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METHODS FOR THE SYNTHESIS OF CARBOCYCLES

by

A. GAETAN ANGOH

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH

IN PARTIAL FULFILMENT OF THE REQUIREMENTS FOR THE DEGREE

OF DOCTOR OF PHILOSOPHY

DEPARTMENT OF CHEMISTRY

EDMONTON, ALBERTA

SPRING 1985

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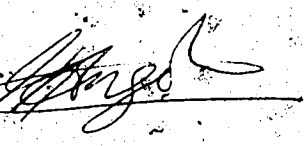
(Signed) 

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submitted by A. GAETAN ANGOH

in partial fulfilment of the requirements for the degree of DOCTOR OF PHILOSOPHY

D. L. J. Clive

Supervisor

Peter Sporns

DATE February 22, 1985

A mes Parents

et à

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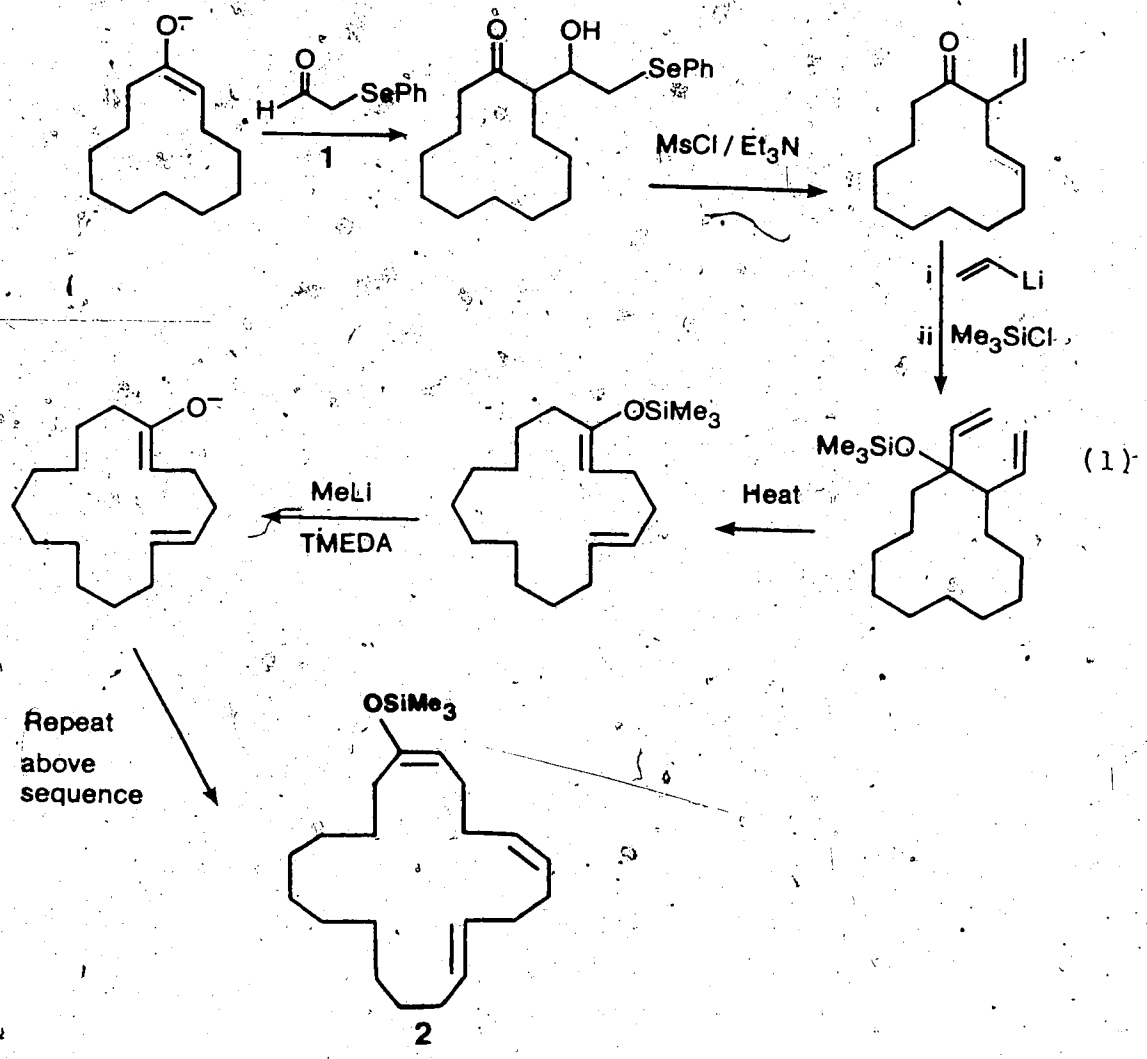
ABSTRACT

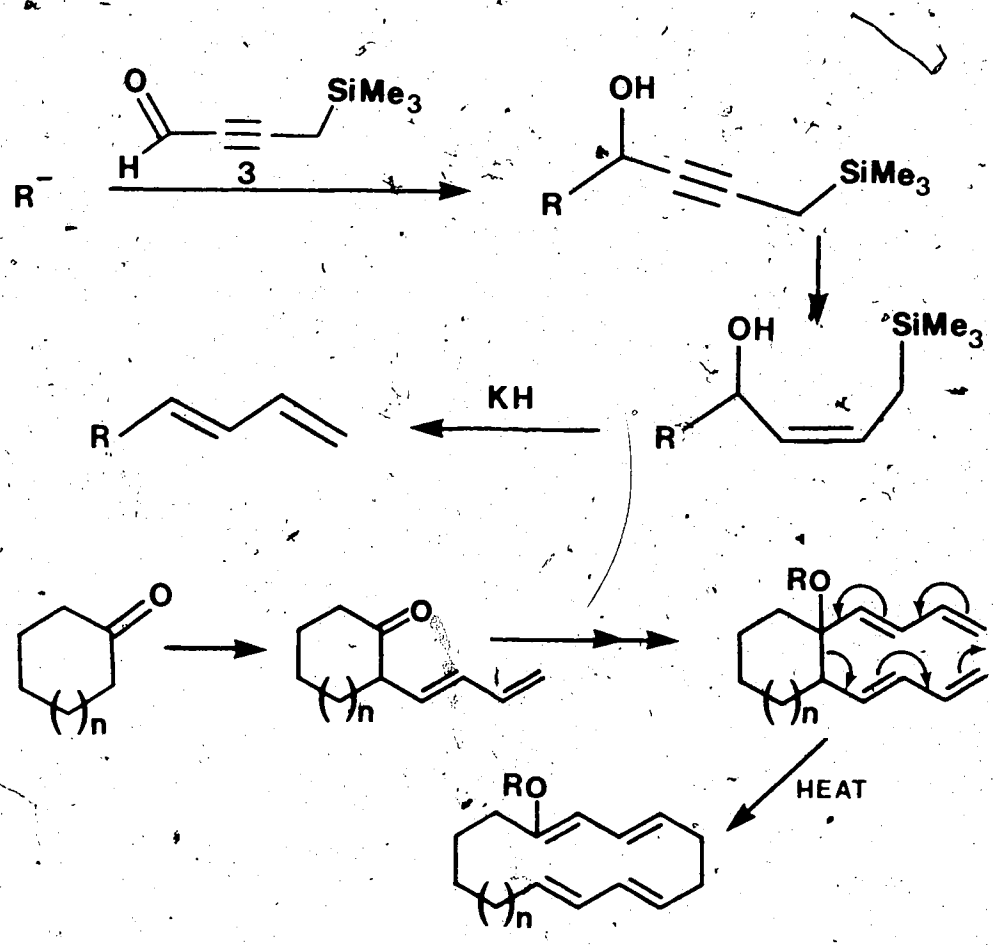
This thesis describes the development of the following methodology:

(1) A procedure for repetitive ring expansion of cyclic ketones with control of regiochemistry. For example, cyclododecanone was converted into the 20-membered cycloalkenes 2 by use of phenylselenoacetaldehyde 1 and the siloxy-Cope rearrangement (eq. 1).



(1)

(2) A method for macroexpansion of cyclic ketones by eight-carbons. 4-(Trimethylsilyl)but-2-ynal **3** was developed as a synthetic equivalent for the butadienyl carbonium ion and was used for preparation of terminal dienes (eq. 2) and for macroexpansion of cyclic ketones (eq. 3).



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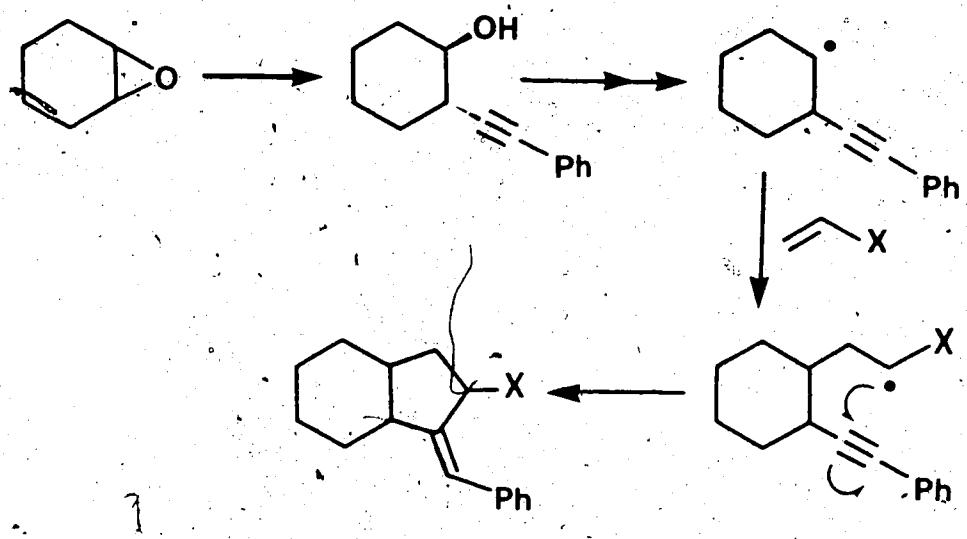
(3) A method for making five-membered carbocycles, using β-acetylenic radicals and electron-deficient olefins

by a novel radical annulation reaction (eq. 4).



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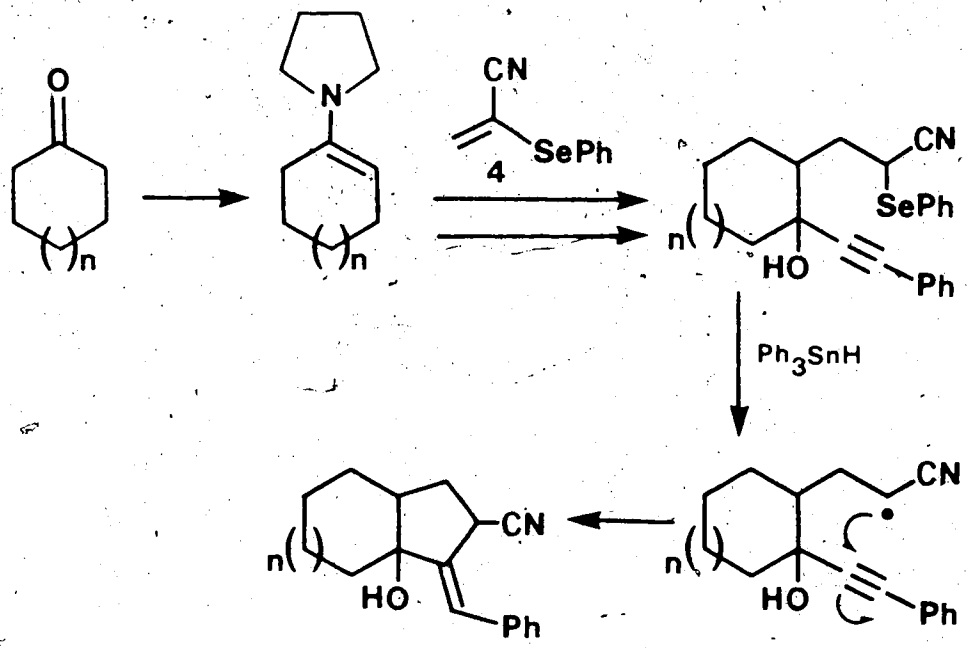
(4) A method for radical cyclization that makes use of 2-(phenylseleno)acrylonitrile, 4 (eq. 5).



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CHAPTER 1

RING EXPANSION OF CYCLIC KETONES

Carbocyclic Ring Expansion - Introduction

The first research sections of this thesis deal with a method of repetitive ring expansion of ketones by four atoms and a procedure for ring expansion of ketones by eight atoms in one cycle of operations. There is very little prior literature in these areas; however, by way of introduction to the research, some examples of ring expansion of carbocycles are given below.

The majority of organic compounds are cyclic[1] and there are many situations where one ring system is more accessible than another or has certain desirable features, such as those that allow stereocontrolled operations. In these cases the ability to transform one ring into another by ring expansion is obviously useful.*

Medium and large rings are less accessible than small and normal rings.** A growing number of natural products

---

* The process of ring contraction has found few applications, because, with currently available methodology, there is a greater requirement for elaboration of smaller to larger rings.

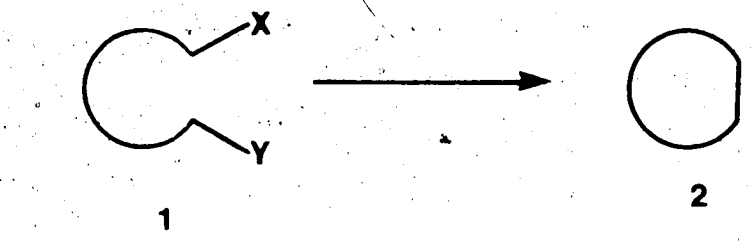
** Ring size classification: Small (3,4); normal (5, 6, 7); medium (8 — 11); large (greater than 11 members).

with both potentially interesting biological properties and medium or large ring structures have been isolated[2] and so the requirement for synthetic methods in this area is increasing.

Since stereochemical control in cyclic and, especially, polycyclic compounds, is often easy, it is worth noting that cleavage of a ring system affords an acyclic molecule. This type of approach can lead to acyclic species that are highly functionalized with regio- and stereochemical features.

Medium and large ring compounds have been studied for over 100 years and early prejudice that large rings could not exist was set aside by the identification in 1926[3] of muscone and civetone as naturally occurring fifteen- and seventeen-membered ring systems and by subsequent synthetic work in the area of cyclic compounds. In more modern times, research on medium[4] and large rings[5] has been stimulated by medicinal,[6] theoretical,[7] and commercial[8] interest in naturally occurring macrocycles and in species such as crown ethers[9] and annulenes.[10]

The main approaches are (1) closure of acyclic chains (**1**→**2**), (2) fragmentation of polycyclic molecules (**3**→**4**);(3) ring expansion — by which is meant attachment of one or more appendages to an existing ring followed by



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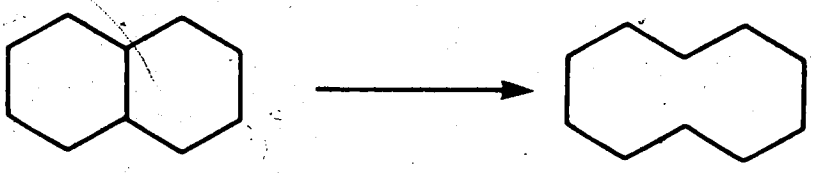


3 4

cleavage (or migration) of a bond in the original ring so as to generate a larger structure.

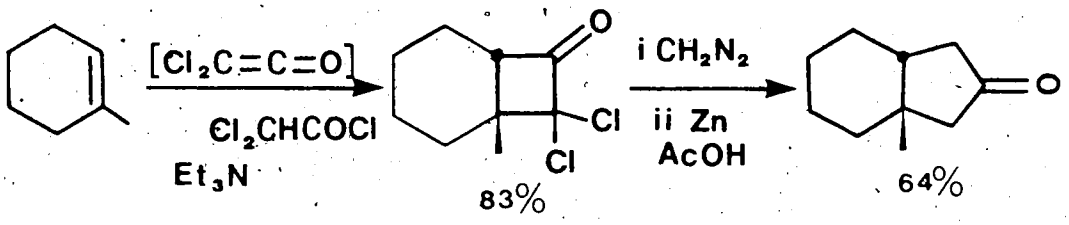
Ring closure techniques, especially for preparation of medium rings, often proceed poorly.[11] Ring enlargement has often been used in synthesis but has almost always been restricted to expansions of one, two, three, or four atoms in one operation. Only a limited number of methods is available for conversion, by one expansion sequence, of the common rings into macrocycles of twelve, or more, members.[12] Prior to our own work, repetitive sequences, in which the same type of expansion is carried out several times, do not appear to have been much investigated for

carbocycles.[13]

The general area of carbocyclic ring expansion has been reviewed several times[13,14] and a brief survey of important procedures is as follows.

Expansion by one atom

Expansion of ketones with diazoalkanes and diazoesters is a method that is frequently used for ring enlargement. Some of the current importance of the method is due to the availability of cyclobutanones by 2 + 2 cycloaddition and the widespread occurrence of 5-membered rings in natural products.[15] The example shown[16] in eq. 1



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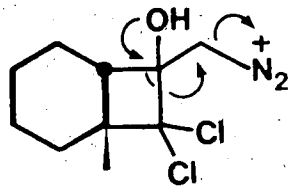

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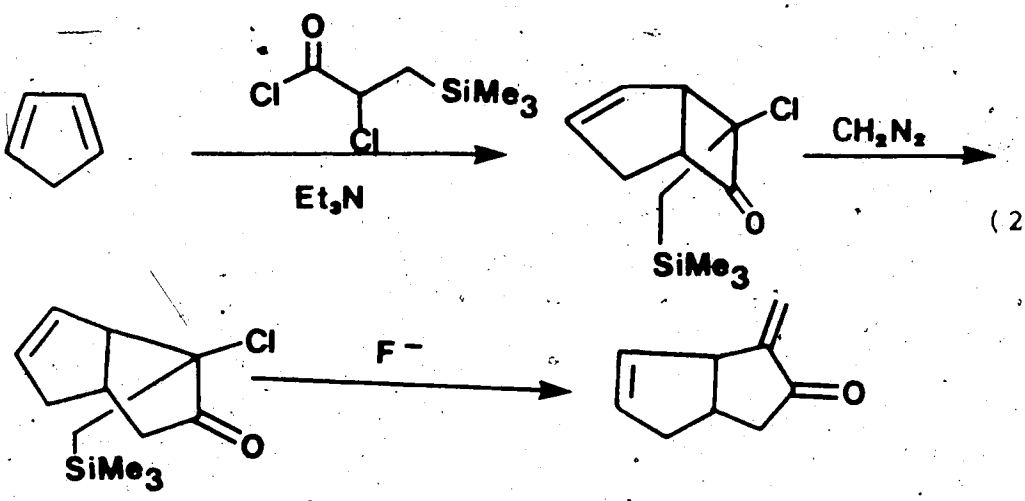
is efficient and the expansion is regiospecific (see 5) due to the presence of the two electron-withdrawing groups. The starting ketone, being strained, is more

reactive than the product and so multiple expansion is not a problem.[17] In an extension of the technique[18] the expansion can be linked with silicon chemistry (eq. 2).



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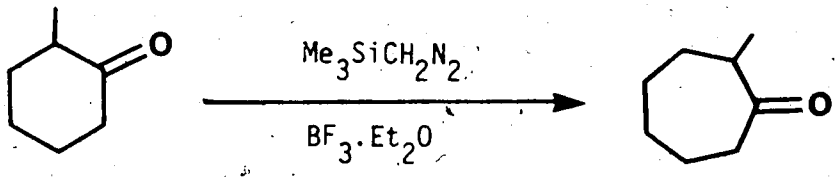
Regiochemical control, attributable to the bulk of the reagent, is also possible with trimethylsilyldiazomethane (eq. 3).[19]



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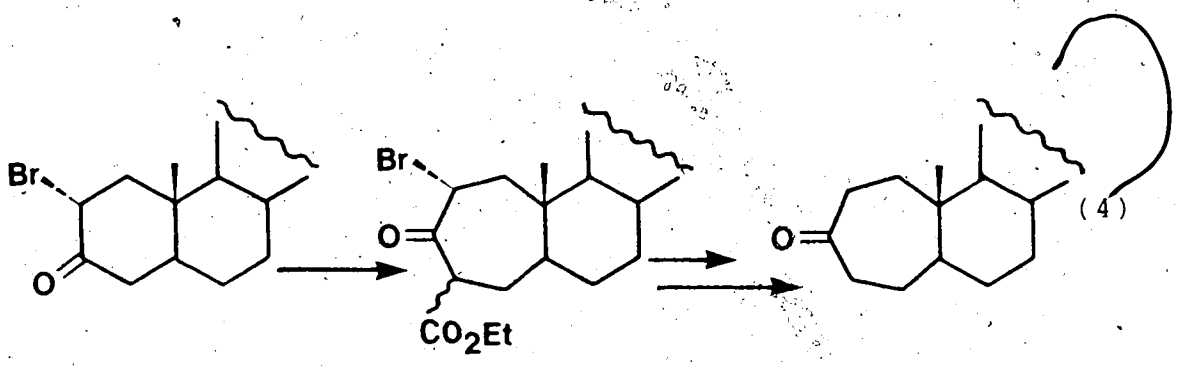
69%

Ethyl diazoacetate is often preferable to diazomethane since multiple expansion is not a problem

with this reagent, nor is epoxide formation. The reaction of ketones with ethyl diazoacetate is catalyzed by boron trifluoride etherate and by triethyloxonium tetrafluoroborate.[20] Carbon insertion occurs[21] on the less hindered side of the ketone carbonyl and high levels of regiochemical control are possible by using α-halo (Cl, Br) ketones (eq. 4).[22]



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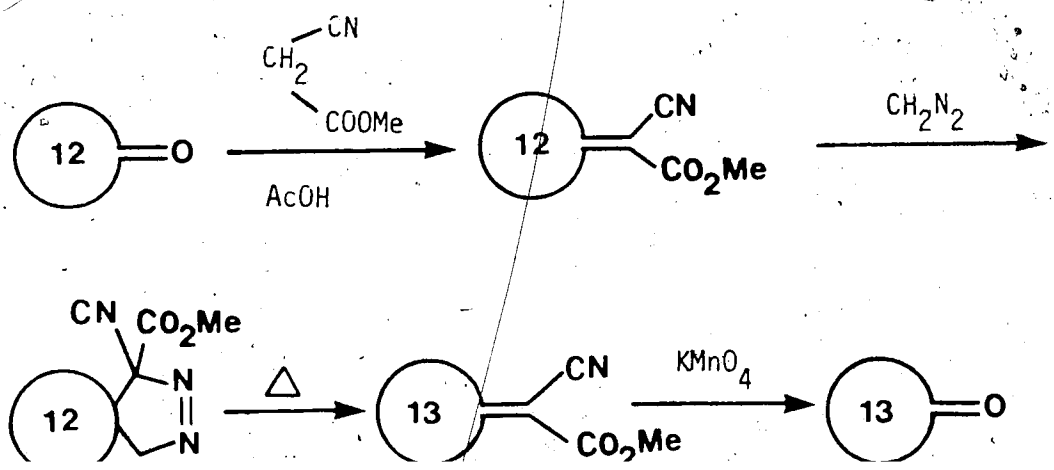
Diazomethane has also been used[23] in the sense shown in eq. 5; unfortunately regioselectivity is poor with unsymmetrical ketones.



