allenic sulfones in a conjugate fashion. Takayama[77] has taken advantage of this selectivity to introduce the appropriate alkyl side chain in a stereoselective synthesis of cholesterol (**158**). The key step in the synthesis is the addition of lithium dimethylcuprate to the steroidal allene **154** to produce only the (Z)-allyl sulfone **155** (mixture of epimers at C-22). Intermediate **155** is then elaborated to cholesterol by the series of transformations shown in Scheme 28.



Scheme 28

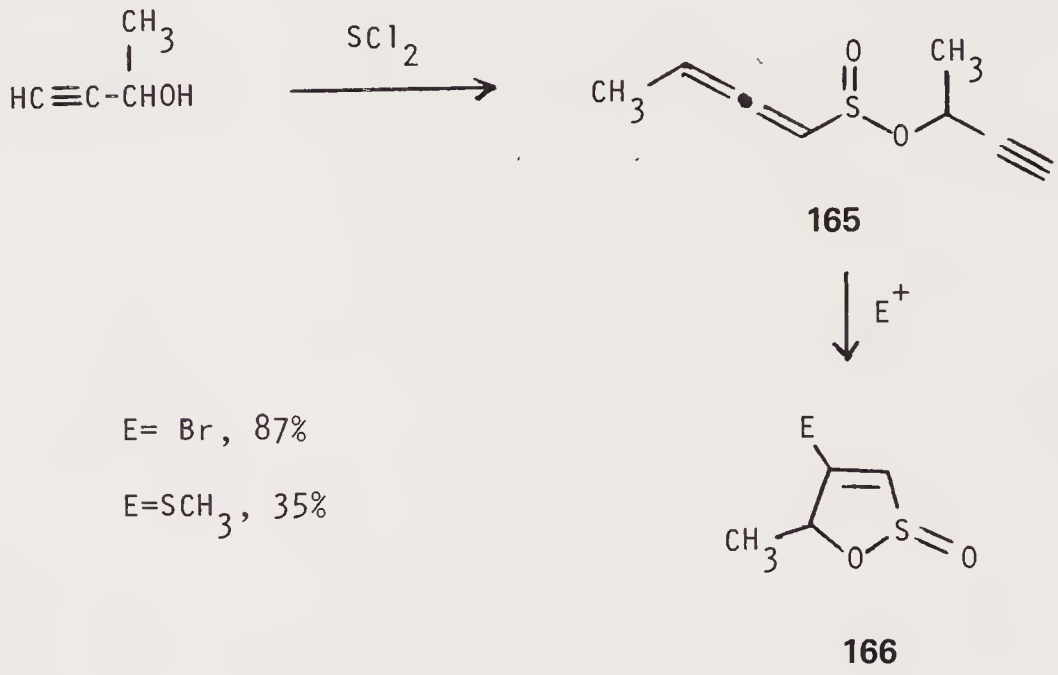
The unusual diallenic sulfone **160** is readily prepared by the reaction of 3-hydroxy-3-methyl-1-butyne with sulfur dichloride.[78] The transformation involves a double [2,3]sigmatropic rearrangement that proceeds through sulfinate **159**. Upon exposure to a variety of reagents, **160** undergoes many interesting reactions illustrated in Scheme 29.



Scheme 29

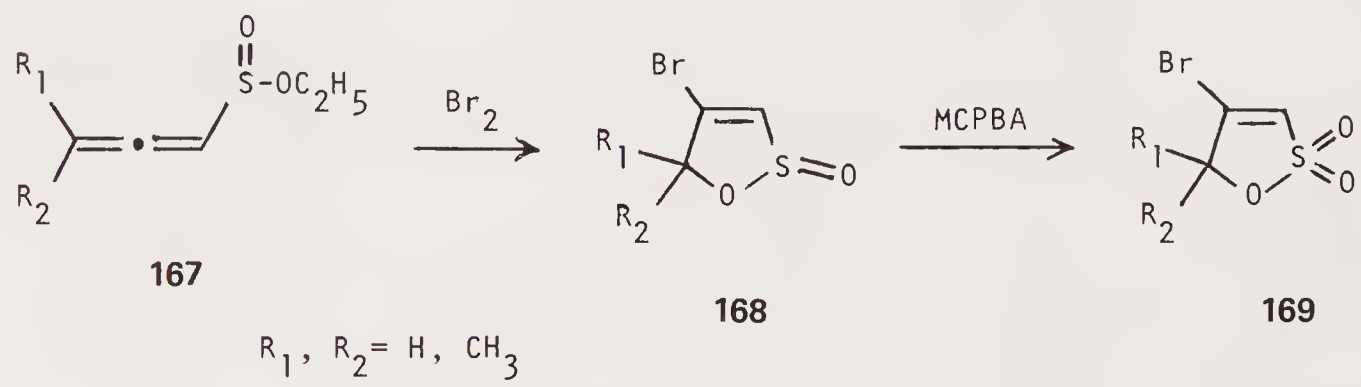
7.2.4. Allenic Sulfinates and Sulfonates

3-Hydroxy-1-butyne, when treated with sulfur dichloride at −78°C, affords the sulfinate **165** in 80% yield. Because of the mechanistic nature of the conversion, the use of a chiral propargyl alcohol produces **165** in optically active form. Reaction of the enantiomers of **165** with electrophiles such as bromine or methanesulfenyl chloride gives optically active γ-sultines **166**[83] (equation 26).



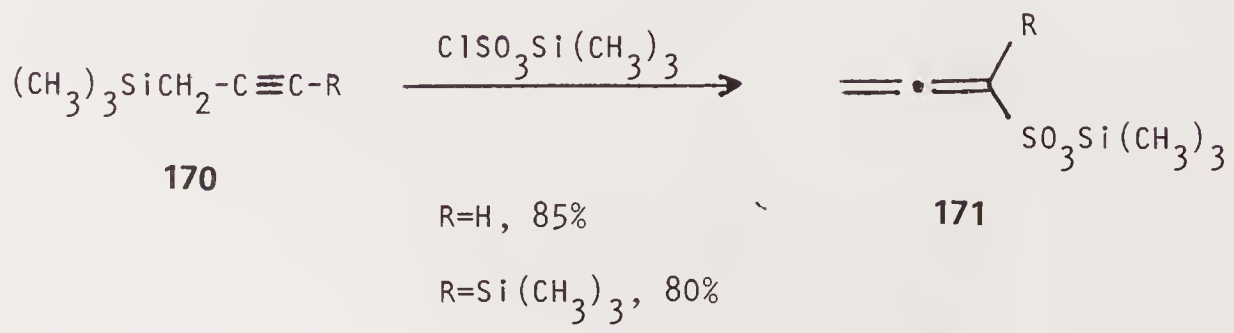
(26)

The bromination of simpler sulfinate esters **167** proceeds analogously (equation 27). Oxidation of the resulting sultines **168** with *m*-chloroperbenzoic acid produces sultones **169**.[82]



(27)

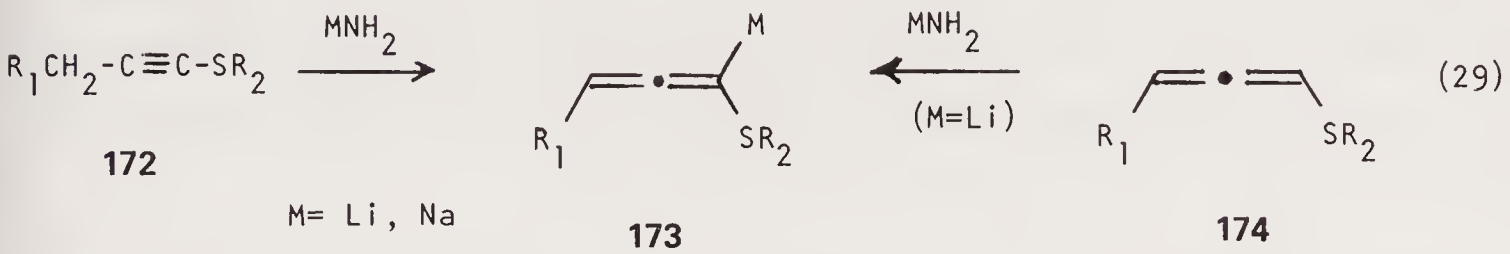
Sulfonating agents such as trimethylsilyl chlorosulfonate react with propargyl silylalkynes (**170**) to give allenic trimethylsilylsulfonates **171** in good yields[84,85] (equation 28).



(28)

7.2.5. Anions Derived from Thioallenes

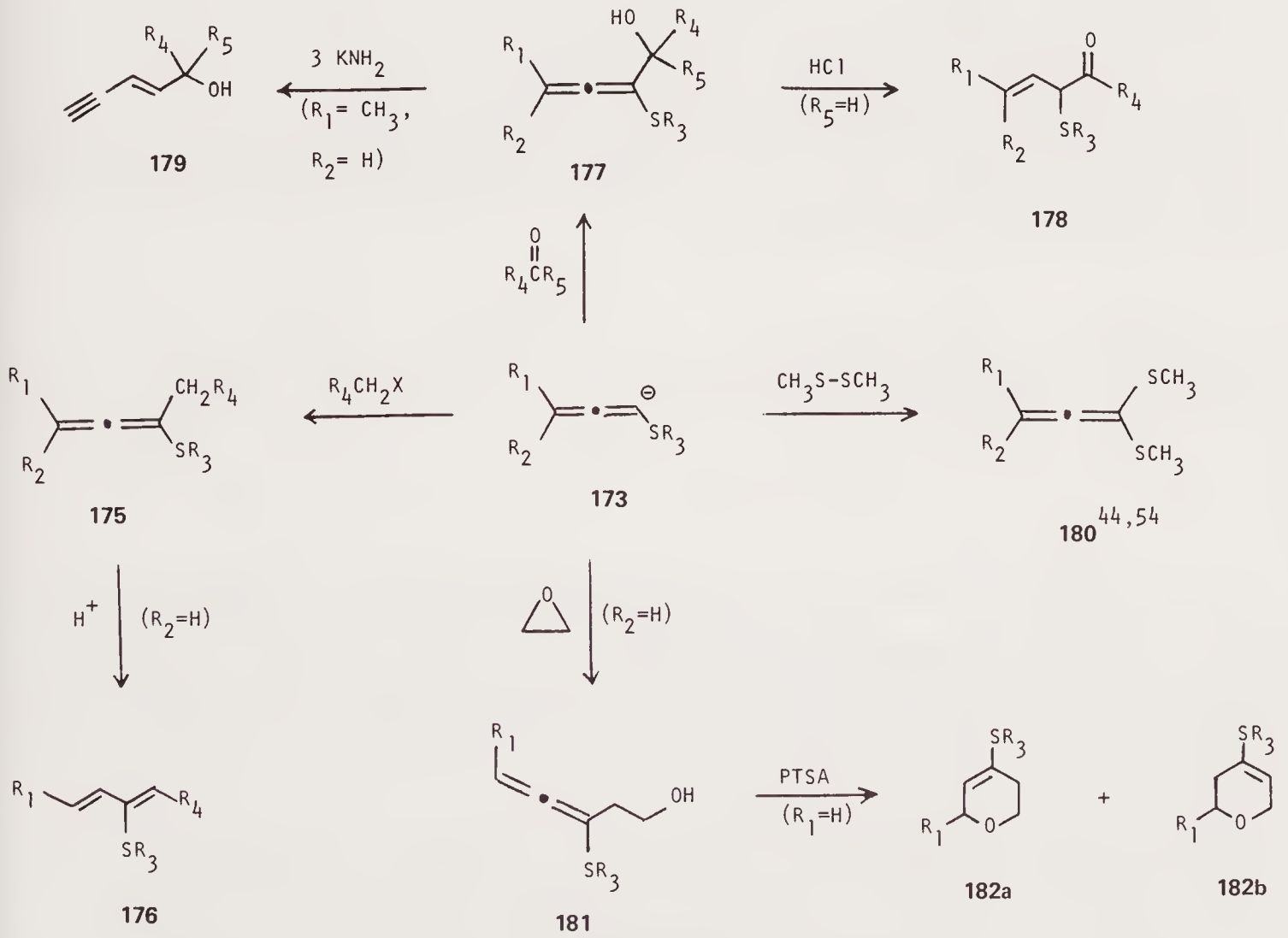
α-Metallated allenyl thioethers (**173**) can easily be generated by the action of an alkali metal amide on either a 1-alkynyl thioether[21,47,86] (**172**) or an allenic sulfide[87] (**174**) (equation 29).



(29)

As shown in Scheme 30, such metallated allenes react with a variety of electrophiles to give interesting products of potential synthetic utility. Quenching the anion **173** with alkyl halides results in the formation of the α-alkylated allenic sulfides **175** in yields ranging from 67 to 89%.[47,86] In the presence of a catalytic amount of picric acid, sulfides **175** isomerize to the conjugated dienes **176** (as a mixture of isomers).

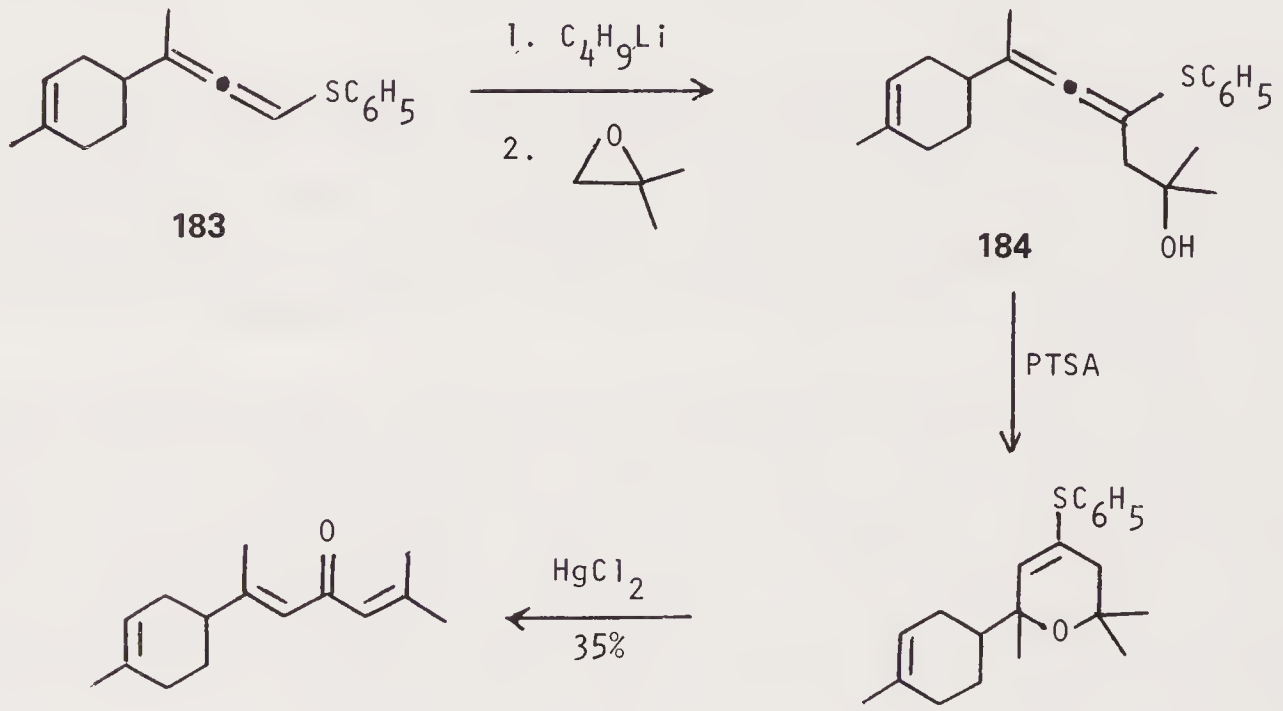
As expected, **173** reacts with aldehydes and ketones to give the allenic alcohols **177** in yields of up to 78%.[87] Upon treatment of these alcohols with 3 equivalents of potassium amide in liquid ammonia, (E)-enyne alcohols **179** are obtained (64–82%) as a result of elimination of alkane thiol. Alternately, exposure of **177** to hydrochloric acid in wet acetonitrile affords the interesting β,γ-unsaturated ketones **178**.[88]



Scheme 30

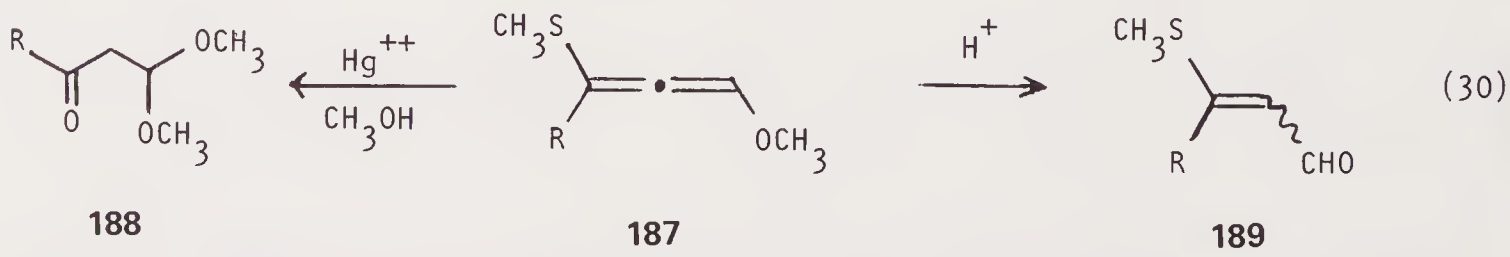
When the anion **173** is allowed to react with ethylene oxide, β-allenic alcohols **181** are produced in good yields.[21] Treatment of **181** with a catalytic amount of *p*-toluenesulfonic acid affords dihydropyran derivatives **182**.[89] If R_1 = H, **182a** is isolated in 54% yield. However, when $R_1 = C_3H_7$, a mixture of **182a** and **182b** (ratio 60:40) is obtained in 91% yield.

Using the **173** → **182** technology, one can synthesize the natural product atlantone (**186**), isolated from the essential oils of *Cedrus atlantica* and *C. deodara*,[90] from phenylthioallene **183**, as shown in Scheme 31.[91] The low yield in the mercury hydrolysis step is a result of retro-aldol condensations.

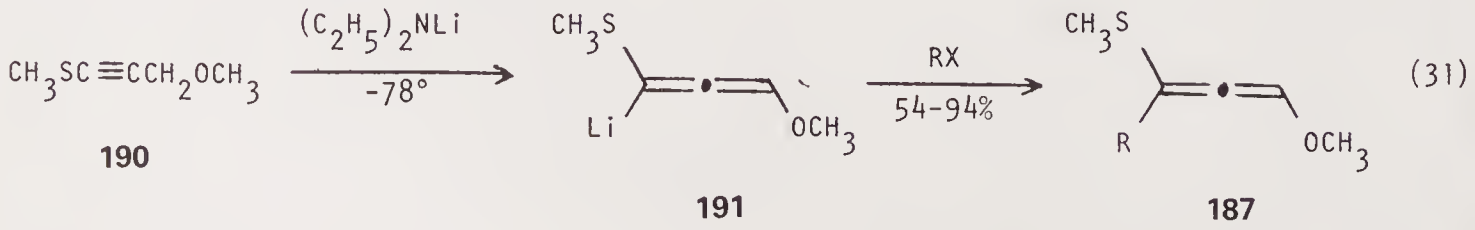


Scheme 31

Allenes that contain both ether and thioether functionalities behave as masked β-ketoaldehydes. Either group can be selectively hydrolyzed, as shown in equation (30), to release the desired substituent.[92]

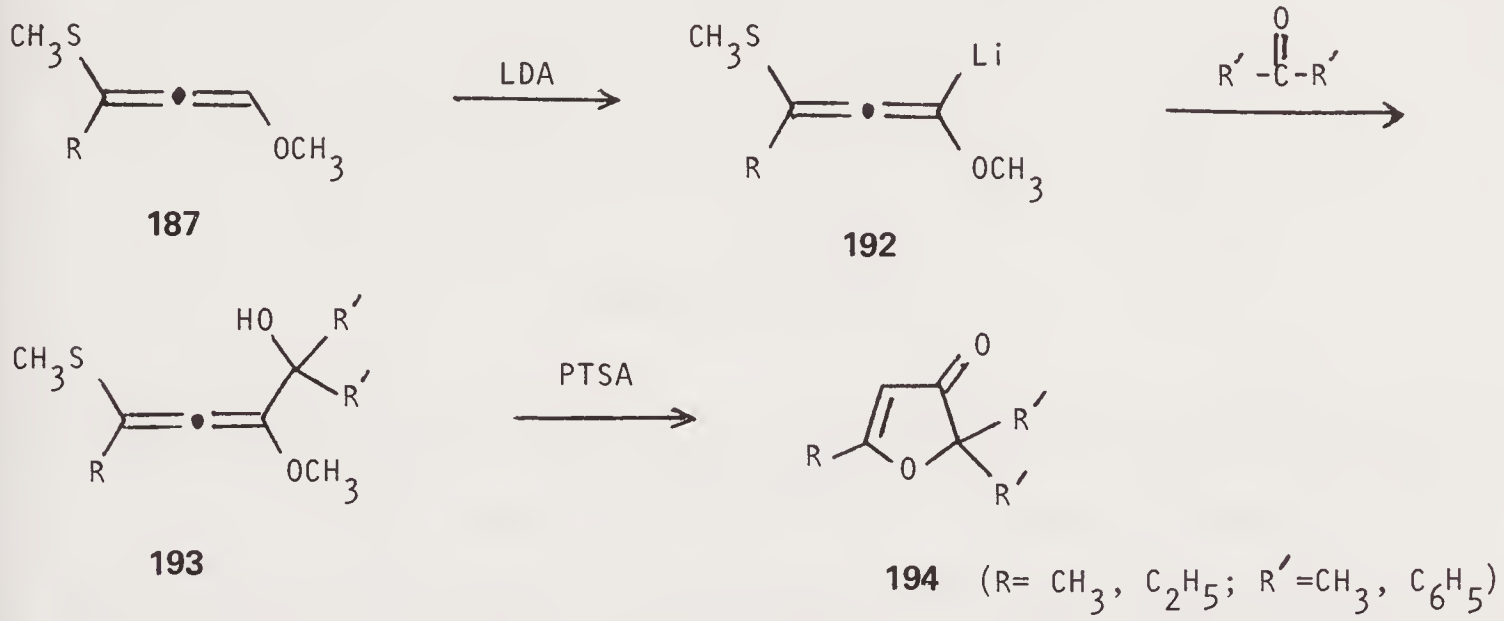


The treatment of 1-methylthio-3-methoxypropyne (**190**) with lithium diethylamide results in the generation of lithioallene **191**. This anion can be alkylated in good yield with alkyl halides to provide the requisite allene **187**. Acid hydrolysis of **187** produces α,β-unsaturated aldehydes **189** in 80–85% yield. In all cases the



Z-isomer is preferentially formed. Alternately, the mercury-assisted hydrolysis of **187** with 2 equivalents of mercuric chloride in methanol gives β-ketoacetals **188** in 42–55% yield.

Allene **187** can be deprotonated α to the methoxy substituent to give **192** by treatment with *n*-butyllithium or LDA below −60°C. Reaction with a slight excess of an aldehyde or ketone produces alcohols **193** that, when subjected to catalytic acid hydrolysis, form dihydrofuranones **194** in 67–93% yields (Scheme 32). The entire sequence **190** → **187** → **193** → **194** can be carried out in one flask.

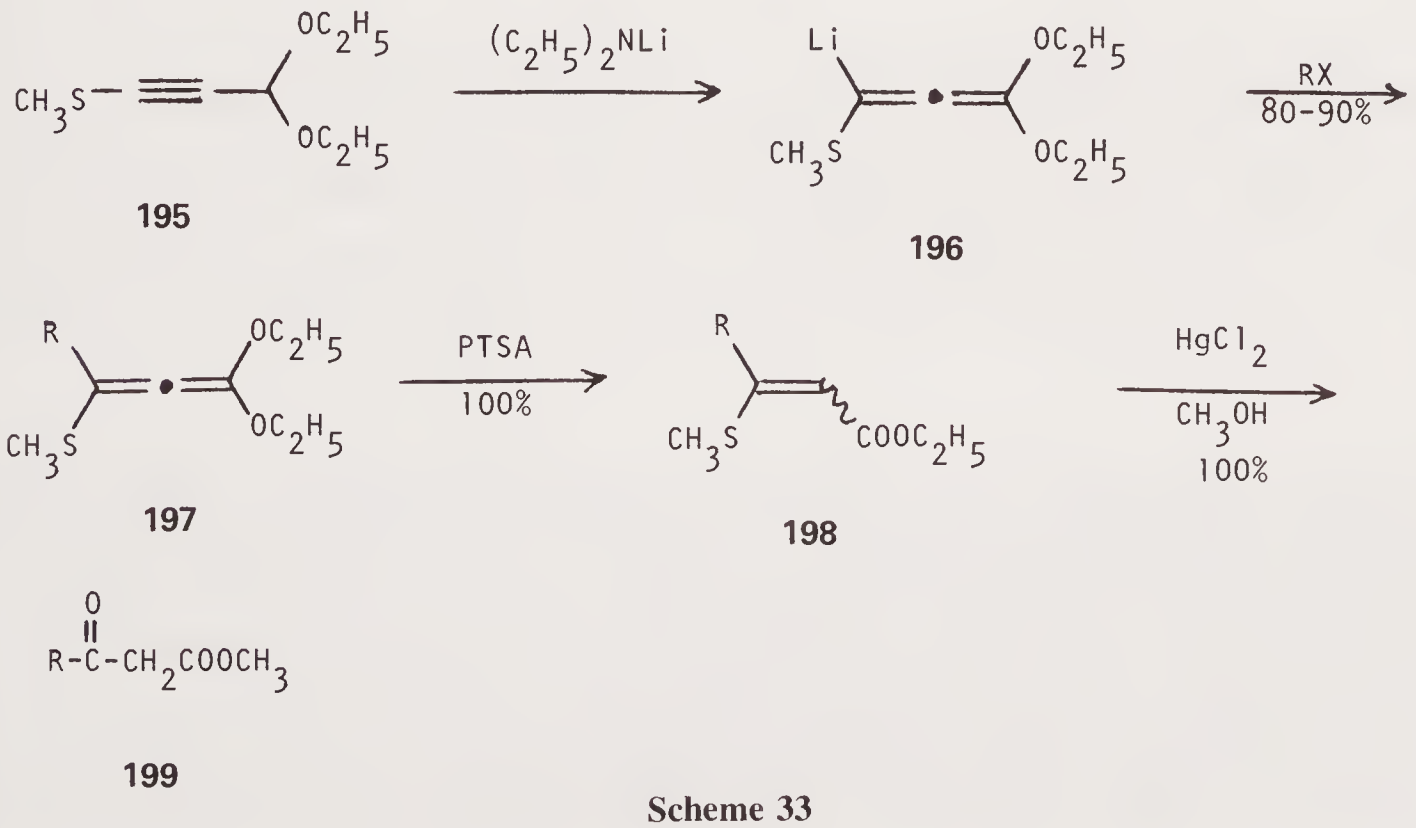


187 **192** **193**

194 (R= CH_3, C_2H_5; R′=CH_3, C_6H_5)

Scheme 32

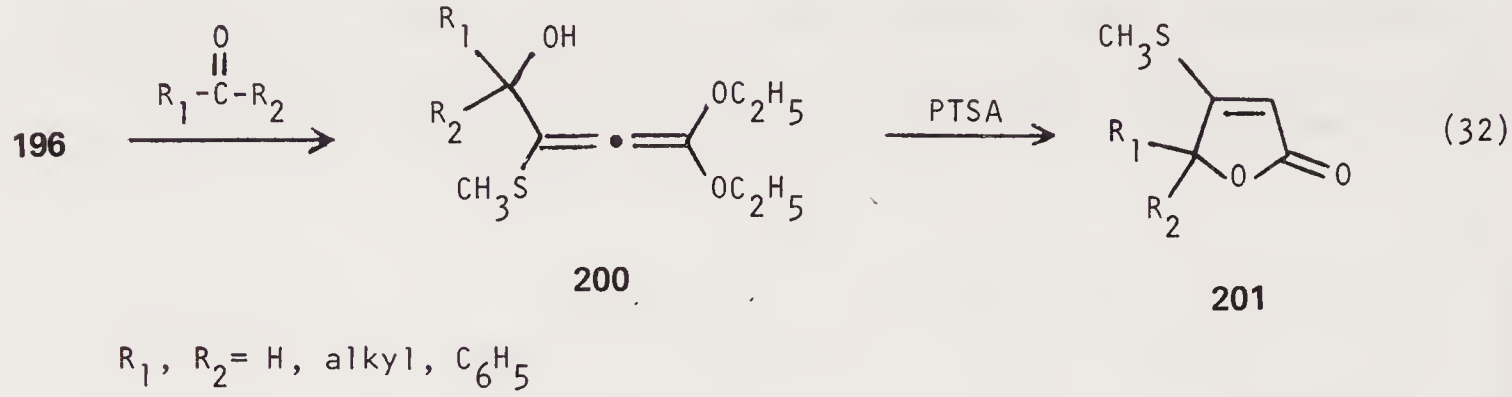
Allenic carbanion **196** is readily generated from 1-methylthio-3,3-diethoxypropyne (**195**) by treatment with lithium diethylamide at −78°C. Alkylation with primary alkyl halides provides ketene acetals **197** in high yields. The addition of halides other than primary results in the formation of elimination products.[93] Allenes **197** are useful as masked β-ketoesters which can be released by sequential acid hydrolysis (to produce β-methylthioacrylates **198**) then mercury hydrolysis to give the β-ketoester **199** (Scheme 33).



195 **196** **197** **198** **199**

Scheme 33

Anion **196** also reacts with aldehydes and ketones to give the rather unstable alcohols **200**. When exposed to *p*-toluenesulfonic acid, these alcohols lactonize to the β-methylthiobutenolides **201**. The overall yield for the sequence shown in equation (32) ranges between 70 and 92%.

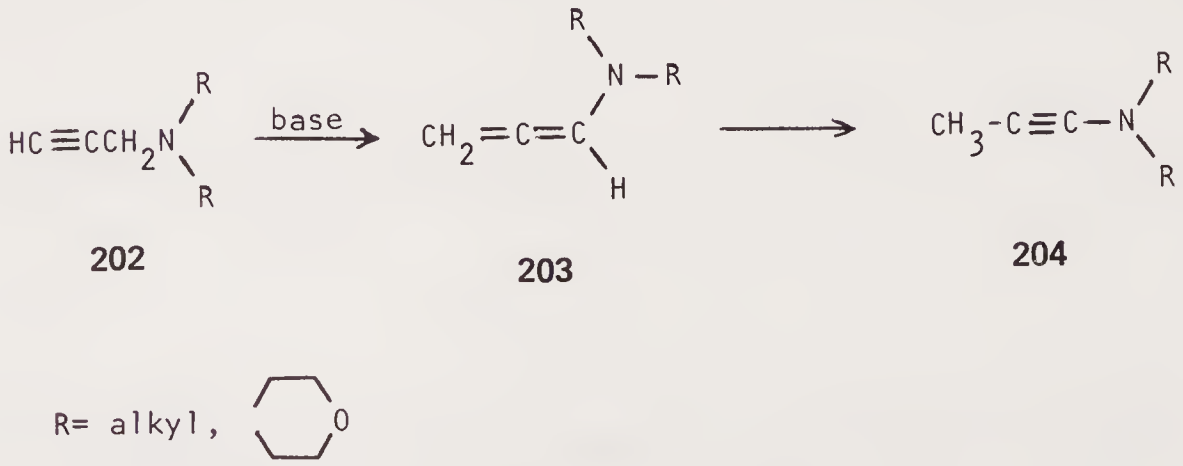


(32)

7.3. NITROGEN

This section discusses only allenes with amino functionalities directly connected to the propadiene framework. These types of compounds are of special interest because of their enaminelike structure which is of great synthetic value.

Aminoallenes (**203**) are generally prepared by the base-catalyzed isomerization of 2-propynylamines **202** (equation 33). The conversion can be effected with a dispersion of potassium amide on alumina, however, the reaction depends on the basicity of the nitrogen to which the propargyl group is linked. When the amine contains alkyl substituents, the resulting allene **203** rearranges further to N,N-dialkylmethyl ynamines **204**.[94] When the amine is represented by heterocycles such as pyrrole, pyrazole, or imidazole, the isomerization can be stopped at the allene stage to give the corresponding propadienyl-substituted heterocycle in 20–40% yields.[95]

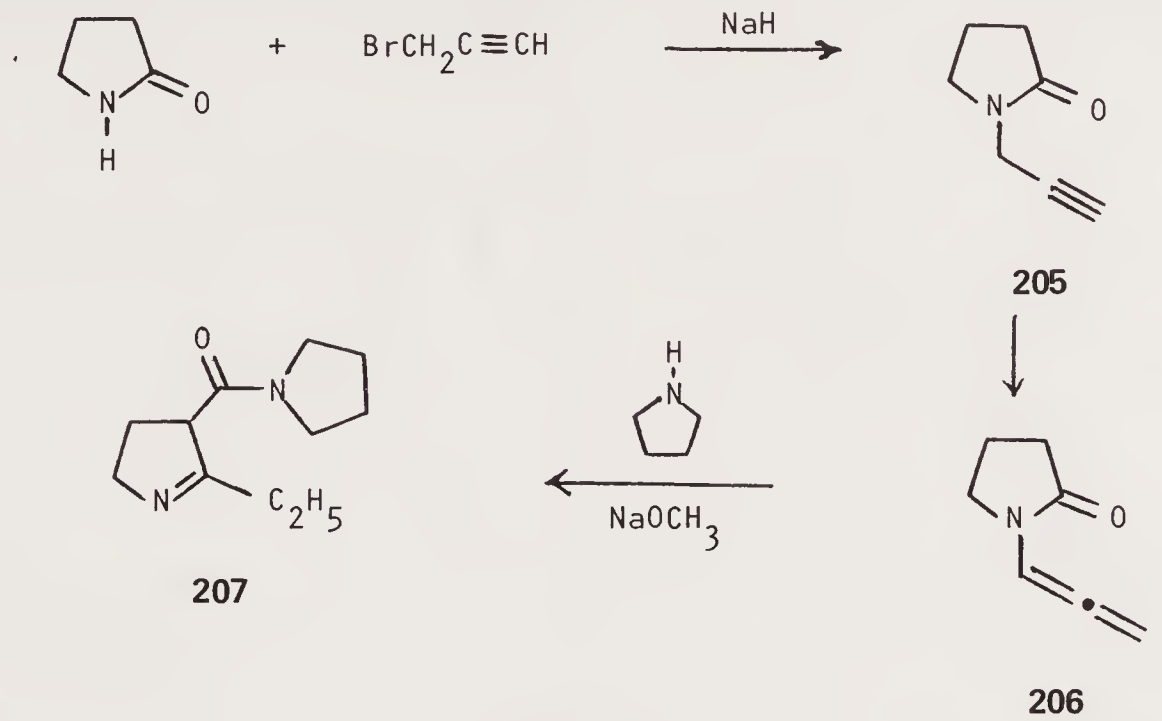


(33)

Dialkylaminoallenes are accessible on a preparative scale from the **202** → **203** rearrangement by using potassium *t*-butoxide in THF or potassium *t*-butoxide/*t*-butanol in HMPA. With these catalysts, allenic amines are consistently isolated in greater than 85% yield and are contaminated only to a minor extent with **204**.[96]

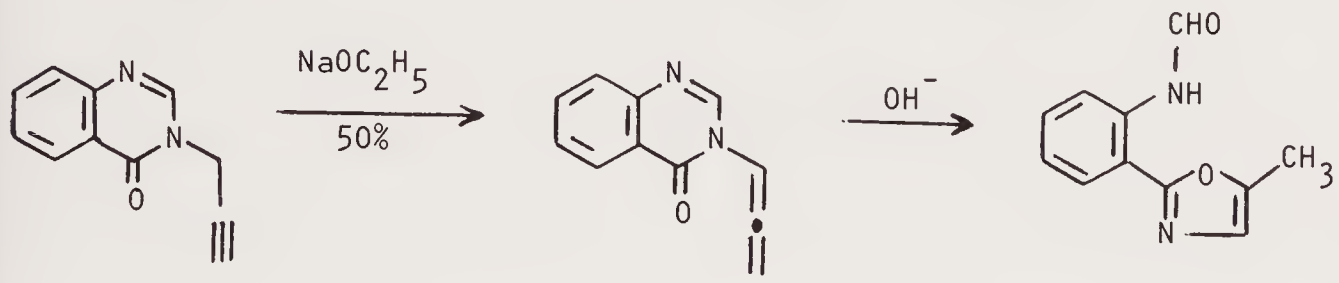
The alkylation of 2-pyrrolidone with propargyl bromide gives only 1-(propadienyl)-2-pyrrolidone (**206**), which presumably arises from the base-catalyzed isomerization of **205**[97] (Scheme 34). When **206** is allowed to react with pyrrolidine

in the presence of sodium methoxide, **207** is produced. The formation of **207** is not a result of the addition of pyrrolidine to any of the allenic carbons, but rather to the pyrrolidone carbonyl followed by ring scission and recyclization.



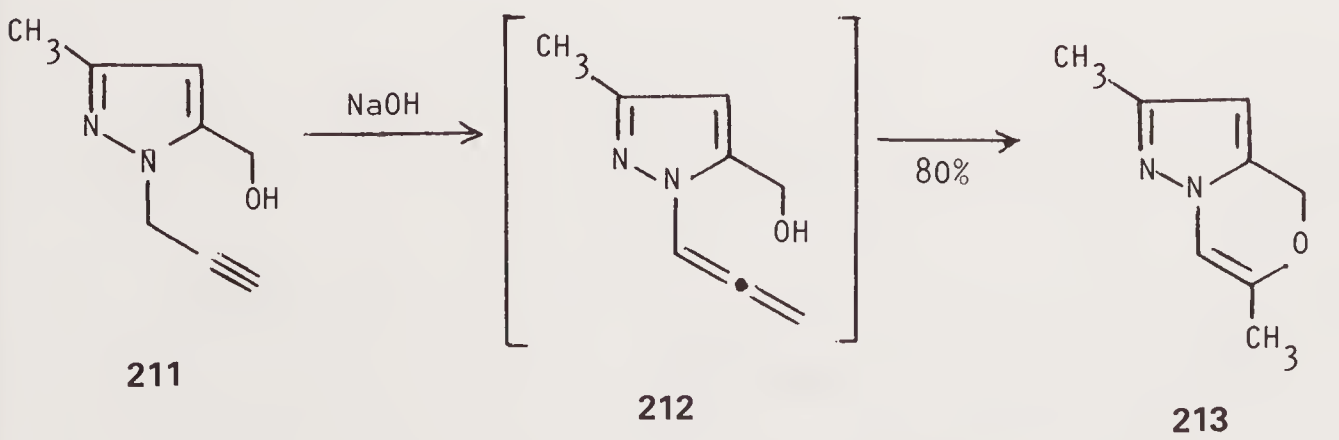
Scheme 34

Propargyl quinazolone **208**, upon treatment with sodium ethoxide in absolute ethanol, isomerizes to the 3-propadienyl quinazolone **209**. If 96% ethanol is used as the reaction medium, oxazole **210** is obtained[98] (equation 34).



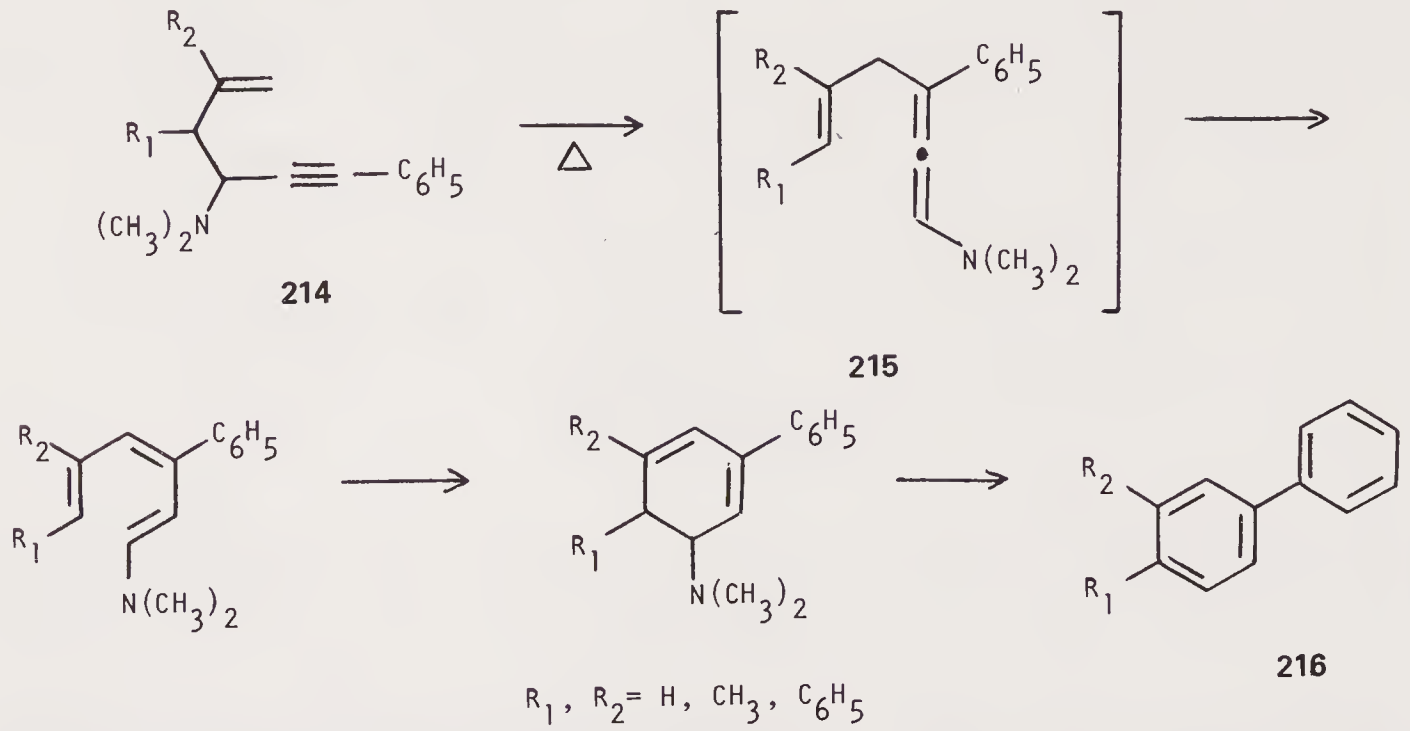
(34)

Under strongly basic conditions, such as those encountered in a phase-transfer system, 5-hydroxymethyl-3-methyl-1-propargylpyrazole (**211**) is converted to the pyrazolooxazine **213**[99] (equation 35). The transformation probably proceeds by the base-catalyzed rearrangement of **211** to its allene isomer **212** followed by intramolecular nucleophilic addition of the alcohol to the central allene carbon.



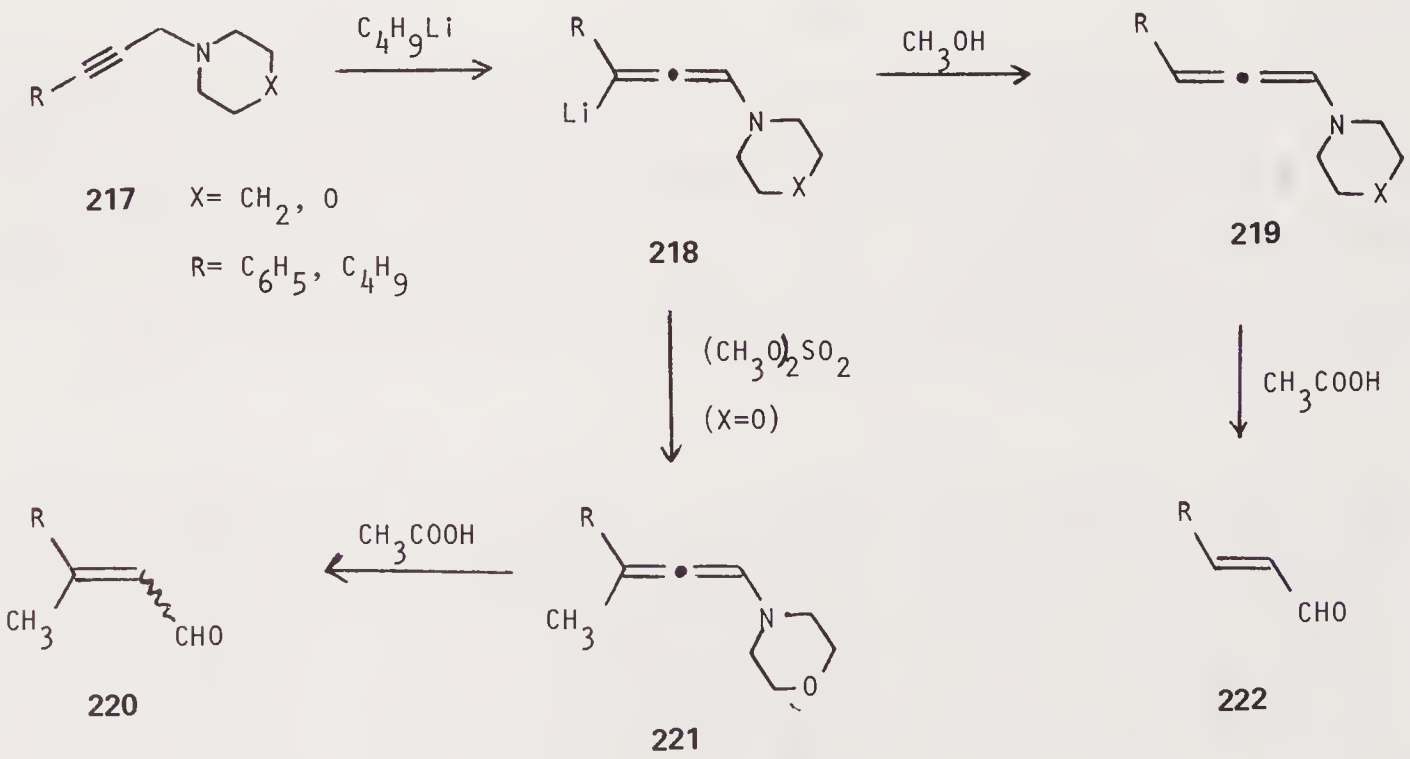
(35)

The thermal isomerization of allylpropynyl amines **214** provides direct access to substituted biphenyls.[100] As shown in Scheme 35, the transformation is possibly initiated by a [3,3]sigmatropic rearrangement to give the allene **215**, which subsequently isomerizes, cyclizes, and then aromatizes (by loss of dimethylamine) to give **216** (58–95% yields).



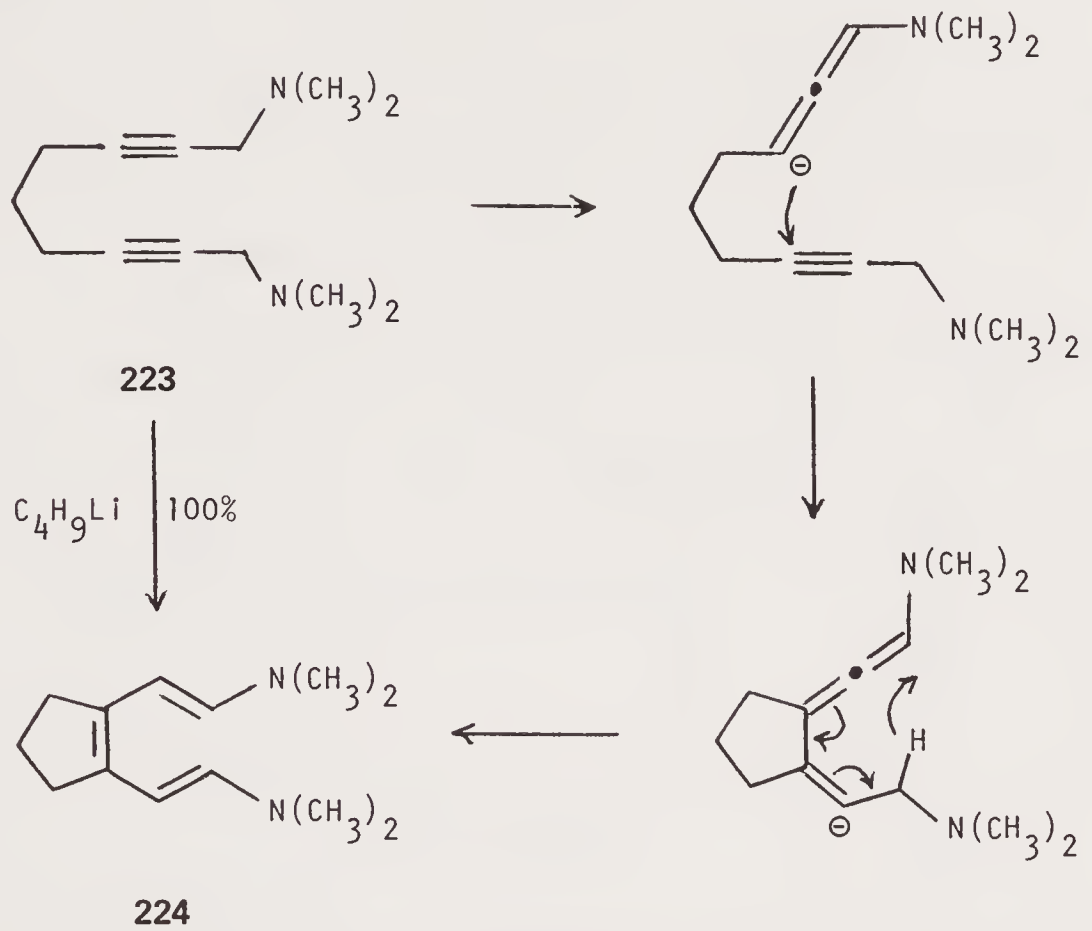
Scheme 35

γ-Lithio aminoallenes **218** are generated by the isomerization of 2-propynylamines **217** with *n*-butyllithium at −76°C.[101] The allene **219** can be obtained by protonation with methanol at 0°. Hydrolysis of allenes **219** with aqueous acetic acid proceeds quantitatively to give α,β-unsaturated aldehydes **222** in overall yields ranging from 68 to 88%. Methylation of **218** with dimethyl sulfate gives the alkylated allene **221** that, after hydrolysis, furnishes the methylated unsaturated aldehydes **220** (overall yield, 86%).



Scheme 36

The diacetylenic diamine **223**, when treated with *n*-butyllithium at −10°C, instantaneously and quantitatively rearranges to the cyclopentene derivative **224**.[102,103] The mechanism (Scheme 37) involves the cyclization of an initially formed allenic carbanion followed by a [1,5]sigmatropic hydrogen shift. In the presence of acids, **224** immediately forms a black polymer.

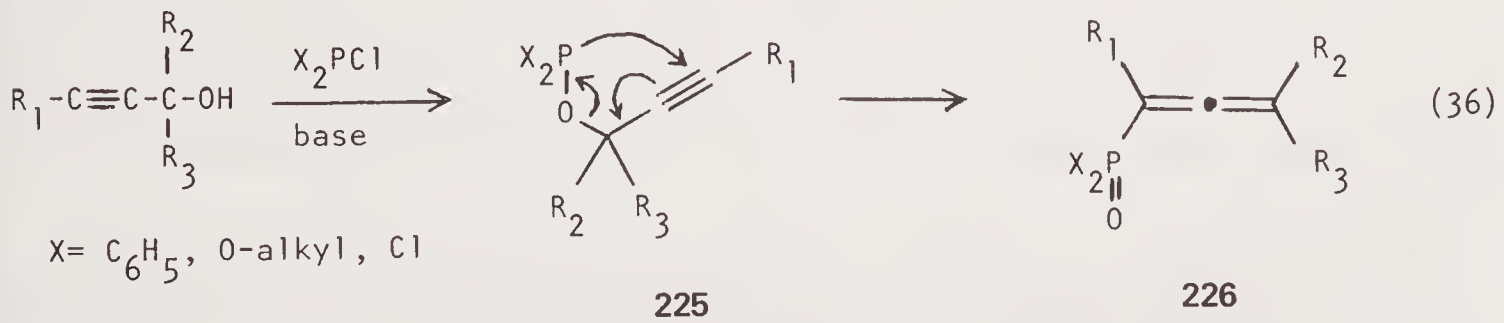


Scheme 37

7.4. PHOSPHORUS

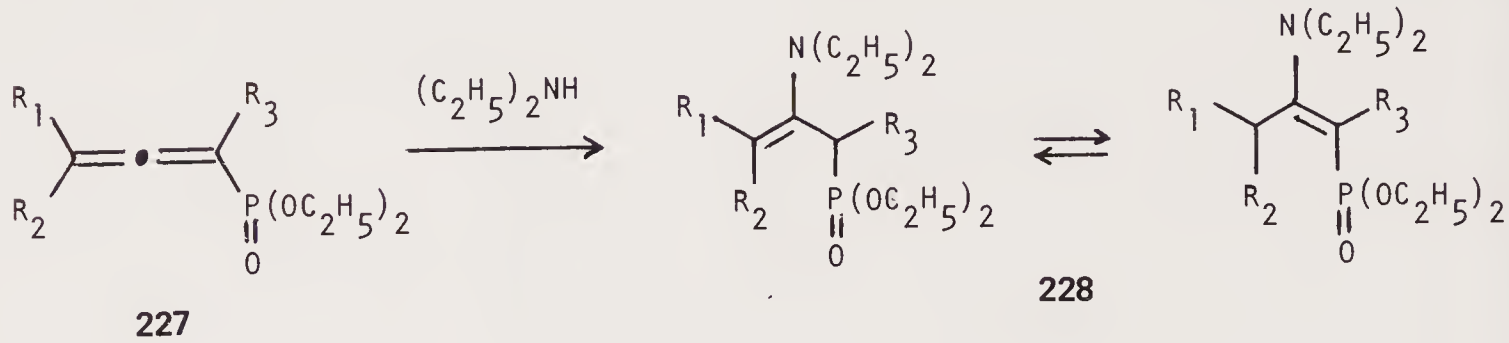
The importance of organophosphorus compounds has long been recognized in the field of synthetic organic chemistry. It was only a matter of time until the phosphorus atom and the allene unit were joined and the chemistry of the resulting phosphoallenes investigated.

A generally reliable method for the preparation of phosphoallenes is the reaction of a propargyl alcohol with a trivalent phosphorus chloride in the presence of an organic base such as pyridine, triethylamine, N-methylmorpholine, or methyllithium (equation 36). The initially formed intermediate **225** undergoes a pseudo-Claisen-type rearrangement, usually at temperatures less than 25°C, to form the pentavalent phosphoallene **226**.[104–113]



(36)

Allenic phosphonates (**227**), which are obtainable in 62–87% yield by this process, can be converted to β-ketophosphonates (**229**) by nucleophilic addition of diethylamine followed by acid hydrolysis of the resulting enamines **228**[114] (Scheme 38).



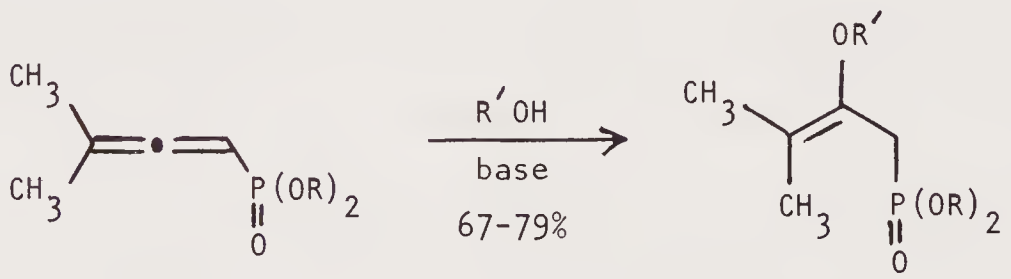
227 **228**

R_1	R_2	R_3	Yield **229** %
H	H	H	59
H	CH_3	H	71
H	H	CH_3	68
CH_3	CH_3	H	78
—$(CH_2)_5$—		H	80

229

Scheme 38

Alcohols add exothermically to 3-methyl-1,2-butadienylphosphonates (**230**) in the presence of sodium ethoxide or triethylamine to produce enol ethers **231** as the only product (equation 37). The nonconjugated position of the double bond was established by ozonation of the addition products.[115,116]



(37)

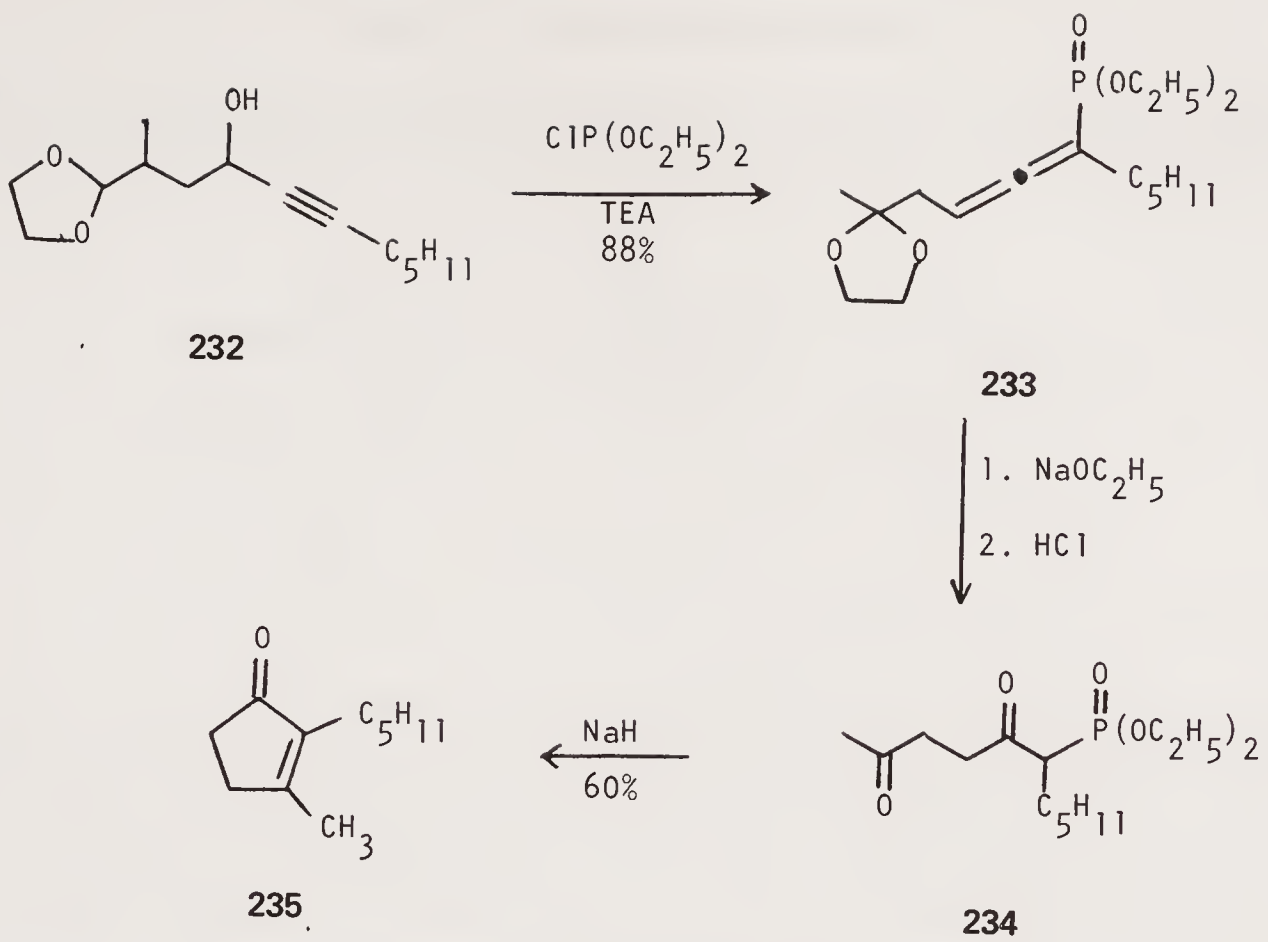
230 **231**

R= C_2H_5, C_3H_7

R′= CH_3, C_2H_5, C_3H_7

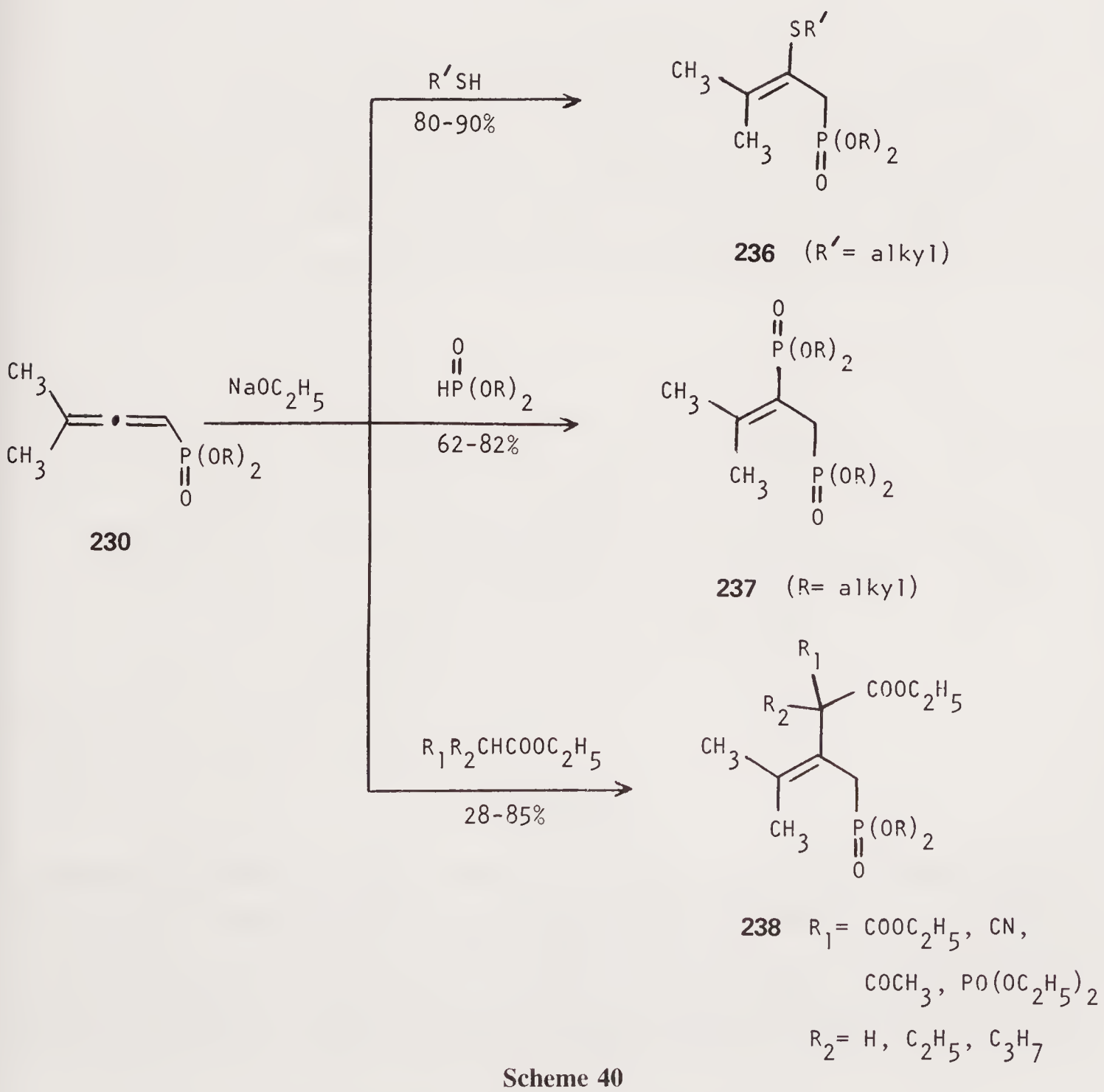
In this manner dihydrojasmone (**235**) can be synthesized as outlined in Scheme 39.[117] The addition product obtained from the reaction of sodium ethoxide with **233** is directly hydrolyzed with dilute HCl to give the diketophosphonate **234**. Treatment with sodium hydride gives the desired product by means of an intramolecular Wittig reaction.

Nucleophiles such as sulfides,[118] dialkyl hydrogen phosphites,[115,116] and anions derived from active methylene compounds[118] also add readily to phosphonate **230** and are summarized in Scheme 40.



232 **233** **234** **235**

Scheme 39



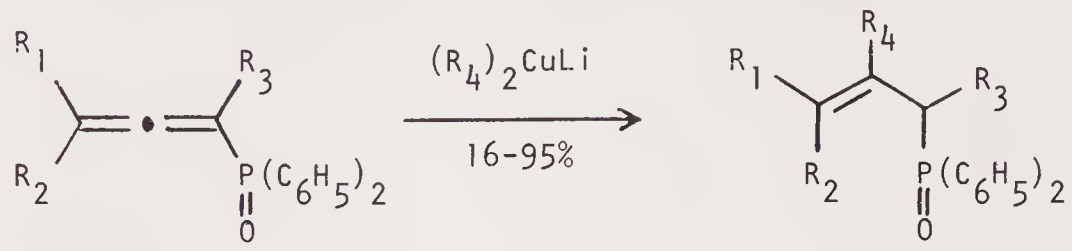
230 **236** (R'= alkyl) **237** (R= alkyl)

238 R_1= $COOC_2H_5$, CN, $COCH_3$, $PO(OC_2H_5)_2$

R_2= H, C_2H_5, C_3H_7

Scheme 40

Lithium dialkylcuprates add in a 1,2-fashion to allenic phosphine oxides **239** to give adducts **240** as the principal product[119–122] (equation 38).

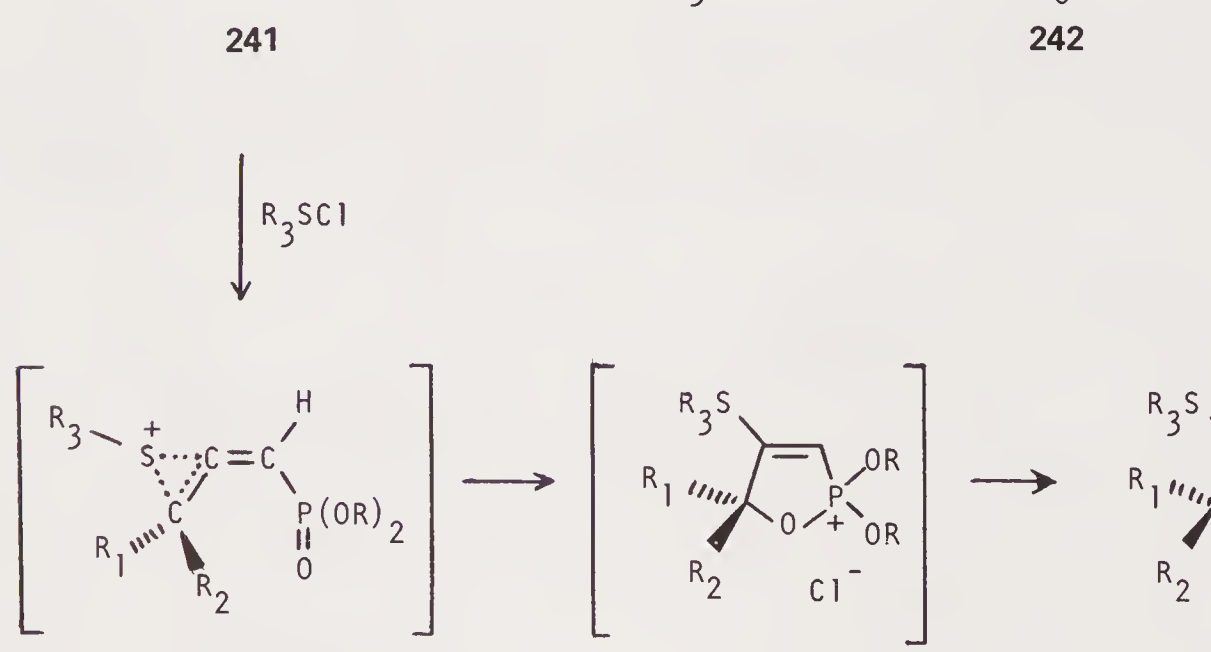


(38)

239 **240**

R_1-R_3= H, CH_3, $(CH_2)_5$, C_6H_5

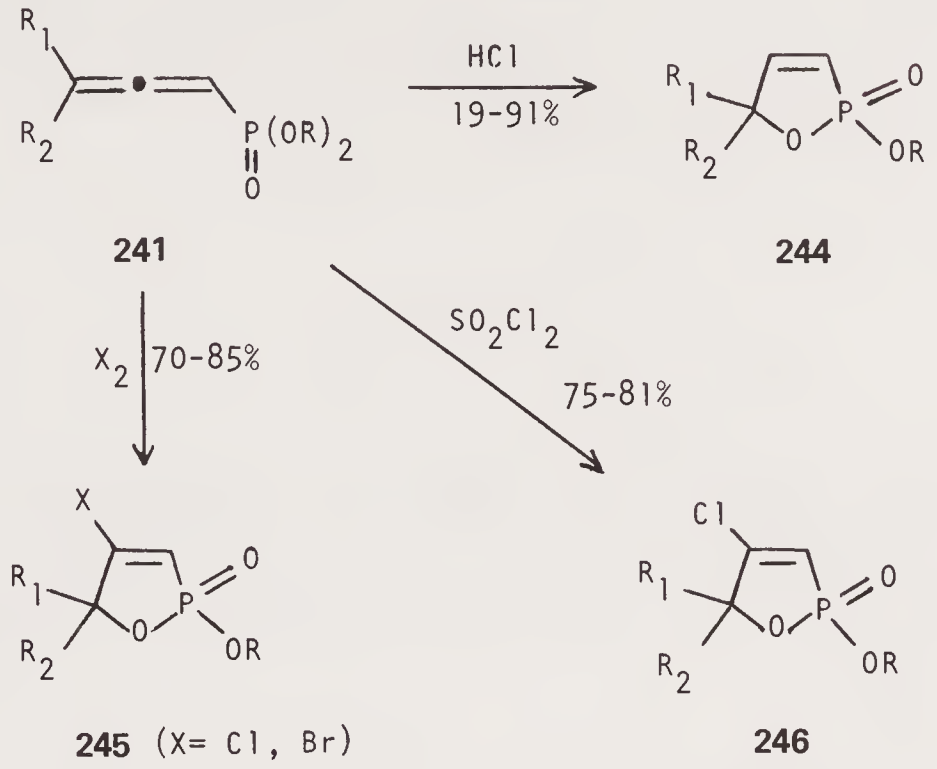
Allenyl phosphonates are also susceptible to electrophilic substitution reactions. The addition of benzenesulfenyl chloride to dimethyl propadienylphosphonate (**241**, $R_1 = R_2 = H$, $R = CH_3$) at 15–16°C affords the acyclic monoadduct **242**.[123] However, when the terminal carbon of the allene is disubstituted, a cycloaddition of the reactants occurs to produce 4-thio-1,2-oxaphosphol-3-ene 2-oxides (**243**) in 63–82% yields by way of an episulfonium ion[124] (Scheme 41).



Scheme 41

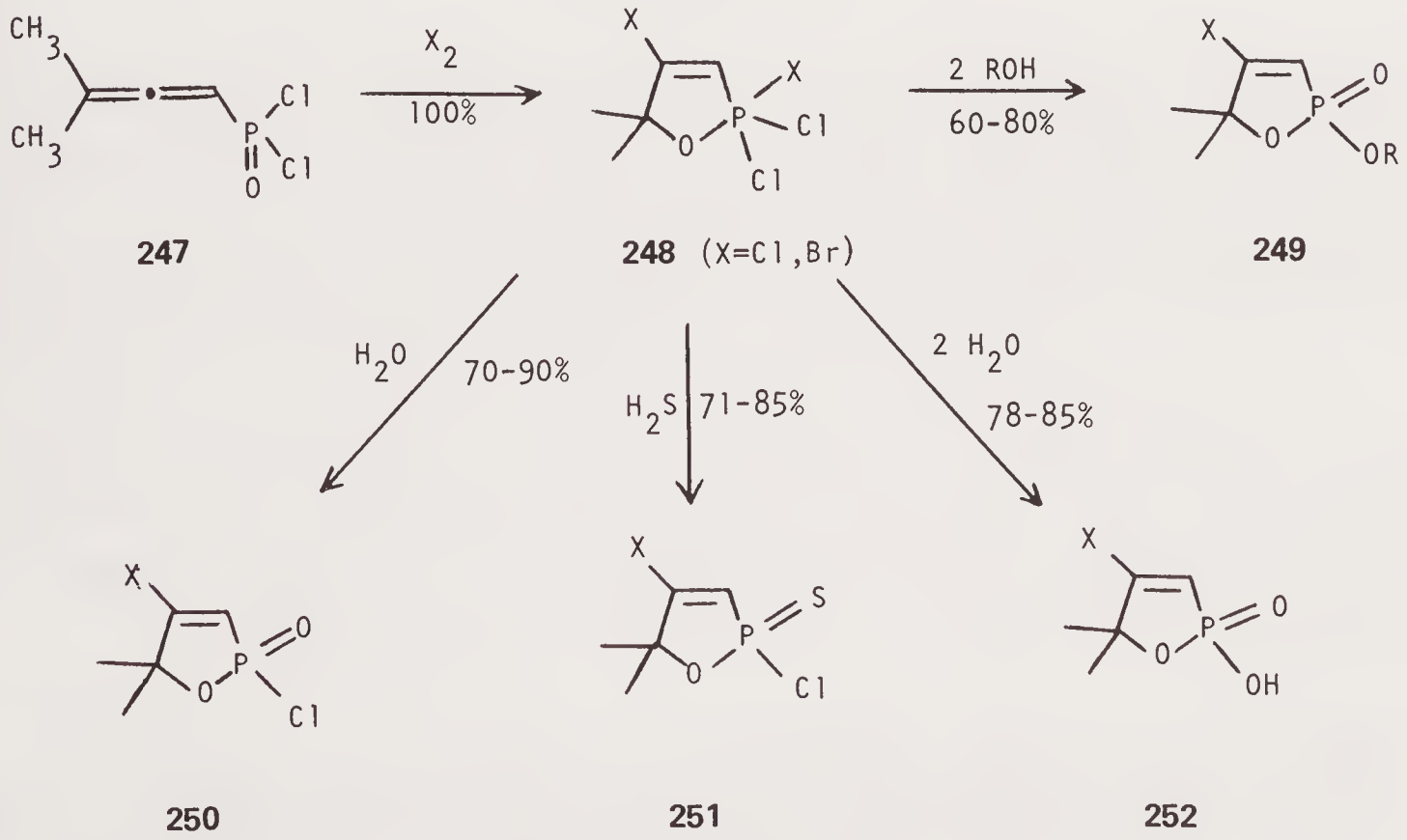
Allenes **241**, when treated with gaseous HCl, produce 2-alkoxy-1,2-oxaphosphol-3-ene 2-oxides (**244**), generally in good yields.[125] Halogenation of **241** provides the corresponding 4-halo derivatives **245**.[82,126–129] Alternately, the 4-chloro heterocycles **246** can be obtained by the reaction of equimolar amounts of **241** and sulfuryl chloride. With 3,3-disubstituted derivatives of **241**, the reaction proceeds

at 8–10°C, but with monosubstituted compounds heating (30–40°C) is required to effect the conversion.[130]



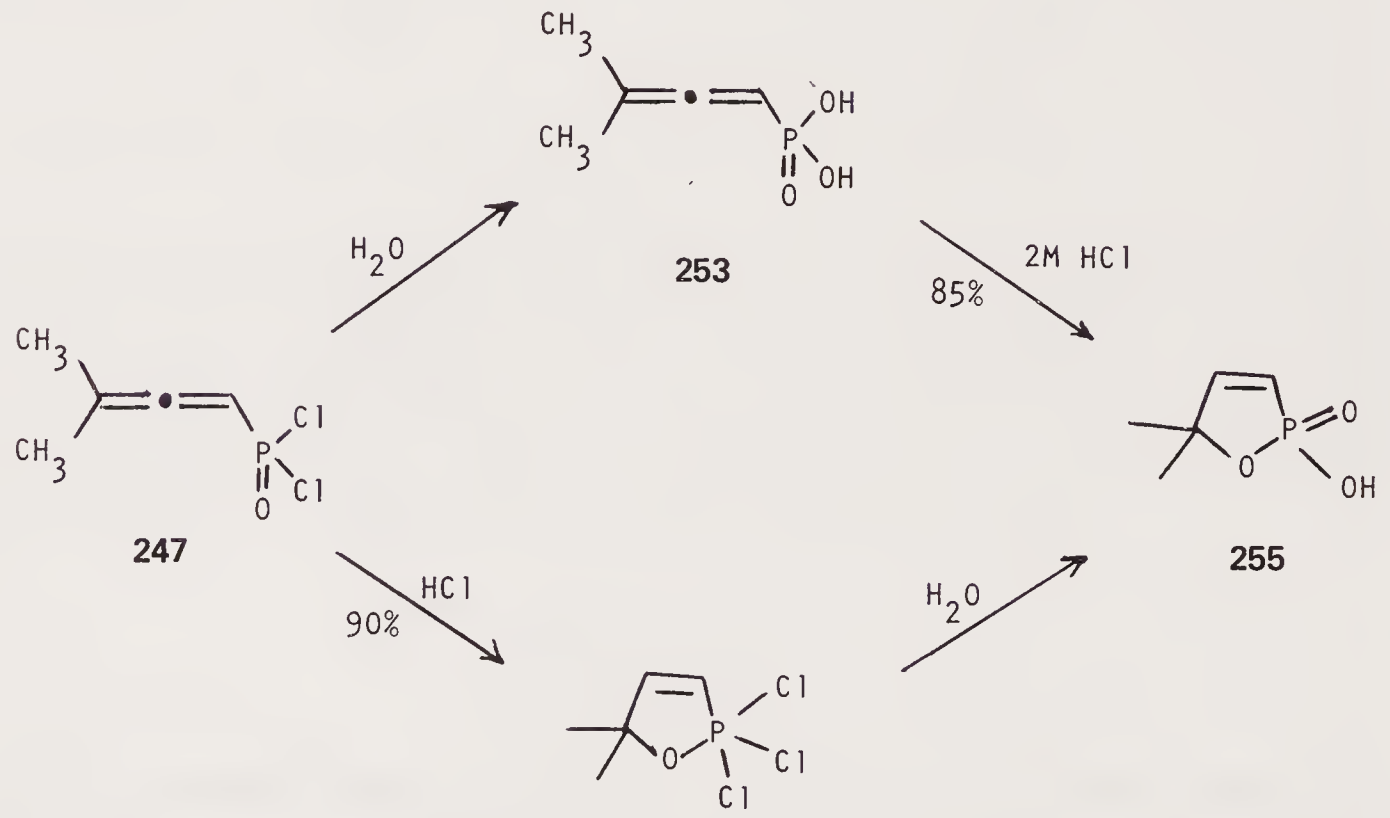
Scheme 42

The halogenation of (3-methyl-1,2-butadienyl)phosphonic dichloride (**247**) proceeds analogously and rapidly produces tetrahalooxaphosphol-3-ene **248** in essentially quantitative yield.[131] By exposing **248** to varying amounts of water, alcohols, or hydrogen sulfide, oxaphosphol-3-ene 2-oxides **249–252** are obtained[132] (Scheme 43).



Scheme 43

Addition of water to **247** results in the formation of allenyl phosphonic acid **253**. In the presence of aqueous 2M HCl, **253** cyclizes cleanly to the relatively unstable 5,5-dimethyl-2-hydroxy-1,2-oxaphosphol-3-ene 2-oxide (**255**; half-life 10.3 hours at 66°C). Alternately, **255** can be prepared from **247** by treatment with gaseous HCl (25 days), to give **254**, followed by hydrolysis with aqueous dioxane (60% overall yield from **247**)[113] (Scheme 44).



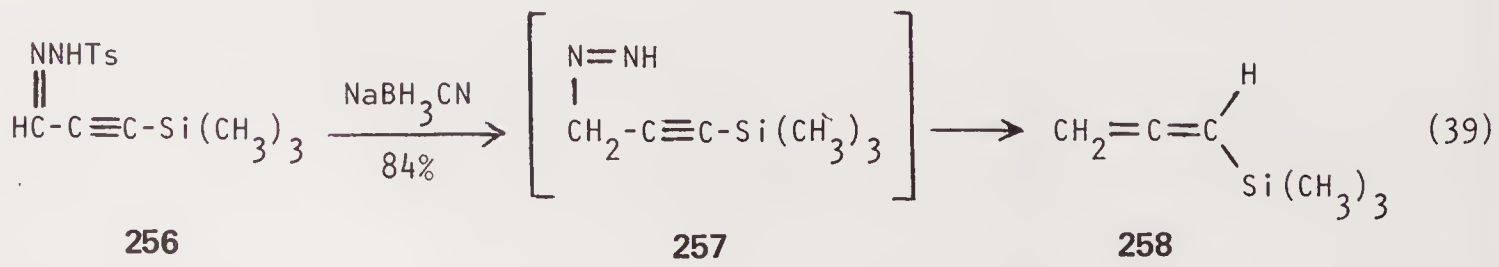
254

Scheme 44

7.5. SILICON

Silylallenes, a relatively new class of compounds in the field of organic chemistry, have only recently found applicability as useful molecules in organic synthesis. Several interesting routes leading to functionalized allenyl silanes have been reported, however, the products suffer from contamination with varying amounts of their isomeric acetylene derivatives.[133–136] Within the last few years, methods have been developed to minimize the amount of acetylene formation in such preparations.

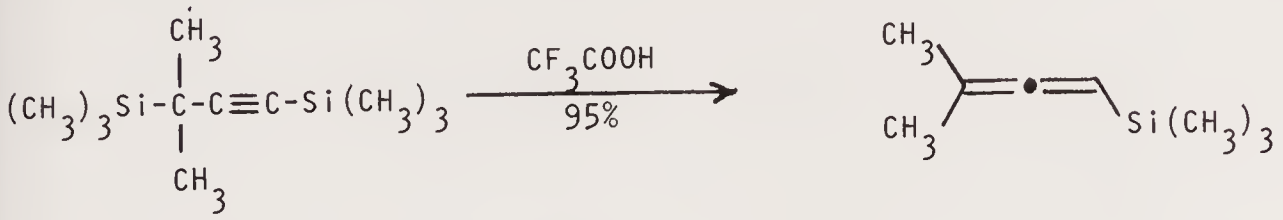
Trimethylsilylallene (**258**), the simplest member in the family, can be synthesized by an interesting approach illustrated in equation (39).[137] The treatment of tosylhydrazone **256** with 8 equivalents of sodium cyanoborohydride in DMF/sulfolane/hexane results in the formation of propargyl diazene **257**. A concerted [1,5]sigmatropic rearrangement then furnishes the allene **258** free of any acetylenes.



(39)

256 **257** **258**

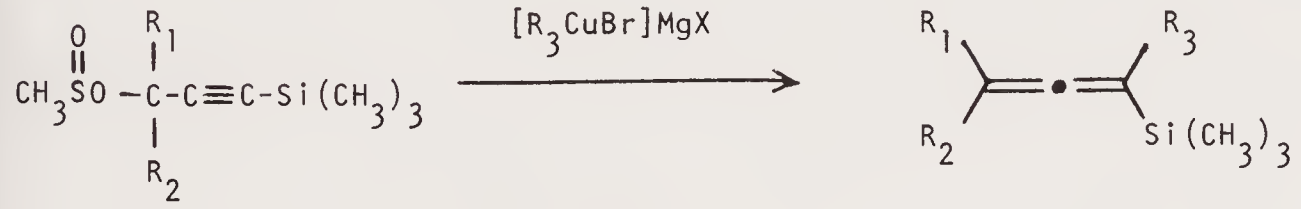
The dimethyl analog **260** is readily obtainable in essentially quantitative yield from the desilation of 1,3-bis(trimethylsilyl)-3-methyl-1-butyne (**259**) with trifluoroacetic acid (0°C, 5 minutes)[138,139] (equation 40). However, the generality of this method has yet to be demonstrated.



(40)

259 **260**

To date, the most versatile approach for the preparation of silylallenes is a 1,3-addition of an organoheterocuprate to a trimethylsilyl propargyl mesylate (equation 41). Conversions are in excess of 85%, and only in selected cases (where R_3 = *t*-C_4H_9 or C_6H_5) are any acetylenes produced.[140,141]



(41)

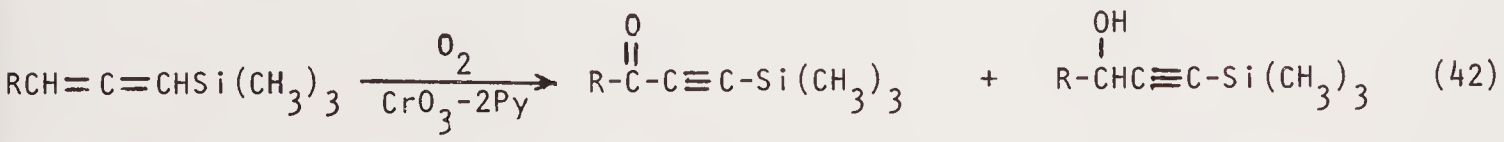
261 **262**

R_1, R_2= H, CH_3, t-C_4H_9, $(CH_2)_n$ (n=4,5,6)

R_3= CH_3, C_2H_5, C_3H_7(n,i), C_4H_9(n,s,t), C_6H_5

X= Cl, Br

Trimethylsilylallenes can be oxygenated to give either α,β-acetylenic ketones **264** or propargyl alcohols **265**[142] (equation 42). Allene **263**, when stirred under an oxygen atmosphere, forms propargylic hydroperoxides. Subsequent treatment with Collins reagent affords ketones **264** (43–74% yield) contaminated with 2–9% of **265** and 10–15% of the corresponding desilated ketones. Alternately, oxygenation of **263** in the presence of boronic anhydride (B_2O_3) gives alcohols **265** as the major product (41–53% yield) contaminated with 5–32% of **264**.



(42)

263 **264** **265**

R= alkyl, cyclopentyl

Cyclopentenes are important intermediates in the synthetic pursuit of prostaglandins, steroids, and other natural products. Danheiser[141,143] has ingeniously developed a one-step [3 + 2] approach to cyclopentene derivatives by way of a (trimethylsilyl)cyclopentene annulation. The reaction involves the combination of

Table 7.1. (Trimethylsilyl)cyclopentenes Prepared According to the Reaction Shown in Equation (43)[a]

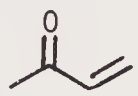
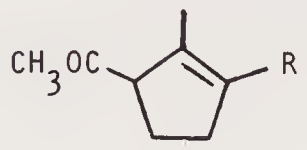
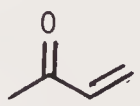
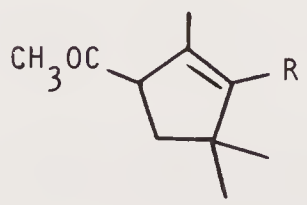
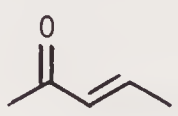
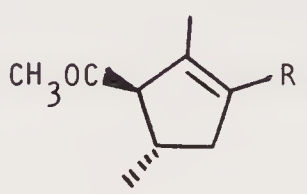
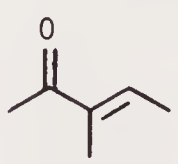
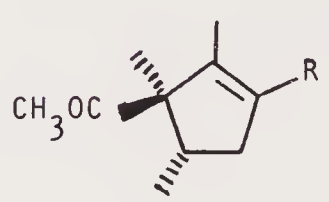
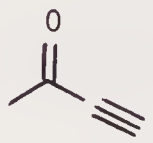
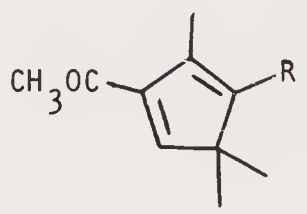
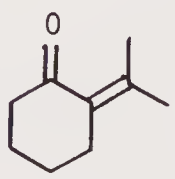
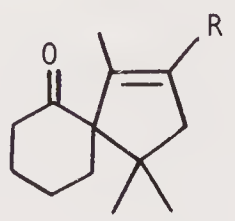
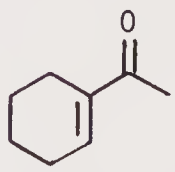
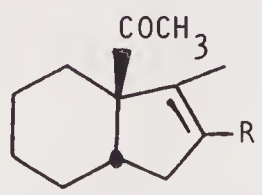
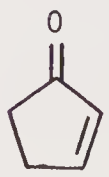
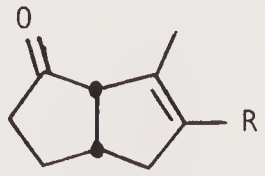
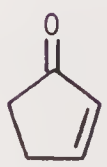
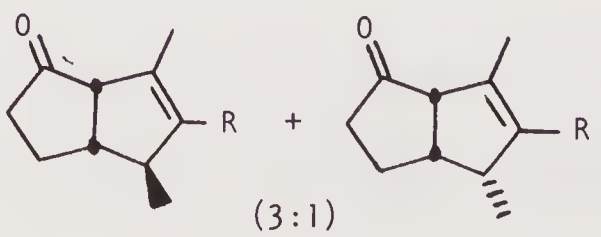
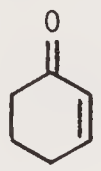
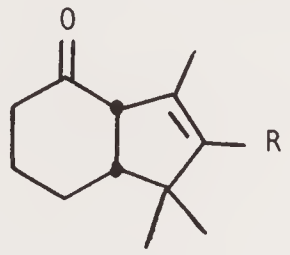
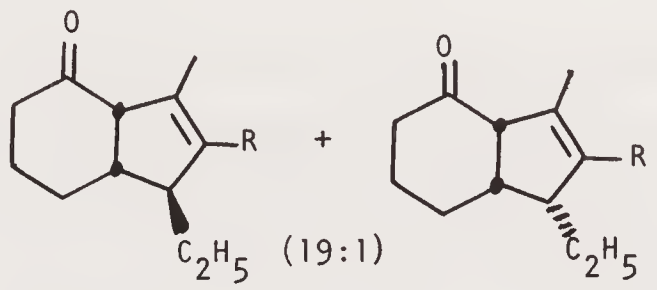
ALLENE R_1	ALLENE R_2	ALLENE R_3	ENONE	PRODUCT [R=Si(CH$_3$)$_3$]	Yield,%
H	H	CH_3			71-75
CH_3	CH_3	CH_3			80
H	H	CH_3			79
H	H	CH_3			71
CH_3	CH_3	CH_3			53
H	H	CH_3			86
H	H	CH_3			91
H	H	CH_3			48
CH_3	H	CH_3		 (3:1)	68

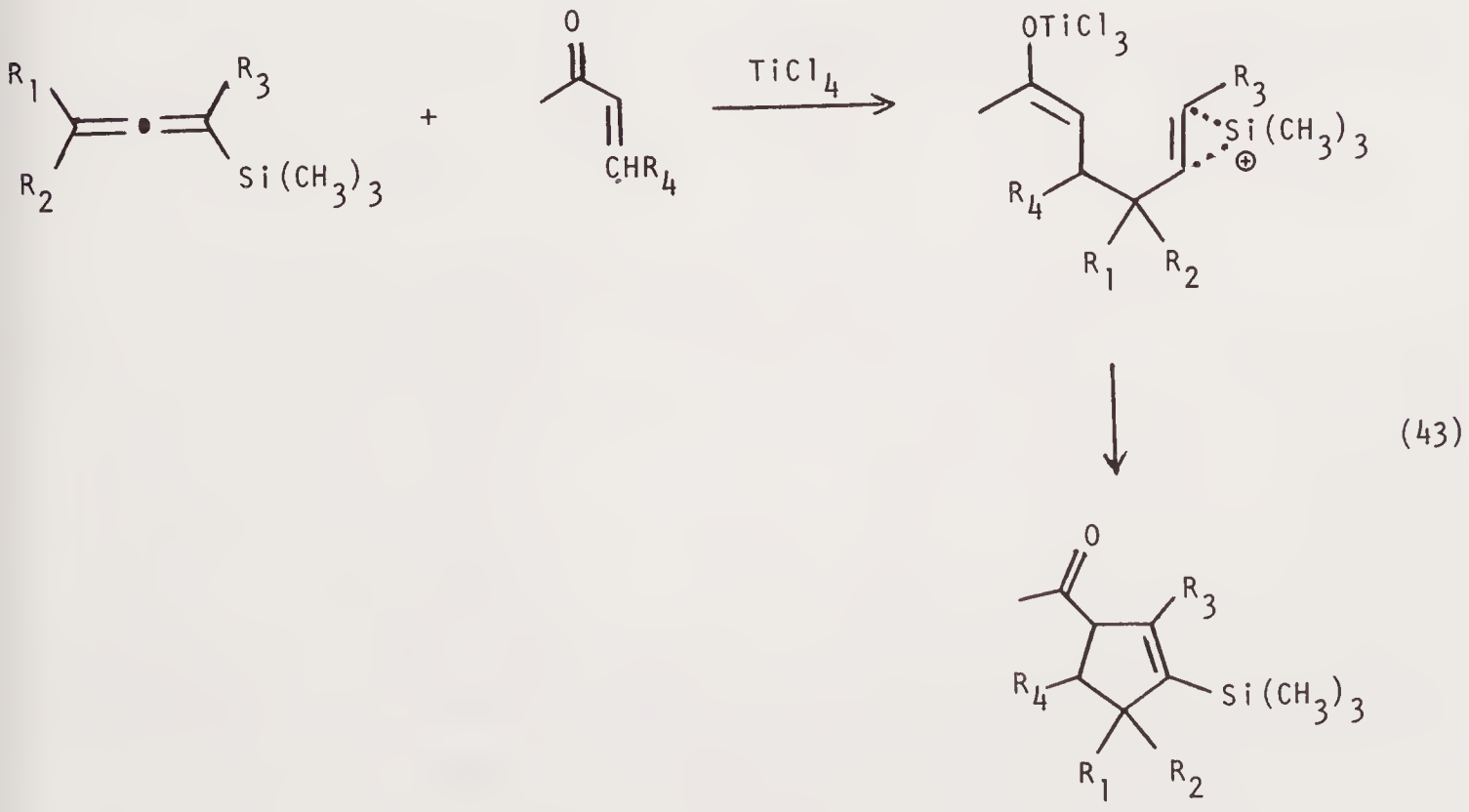
Table 7.1. (*Continued*)

ALLENE R_1	R_2	R_3	ENONE	PRODUCT [R=Si(CH$_3$)$_3$]	Yield,%
CH_3	CH_3	CH_3			63
C_2H_5	H	CH_3			79

[a]Reprinted in part from refs. 141 and 143 with permission from the authors. Copyright 1981 American Chemical Society.

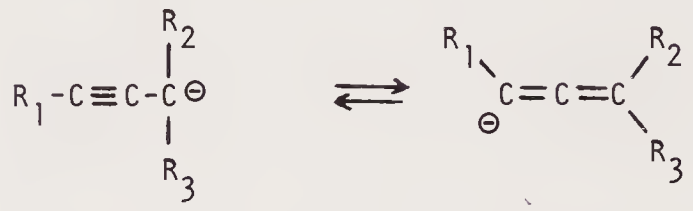
a trimethylsilylallene with an enone in the presence of titanium tetrachloride (equation 43).

A unique feature of this reaction is its capacity to regiospecifically generate five-membered rings substituted at each position and functionally equipped for further synthetic elaboration. This high stereoselectivity is a result of the preferential suprafacial addition of the allene to the electron-deficient olefin. Table 7.1 provides selected examples of this highly efficient transformation.



(43)

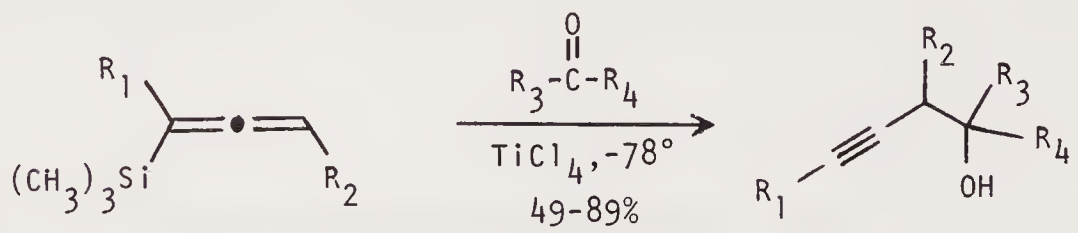
Propargyl anion equivalents are potentially useful synthons in the preparation of acetylenic compounds. Unfortunately, metallated derivatives of this type are in equilibrium with their allene tautomer (equation 44) and combine with electrophiles to produce both allenic and acetylenic products.



(44)

266a **266b**

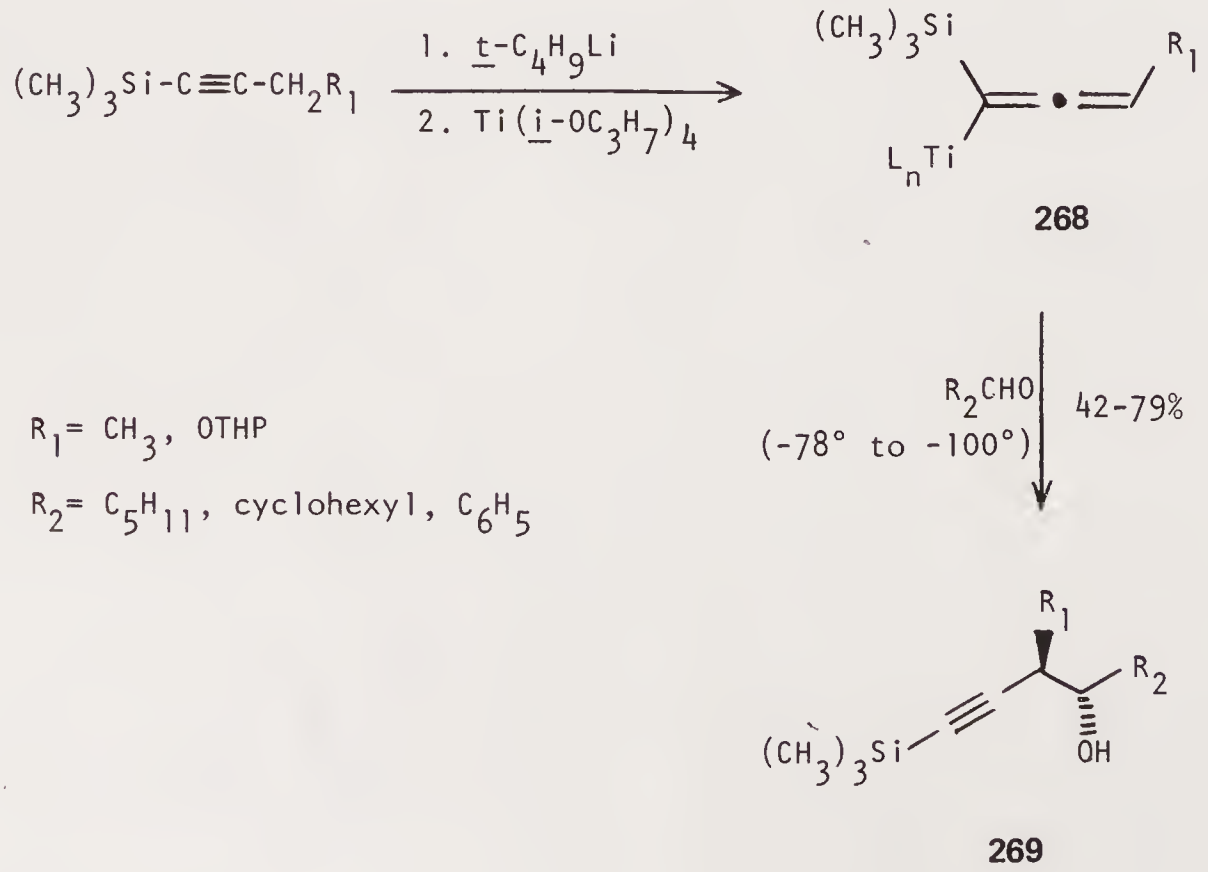
Trimethylsilylallenes can be used as a synthetic equivalent of **266a**. They react regiospecifically with ketones, aldehydes, and acetals in the presence of titanium tetrachloride to give homopropargylic alcohols **267** or ethers (equation 45).[137] In reactions with allenes where R_1 = H, the products are accompanied by minor amounts of (trimethylsilyl)vinyl chlorides.



(45)

267

In a somewhat similar study, Yamamoto[144] investigated analogous reactions using metallated trimethylsilylallenes. These reactions exhibit enhanced diastereoselection and produce *threo*-β-acetylenic alcohols **269** or, in the case of R = OTHP, *erythro*-α,β-acetylenic diols (after hydrolysis) (equation 46). In all cases titanyl allenes



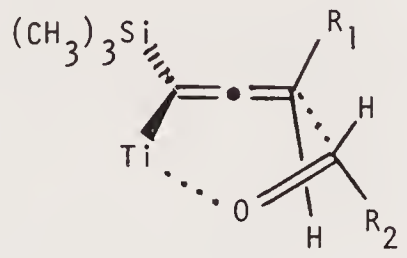
268

(46)

269

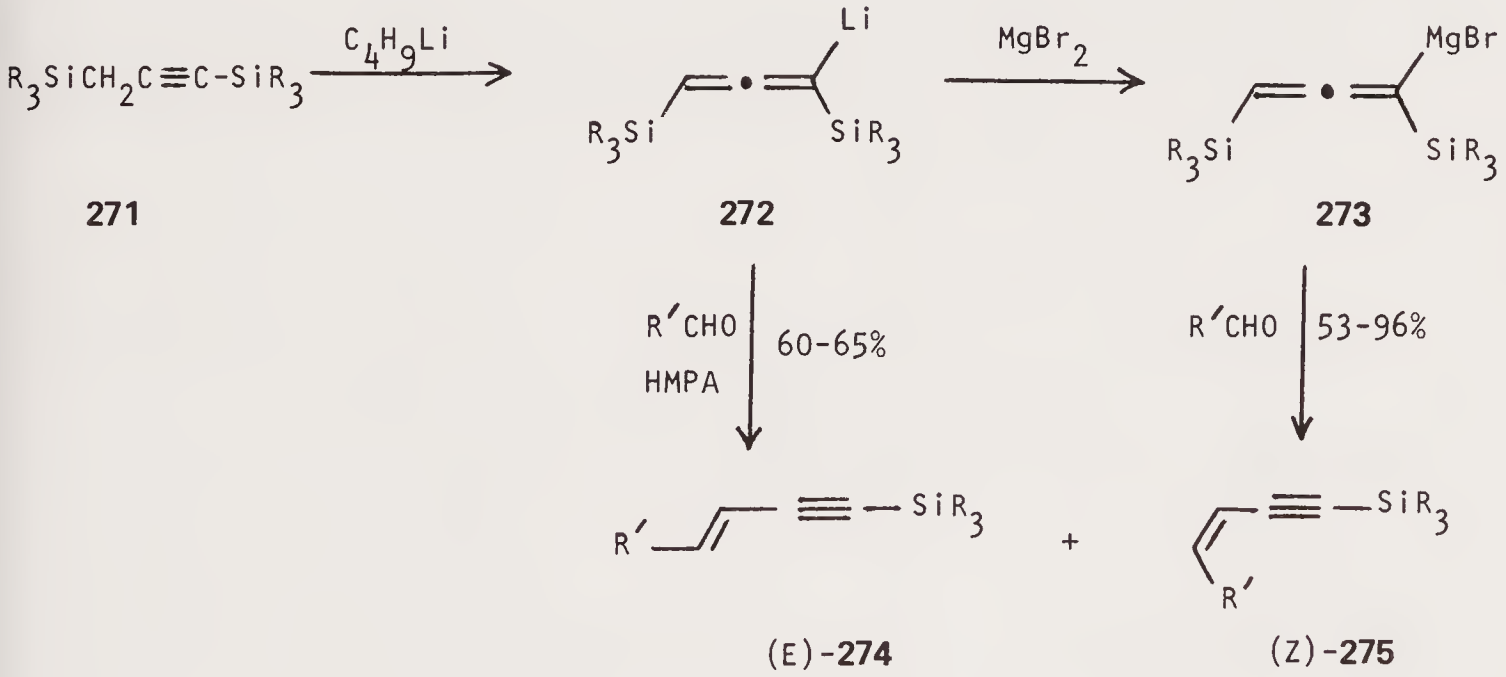
(**268**) are superior to the corresponding lithium, magnesium, or zinc derivatives and provide stereochemical purities in excess of 90%.

The high stereoselectivity exhibited by the reaction can be rationalized by invoking a transition state such as **270**.



270

Bis-1,3-disilylpropynes (**271**) are rapidly metallated with *t*-butyllithium (−78°)[145] or *n*-butyllithium (−20°C)[146] to generate allenyl lithio derivatives **272**. These anions react with aldehydes to give Z- or E-enynes, the ratio of which depends on the size of the silyl group, the counter ion, or reaction conditions (Scheme 45). The formation of Z-enynes **275** is favored, and transmetallation to magnesium (**273**) or titanium[147] increases the ratio dramatically. In contrast, when the reaction is performed in the presence of 5 equivalents of HMPA, *trans*-enynes **274** are obtained with E/Z ratios in the range of 20:1 to 10:1 (R = *i*-C_3H_7).[146]



271 **272** **273**

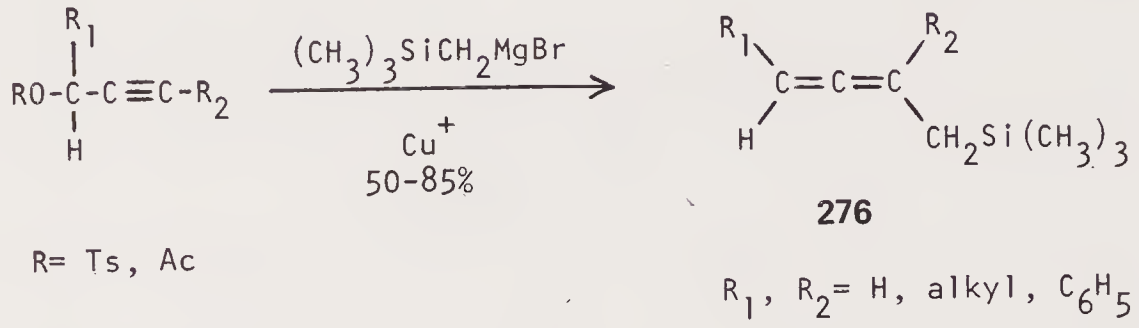
(E)-**274** (Z)-**275**

Enyne Product Distribution for R′ = Cyclohexyl[145]

R	Metal	Yield **274** + **275** (%)	E/Z Ratio
CH_3	Li	69	1:8
CH_3	MgBr	84	1:20
C_2H_5	Li	88	1:10
C_2H_5	MgBr	96	1:23
t-$C_4H_9(CH_3)_2$	Li	55	1:12
t-$C_4H_9(CH_3)_2$	MgBr	75	1:30

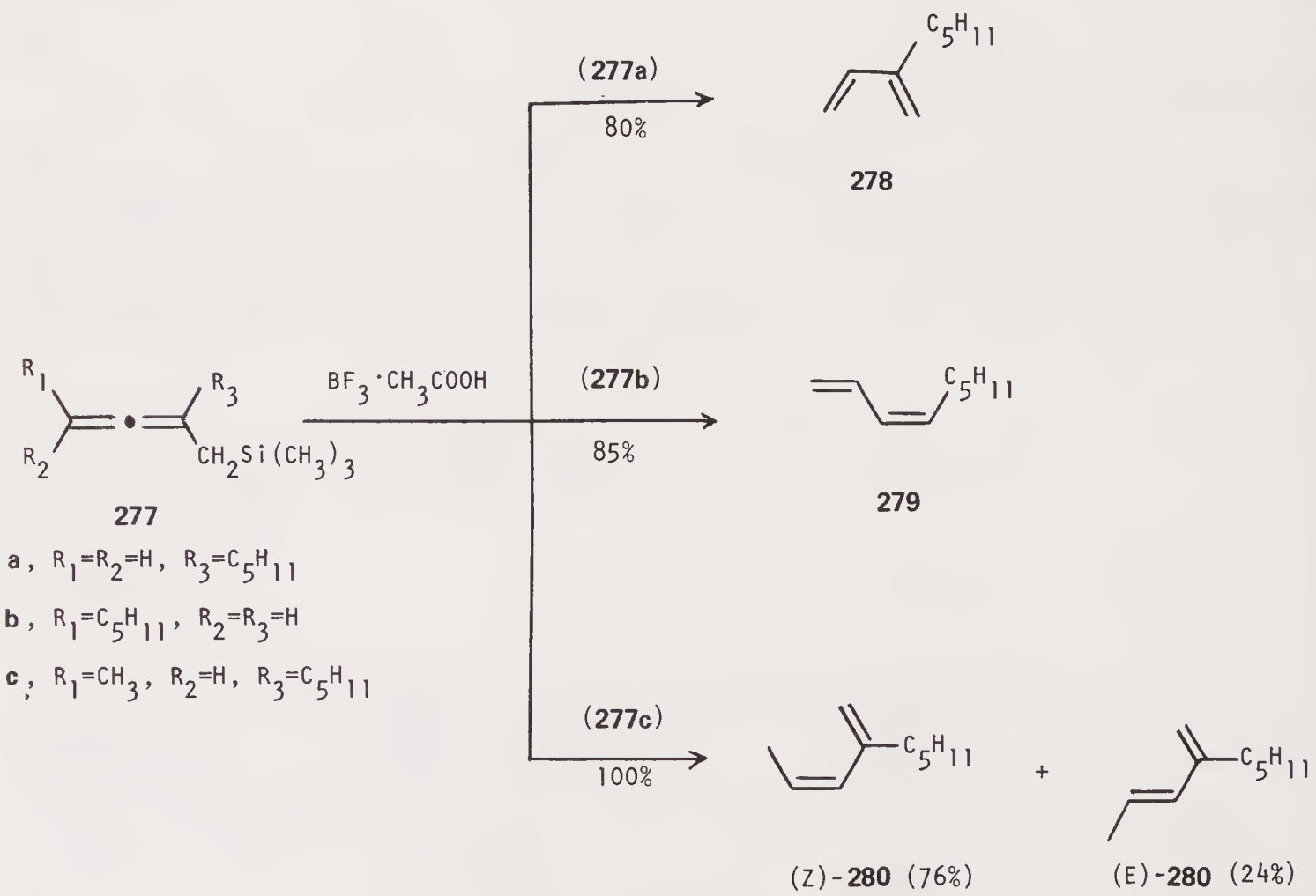
Scheme 45

The interaction of propargylic tosylates or acetates with the Grignard derivative of chloromethyltrimethylsilane in the presence of copper (*I*) ions leads to the formation of α-(trimethylsilyl) allenes **276**[148] (equation 47).



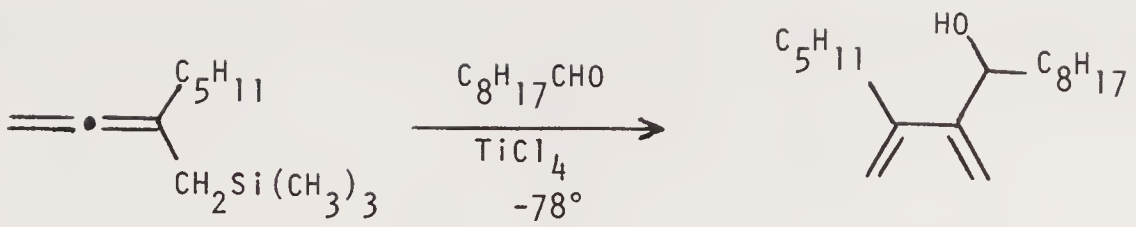
(47)

In the presence of a slight excess of boron trifluoride–acetic acid complex, these allenes are protodesilated to give, 1,3-dienes[149] (Scheme 46). Allene **277a** is transformed to 2-pentyl-1,3-butadiene (**278**) within 30 minutes at −78°C. Within the same time span but at −40°C, **277b** is converted to (Z)-1,3-nonadiene (**279**). Prolonged reaction times result in partial isomerization to the *trans*-diene. Allene **277c**, however, leads to a mixture of (E)- and (Z)-2-pentyl-1,3-pentadienes **280**, with the Z-isomer predominating.



Scheme 46

Allene **277a** also reacts with nonyl aldehyde in the presence of titanium tetrachloride to give the α-hydroxydiene **281** in 56% yield[148] (equation 48).

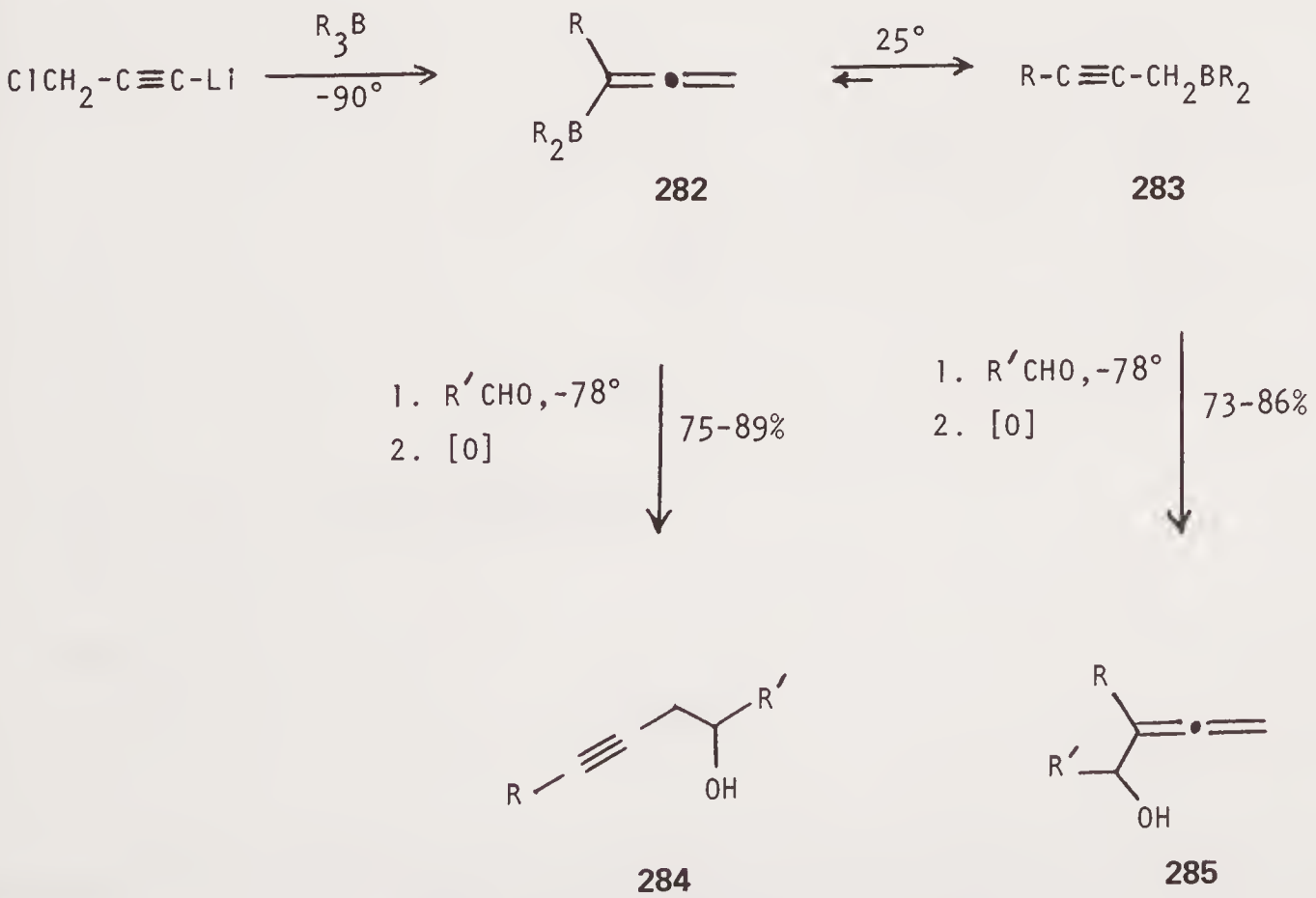


277a 281 (48)

7.6 BORON

Allenic boranes **282** have been introduced briefly in Chapter 2 (equation 26) as precursors for the preparation of terminal allene hydrocarbons. The allenes are stable at −78°C, however, at room temperature they rearrange to the thermodynamically more stable propargylic boranes **283** (Scheme 47). These organoboranes react with aldehydes to produce either homopropargylic alcohols (**284**) or α-allenic alcohols (**285**).

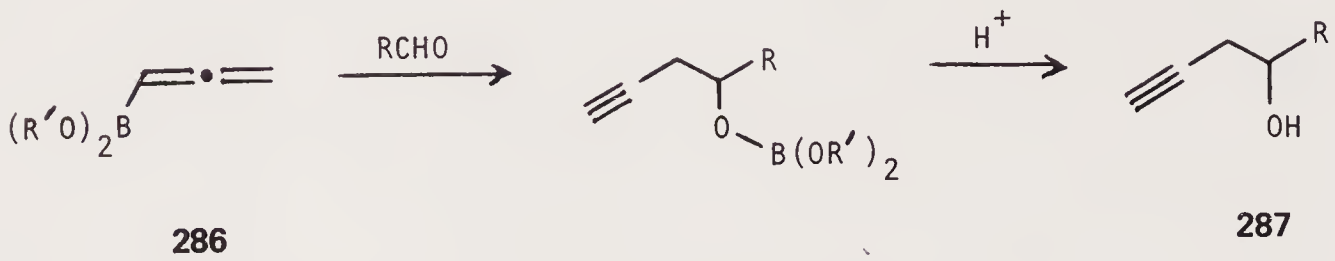
The most remarkable feature of the reaction is that the alcohol formed depends specifically on the temperature at which the organoborane is maintained prior to its reaction with the aldehyde. Addition of the aldehyde to the organoboron intermediate at −78°C produces, after oxidative workup, nearly exclusively **284**. If the organoborane is first brought to room temperature and then treated with the aldehyde at −78°C, alcohol **285** is obtained essentially free of contamination by the corresponding homopropargylic alcohol **284**.[150,151]



282 283 284 285

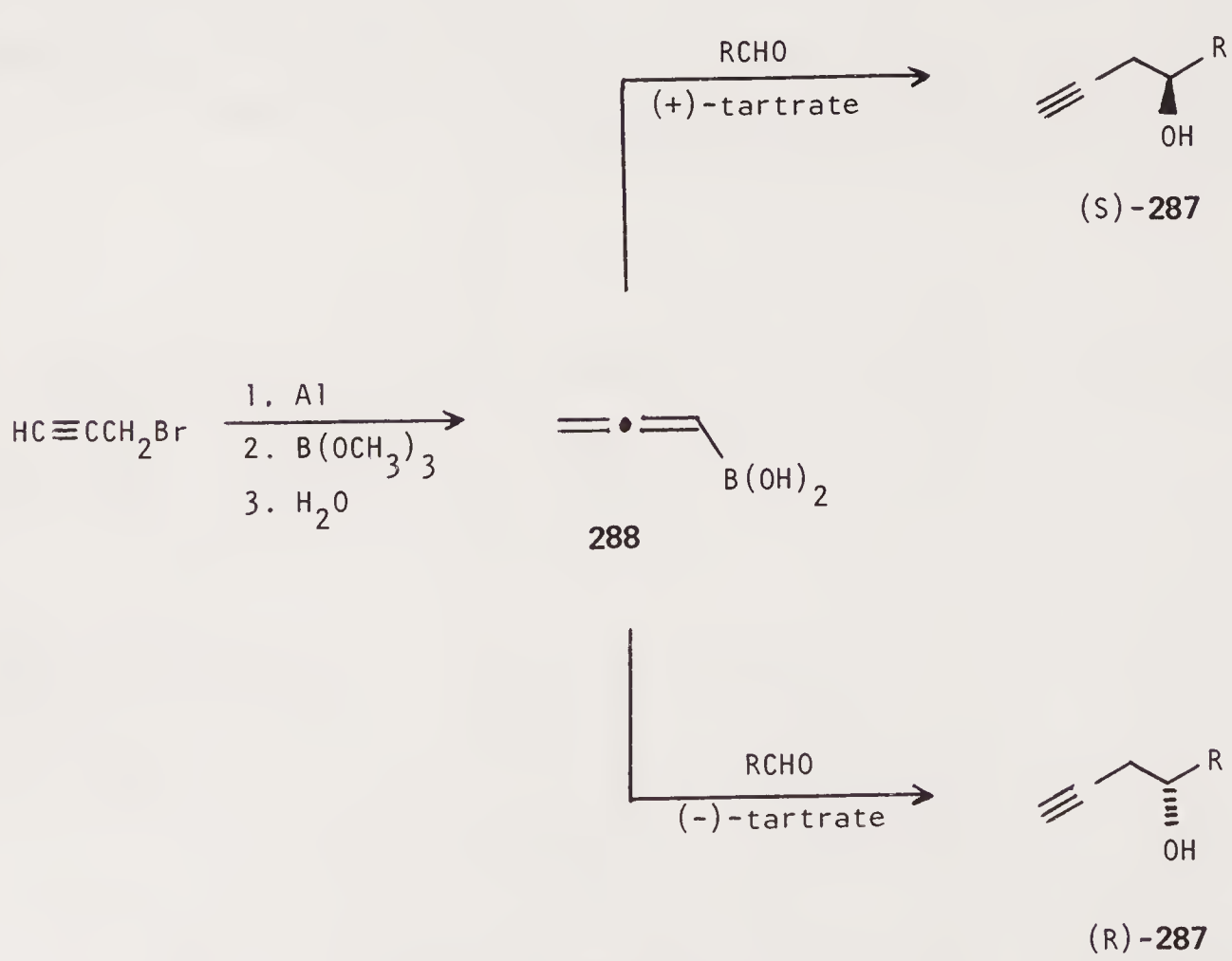
Scheme 47

A similar approach to the synthesis of β-hydroxyacetylenes makes use of allenylboronates **286** (equation 49).[152–155]



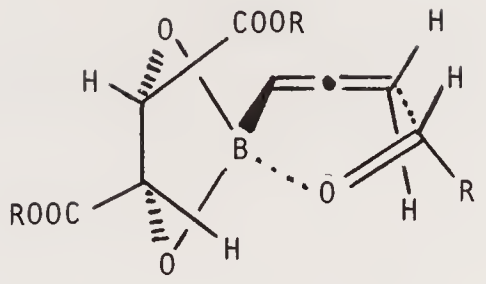
286 **287** (49)

A particularly exciting aspect of this method resides in those reactions employing optically active allenylboronates. Such chirally modified borate esters enantioselectively condense with aldehydes to provide homopropargylic alcohols with high enantiomeric excesses (60 to >95%).[156] Thus, when allenylboronic acid[157] (**288**) (pyrophoric) is treated with a (+)- or (−)-dialkyltartrate at 25°C (14 hours) followed by an aliphatic aldehyde at −78°C (12–24 hours), the (S)- or (R)-alcohol **287** is obtained in 42–85% yield (Scheme 48).



Scheme 48

The high optical induction in these reactions can be rationalized by the molecules adopting the relatively noncrowded transition state **289**.