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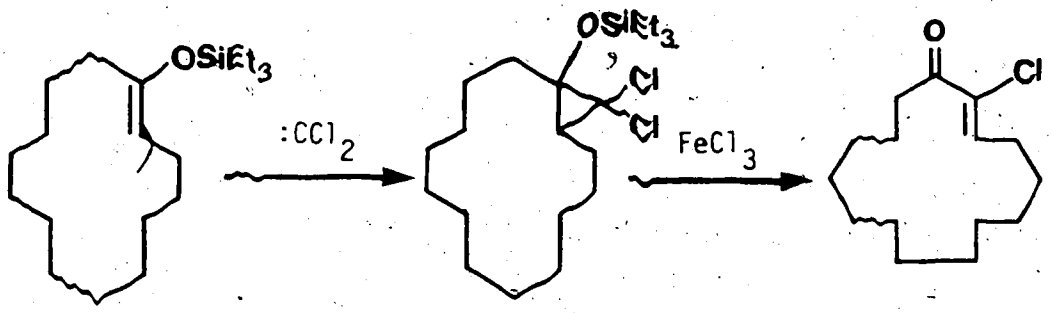
Another type of one-carbon expansion involves formation and opening of cyclopropanes.[24] Four variations of this theme[25] are shown in eqs. 6 — 9. In the first three examples carbene addition to a double bond takes place, while the last example involves intramolecular rearrangement of a carbene.



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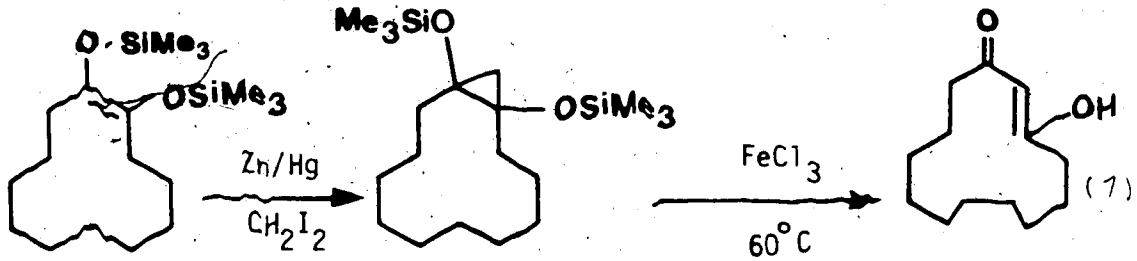

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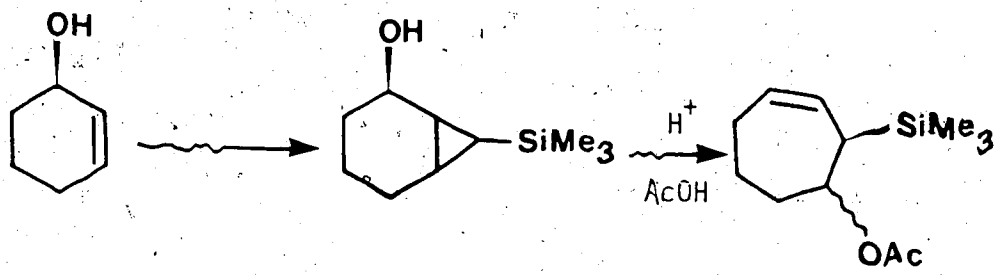

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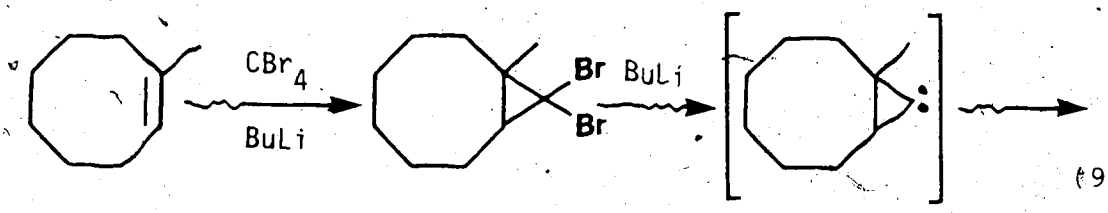

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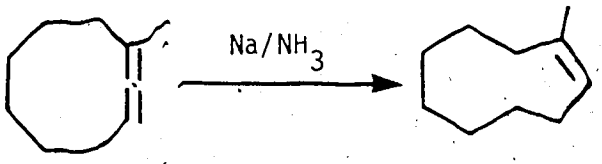
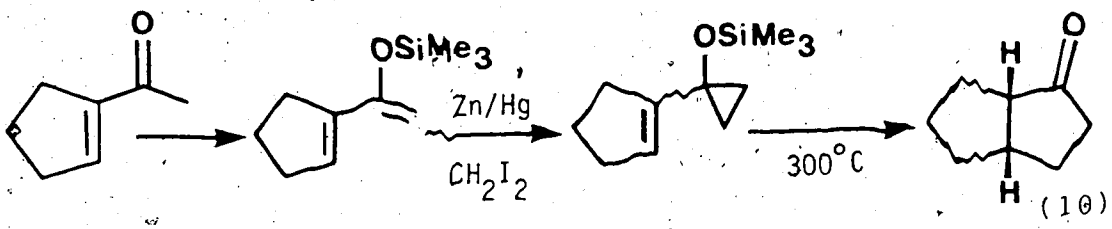


Ref. 28

Expansion by two atoms

Thermal rearrangement[29] of vinylcyclopropanes constitutes a popular method of access to five-membered rings (eqs. 10, 11).

The cyclobutene → butadiene rearrangement can also serve to expand rings by two atoms and examples of the implementation of this method are shown in eqs 12 – 14.



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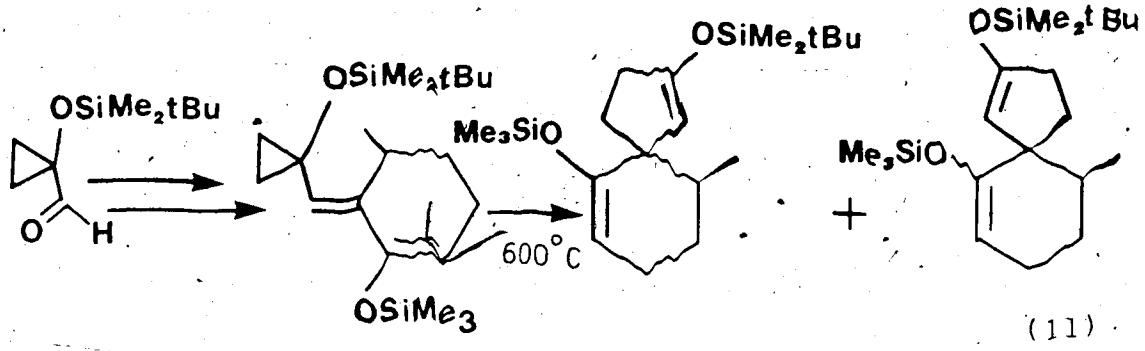

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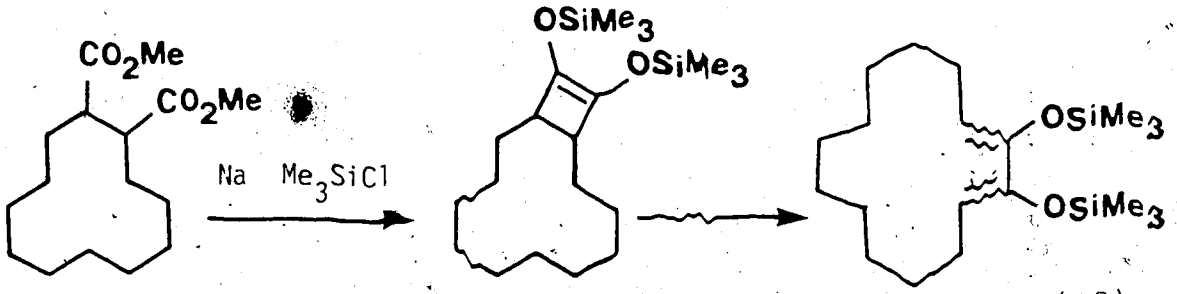

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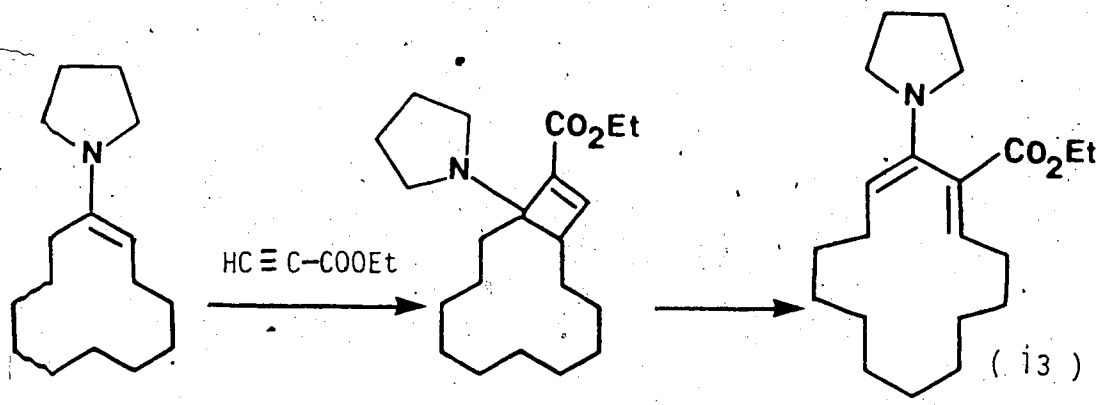

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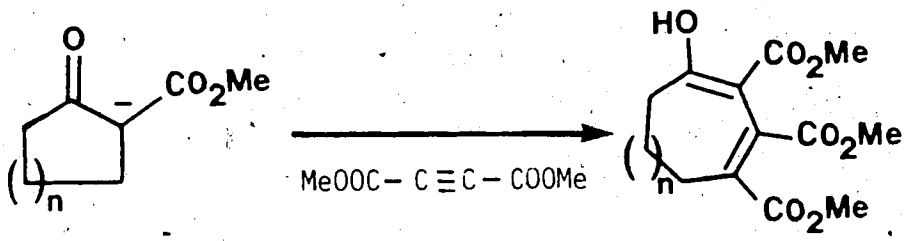
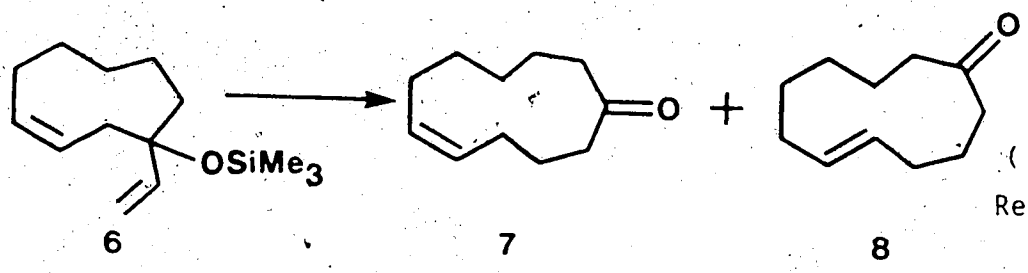


(14)

Ref. 34

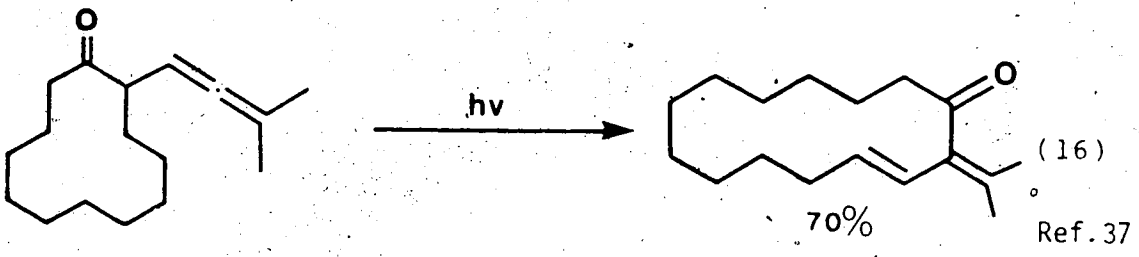
Formal 1,3-sigmatropic rearrangements constitute an expansion by two atoms. Thus at 240 — 300°C compound **6** gives a mixture of **7** and **8** (eq. 15). The mechanism of this process is unclear[36] and the reaction does not seem to have been used in synthesis. It is mentioned here because the allylic silyl ether unit is used in our own research on ring expansion.



6 7 8 (15)

Ref. 35

Photochemical 1,3-migration is also possible (eq. 16)



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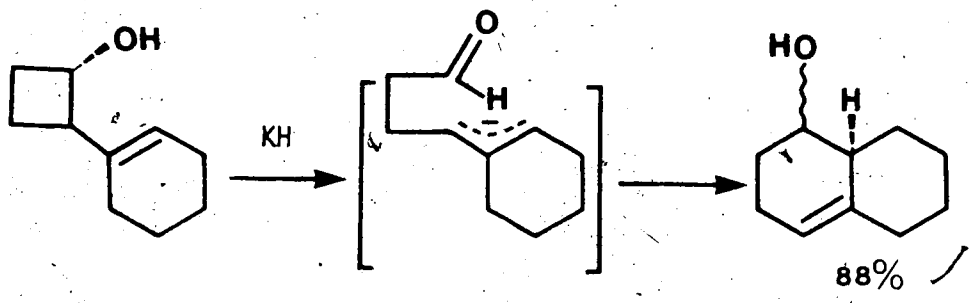
Finally, in the context of two-atom expansions, mention must be made of the fragmentation-recombination approach exemplified by eq. 17.



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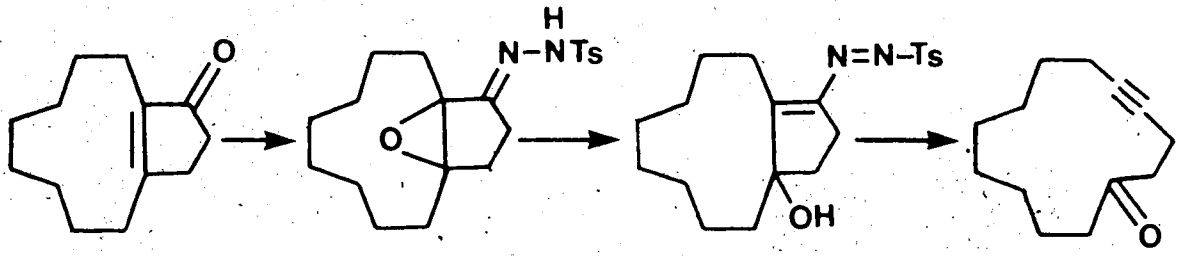
Expansion by three atoms

Because of the ready availability[39] of cyclododecanone and the interest of the perfume industry in muscone, a C-15 compound, a number of methods have been developed for expansion by three atoms so as to convert cyclic C-12 into C-15 systems. Eqs. 18 to 24 show a number of these methods. (In the case of eq. 21 the mechanism is not clear).

Ring expansion by four atoms

Ring expansions by four atoms generally involve electrocyclic processes such as the cyclohexadiene ⇄ hexatriene interconversion (eq. 25), electrocyclic opening of cyclobutanones (eq. 26), or sequences based on the oxy-Cope or Cope rearrangement. In the case of the



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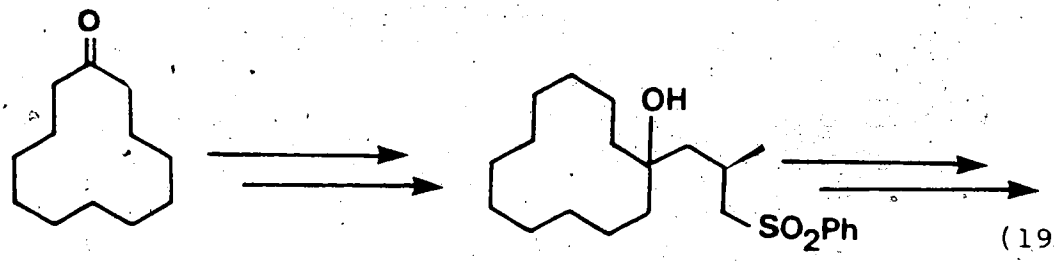
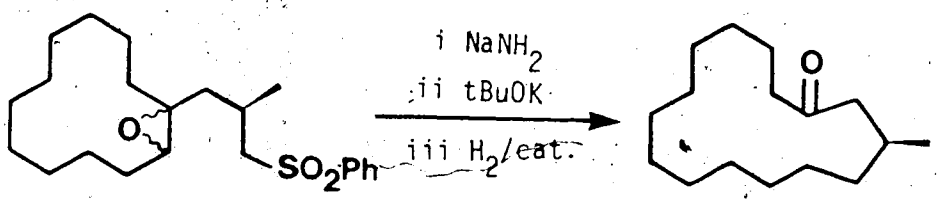
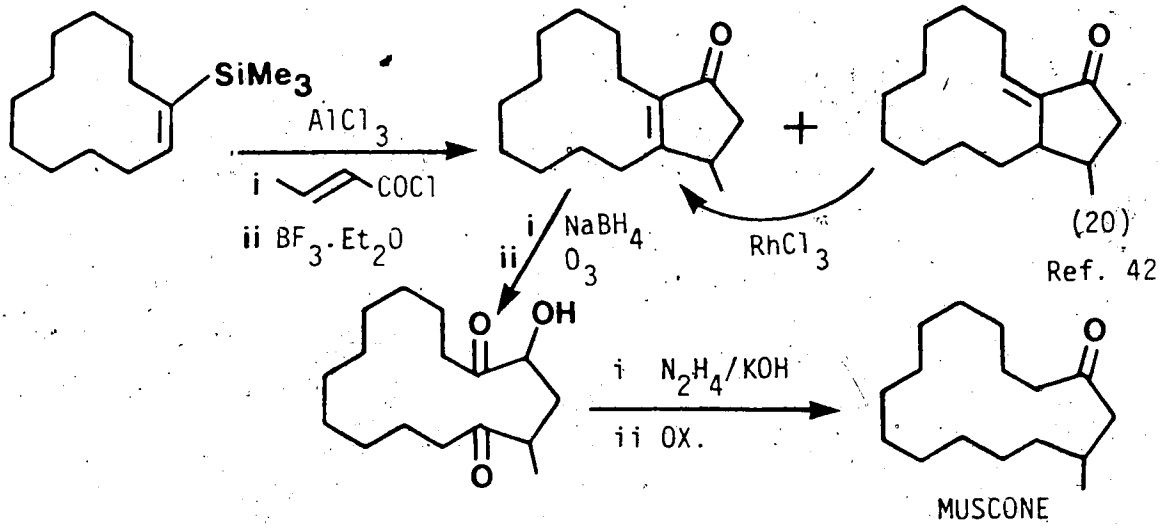


(19)

Ref. 41



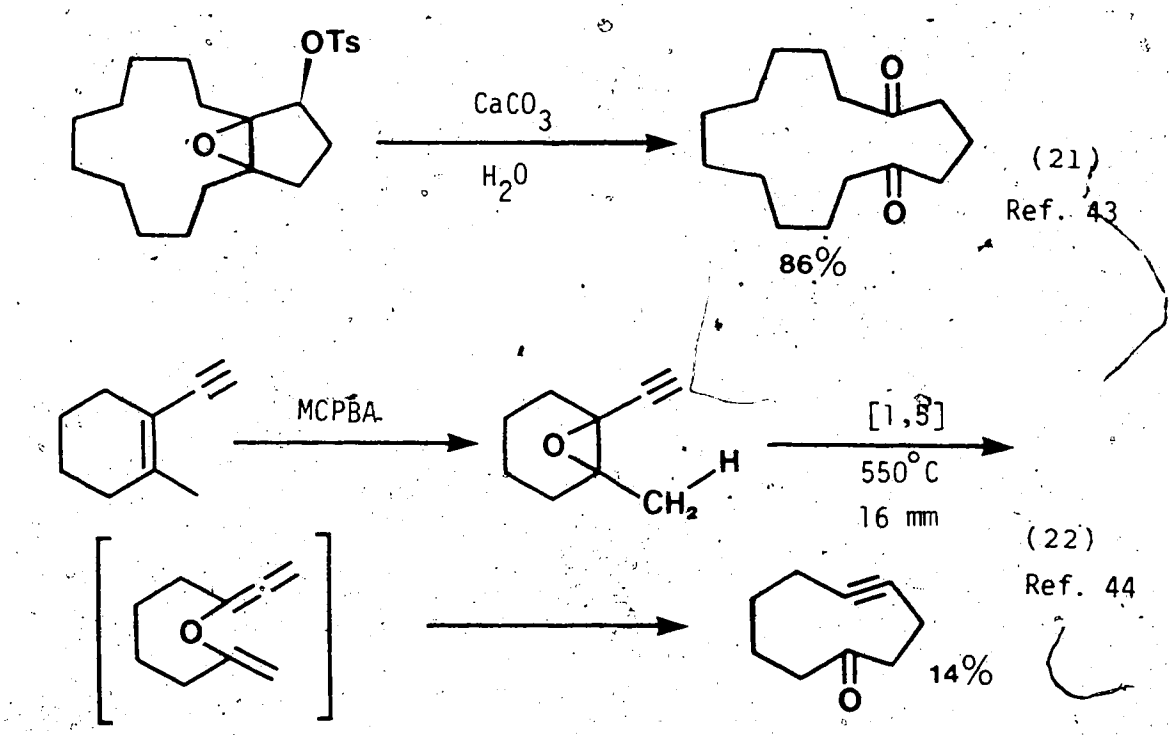
MUSCONE

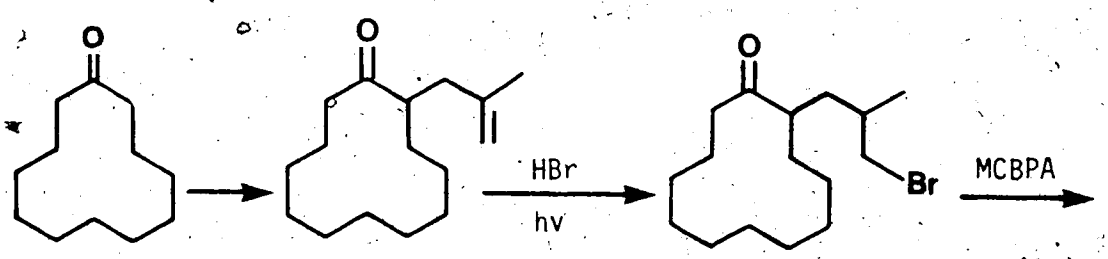


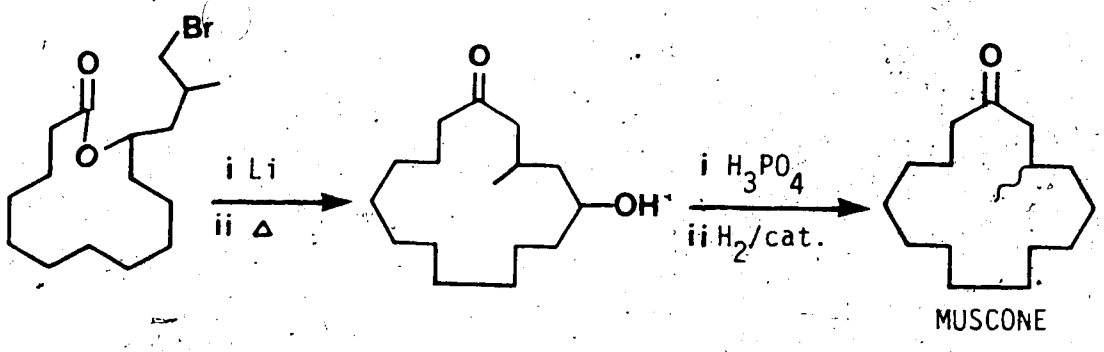
(20)