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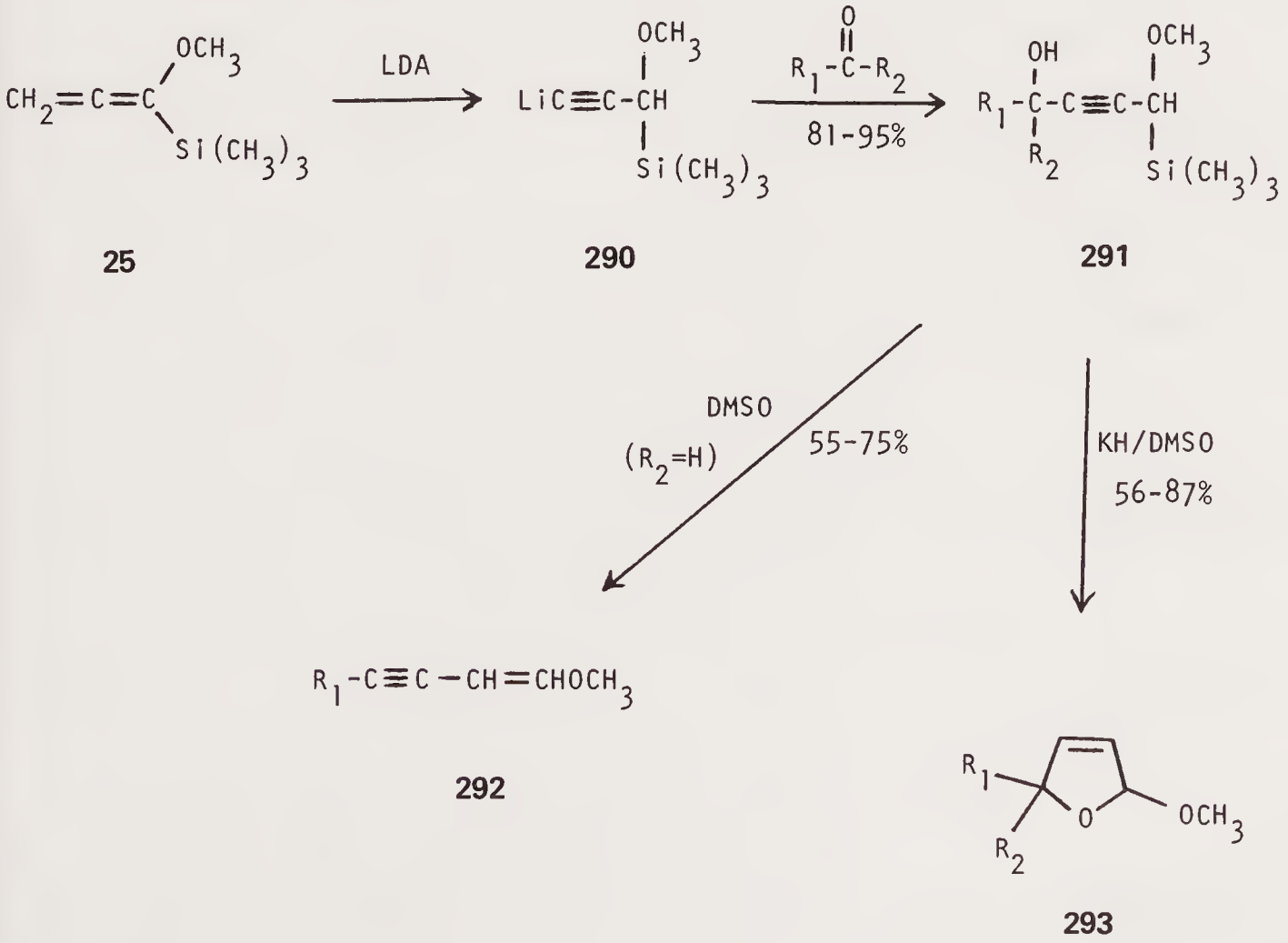
7.7 ADDENDA

1-Trimethylsilyl-1-methoxyallene (**25**), upon treatment with an alkyllithium reagent, undergoes selective γ-lithiation that reacts wholly in the allenyl form (see Schemes 10 and 11). On the other hand, reaction of **25** with lithium diisopropylamide causes isomerization to the lithio acetylene **290**. Addition of an aldehyde or a ketone to this anion leads to the formation of the propargyl alcohol **291** in high yields. If the alkoxide of **291** is allowed to stand in dry DMSO, the corresponding 1-methoxy-1-alken-3-yne (**292**) is obtained (E/Z ratio approximately 75:25). However, under the influence of 0.1 equivalent of potassium hydride in DMSO, **291** is readily converted to 2-methoxy-2,5-dihydrofurans (**293**)[161] (Scheme 49).



R_1, R_2= H, alkyl, C_6H_5, $(CH_2)_n$ (n=5,6,7)

Scheme 49

Table 7.2. Allenes as Acyl Anion Equivalents

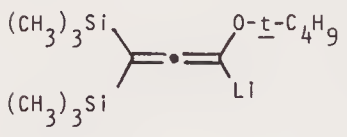
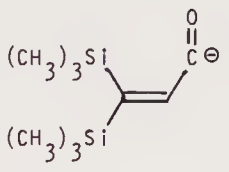
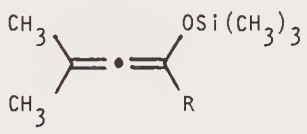
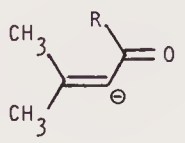
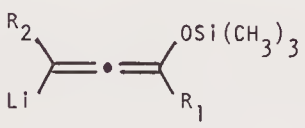
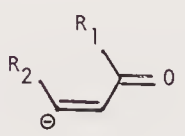
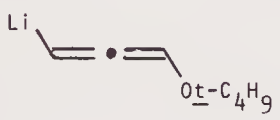
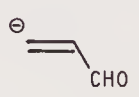
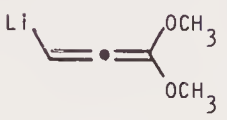
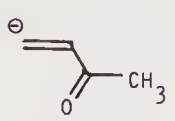
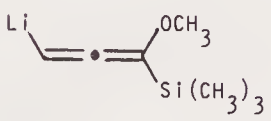
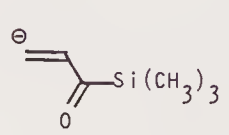
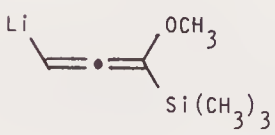
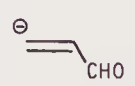
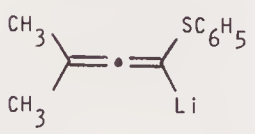
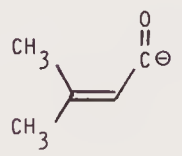
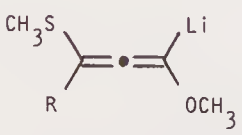
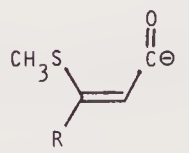
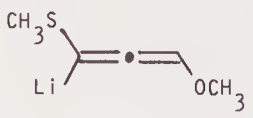
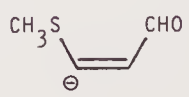
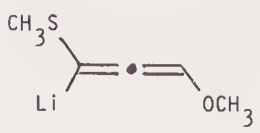
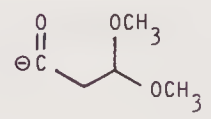
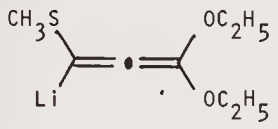
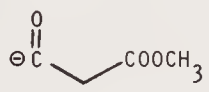
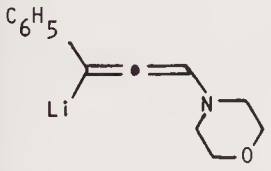
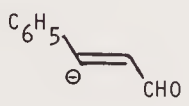
ALLENE	HYDROLYSIS or OXIDATION REAGENT	SYNTHON	REFERENCE
	H_3O^+		158
	H_3O^+		159
	H_3O^+		160
	H_3O^+		24
	H_3O^+		24
	CF_3COOH		17
	F^-		17
	$HgCl_2$		44,54
	H_3O^+		92
	H_3O^+		92
	$HgCl_2/CH_3OH$		92

Table 7.2. (*Continued*)

ALLENE	HYDROLYSIS or OXIDATION REAGENT	SYNTHON	REFERENCE
	1. PTSA 2. $HgCl_2/CH_3OH$		93
	CH_3COOH		101

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CHAPTER EIGHT

HALOALLENES

This chapter discusses those allenes that are directly bonded to one of the four common halogens. The reasonable stability of these allenes, as well as the ability to synthesize them in good yields and with high purity, makes this class of allenes synthetically exciting.

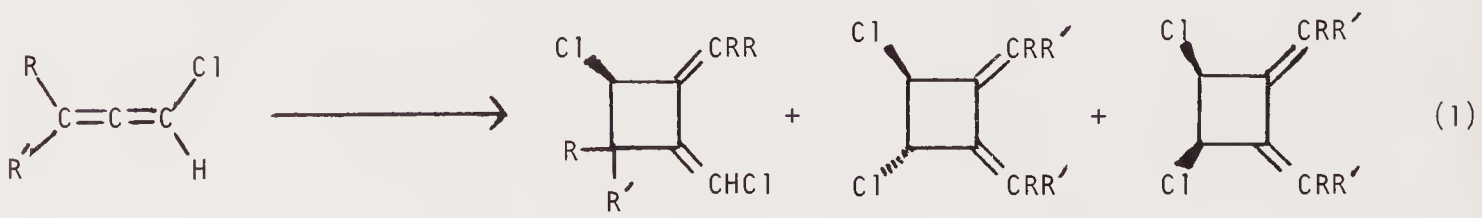
8.1. FLUOROALLENES

Although all possible simple fluoroallenes have been prepared,[1–5] their synthetic utility has not been explored. Spectroscopic studies[6] as well as several addition reactions[7–11] constitute the extent of their development so far.

8.2. CHLOROALLENES

8.2.1. Preparation

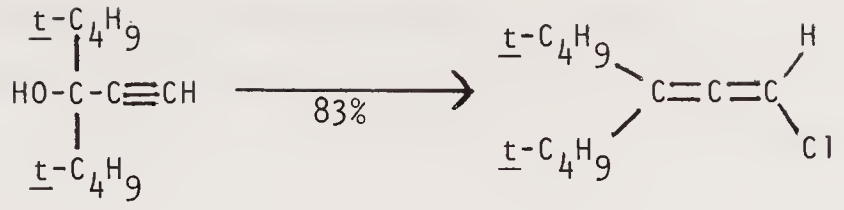
Chloroallenes have a limited synthetic utility. They easily dimerize to derivatives of 1,2-dimethylene cyclobutanes **1**, **2**, and **3**.[12–20]



(1)

1 **2** **3**

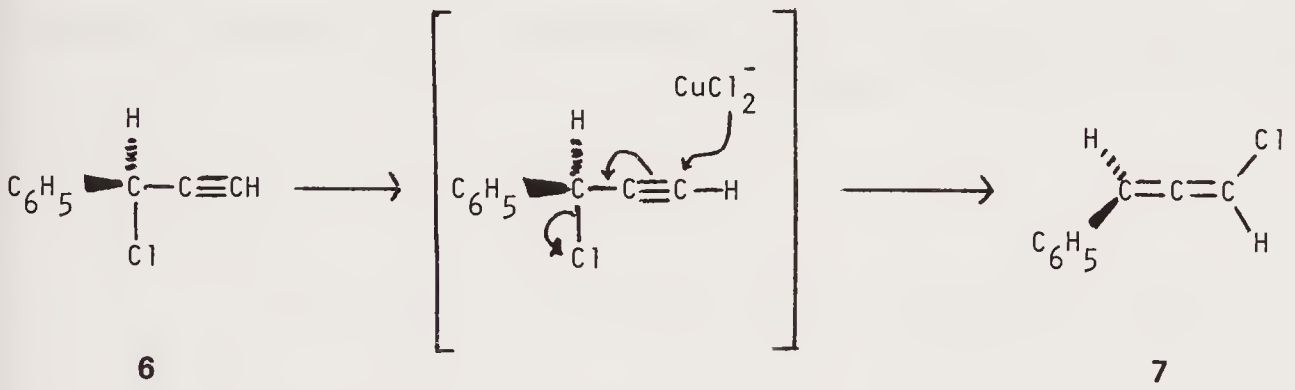
Chloroallenes have been prepared from propargylic alcohols by treatment with concentrated hydrochloric acid in the presence of either cuprous and ammonium chlorides,[21] or calcium chloride.[22,23] The addition of 3-*t*-butyl-4,4-dimethyl-1-pentyne-3-ol (**4**) to an ice-cold slurry of calcium chloride and concentrated hydrochloric acid provides 1-chloro-3,3-di-*t*-butylallene (**5**) in 83% yield after workup[23] (equation 2).



(2)

4 **5**

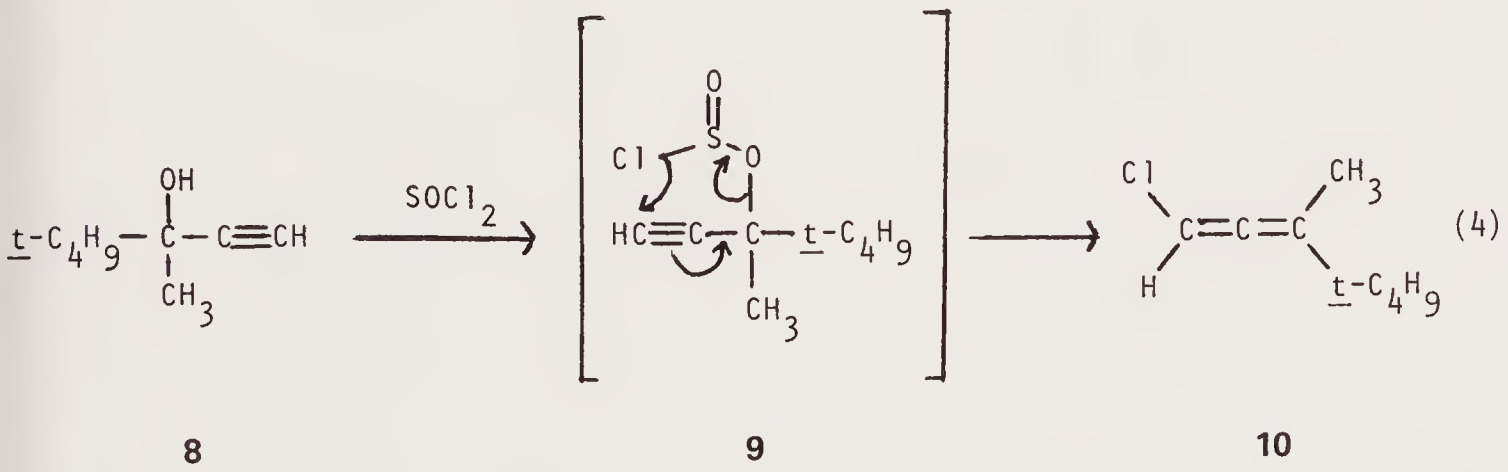
Primary,[24] secondary,[25] and tertiary[21] propargylic halides also undergo a cuprous chloride catalyzed rearrangement reaction to chloroallenes in 50–60% yields. In a stereochemical study of the conversion of 3-chloro-3-phenyl-1-propyne (**6**) to 1-chloro-3-phenyl-1,2-propadiene (**7**) by means of a tetrabutylammonium chloride stabilized cuprous chloride rearrangement, it was found that *anti* attack of the negative nucleophile is preferred[26] (equation 3).



(3)

6 **7**

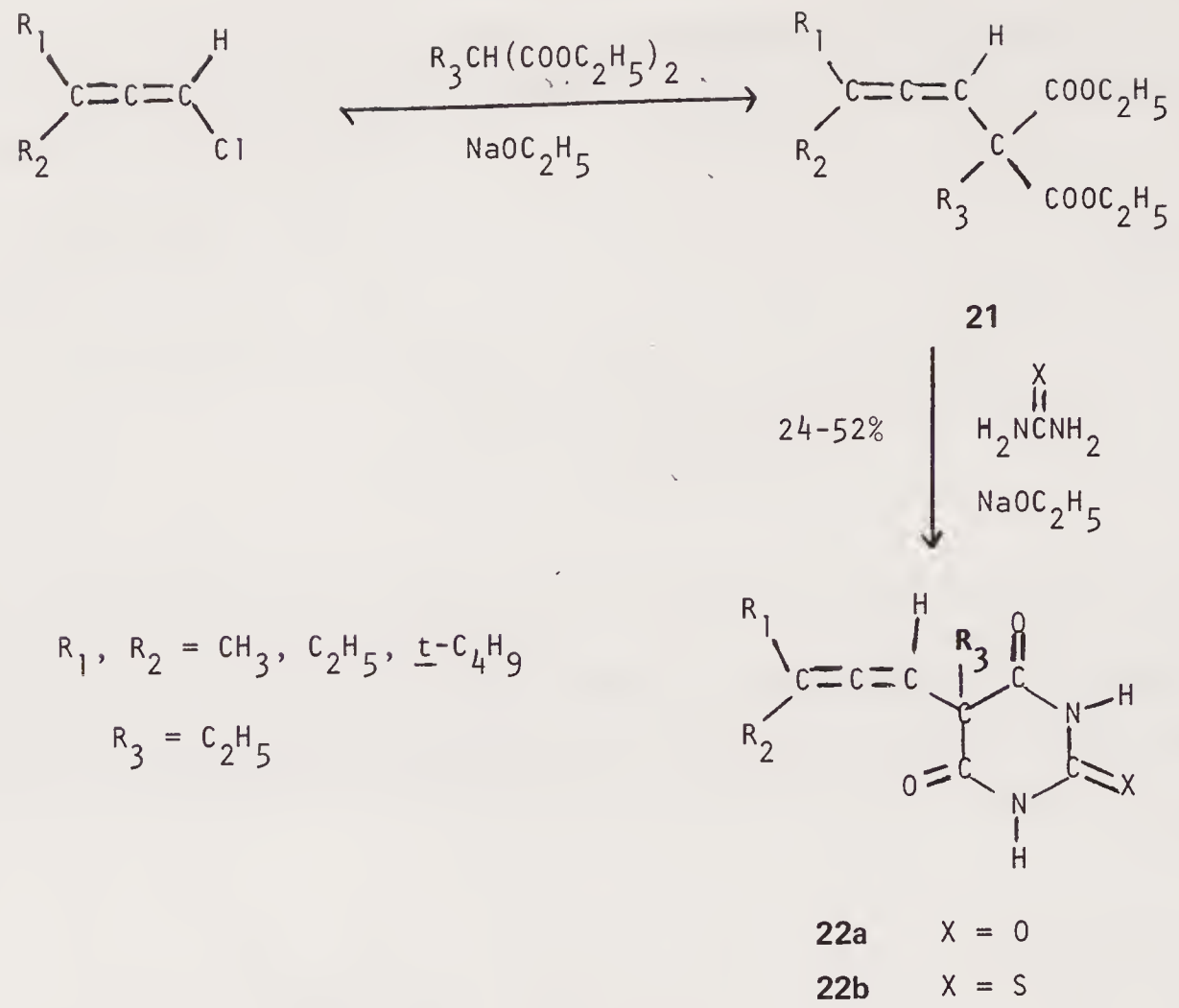
Chloroallenes can also be prepared by treating the corresponding propargylic alcohols with thionyl chloride in the presence of pyridine,[27,28] triethylamine,[29,30] or ether solvents.[31–33] Stereospecificity is observed when the reaction is performed in boiling dioxane without a base. This suggests an S_Ni' rearrangement of an intermediate chlorosulfinate.[32] Thus (R)-(−)-3,4,4-trimethyl-1-pentyne-3-ol (**8**) is converted to (S)-(−)-1-chloro-3,4,4-trimethyl-1,2-pentadiene (**10**) by means of the chlorosulfinate (**9**)[33–35] (equation 4).



(4)

8 **9** **10**

This stereospecificity is very sensitive to the reaction conditions. Racemization occurs if the thionyl chloride is impure or if water is present in the dioxane. Refluxing after addition is complete also leads to racemization.[33] Sterically hindered tertiary propargylic alcohols generally provide better yields of chloroallenes,[27,28] whereas aromatic propargylic alcohols tend to yield chloroallenes that often dimerize under the reaction conditions.[36,37]

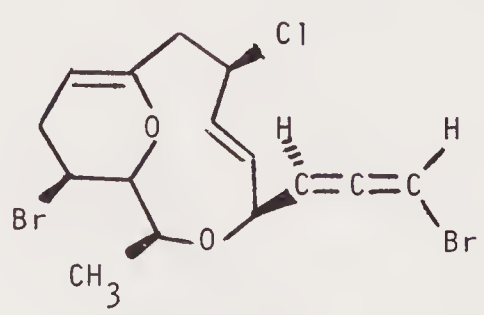


Scheme 2

8.3. BROMOALLENES

8.3.1. Natural Occurrence

The numerous secondary metabolites of the red algal genus *Laurencia* include obtusallene (**23**),[43] isolaurallene (**24**),[44] and okamurallene (**25**),[45] all of them novel nonterpenoid C_{15} bromoallenes.



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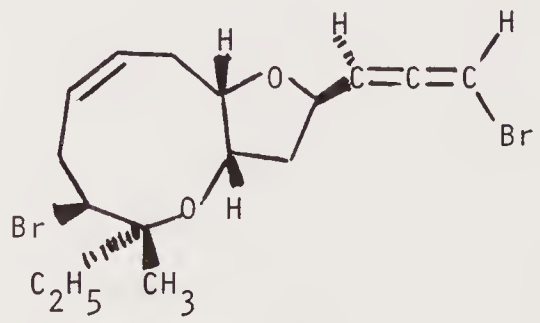
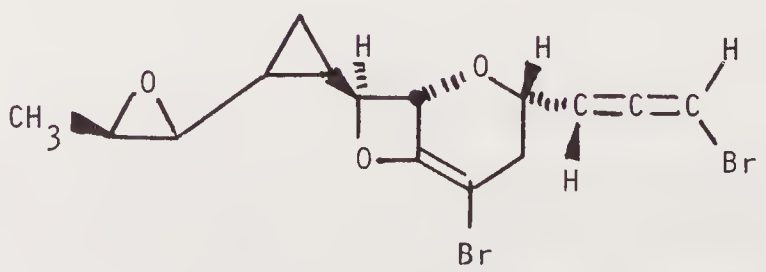


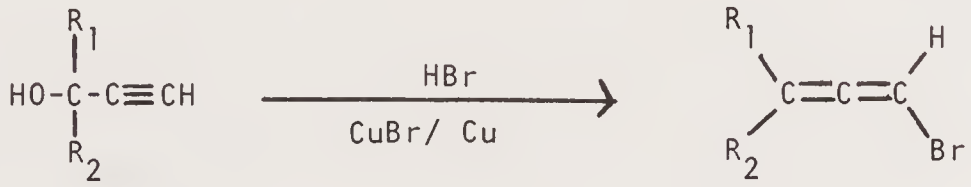
24



25

8.3.2. Preparation and Reactions

1-Bromoallenes can be prepared in excellent yields from the reaction of concentrated hydrobromic acid with either secondary or tertiary propargylic alcohols in the presence of a cuprous bromide–copper catalyst[46–50] (equation 8).

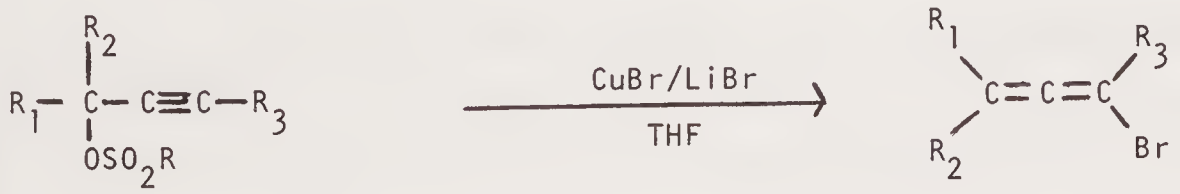


(8)

R_1	R_2	Yield (%)
H	CH_3	37
H	*i*-C_3H_7	43
CH_3	CH_3	65
CH_3	*t*-C_4H_9	81
t-C_4H_9	*t*-C_4H_9	70
—$(CH_2)_5$—		45

Bromoallenes are characterized by a sharp allene band at 1950 cm^{-1} (5.1 μ)[46,47] in the infrared spectrum. Most bromoallenes are mobile, slightly lachrimogenic liquids that are reasonably stable when stored at low temperatures.[49,51]

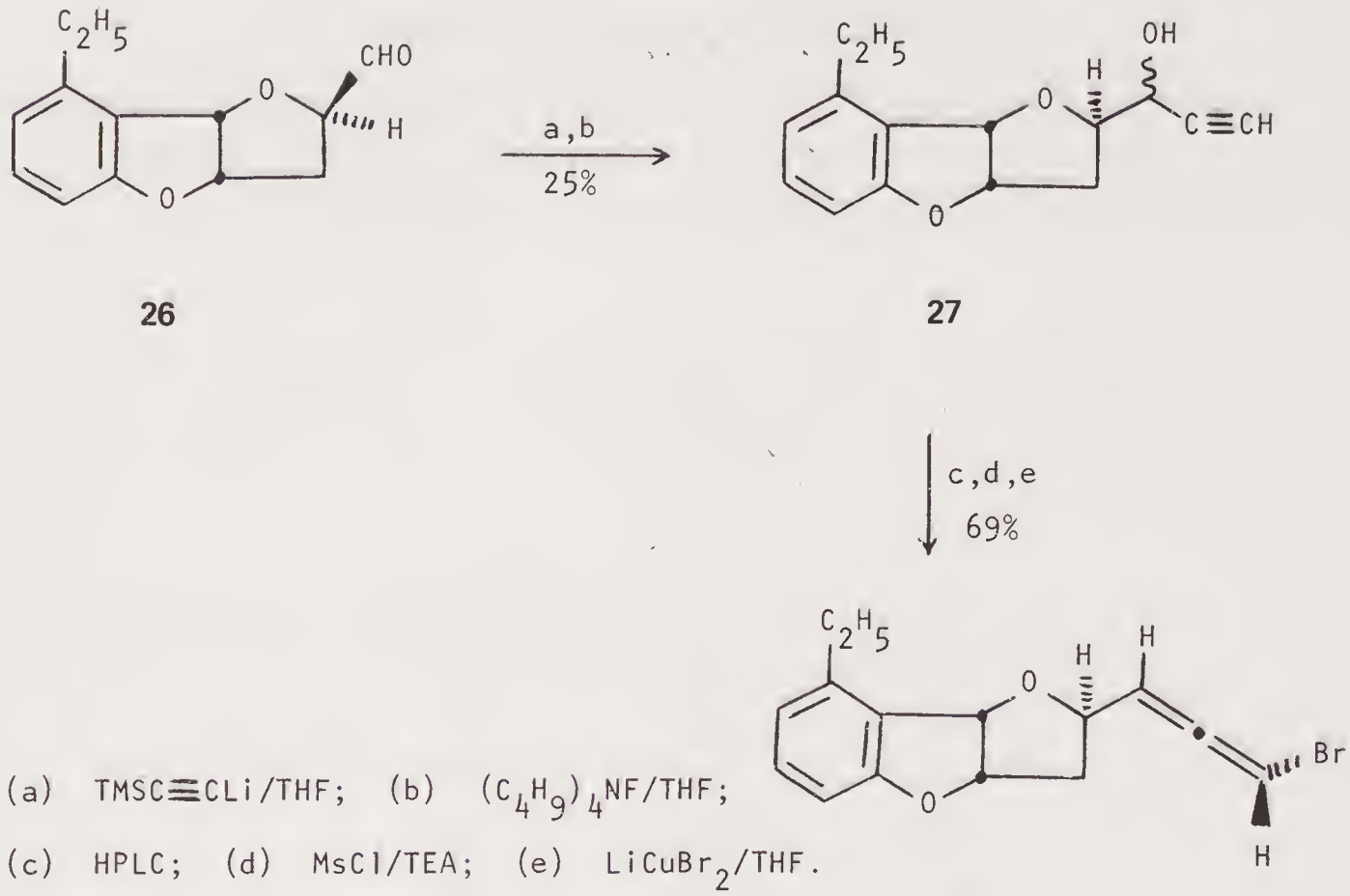
Certain bromoallenes are also produced in good yields with high regioselectivity when propargylic tosylates are treated with $CuBr_2Li$. This is a simple procedure performed under mild, neutral conditions. Complexation of the reagent with the triple bond appears to be the determinant factor to promote the substitution[52] (equation 9).



(9)

R	R_1	R_2	R_3	Yield (%)
p-$C_6H_4CH_3$	H	C_3H_7	H	70
CH_3	CH_3	CH_3	H	65
CH_3	H	C_6H_5	H	71
CH_3	H	C_6H_5	C_6H_5	74

Such a method is used to complete the stereoselective synthesis of (±)-panacene (**28**),[53] a potent feeding deterrent of sharks and other predatory fish, isolated from the sluglike gastropod mollusk *Aplysia brasiliana*[54] (Scheme 3).



26 27 28

(a) $TMSC{\equiv}CLi$/THF; (b) $(C_4H_9)_4NF$/THF;
(c) HPLC; (d) MsCl/TEA; (e) $LiCuBr_2$/THF.

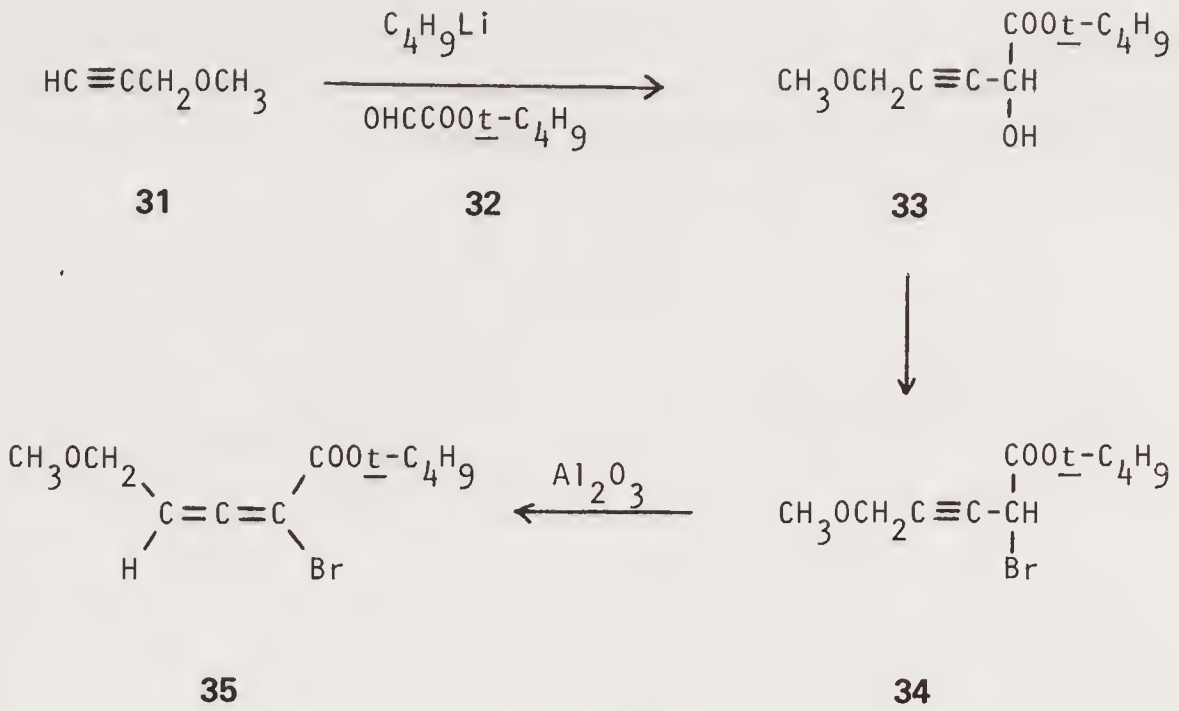
Scheme 3

Ethyl 4-bromobutadienoate (**30**)[55] can be quantitatively prepared from ethyl 3,4-dibromo-2-butenoate (**29**) by the action of excess triethylamine in either ethanol at room temperature or in refluxing diethyl ether[38] (equation 10).

(10)

29 30

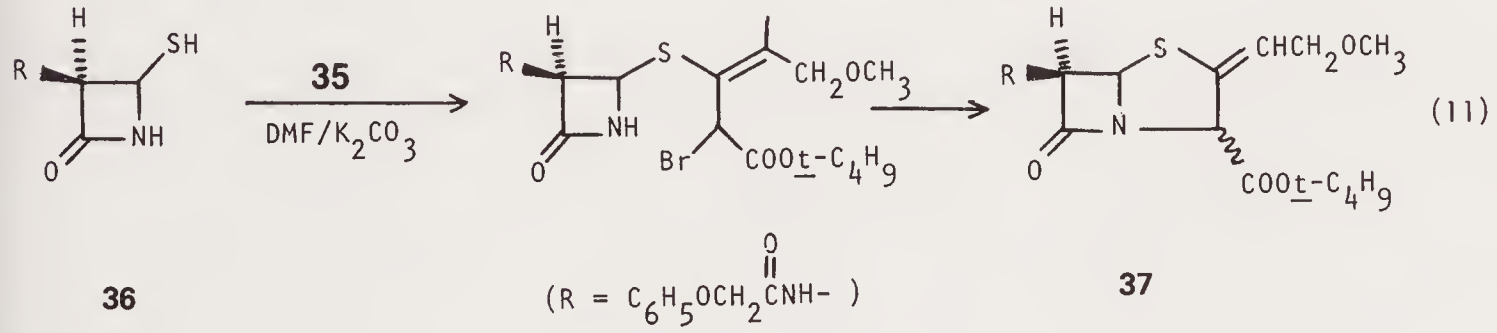
A general method for the preparation of the isomeric α-bromoallenic esters has been developed involving the reaction of an acid chloride with a carboxybromomethylene triphenylphosphorane. Treatment of methyl-2-propynyl ether (**31**) with 1 equivalent of *n*-butyllithium followed by freshly distilled *t*-butyl glyoxylate (**32**) gives the α-hydroxyacetylenic ester **33** that is converted into the bromoacetylenic ester **34** with carbon tetrabromide-triphenylphosphine. Rearrangement to the α-bromo allenic ester **35** is effected with basic alumina[40,56] (Scheme 4).



31 **32** **33** **35** **34**

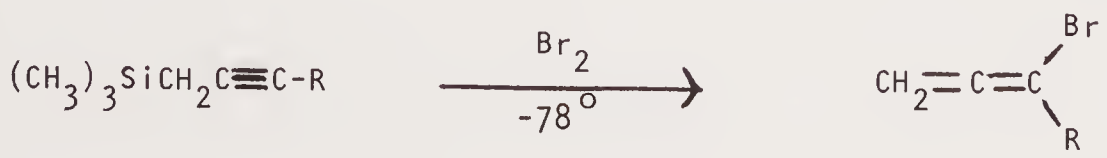
Scheme 4

Michael addition of 4-mercaptoazetidine-2-one (**36**) with **35** followed by an intramolecular N-alkylation provides an entry to the 2-alkylidenepenam esters (**37**)[56] (equation 11).



36 **37** (11)

α-Substituted bromoallenes are accessible in good yields from the cleavage of a silicon propargylic carbon bond with bromine. At −78°C the cleavage occurs, followed by a rearrangement to give the 3-bromoallenes **38–40**[57–59] (equation 12).



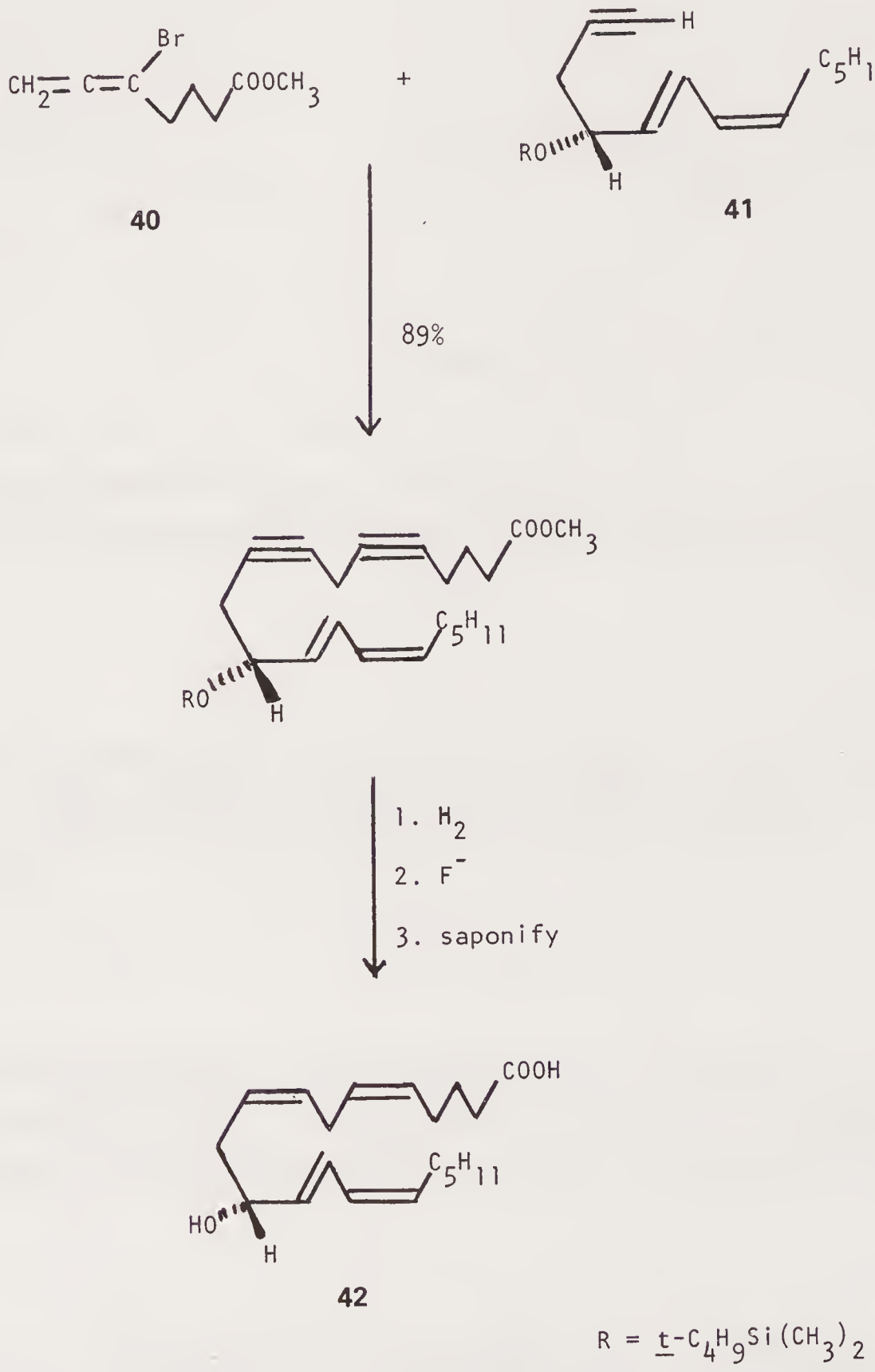
(12)

38) R = C_6H_{13} 58%

39) R = $Si(CH_3)_3$ 95%

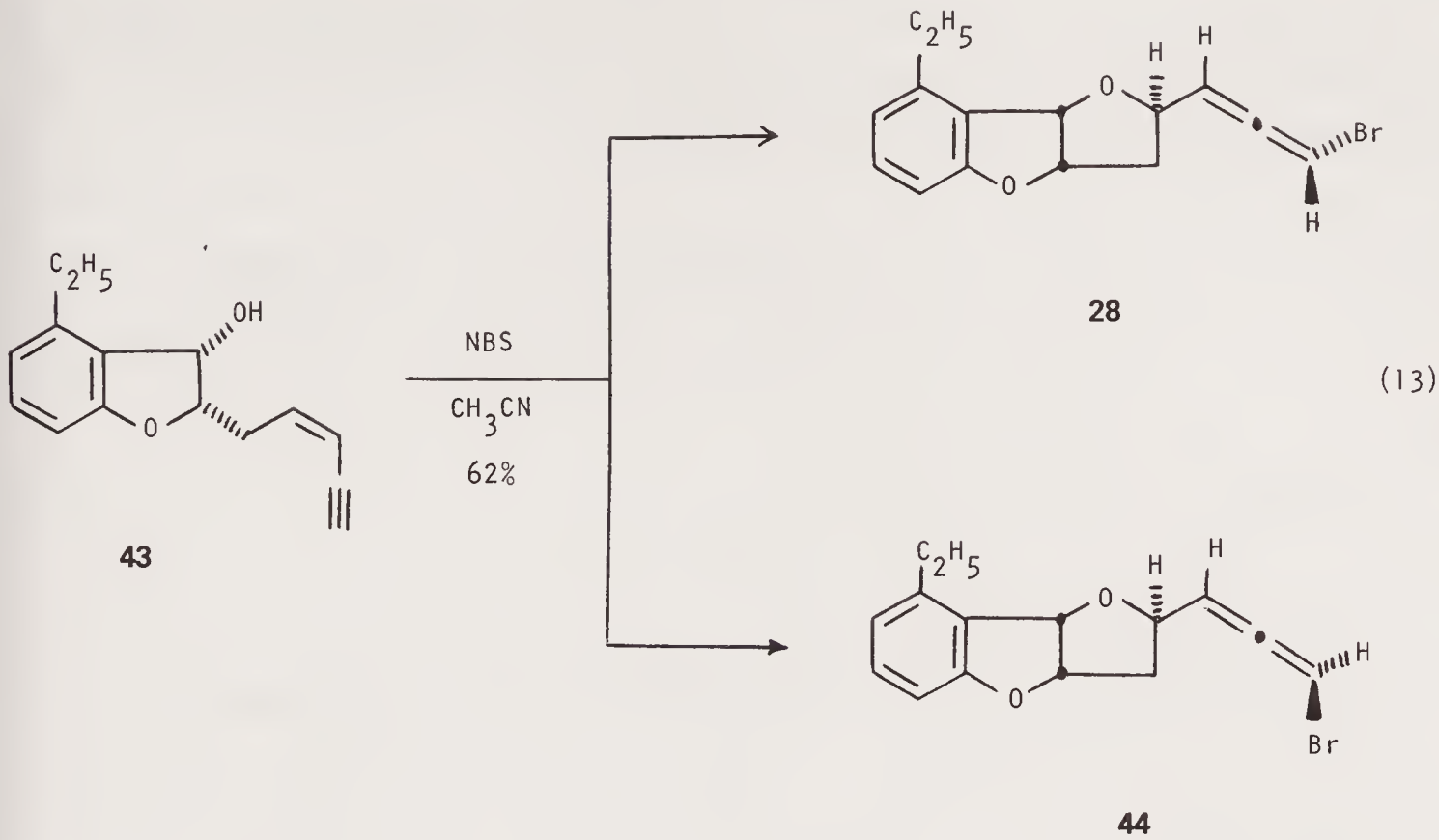
40) R = $(CH_2)_3COOCH_3$ 76%

The stereospecific total synthesis of 11(R)-HETE (**42**) by way of a coupling reaction of **40** with the acetylenic diene **41** illustrates a beautiful application of these bromoallenes to a challenging synthesis[59] (Scheme 5).



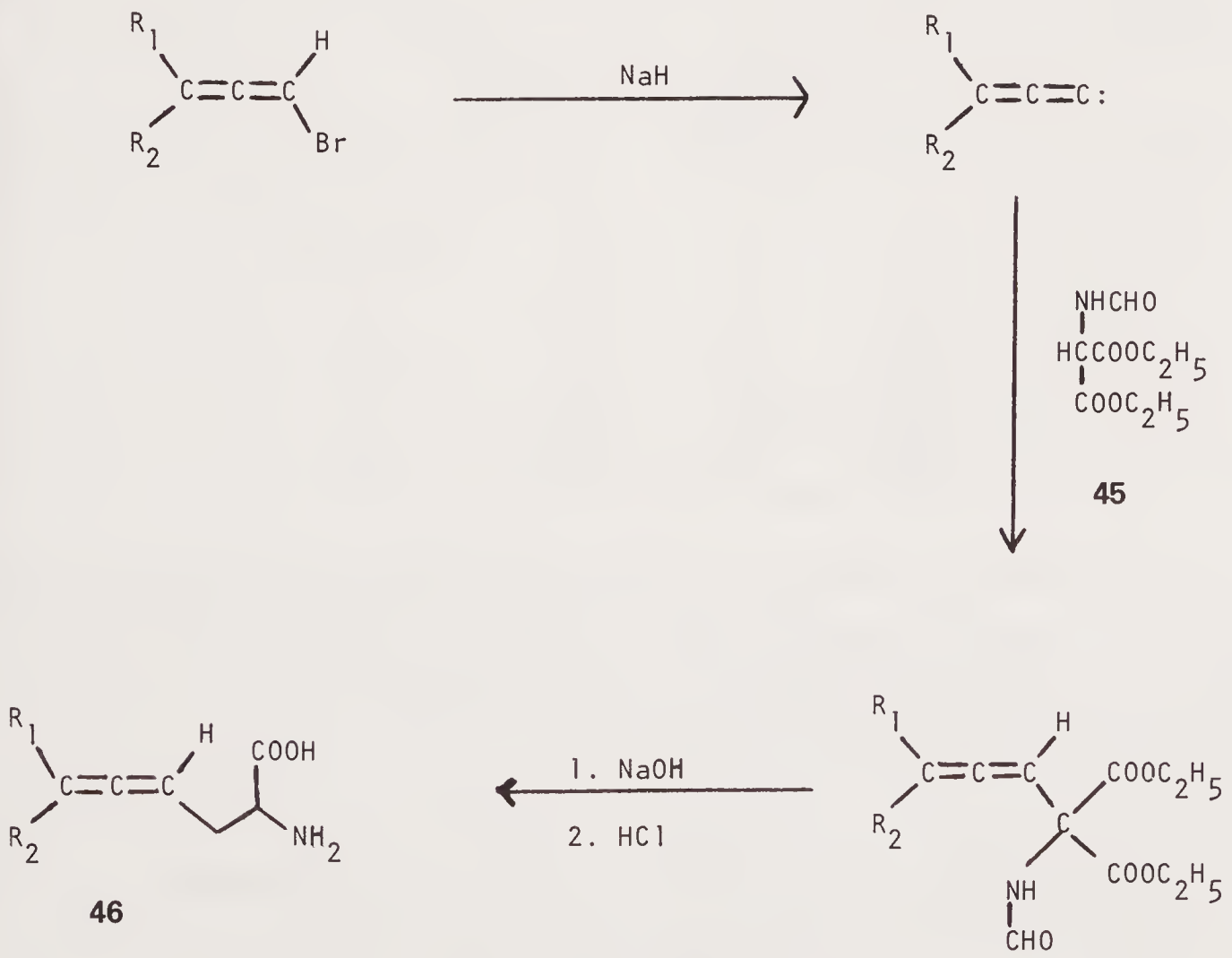
Scheme 5

A very elegant biomimetic brominative cyclization of the hydroxyenyne **43** has been applied to a second synthesis of (±)-panacene (**28**). A 1:1 mixture of **28** and 1-epibromopanacene (**44**) results, presumably by way of competitive *anti* and *syn* (to the OH group) attack of the bromonium ion on the enyne unit of **43**.[60]



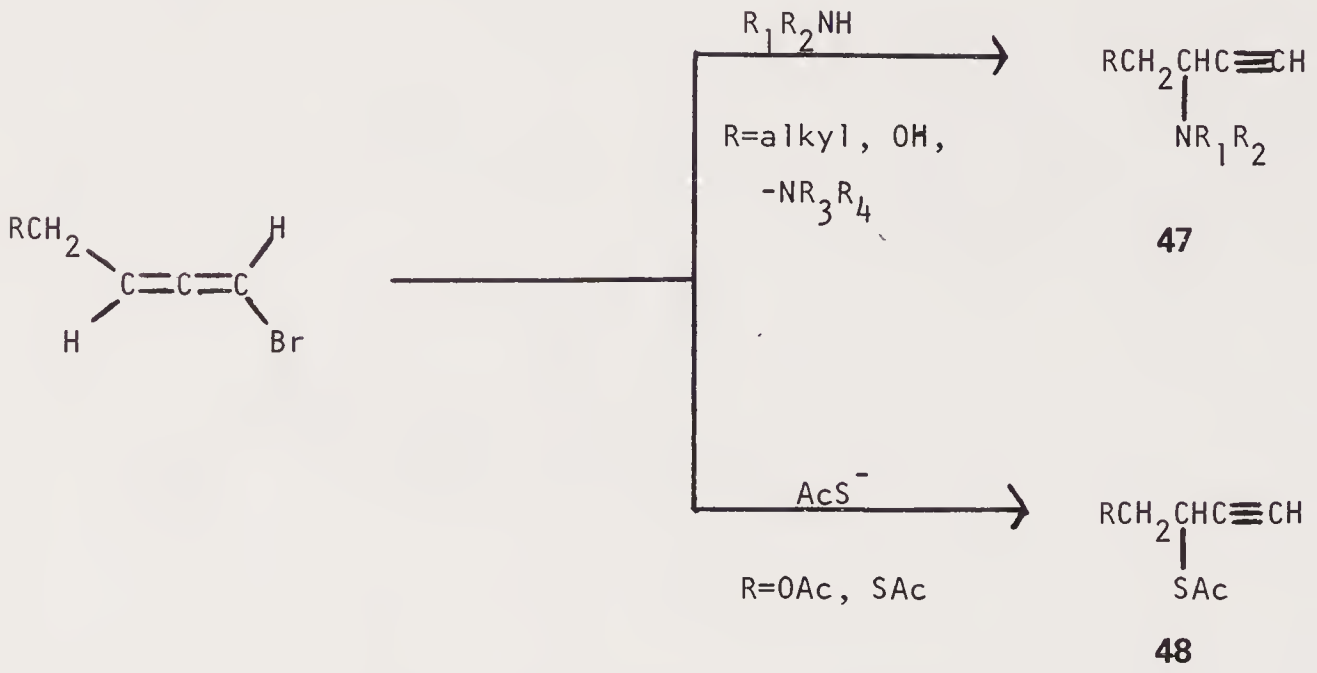
(13)

Allenic amino acids (**46**) can be prepared from the reaction of 1-bromoallenes with diethyl formamidomalonate (**45**) presumably by means of an allenic carbene insertion mechanism (Scheme 6).[61]



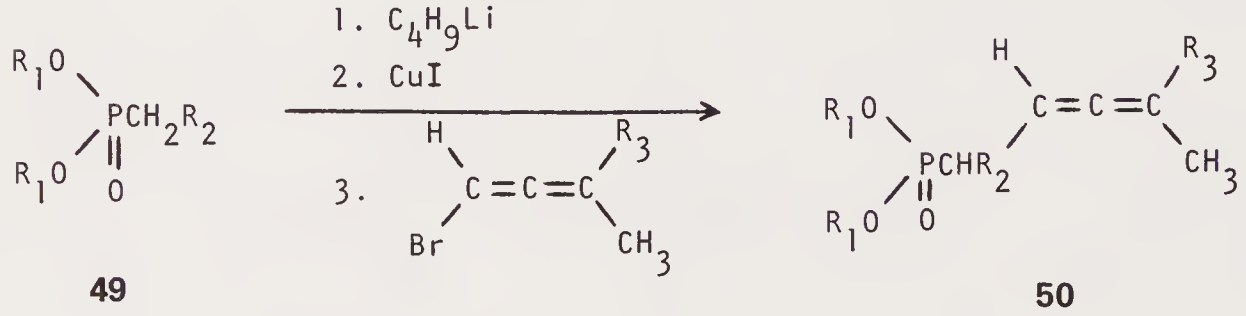
Scheme 6

Interestingly, when 1-bromoallenes react with such nucleophiles as amines or thioacetates, an allene–acetylene rearrangement occurs that affords high yields of functionalized acetylenes **47** and **48**[51] (equation 14).



(14)

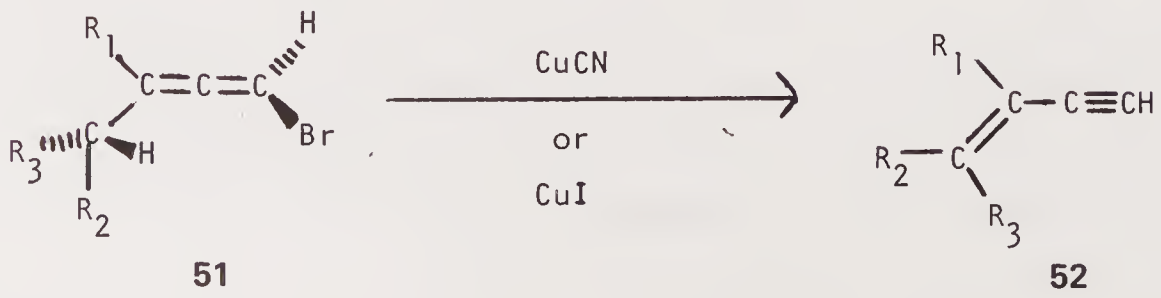
The reaction of 1-copper(I) derivatives of alkyl alkane phosphonates **49** with 1-bromoallenes constitutes a useful general synthesis of dialkyl 2,3-alkadiene phosphonates **50**[62] (equation 15).



(15)

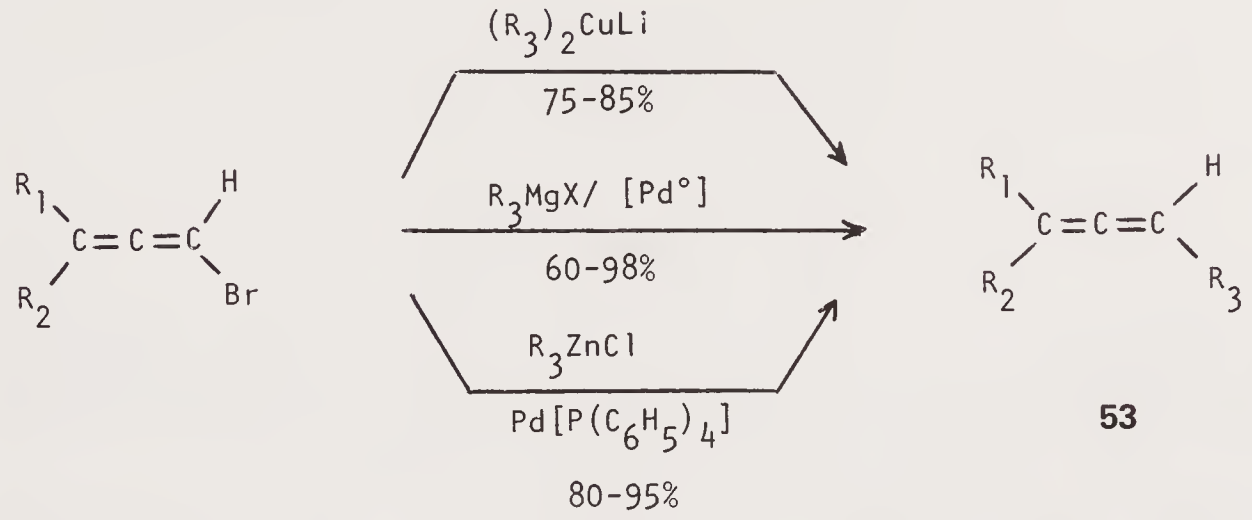
R_1	R_2	R_3	Yield (%)
CH_3	H	CH_3	40
C_2H_5	H	H	65
C_2H_5	H	CH_3	73
C_2H_5	CH_3	CH_3	69

The 1,4-elimination of hydrogen bromide from 1-bromoallenes **51** in the presence of either dry cuprous cyanide or cuprous iodide (or bromide) in DMF provides a good route to alkenynes **52**. Both the *cis* and *trans* geometries are usually obtained, with the *trans* predominating[63] (equation 16).



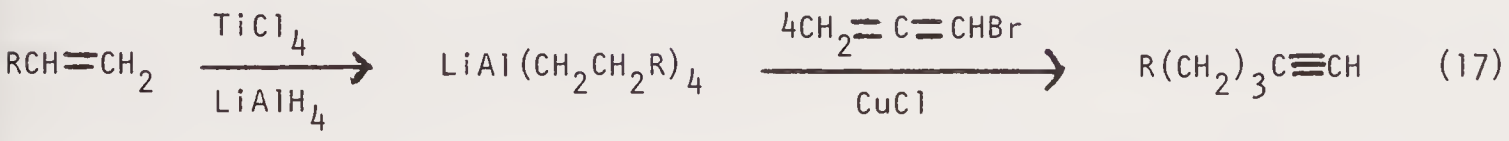
(16)

Allenic bromides can also be treated with lithium dialkyl cuprates at low temperature for the preparation of allenic hydrocarbons **53**.[64,65] Alternately, these allenes can be prepared from the reaction of Grignard reagents with 1-bromoallenes in the presence of a catalytic amount of palladium chloride, triphenyl phosphine, and DIBAH in THF at room temperature.[66] Good yields and high allenic purity are usually obtained. Aryl, vinyl, 1-alkynyl allenes, and diallenes are also accessible by means of (tetrakis–triphenylphosphine) palladium-promoted reaction of an allenic bromide with appropriate organozinc halides[67] (Scheme 7).

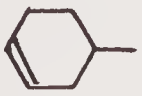


Scheme 7

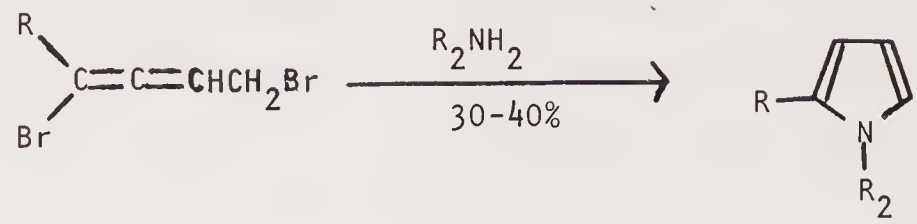
The hydroalumination of 1-alkenes followed by treatment with bromopropadiene provides a convenient method for preparing terminal acetylenes **54** in moderate yields[68] (equation 17).



(17)

R	Yield, %
H	43
C_3H_7	49
C_4H_9	50
$CH_3CH{=}CHCH_2$	52
$CH_2{=}C(CH_3)CH_2CH_2$	55
	54

Substituted dibromoallenes **55**, upon heating with an amine, provide pyrroles **56** or more interestingly, 2-alkoxymethyl pyrroles **57**.[69,70]



(18)

55a R = H

55b R = R'OCH$_2$-

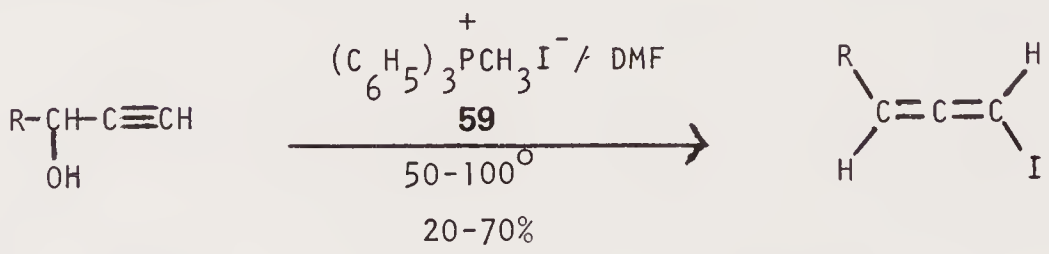
56 R = H

57 R = R'OCH$_2$-

8.4. IODOALLENES

Although iodoallenes have not been used in synthesis as extensively as bromoallenes, new methods for their synthesis will undoubtedly provide more opportunities for studying these interesting allenes in synthetic applications.

Iodoallenes can be synthesized by the addition of 1-alkyl-2-propynols **58** to a solution of triphenyl phosphite methiodide **59** in DMF (equation 19). An S_Ni' mechanism is suggested to explain their formation. In most cases the iodoallenes are distilled directly from the reaction mixtures. These iodoallenes are reasonably stable over a period of several weeks.[71]

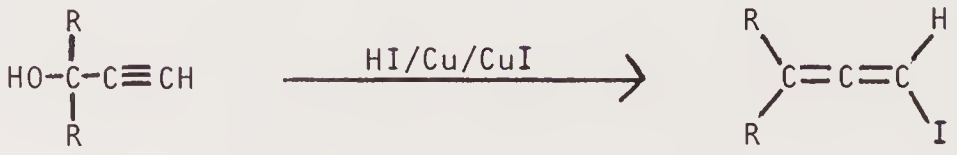


(19)

58

R = alkyl, HC≡C-, C_6H_5

However, 1,1-dialkyl-2-propynols **60** do not react with **59** for steric reasons. In these cases treatment of **60** with 45% hydriodic acid in the presence of copper(I) iodide provides good yields of 1,1-dialkyl-3-iodoallenes **61**.[72]



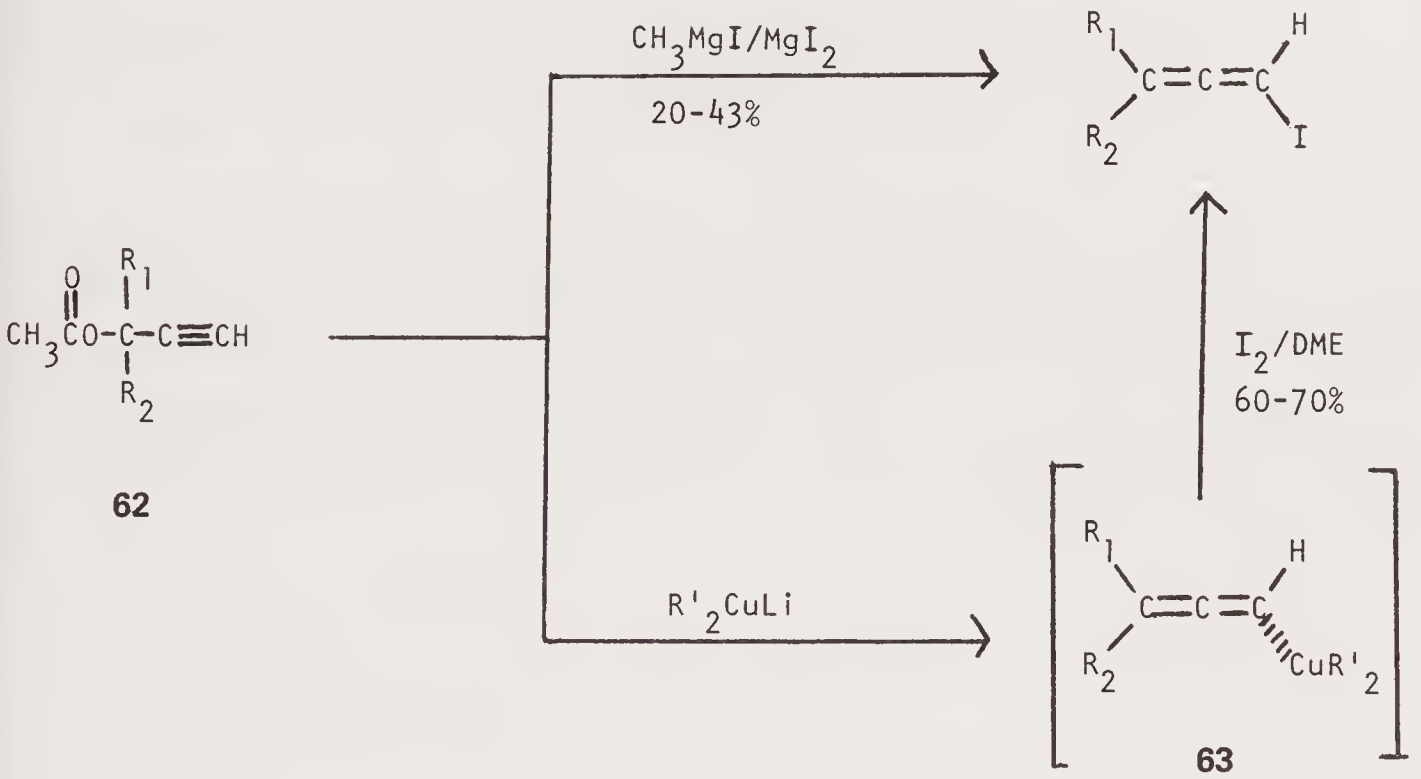
(20)

60 **61**

R = CH_3 61%

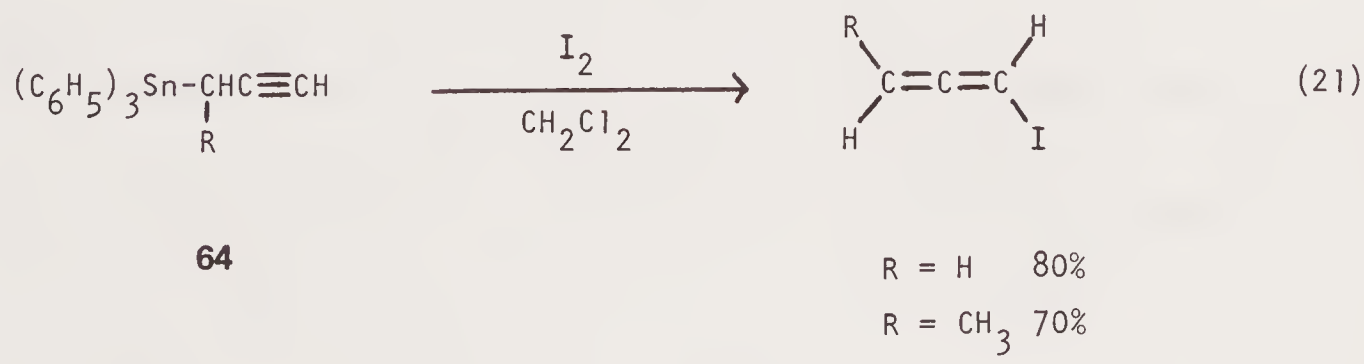
R = C_2H_5 65%

When propargylic acetates **62** are treated with methylmagnesium iodide in the presence of an excess of magnesium iodide, moderate yields of iodoallenes are obtained.[73–75] However, the presence of considerable amounts of unwanted products makes this method synthetically unattractive. A preferred method is to treat **62** with lithium dialkylcuprate reagents followed by iodine addition to the intermediate **63**. In this way, optically active iodoallenes are prepared easily from optically active acetates[76] (Scheme 8).



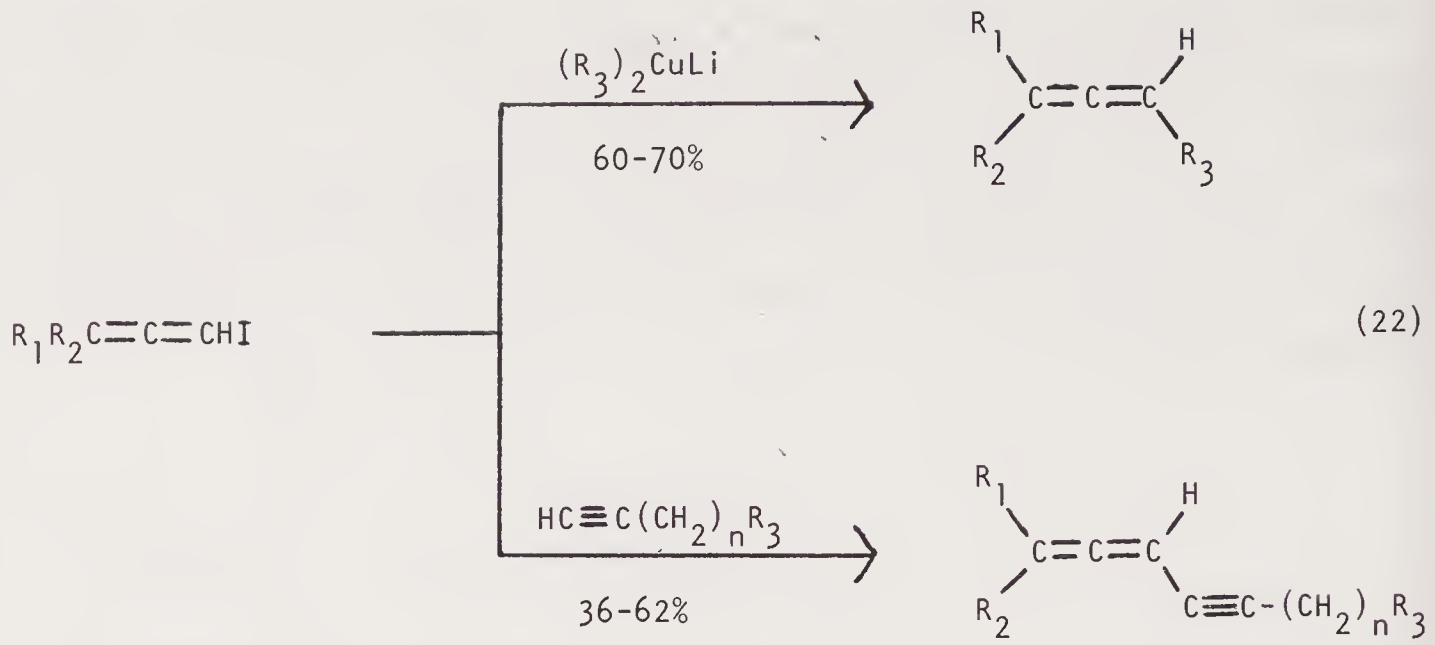
Scheme 8

An unusual synthesis of iodoallenes involves the cleavage of propargylic tin compounds **64** with iodine[77] (equation 21).

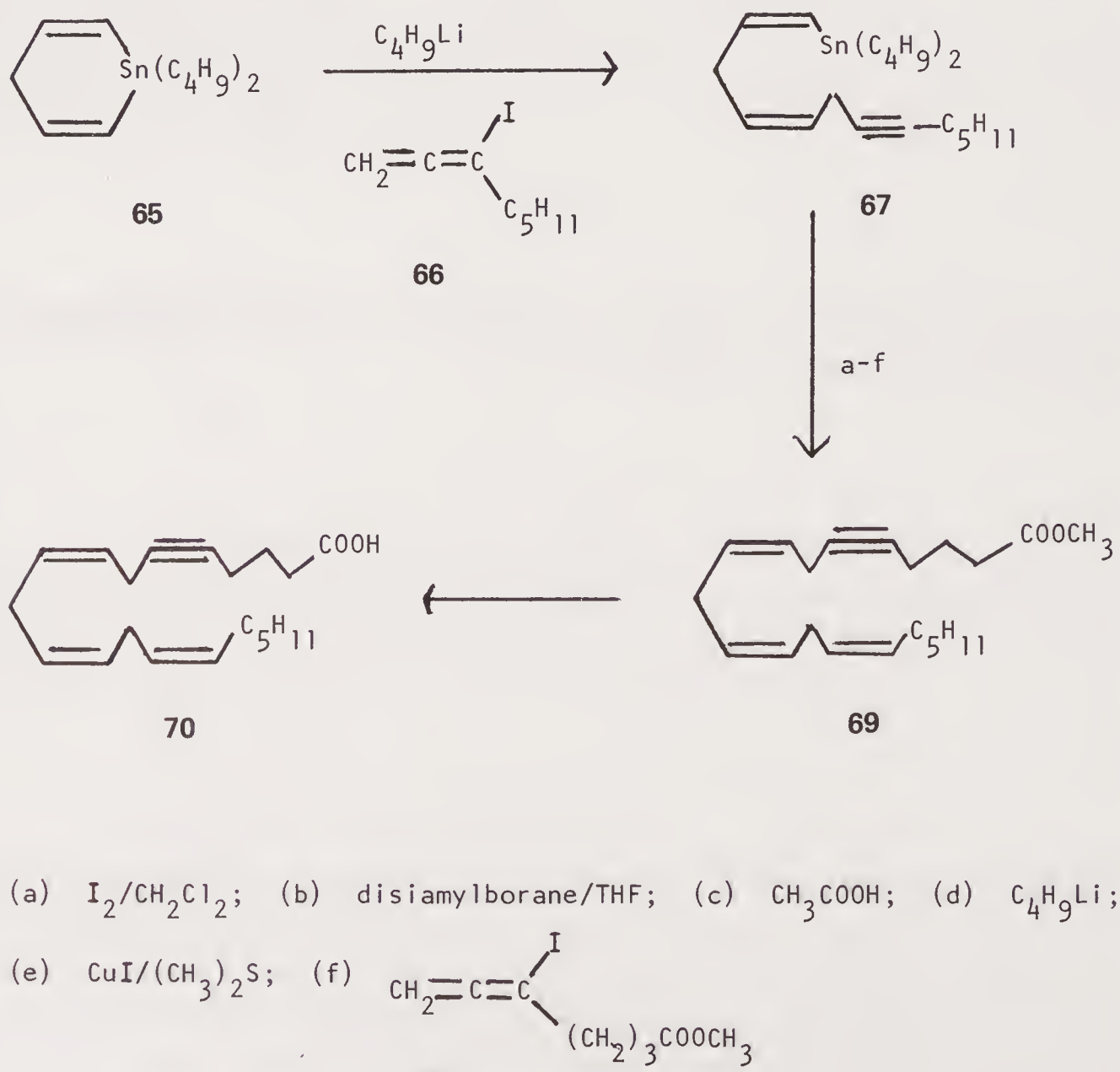


(21)

Iodoallenes can be used in the same reactions as bromoallenes with the advantage that they provide greater reactivity. When treated with lithium dialkylcuprates at low temperature, iodoallenes provide good yields of the corresponding allenic hydrocarbons.[64,65] Iodoallenes also couple with terminal acetylenes in the presence of cuprous ions and a suitable amine base to provide moderate yields of allenynes[78] (equation 22).

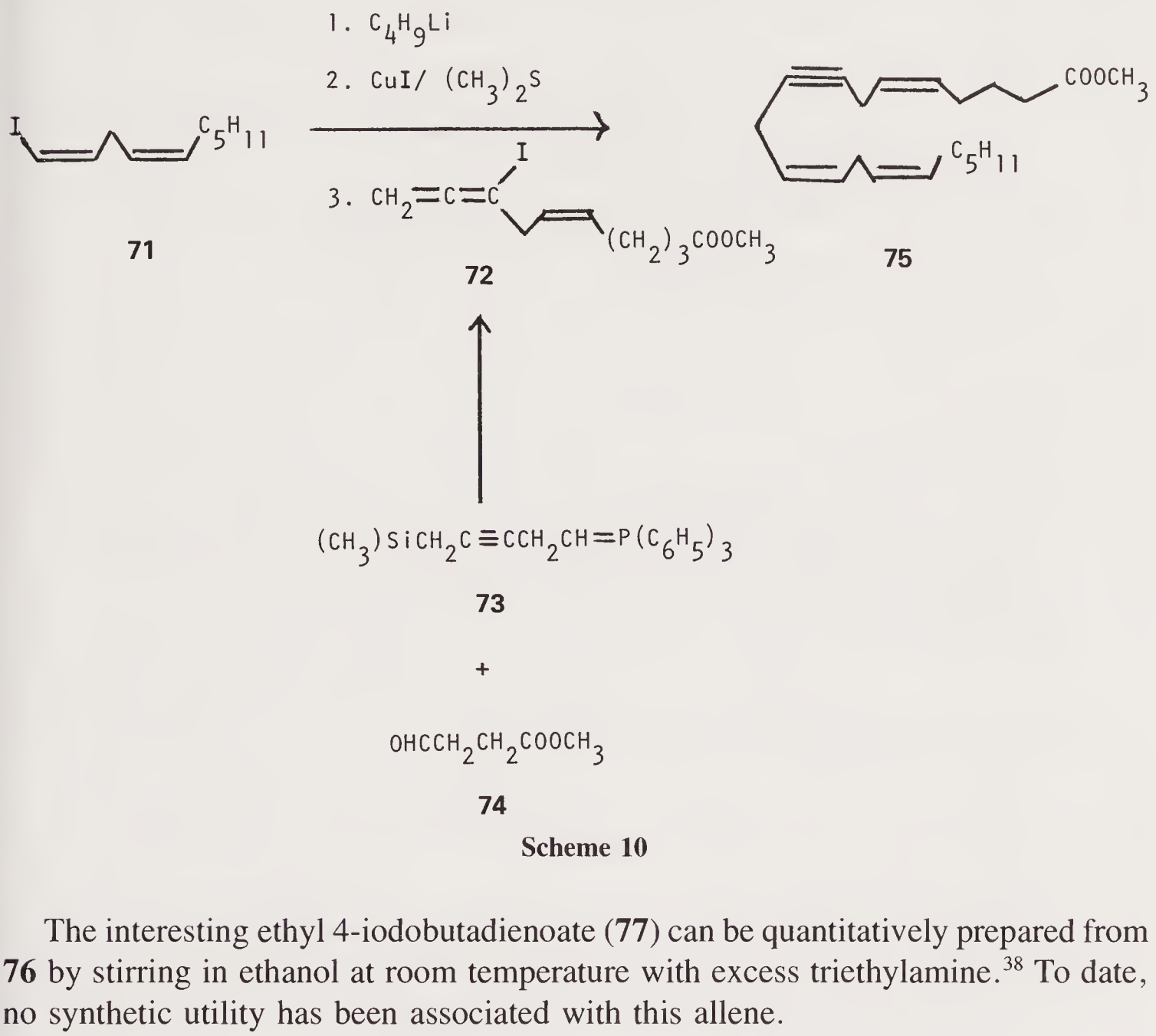


An elegant stereocontrolled synthesis of the irreversible eicosanoid biosynthesis inhibitor, 5,6-dehydroarachidonic acid (**70**) uses both 3-iodo-1,2-octadiene (**66**) and methyl 5-iodo-5,6-heptadienoate (**68**) to introduce the appropriate carbon segments of the molecule (Scheme 9). Each iodoallene is prepared from the corresponding propargyl trimethylsilane by treatment with iodine–silver tetrafluoroborate in methylene chloride at $-78°C$.[58,59]



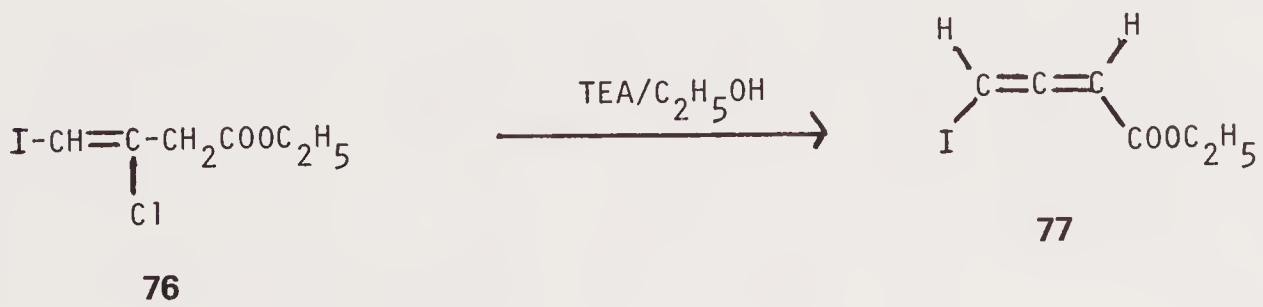
Scheme 9

Similarly, 8,9-dehydroarachidonic acid (**75**) is prepared from (1Z,4Z)-1-iodo-1,4-dodecadiene (**71**) and methyl (5Z)-8-iodo-5,8,9-decatrienoate (**72**), prepared by coupling 5-trimethylsilyl-3-pentynylidenetriphenylphosphorane (**73**) with methyl 4-formylbutyrate (**74**) followed by iodination with iodine–silver tetrafluoroborate[79] (Scheme 10).



Scheme 10

The interesting ethyl 4-iodobutadienoate (**77**) can be quantitatively prepared from **76** by stirring in ethanol at room temperature with excess triethylamine.[38] To date, no synthetic utility has been associated with this allene.



(23)

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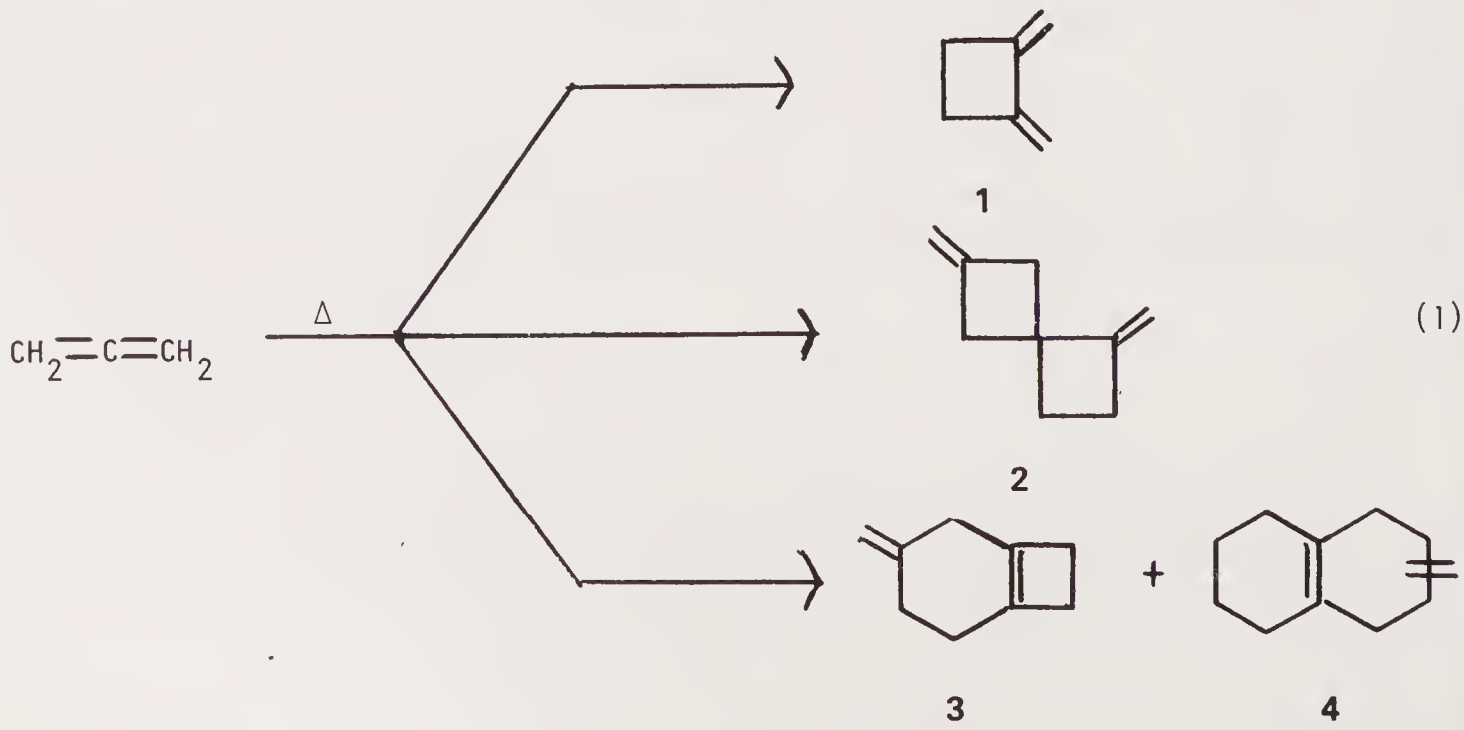
CHAPTER NINE

CYCLOADDITION REACTIONS OF ALLENES

The ability of allenes to undergo either inter- or intramolecular cycloaddition reactions with a variety of unsaturated functionalities provides the synthetic chemist with a convenient route for the construction of complex ring systems. The application of these kinds of reactions to the synthesis of natural products has greatly increased the value of these reactions in preparative organic chemistry.

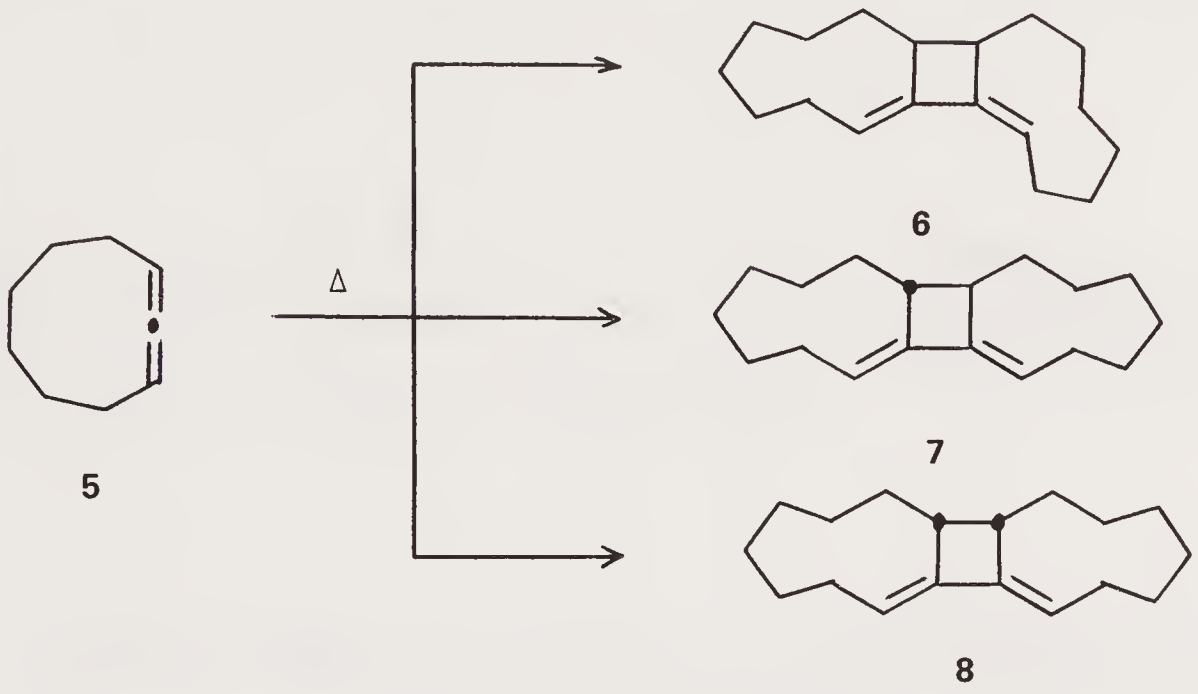
9.1. ALLENE–ALLENE DIMERIZATIONS

Thermal homocyclization or oligomerization of allene either in the gas phase[4] or neat[6,8,9] leads to 1,2-dimethylenecyclobutane (**1**) and higher oligomers, such as **2**, **3**, and **4**, that are derived from further cycloaddition reactions of **1**.[5,7] Only when the reaction is performed in benzene with careful control of temperature and concentration does this reaction offer some synthetic utility. Codimerizations between different allenic species can be achieved by using an excess of the less reactive allene; otherwise, the dimer of the more reactive species results.[10] Sensitized photoreactions yield a complex mixture of products.[11]



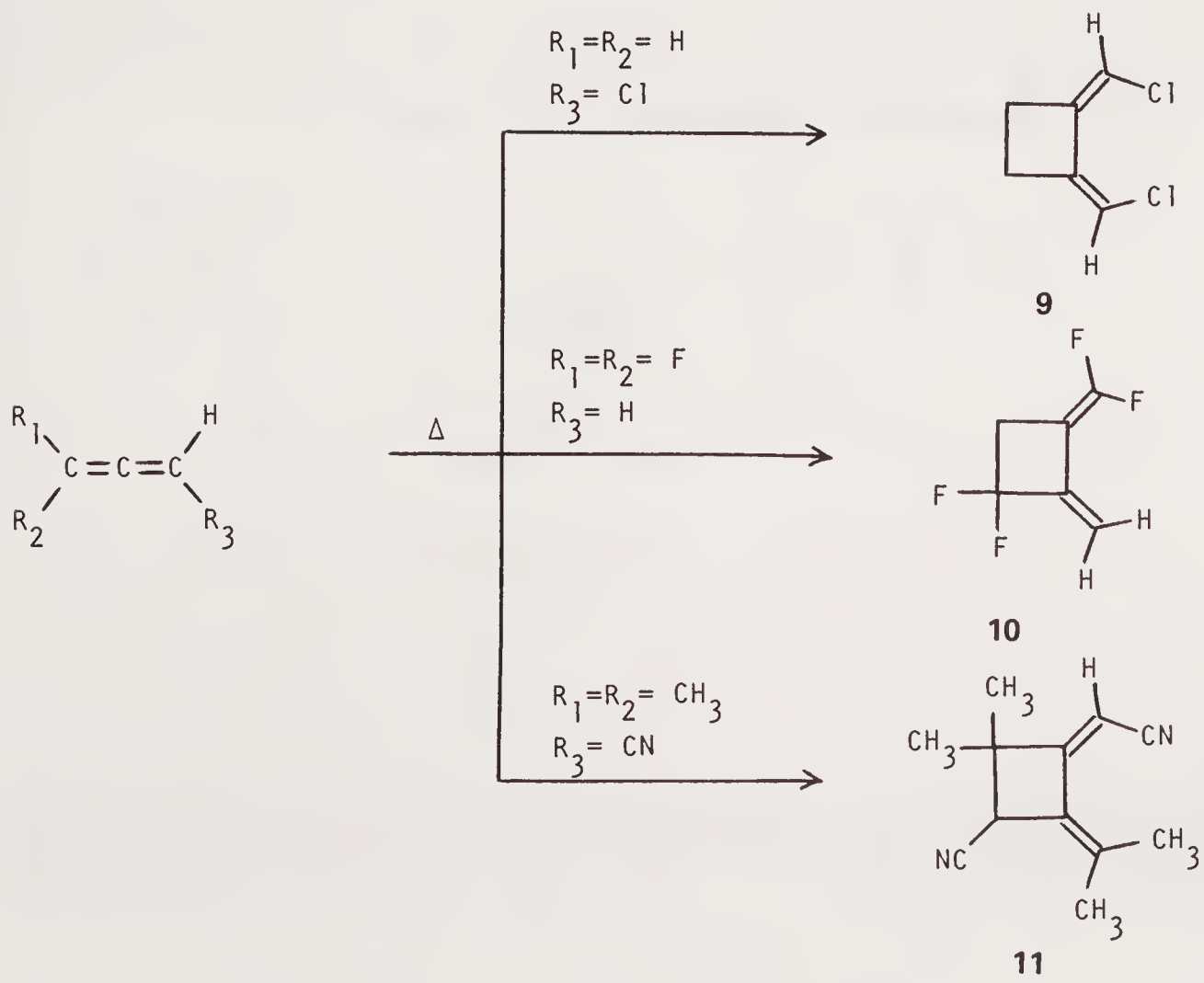
(1)

1,2-Cyclononadiene (**5**) dimerizes with a high degree of stereoselectivity[3,12,13] to give a quantitative yield of three isomers **6**, **7**, and **8** in a ratio of 6.3:62.5:31.2 (equation 2). Although this seems to indicate the possibility of a concerted [π^2s + π^2a] symmetry-allowed cycloaddition, studies with secondary deuterium isotope effects suggest that the reaction may proceed through a two-step nonsynchronous process in which each step is stereospecific.[14]



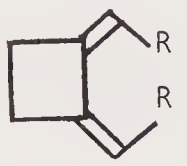
(2)

The regioselectivity of the cyclodimerization also depends on the nature of the allenic substitution. Chloroallene dimerizes in a head-to-head manner,[15] whereas 1,1-difluoroallene[16] and 3,3-dimethyl-1-cyanoallene[17] dimerize in a head-to-tail manner, a result not rationalized by either a [π^2s + π^2a] concerted or a nonconcerted process[18] (equation 3).

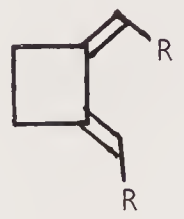


(3)

The stereochemistry obtained from these dimerizations shows that both of the vinyl R groups of the product have a strong preference for orientation in an inward direction **12**. This result suggests that the electrocyclization occurs by a conrotatory ring closure. In fact, the reaction can accommodate R groups such as mesityl[19] and retain the *syn* relationship. Only when R is represented by an adamantyl group[20] does a change in stereochemistry occur. In this case, the adamantyls are oriented as shown in structure **13**.



12

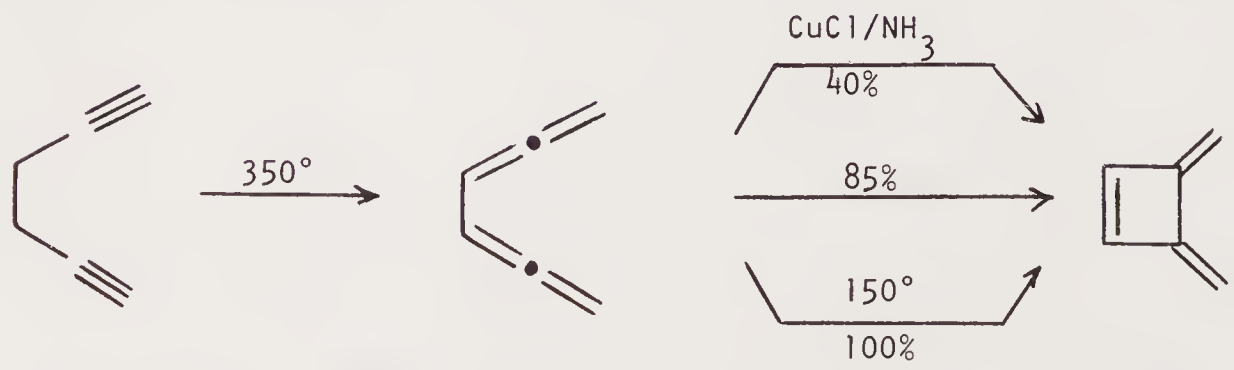


13

Substituents on the allene that will eventually reside on the cyclobutane ring favor a *trans* relationship, although this is not exclusive.[15,21]

The application of second-order PMO theory to the cyclodimerization of allenes predicts a concerted $[\pi^2s + (\pi^2s + \pi^2s)]$ mechanism in which the regio- and stereoselectivity is consistent with experimental observations.[18]

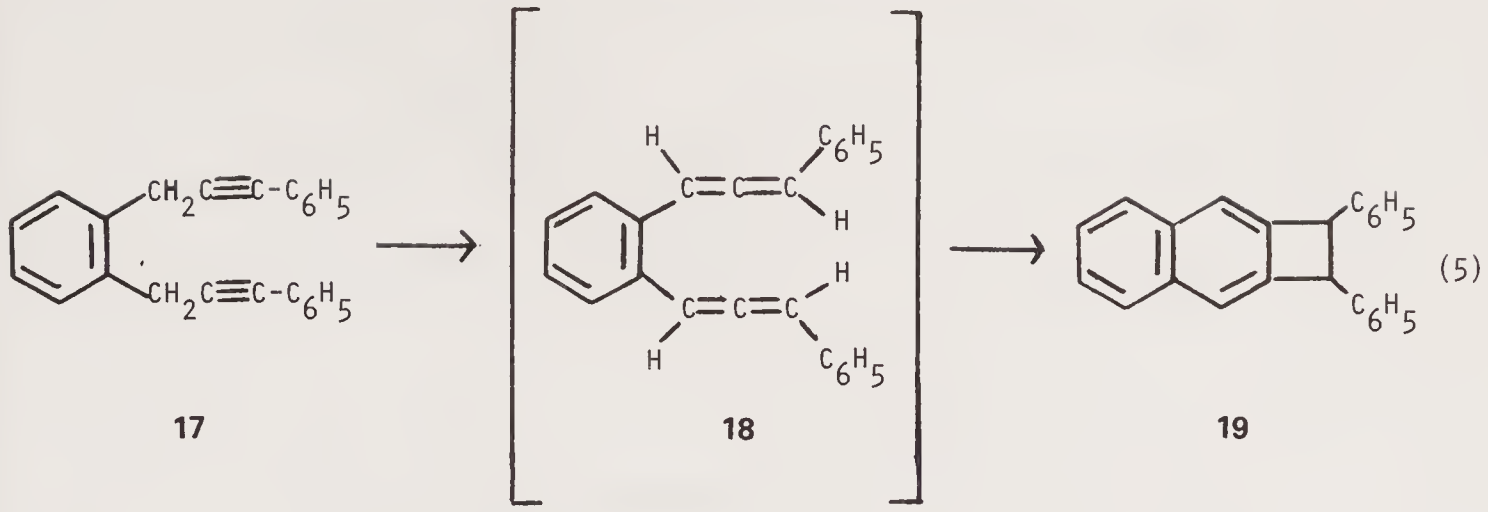
Intramolecular allene dimerizations have some interesting synthetic potential. The thermolysis of 1,5-hexadiyne (**14**) at 350° affords 3,4-dimethylenecyclobutene (**16**) in 85% yield, presumably by way of a conrotatory ring closure of 1,2,4,5-hexatetraene (**15**).[22,23] Although stable at room temperature, **15** quantitatively isomerizes to **16** at 150°C.[24] This also occurs when **15** is treated with cuprous chloride in liquid ammonia, although the yield drops to 40%[25] (equation 4).



14 **15** **16**

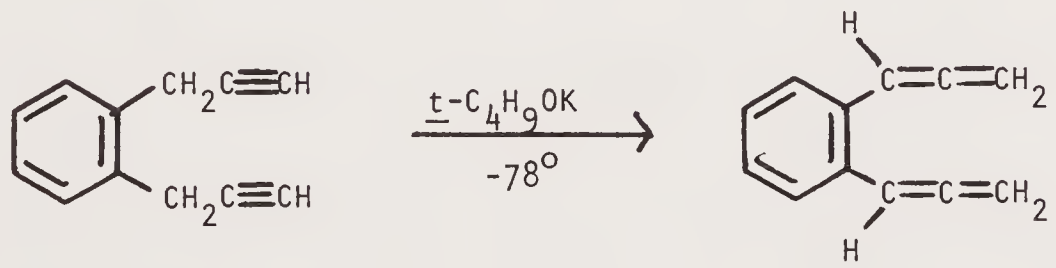
(4)

The thermal rearrangement of 1,2-bis-(3-phenyl-2-propynyl)-benzene (**17**) with basic aluminum oxide results in a 55% yield of *trans*-1,2-diphenylnaphtha[b]cyclobutane (**19**) probably by way of the diallene **18**.[26]

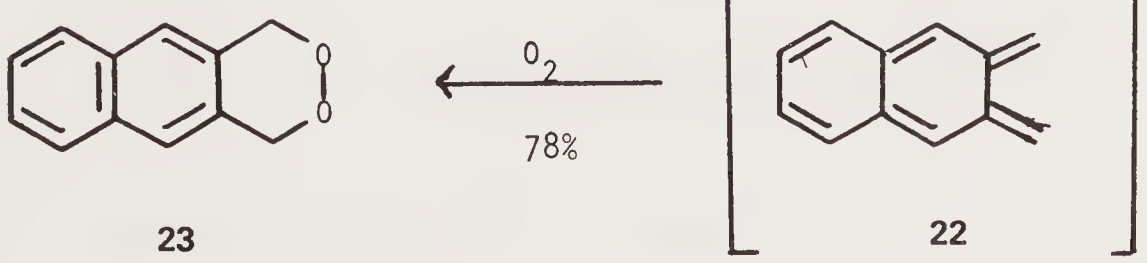


17 18 19 (5)

When *o*-dipropargyl benzene (**20**) is treated with potassium *t*-butoxide in *t*-butanol at −78°C, the unstable but isolable diallene **21** is formed. Bubbling oxygen through an ethereal solution of **21** produces the peroxide **23** in 78% yield, presumably from the 2,3-naphthoquinodimethide (**22**).[27]

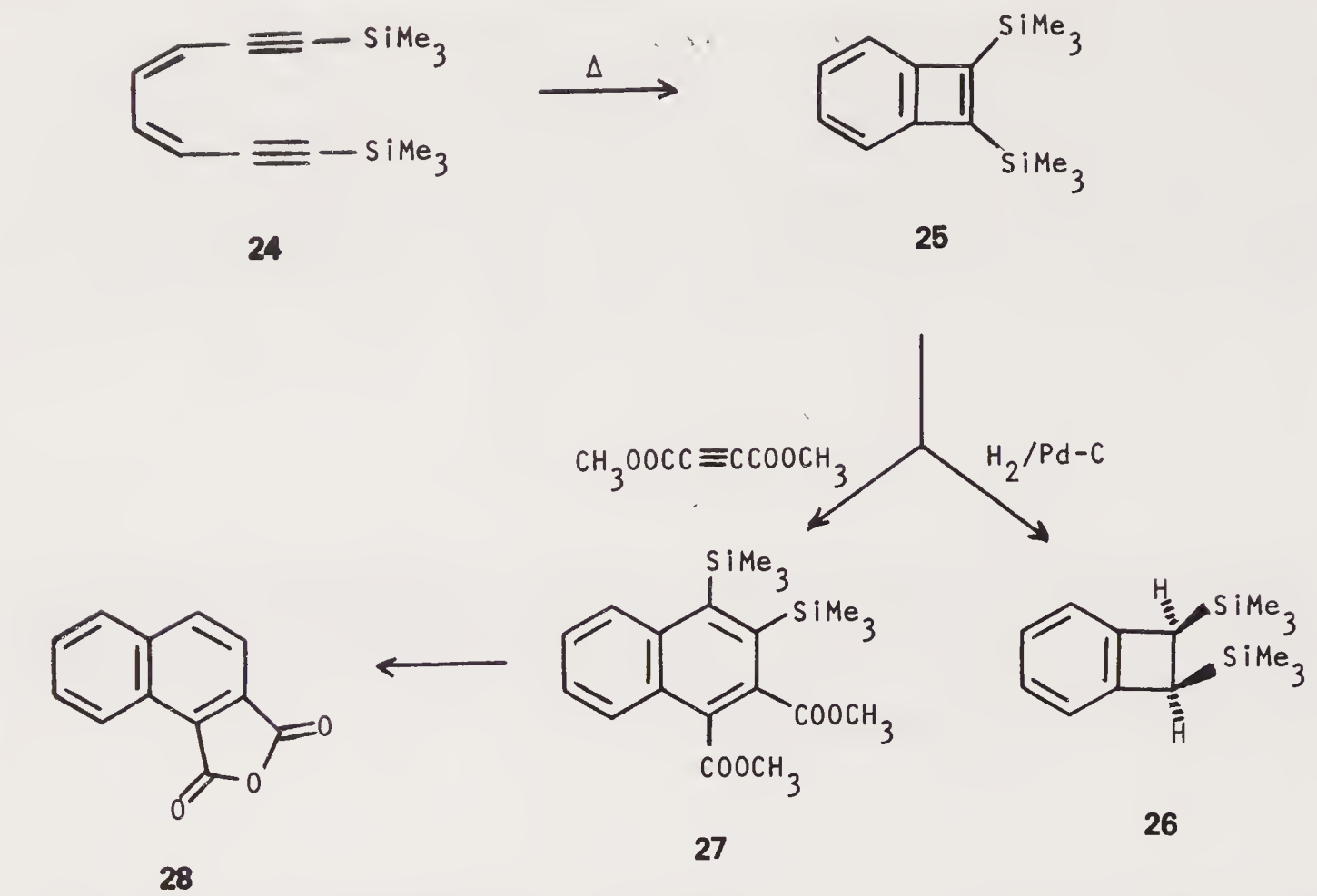


20 21 (6)



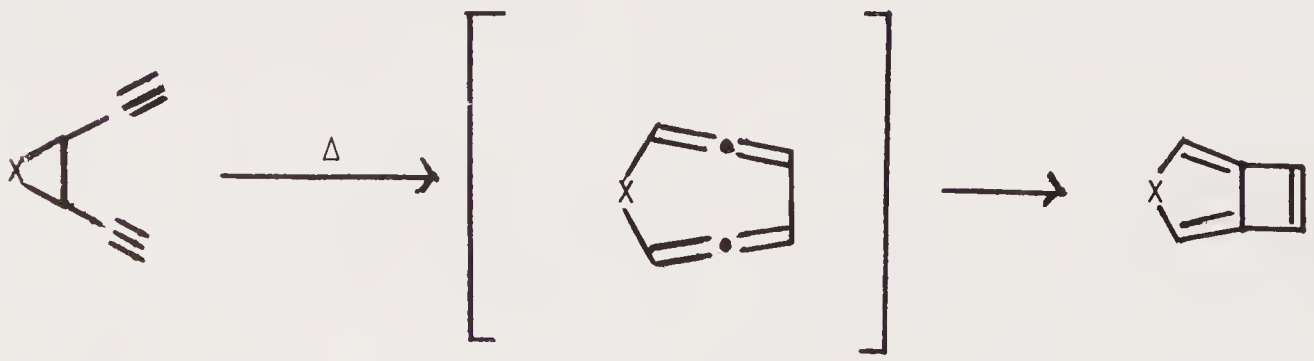
23 22

The antiaromatic 8π-electron system, 1,2-bis(trimethylsilyl)benzocyclobutadiene (**25**), can be cleanly prepared by flash vacuum pyrolysis of **24** in a quartz tube at 650°/0.001 torr. This substance is remarkably stable but extremely reactive, especially toward oxygen. Hydrogenation smoothly converts **25** to the dihydro derivative **26**. Angular addition occurs when **25** is treated with dimethylacetylene dicarboxylate to afford the crystalline **27**. This can be converted to naphthalene-1,2-dicarboxylic acid anhydride (**28**) by treatment with a 1 : 1 : 1 mixture of $CF_3COOH/H_2SO_4/CCl_4$[28] (Scheme 1).



Scheme 1

Cyclopropanes **29**,[29] epoxides **30**,[30,31] or thiaepoxides **31**[32] undergo thermal rearrangement to the corresponding cyclic diallenes **32**, which then spontaneously undergo electrocyclic ring closure to bicyclic 3,4-bis-methylenecyclobutenes **33**, although in poor yields (equation 7).



(7)

29 X = CH_2

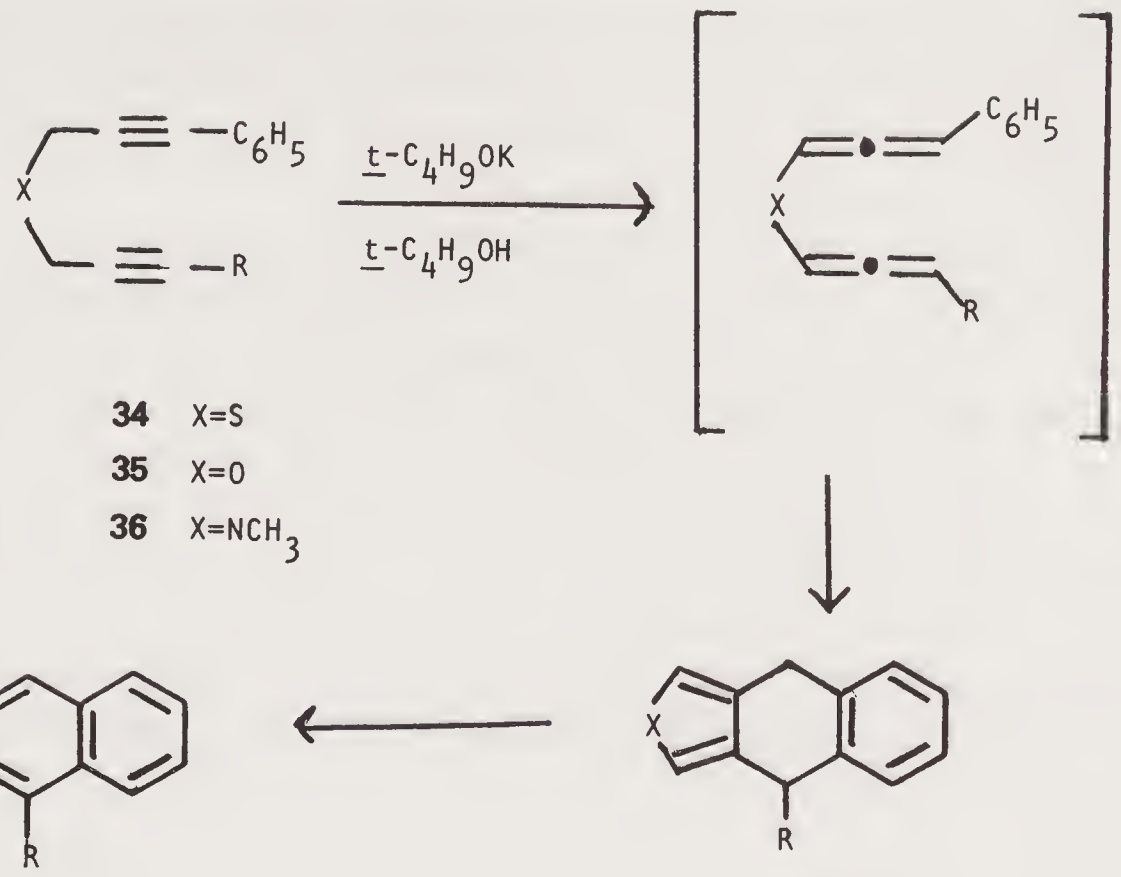
30 X = O

31 X = S

32

33

The base-catalyzed rearrangement of bis(3-phenyl-2-propynyl)sulfide (**34**), ether (**35**), or N-methylamine (**36**) leads to novel heterocyclic ring systems **37** in moderate yields.[33] The naphthalenic systems **38** can be obtained when **37** is treated with base under more vigorous conditions. A diradical mechanism can be invoked to explain these results[33–35] (Scheme 2).



34 X=S
35 X=O
36 X=NCH_3

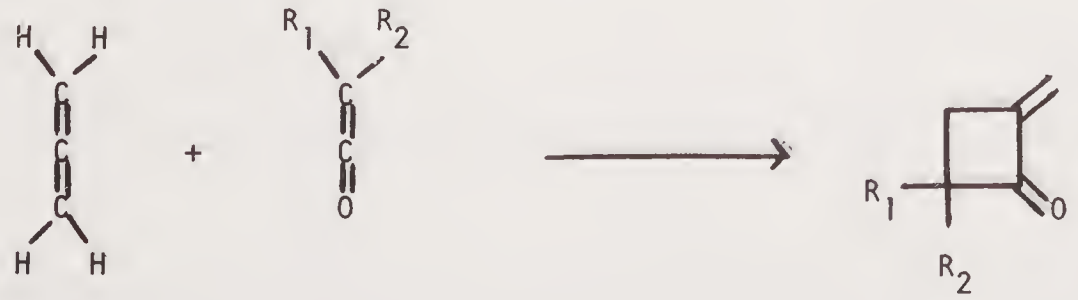
38 **37**

X	R	Yield **37**, %
S	C_6H_5	50
O	C_6H_5	54
NCH_3	C_6H_5	--
O	H	20

Scheme 2

9.2. ALLENE-KETENE CYCLOADDITIONS

Thermal cycloaddition reactions of allenes with ketenes provide the chemist with a practical route to α,β-ethylidene cyclobutanone derivatives **39**. When either the allene or ketene is functionalized by one or more substituents, the stereochemistry of the product cannot be controlled, and the reaction furnishes a mixture of isomers.[36]



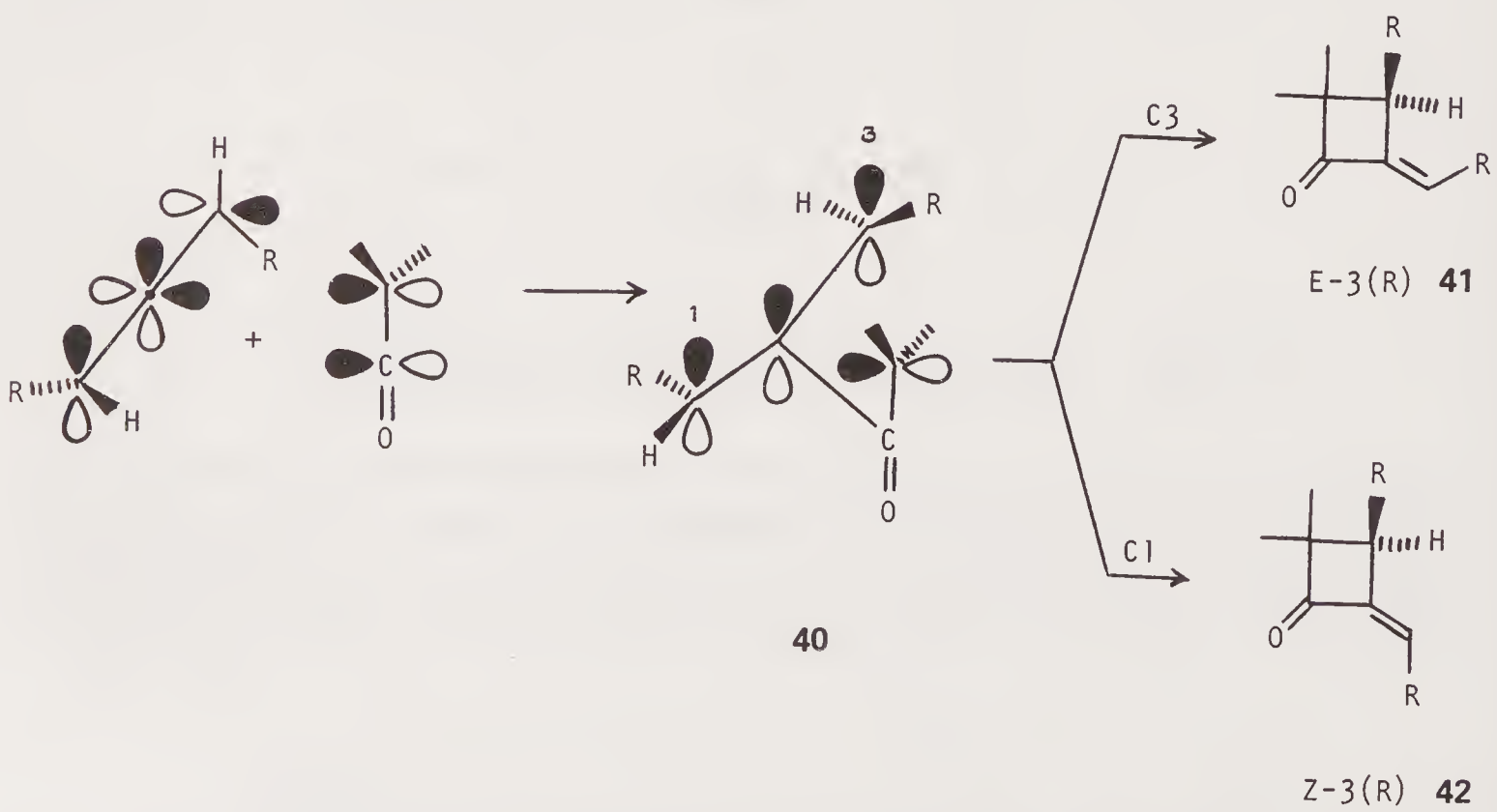
(8)

39

Allenes, particularly those that have a high electron density at the central sp carbon,[38] exhibit greater chemical reactivity toward cycloaddition reactions.[18] Ketene reactivity follows the increasing order ketene < butylethylketene < dimethylketene < diphenylketene.[43]

The cycloaddition product results from the nucleophilic central allene carbon combining regiospecifically with the central ketene carbon atom. In the case of partially resolved chiral allenes, the cycloaddition leads to optically active products. Thus a 1,3-disubstituted allene of R-configuration produces cyclobutanones in which the newly formed asymmetric carbon also has an R-configuration, regardless of whether the adduct is pure E or Z, or a mixture.[41,42] To explain these results, mechanisms such as a concerted $[\pi^2s + \pi^2a]$[41,44–46] and a diradical intermediate[38,47,48] are proposed. However, neither of these mechanisms adequately explains all of the experimental results. In acyclic allenes, the retention of configuration at the newly formed asymmetric center, regardless of the olefin geometry, is not consistent with a single concerted mechanism. Solvent effects are not sufficiently large to satisfy the criteria for a dipolar mechanism,[49] whereas the large negative entropy change observed for the reaction seems to indicate some sort of a concerted process.[36]

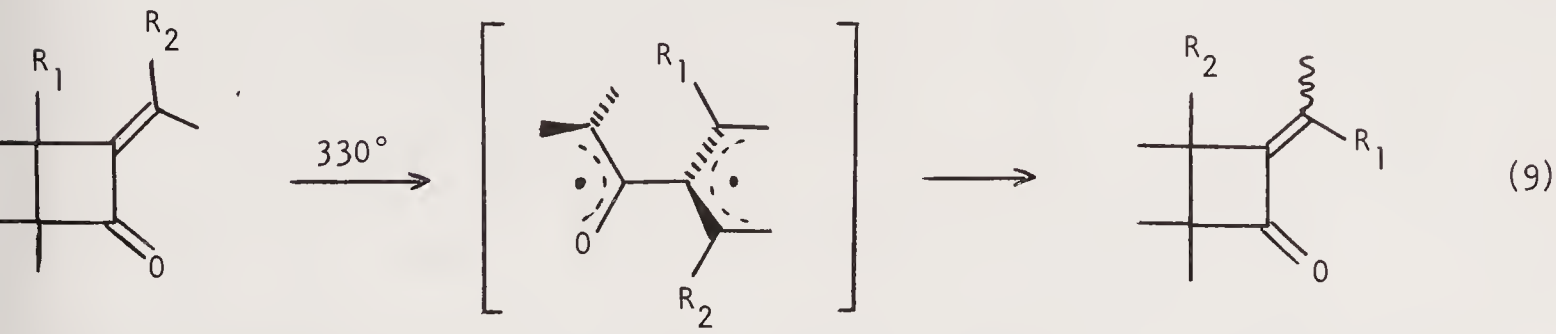
All experimental results seem to agree well with a general mechanism involving the 4π electrons of the 1,2-dienes in a $[\pi^2s + (\pi^2s + \pi^2s)]$ process leading to the formation of a bisallylene kind of transition species **40** where the two diagonal sp carbon atoms of the reaction partners can bond together. Disrotatory ring closure results in bond formation of the second carbon of the ketene with either allene carbon three to give **41** or carbon one to give **42**.[36]



Scheme 3. Reprinted from ref. 36 with permission from the authors.

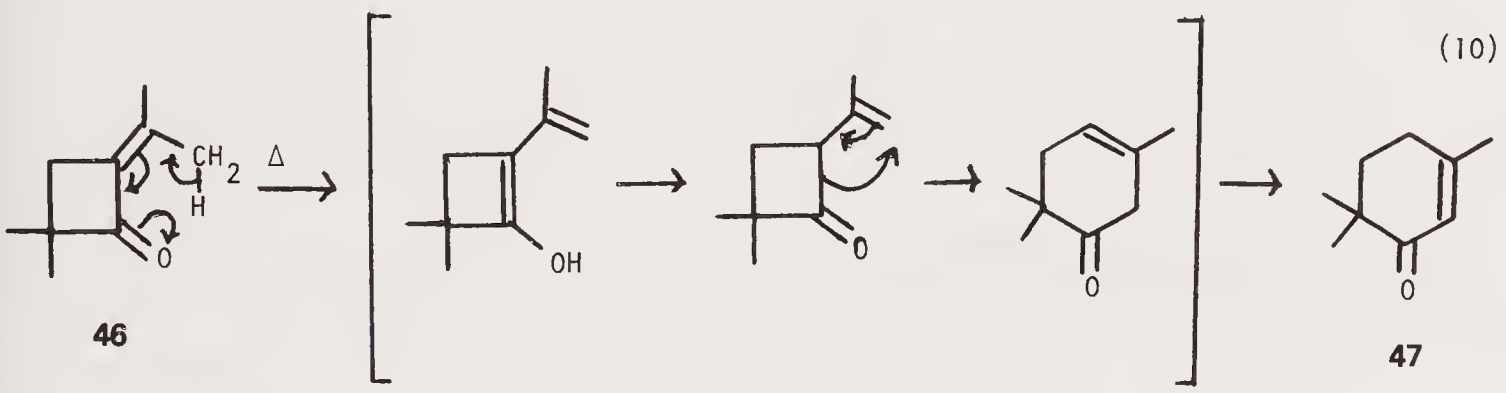
Alkylidene cyclobutanones **43** substituted in the three position thermally isomerize to the analogous hydrocarbons **45** by way of the orthogonal diallylic diradical

44. Retention of configuration at the migrating C4 carbon and antarafacial intervention of the allylic group result in the observed stereochemistry.[50,51]



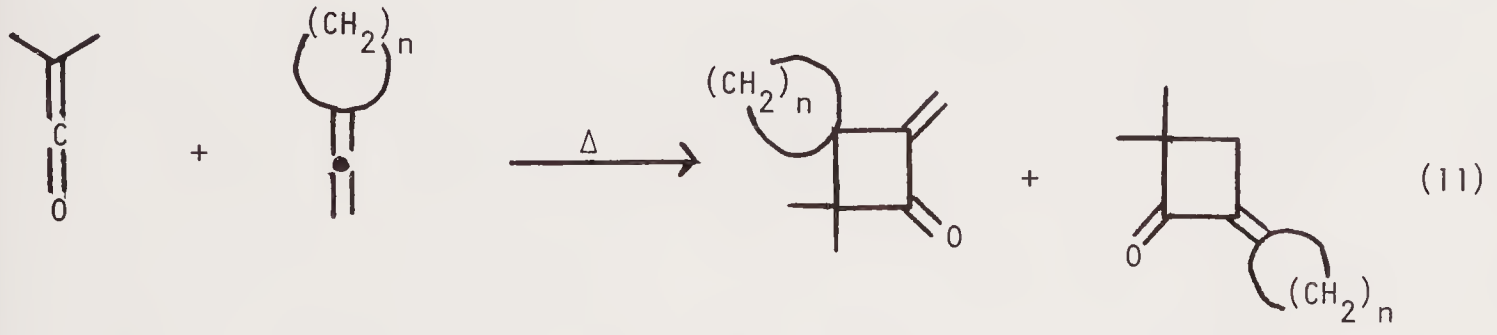
43 **44** **45** (9)

If there is no substitution at C3, then **46** undergoes a [1.5] sigmatropic rearrangement to the conjugated cyclohexenone **47** in 35% yield.[51–53]



46 **47** (10)

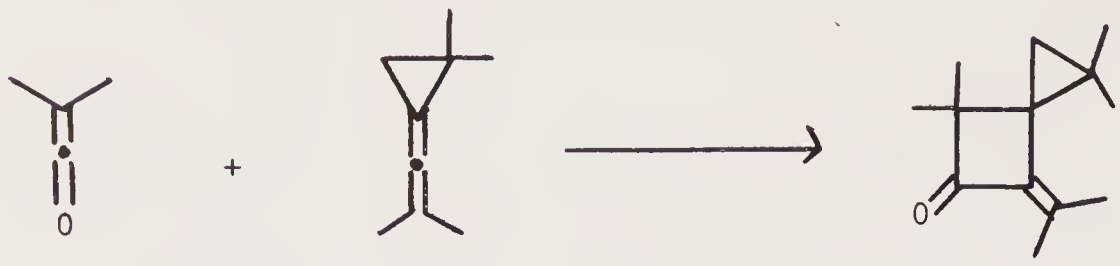
The cycloaddition of dimethylketene with a variety of exocyclic allenes **48** results in a mixture of two products **49** and **50** whose ratio depends on the ring size.[36,39,53]



48 **49** **50** (11)

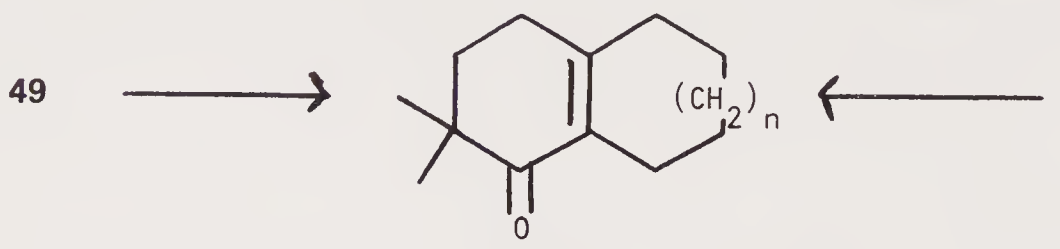
			Ratio	
n	Temperature (°C)	Yield (%)	**49**	**50**
1	50	68	76	24
2	120	75	30	70
3	120	72	49	51
5	120	60	—	100

In the case of 2,2-dimethyl-1,1-dimethylvinylidene cyclopropane (**51**), only the spiro product **52** is obtained in 60% yield.[39]



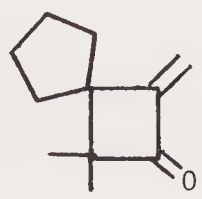
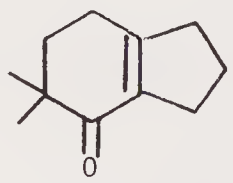
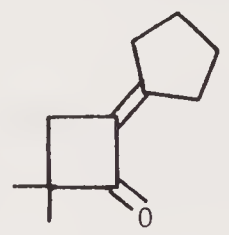
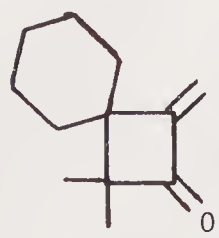
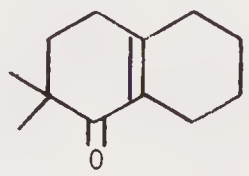
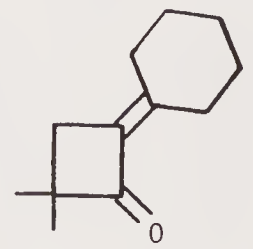
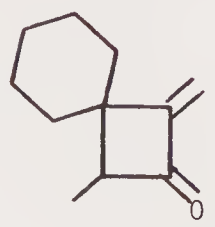
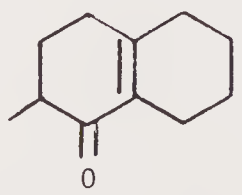
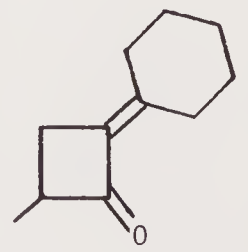
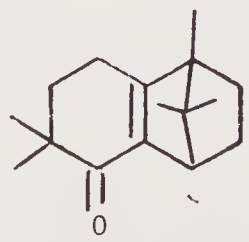
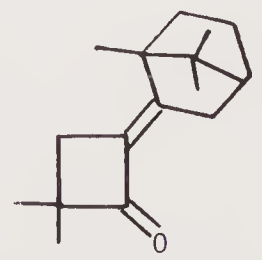
51 **52** (12)

Heating either the conjugated methylene cyclobutanones **49** or the cycloalkylidene cyclobutanones **50** results in the formation of bicyclo[4.n.0] alkenones (**53**).[51–53] Table 9.1 illustrates these results.