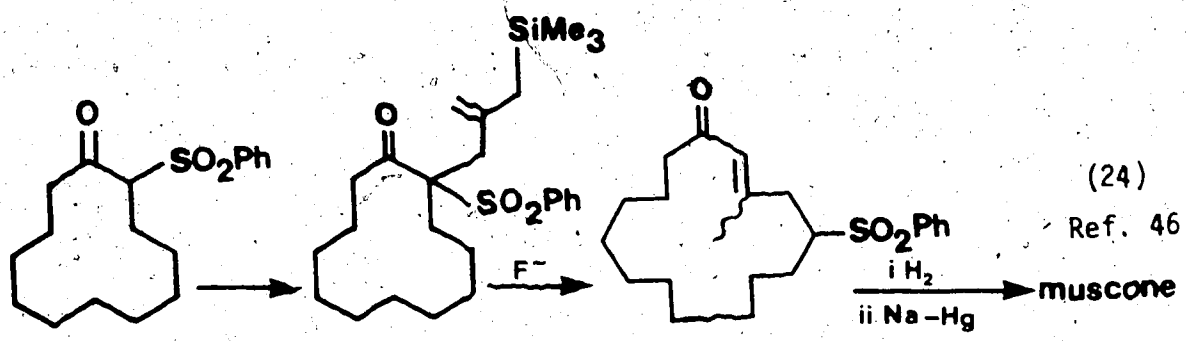
Ref. 42

MUSCONE

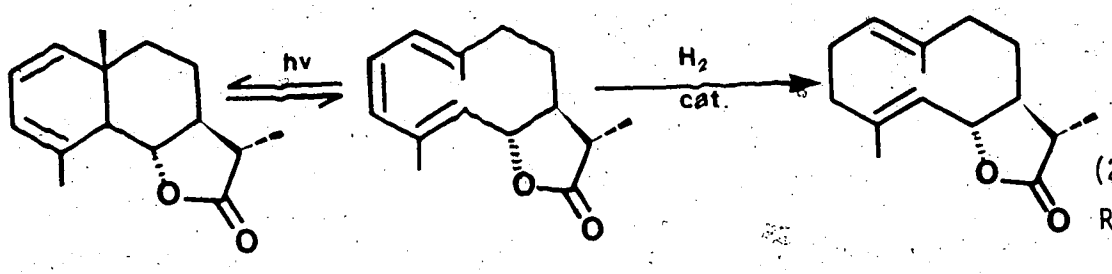

OTs
O
$CaCO_3$
H_2O
O
O
86%
(21)
Ref. 43
MCPBA
O
H
CH_2
[1,5]
550°C
16 mm
(22)
Ref. 44
O
14%


O
O
HBr
hv
O
Br
MCBPA
(23)
Ref. 45

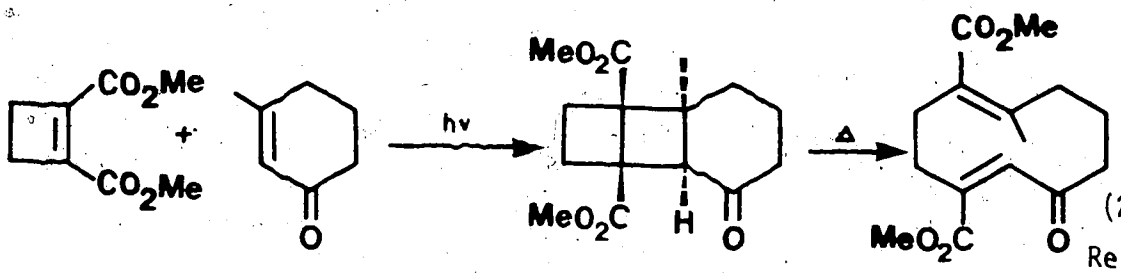

Br
O
O
i Li
ii Δ
O
OH
i H_3PO_4
ii H_2/cat.
O
MUSCONE



(24)
Ref. 46



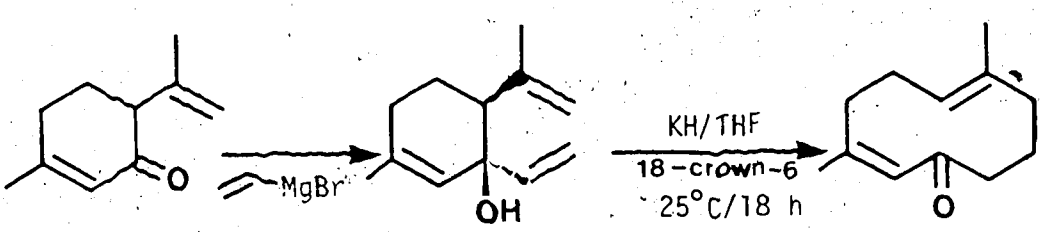
(25)
Ref. 47



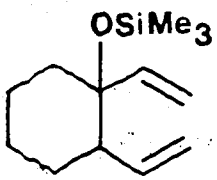
(26)
Ref. 48

oxy-Cope reaction, the anionic version (eq. 27) is preferred since it generally operates under very mild conditions and gives better yields. A mechanistic study[50] showed that it involves a concerted process predominantly via a chair[51] transition state. Mechanistic studies for the siloxy-Cope rearrangement of divinyl species such as **9** have not been reported, but related studies[52] suggest that it too must follow the normal concerted chair pathway[53] of

the classical Cope rearrangement.

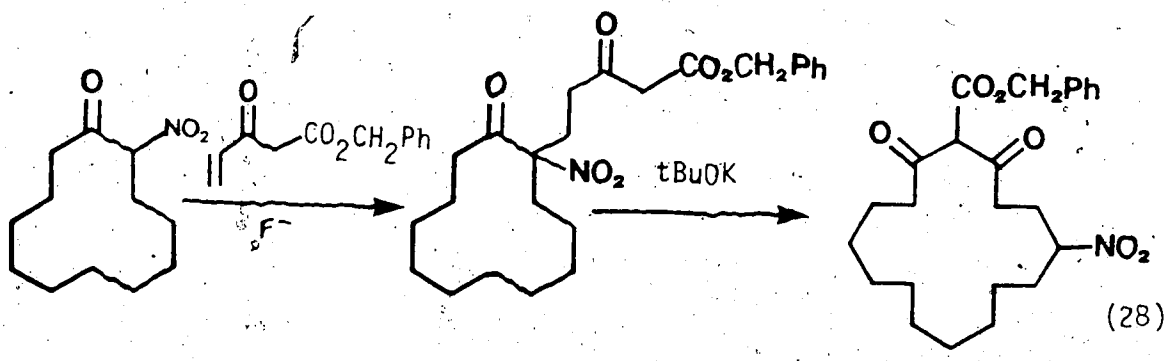


(27)
Ref. 49



9

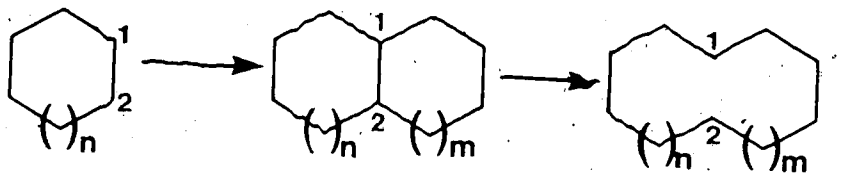
A different approach to four atom expansion, and known as the "carbon-zip reaction", has been published[54] (eq. 28).



(28)

Fragmentation processes

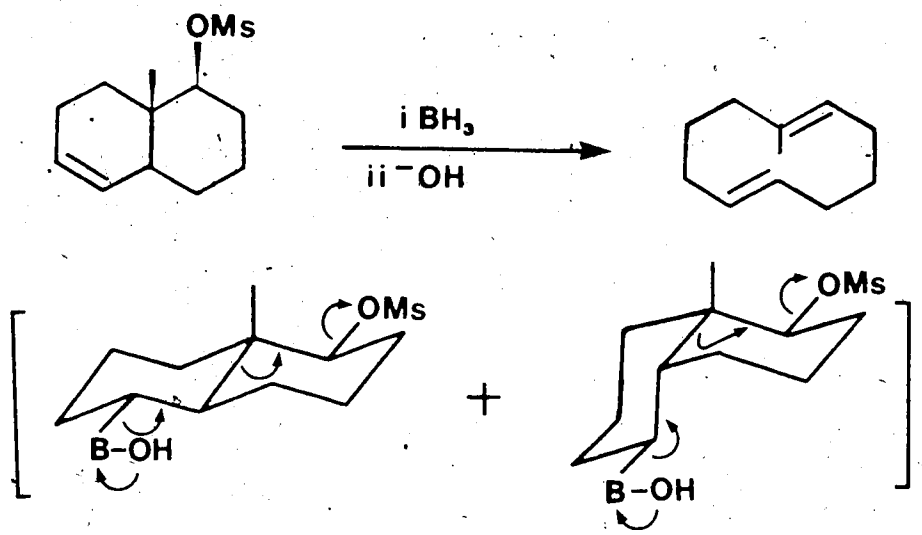
In the context of ring expansion we mean by the term "fragmentation process" a reaction in which a bicyclic[a.b.c] system is converted by bond cleavage into a monocyclic compound of (a+b) atoms.* Several examples have been mentioned already (see eqs. 18, 20, and 21), especially cases in which two contiguous atoms of a ring are used for annulation and are then separated by cleavage (eq. 29).



(29)

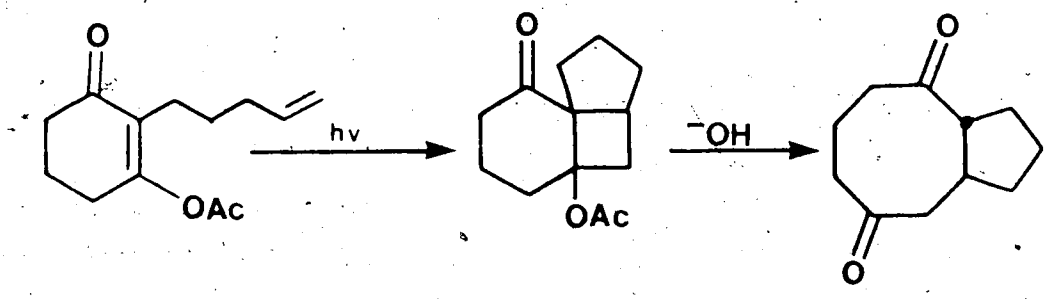
In this section we mention briefly a few examples that do not fit into the earlier classifications. The fragmentation described above is illustrated by the simple reactions shown in eq. 30.

*We do not imply by our notation any order in the relative numerical values of a, b, c.

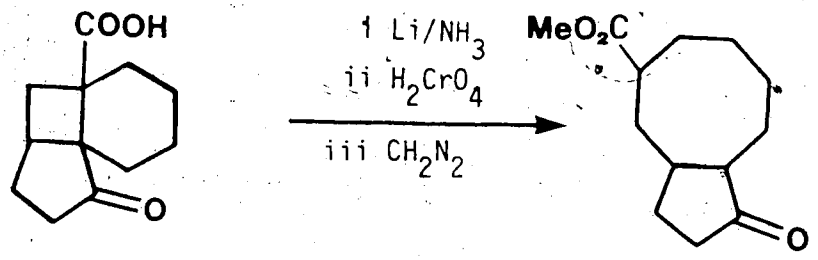


(30)
Ref. 55

These, and related processes[56] are of interest in the context of stereoelectronic effects[57] and they also provide a route to medium ring compounds. Fragmentation processes, beyond those closely related to pathways mentioned in other sections, do not appear to have been much used, if at all, for construction of large rings and eqs. 31 — 34 represent applications in the area of medium ring compounds.

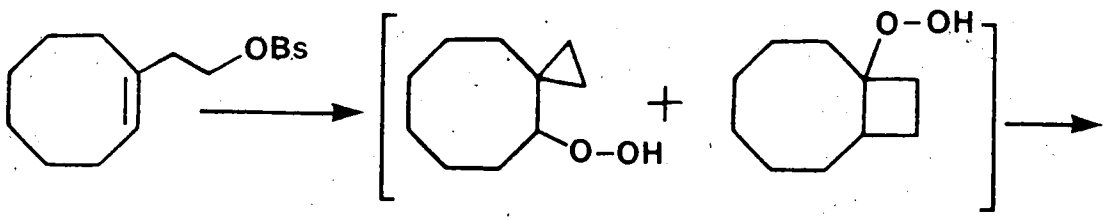


(31)
Ref. 58

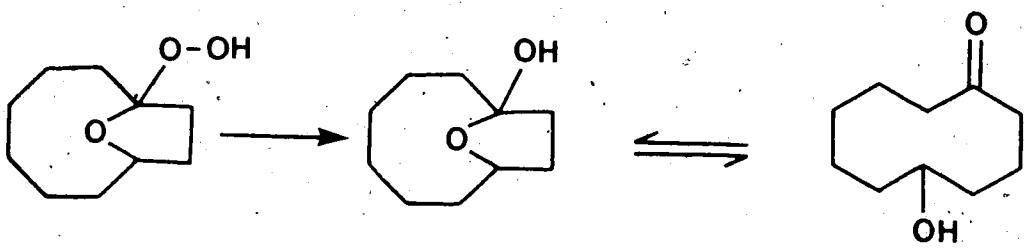


(32)

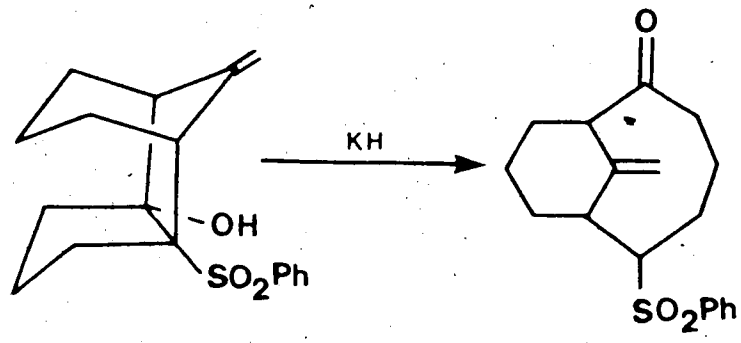
Ref. 59



(33)



Ref. 60



(34)

Ref. 61

Examples such as eq. 30 and eq. 32 give the impression that such reactions have to be incorporated at an early stage into the strategy,[62] whereas processes of the annulation-cleavage type (see eq. 19) can be used almost with the freedom of a functional group transformation. The latter case is, accordingly, more widely applicable, while the former, in particular selected cases, can constitute very interesting and concise approaches to a synthetic target.

Repetitive Ring Expansions

Repetitive ring expansions can operate at two levels of sophistication. In both of them the same compound class* must be generated at the end of the expansion sequence as was used to begin the sequence. In the second level a further requirement is met: A regiochemical bias in the starting material is preserved throughout the expansion sequence so that, after several applications of the method, the precise origin of all atoms in the product is known.

Reaction of a diazo-alkane with a ketone represents

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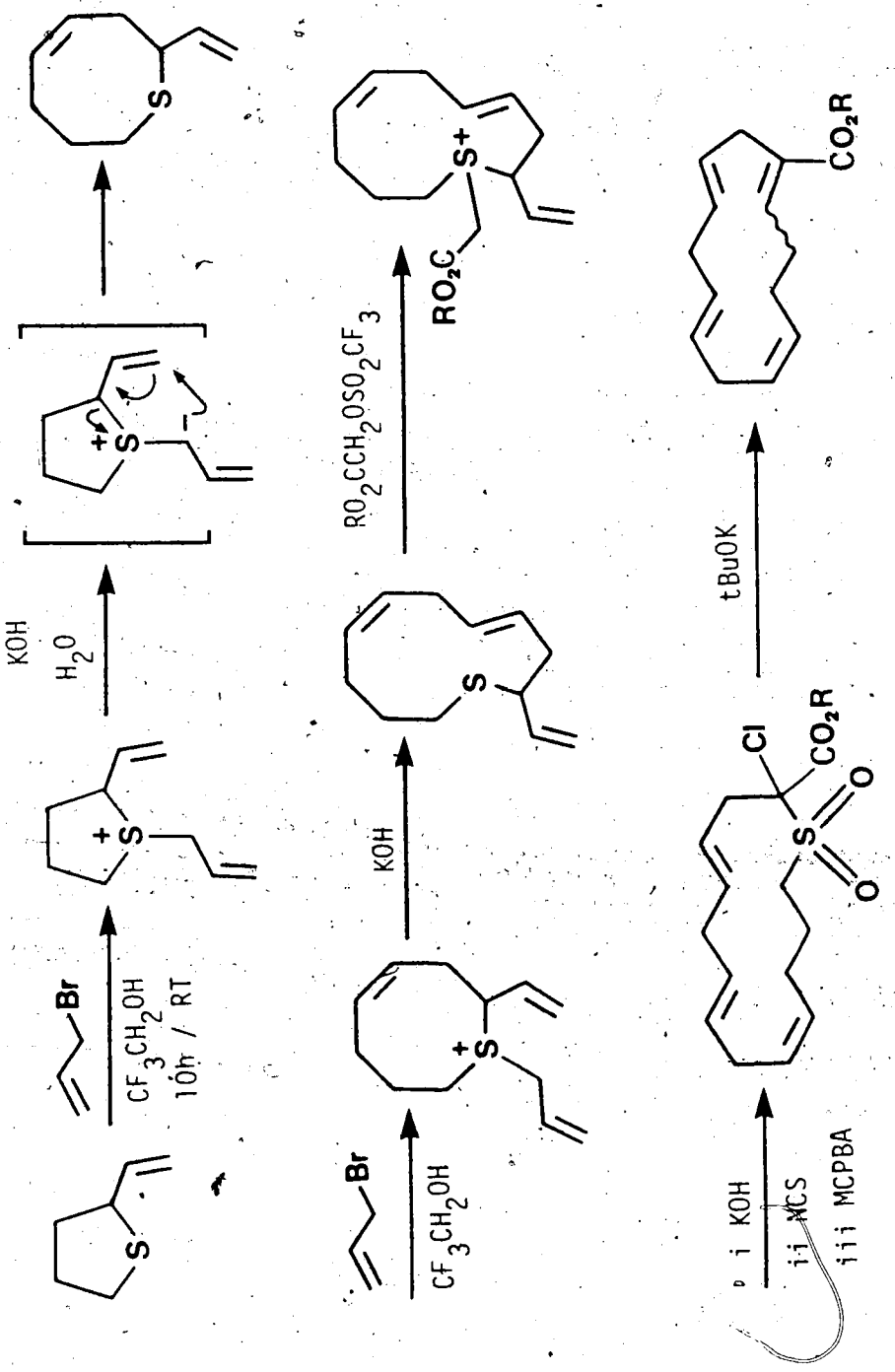
*Or a substance easily convertible to it.

the first category just mentioned and also serves to illustrate another point. The purpose of a repetitive sequence is to interpolate a number of atoms into the periphery of an existing skeleton. For maximum efficiency, it is desirable to incorporate several atoms — not just one — in each complete set of operations.

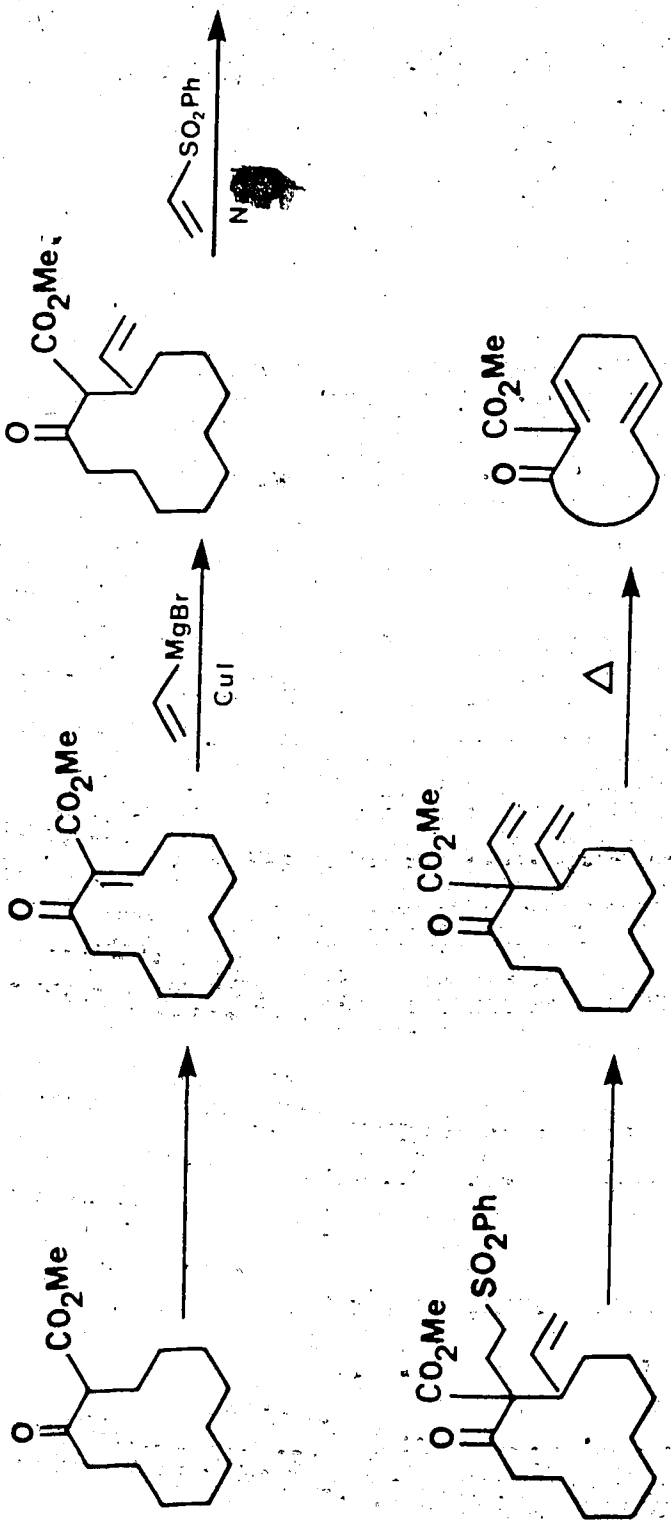
The following prior work has been done in this area (Schemes 1 and 2). [2,3]-Sigmatropic rearrangement of sulfonium ylides, as in Scheme 1,[25,63] generates a sulfur-containing macrocycle from which a carbocycle can be produced by use of the Ramberg-Bäcklund rearrangement. Related methodology has been used to construct the 11-membered carbocyclic portion of cytochalasin D.[63,64] Scheme 2,[65] on the other hand, summarizes an approach based on the Cope rearrangement. However, because of the low yield — 10-20% per sequence — with the second Michael reaction being the poor step, this method (at least without further refinement) does not represent a useful process of repetitive expansion.