49 **50** **53** (13)

Table 9.1. Bicyclo[4.n.0]alkenone (53) Synthesis[a]

Substrate **49**	Yield, %	**53**	Yield, %	Substrate **50**
	40		50	
	35		40	
	40		40	
	--		55	

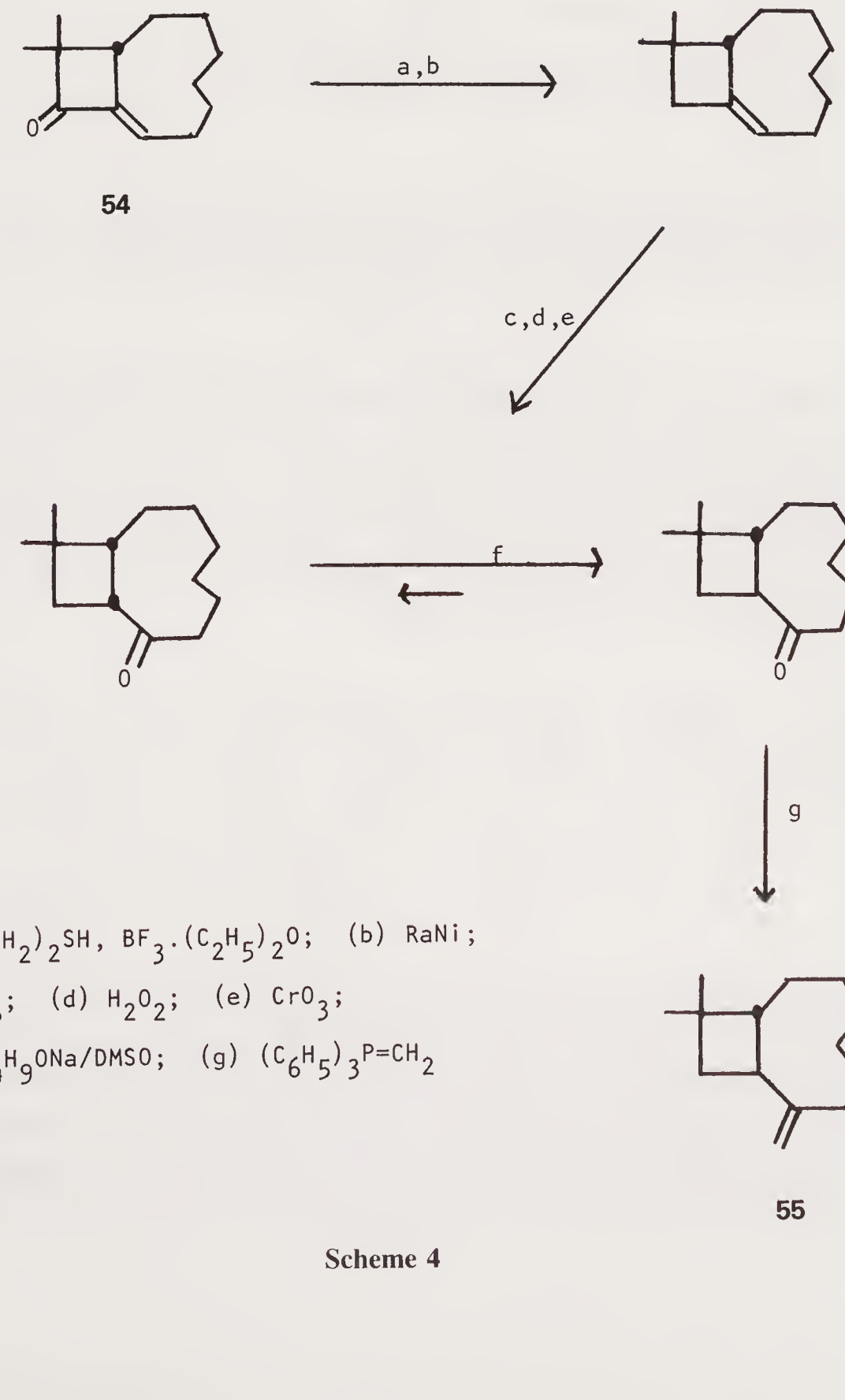
[a]Reprinted from refs. 51 and 53 with permission from the authors.

When dimethylketene reacts with 1,2-cyclononadiene (**5**), a single product **54**, possessing the bicyclo[7.2.0] undecane system, is obtained in 85–90% yield.[39,44] The steric hindrance provided by the hexamethylene chain directs the cyclo-addition exclusively from the less hindered side.[36] Partially resolved (S)-**5** translates to a (3S)-configuration in the product.[44]

(14)

5 **54**

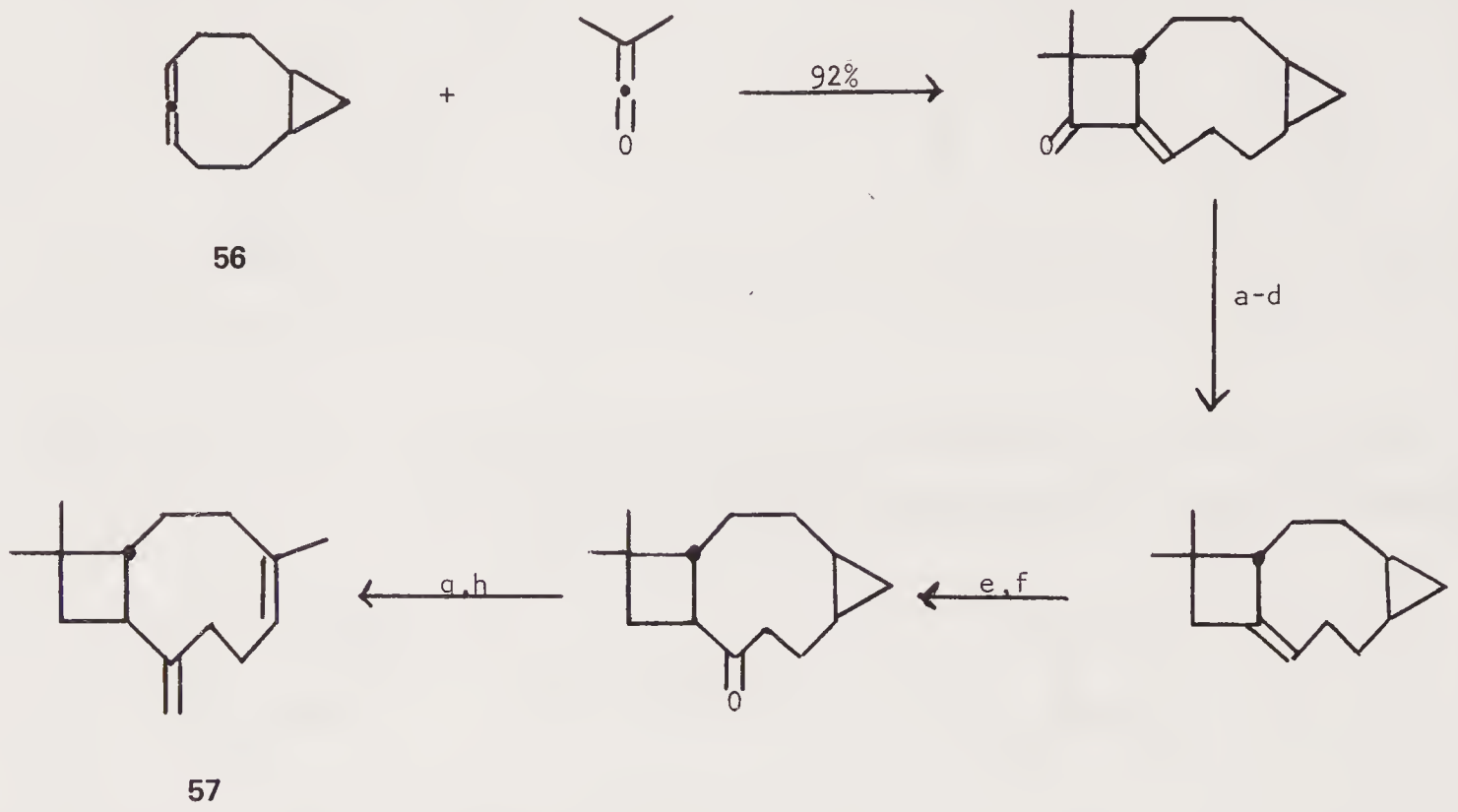
Through a series of standard functional group manipulations, **54** is easily transformed to dihydro-5,6-norcaryophyllene **55**[54] (Scheme 4).



54 **55**

Scheme 4

The cycloaddition of dimethylketene with bicyclo[7.1.0]-4,5-decadiene (**56**) provides an entry to the stereoselective total synthesis of (+)-isocaryophyllene (**57**). The 4,5-double bond of the product is protected as a cyclopropane to make the necessary chemical transformations[55] (Scheme 5).

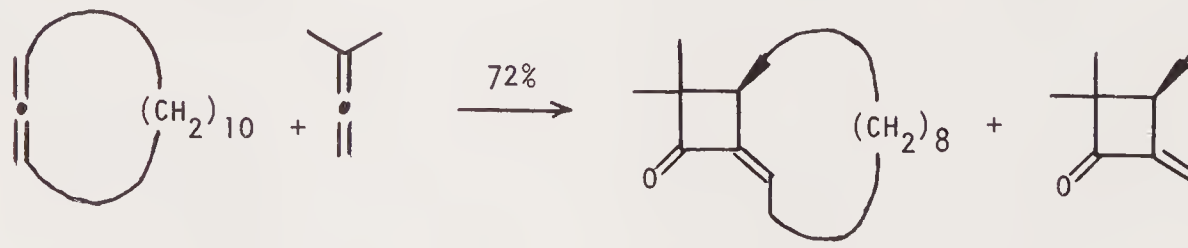


56 **57**

(a) $LiAlH_4$(95%); (b) $TsCl/C_6H_6$(84%); (c) $LiAlH_4$(94%); (d) Carbowax 20M, 150°(90%); (e) B_2H_6; (f) CrO_3(77%); (g) 360°/7hrs(80%); (h) $(C_6H_5)_3P{=}CH_2$(72%).

Scheme 5

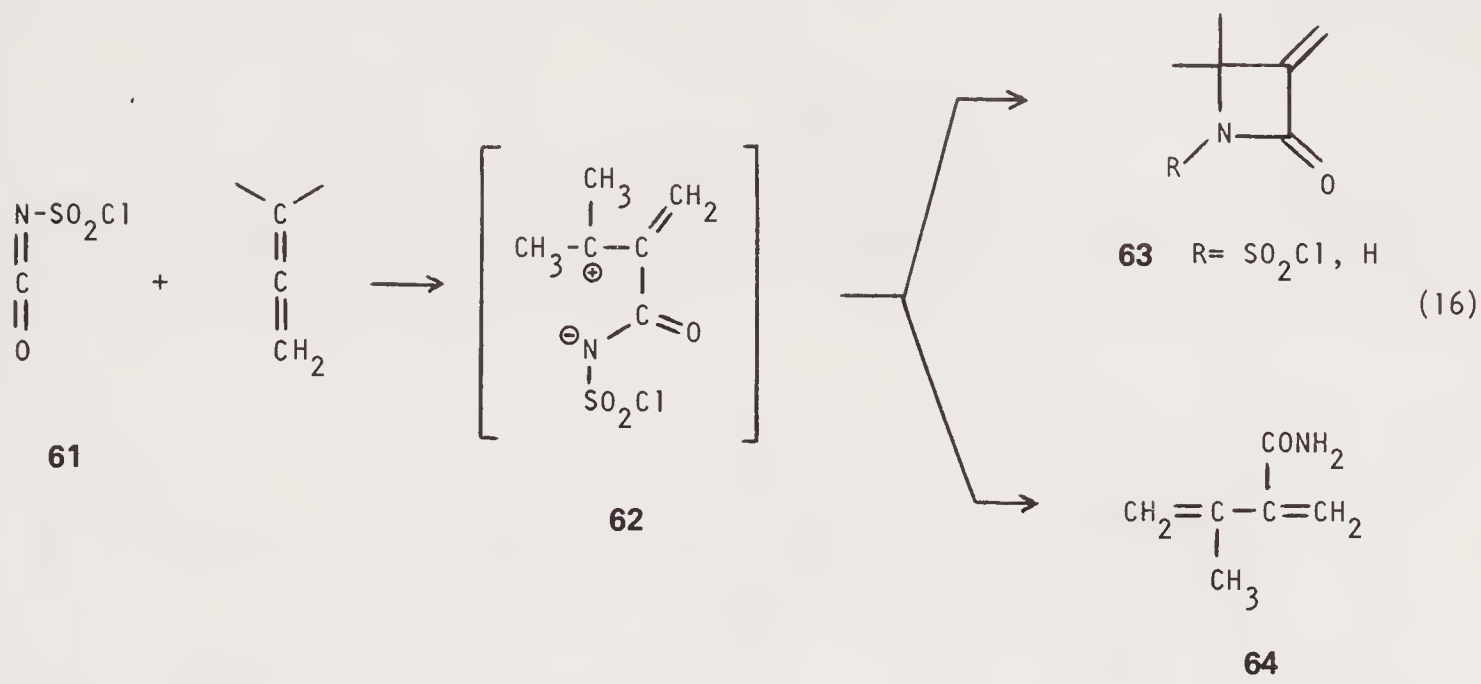
As the ring size of the cycloallene increases, the stereospecificity of the cycloaddition decreases because the steric constraints are reduced by the increased flexibility of the methylene chain. Consequently, 1,2-cyclododecadiene (**58**) reacts with dimethylketene at 120°C to afford a mixture of the *trans*-**59** and *cis*-**60** cycloadducts in a ratio of 55:45. An R-configuration in the starting allene produces an R-configuration at C3 in both products.[39,42]



58 **59** **60** (15)

Symmetrically and unsymmetrically substituted allenes also react with chlorosulfonyl isocyanate (**61**) to form β-lactams **63**, containing an exocyclic double bond, and 2-carboxamido-1,3-butadiene derivatives **64**[56] (equation 16). A concerted mechanism is disallowed in this case.[57] The results, however, suggest a two-step 1,2-dipolar cycloaddition where **61** adds electrophilically to the central allene carbon to generate an allyl-type stabilized transition state **62**. Cyclization of this zwitterion

leads to **63**, whereas proton transfer from carbon to nitrogen produces the butadiene **64**.[56,58]

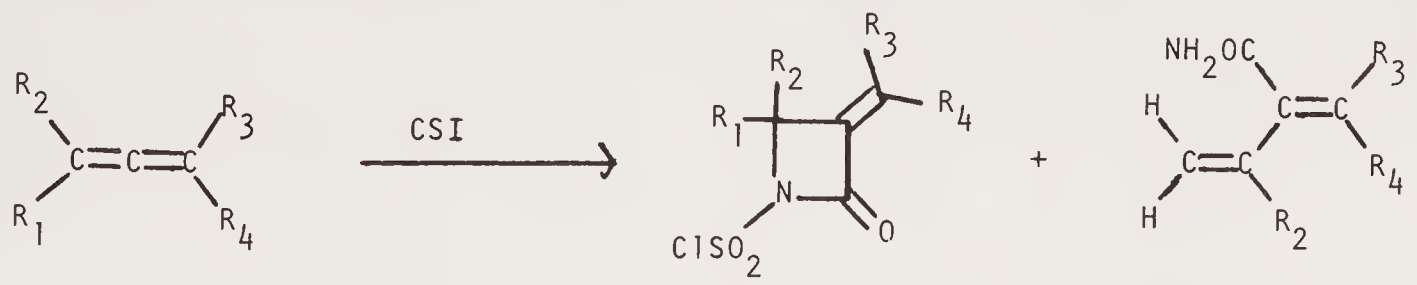


(16)

Table 9.2 shows a variety of such products. Reduction of the *N*-chlorosulfonyl-β-lactams **63** with benzenethiol and pyridine in acetone[60] affords the lactams (R = H) in reasonable yields.[56]

p-Tolylsulfonyl isocyanate **65** (R = Ts) analogously reacts with tetramethylallene to give only 3-isopropylidene-4,4-dimethyl-1-(*p*-tolylsulfonyl)-2-azetidinone (**66**). On the other hand, replacement of the tosyl moiety with a trichloroacetyl

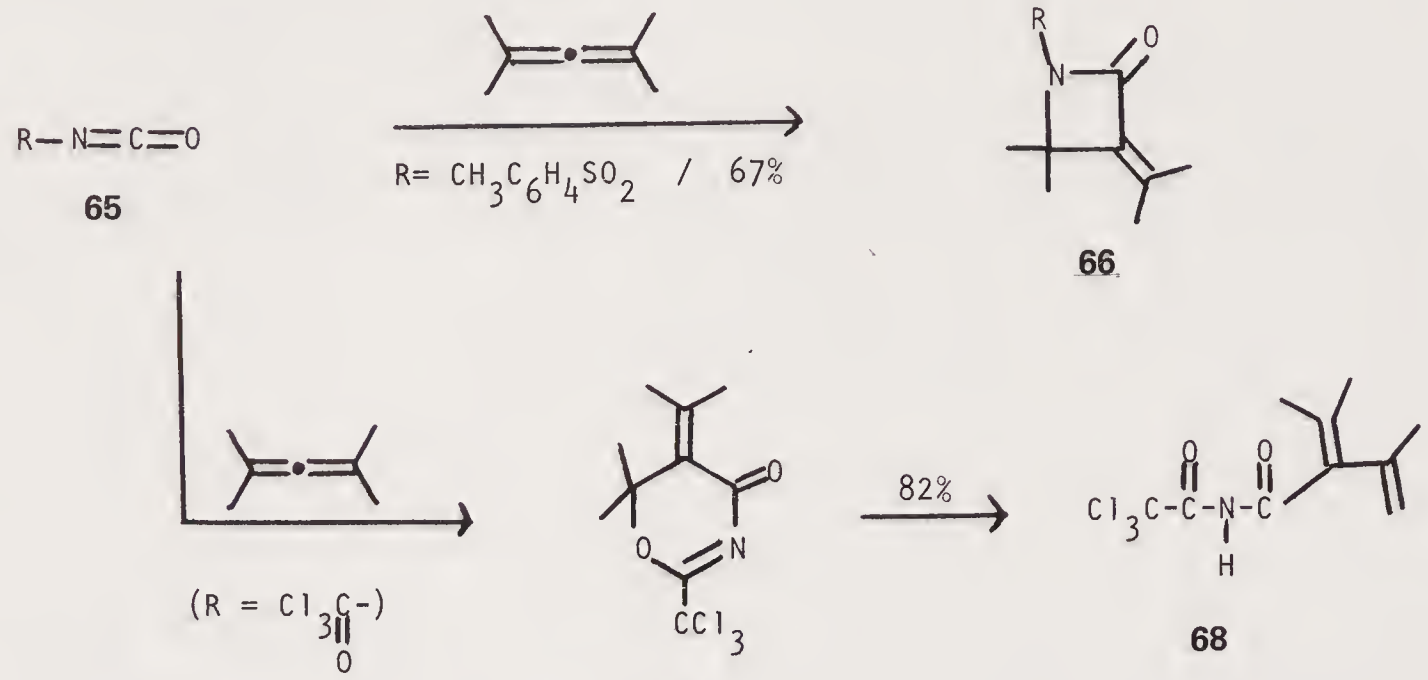
Table 9.2. Product Distributions of CSI Addition to Allenes



R_1	R_2	R_3	R_4	Yield (%) **63**	Yield (%) **64**
CH_3	CH_3	CH_3	CH_3	73	22
CH_3	CH_3	CH_3	H	37[a]	25[b]
H	CH_3	CH_3	H	—	31
CH_3	CH_3	H	H	23	36
	$—(CH_2)_5—$	H	H	40	32
H	C_6H_5	H	C_6H_5	63	—
	$—(CH_2)_6—$	H	H	89	—

[a] 13% *cis*:87% *trans*.
[b] 29% *cis*:71% *trans*.

group results in a facile [4 + 2] cycloaddition to afford cycloadduct **67**, which readily rearranges to 2-isopropenyl-3-methyl-*N*-(trichloroacetyl)-crotonamide (**68**)[59] (Scheme 6).



Scheme 6

9.3. ALLENE–OLEFIN CYCLOADDITION REACTIONS

The thermal cycloaddition of olefins with allenes provides the synthetics chemist with a route to substituted methylenecyclobutanes **69** (R groups omitted for clarity).[1,3]

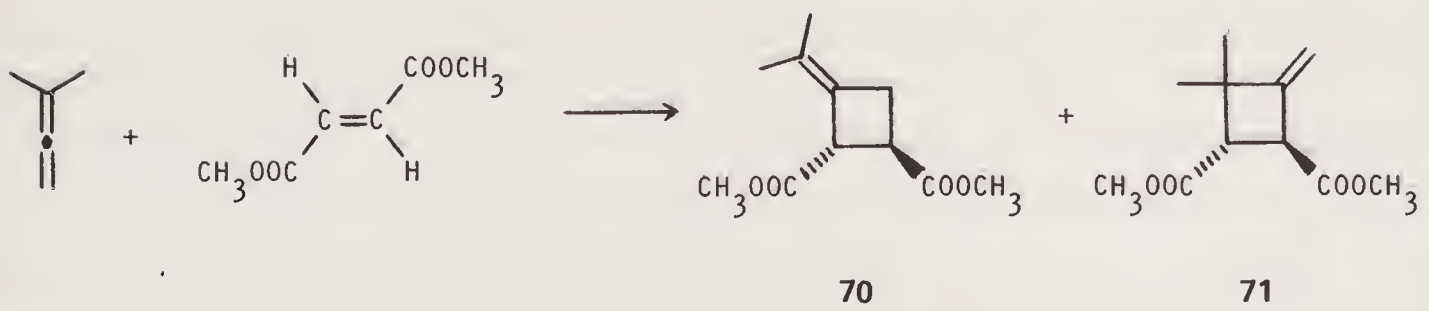
(17)

69

The usefulness of this reaction is governed by three factors that either help or hinder the reaction.[61]

1. The olefin must be sufficiently electron rich for a smooth reaction to occur and follows the increasing order: 1,2-dialkyl < 1,1,2-trialkyl < 1,1,2,2-tetraalkyl ethylene. Both 1-alkenes and cyclohexene do not react.
2. Steric hindrance due to large bulky groups on the olefin hinders cycloaddition.
3. The tendency of the alkene to undergo cationic polymerization.

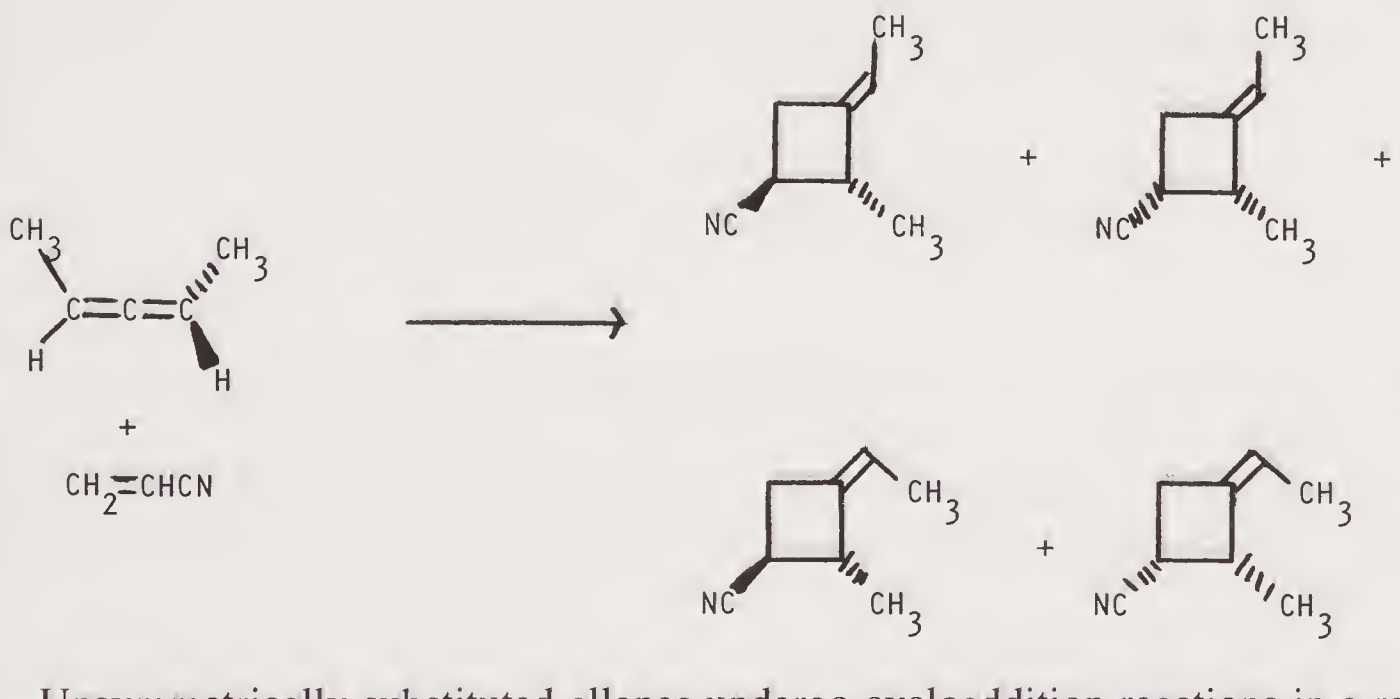
The stereochemistry about the alkene is retained in the cycloaddition.[62] The reaction of 1,1-dimethylallene with dimethyl fumerate affords two cycloadducts **70** and **71** (ratio 11.5:1) in which >99% of the *trans*-relationship is retained.[63]



(18)

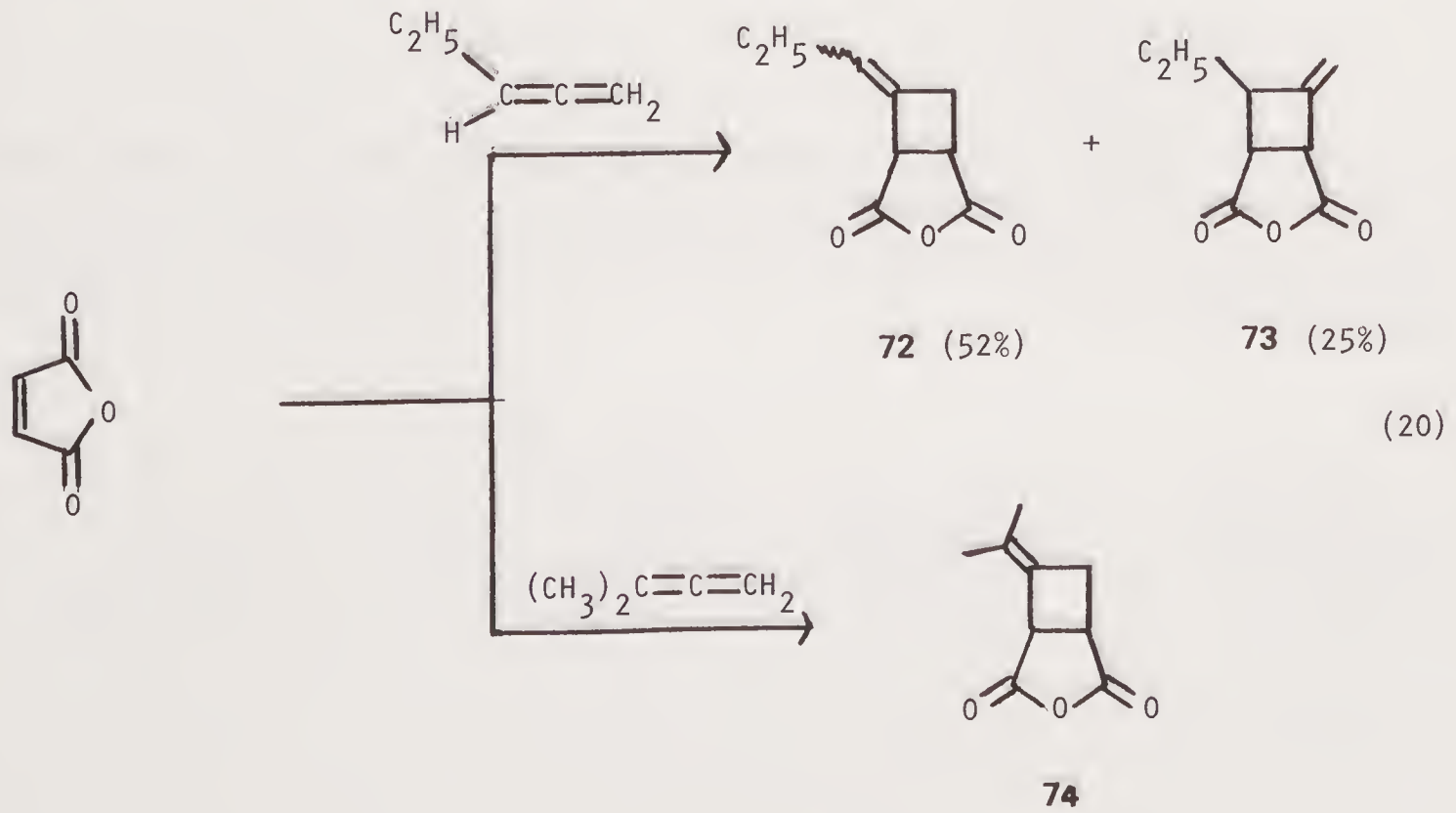
70 **71**

Optically active R-(−)-1,3-dimethylallene reacts with acrylonitrile to produce four stereoisomers in approximately equal proportions, all having the R-configuration at C2.[64]



(19)

Unsymmetrically substituted allenes undergo cycloaddition reactions in a regioselective manner. Reaction takes place predominantly at the less substituted double bond of the allene. A monosubstituted allene, such as 1,2-pentadiene, reacts with maleic anhydride to give a mixture of **72** and **73**, with **72** being formed as the major product. Alternately, 1,1-dimethylallene affords only a single product **74**[65,66] (equation 20).



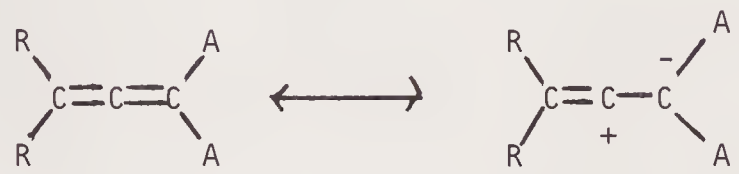
72 (52%) **73** (25%)

(20)

74

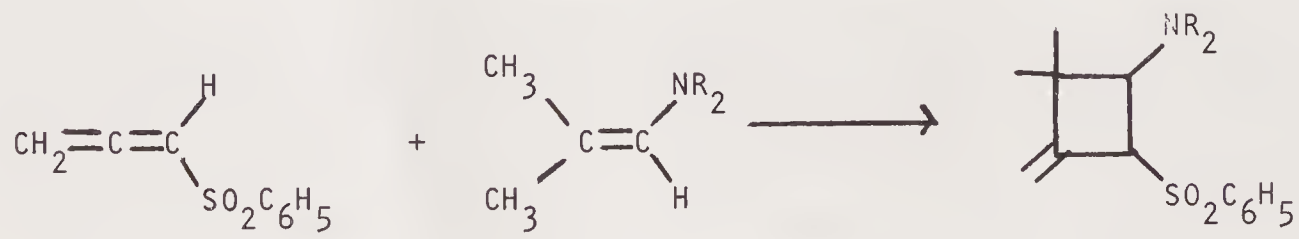
Various mechanistic interpretations have been advanced to explain these results.[67–70] However, in most cases the [π^2s + π^2a] concerted process is insufficient to explain the chemoselectivity and relative reactivity of the allenes.[70] PMO calculations suggest that a six-electron process should be favored over a four-electron process.[17] A study of the cycloaddition reaction of substituted allenes with 1,1-dichloro-2,2-difluoroethane reveals that the steric interactions that occur in the transition state effect both the rate of reaction and the chemoselectivity, thus indicating that the cycloaddition may occur by means of a two-step diradical intermediate.[62,71]

Electron-deficient allenes exhibit a polarity similar to that of ketenes, whose cycloadditions to olefins are either a concerted or two-step reaction proceeding by way of dipolar intermediates.



A = electron withdrawing group

Consequently, 1-benzenesulfonylallene (**75**) reacts with aminoisobutenes to give methylene cyclobutanes **76**, which are formed by reaction with the 1,2-double bond of the allene.[72]

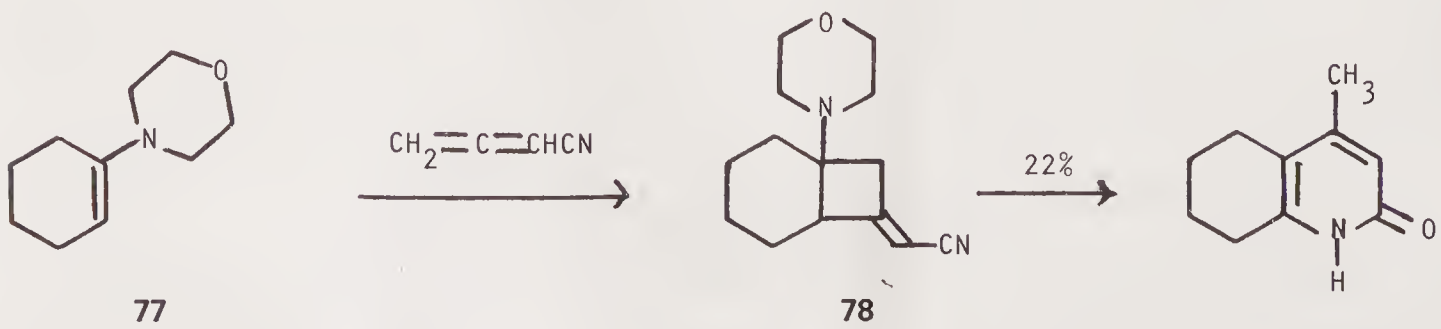


75 **76**

(21)

R = CH_3, $-(CH_2)_4-$

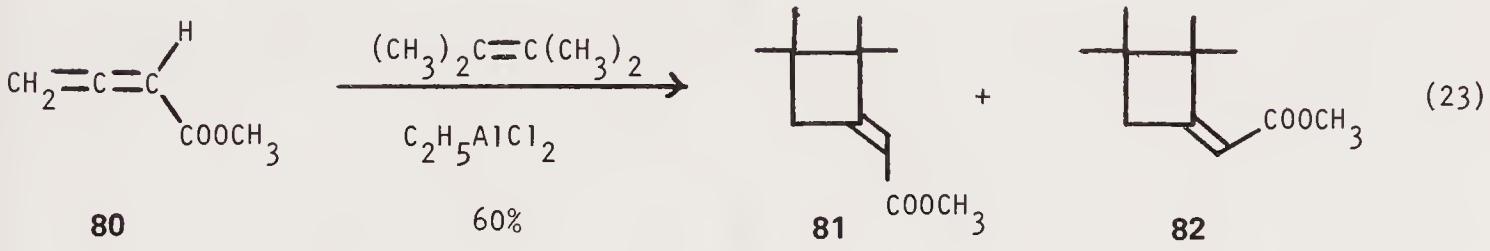
On the other hand, 1-(N-morpholino)-cyclohexene (**77**) reacts with 1-cyanoallene at the 2,3-double bond affording 1-(N-morpholino)-(E)-7-cyanomethylene-*cis*-bicyclo[4.2.0]octane (**78**). Treatment with mild base gives 4-methyl-5,6,7,8-tetrahydrocarbostyril (**79**).[73]



77 **78** **79**

(22)

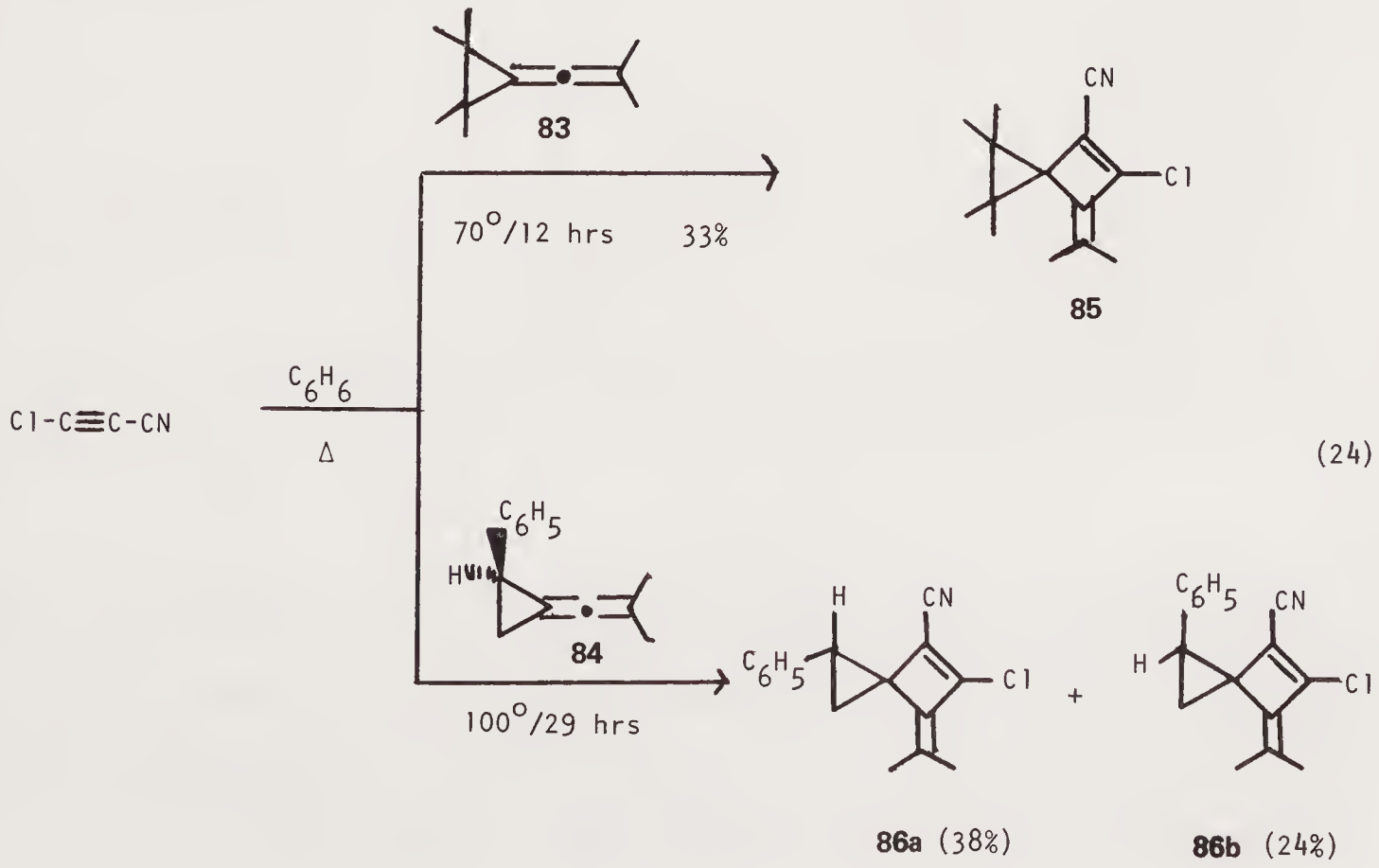
Reactions giving methylenecyclobutanes can also be performed in the presence of Lewis acid catalysts. The order of reactivity is $C_2H_5AlCl_2 > GaCl_3 > AlBr_3 > AlCl_3 > FeCl_3$.[61] A vinyl cation, formed by complexation of the Lewis acid to the double bonds of allenes, is electronically similar to ketene and is expected to undergo a stereospecific [$\pi^2s + \pi^2a$] cycloaddition. With methyl 2,3-butadienoate (**80**), cycloaddition occurs regiospecifically at the 3,4-double bond of the allene to afford a mixture of cycloadducts in moderate yield. The (E)-isomer **81** predominates.[74] For additional examples see Table 9.3.



(23)

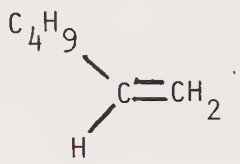
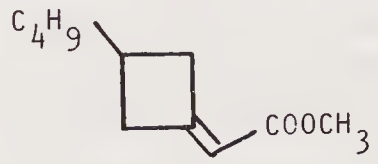
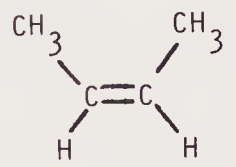
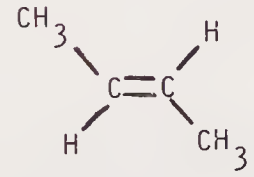
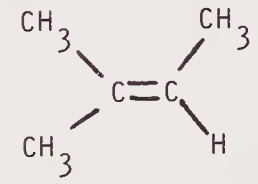
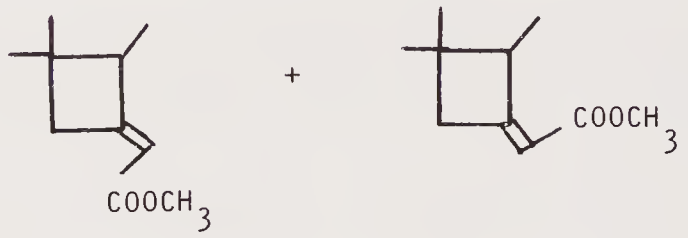
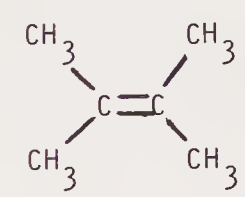
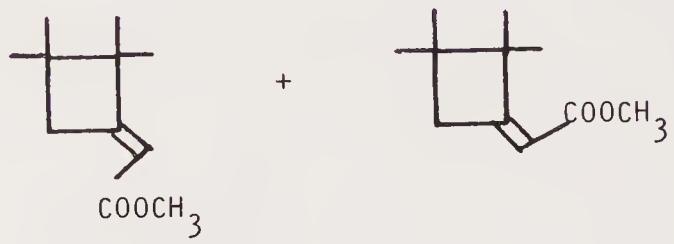
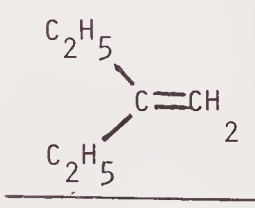
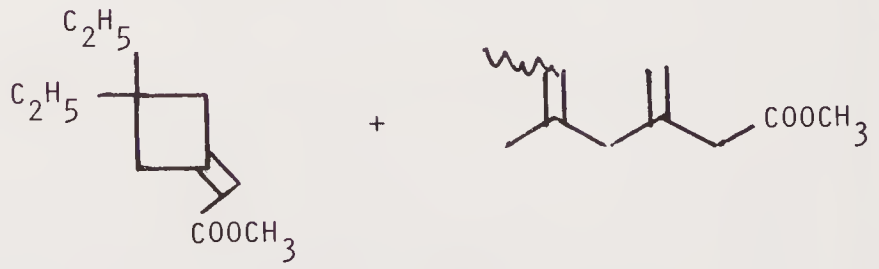
The reaction of allenes with acetylenic enophiles seems to proceed by a [2 + 2] cycloaddition mechanism. In the reaction of benzyne with allenes, hydrogen abstraction predominates except in cases of electron-rich allenes, and even then yields are too low for any synthetic utility.[75]

When 2,2,3,3-tetramethylisobutylidenecyclopropane (**83**) or 2-phenylisobutylidenecyclopropane (**84**) react with chlorocyanoacetylene in benzene at elevated temperatures, the interesting spiro–cycloadducts **85** and **86** are formed exclusively.[76]



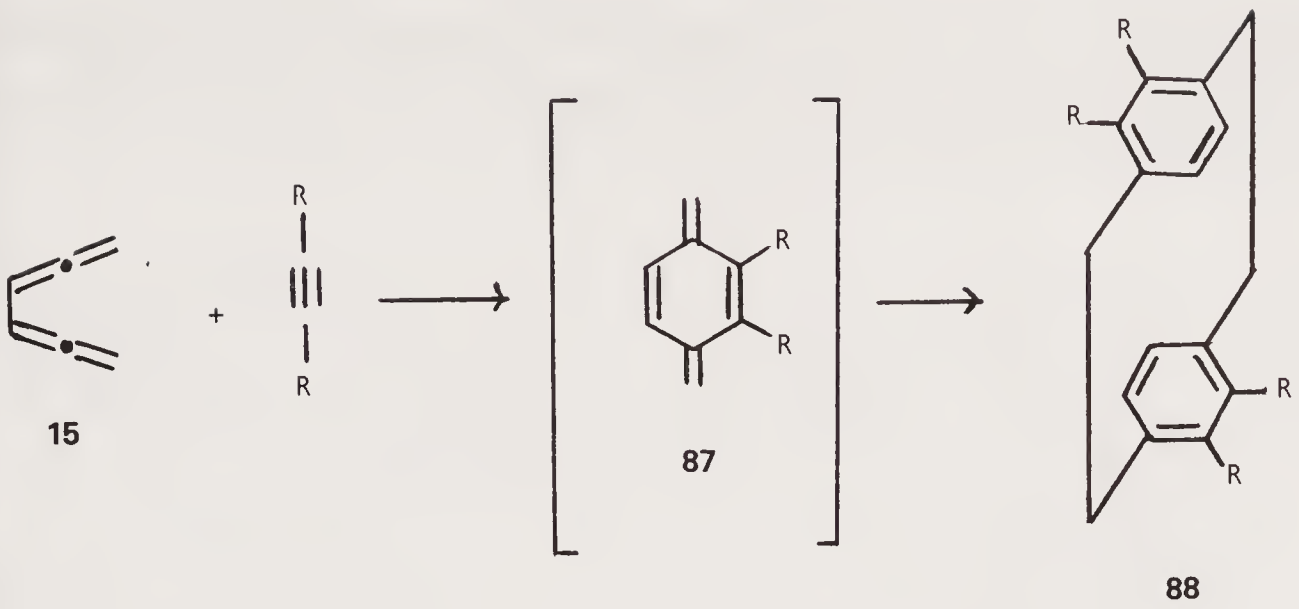
(24)

Table 9.3. Adducts from the Cycloaddition of 80 with Alkenes under $C_2H_5AlCl_2$ Catalysis[a]

Alkene	Yield, % (ratio)	Adducts
	65	
	77(14:1)	
	90(1.27:1)	
	65(3.1:1)	
	60(12.5:1)	
	48(7.7:1)	

[a]Reprinted from ref. 74 with permission from the American Chemical Society, Copyright 1980.

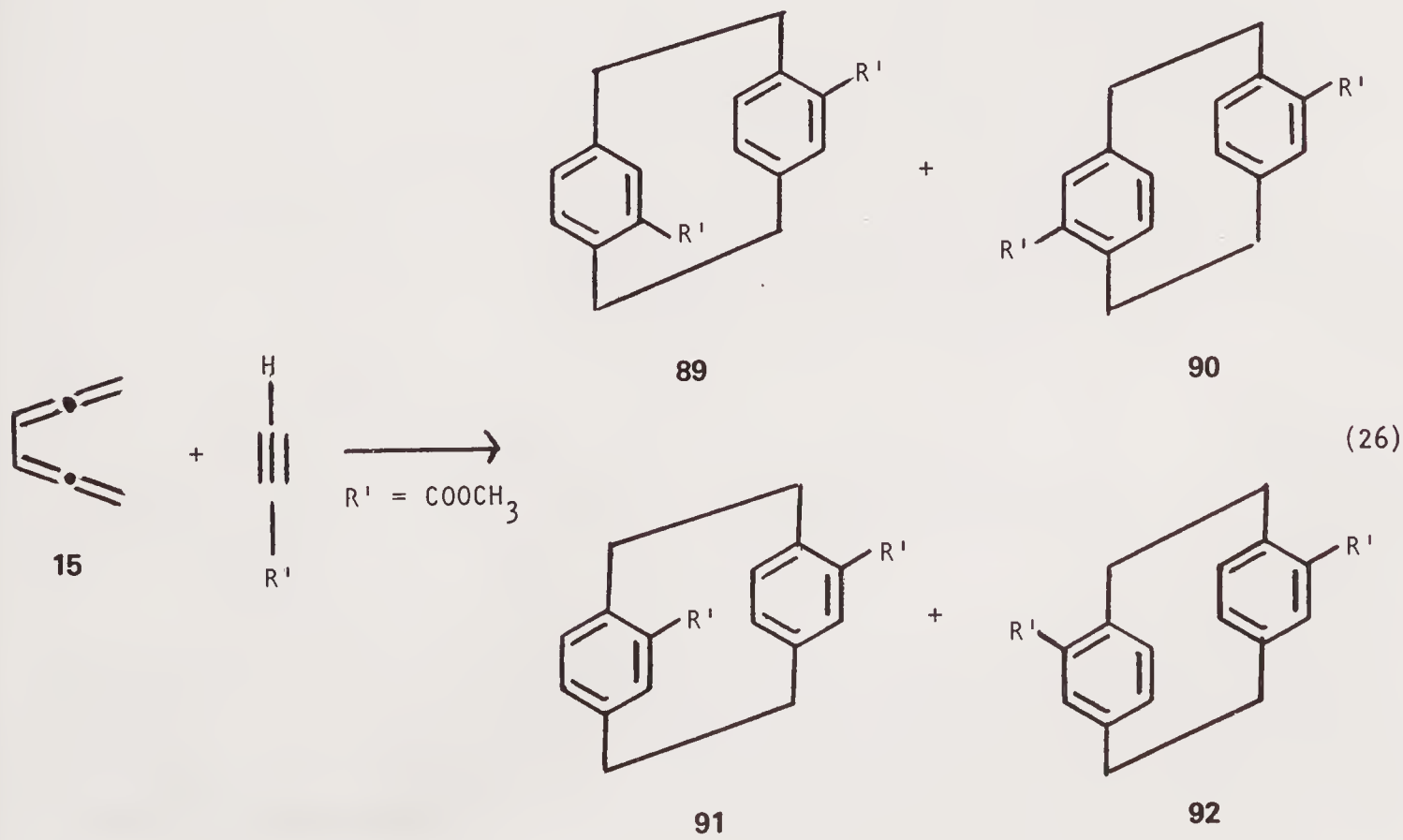
One of the most synthetically interesting and useful allene cycloaddition reactions has been applied to the synthesis of paracyclophane derivatives. This reaction involves a [4 + 2] Diels–Alder cycloaddition of 1,2,4,5-hexatetraene (biallenyl) (**15**) with an electron-poor acetylenic enophile where **15** behaves as the 4-electron partner in the reaction. The initially formed *p*-xylylene intermediate **87** reacts with itself to produce the [2.2] paracyclophanes **88**[77–80] (equation 25).



15 87 88 (25)

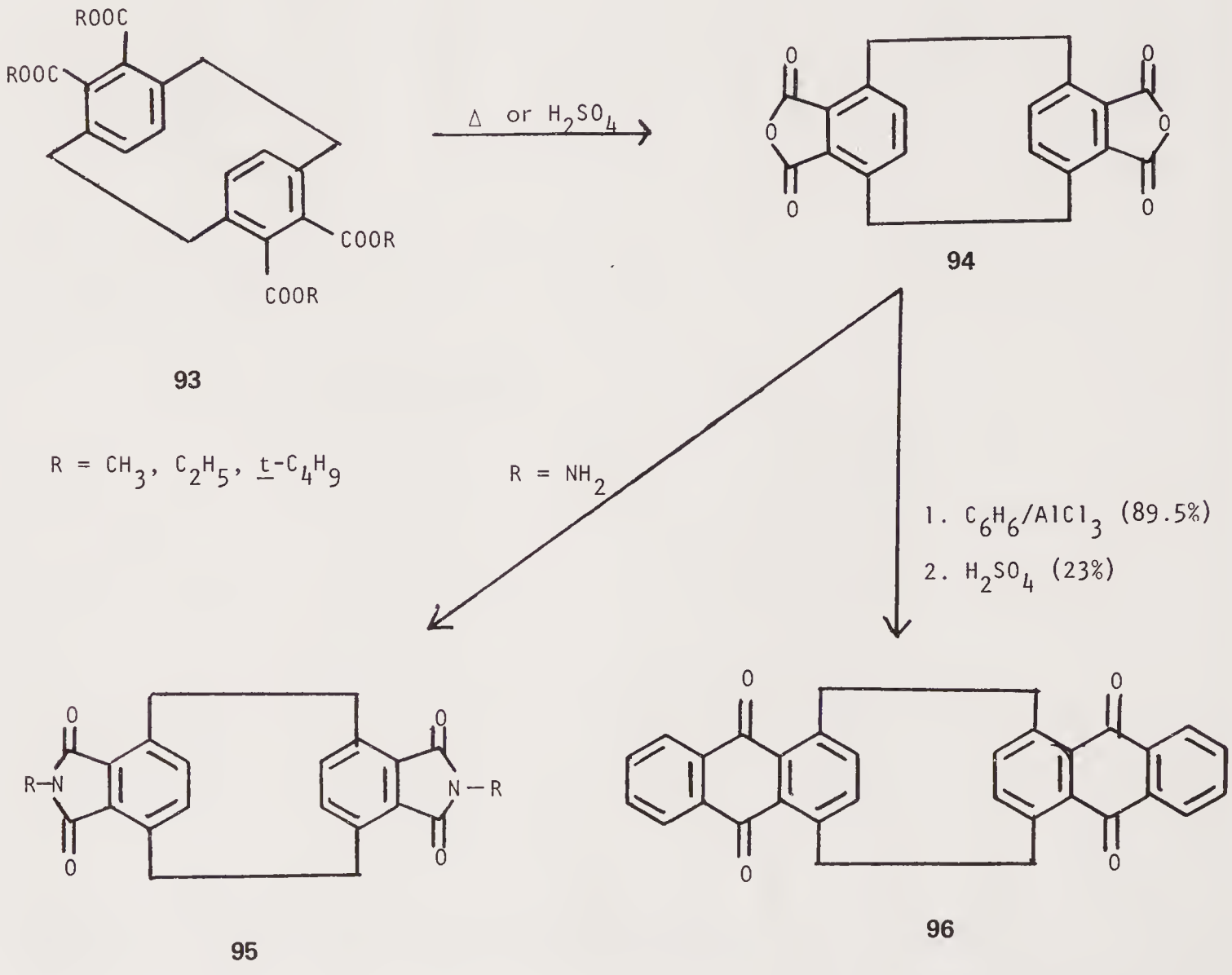
R	Yield **88** (%)
$COOCH_3$	47
$COOC_2H_5$	30
$COOCH(CH_3)_2$	37
$COOC(CH_3)_3$	20
COOH	5
$COOCH_2CH(CH_3)_2$	28
$COOCH_2C(CH_3)_3$	24
CN	37
CF_3	21

Unfortunately, an analogous reaction with methyl propiolate results in the formation of all four possible disubstituted [2.2] paracyclophanes **89–92**, which must be chromatographically separated.[79]



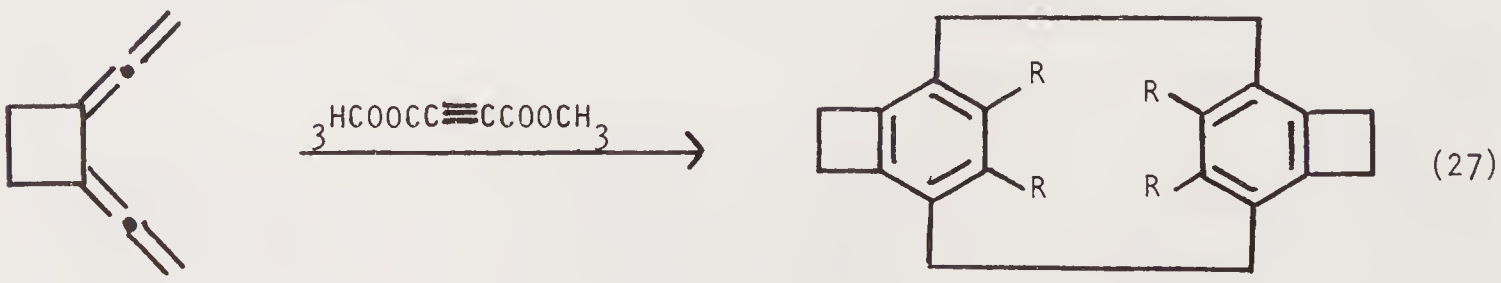
15 89 90 91 92 (26)

The tetrasubstituted esters **93** can be conveniently converted to the bis-anhydride **94** that serves as starting material for the preparation of the bis-imides **95** or the anthraquinophane (**96**)[80] (Scheme 7).



Scheme 7

An unusual extension of this reaction involves the cycloaddition of dimethyl acetylene dicarboxylate with 1,2-bis(vinylidene)cyclobutane (**97**) to afford in 7.5% yield the interesting benzocyclobutenophane (**98**).[81]



The interesting [2.2.2] (1.2.4)-cyclophane (**100**) can be prepared in good yield from dimethyl [2.2] paracyclophane-4,13-dicarboxylate (**99**) (prepared in 5.4% yield after chromatographic separation of the products in equation 26[79]).[82]

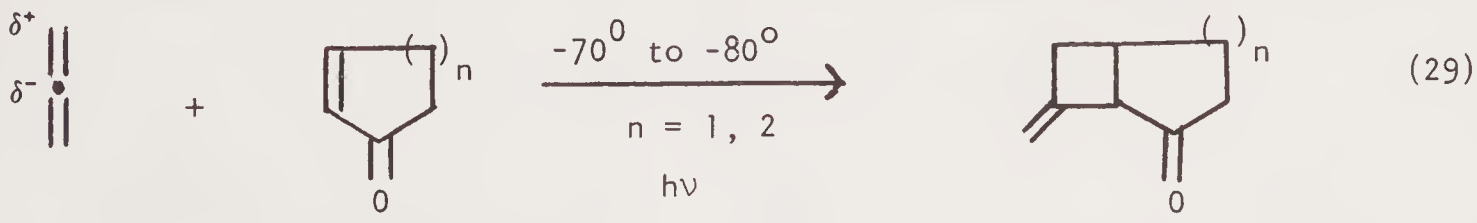
(28)

99 **100**

9.4. ALLENE–ENONE PHOTOCHEMICAL CYCLOADDITIONS

The photochemical [2 + 2] cycloaddition of allene with a variety of α,β-unsaturated ketones or aldehydes results in a regioselective formation of *exo*-methylene cyclobutanes that can undergo facile functional group manipulation reactions.

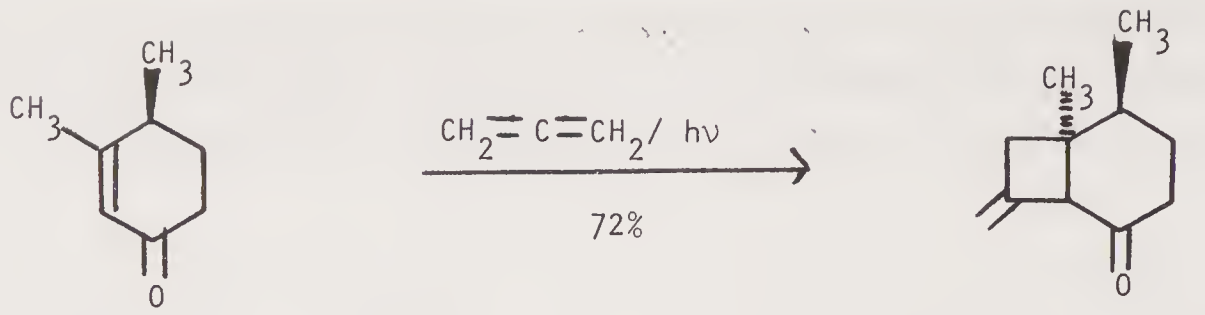
When cyclohexenone (**101**, $n = 2$) is irradiated in the presence of excess allene at low temperature, a 55% yield of 8-methylenebicyclo[4.1.0]octan-2-one (**102**) is obtained as the major product (equation 29). This head-to-head cycloadduct is controlled by the geometry of the intermediate π-complex resulting from the n–π* excited state of the enone and the polarity of the allene, since the sp-hybridized carbon is more electronegative than the sp^2-hybridized carbon.[83] A similar reaction is observed with 2-cyclopentenones.[83,84] In both cases the ring fusion is *cis*.



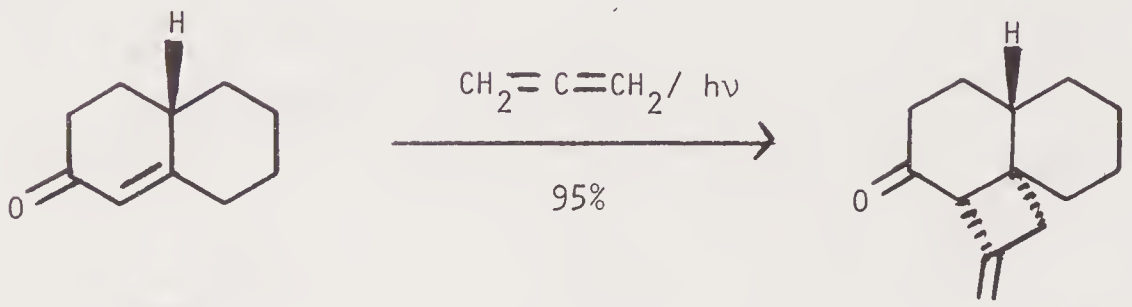
(29)

101 **102**

The irradiation of 3,4-dimethylcyclohexenone (**103**) with an excess of allene yields the *transoid* adduct **104** as the major product[85] (equation 30). With the unsubstituted octalone **105**, the allene adduct **106** is obtained stereospecifically in 95% yield[86] (equation 31).

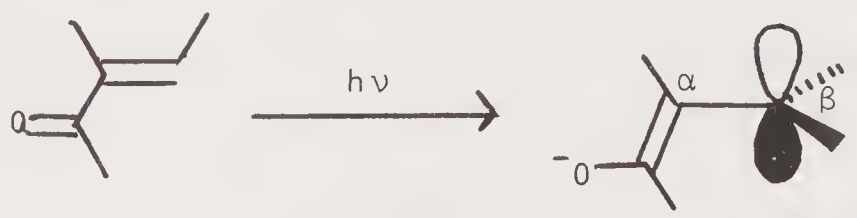


103 104 (30)



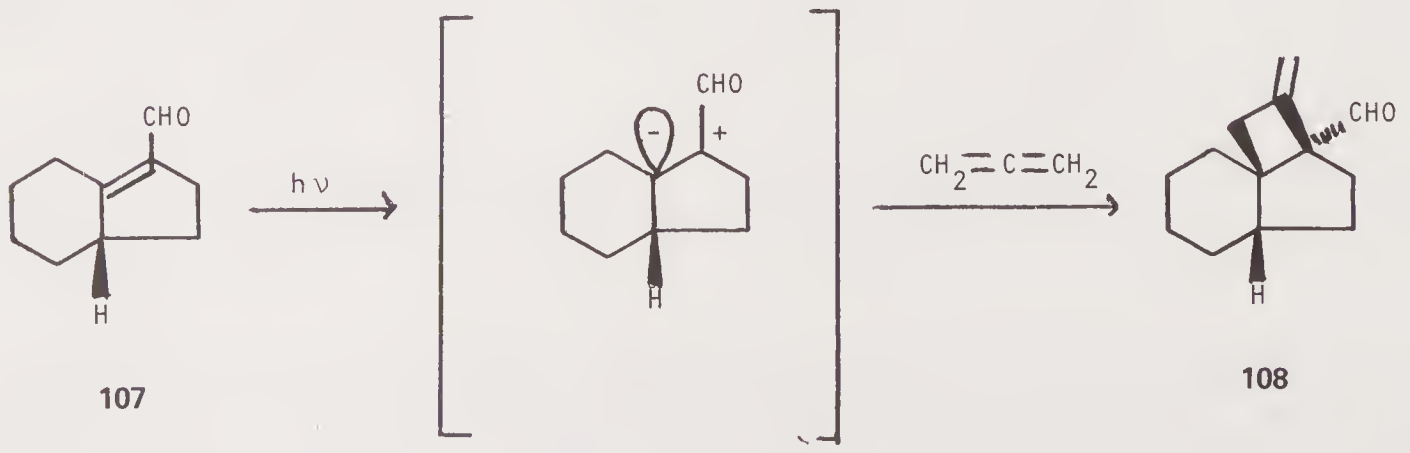
105 106 (31)

Such observations lead to the establishment of an empirical rule for the prediction of the configuration of such photocycloadditions between allene and α,β-unsaturated carbonyls. It is postulated that the preferred configuration of the excited state determines the configuration of the major photocycloadduct. It is assumed that the geometry of the excited state is trigonal at the α-carbon and pyramidal at the β-carbon, thus establishing an additional chiral center in the excited state. It is this chirality that dictates the more stable of the two possible epimeric configurations.[86,87]



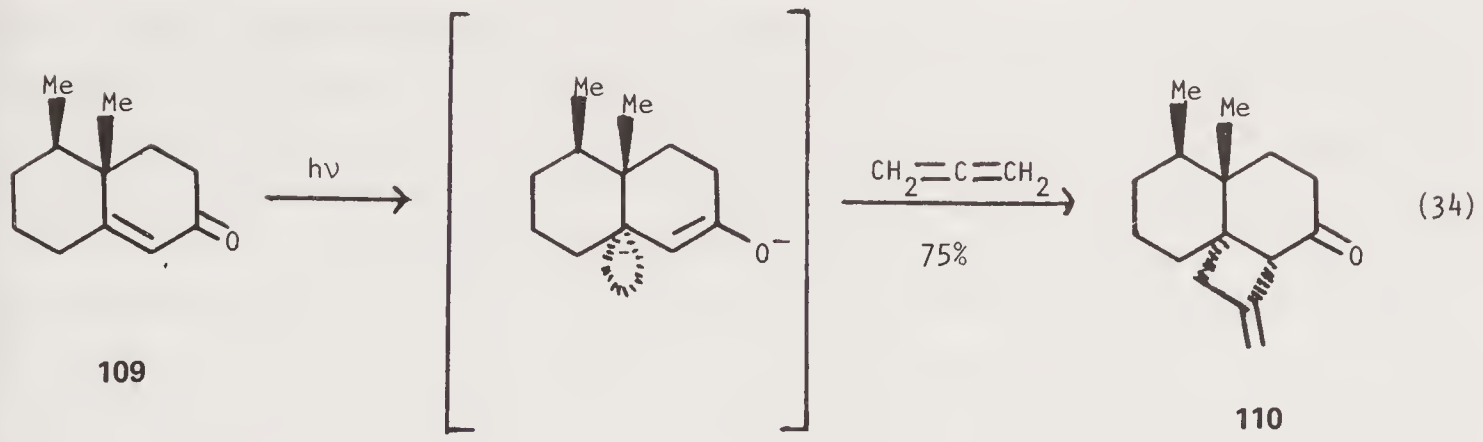
(32)

As illustrated by the indene aldehyde **107**, the preferred excited state configuration is *cisoid* at the ring junction[88] to produce the *cis*-adduct **108** (equation 33).



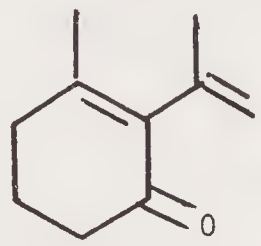
107 108 (33)

On the other hand, the bicycloenone **109** has a *transoid* ring junction preference to afford adduct **110** in 75% yield.[89]

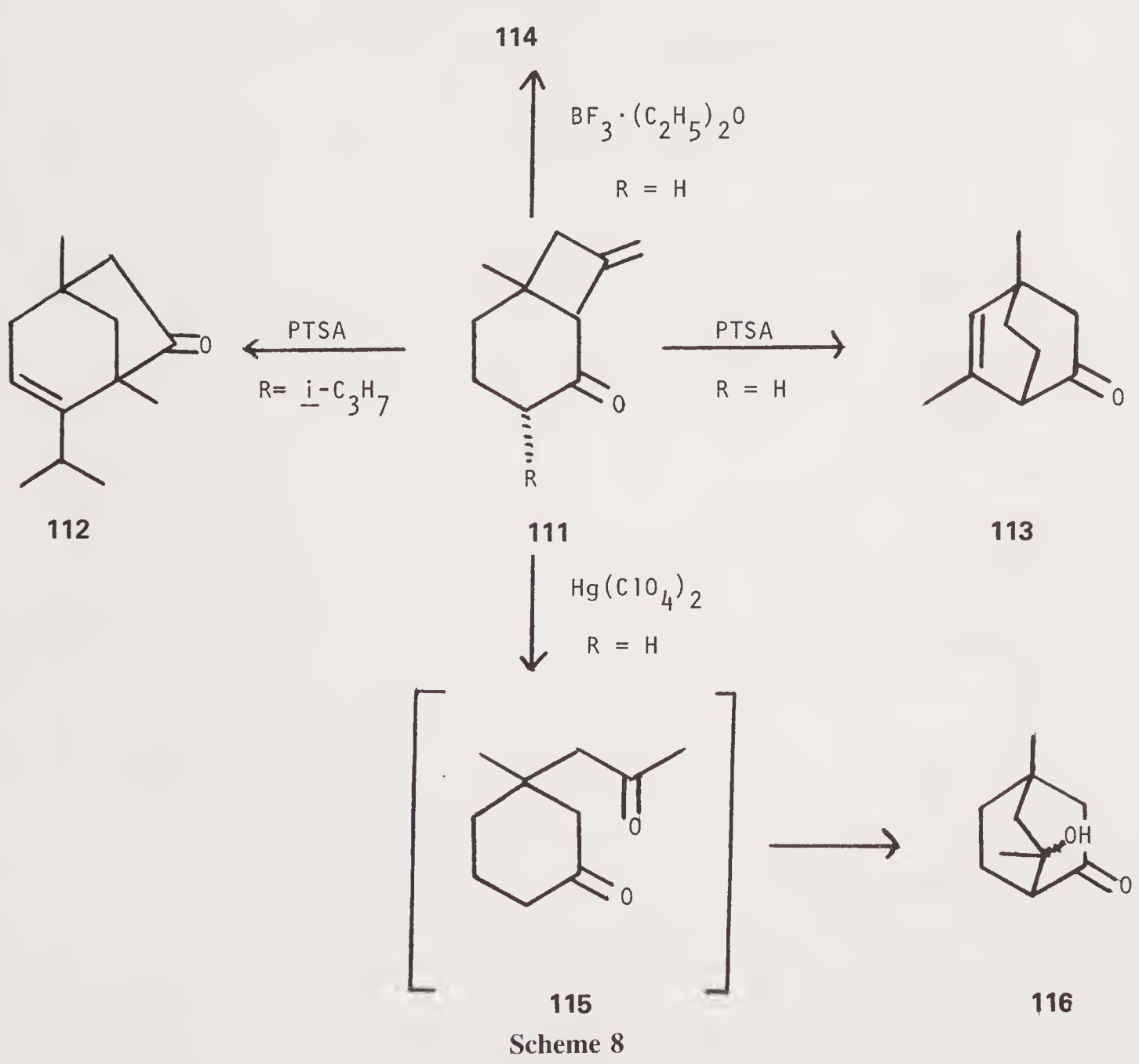


109 110 (34)

The methylene cyclobutanes resulting from these photocycloaddition reactions are extremely versatile intermediates which are easily transformed into more desirable and useful functionalities. For example, in the presence of *p*-toluenesulfonic acid, bicyclo[4.1.0]-oct-7-en-2-one (**111**) undergoes an acid-catalyzed rearrangement to afford either bicyclo[3.2.1]octene (**112**) or bicyclo[2.2.2]octene (**113**)[90] (Scheme 8).



114



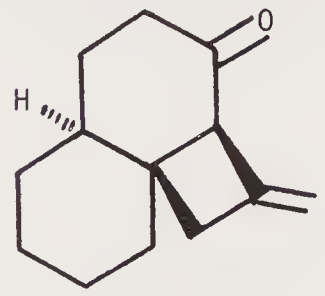
112 111 113

115 116

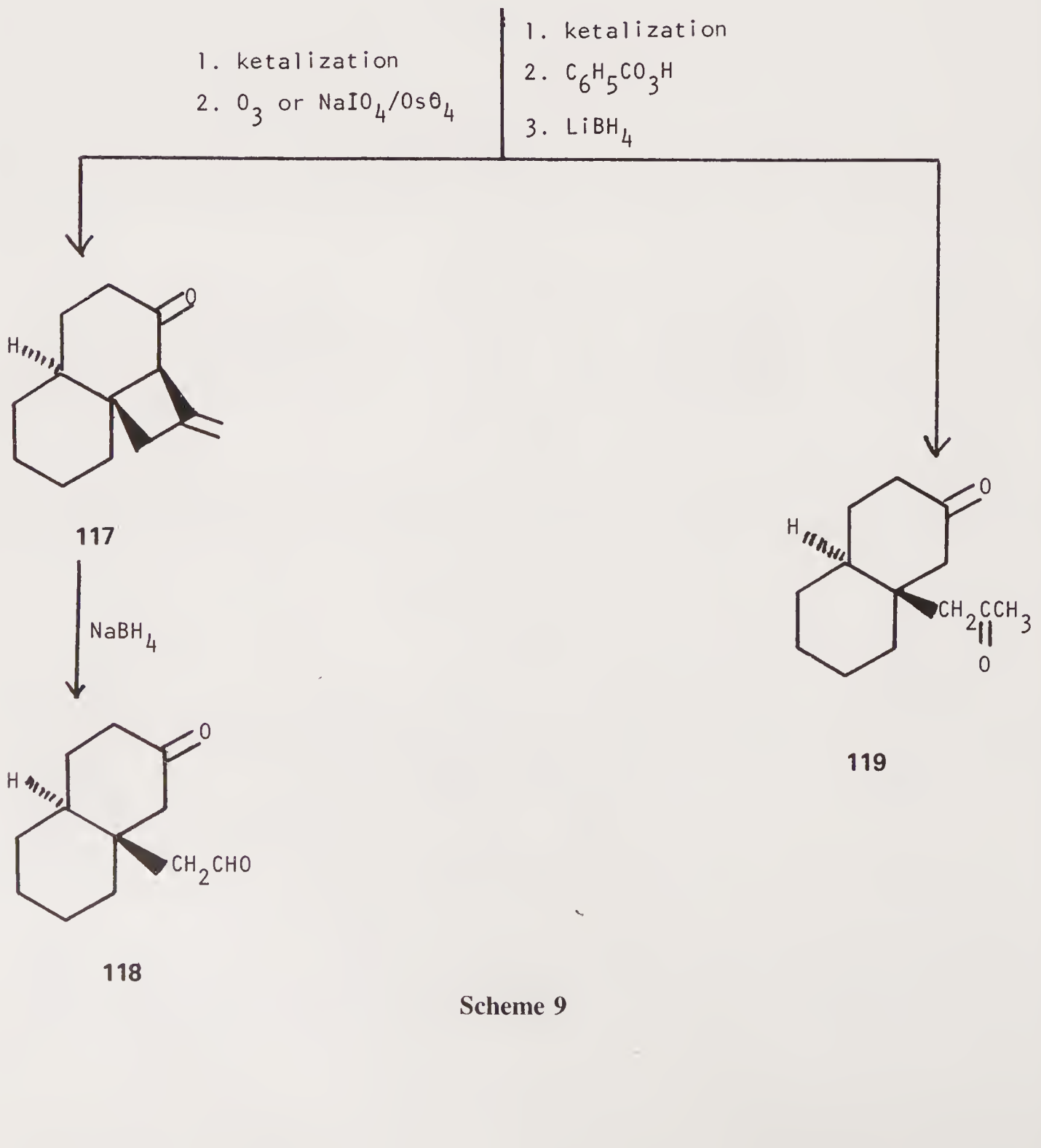
Scheme 8

The isopropenyl group can be introduced to an α,β-unsaturated ketone by refluxing **111** in benzene with boron trifluoride etherate. Yields vary from 25 to 95% depending on the substrate.[91] Treatment of **111** with mercuric perchlorate in acetone produces the diketone **115** which under the reaction conditions leads to bicyclic ketone **116** by way of an intramolecular aldol condensation.[92]

Stereospecific introduction of an acetaldehyde or methyl ketone constitutes another excellent synthetic use for these methylenecyclobutanes. The treatment of cycloadduct **106** with ozone[93,94] or $OsO_4/NaIO_4$[95,96] results in the formation of ketone **117** which, when reduced with sodium borohydride, leads to a cyclobutanol that undergoes a retro-aldol reaction to **118**. Alternately, epoxidation of ketalized **106** with peracid followed by lithium borohydride reduction gives a tertiary alcohol that also undergoes a retro-aldol reaction to produce the methyl ketone **119**.[97–101] In



106



117

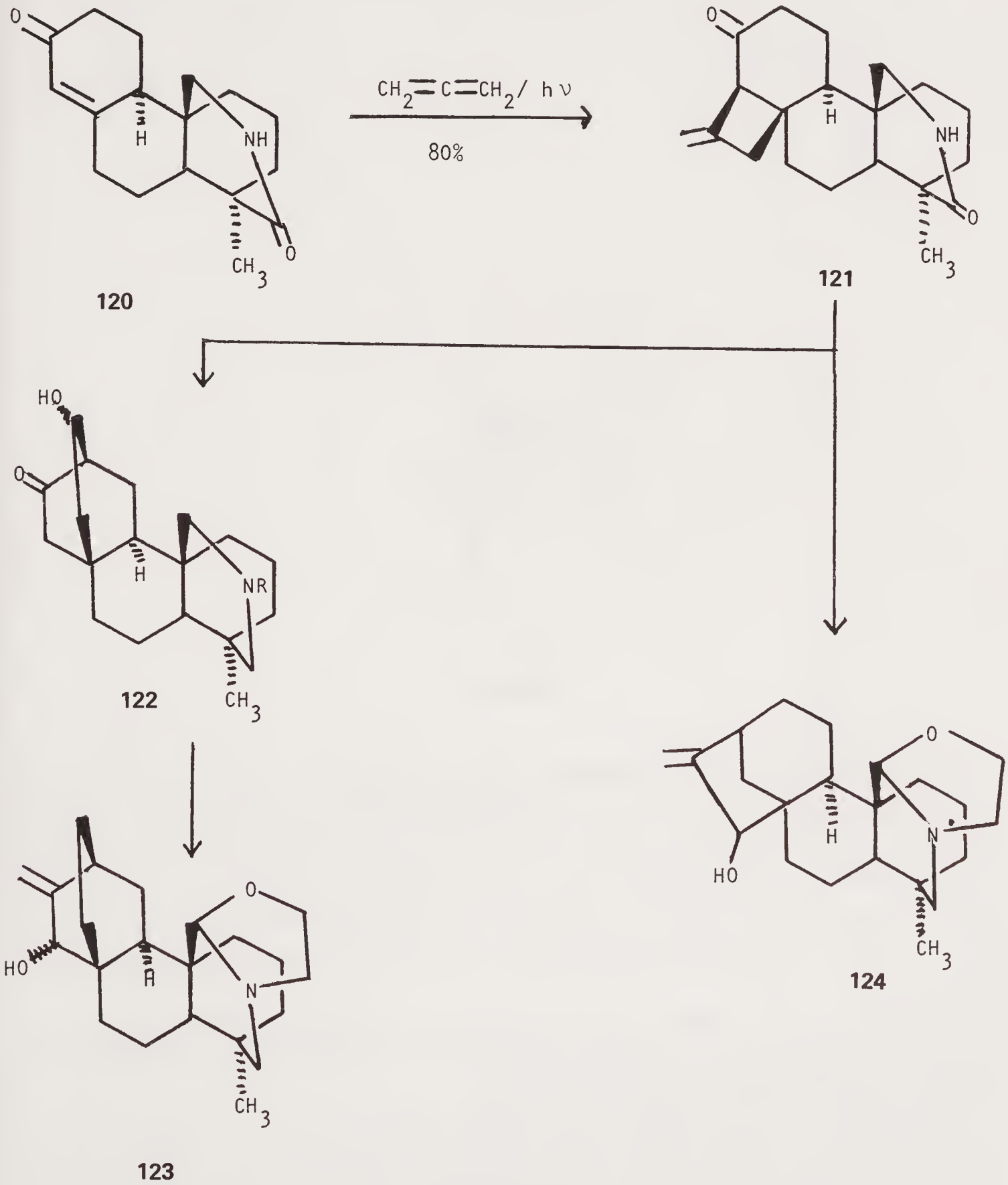
118

119

Scheme 9

both cases, a further aldol reaction to a new bicyclic system usually occurs under the reaction conditions (Scheme 9).

The application of this cycloaddition to the synthesis of complex natural products gives this method its greatest value. Atisine (**123**), the principal alkaloid of the rhizomes of *A. heterophyllum wall*,[102] is a C-20 diterpenoid alkaloid that can be synthesized from the α,β-unsaturated enone **120**.[95] Irradiation of **120** in the presence of a large excess of allene for 18 hours affords photoadduct **121** in 80% yield.[96] Ketalization followed by $OsO_4/NaIO_4$ oxidation and sodium borohydride reduction proceeds as previously described to give the aldol product **122**. Further chemical transformations lead to **123**. The related skeleton system of veatchine (**124**) is accessible by further elaboration of **121** (Scheme 10).



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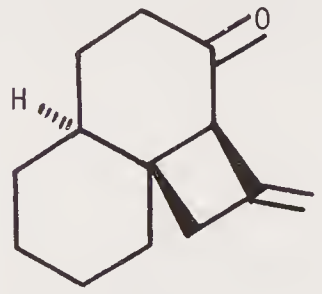
The isopropenyl group can be introduced to an α,β-unsaturated ketone by refluxing **111** in benzene with boron trifluoride etherate. Yields vary from 25 to 95% depending on the substrate.[91] Treatment of **111** with mercuric perchlorate in acetone produces the diketone **115** which under the reaction conditions leads to bicyclic ketone **116** by way of an intramolecular aldol condensation.[92]

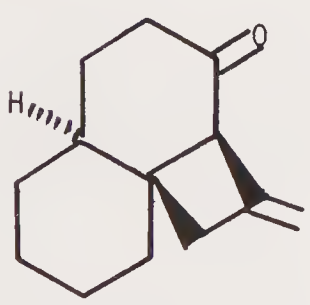
Stereospecific introduction of an acetaldehyde or methyl ketone constitutes another excellent synthetic use for these methylenecyclobutanes. The treatment of cycloadduct **106** with ozone[93,94] or $OsO_4/NaIO_4$[95,96] results in the formation of ketone **117** which, when reduced with sodium borohydride, leads to a cyclobutanol that undergoes a retro-aldol reaction to **118**. Alternately, epoxidation of ketalized **106** with peracid followed by lithium borohydride reduction gives a tertiary alcohol that also undergoes a retro-aldol reaction to produce the methyl ketone **119**.[97–101] In



106

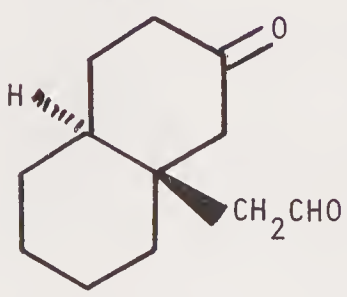
1. ketalization
2. O_3 or $NaIO_4/OsO_4$

1. ketalization
2. $C_6H_5CO_3H$
3. $LiBH_4$

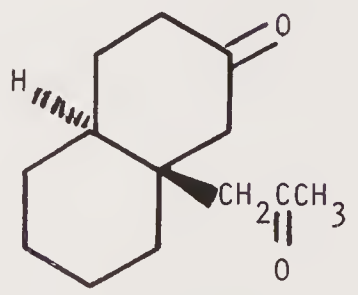


117

$NaBH_4$



118

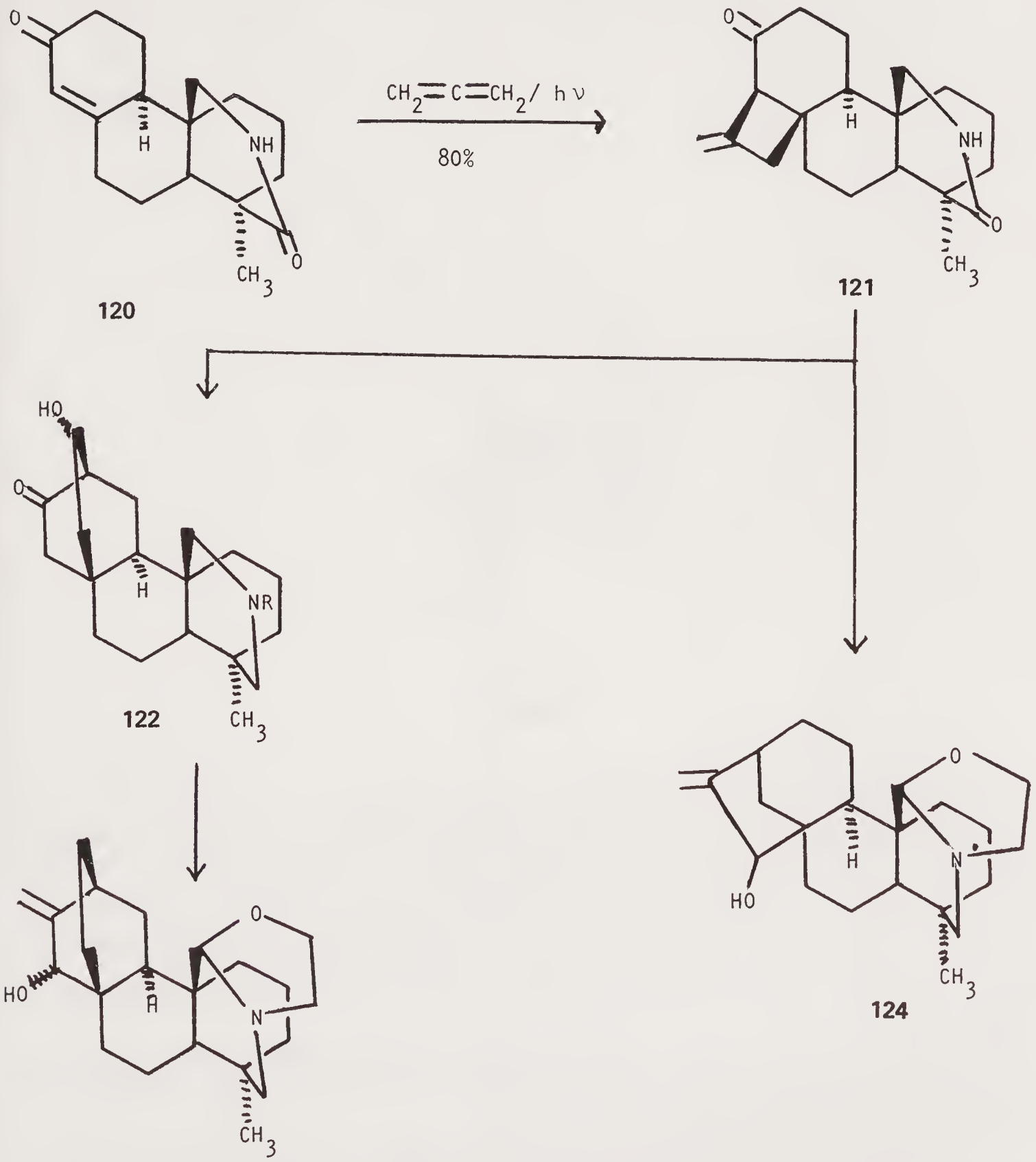


119

Scheme 9

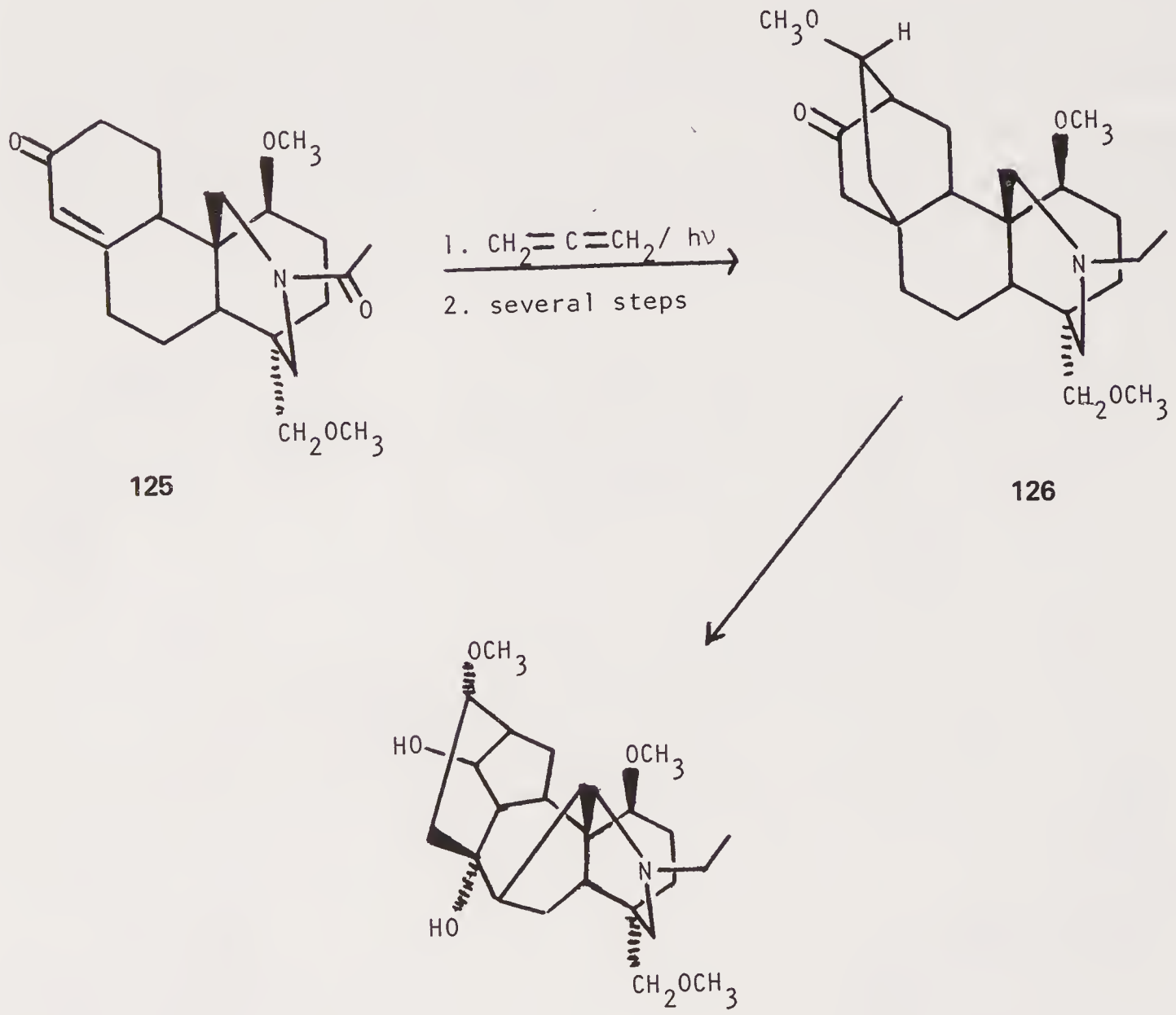
both cases, a further aldol reaction to a new bicyclic system usually occurs under the reaction conditions (Scheme 9).

The application of this cycloaddition to the synthesis of complex natural products gives this method its greatest value. Atisine (**123**), the principal alkaloid of the rhizomes of *A. heterophyllum wall*,[102] is a C-20 diterpenoid alkaloid that can be synthesized from the α,β-unsaturated enone **120**.[95] Irradiation of **120** in the presence of a large excess of allene for 18 hours affords photoadduct **121** in 80% yield.[96] Ketalization followed by $OsO_4/NaIO_4$ oxidation and sodium borohydride reduction proceeds as previously described to give the aldol product **122**. Further chemical transformations lead to **123**. The related skeleton system of veatchine (**124**) is accessible by further elaboration of **121** (Scheme 10).



Scheme 10

The first synthesis of the hexacyclic aconite alkaloid talatisamine (**127**), isolated from *Aconitum variegatum,*[103,104] incorporates the photochemical cycloaddition of allene to enone **125**, which is then transformed to an atisine type intermediate **126**. A biogenetic rearrangement yields racemic **127**[105] (Scheme 11).



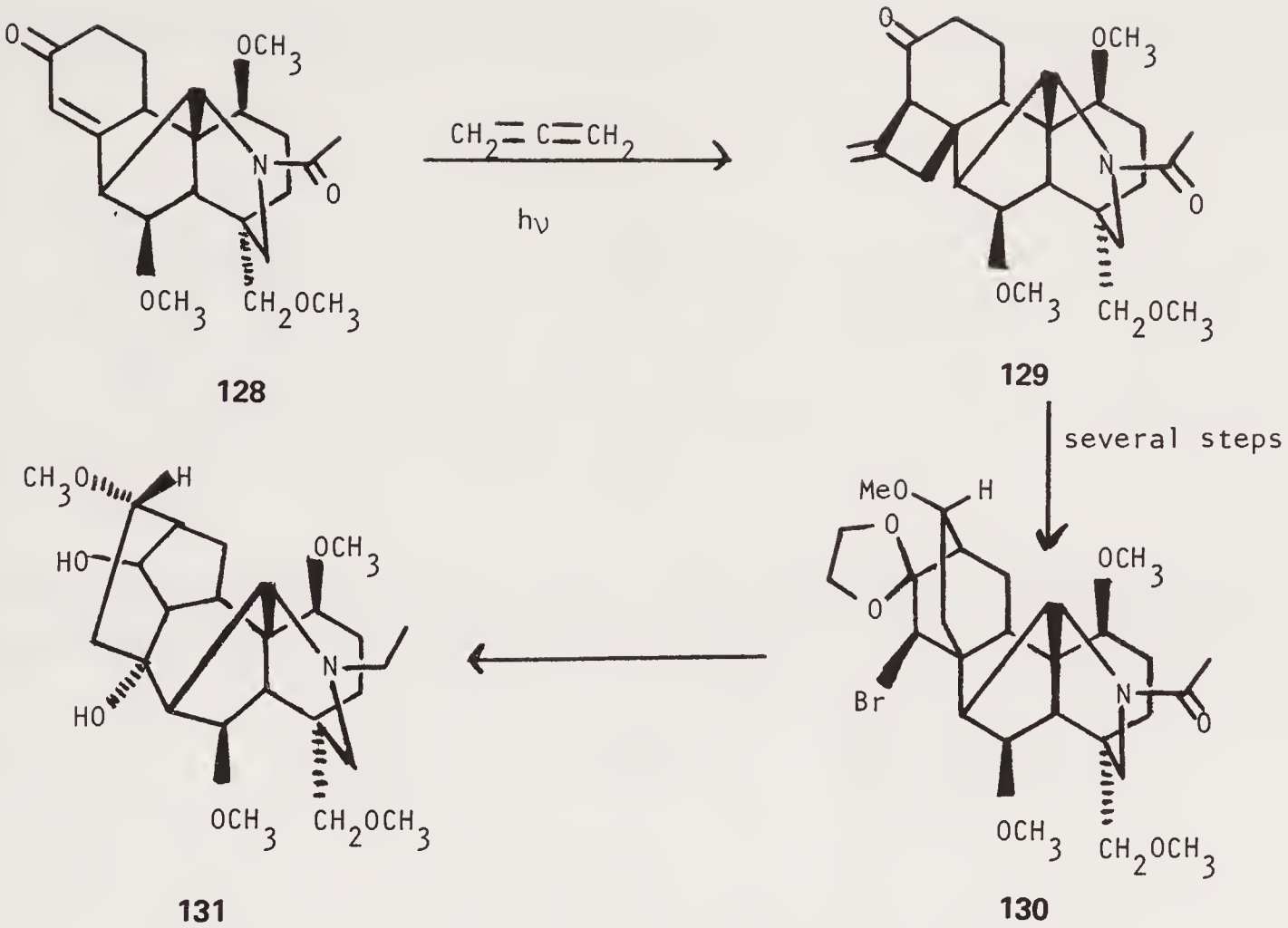
125 **126** **127**

Scheme 11

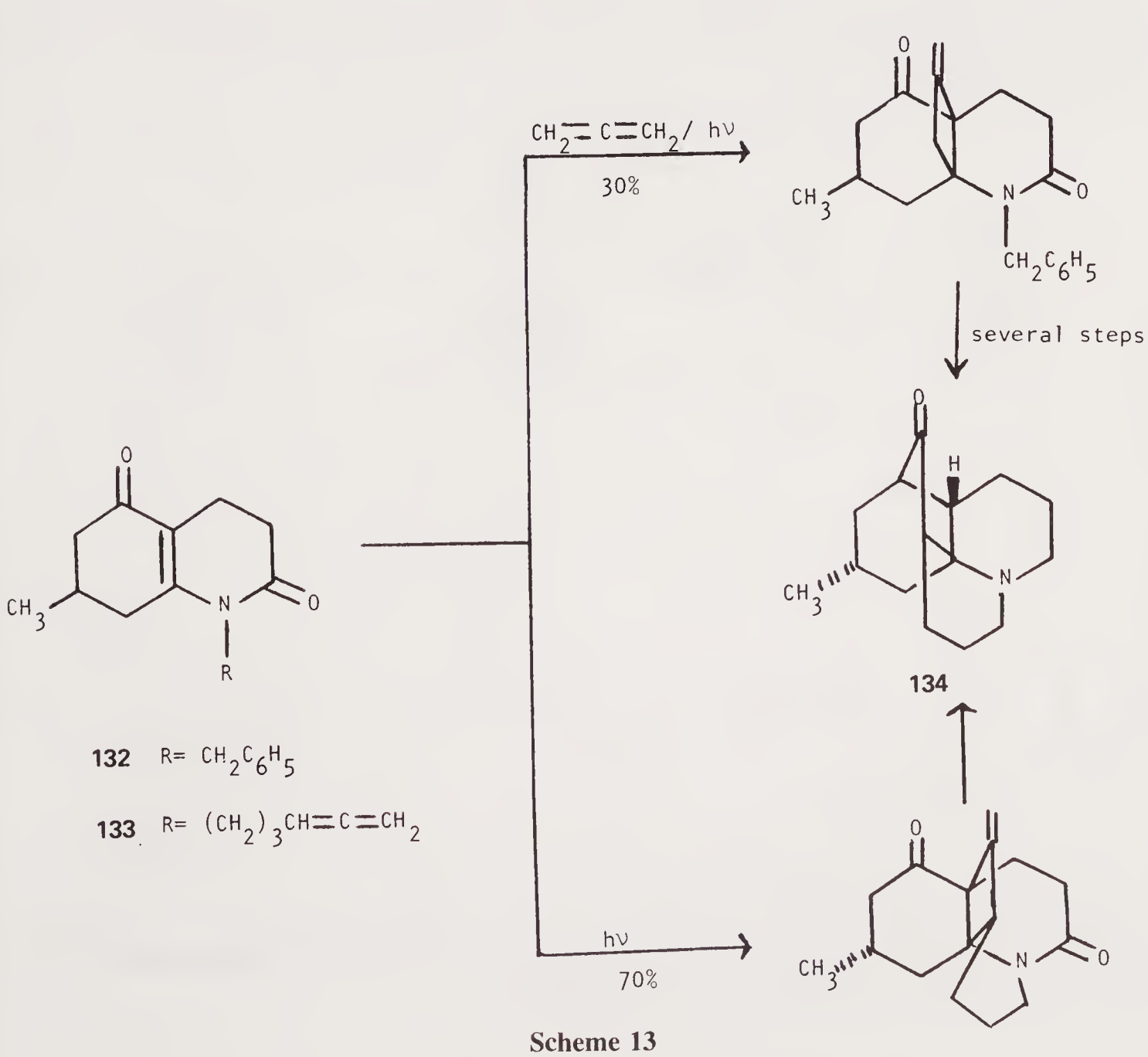
Chasmanine (**131**), a C-19 delphinine-type alkaloid,[104] can be stereospecifically synthesized by the photochemical cycloaddition of allene to **128**. Rearrangement and proper functionalization yields racemic **131**.[106–109] Model studies[93,94] indicate that the preferred excited state of the cyclohexane ring annelated to the bicycloheptene system adopts the *cis* configuration. Therefore this directs the allene molecule to add to the sterically more hindered *endo* face to give the observed stereospecificity.[87]

12-epi-Lycopodine (**134**), a diastereoisomer of the naturally occurring alkaloid, lycopodine, is easily accessible from an inter-[110,111] or intramolecular[100] addition of an allene to either **132** or **133** (Scheme 13).

The alkaloid annotinine (**137**) can be synthesized by employing the photoaddition of allene to the tricyclic enone **135**.[97] This occurs quantitatively with the stereochemistry being determined by a diaxial preference in the excited state, thus af-

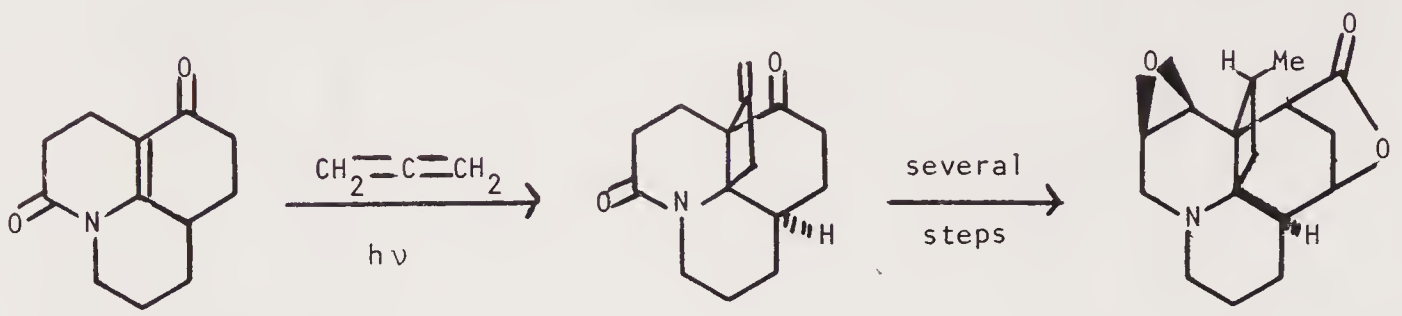


Scheme 12



Scheme 13

fording the *trans*-product.[101] Standard chemical transformations then provide **137**[98,99,101] (equation 35).

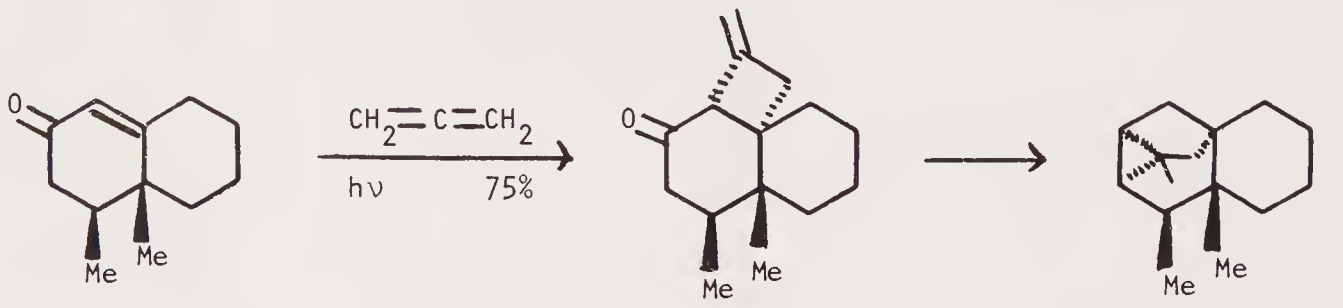


135 **136** **137** (35)

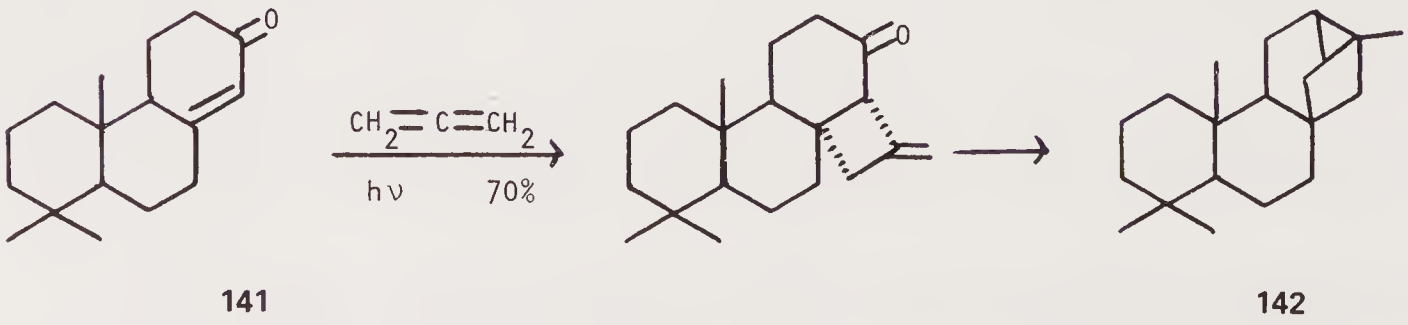
The sesquiterpene ishwarane (**140**)[112] and the diterpene trachylobane (**142**)[113] both possess a tricyclo[3.2.1.$0^{2,7}$]octane system **138**. Both are obtained from the

138

regio- and stereospecific addition of allene to either enone **139** or **141** (equations 36 and 37). Subsequent elaboration of the exomethylene cyclobutane then leads to the products.

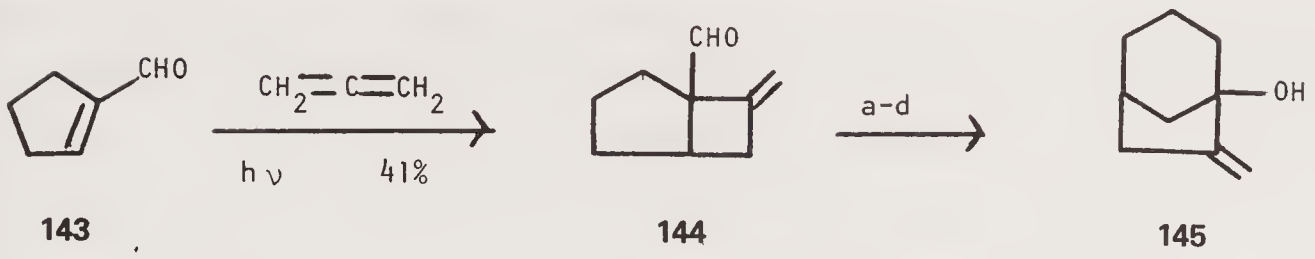


139 **140** (36)



141 **142** (37)

1-Hydroxy-7-methylene bicyclo[3.2.1]octane (**145**), a ring system common to gibbanes, is obtained from 1-cyclopentene-1-carboxaldehyde (**143**) according to the series of reactions outlined in equation (38).[114]

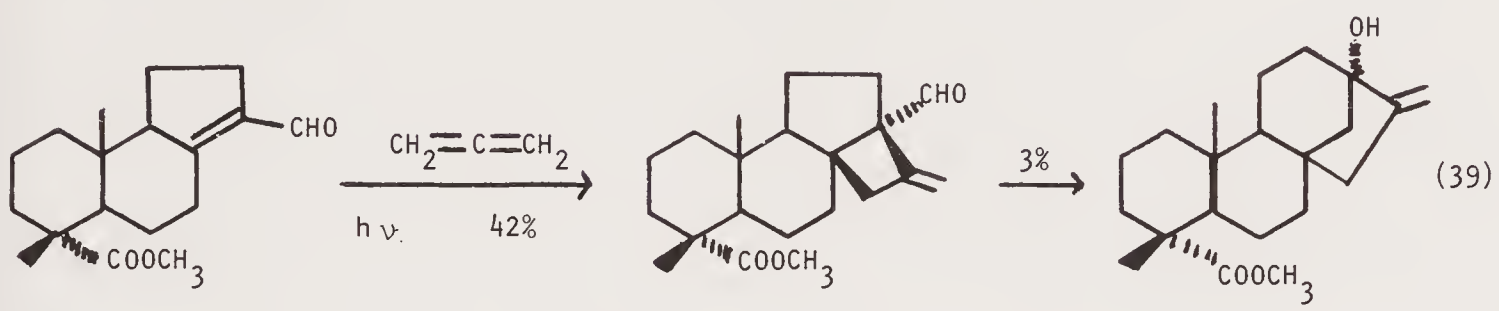


(38)

143 **144** **145**

(a) $LiAlH_4$ (69%); (b) TsCl/pyridine (80%); (c) NaOAc/AcOH (46%); (d) $LiAlH_4$.

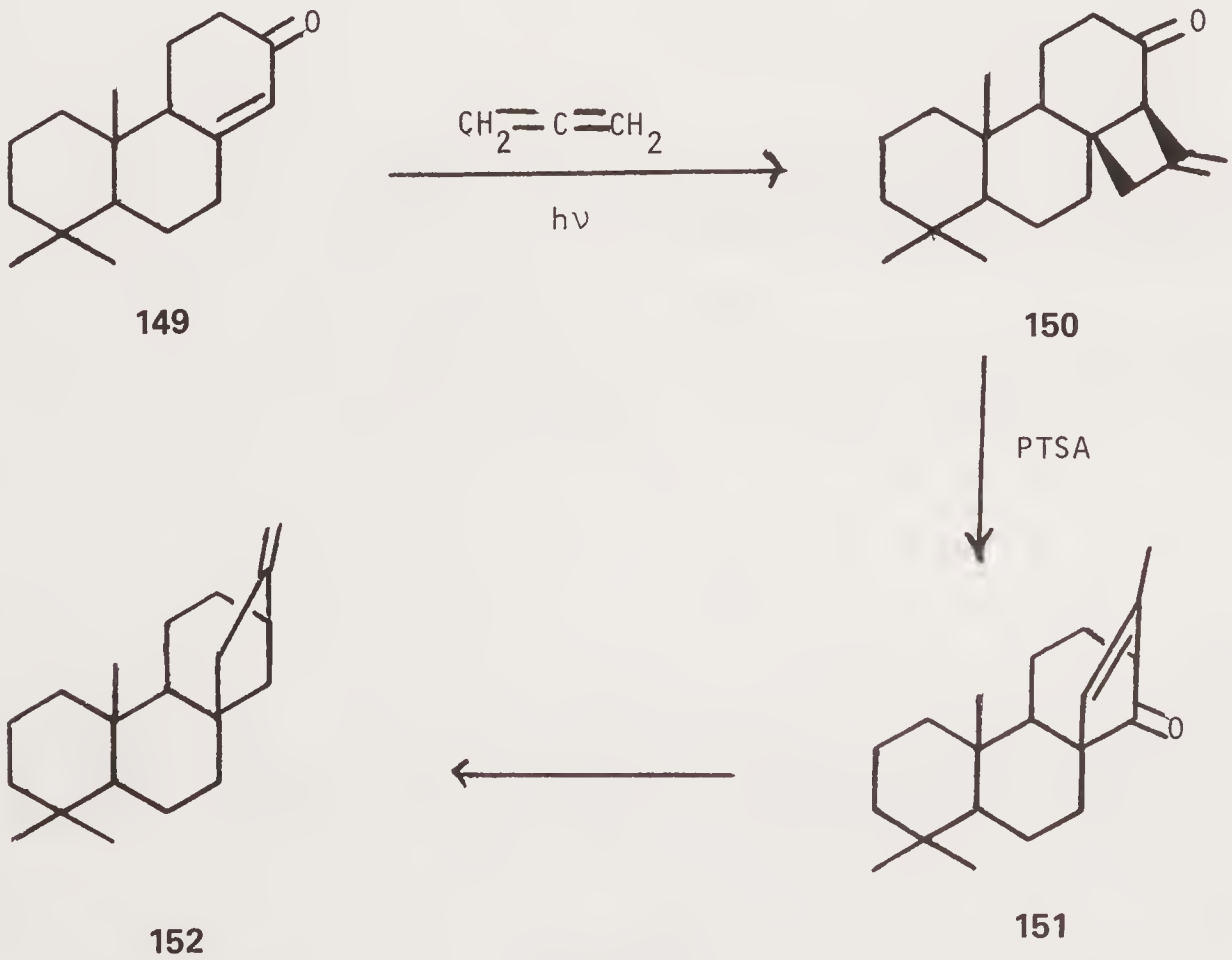
Actual application of this method to the synthesis of (±)-steviol methylester (**148**) results in a low yield of product.[115]



(39)

146 **147** **148**

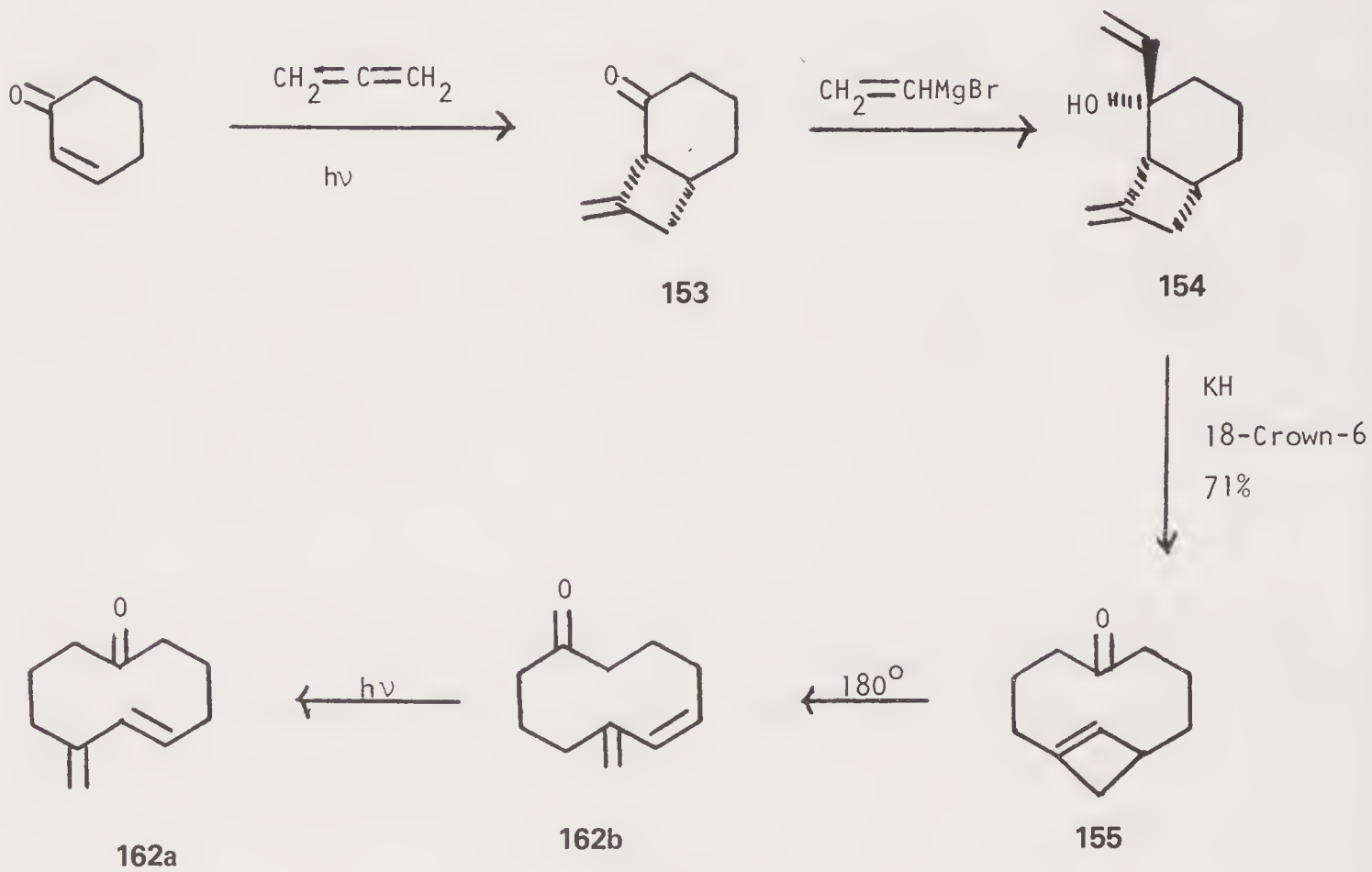
Isophyllocladene (**151**) and phyllocladene (**152**) occur in the leaf oils of various conifers.[116] The photoaddition of allene to (+)-$\Delta^{8(14)}$-podocarpen-13-one (**149**) proceeds as expected to give adduct **150**. Refluxing **150** in benzene in the presence of a large amount of *p*-toluenesulfonic acid results in a 50% yield of **151**. Wolff–Kishner reduction of **151** followed by bromination with N-bromosuccinimide then zinc–acetic acid reduction affords **152**[117] (Scheme 14).



149 **150** **151** **152**

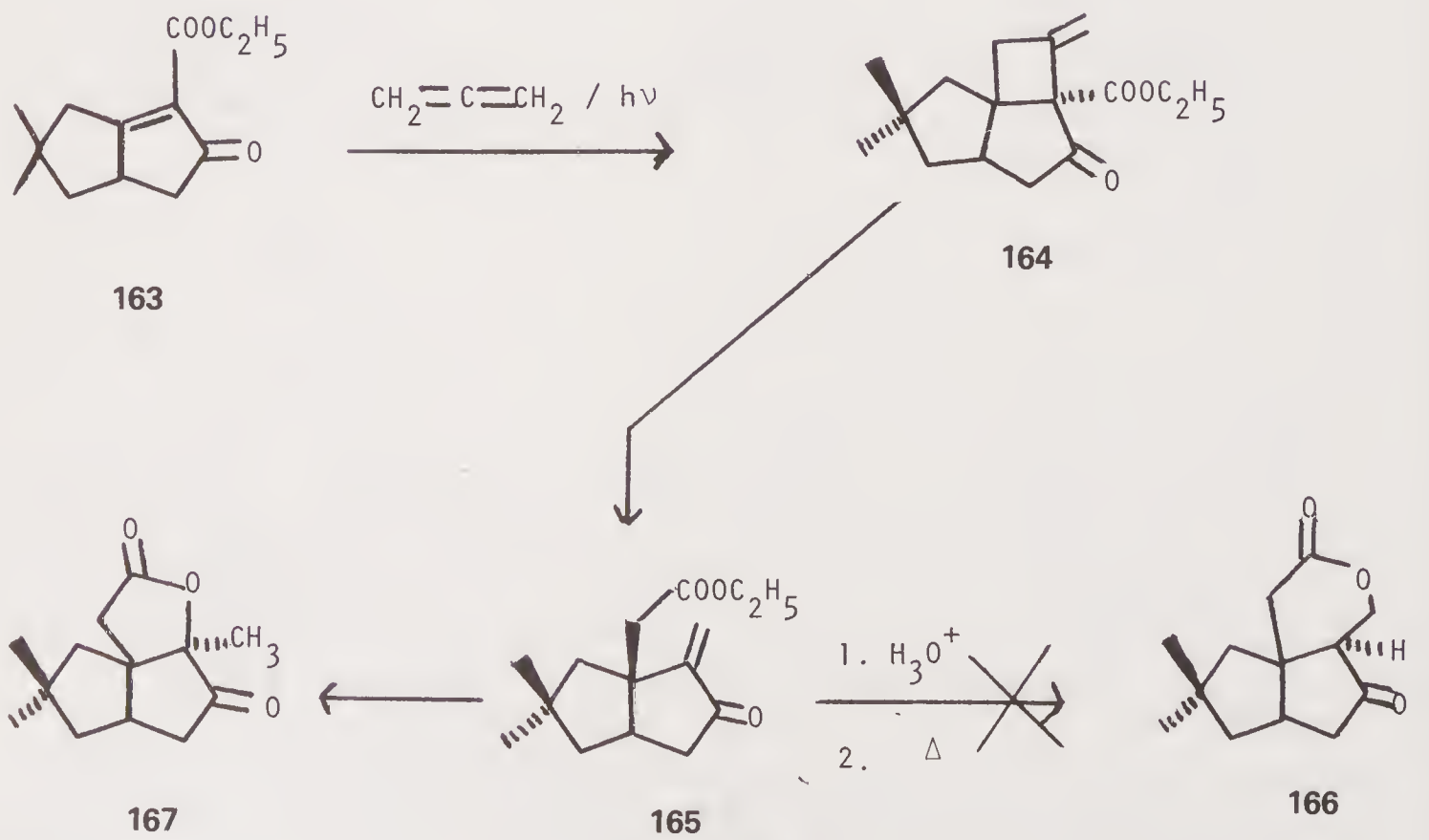
Scheme 14

In a model study for the synthesis of germacranes, the β,γ-unsaturated enone **153** adds vinyl magnesium bromide to afford **154** in 79% yield. This undergoes a consecutive oxy-Cope cyclobutene rearrangement to provide **162b** (5:1 *cis*/*trans* mixture). Photolysis gives a photostationary state consisting of a 10:1 mixture of *trans* and *cis* isomers. Thus in this fashion an enriched mixture of *cis* **162b** or *trans* **162a** isomers can be established[118] (Scheme 15).



153 **154** **155** **162b** **162a**

Scheme 15

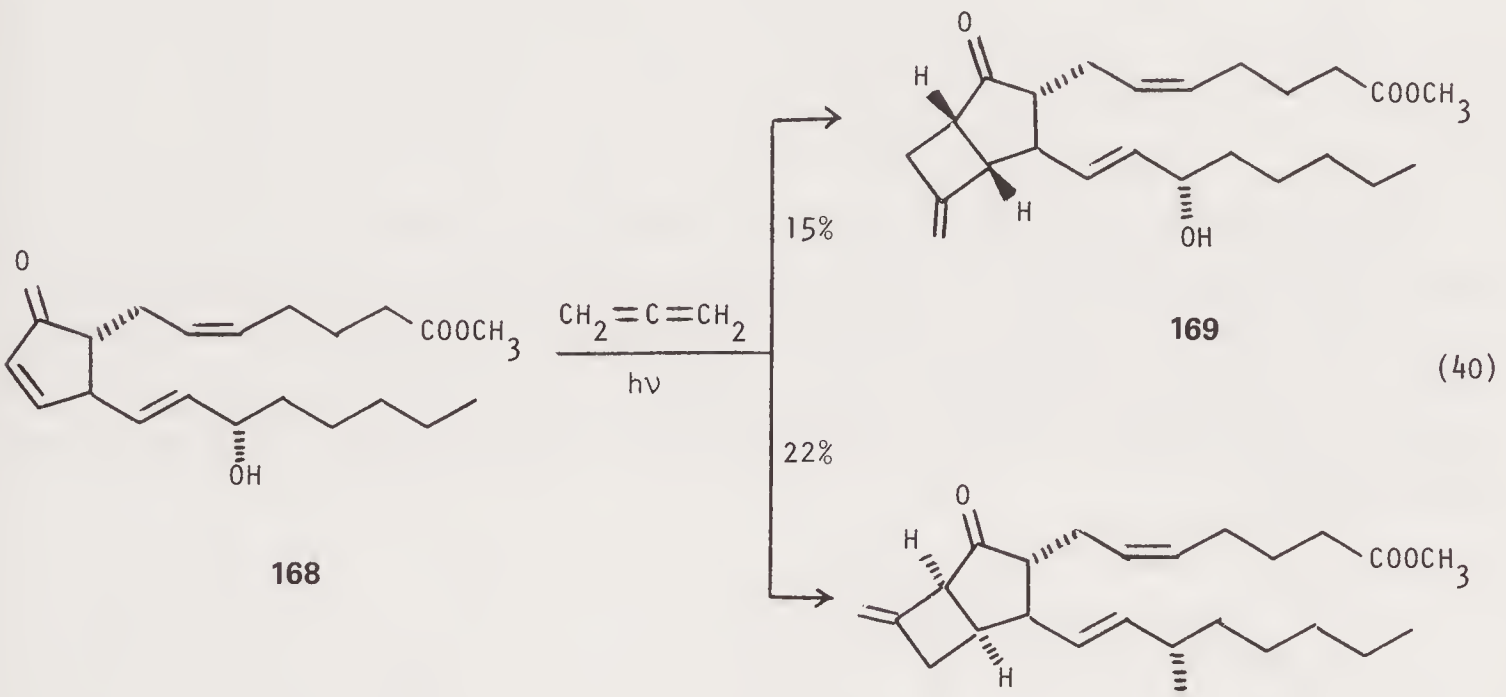


163 **164** **165** **166** **167**

Scheme 16

The photochemical addition of allene to 2-ethoxycarbonyl-7,7-dimethylbicyclo[3.3.0]oct-1-en-3-one (**163**) provides adduct **164** in 83% yield. Elaboration through a fragmentation sequence gives 7,7-dimethyl-1-(carbomethoxymethyl)-2-methylenebicyclo[3.3.0]octan-3-one (**165**) which, when converted to the acid, fails to lactonize to pentalenolactone E (**166**). Instead, the γ-lactone **167** is produced in 78% yield[119] (Scheme 16).