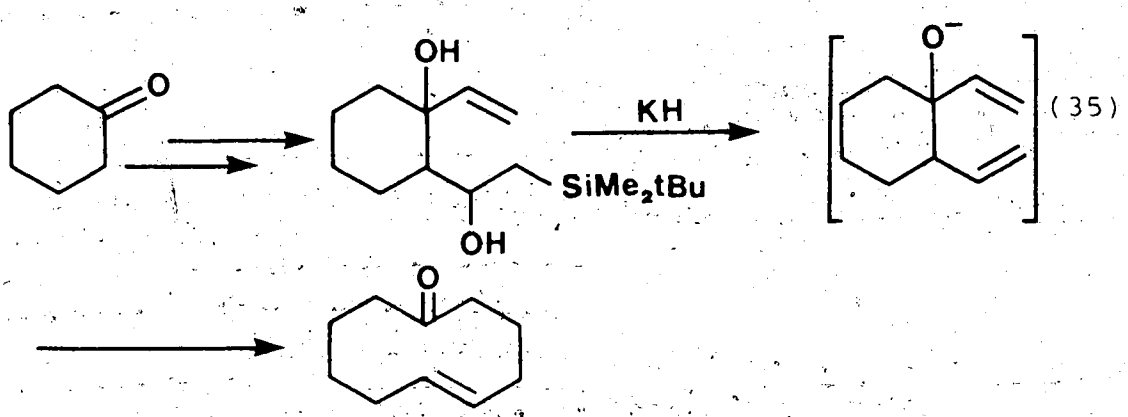
The possibility of repetitive expansion by the anionic oxy-Cope rearrangement has been mentioned in the literature.[66] The first cycle was carried out (eq. 35). The potential problems with this approach are discussed with our own results.

Scheme 1


Br
CF_3CH_2OH
10hr / RT
KOH
H_2O
KOH
$RO_2CCH_2OSO_2CF_3$
RO_2C
tBuOK
CO_2R
i KOH
ii MCS
iii MCPBA
Cl
CO_2R

Scheme 2

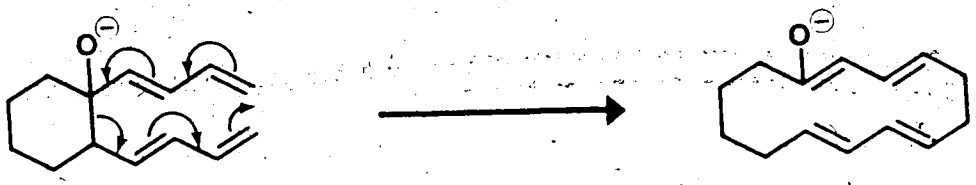




(35)

Macroexpansion

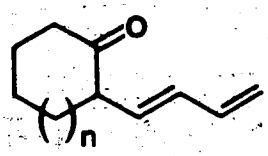
The overall process summarized in eq. 36 is termed "macroexpansion". It represents an interesting contribution to the rapid synthesis of large rings.



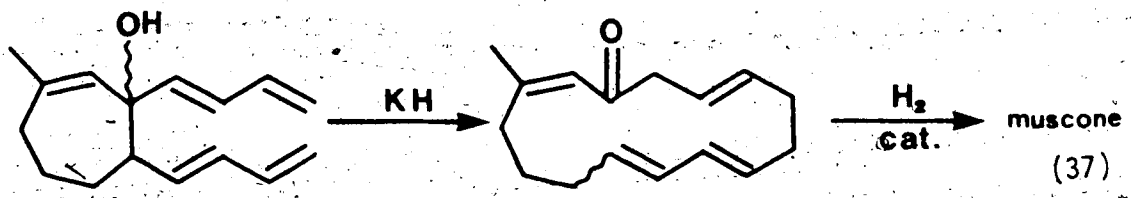
(36)

Full experimental details are available for the case shown in eq. 36[67] but it is not known if two successive [3,3] sigmatropic rearrangements occur or whether a single [5,5]

process takes place. When originally published, the preparation of α-butadienyl ketones **10** was a lengthy process but now, at least for 5- and 6-membered ketones, an elegant and simple approach is available[68] besides the method reported in this thesis. Two examples (apart from our own work) of macroexpansion are known[67,68] (eqs. 36 and 37)*.



10



(37)

Our own finding is that the reaction is not general and must be modified in some cases.

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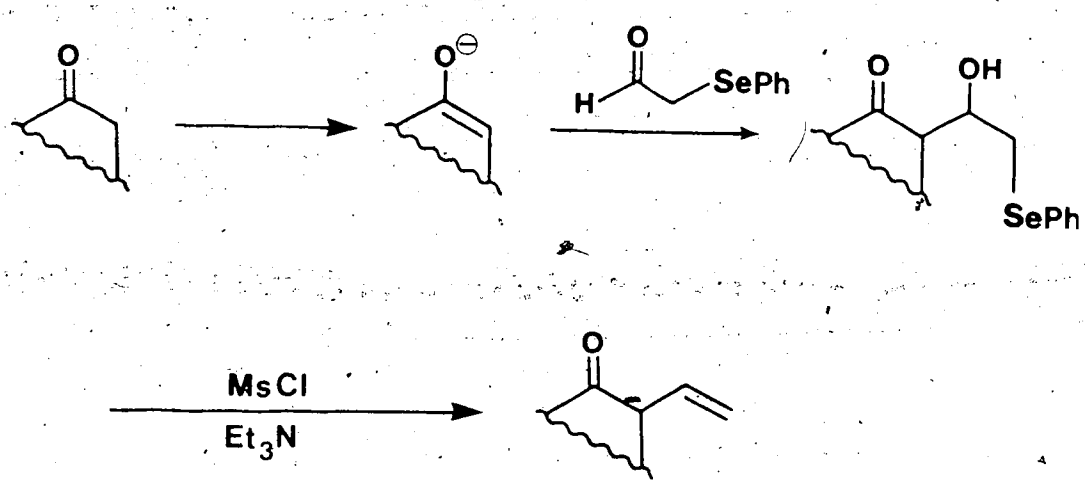
*A third example (Wender — 188th ACS meeting, Philadelphia, August 26-31, 1984; Abstract No. 90) may have been studied.

RESULTS AND DISCUSSION

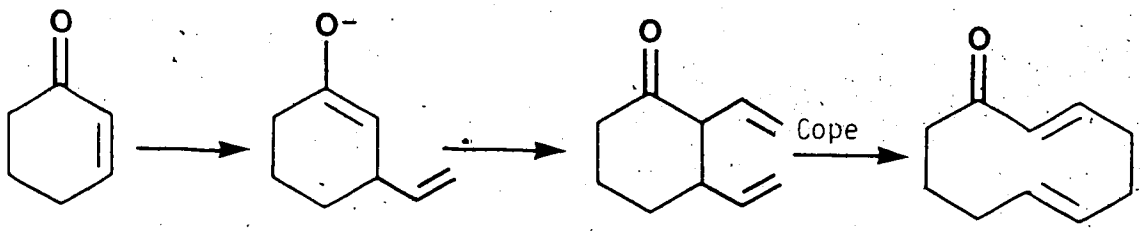
Previous work in this laboratory[69] had developed the use of (phenylseleno)acetaldehyde as a synthetic equivalent for the vinyl carbonium ion, $CH_2=\overset{+}{C}H$. The reagent was used (see Scheme 3) to convert ketones into β,γ-unsaturated ketones. These substances are properly

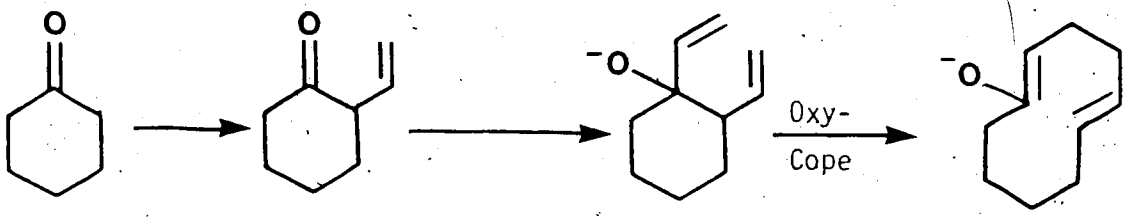


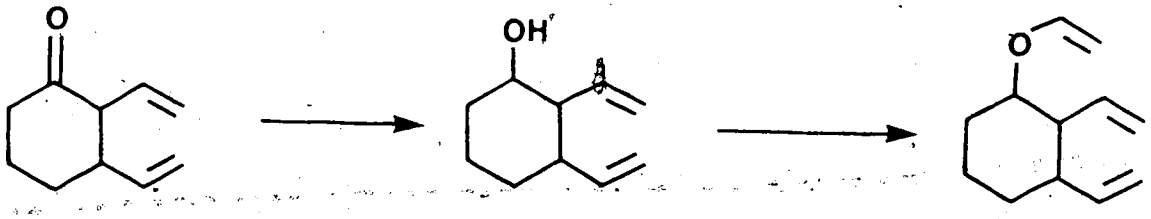
Scheme 3

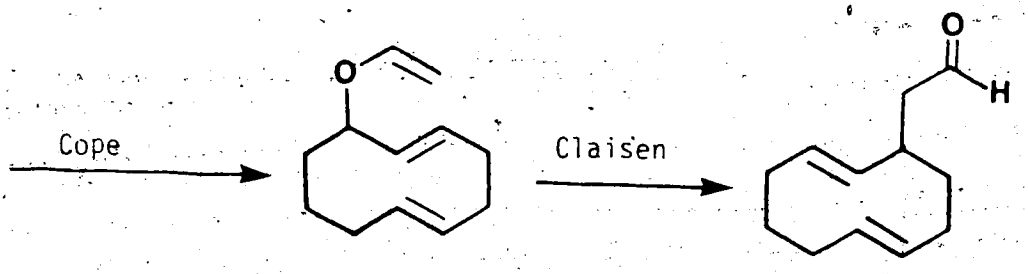
constituted to undergo Cope[70], oxy-Cope,[49,71] and Cope-Claisen[72] rearrangements, as shown in Scheme 4. Such electrocyclic processes are, of course, permanently established as synthetic methods of considerable importance, and so efficient equivalents for the vinyl carbonium ion[69,73] are likely to be very useful species.

Scheme 4







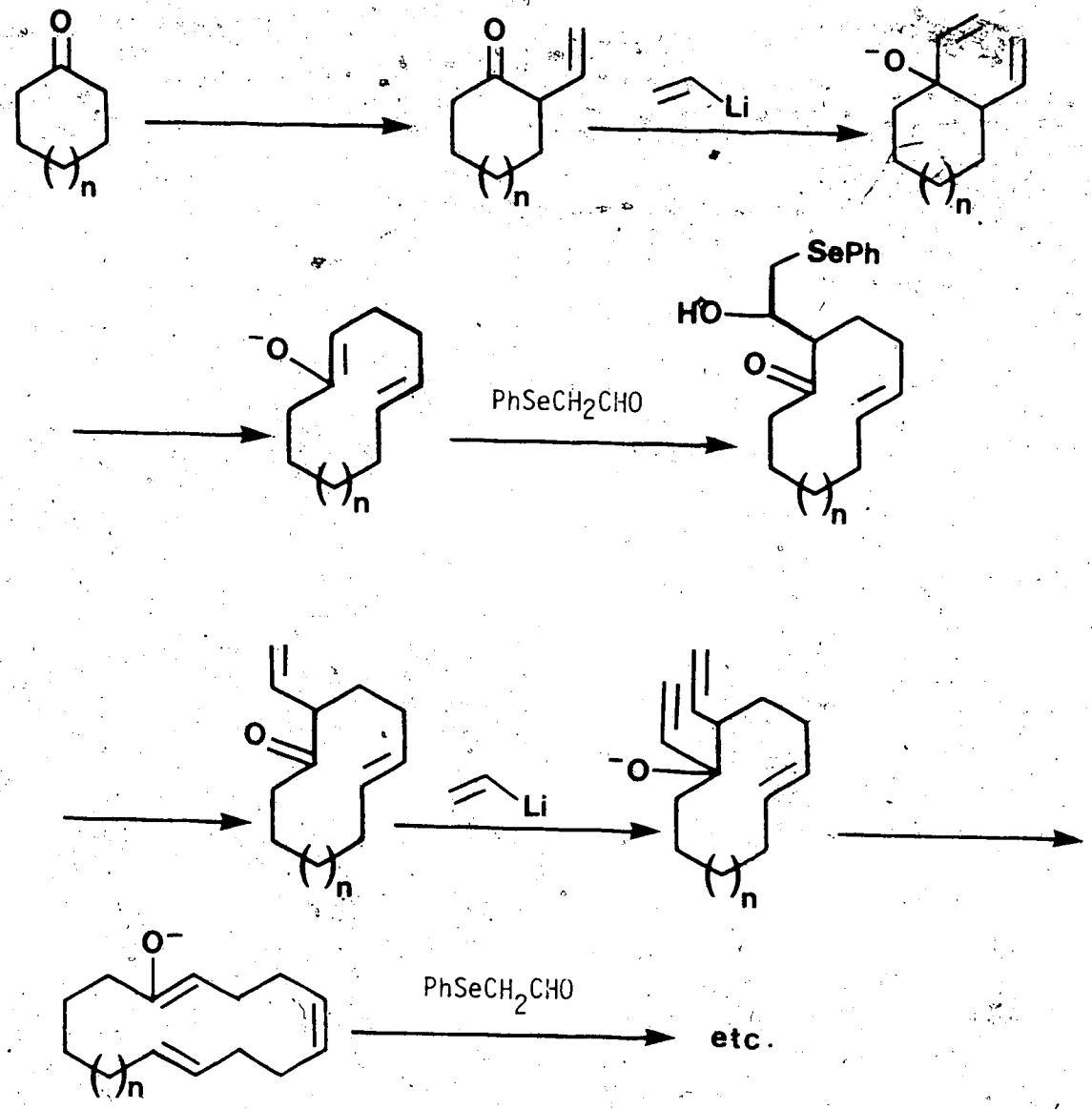


We recognized that the anionic oxy-Cope rearrangement could be made into a repetitive process using (phenylseleno)acetaldehyde. The sequence would allow multiple expansion of cyclic ketones in the sense shown in Scheme 5.

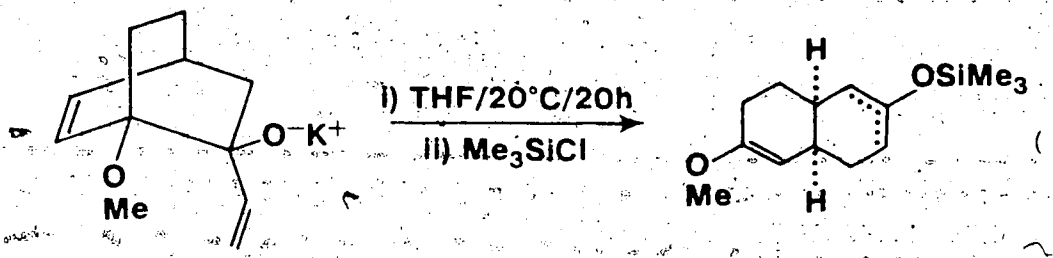
Ideally, a procedure for ring expansion of ketones in a repetitive fashion has to satisfy two criteria: Each cycle must regenerate a member of the same compound class, or a substance easily converted to it. This has to be so in order that identical methodology can be applied again. The second requirement is that the regiochemical bias of the starting material must be preserved during the homologation.

In general, the simple route depicted in Scheme 5, is not expected to satisfy the second requirement because it is known that the anionic oxy-Cope rearrangement can proceed with loss of regiochemical integrity: For example, the rearrangement shown in eq. 38 does not give a single enolate.[74] The reasons for scrambling of the enolate regiochemistry, and the generality of the phenomenon are not known. Potassium enolates do not attack THF,[75] at least at room temperature. A very small amount of attack, however, would provide ketonic material that

Scheme 5



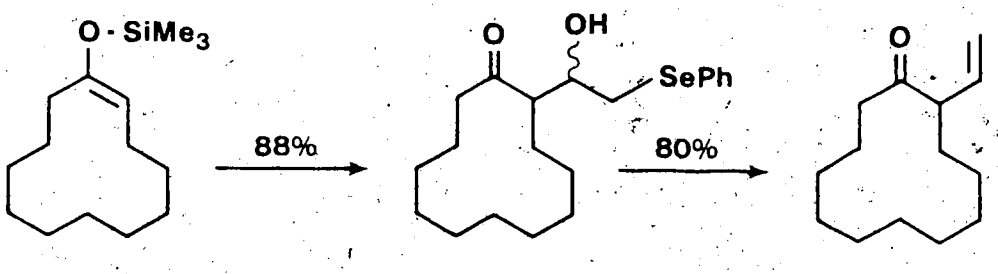
could mediate proton-transfer and lead to both enolates as



(38)

shown in eq. 38. We modified Scheme 5 to bypass this regiochemical problem and our procedure is discussed below.

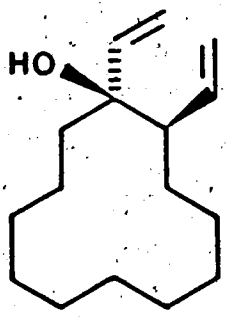
The silyl enol ethers of cyclododecanone were converted in 88% yield into the diastereomeric hydroxyselenides **12** by using our published[69] procedure as follows:



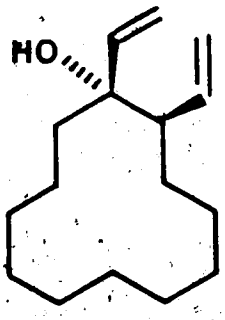
(39)

11 **12** **13**

The silyl enol ethers were treated with methyllithium and then ethereal zinc chloride[76] and (phenylseleno)-acetaldehyde were added. The stereochemistry at the hydroxyl-bearing carbon in the product, **12**, is not relevant to the overall transformation because that centre is eventually converted to sp^2-hybridization. The mixture of alcohols **12** was treated with methanesulfonyl chloride and triethylamine to generate the desired double bond (eq. 39; **12**→**13**). When compound **13** was added to vinyllithium in THF at low temperature, the two alcohols **14** and **15** were formed in more than 90% yield in a ratio of ca. 2.3:1. Although **13** has a hydrogen that is both α to a carbonyl group and allylic, we did not encounter problems due to enolization by the (basic) reagent. In contrast, vinylmagnesium bromide caused extensive enolization. For



14

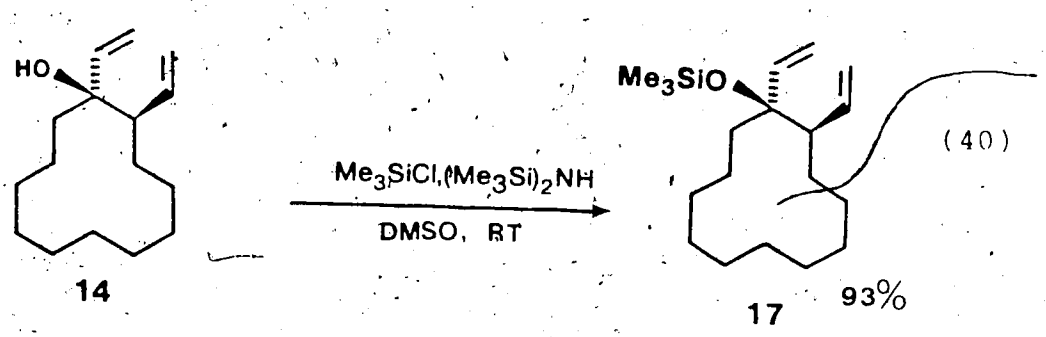


15

exploratory purposes the alcohols **14** and **15** were separated

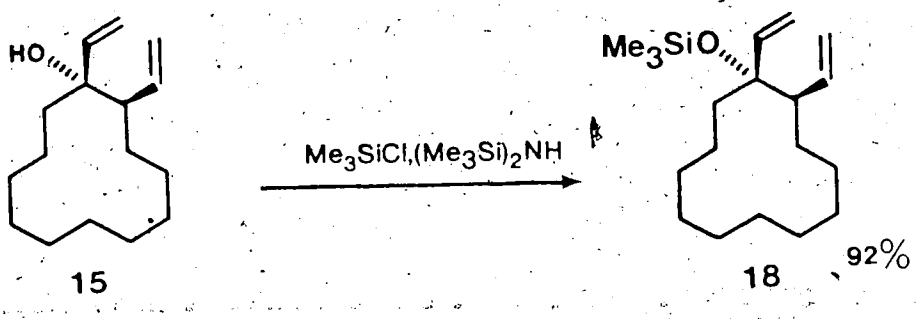
When we worked through the sequence with a methyl group present as a label (see 16), ring expansion by the anionic oxy-Cope method[71] and condensation with (phenylseleno)acetaldehyde gave a small amount of material (see Scheme 6) that had obviously come from the undesired regioisomer of the enolate. It should be stated, however, that we did not reinvestigate the reaction in order to see if refinement of experimental technique could remove the problem. Instead we sought an alternative procedure.

Each of the tertiary alcohols **14** and **15** was silylated in DMSO by using a mixture of chlorotrimethylsilane and hexamethyldisilazane.[77] The corresponding silyl ethers **17** and **18** were obtained in excellent yields (93% and 91%, respectively) (eqs. 40, 41).



14 **17** 93%

(40)

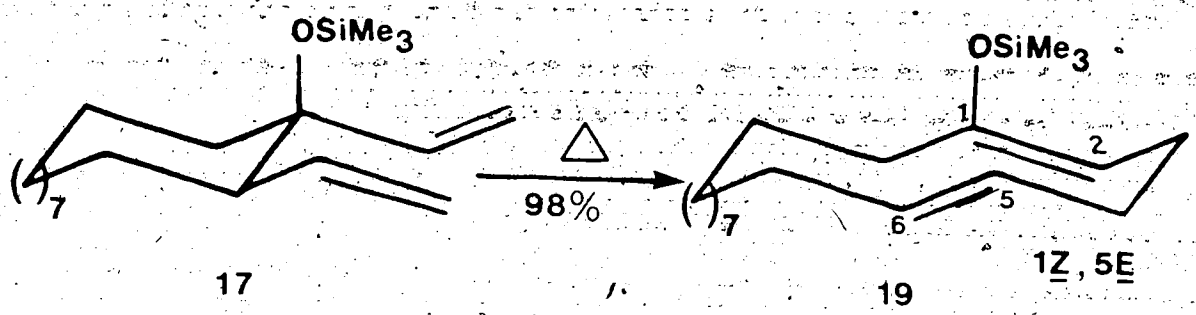


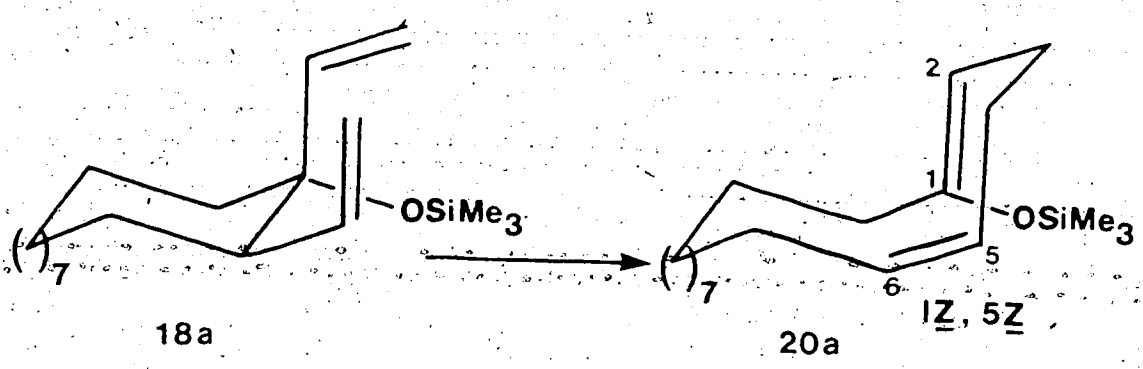
15 18 92% (41)

Each silyl ether underwent siloxy-Cope rearrangement[52,78] upon heating (200°C) under nitrogen in a sealed ampoule for 15 minutes (see Scheme 7) to generate a 16-membered ring in the form of a silyl enol ether. This is exactly the compound class we started with. Also, we know the origin of all the carbon atoms in the large ring. The trans-divinyl ether **17** gave product **19** (see Scheme 7) in 98% yield. The material was a single isomer on the basis of its high field ^{1}H and ^{13}C NMR spectra. Such a result is understandable in terms of a chair transition state for the rearrangement **17→19**. Moreover, silyl enol ether **19**, on treatment with tetrabutylammonium fluoride in THF gave (83%) (5E)-cyclohexadecen-1-one **21**[79] (eq. 42), identified by its IR spectrum (970 cm^{-1} for (E)-geometry).

On the other hand, the cis-divinyl compound **18** gave, on thermolysis, a mixture of two products in 94% yield.

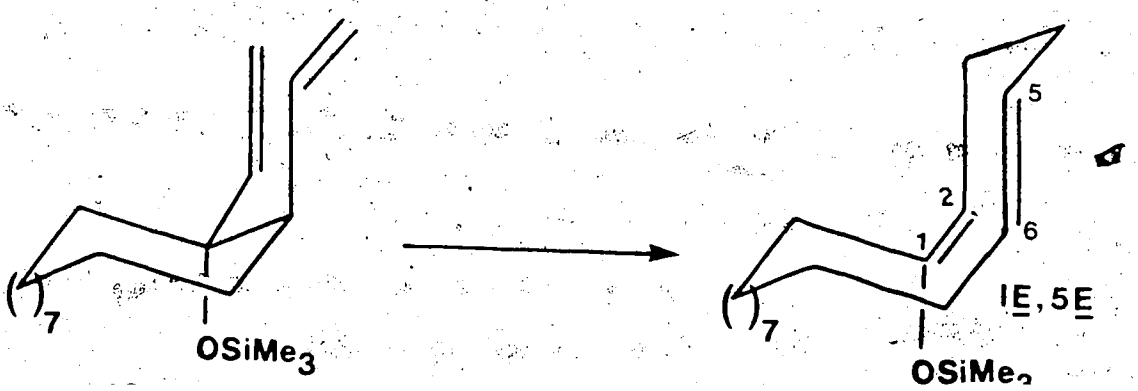
Scheme 7

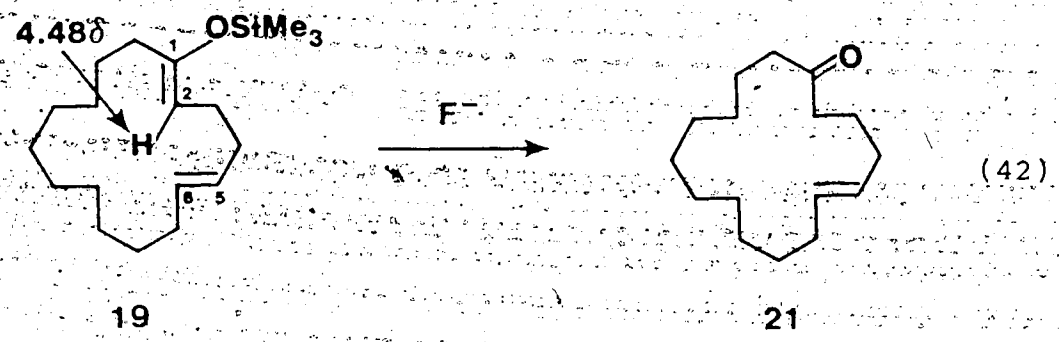

OSiMe3
7
98%
17
OSiMe3
1
2
5
6
7
19
1Z, 5E


OSiMe3
7
18a
2
1
OSiMe3
5
6
7
20a
1Z, 5Z


b

94%


OSiMe3
7
5
2
1
6
1E, 5E
7
OSiMe2



(42)

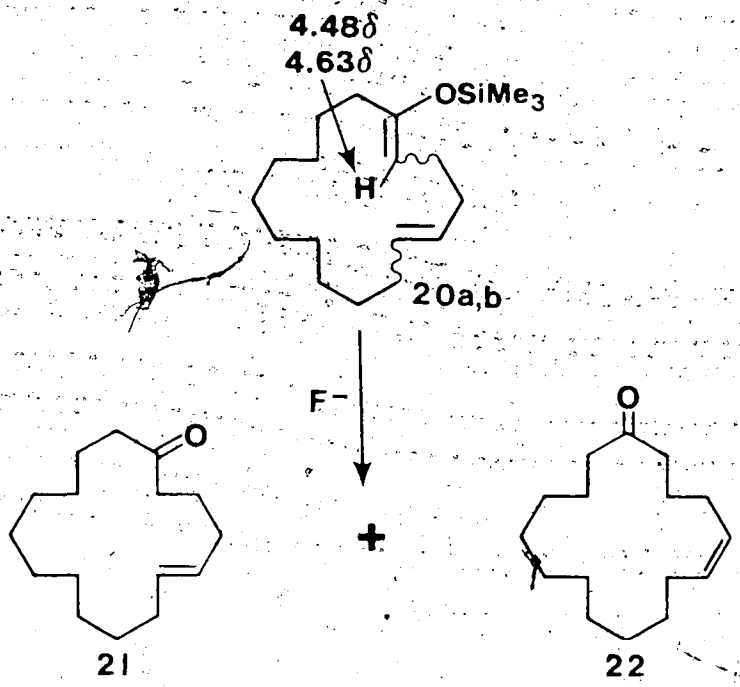
19 21

In this case there are, in principle, two chair transition states (see **18a** and **18b**) available for the concerted [3,3] rearrangement and we actually obtained a 1:1 mixture of silyl enol ethers **20a** and **20b** (see Scheme 7).* The action of fluoride ion in THF converted the mixture of **20a** and **20b** into a separable mixture of (5E)-cyclohexadecen-1-one **21**[79] (40% yield) and (5Z)-cyclohexadecen-1-one **22**[79] (48% yield) (eq. 43). Again the structures were assigned by the respective IR spectra (970 cm^{-1} for (E)-geometry, and 720 cm^{-1} for (Z)-geometry).

The next step in the ring expansion procedure called for regiospecific generation[81] of the enolates from **19**,

---

*Our data do not give direct evidence for the geometry of the trisubstituted double bond in **19**, **20a**, or **20b**. Pascual's rules[80] suggest δ4.63 for the (E)-isomer and δ4.38 for the (Z)-isomer. The observed values are δ4.63 for the (E)-isomer and δ4.48 for the (Z)-isomer.



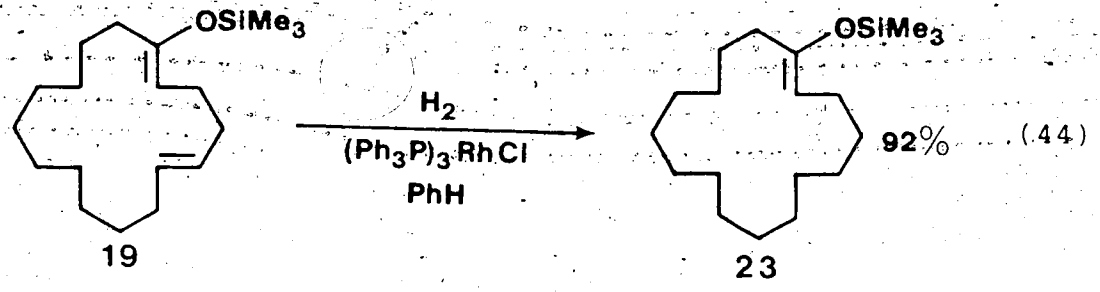
(43)

20a, and 20b. This would be followed by condensation with (phenylseleno)acetaldehyde.

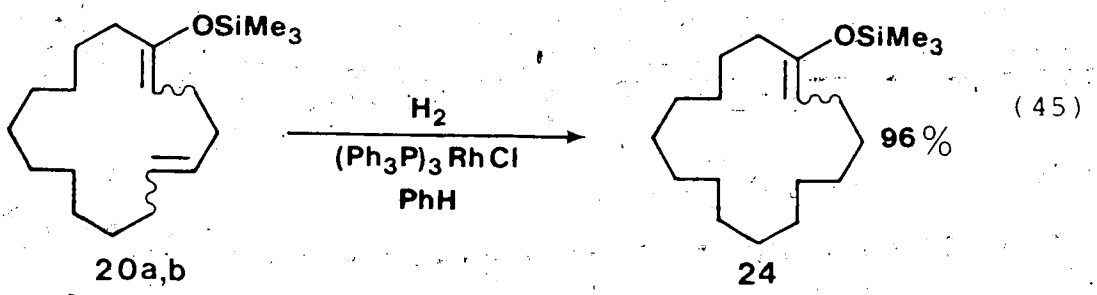
Reaction of silyl enol ether 19 with methyllithium was too sluggish to be useful and so we sought to mediate the aldol reaction with titanium(IV)chloride.[82]* However the second double bond in 19 appeared to interfere in the reaction as the aldol product contained chlorine. Clearly, the double bond had to be removed and we tried hydrogenation using Wilkinson's catalyst. The reaction appeared to proceed well and it afforded a silyl enol

*This reaction was done by Dr. S. Suri.

ether 23 in 92% yield. Likewise, the mixture of silyl enol ethers 20a and 20b gave the hydrogenated product 24 as a mixture of isomers (96%) (eqs. 44 and 45).



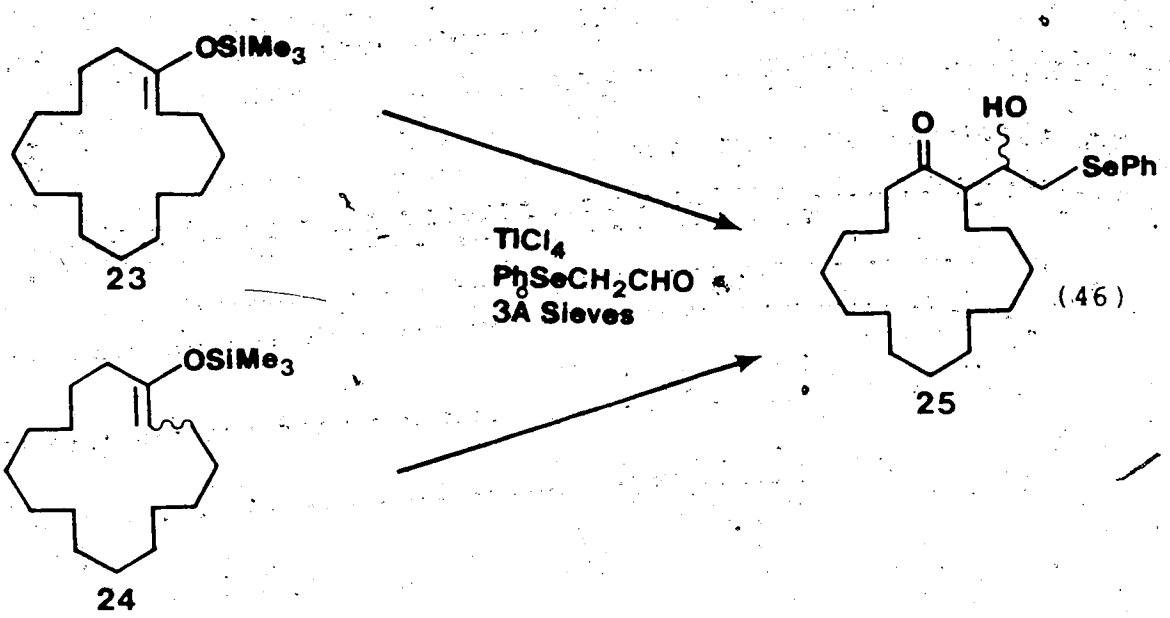
(44)



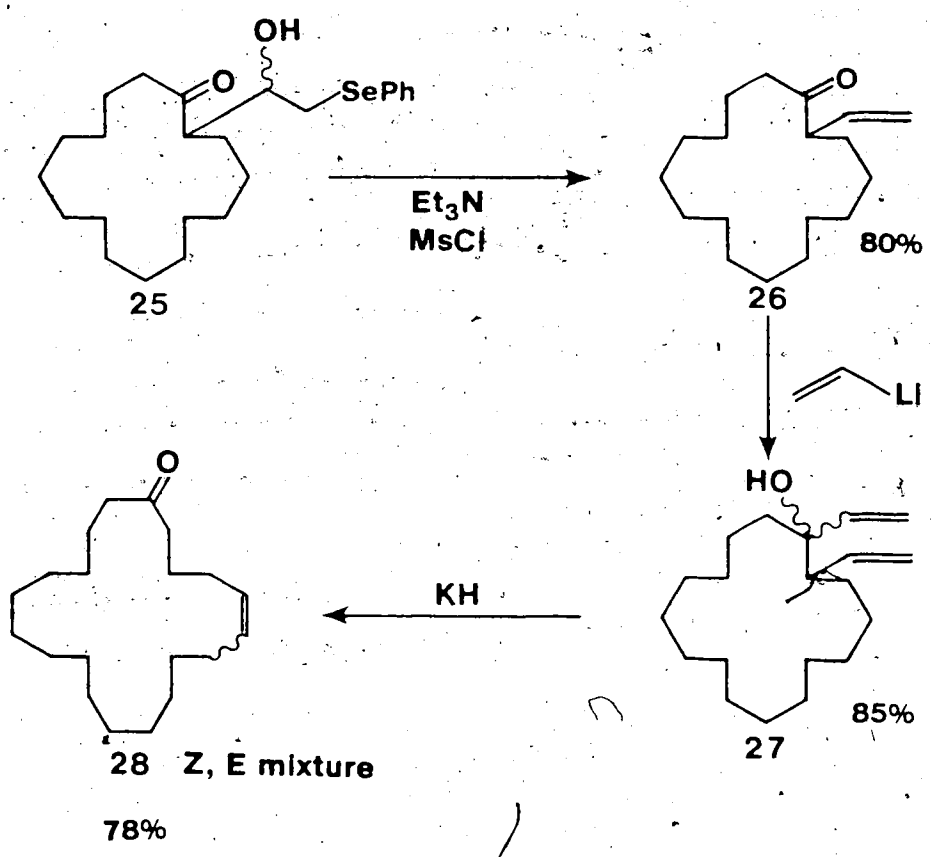
(45)

Compound 23 underwent aldol condensation in 80% yield (23→25) when treated with (phenylseleno)acetaldehyde, titanium tetrachloride,[81] and 3Å molecular sieves. The

mixture **24**, without separation, was also condensed with (phenylseleno)acetaldehyde to give the aldol **25** in 75% yield (eq. 46).



With the hydroxyselenides **25** in hand the next steps were straightforward. Treatment with triethylamine and methanesulfonyl chloride generated the α-vinyl ketone **26** in 80% yield and reaction with vinyllithium proceeded smoothly to afford the divinyl alcohols **27** (85%) as a mixture of isomers. At this stage the sequence overlaps with an earlier cycle and so we terminated the whole process by treating the alcohols with potassium hydride in warm tetrahydrofuran to obtain, after workup, 5-cyclo-eicosen-1-one **28** (78%) as a (5Z,5E)-mixture (eq. 47)

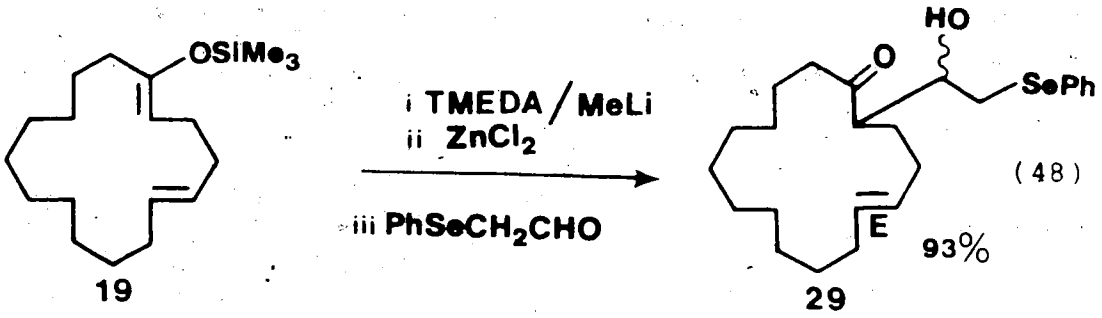


(47)

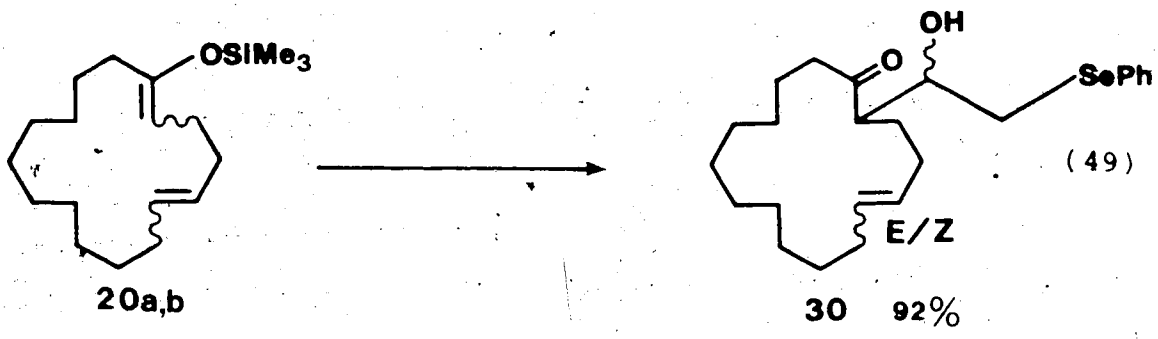
At this point the high field ^{1}H NMR spectrum of the hydrogenation product **23** became available. Close examination revealed that there may have been a small amount of regiochemical scrambling of the silyl enol ether. That is, the starting material **19** was a single isomer (^{1}H and ^{13}C) and had clean (Z)-geometry (δ4.48) at the trisubstituted double bond, but, after hydrogenation 3 — 5% of the product had (E)-geometry (δ4.63) for the C(1) — C(2) double bond. On mechanistic grounds it is

likely that the double bond stays in its original position but we do not have any experimental proof of this.

In our earlier experiments we could not generate an enolate from silyl enol ethers of type **19** and **20a,b** using methyllithium. Subsequently, we found that it is indeed possible to make an enolate from large ring silyl enol ethers if one uses methyllithium in the presence of a full equivalent of tetramethylethylenediamine (TMEDA). Thus, the silyl enol ethers **19** and the mixture **20a,b** were individually treated with methyllithium in ether in the presence of TMEDA, and the resulting enolates were converted into the corresponding zinc enolates.[76] They were then condensed with (phenylseleno)acetaldehyde. These operations produced the hydroxyselenides **29** and **30** in excellent yields (eqs. 48, 49).



(48)



20a,b

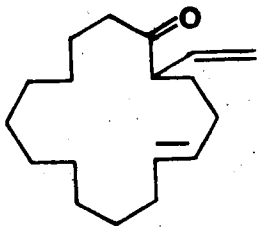
30 92%

(49)

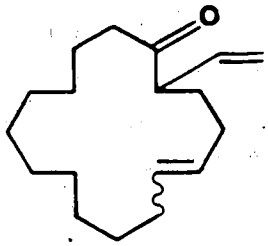
Both **29** and **30** were individually subjected to the early stages of the sequence: Treatment with triethylamine and methanesulfonyl chloride gave the corresponding 2-vinylcycloakenones **31** (82% yield from **29**) and **32** (85% yield from **30**). ^{13}C NMR measurements showed, as expected, that **31** was a single compound, but that **32** was a mixture of two isomers.

The action of vinyllithium in THF at -78°C produced the divinyl alcohols **33** (89% yield from **31**) as a cis/trans pair, each having (5E)-geometry. Sample **32** gave in slightly lower yield (85%) the divinyl alcohols **34**.

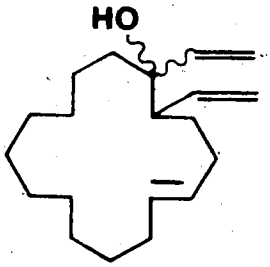
With the formation of **33** and **34**, the sequence had been brought to a stage where, except for the presence of endocyclic unsaturation, it overlaps with the first cycle. Silylation of **33** by our usual method gave the corresponding trimethylsilyl ether **35** (95% yield from **33**)



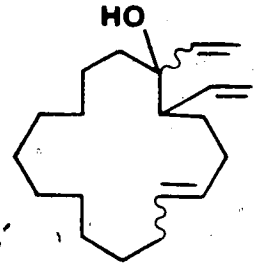
31



32*



33



34

and thermolysis (200°C, 15 minutes) produced the 20-membered ring system **36** in 92% yield (eq. 50). The product **37** is a mixture of isomers, but each component must have (9E)-geometry. The corresponding stages with **34** (i.e. **34**→**38***→**39**) were effected in yields of 92% and 95% respectively (eq. 51).