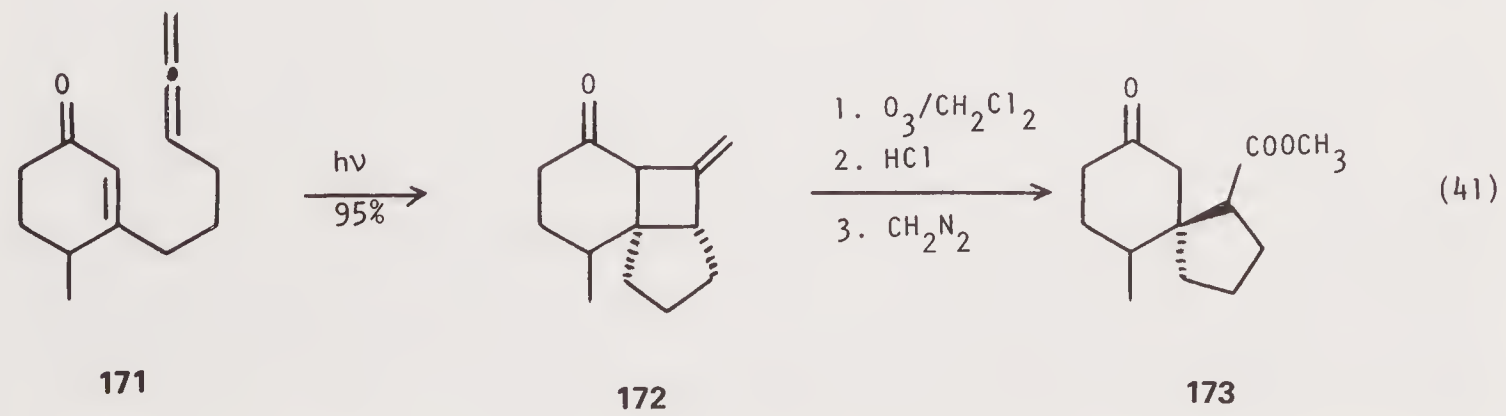
If the scope of the reaction is extended to include the prostaglandin nucleus, the regiospecificity inherent in the photoaddition vanishes. When PGA_2-methyl ester (**168**) is irradiated in the presence of allene, almost a statistical mixture of adducts **169** and **170** is produced[120] (equation 40).



168 **169** **170** (40)

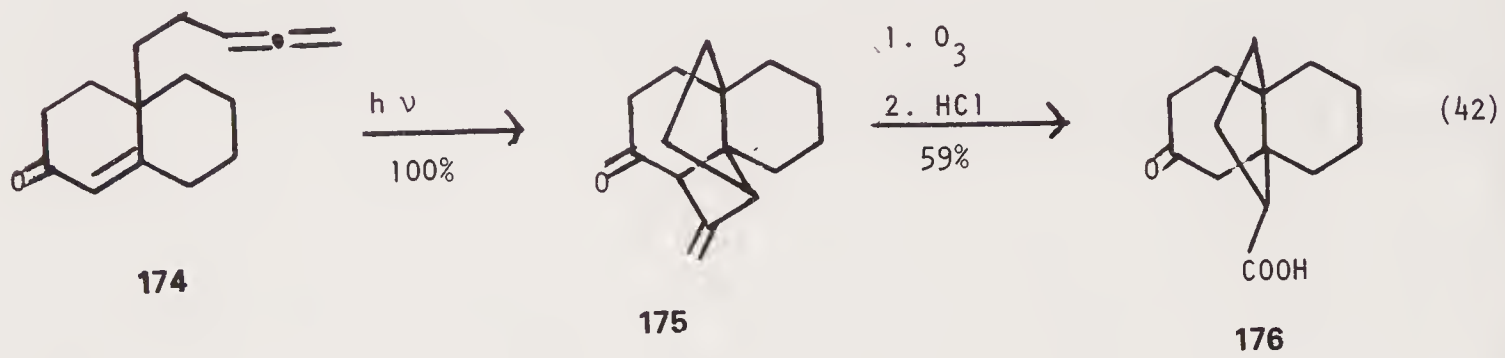
In addition to the synthetic value of the intermolecular photocycloaddition of allene to conjugated carbonyls, an intramolecular photocyclization offers the opportunity for extending this reaction even further.

Irradiation of the keto allene **171** in cyclohexane at room temperature for one hour results in a 95% yield of cycloadduct **172**, which can be easily converted to the spiro system **173**.[121–123]



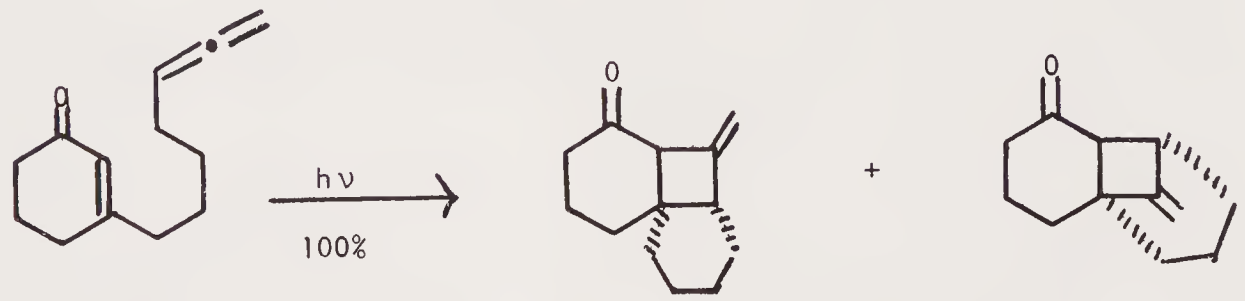
171 **172** **173** (41)

The synthetic potential of this reaction is shown for the synthesis of a [4.4.3]-propellane (**176**).[122] Irradiation of 4a-(3,4-pentadienyl)-4,4a,5,6,7,8-hexahydro-2-(3H)naphthalenone (**174**) yields a single adduct **175** in quantitative yield. Ozonolysis to an unstable 1,3-diketone followed by decomposition with hydrochloric acid in THF results in the formation of 9-carboxy[4.4.3]propellan-2-one (**176**)[122] (equation 42).



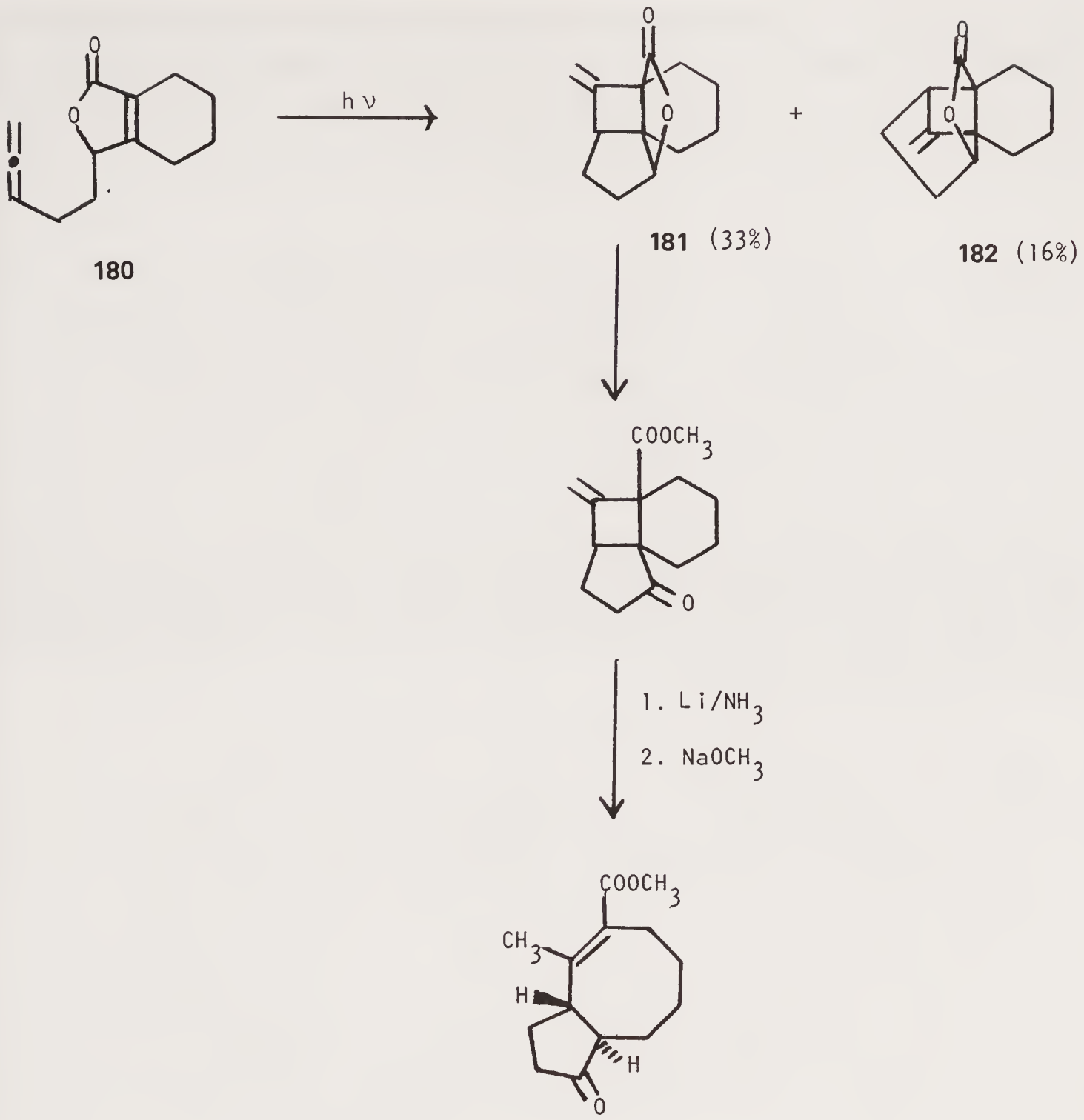
174 **175** **176** (42)

The regiospecificity obtained in these intramolecular additions is a function of chain length between the enone and the allene. The molecule can accommodate two or three methylene units (e.g., **133**, **171**, **174**) and retain regiospecificity. However, when the length is increased to four methylenes, as in 3-(5,6-heptadienyl)-2-cyclohexen-1-one (**177**), a mixture of cycloadducts (**178** and **179**) is obtained in an 85:15 ratio.[122]



177 **178** **179** (43)

A new annelative two-carbon ring expansion of fused α,β-unsaturated γ-lactones that incorporates an intramolecular [2 + 2] photoaddition has been successfully applied to the synthesis of compounds bearing structural similarities to the A/B rings of the fusicoccin and ophiobolane natural products.[124,125] Irradiation of 3-(3,4-pentadienyl)-4,5,6,7-tetrahydro-1(3H)-isobenzofuranone (**180**) in *p*-xylene results in a mixture of fused adduct **181** and bridged adduct **182**. Treatment of **181** with sodium ruthenate in water results in the efficient conversion of the lactone to a keto acid. Esterification with diazomethane produces methyl 6-methylene-2-oxotricyclo[5.4.0.$0^{1,5}$]undecane-7-carboxylate (**182**) in 75% yield. Reductive fragmentation with lithium in liquid ammonia and THF followed by equilibration of the isomeric mixture with sodium methoxide in refluxing methanol affords a single conjugated ester, methyl 2,3,3a,6,7,8,9,9a-octahydro-4-methyl-1-oxo-1H-cyclopentacyclooctane-5-carboxylate (**183**) in 72% yield (Scheme 17).



180 **181** (33%) **182** (16%)

183

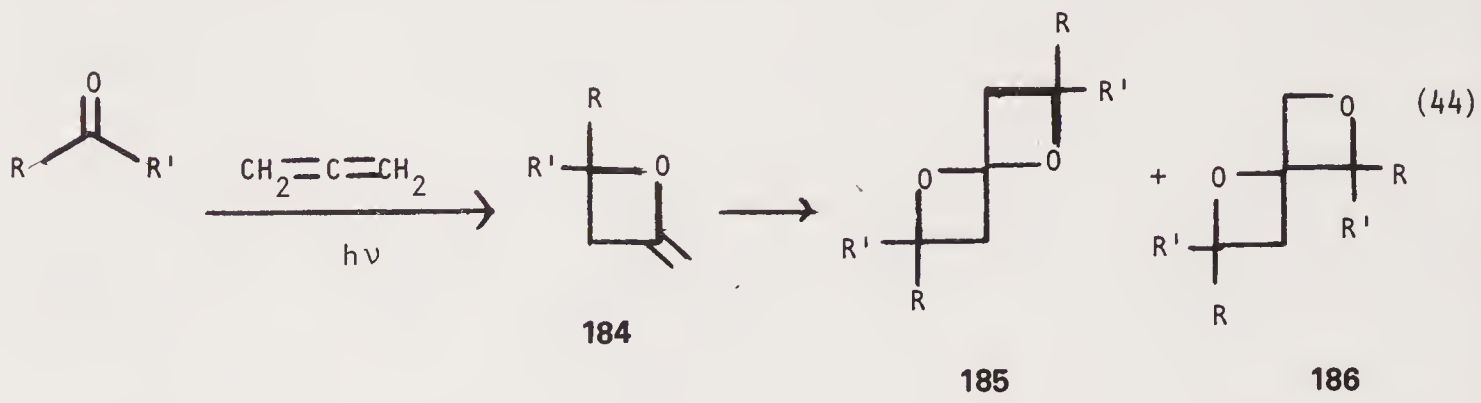
Scheme 17

9.5 HETEROCYCLES BY WAY OF ALLENE CYCLOADDITIONS

Although numerous heterocyclic systems are available through the cycloaddition reaction of allenes with hetero-olefinic systems, the synthetic utility is limited by low yields and product mixtures. Nevertheless, there is considerable opportunity for the development of this reaction, and for this reason various useful applications are discussed.

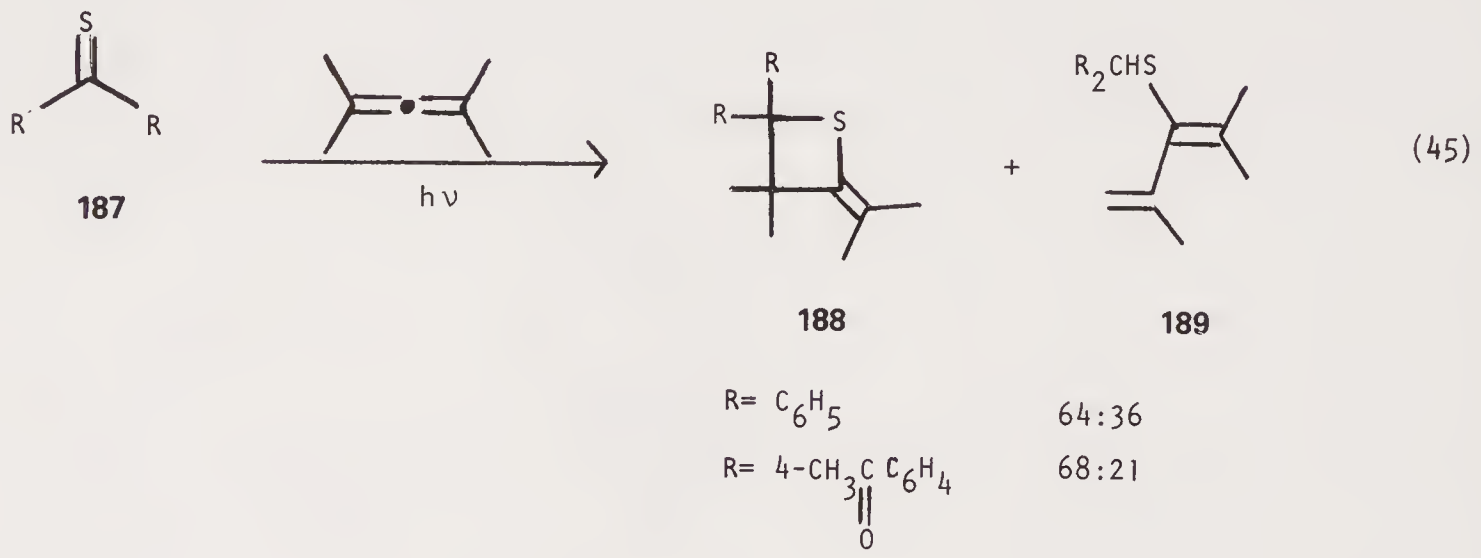
Carbonyl compounds in an excited state add to allenes to give 2-alkylidene oxetanes **184**, which occasionally react further, forming 1,5- and 1,6-dioxospiro-[3.3]heptanes, **185** and **186** respectively[126–128] (equation 44). In some cases the oxetanes undergo further photoisomerization to cyclobutenones.[127,128] The addition

giving the oxetane is highly selective owing to the preference of an intermediate biradical in which allylic stabilization is favored over an alternate vinylic radical.[128] All the cycloaddition products arise from an initial attack by the oxygen of the carbonyl n,π^* state on the central allene carbon.[126]



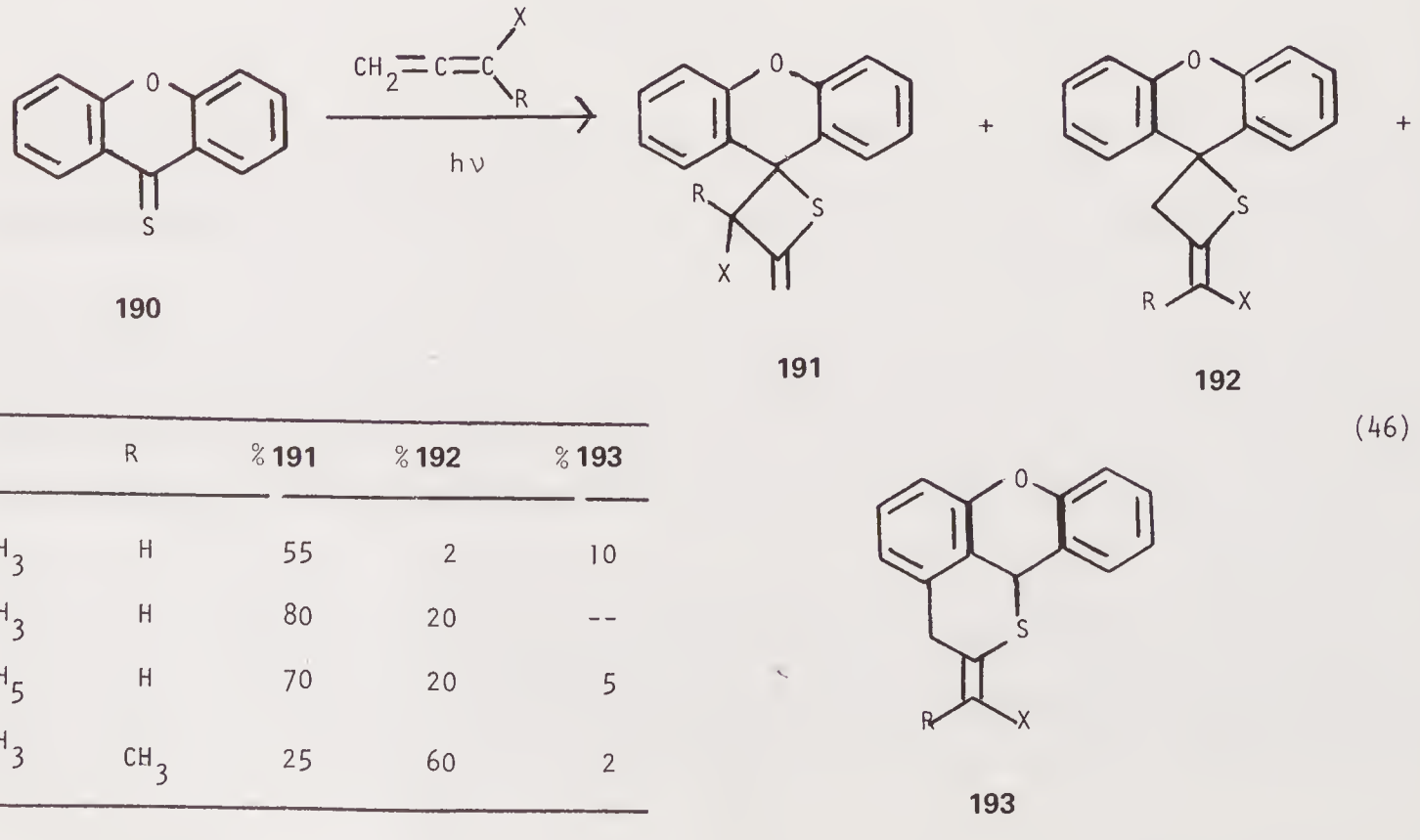
(44)

Thiones **187** in their n,π^* triplet state also react with allenes to give a thietane **188**, as well as the nucleophilic addition product **189**[129] (equation 45). It is interesting to note that when the reaction is performed thermally (R = C_6H_5), only **189** is produced in quantitative yield.[130]



(45)

R= C_6H_5	64:36
R= 4-$CH_3C(=O)C_6H_4$	68:21



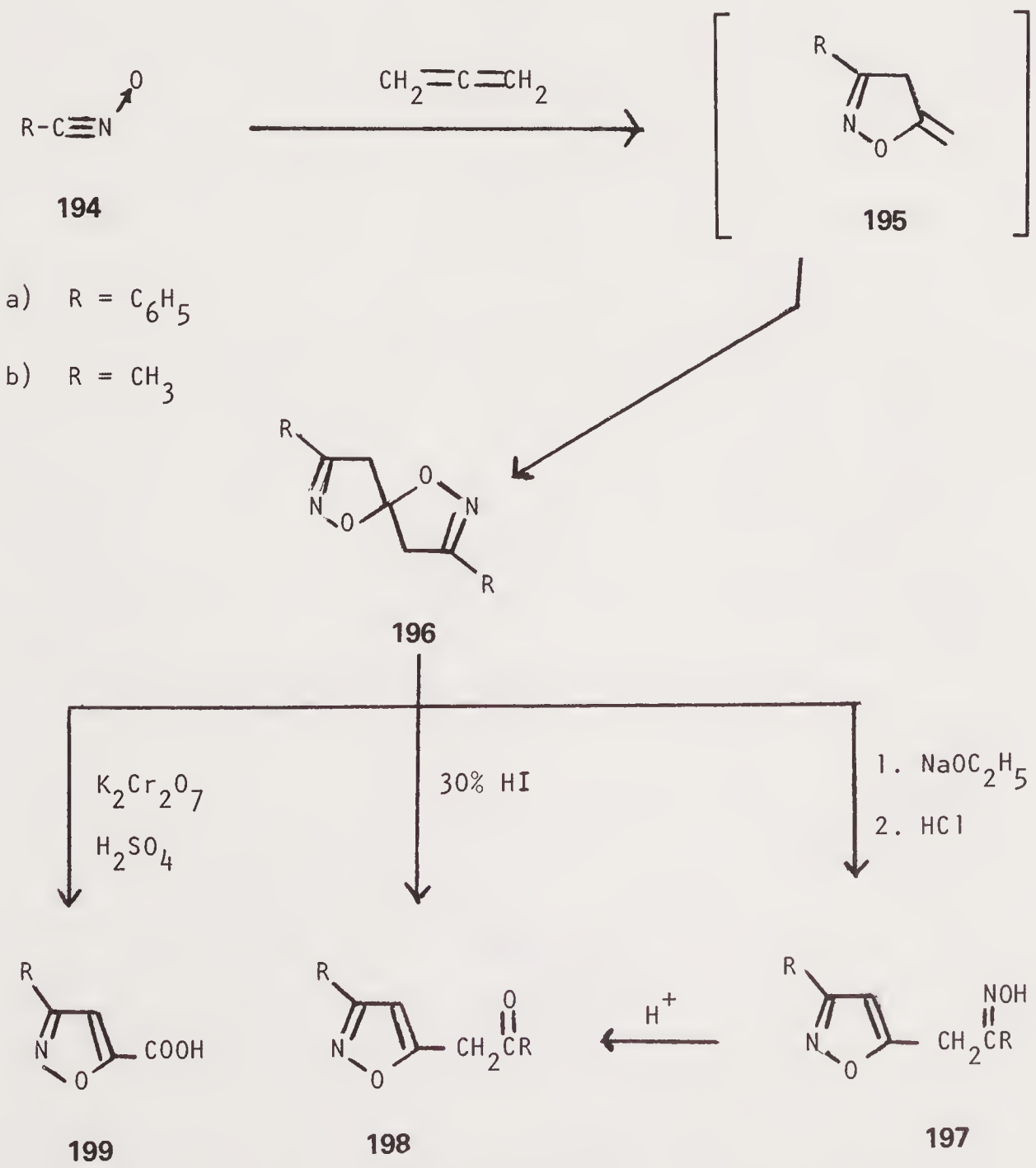
(46)

X	R	% **191**	% **192**	% **193**
OCH_3	H	55	2	10
SCH_3	H	80	20	--
C_6H_5	H	70	20	5
CH_3	CH_3	25	60	2

Triplet xanthanethione **190** undergoes a photochemical [2 + 2] and [4 + 2] cycloaddition with various allenes giving rise to thietanes **191** and **192** and to thiopyranes **193**, respectively[131] (equation 46). The reaction appears to occur by way of attachment of the sulfur atom to the central allene carbon atom with ultimate formation of an allylic biradical that undergoes ring closure to form either thietanes or thiopyran.

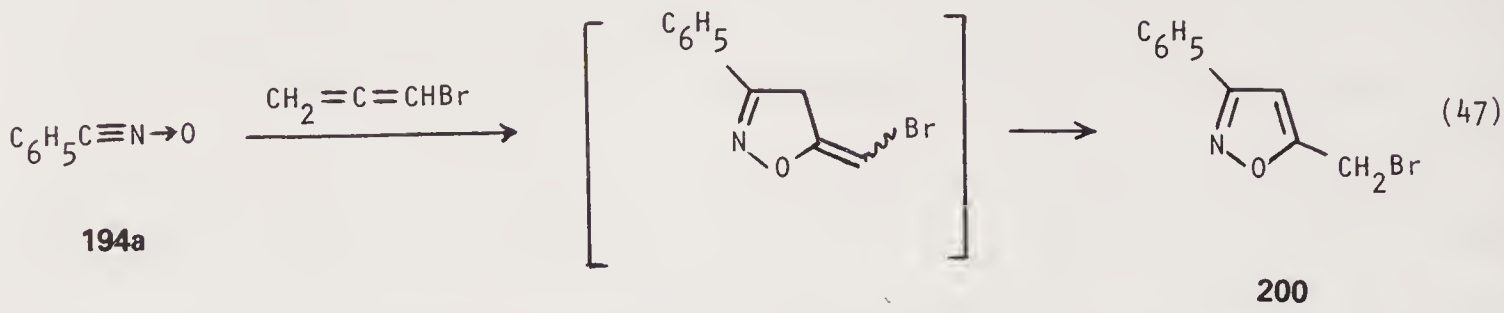
The thermal reaction of **190** with allenes results in the same cycloadducts. Because of this similarity between the photochemical and thermal cycloaddition reactions a common intermediate is suspected.[131,132]

The 1,3-cycloaddition of benzonitrile oxide (**194a**)[133] or acetonitrile oxide (**194b**)[134] with allene results in the initial formation of **195** which reacts further with another molecule of **194** to form the spiro bis-isoxazole **196**. Treatment of **196** with sodium ethoxide followed by dilute hydrochloric acid yields the oxime **197**, which upon acidic hydrolysis, affords the corresponding ketone **198**. (This compound may also be obtained directly from **198** by treatment with 30% hydriodic acid.) Oxidation of **196** with potassium dichromate in sulfuric acid provides the 5-carboxyisoxazole **199** (Scheme 18).



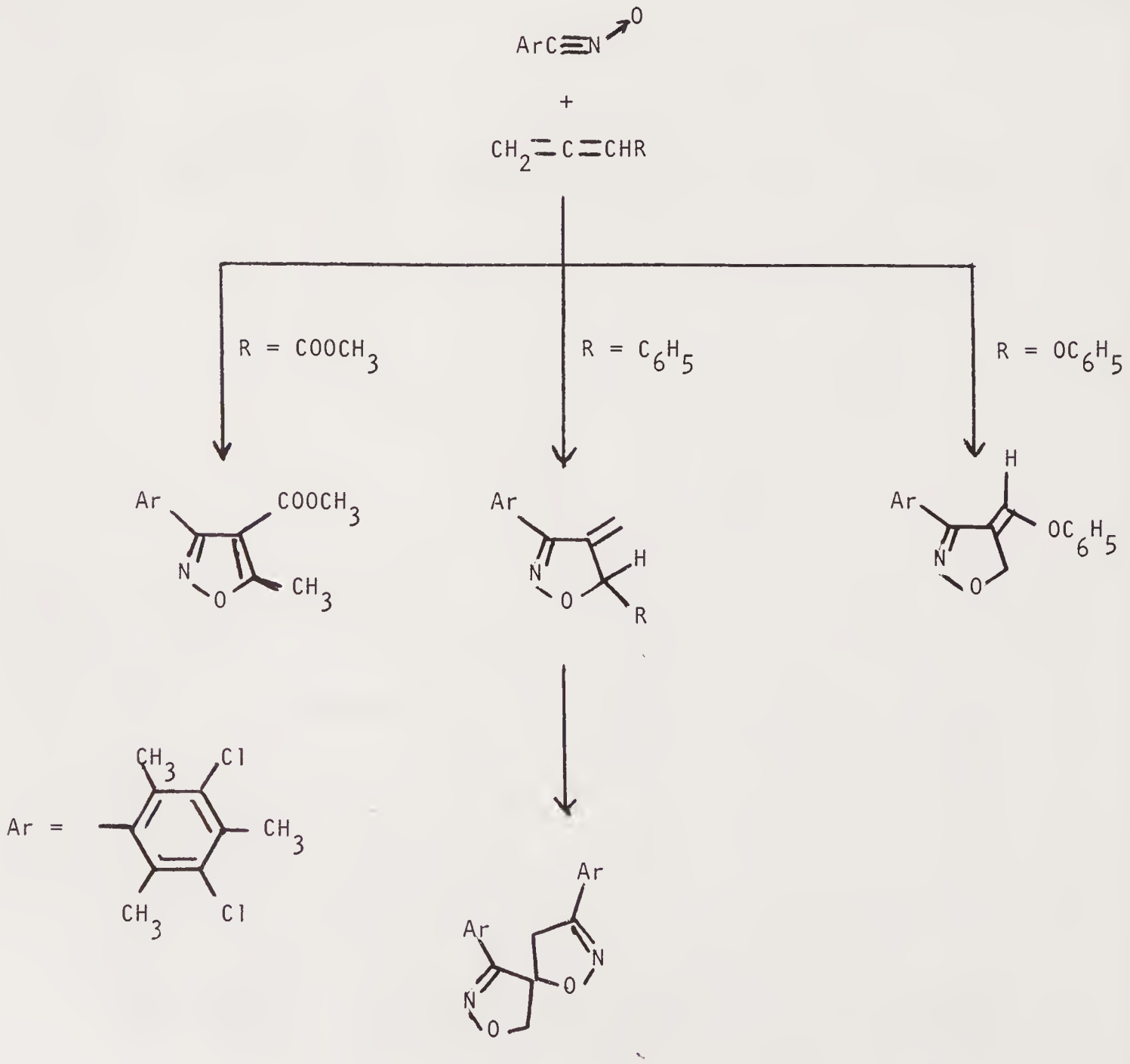
Scheme 18

Interestingly, the reaction of **194a** with bromoallene results in a 41% yield of 5-bromomethyl-3-phenylisoxazole (**200**)[135] (equation 47).



194a **200** (47)

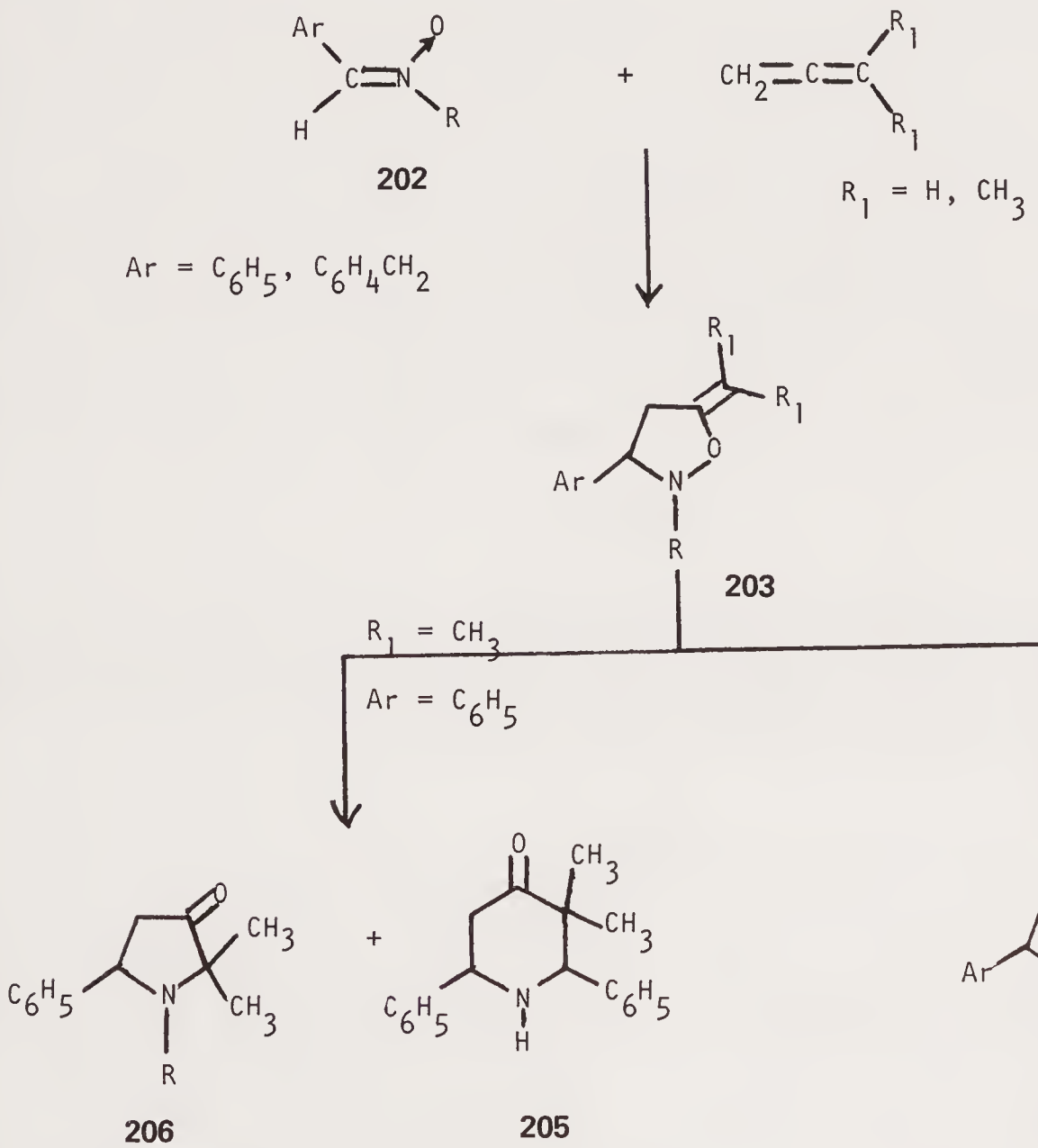
With substituted allenes, the possibility of attack at either the α,β-double bond or the β,γ-double bond exists. The cycloaddition occurs preferentially at the α,β-double bond when the substituent on the allene is electron withdrawing (e.g., $COOCH_3$,[136] C_6H_5[137,138]) and at the β,γ-double bond when the substituent is electron donating such as phenoxy.[139] When the product contains an unsubstituted exomethylene, further cycloaddition occurs to produce the dimer **201**[138] (Scheme 19).



201

Scheme 19

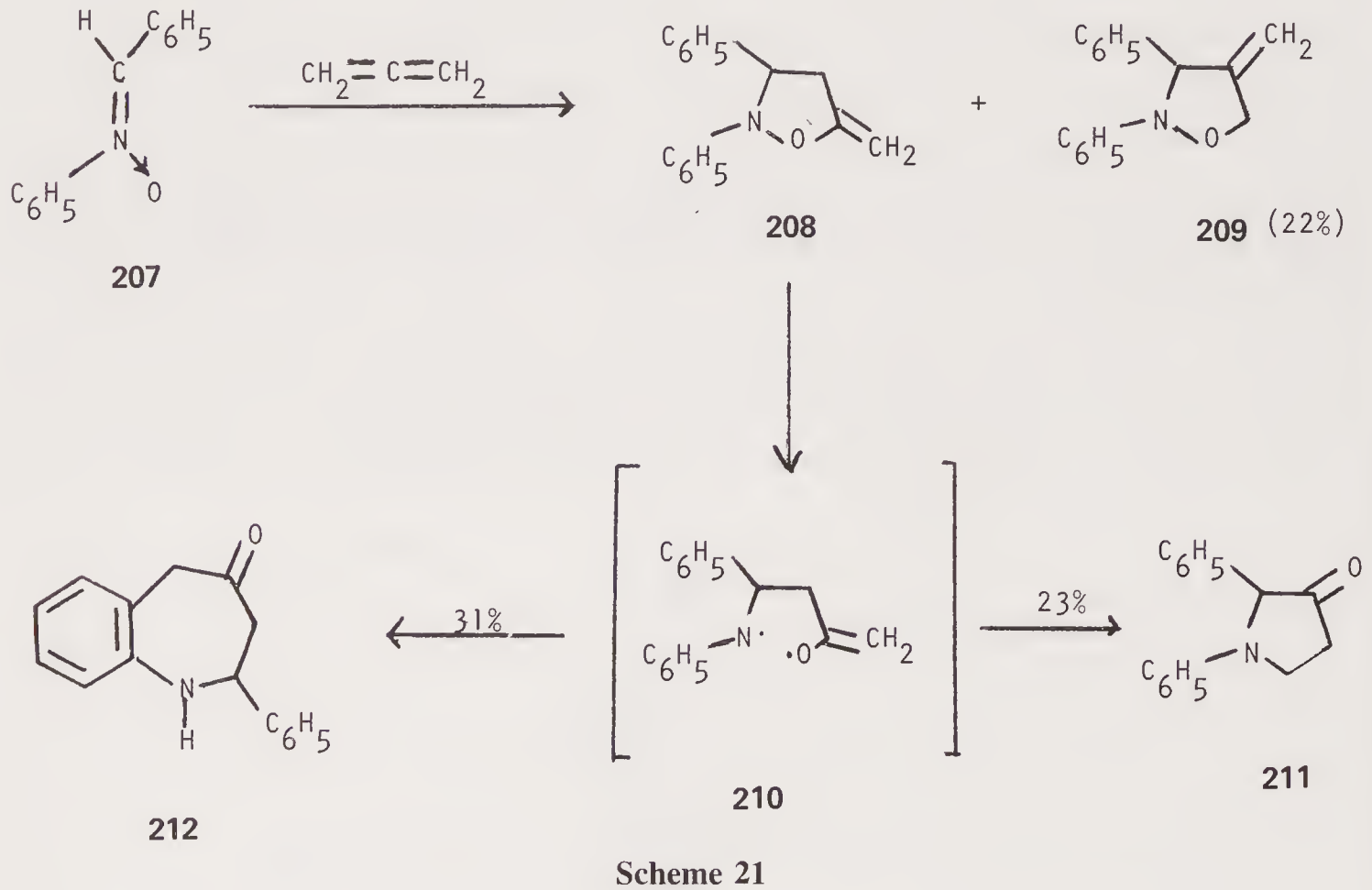
Nitrones **202** behave as 1,3-dipoles in thermal cycloaddition reactions.[140] With allenes, nitrones undergo an initial [π^4s + π^2s] cycloaddition to the less hindered double bond of the propadiene. This provides a regioselective bias in which the oxygen atom of the dipole bonds to the more hindered end of the dipolarophile. The resulting isoxazolidine **203**, however, is unstable and, in the case of N-aryl substituents[141] undergoes internal rearrangement to the pyrrolidin-3-one (**204**). The transformation occurs by way of heterolysis of the N–O bond, ring opening, rotation around the 4,5-bond, and then C–N bond formation. In N-alkyl substitution, destabilization of the zwitterionic intermediate (the nitrenium ion) by the alkyl group allows for a competitive reaction to occur. This involves an additional nitrone molecule and consequently forms a substituted piperidin-4-one (**205**) along with **206**[142] (Scheme 20).



R	% **205**	% **206**
CH_3	35	20
C_2H_5	20	20
C_6H_{11}	--	60

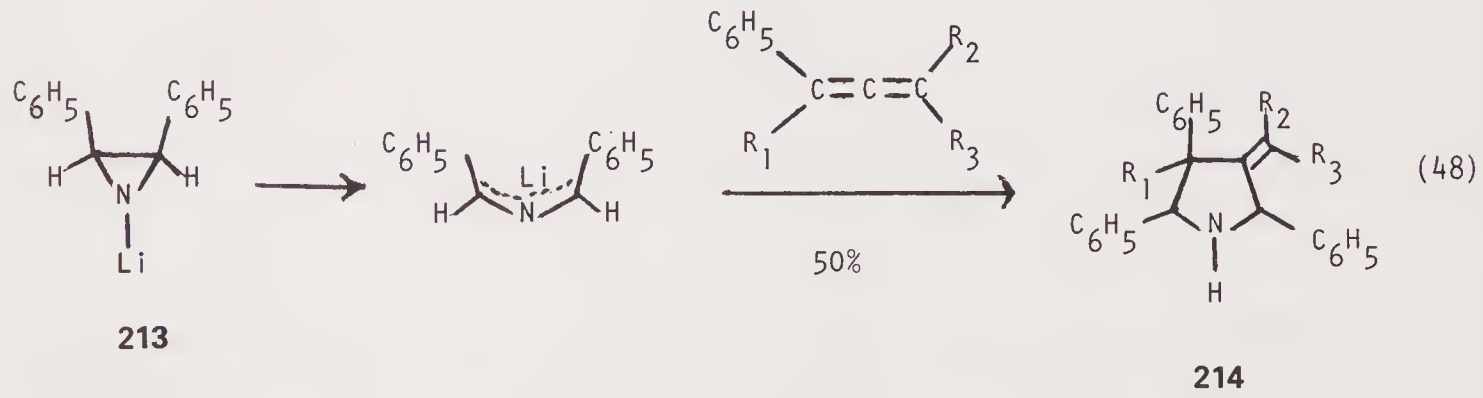
Scheme 20

In contrast to these results, the reaction of C,N-diphenylnitrone **207** with allene affords **208** and **209**. Subsequent spontaneous nitrogen–oxygen bond cleavage in **208** to the diradical **210** results in the observed products **211** and **212**. In the absence of an N-aryl substituent in **207**, no **212** is formed[143] (Scheme 21).

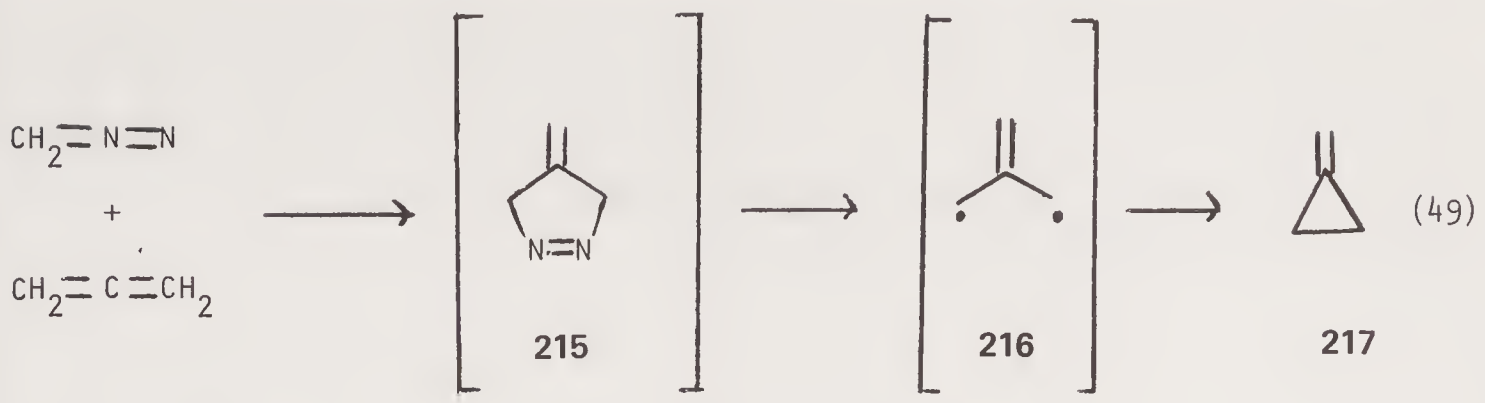


Scheme 21

1,3-Diphenyl-2-azallyllithium (**213**) undergoes a 1,3-cycloaddition with aryl-allenes to provide a general synthetic method for arylmethylenepyrrolidines (**214**), a new class of five-membered heterocycles[144] (equation 48).



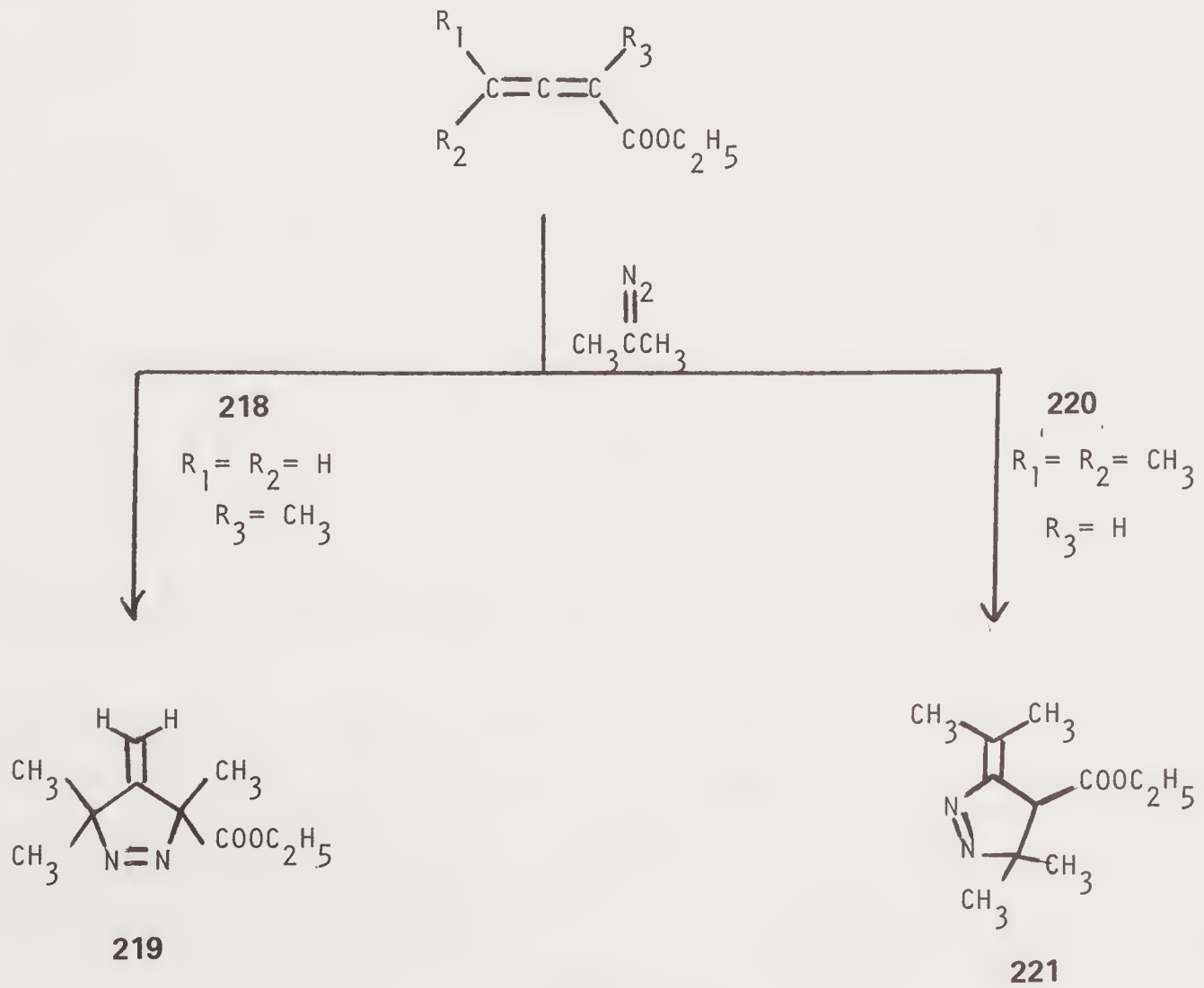
The 1,3-dipolar cycloaddition of diazomethane with allenes affords 4-methylene-1-pyrazoline (**215**) in almost quantitative yield.[145,146] This product is sensitive to water, heat, light, and oxygen and is best handled under vacuum.[147] Gas-phase pyrolysis of **215** results in a quantitative conversion to methylenecyclopropane (**217**), a process believed to involve the formation of the 1,3-diradical trimethylene methane (**216**)[146,147] (equation 49).



(49)

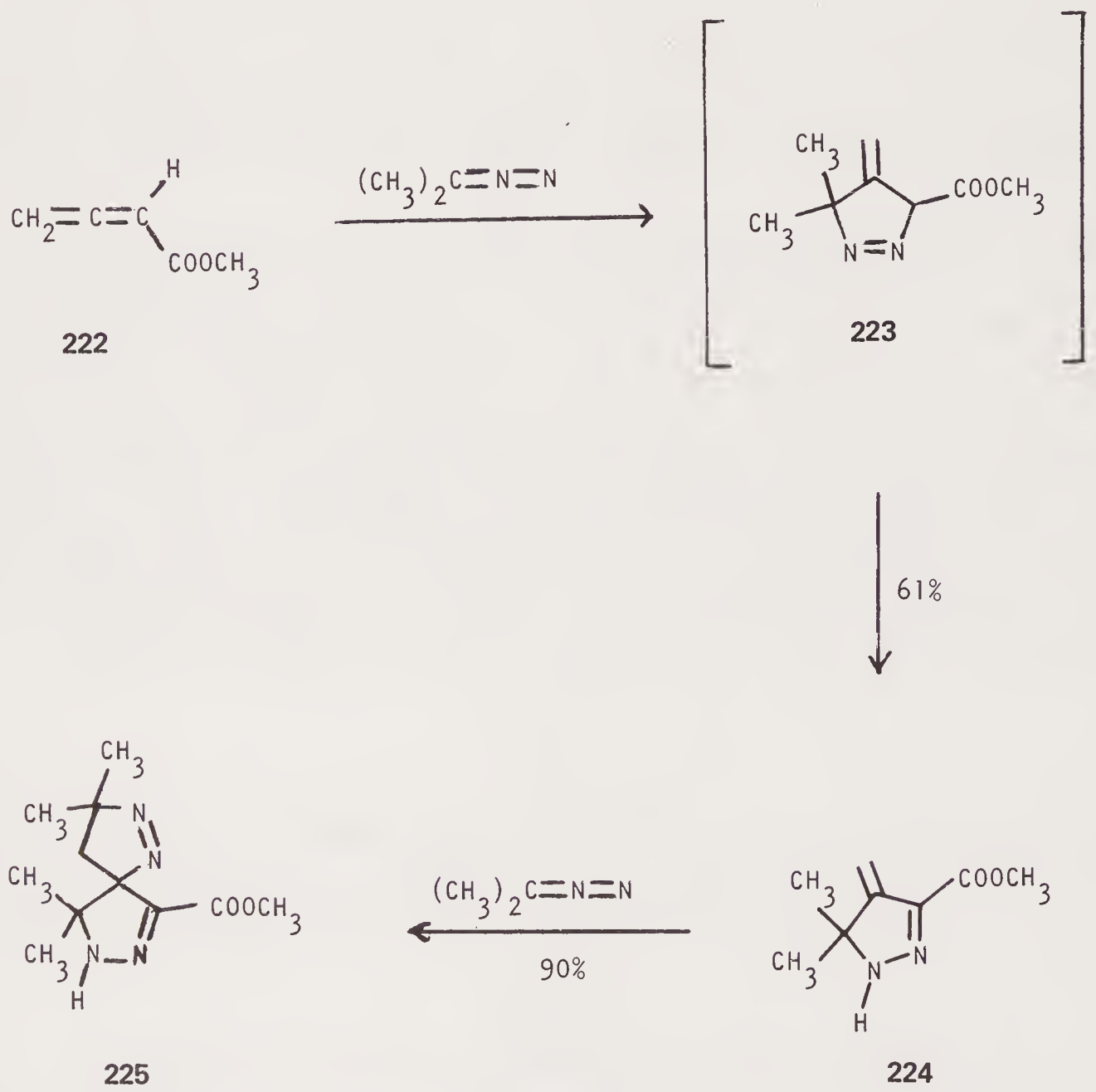
Diazomethane adds selectively to the α,β-double bond of allenic esters and ketones and to the β,γ-double bond of allenic ethers and thio ethers.[148] However, the orientation depends on the degree of substitution at the γ-carbon atom of the allene.

Ethyl 2-methyl-2,3-butadienoate (**218**) reacts with an excess of ethereal 2-diazopropane at 0°C to afford 3-ethoxycarbonyl-4-methylene-3,5,5-trimethyl-1-pyrazoline (**219**) in 98% yield. In contrast, the γ,γ-disubstituted allenes do not produce **219** heterocycles but rather the isomeric 3-alkylidene pyrazolines as a result of addition of 2-diazopropane to the β,γ-unsaturated bond. This reversed regioselectivity is due to the severe crowding of the alkyl groups that occurs in the transition state.[149] Thus ethyl 4-methyl-2,3-pentadienoate (**220**) reacts with 2-diazopropane affording 3,3-dimethyl-4-ethoxycarbonyl-5-isopropylidene-1-pyrazoline (**221**) in 96% yield[150] (Scheme 22). Tetramethyl allene with two eclipsing interactions in the transition state shows very low reactivity toward cycloaddition reactions.



Scheme 22

Methyl 2,3-butadienoate (**222**) reacts with 2-diazopropane to give 4-methylene-Δ^2-pyrazoline (**224**) as the result of a rapid tautomerization of the initial adduct **223**. Because of the activated *exo*-double bond, **224** can react further with diazopropane to give 5,5-dimethyl-3-methoxycarbonyl-2-pyrazoline-4-spiro-3′-(5′,5′-dimethyl-1′-pyrazoline) (**225**)[150] (Scheme 23).

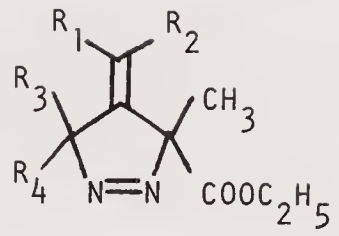


Scheme 23

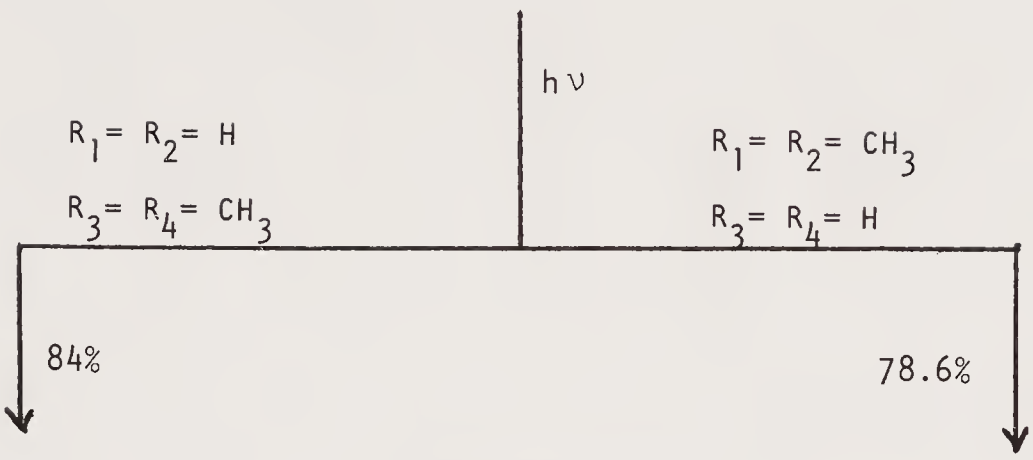
The photolysis of these 4-alkylidene-Δ^1-pyrazoline-3-carboxylates, such as **219**, leads to two possible alkylidenecyclopropanes, **226** and **227**, possibly by way of **216**[151,152] (Scheme 24).

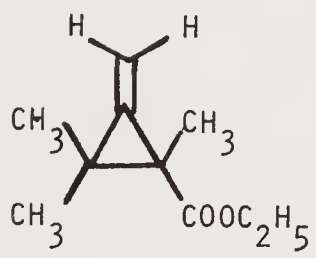
By the use of such an approach, it was determined that the proposed structure for the sex attractant of the American cockroach was not correct.[153,154]

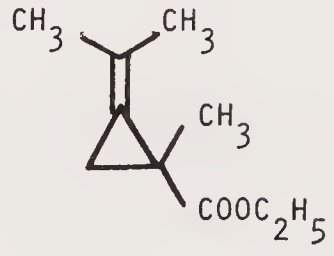
The thermal intramolecular cycloaddition of allenyl azine **229**, generally prepared by a Wittig reaction of the corresponding 2-(alkylidenehydrazono)propylidene phosphorane **228** with substituted ketenes, affords moderate yields of pyrazolo[5,1-c]-1,4-oxazines (**230**)[155] (equation 50).



219

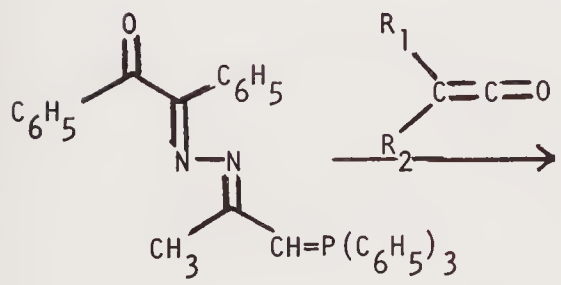




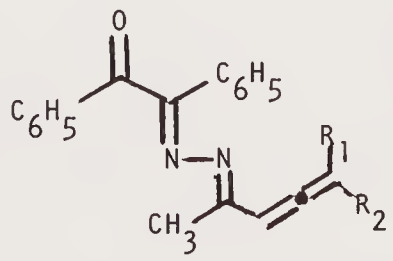


226 **227**

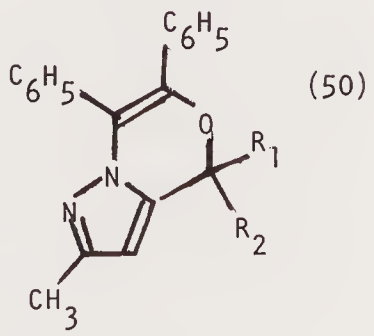
Scheme 24



228



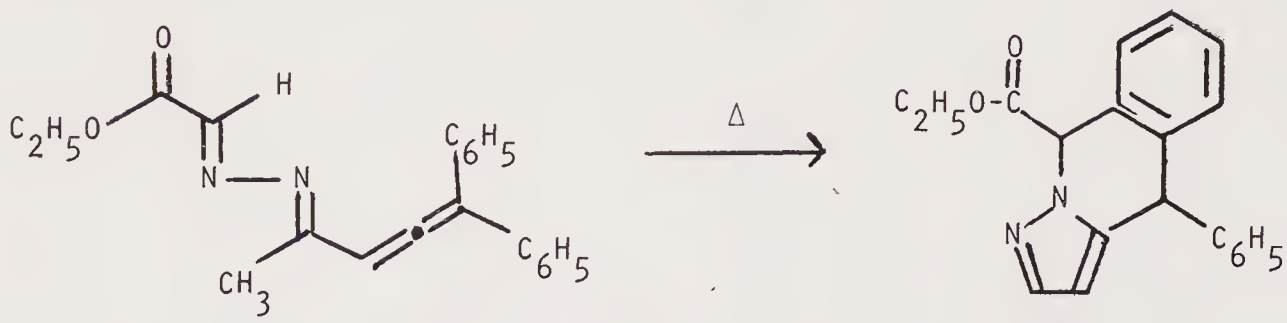
229



230 (50)

R_1	R_2	Yield **230** (%)
H	H	65
H	C_6H_5	67
H	—CH=CH_2	35

On the other hand, allenyl azine **231** affords only 2-methyl-4-phenyl-4,9-dihydropyrazolo[1,5-b]-isoquinoline-9-carboxylic acid ethyl ester (**232**) in 80% yield. Subject to the nature of the substituents introduced by way of the ketenes, both oxazines and isoquinolines may be isolated as a mixture or pure.[155]



231 232 (51)

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CHAPTER TEN

MISCELLANEOUS REACTIONS OF ALLENES

This chapter is concerned with those synthetically useful allene reactions that do not belong to any of the previous chapters. Only those reactions of practical synthetic value are discussed here.

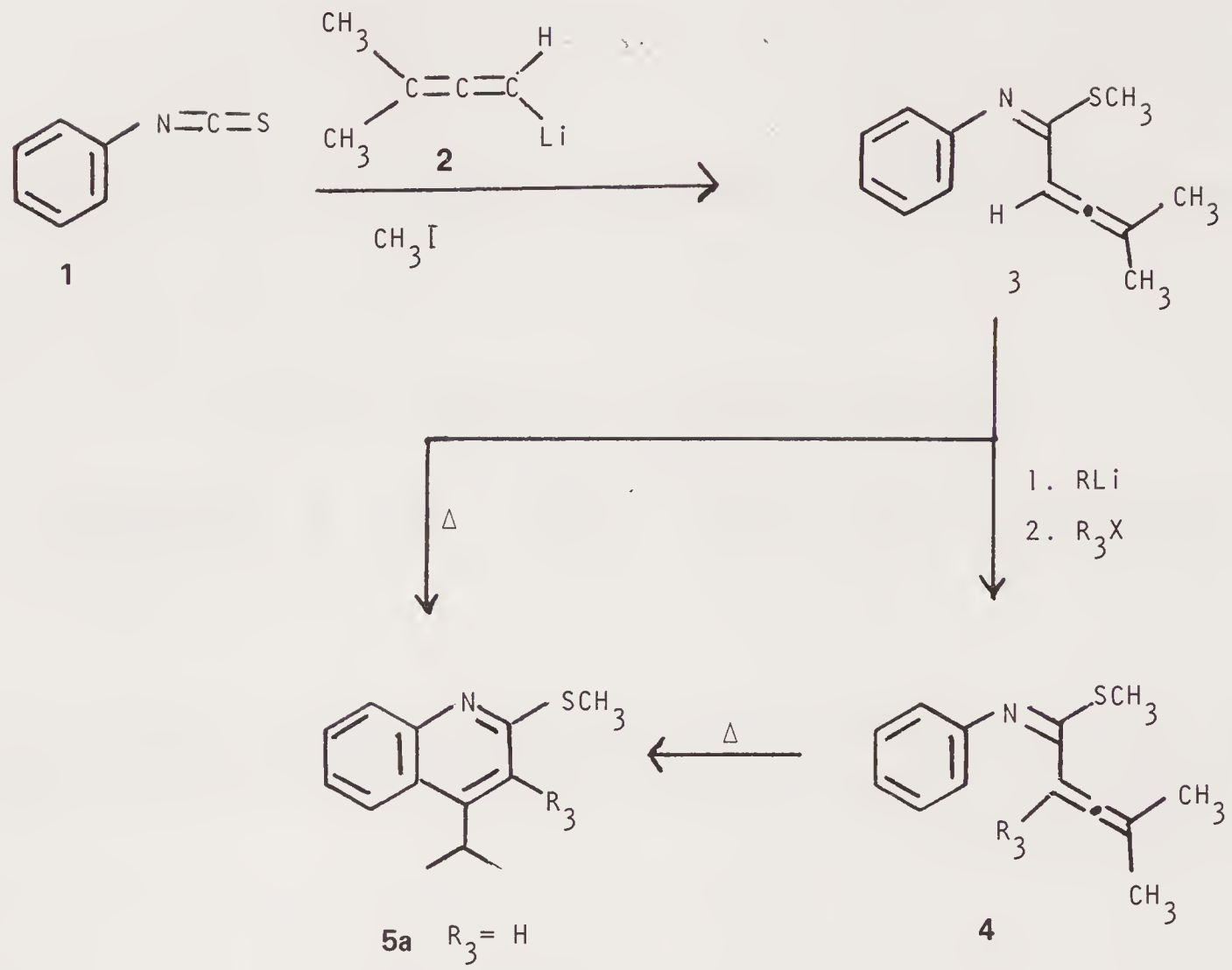
10.1. ORGANOMETALLIC ALLENES

Moreau provides an excellent review on the preparation, properties, and reactivities of the many allene–metal compounds.[1] Although these are interesting from a chemical viewpoint, they have as yet found little synthetic use.

10.1.1. Lithium

Lithium allenes are easily generated and can be used for a variety of synthetic applications. Many of these have been discussed in previous chapters. Lithium allenes can function as nucleophiles for the synthesis of quinolines. The reaction of 3-methyl-1,2-butadienyl lithium (**2**) with phenyl isothiocyanate (**1**) in THF at $-70°C$ produces the allenyl thiocarboximidate (**3**) which can be thermally cyclized to 2-methylthioquinoline (**5a**). When **3** is treated with an alkyllithium, the resulting lithium allene can be alkylated with alkyl halides to obtain **4**. Upon thermal cyclization, **5b** is obtained. Yields range from 60 to 80%[3] (Scheme 1).

Lithium–metal exchange occurs easily to provide allene–metal intermediates not easily accessible by direct allene–metal interactions.[1] Metallation of 1-methoxy-2-butyne (**6**) with *n*-butyllithium at $-70°C$ followed by the addition of one equivalent of zinc chloride generates the very reactive and unisolable organozinc intermediate *7*. Reactions of **7** with cyclohexenone affords the acetylenic alcohol **8** in 95% yield

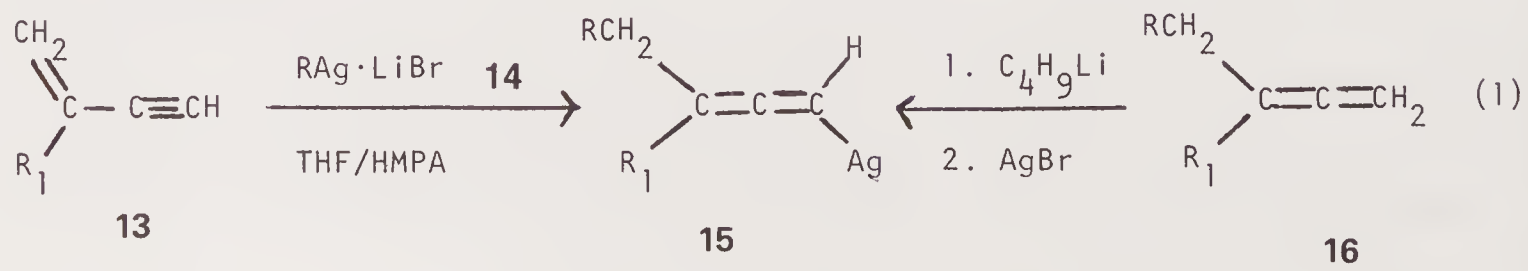


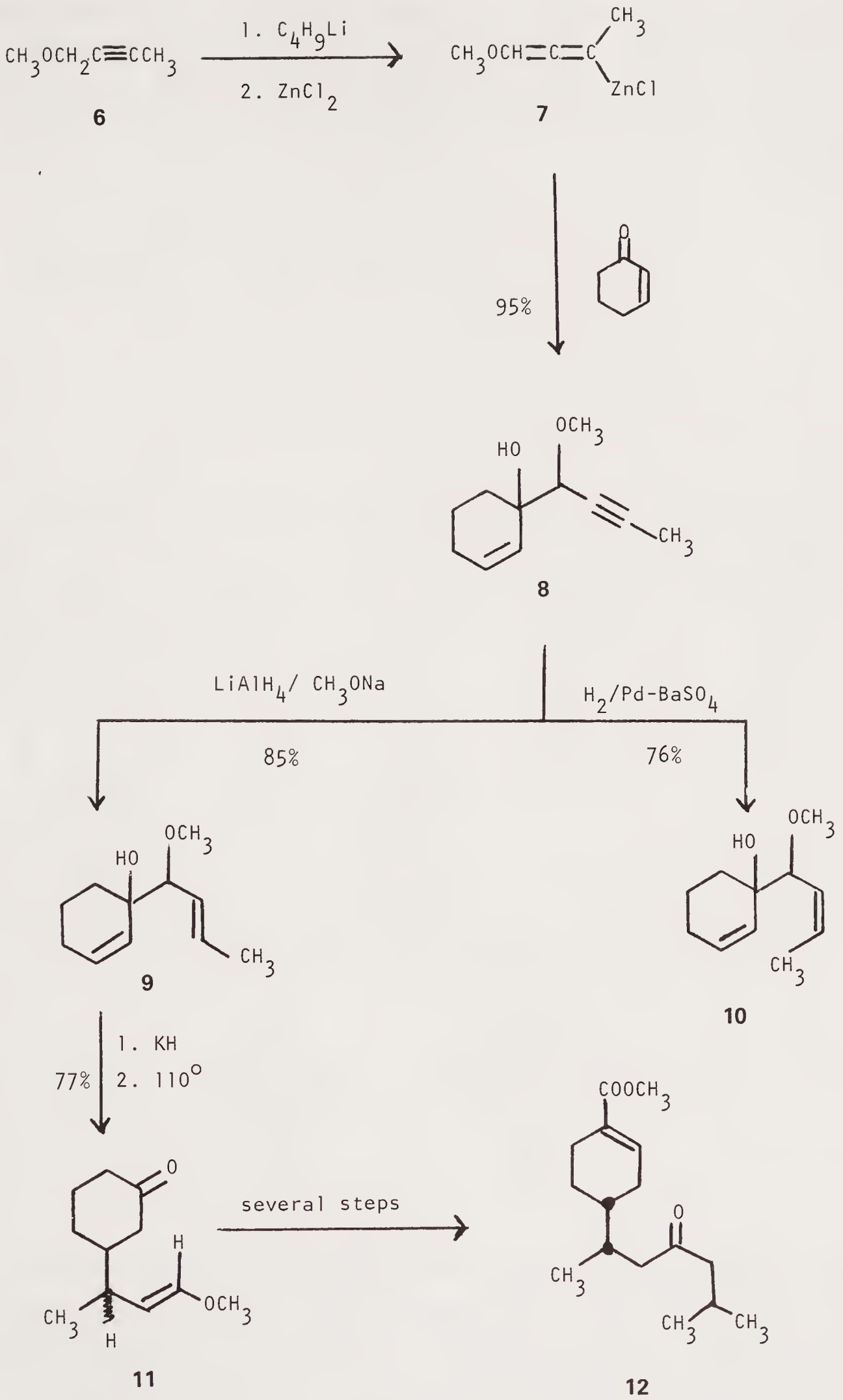
Scheme 1

as a 65:35 mixture of diastereomers. Subsequent reduction provides either the *trans*-olefin **9** or the *cis*-olefin **10**. A modified oxy-Cope rearrangement of **9** provides the diastereomeric ketones **11** that have been successfully applied to the synthesis of (±)-*erythro*-juvabione (**12**)[4] (Scheme 2).

10.1.2. Silver

Allenyl silver(I) compounds **15** are prepared *in situ* by the addition of alkyl silver(I) lithium bromide complexes **14** to butenynes **13**.[5,6,7] However, a more general and convenient preparation of **15** uses the fact that allenyllithium compounds are easily accessible and readily undergo metal exchange. Thus deprotonation of the allenic hydrocarbon **16** with *n*-butyllithium and subsequent treatment with silver bromide provides **15**[6] (equation 1).

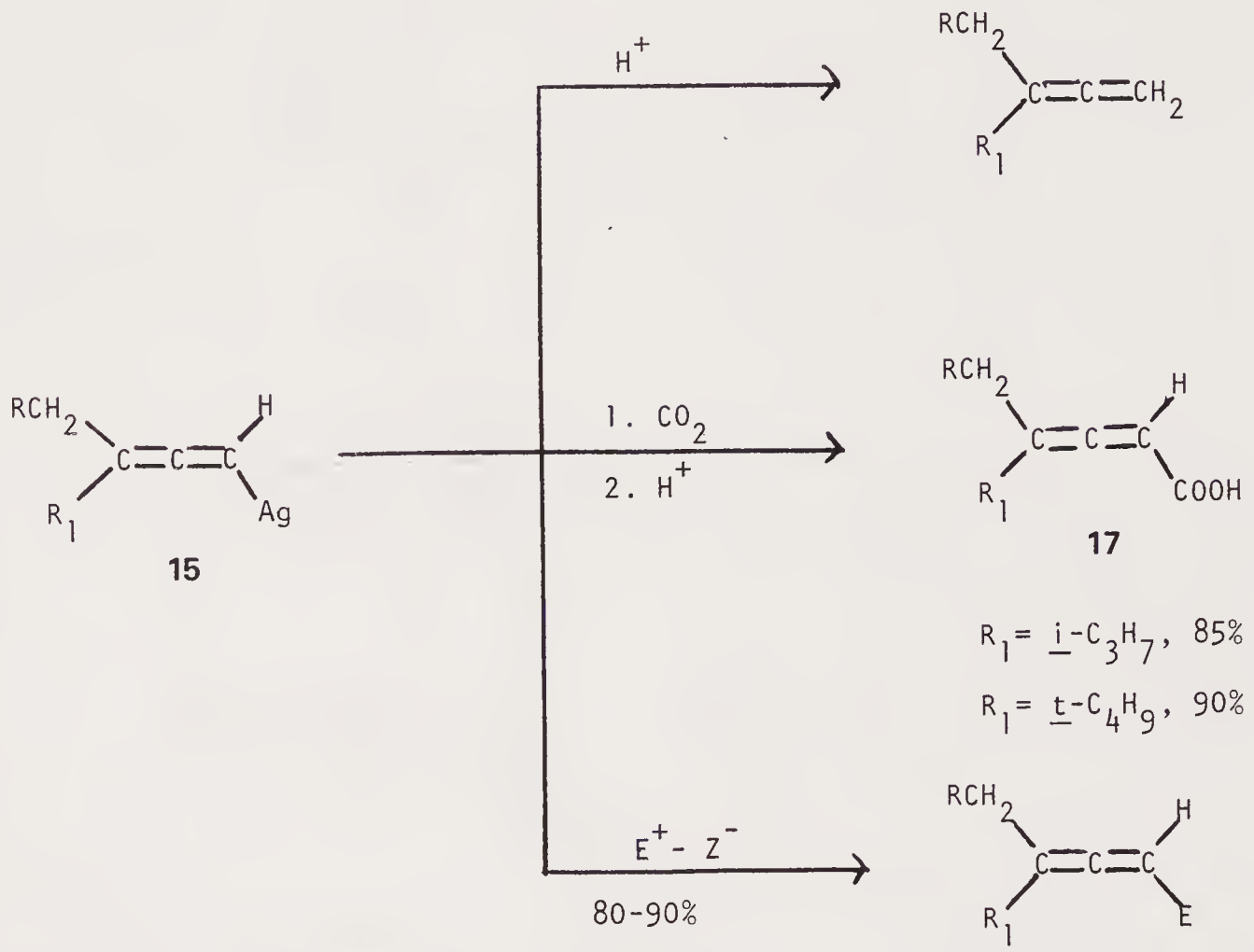




6 **7** **8** **9** **10** **11** **12**

Scheme 2

Allenyl silver compounds **15** afford allenic hydrocarbons in 70–90% yield when protonated.[8] They also react with a variety of electrophiles, preferrably at the terminal end without significant isomerization to the propargyl system.[5] Reaction with carbon dioxide provides nearly pure allenyl carboxylic acids in excellent yields[5] (Scheme 3).

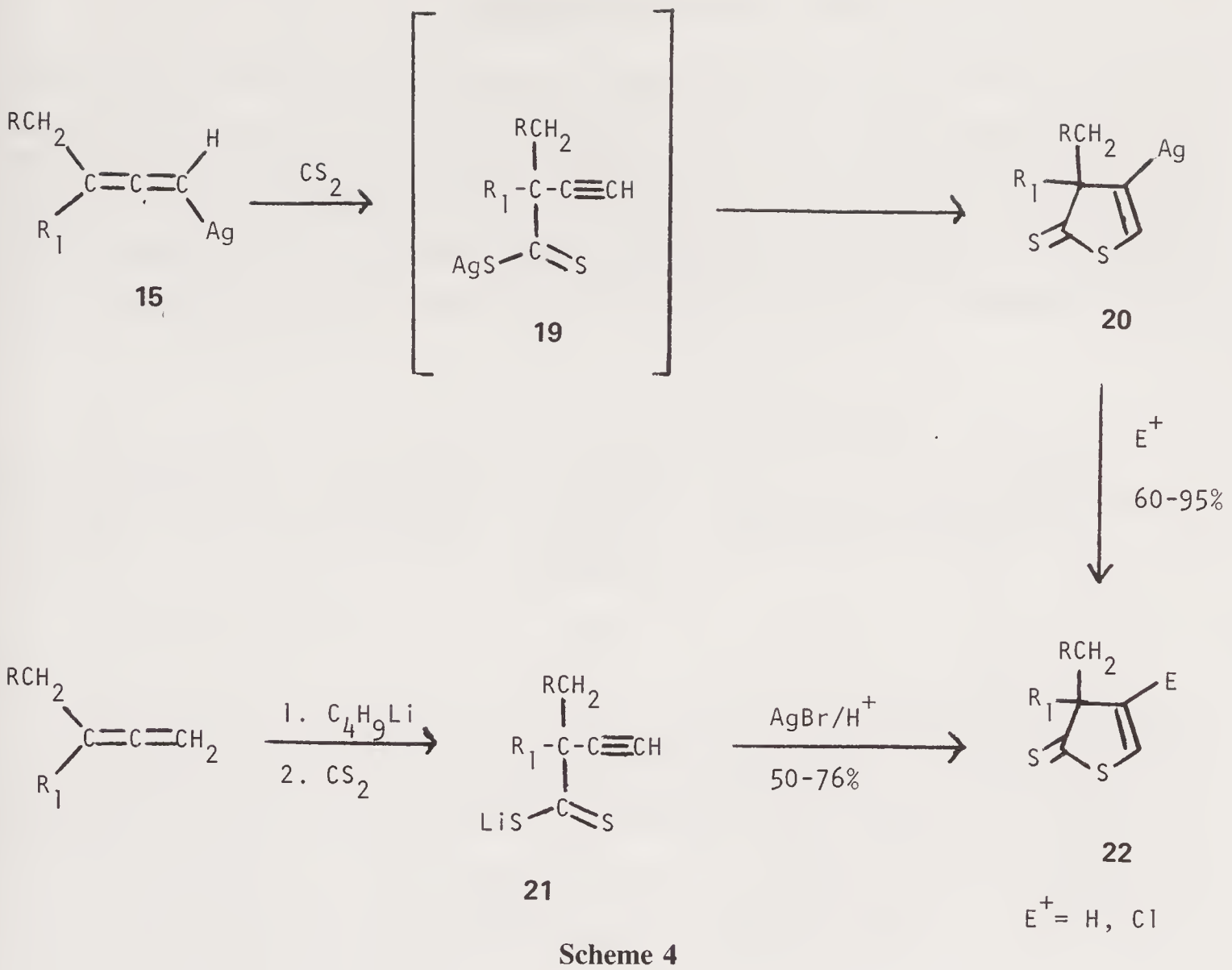


Scheme 3

$E^+ - Z^-$	E^+ in **18**
BrCN	Br
$CH_3SSO_2CH_3$	CH_3S
$CH_2{=}CHCH_2Br$	$CH_2{=}CHCH_2$
$(CH_3)_3SiCl$	$(CH_3)_3Si$
NBS	Br
NCS	Cl

The reaction of **15** with carbon disulfide provides a facile approach to β,γ-unsaturated γ-dithio lactones **22**, presumably by way of the silver salts **19** and **20**.[6,7] Alternately, **22** may be prepared from the corresponding allenyllithium intermediates by treatment with carbon disulfide followed by the addition of silver bromide. In the latter case, the lithium salt **21** is stable and isolable[6] (Scheme 4).

The silver nitrate or mercuric chloride promoted cyclization of secondary γ-allenic (**23**), and δ-allenic amines (**24**) provides an excellent method for the synthesis of 2-alkenylpyrrolidines (**25**) and 2-alkenylpiperidines (**26**), respectively, in good yields and exclusively with the E-configuration. Silver catalysis usually provides better yields than does mercury catalysis[9] (equation 2).



15

19

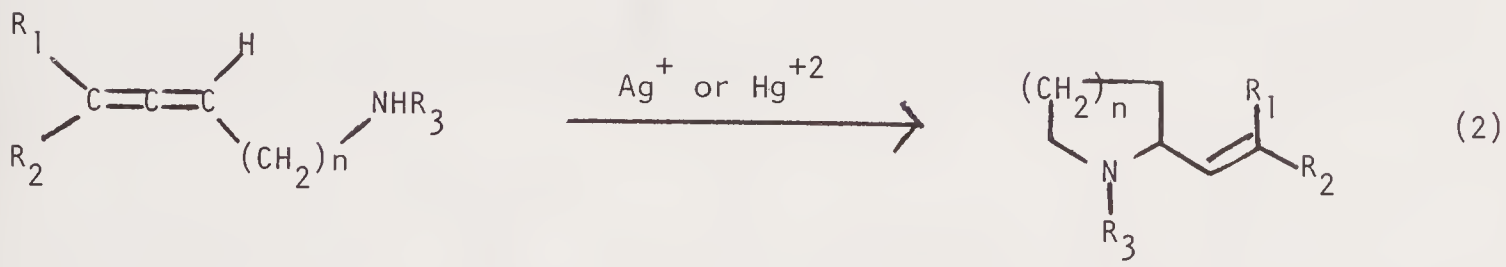
20

21

22

E^+ = H, Cl

Scheme 4



(2)

23 n=3

24 n=4

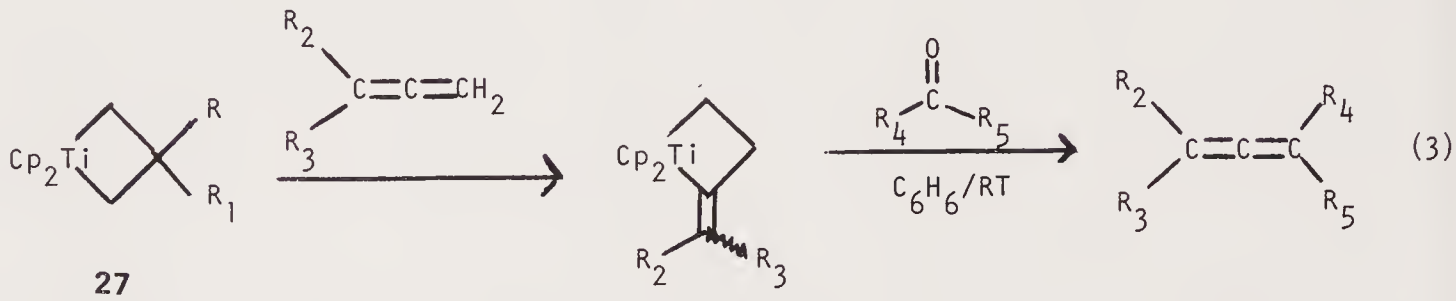
25 n=1

26 n=2

				Yields	
R_1	R_2	R_3	*n*	Hg^{+2}	Ag^+
H	H	C_3H_7	3	70	95
H	H	$CH_2C_6H_5$	3	52	79
H	H	C_6H_5	3	70	82
CH_3	CH_3	C_3H_7	3	70	71
CH_3	CH_3	$CH_2C_6H_5$	4	52	79
H	H	C_3H_7	4	55	95
H	H	$CH_2C_6H_5$	4	54	89
C_2H_5	H	C_3H_7	4	50	76
C_2H_5	H	$CH_2C_6H_5$	4	35	94

10.1.3. Titanium

A general synthesis of substituted allenes that allows the preparation of a variety of structural types of these products is available by way of the titanium metallocycle **28**. The reaction of the titanacyclobutane **27** with one equivalent of a 1,1-disubstituted allene (terminal allene) produces a quantitative yield of **28** as a single regioisomer. When a benzene solution of **28** is treated with one equivalent of a ketone, a good-to-excellent yield of substituted allene is formed[10] (equation 3).



(3)

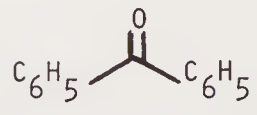
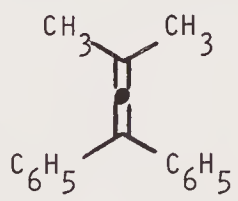
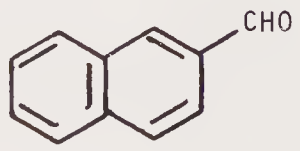
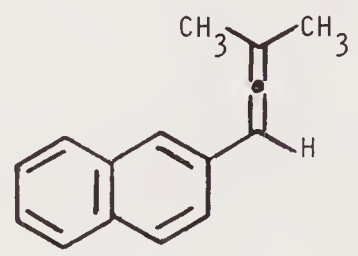
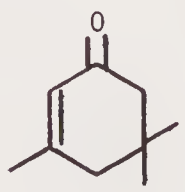
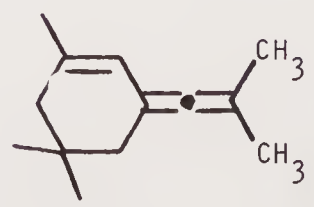
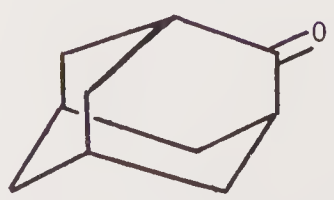
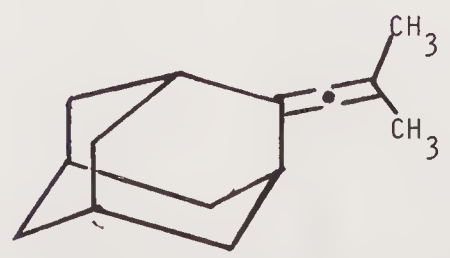
27

a $R=R_1=CH_3$

b $R=CH_3$, $R_1=C_3H_7$

28

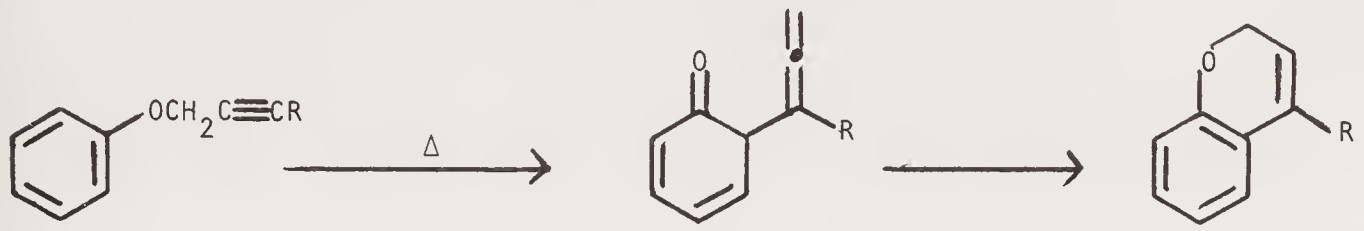
29

Allene	Carbonyl	Product	Yield, %
$CH_2=C=CH_2$			58
$(CH_3)_2C=C=CH_2$			80
$(CH_3)_2C=C=CH_2$			53
$(CH_3)_2C=C=CH_2$			55
$(CH_3)_2C=C=CH_2$			75

10.2. CLAISEN REARRANGEMENTS[2]

10.2.1. Oxy-Claisen

Both aliphatic and aromatic propargyl ethers undergo the Claisen rearrangement. Aryl propargyl ethers **30** undergo a thermal [3.3] rearrangement at 200°C to the allene intermediate **31**. Subsequent tautomerization, a [1.5] hydrogen shift, and finally an electrocyclization provides the corresponding 2H-1-benzopyran (3-chromene) **32**[11] (equation 4).

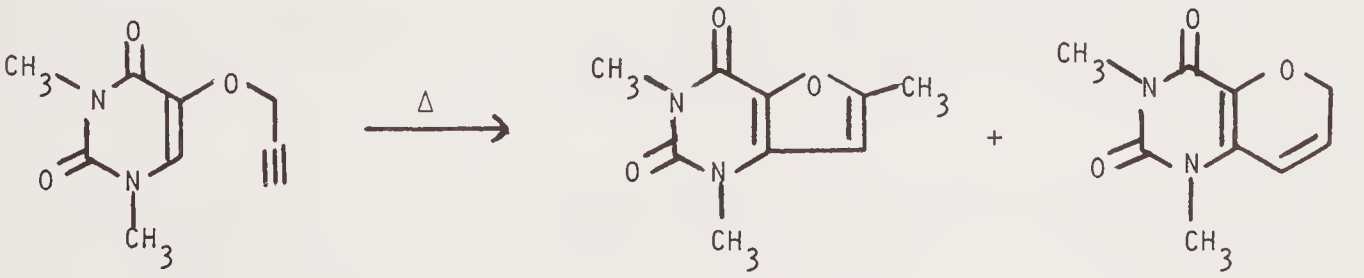


(4)

30 **31** **32**

The contribution of the electronic character of *para*-substituents to the relative rate of rearrangement is greatly outweighed by the degree of substitution at the propargyl carbon.[12] In *meta*-substituted propargylic ethers, both the 5- and 7-substituted 3-chromenes are obtained. Both electron-donating and electron-withdrawing groups appear to have an adverse effect upon the yield of product.[13] Such mixtures make *meta*-substituted derivatives synthetically unattractive.

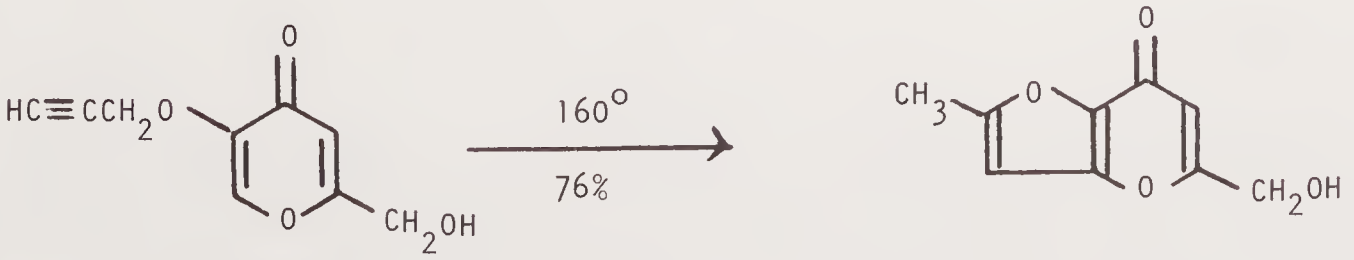
The thermal rearrangement in the presence of certain bases produces benzofurans.[14] In **33**, the ratio of products is strongly solvent dependent and can be directed to give mostly **34** (with DMF), equal amounts of **34** and **35** (in DMSO), or predominantly **35** (in xylene)[15] (equation 5).



(5)

33 **34** **35**

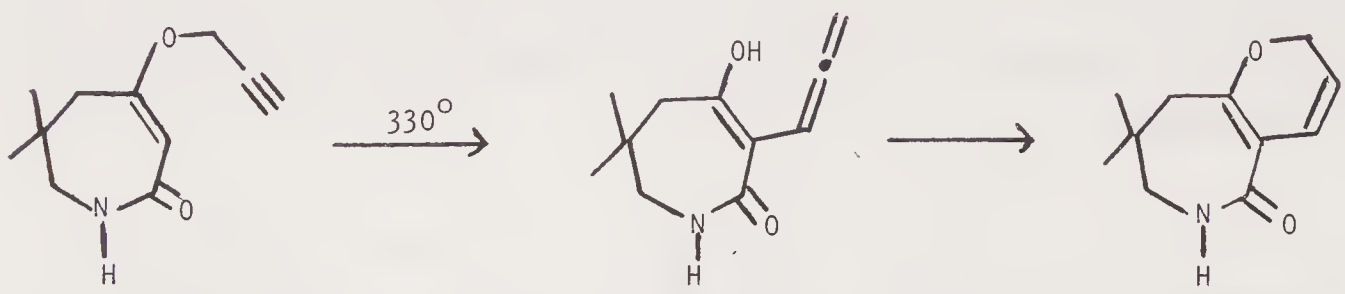
The novel heterocycle furo[3,2-b]pyrone (**37**) is produced in high yield from the thermal rearrangement of 2-propynylkojate (**36**)[16] (equation 6).



(6)

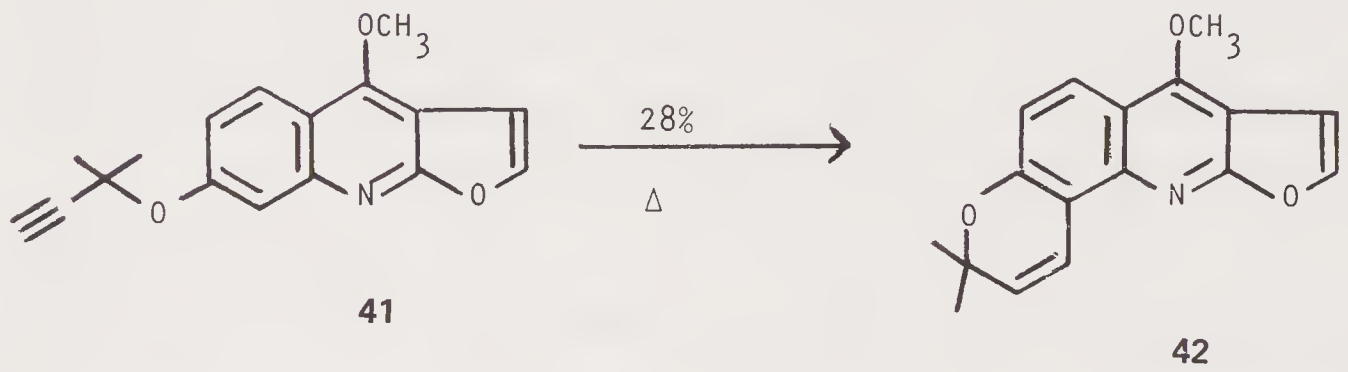
36 **37**

Central nervous system active compounds can be prepared by the Claisen rearrangement of alkyl propargyl ethers of caprolactams **38**. 6,6-Dimethyl-4-(2-propynyloxy)-2,5,6,7-tetrahydro-1H-azepin-2-one (**38**) rearranges readily to the allene **39**, which cyclizes to **40**[17] (equation 7).



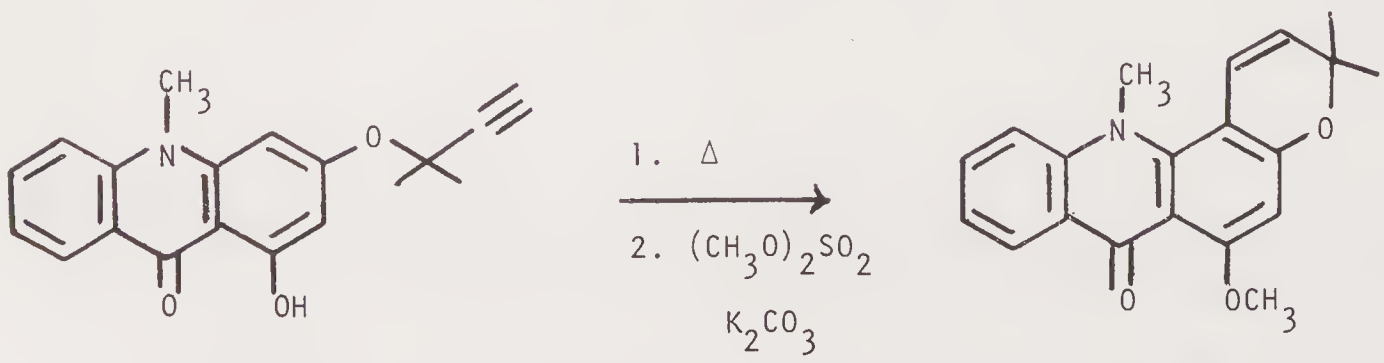
38 **39** **40** (7)

Dutadrupine (**42**), a novel alkaloid isolated from *Dutaillyea drupacea* (Rutaceae)[18] depends on a Claisen rearrangement of the propargyl ether **41** as a key step in its synthesis. The rearrangement occurs in refluxing acetone[19] (equation 8).



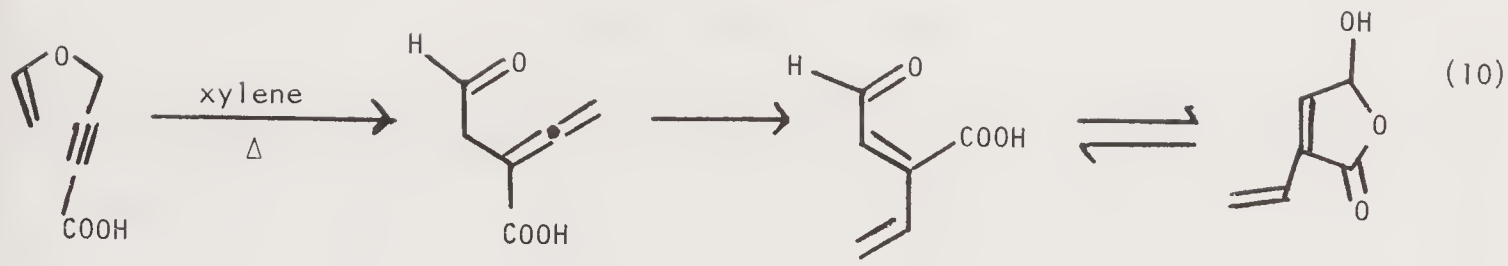
41 **42** (8)

A similar reaction, also occurring at only 70°C, is used to prepare the acridone alkaloid acronycine (**44**),[20] isolated from the bark of *Acronychia baueri Schott*[21] (equation 9).



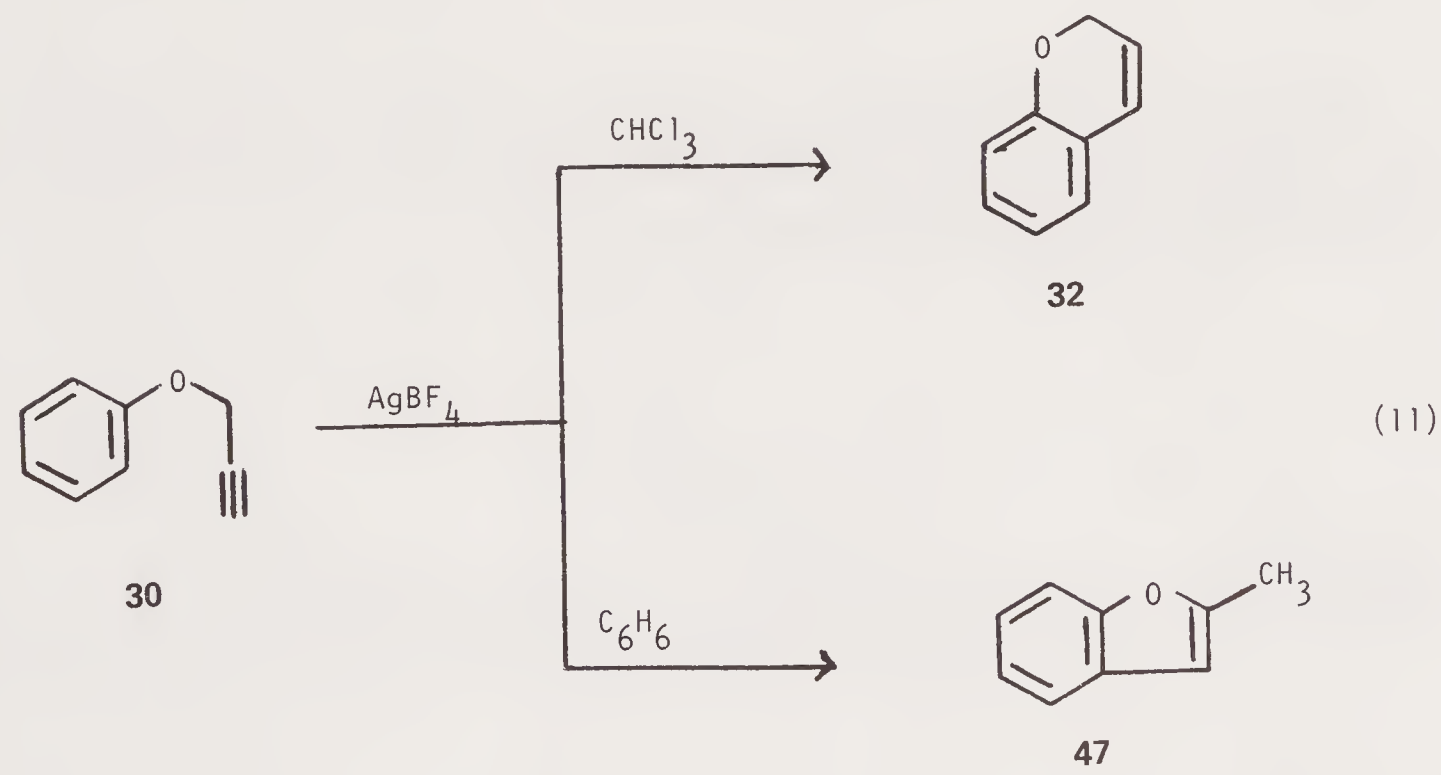
43 **44** (9)

The naturally occurring antibiotic 4-hydroxy-2-vinyl-2-buten-4-olide (**46**) is prepared by way of the Claisen rearrangement of 3-carboxy-2-propynyl vinyl ether (**45**). This is an example of an aliphatic propargylic ether rearrangement.[22,23]



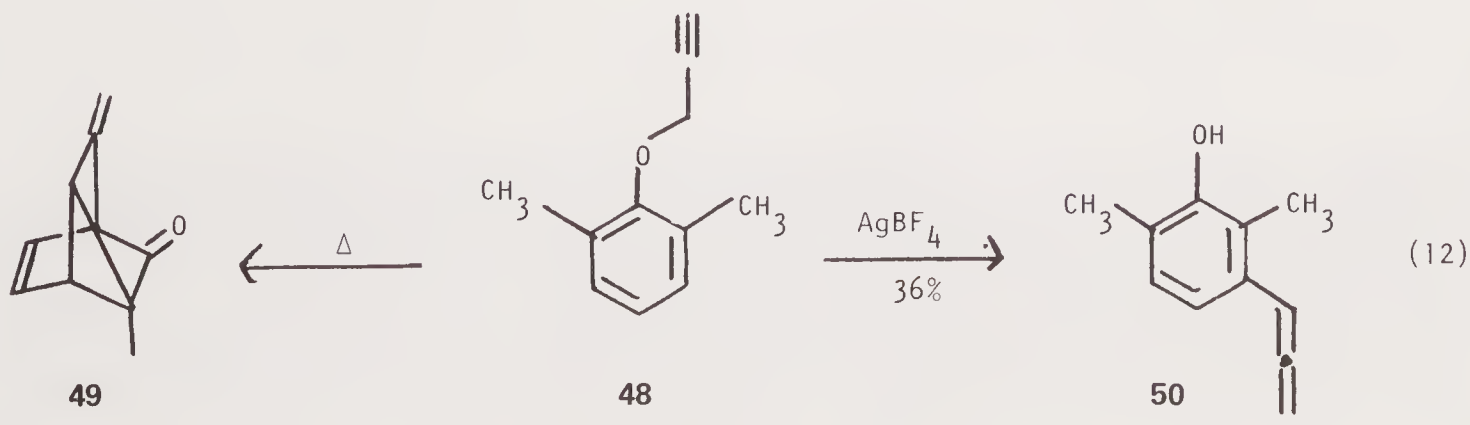
45 46 (10)

Silver tetrafluoroborate exerts a significant catalytic effect on the Claisen rearrangement. Reactions normally performed at elevated temperatures (160–200°C) can now be carried out at 20–80°C. There is a solvent effect. Rearrangement of **30** (R = H) in chloroform results in the formation of **32** in 49% yield, whereas, in benzene a 3:1 mixture of 2-methylbenzofuran (**47**) and **32** is obtained[24] (equation 11).



30 32 47 (11)

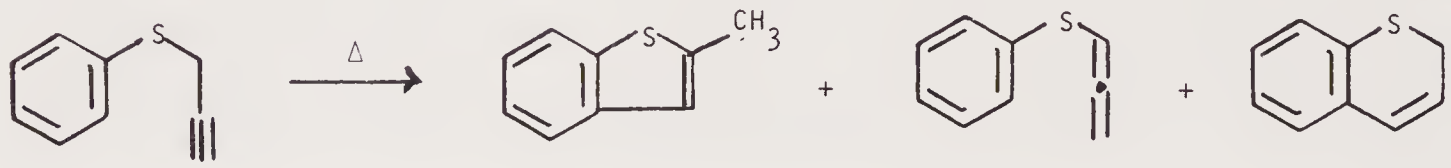
Interestingly, 2,6-disubstituted propargylic phenols **48** undergo an intramolecular Diels–Alder reaction to **49** under thermal conditions[11] but rearrange in the presence of silver tetrafluoroborate in benzene at room temperature to 3-allenylphenols **50**[24] (equation 12).



49 48 50 (12)

10.2.2. Thio-Claisen

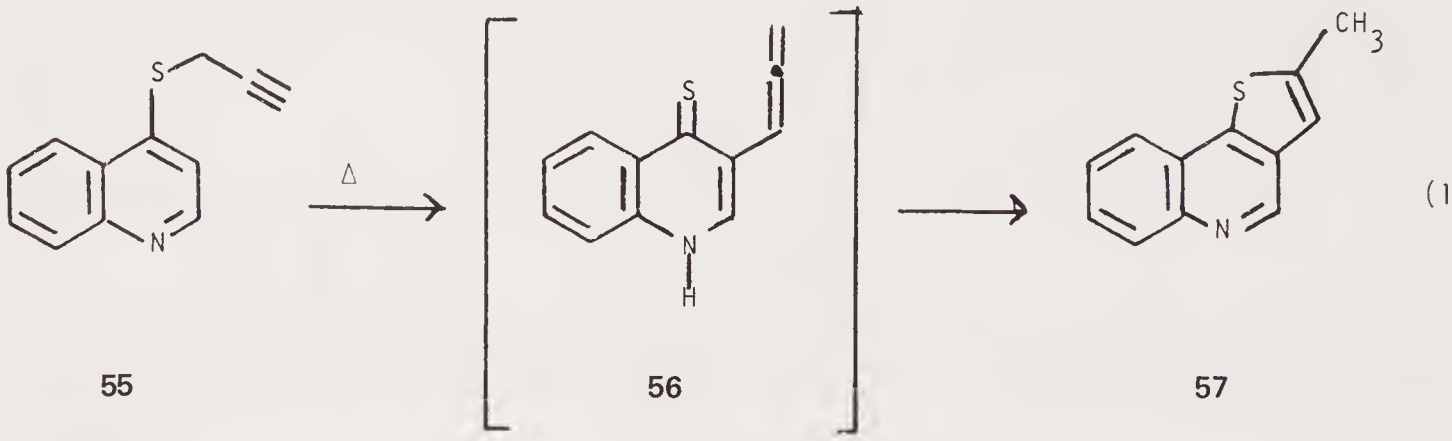
Like propargylic ethers, the thioethers also undergo thermal [3.3] rearrangements providing a variety of sulfur heterocycles. Thermolysis of 2-propynyl phenylsulfide (**51**) in quinoline at 200°C yields a mixture containing 2-methylbenzo[b]thiophene (**52**) and phenyl allenyl sulfide (**53**). At higher temperatures, 2H-thiachromone (**54**) is also obtained,[25] but such a mixture is not synthetically useful (equation 13).



(13)

51 52 53 54

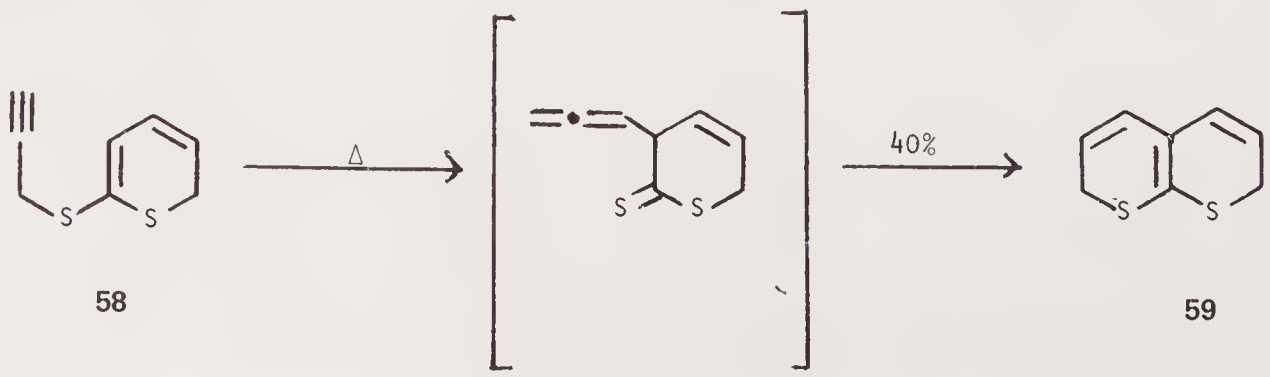
Heating the 4-quinolyl propargyl sulfide (**55**) at 200°C in dimethylaniline produces 2-methylthieno [3,2-c] quinoline (**57**) in 80% yield, presumably by way of the allenic intermediate **56**[26] (equation 14).



(14)

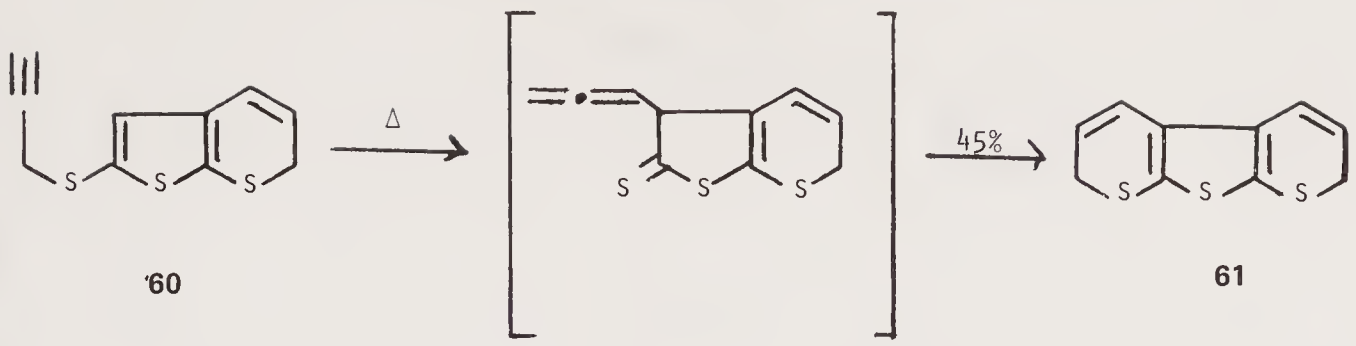
55 56 57

The novel heterocyclic compounds 2H,7H-thiopyrano[2,3-b]thiopyran (**59**) and 2H,7H-dithiopyrano[2,3-b:3′,2′-d]thiophene (**61**) are prepared by way of a thio-Claisen rearrangement of the propargylic sulfides **58** and **60**, respectively.[27]



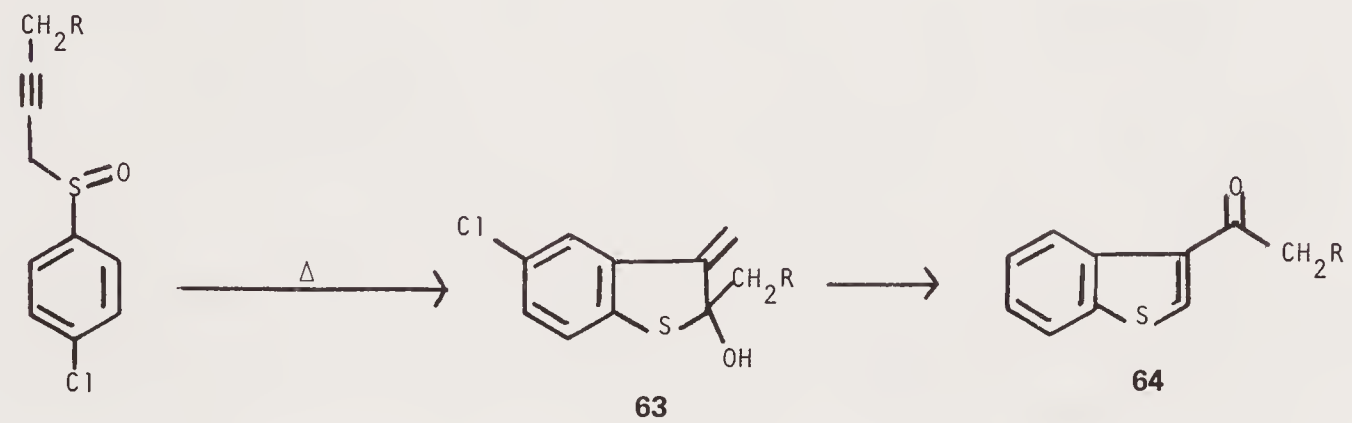
(15)

58 59



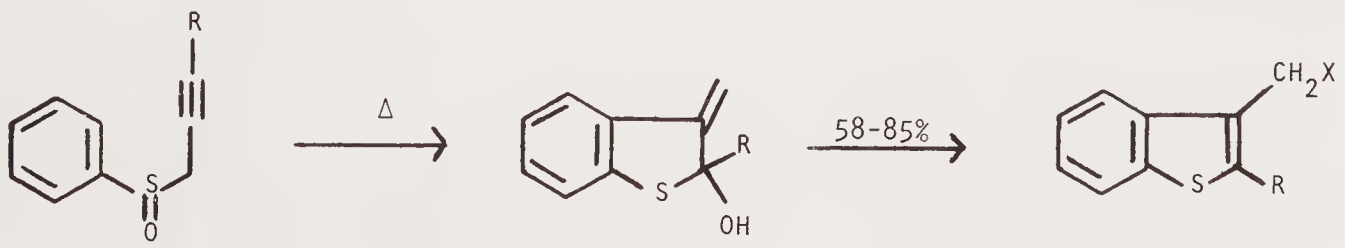
60 61 (16)

An unusual *ortho*-Claisen rearrangement occurs when aryl 2-propynyl sulfoxide **62** is heated under reflux in carbon tetrachloride. A quantitative yield of **63** is obtained. Treatment of **63** with 20% potassium hydroxide at room temperature affords **64** in 90% yield.[28]



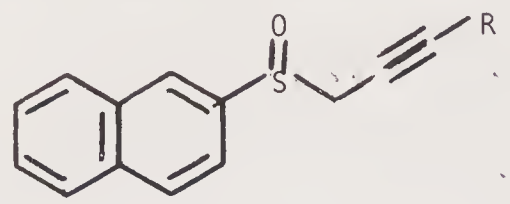
62 R= p-chlorophenoxy 63 64 (17)

By this method phenyl 2-propynyl sulfoxide **65** produces the corresponding benzo[b]thiophenes **67** by way of the intermediates **66**.[29]

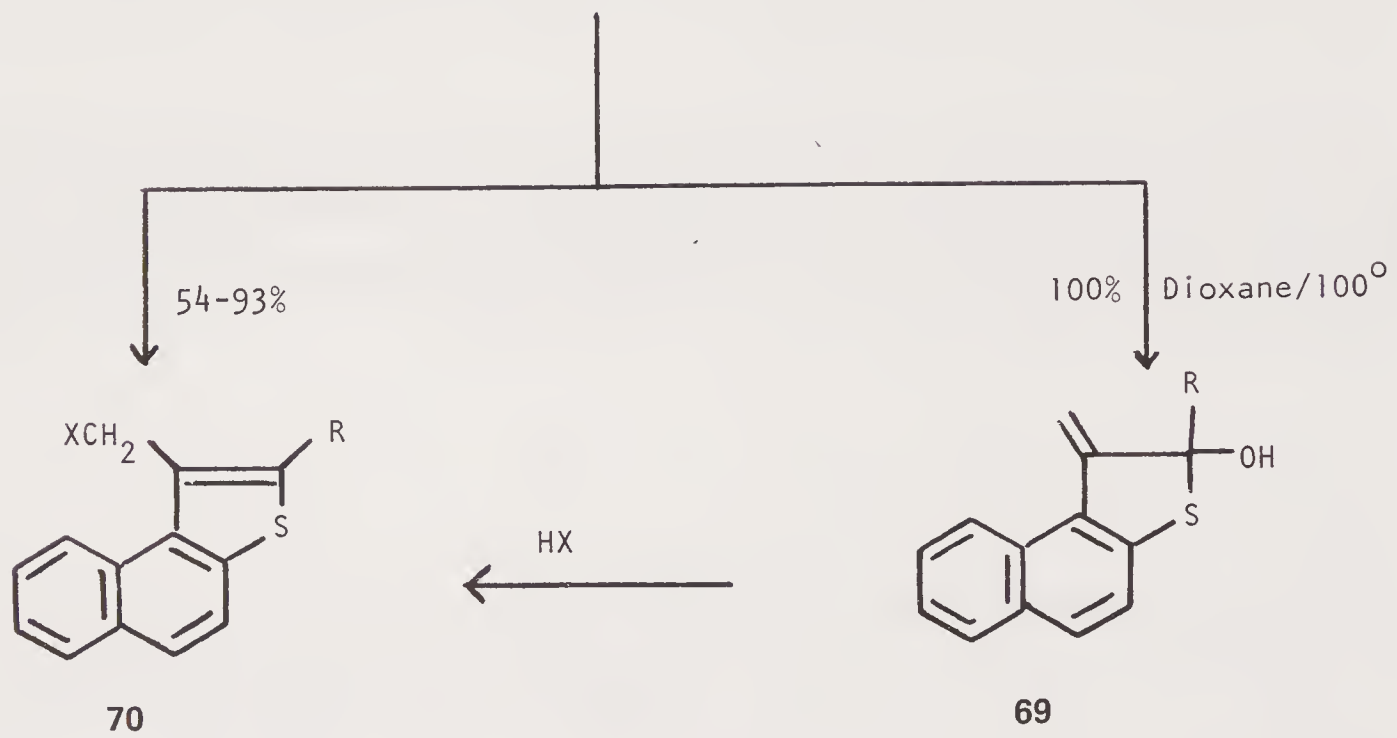


65 R= H, CH_3 66 67 X= C_6H_5S, C_2H_5O, HO (18)

Condensed thiophenes **70** are formed when naphthyl 2-propynyl sulfoxides (**68**) are heated in a suitable protic solvent, such as benzenethiol, ethanol, or acetic acid. Heating in dioxane at 100°C quantitatively affords the hemithioacetals **69** which can be transformed to **70** by treatment with the previously mentioned protic solvents[29] (Scheme 5).



68



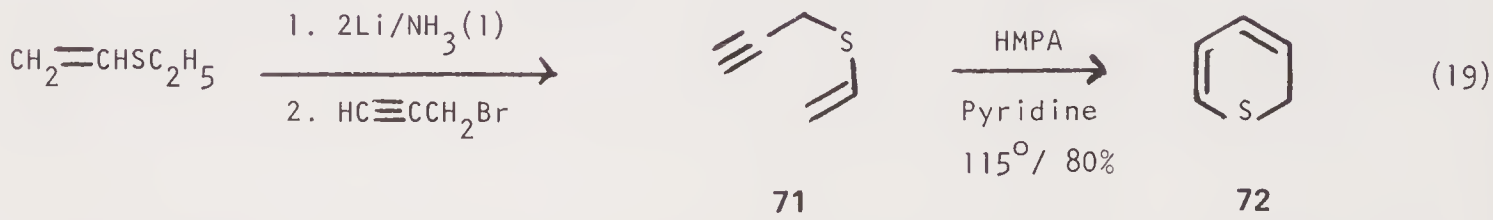
70 **69**

R= H, CH_3

X= C_6H_5S, C_2H_5O, AcO

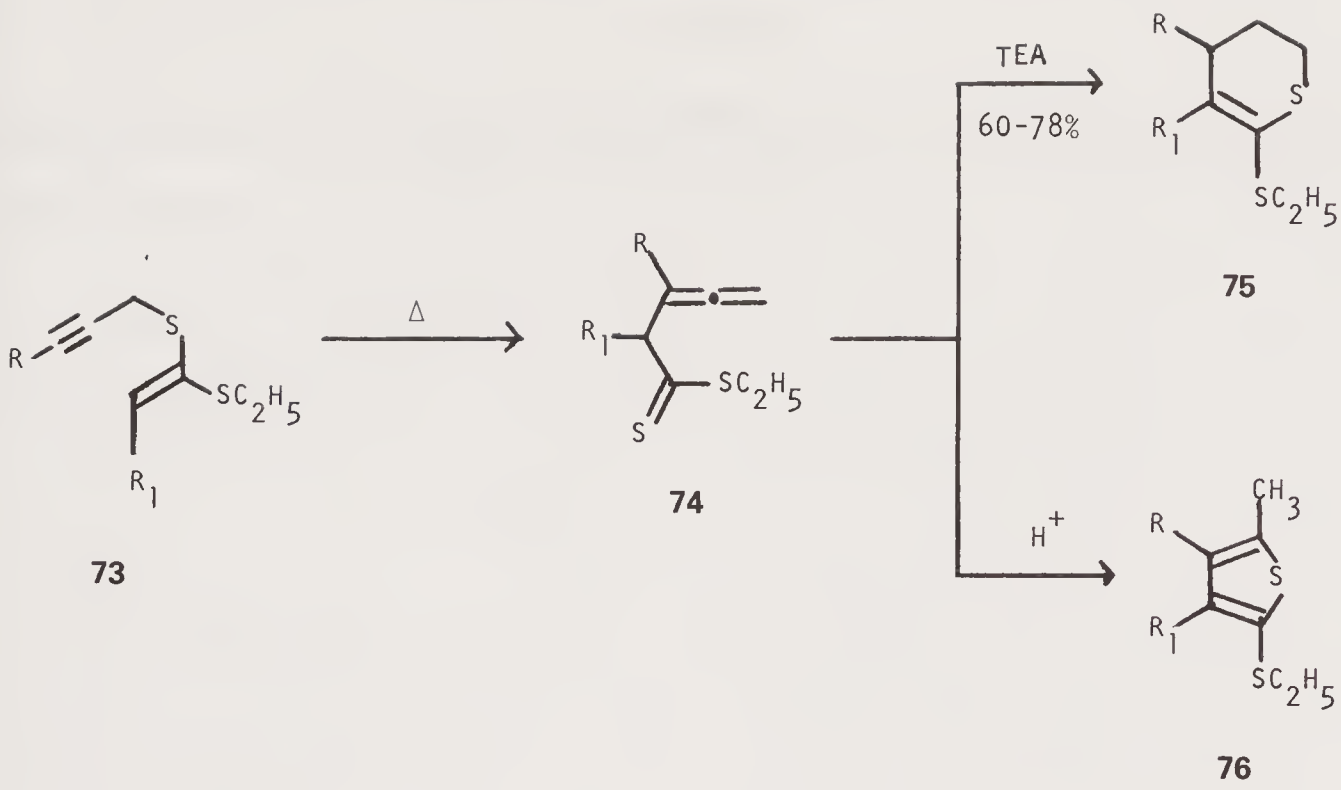
Scheme 5

The thio-Claisen rearrangement can also be done with aliphatic thioethers. The thermal rearrangement of propargyl vinyl sulfide (**71**) produces a high yield of α-thiopyrane (**72**).[30]



71 **72** (19)

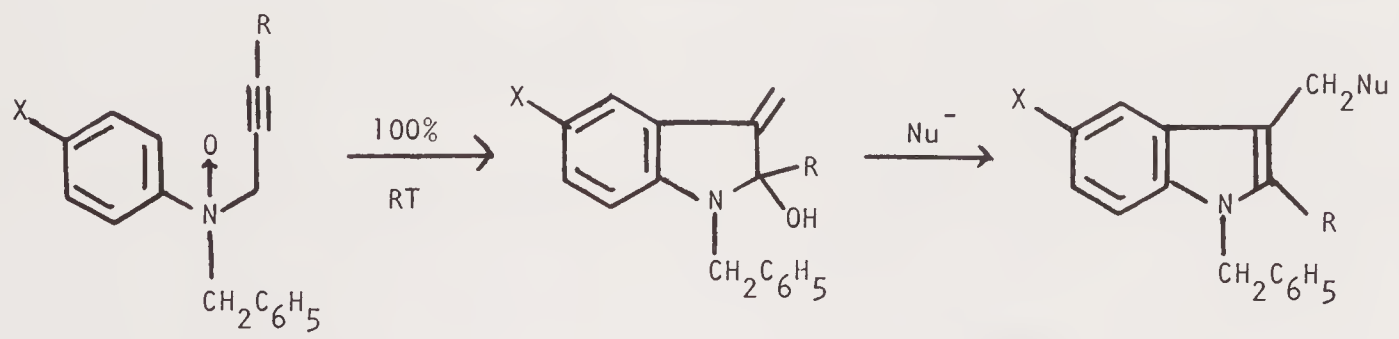
Rearrangement of **73** at elevated temperatures produces first the allenic dithio ester **74**, which can cyclize either to 2H-thiopyrane derivatives **75** or to a substituted thiophene **76**. The formation of **75** is accelerated by the addition of triethylamine, whereas traces of acid favor **76**[31] (equation 20).



(20)

10.2.3. Amino-Claisen

N-propargylaniline does not undergo the Claisen rearrangement.[32] However, the thermal rearrangement of N-propargylaniline N-oxides (**77**) provides a general route for the synthesis of 3-(substituted methyl) indoles **78–80**[33] (equation 21).



(21)

77

R= H, CH_3

X= Cl, OCH_3, H

78 Nu= C_6H_5S

79 Nu= N_3

80 Nu= CN

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