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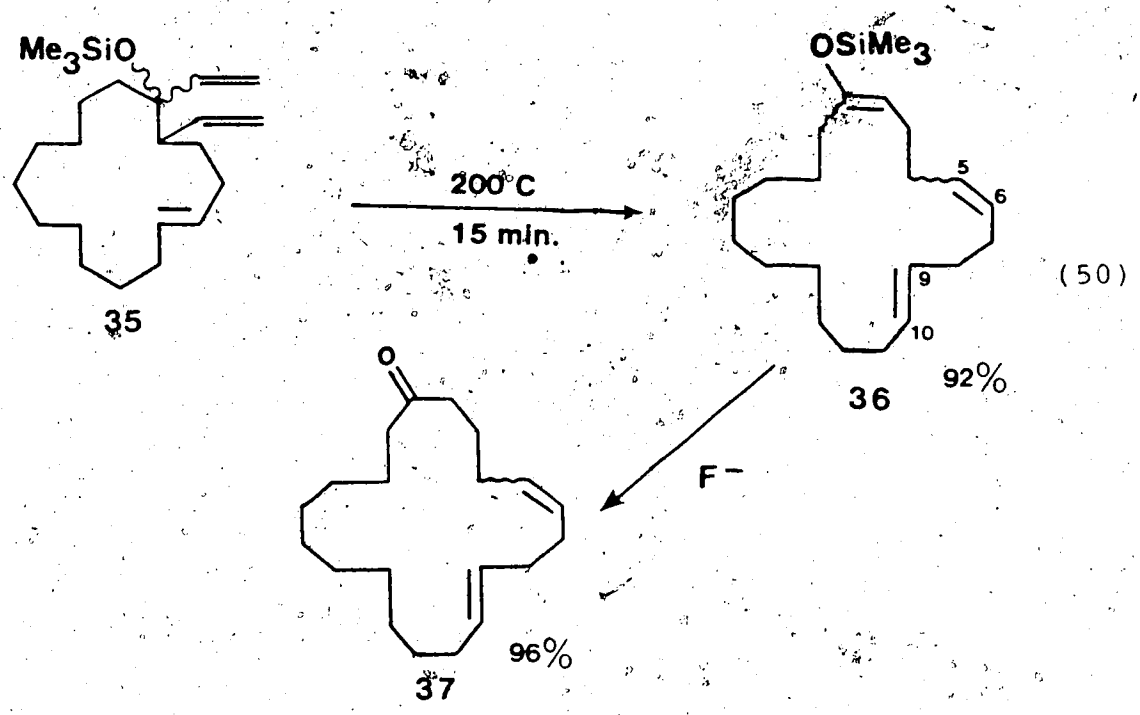
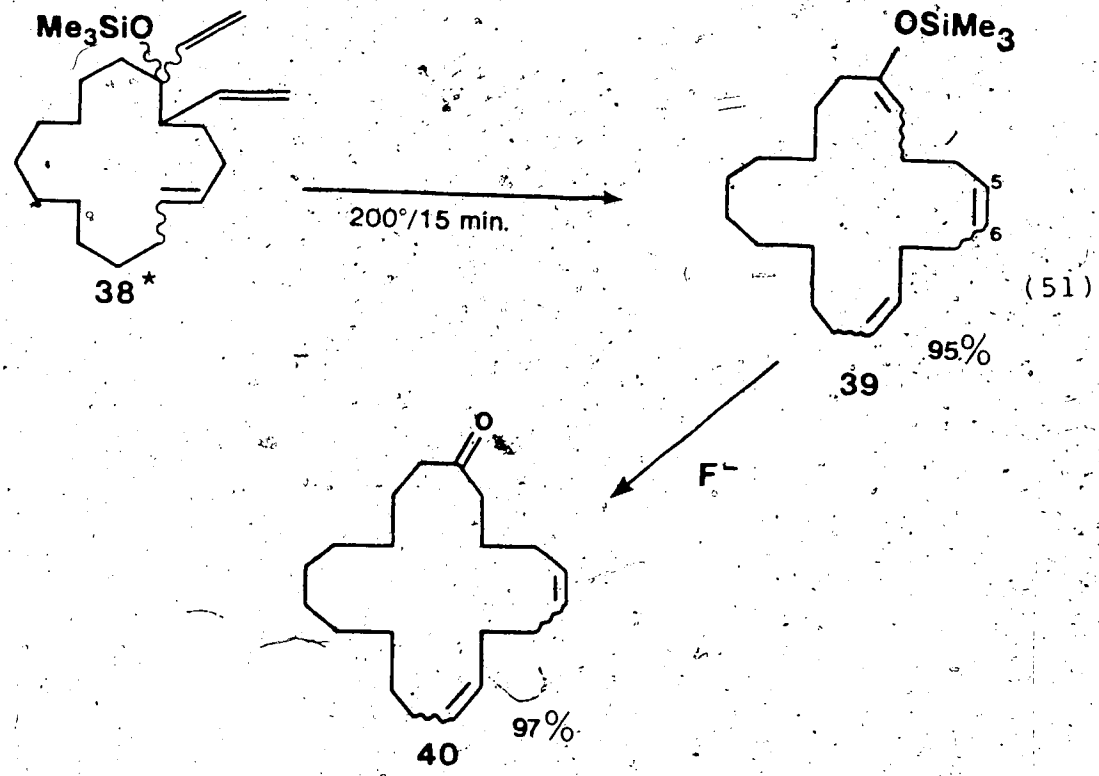
*Compound **32** is a mixture of (5E)- and (5Z)-isomers.



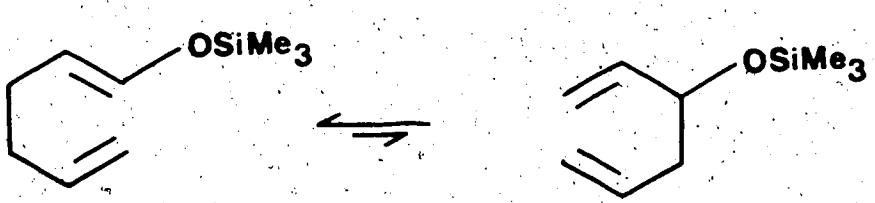
(50)



(51)

*This compound is a mixture of (5E)- and (5Z)-isomers.

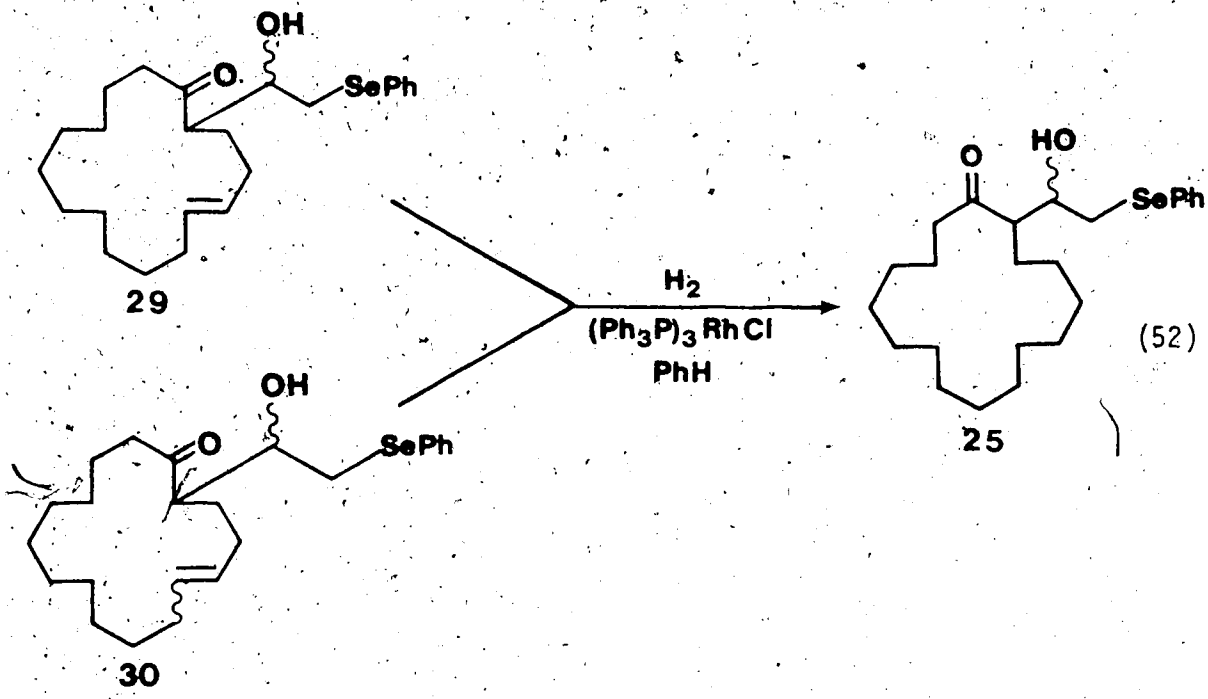
In principle, systems of the type **36** and **39** can undergo ring contraction by a [3,3] rearrangement involving the 5,9-diene system. [The 1,5-diene system would not be expected to rearrange because, at least for open-chain systems (**41a**)⇌(**41b**) the equilibrium lies on the



41a **41b**

side of **41a** to the extent of 99%.[83]] We did not detect any evidence for ring contraction involving the 5,9-diene unit: the high field ^{1}H and ^{13}C NMR spectra of the ring expanded products **36** and **39** showed no evidence for vinyl groups. However, we could not separate the isomers of **36** and **39** for individual characterization. For this reason, and in order to accommodate situations where ring contraction might occur, we developed a variation of the ring expansion process. The hydroxyselenides **29** and **30** were individually hydrogenated — both in 80% yield — in

benzene at room temperature using Wilkinson's catalyst (eq. 52). Hydrogenation over palladium on carbon gave mostly starting material and, in fact, hydrogenation of sulfur and selenium compounds is unusual: Sulfur is normally regarded as a catalyst poison and hydrogenation



(52)

of selenides appears to be unprecedented. The discovery of a satisfactory hydrogenation system may extend the utility[84] of organoselenium chemistry.

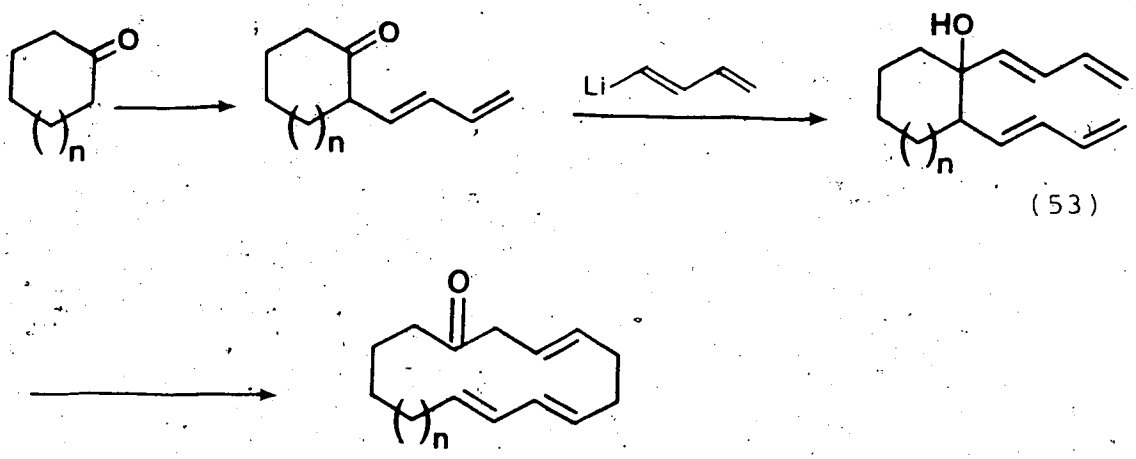
The hydrogenation product **25** was identical (^1H NMR, 400 MHz) with the sample obtained via the titanium tetrachloride induced aldol condensation, thus generating a compound that had already (see eq. 47) been converted

into 5-cycloeicosen-1-one **28**.

In summary, we had developed a repetitive four-carbon expansion which we had carried out over two cycles. The overall yield of 5-cycloeicosen-1-one **28** is 30% from the silyl enol ethers of cyclododecanone and the overall yield of silyl enol ethers **36** and **39** is 35%. In the next section we report an alternative approach to very large ring systems.

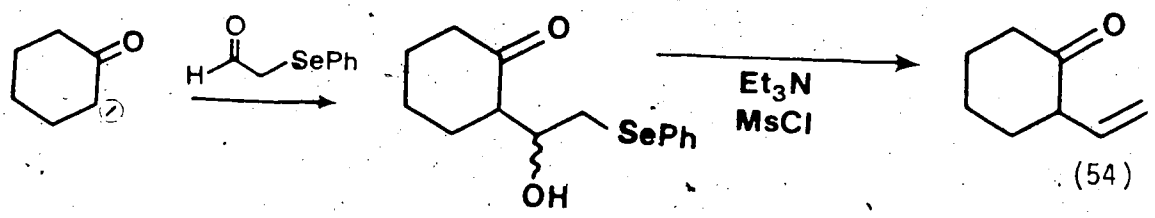
MACROEXPANSION

As stated above, we now sought to develop an easy route to α-butadienyl ketones in the expectation that the method would facilitate access to large ring compounds by the macroexpansion process summarized in eq. 53:

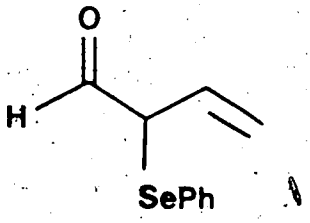


(53)

Because of our experience[69] with (phenylseleno)-acetaldehyde (see eq. 54), it was natural to regard the corresponding vinyl homologue **42** as a synthetic equivalent to the butadienyl carbonium ion. If we could prepare **42**, then aldol condensation followed by removal of the elements of the benzeneseleno-group and hydroxyl, using the method that had worked well with (phenylseleno)-acetaldehyde itself, would serve to generate an α-butadienyl ketone (eq. 55).

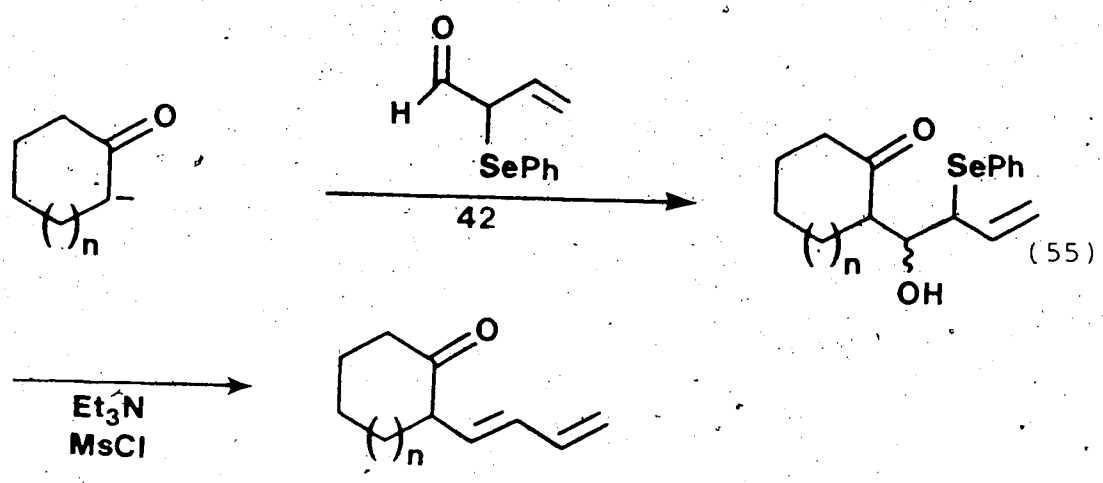


(54)

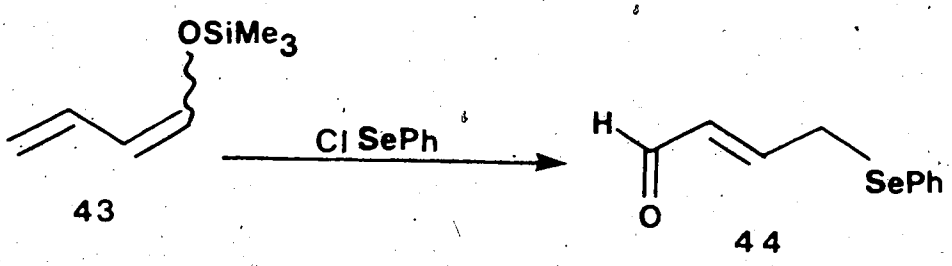


42

However, we were not able to make compound **42**. Our initial attempt involved treating the known[85] silyl enol ether **43**, derived from crotonaldehyde, with benzeneselenenyl chloride. The product isolated **44** (91%) carried the benzeneseleno-group at C(4). This result exactly parallels that reported[86] for the corresponding reaction with benzenesulfenyl chloride. It should be noted that the usual reaction[87] between extended enolates (at least those derived from ketones) and electrophiles is reaction at the α-position, to give the thermodynamically



(55)



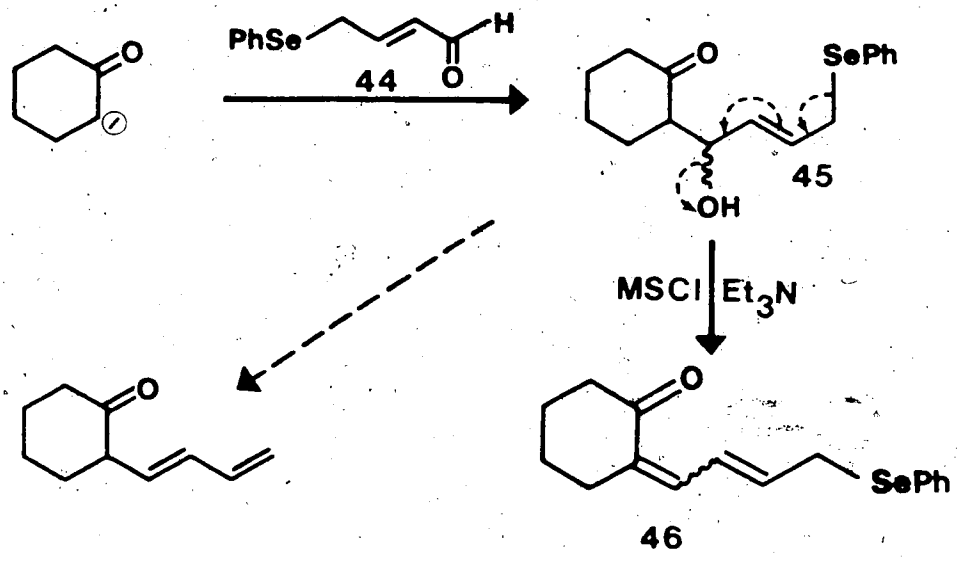
(56)

less stable (i.e. non-conjugated) product.

We did not pursue the question as to whether **44** is the initial product or the result of α-selenation followed by rapid 1,3-migration.[88]

The structure, as well as the stereochemistry of **44** was obvious from its simple ^1H NMR (200 MHz) spectrum [$^3J_{HC=CH}$ = 16 Hz] and, although the compound did not have the desired structure, it could, in principle, still serve

our requirements: Aldol condensation with cyclohexanone proceeded efficiently (82%) in the desired manner (eq. 57) and we expected that we would be able to remove the



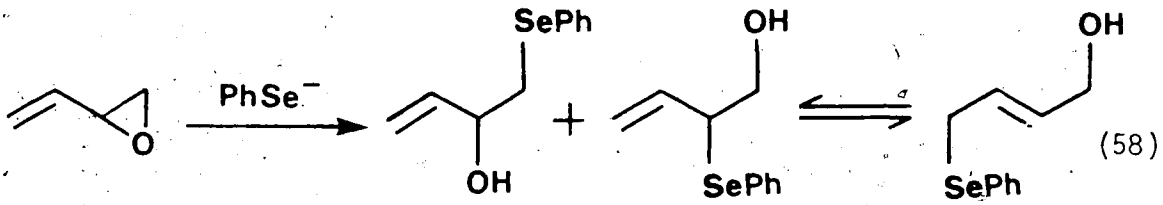
(57)

phenylseleno- and hydroxyl-groups [see **45**, arrows] by treatment of the aldol with methanesulfonyl chloride and triethylamine. When the experiment was performed, under the standard conditions,[69] an unstable ketone carrying a benzeneseleno-group (NMR) and having a conjugated carbonyl (IR, 1690 cm^{-1}) was formed. Presumably the material is one, or both, of the geometrical isomers shown in **46**.

Evidently the vinylogous removal of phenylseleno- and hydroxyl-groups (see **45**) is not a viable process and so we examined an alternative route to aldehyde **42**.

Treatment of epoxide **47**[89] with phenylselenide anion,

which we generated in the normal way[90] from diphenyldiselenide and sodium borohydride, gave the two alcohols

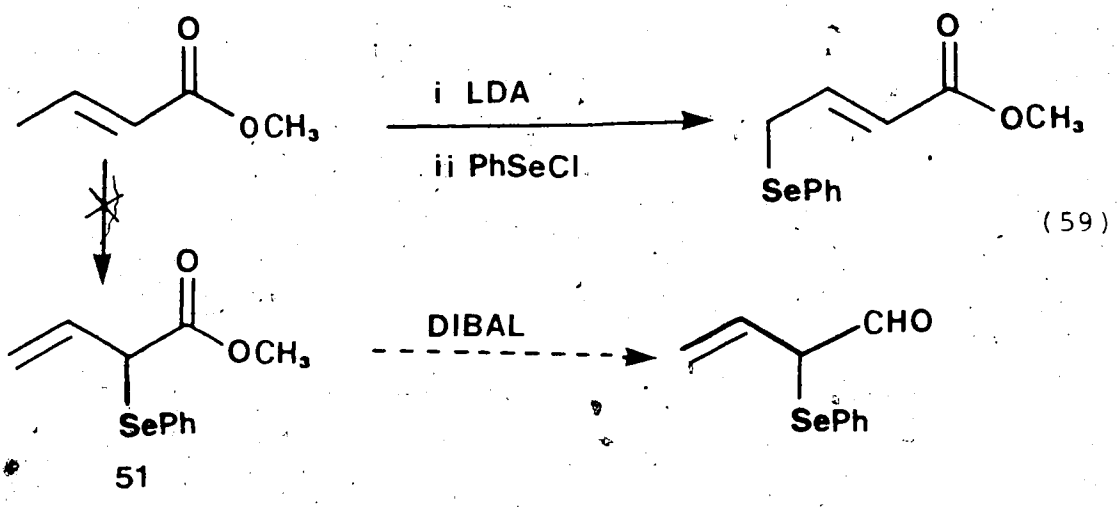


47 48 49 50

48 and 49. These were separated by flash chromatography and characterized on the basis of ^{1}H NMR, IR, and mass measurements. The desired isomer, 49 was not thermally stable; it would be expected[88] to isomerize to 50 but we did not establish this point because attempts to oxidize the compound using methodology known to be compatible with the presence of selenium [Swern oxidation;[91] triphenylbismuth carbonate;[92] N-chlorosuccinimide, dimethylsulfide, triethylamine[93]] were all unsuccessful. Each experiment produced mainly diphenyldiselenide.

Our final attempt to prepare phenylseleno-aldehyde 42 involved generation of the lithium enolate of methyl crotonate. Treatment with benzeneselenenyl chloride, once again gave (37% yield) the product of substitution at the

terminal position (eq. 59) as judged from the ^1H NMR spectrum; if the isomeric product **51** had formed we would have subjected it to DIBAL reduction.



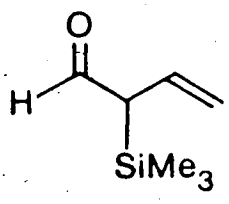
(59)

51

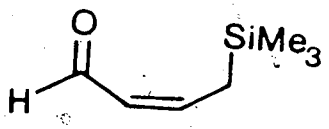
Our efforts to generate a synthetic equivalent for the butadienyl carbonium ion, using selenium chemistry, did not seem very promising and so we turned our attention to corresponding ideas based on the properties of silicon.

We felt that if we could prepare aldehyde **52** or **53** then we would be able to make α-butadienyl ketones by a route involving aldol condensation, because the aldols (**54** and **56**) would be correctly constituted to undergo a classical Peterson reaction[94] (**54**→**55**) or, in the case of **56**, a vinylogous counterpart of the Peterson olefination. We could find no example in the literature of a vinylogous Peterson reaction but, on mechanistic grounds (eq. 62 and eq. 63), the transformation should

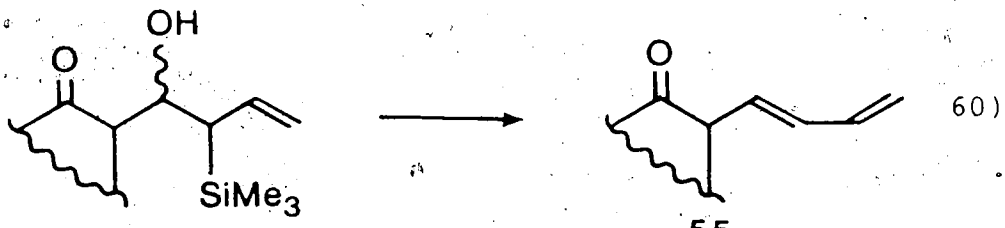
proceed.



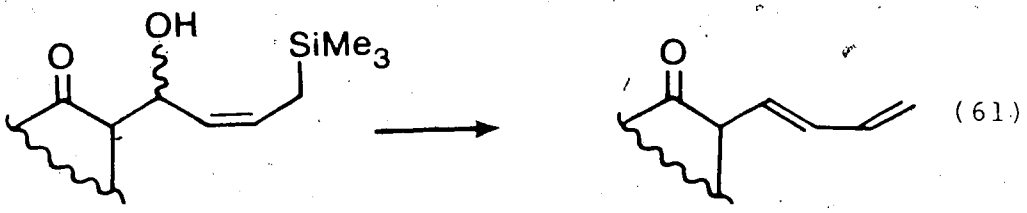
52



53



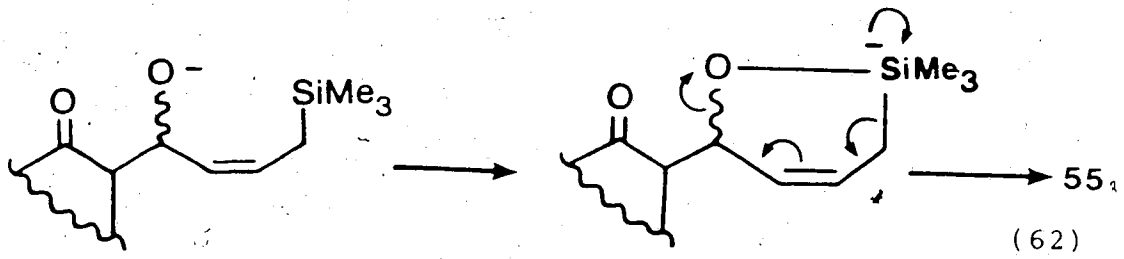
54 55 (60)



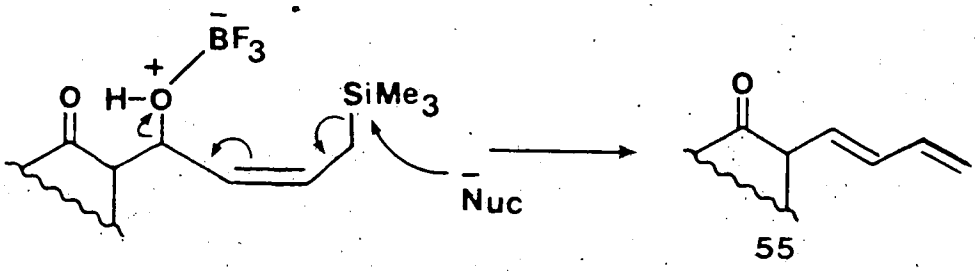
56 55 (61)

The synthesis of either aldehyde 52 or 53 is likely to be very difficult.* The reason for this, in the case

*Neither 52 nor 53 [or its (E)-isomer] have been reported.

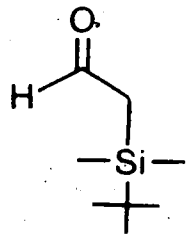


(62)



(63)

of **52**, lies in the ease of 1,3-migration of silicon from carbon to oxygen[95] and, in fact, α-silylated aldehydes are not well-known species. Compound **57** is the best



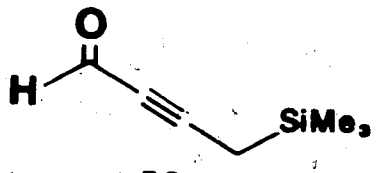
57

characterized example:[66] it has to be prepared under carefully defined conditions and it appears that the hindered silyl group does not allow good yields in the Peterson olefination. 1,3-Migration in **52** would be anticipated to be especially easy because of extended conjugation in the product which is the silyl enol ether of crotonaldehyde.

In the case of **53** an exothermic electrocyclic process (eq. 64) is easily envisioned, which results in breakage of a carbon — silicon bond (bond strength ≈ 318 kJ mol^{-1})[96] and formation of a silicon — oxygen bond (bond strength ≈ 531 kJ mol^{-1}).[96]

It occurred to us that the electrocyclic pathway (eq. 64) could be blocked by enforcing a geometrical change in the molecule. It seemed unlikely that aldehyde **58** would decompose by the electrocyclic intramolecular pathway.

53 (64)

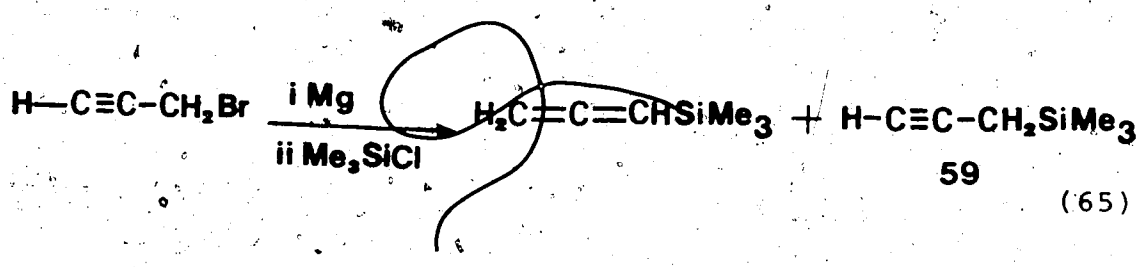


58

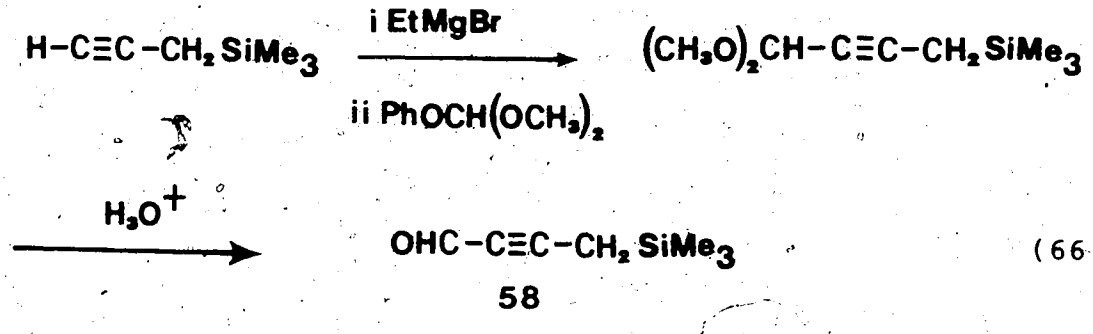
At the same time the compound is synthetically equivalent to **53** — by the process of semihydrogenation, which would be carried out at a suitable stage. We recognized that it might be necessary to protect **58** against intermolecular pathways — perhaps by storing it in dilute solution — but we decided to attempt preparation of the substance.

Propargyl bromide was converted into the silane **59** (80% yield) following the literature procedure[97] and was isolated as a 92% pure (v.p.c.) liquid by spinning band distillation. We attempted to introduce the formyl group by the sequence shown in eq. 66.[98] The first step worked in a satisfactory manner (66% yield), but attempts to hydrolyze the acetyl function led mainly to loss of the trimethylsilyl-group as judged by ^1H NMR measurements. Fortunately, a successful route to the desired aldehyde was quickly developed.

Deprotonation of silane **59** and hydroxymethylation with paraformaldehyde generated the alcohol **60** in almost

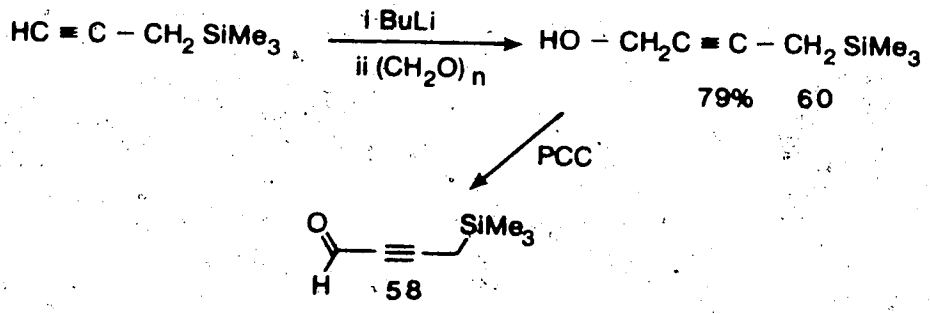


(65)



(66)

80% yield as a distillable liquid (eq. 67). The obvious



(67)

choice for oxidation of **60** is active manganese dioxide but the reagent did not work properly in this case and examination of the review literature[99] showed that manganese dioxide often gives poor (<50%) yields with propargylic alcohols. Pyridinium chlorochromate[100] was the next reagent examined. It effected the oxidation nicely and the reaction seemed clean as judged by thin layer chromatography.* Aldehyde **58** appeared to be volatile** and considerable losses were incurred during complete evaporation of the hexane used to extract it. Also, the aldehyde is sensitive and decomposes when stored overnight as a neat liquid. For these reasons we used the following technique in the preparation: The oxidation is carried out in dichloromethane and then inorganic material is precipitated by pouring the mixture into ice-cold hexane. Filtration through a pad of Celite and removal of most of the solvent gives a stock solution of the aldehyde*** which was stored at 0°C over 3Å molecular

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* Admittedly, an undetermined amount of "decomposition products" may remain at the origin of the TLC plate.

** E.g. We monitored weight loss under water pump vacuum.

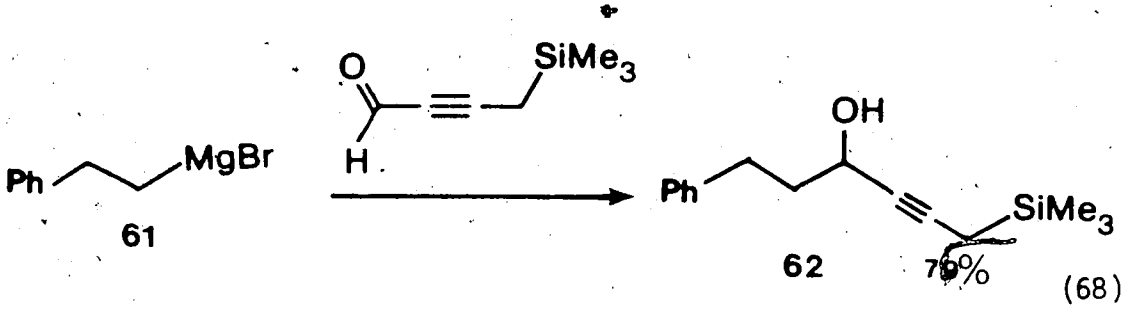
*** We always used an aliquot of the stock solution that would correspond to a 3-fold excess (on the basis of 100% yield in the oxidation).

sieves.

The aldehyde was too unstable for combustion analysis; its structure rests on the mass, infrared, and ^1H NMR spectra, the latter being very simple and characteristic [(200 MHz, $CDCl_3$) δ0.05 (s, 9H), 1.65 (d, J = 2.0 Hz, 2H), 9.04 (t, J = 2.0 Hz, 1H); IR (neat) 2200, 1665, 1250, 850 cm^{-1}].

With the aldehyde in hand we tested its suitability as a synthetic equivalent of the butadienyl carbonium ion by examining, first of all, its reaction with Grignard reagents.

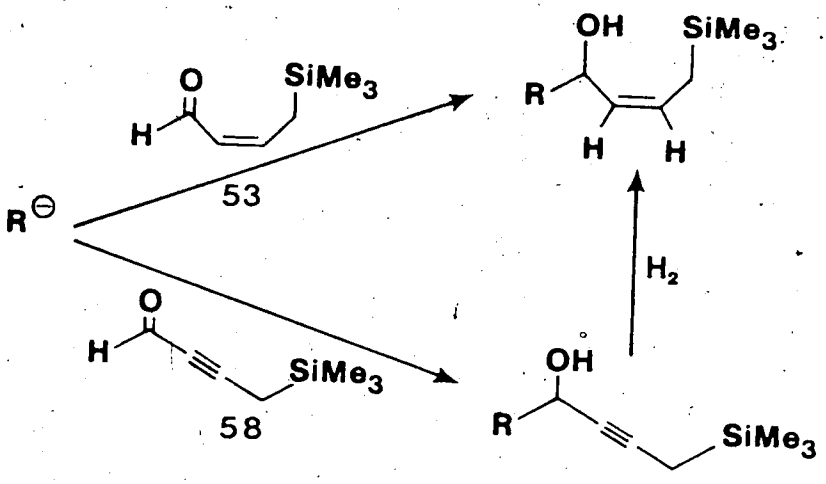
Treatment with 2-phenylethylmagnesium chloride (**61**) proceeded in the expected way (**61**→**62**) (eq. 68). The next step involved semihydrogenation of the triple bond.



(68)

As shown in Scheme 8, by performing a semihydrogenation, the overall result is exactly what one would obtain if the olefinic aldehyde **53** itself had been used in the first

instance. The hydrogenation proceeded efficiently using the classical Lindlar catalyst[101] and, when the resulting



Scheme 8

alcohols **63*** were treated with potassium hydride at room temperature the hexadienylbenzene **64** was produced in 74% yield (eq. 69).

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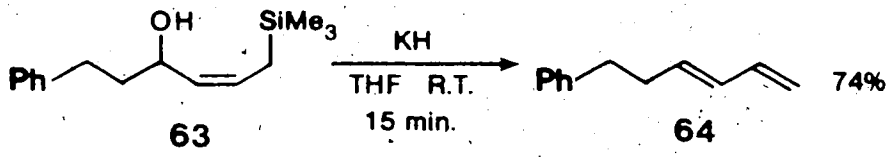
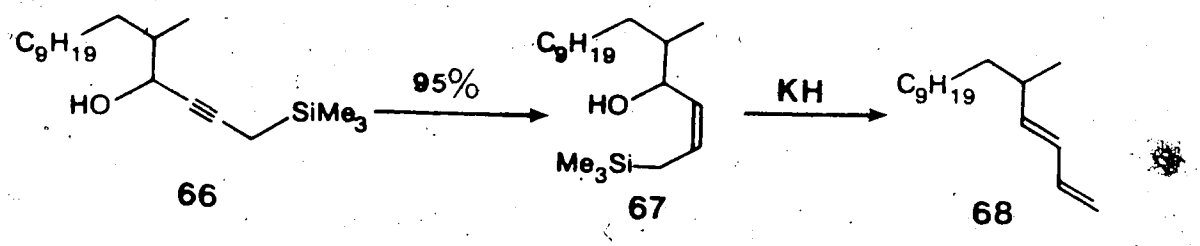
*Appropriate decoupling experiments gave $^{3}J_{HC=CH}$ = 10 Hz; hence the geometry is (Z), as expected.

In a similar fashion, 1-methylundecylmagnesium bromide (**65**) was converted (60%) into the acetylenic



63 **64** (69)

alcohol **66** and this, too, was transformed in very high yield into the (Z)-olefin **67**. The latter gave terminal diene **68** (84%) when exposed to the action of potassium hydride at room temperature. Each olefin, **64** and **68** was a pure compound. In such cases, thin layer chromatography is not a reliable measure of isomeric purity; however, the

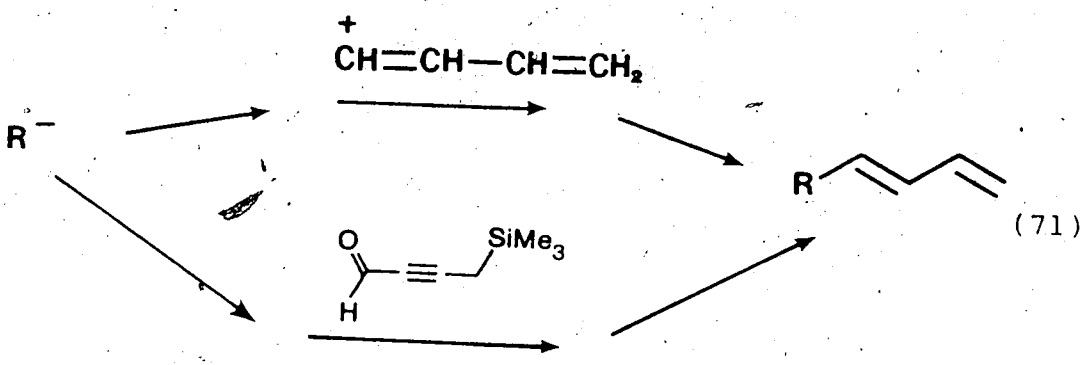


66 **67** **68** (70)

^{13}C NMR spectra (100.6 MHz) were of good quality and showed the presence of only one substance. The internal double bond of both olefins was assigned (E)-geometry on the basis of the values 14.9 and 16.1 Hz for $^{3}J_{HC=CH}$.

The above experiments established that our acetylenic aldehyde 58 did indeed function as an equivalent for the butadienyl carbonium ion (eq. 71) and we were ready to use the sequence for macroexpansion.

First of all we carried out an aldol condensation between the enolate of cyclohexanone and our acetylenic aldehyde. We followed a general procedure that has frequently been used in this laboratory:[69] the enolate was generated in ether from the silyl enol ether by the



(71)

action of methyllithium in the presence of tetramethylethylenediamine* and the resulting lithium enolate was arbitrarily converted into a zinc enolate by addition of

*This additive is essential with some large ring silyl enol ethers: they do not react with methyllithium in its absence. The additive is not needed for a 6-membered ring but we used it to speed up the reaction.

zinc chloride in ether.[76] Finally, a solution containing an excess of the acetylenic aldehyde was added and, after a reaction period of 20 minutes at ice-bath temperature, it was possible to isolate the acetylenic aldol **70** (see Table 1) in 76% yield. The compound is a mixture of isomers, but this fact is of no consequence because one stereocentre is destroyed at a later stage.

In a similar fashion, the silyl enol ethers derived from 7-, 12-, and 13-membered cycloalkanones were converted into the corresponding acetylenic aldols (see Table 1).

The next step in the sequence required semihydrogenation of the triple bond of **70** and we used a procedure (5% Pd on barium sulfate in pyridine) that had been praised in the current literature.[102] The olefinic aldol **71** was formed in 96% yield. The geometry shown (see Table 2) follows from the observed coupling constants. The other aldols that we had made were also semihydrogenated in the same way and also in excellent yields (see Table 2).

TABLE 1

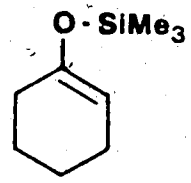
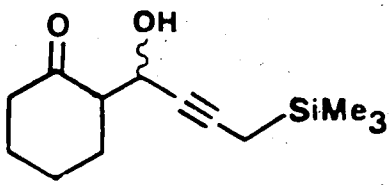
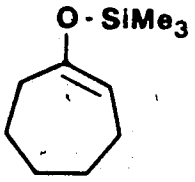
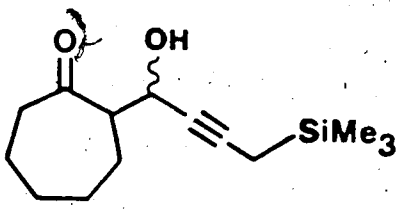
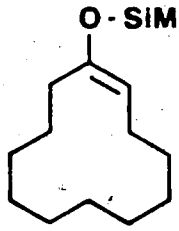
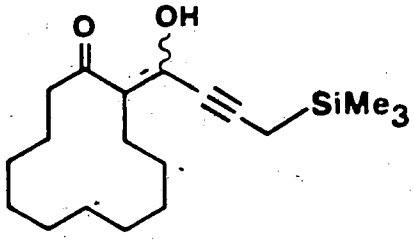
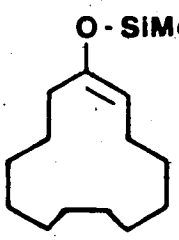
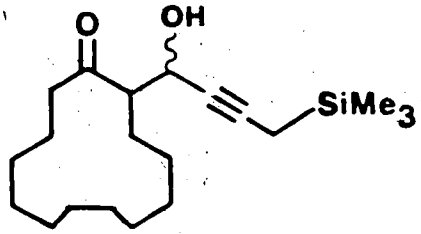
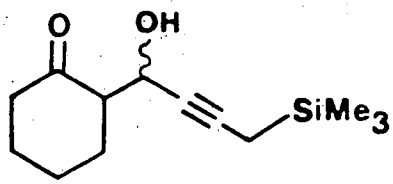
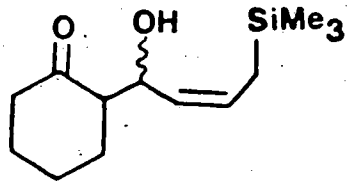
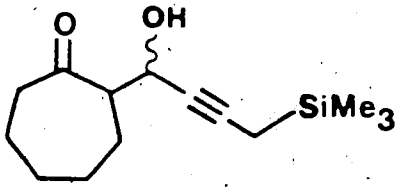
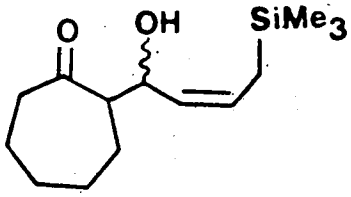
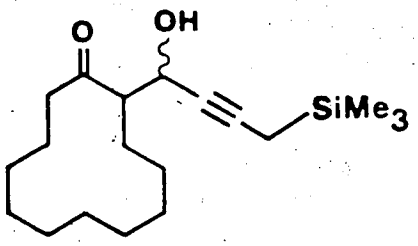
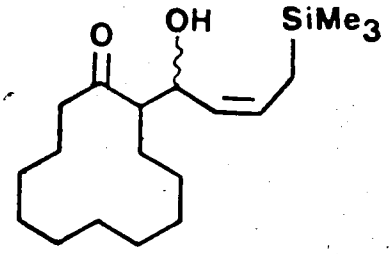
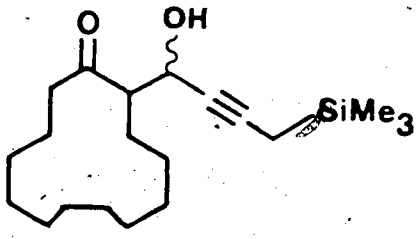
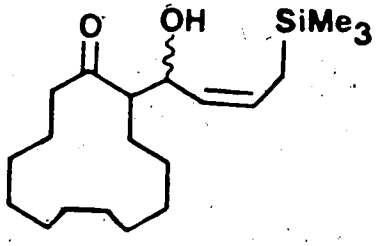
Entry	Silyl Enol Ethers	Aldol Products (%)
1	 69	 70 (76%)
2	 73	 74 (85%)
3	 77	 78 (78%)
4	 81	 82 (70%)

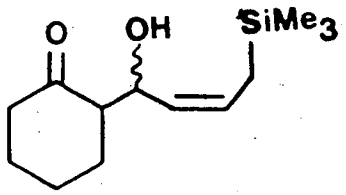
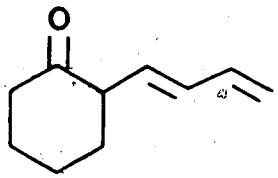
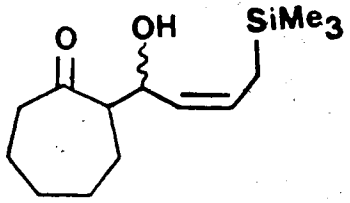
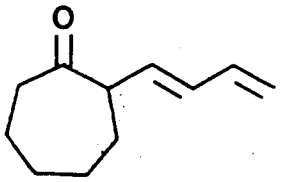
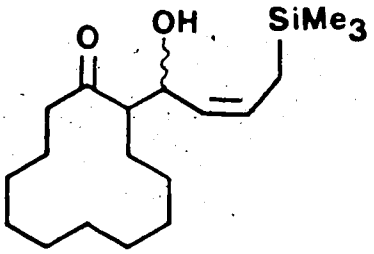
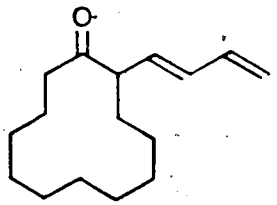
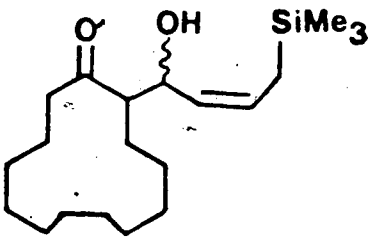
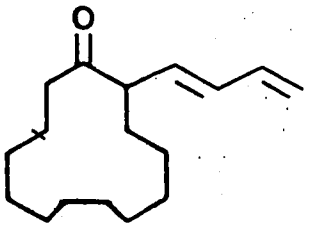
TABLE 2

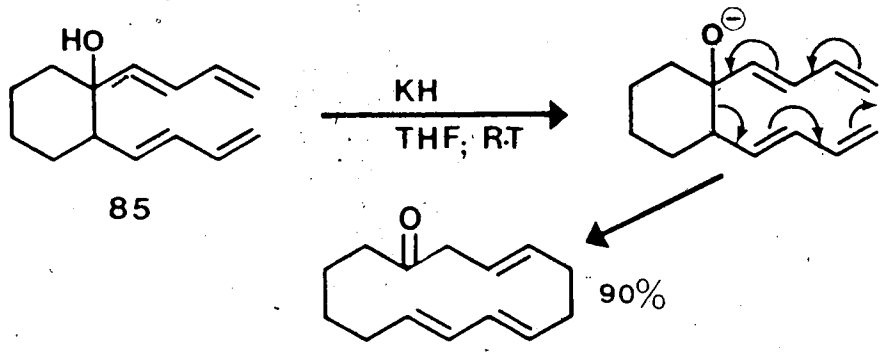
Entry	Acetylenes	Hydrogenation Products (%)
1	 70	 71 (96%)
2	 74	 75 (97%)
3	 78	 79 (96%)
4	 82	 83 (95%)

When we treated compound **71** with potassium hydride under the conditions used successfully in the case of **63** and **67** we obtained a complex mixture and so we sought an alternative method of generating the diene. We found that olefinic alcohol **71** reacted smoothly in less than 10 minutes at -20°C when it was treated with a solution of tin tetrachloride in dichloromethane. The resulting α-butadienyl ketone **72** could be isolated in 69% yield. Boron trifluoride etherate has been used before[94] in Peterson olefinations but we are not aware of the use of tin tetrachloride in this connection. The reaction is general; it worked efficiently for the other examples shown in Table 3. Once again, the stereochemistry of the internal double bond is cleanly (E) as judged by ^1H NMR measurements, the diagnostically significant values of $^3J_{HC=CH}$ ranging from 15.1 to 15.3 Hz. The IR spectrum in each case showed the presence of a non-conjugated ketone.

With these results in hand, we had developed a new route to α-butadienyl ketones, making such substances fairly readily available for macroexpansion. That process had been used, at the time we did these experiments, for expansion of compound **85** as in eq. 72[67] and we decided to apply the method to some other examples, since we had the necessary α-butadienyl ketones. These should be

TABLE 3

Entry	Hydroxy-silanes	Dienes (%)
1	 71	 72 (69%)
2	 75	 76 (80%)
3	 79	 80 (78%)
4	 83	 84 (73%)

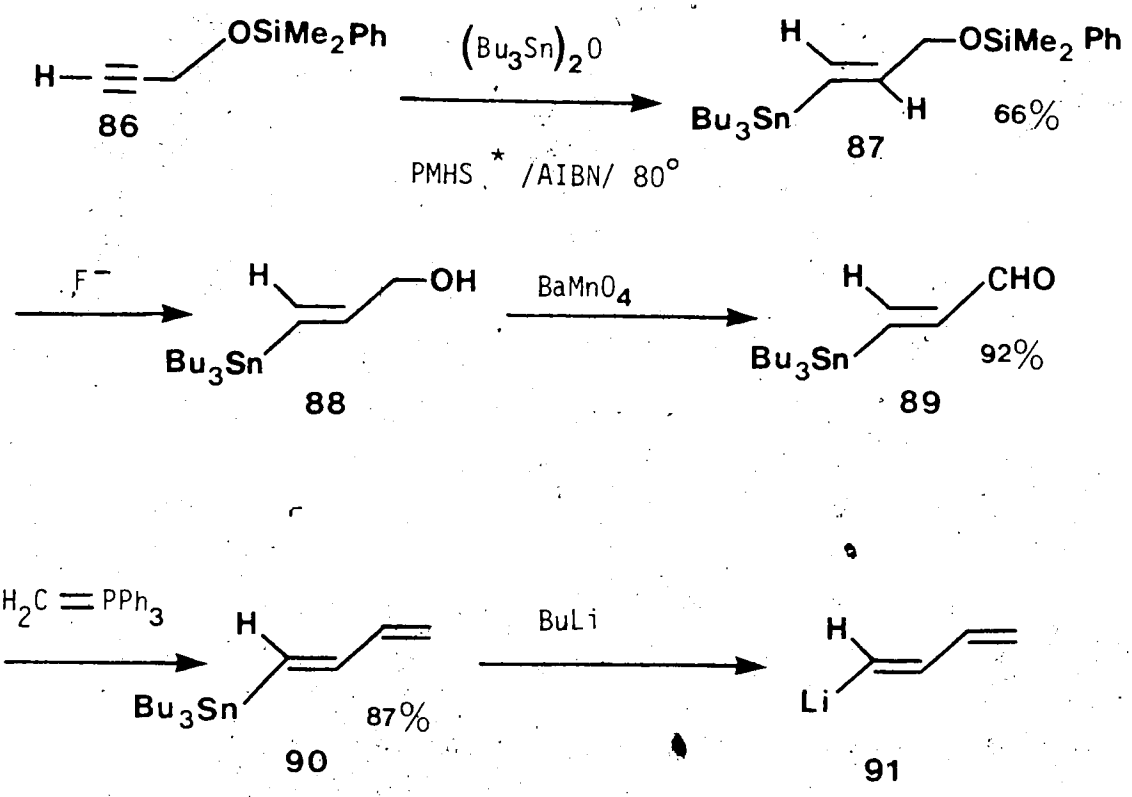


85 (72)

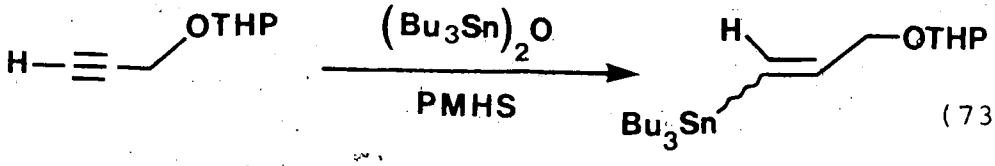
convertible, by the action of 1-lithio-1,3-butadiene[67] into appropriate substances for macroexpansion.

We initially found the preparation of the organometalic to be very difficult. The reported procedure[67] is shown in Scheme 9. In our hands the first stage (**86**→**87**) does not proceed as indicated, but produces two products as judged by thin layer chromatography. Likewise, an analogous literature[103] procedure (eq. 73) also gives two products and not just one as reported. An attempt to use tributylstannane as in eq. 74 was no more successful. Hydrostannylation of propargyl alcohol itself had been claimed[104] to proceed cleanly. We were not able to repeat such a result and the work,[104] in fact, has been criticized in a detailed study[105] of the hydrostannylation. If the conditions of eq. 75 are followed exactly then a satisfactory ratio (17:1) of (E):(Z) stannane is obtained. The distilled total stannylation

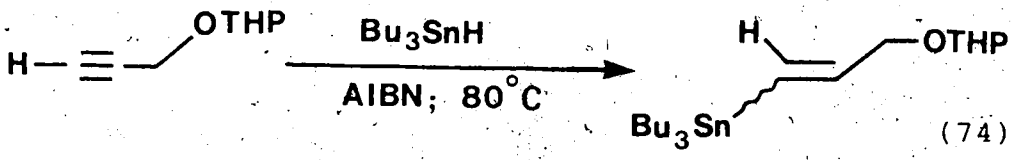
Scheme 9



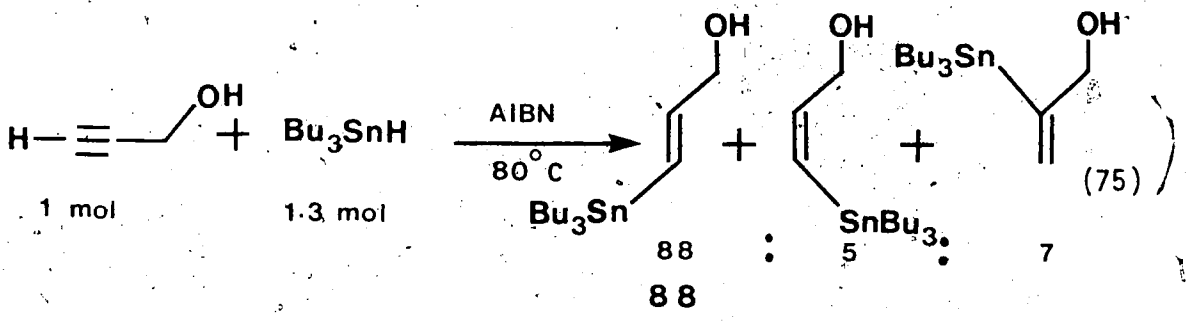
*Polymethylhydrogensiloxane



(73)



(74)



(75)

product was used directly for the next step — oxidation to aldehyde **89** (see Scheme 9). We found barium manganate

unsuitable, despite its reported use[67] for this purpose. In our hands commercial active manganese dioxide worked well and gave aldehyde **89** in 74% yield (corrected for recovered starting material). The material was a 17:1 mixture of isomers with the required (E) geometry — as shown by a value of 19.7 Hz for $^{3}J_{HC=CH}$ — predominating. The final chain extension (see Scheme 9; **89**→**90**) by Wittig reaction proceeded without incident (83% yield). The material appeared to be isomerically pure on the basis of its ^{13}C NMR (100.6 MHz) spectrum.*

Ketone **76** was then treated with lithio-1,3-butadiene derived from stannane **90** in the reported fashion.[67] Some enolization occurred during this process because on workup we obtained an inseparable mixture of the desired bis(butadienyl)alcohol **92** and the starting ketone **76** (eq. 76). This mixture was used directly for the subsequent stages.

We did not detect (^{1}H NMR) any isomer of **92** (i.e. material with 1α,2β stereochemistry**). The stereochemistry assigned is based on analogy with the

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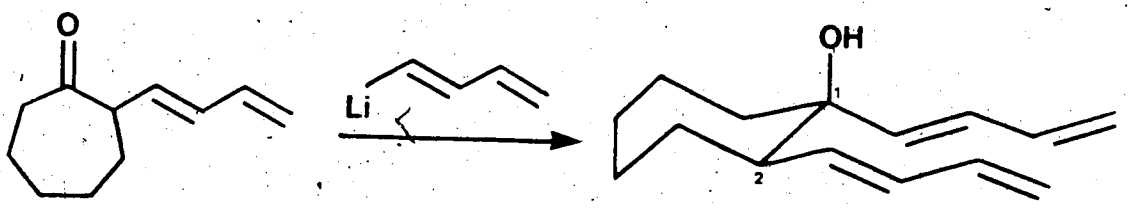
* S/N ratio = ca. 100 for most intense peak.

** The senior group (Sequence Rule) at C-1 defines the α-face.



76 92 (76)

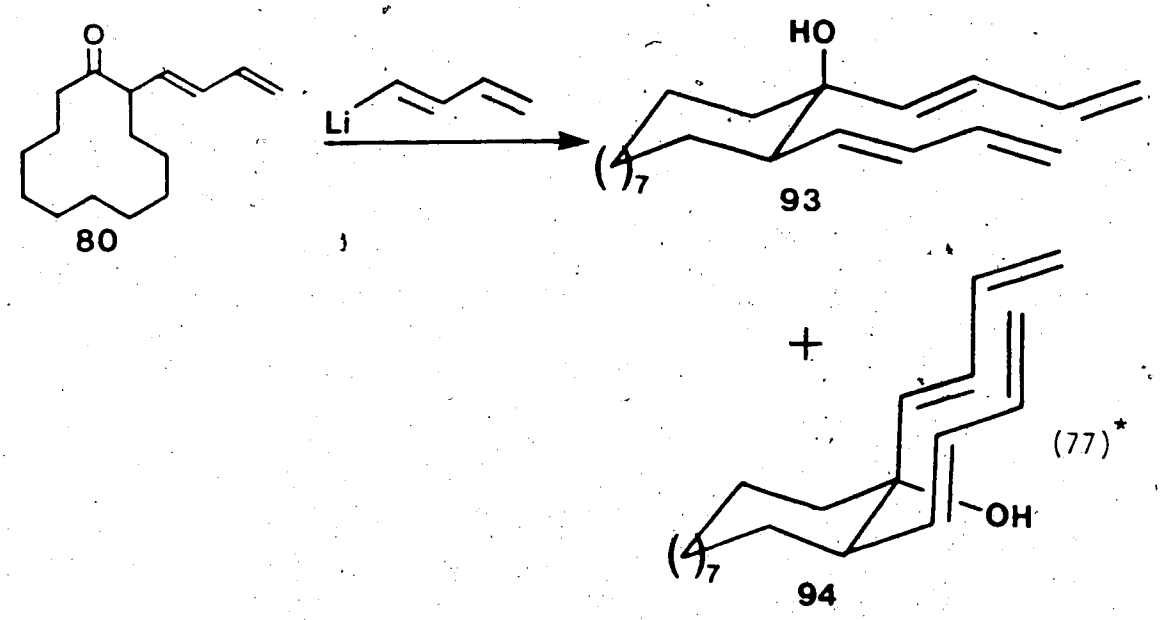
+ 76

corresponding reaction of 2-butadienylcyclohexanone[67] and, in the event, was confirmed by subsequent experiments (see below).

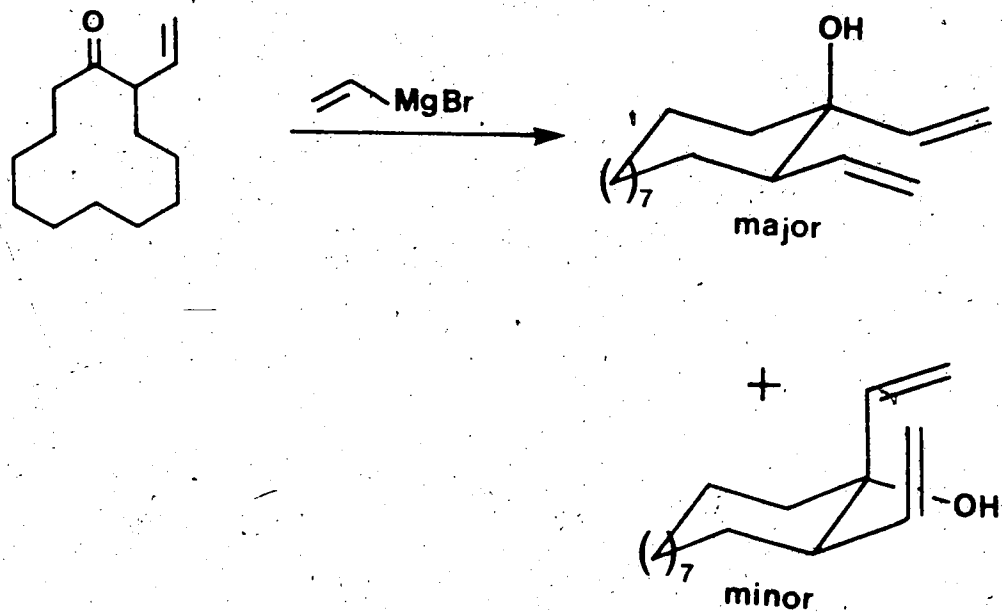
Attempts to induce macroexpansion of **92** by treatment, under the reported[67] conditions, with potassium hydride were unsuccessful as a complex mixture (tlc) of products was generated. Our observations in the cyclododecanone series were also unpromising:

Treatment of 2-butadienylcyclododecanone **80** with 1,3-butadienyllithium gave (74%) two easily separable isomers **93** [1α,2α] and **94** [1α,2β] in the ratio of 3:1.

The stereochemical assignments are tentative: they are made on the basis of analogy with the Japanese work[79] shown in eq. 78, and on the fact that subsequent chemistry (see below) is accommodated in this way, and not if the assignments are reversed.



(77)*

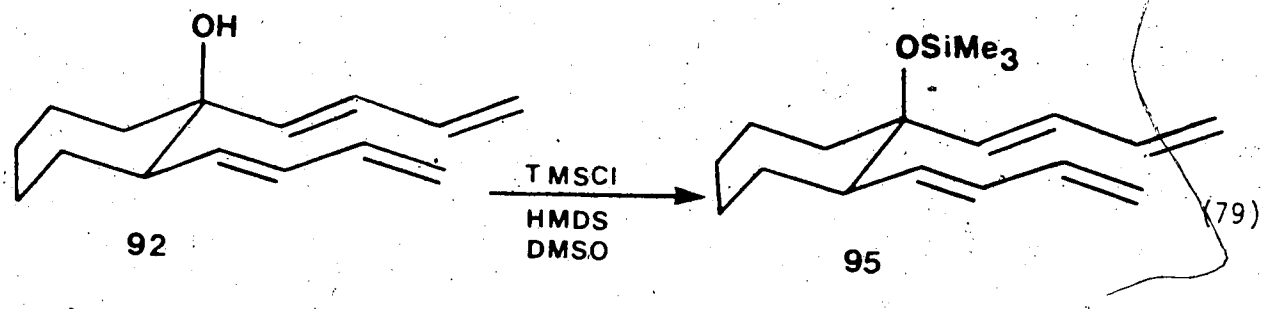


(78)

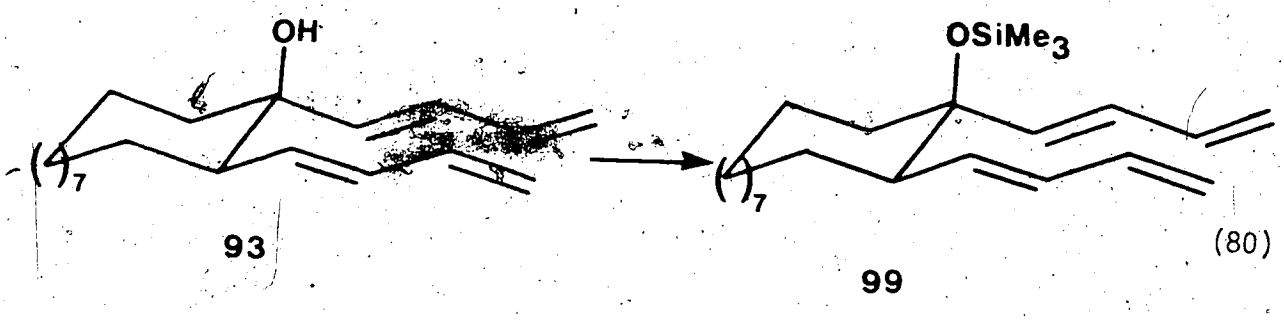
*These diagrams are not meant to imply preferred conformations.

Reaction of **93** with potassium hydride resulted in disappearance of the starting material but the NMR spectrum of the main product showed too many vinyl protons relative to other signals (7H instead of 6H). It was obvious that the anionic macroexpansion reported in the literature was not general. A way round the difficulty was sought and quickly found.

Each of the three alcohols **92**, **93** and **94** was converted into its trimethylsilyl ether. The hydroxyl groups are tertiary and are likely to be hindered, but the reaction worked well in DMSO with chlorotrimethylsilane and hexamethyldisilazane.[77]

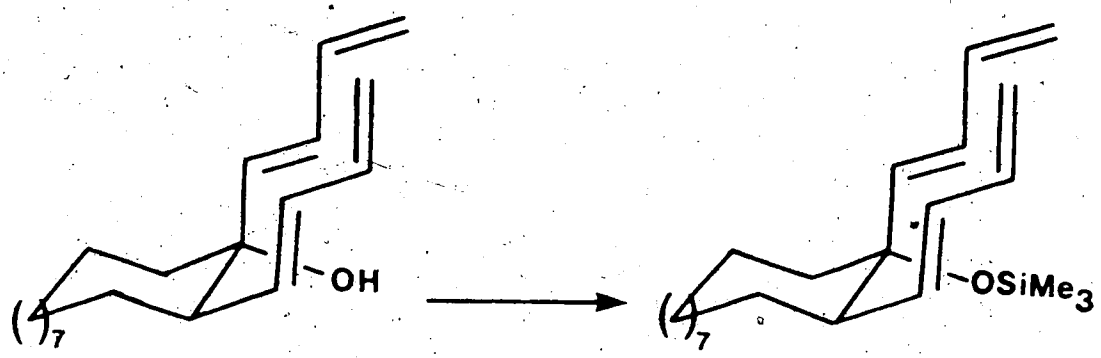


92 **95** (79)

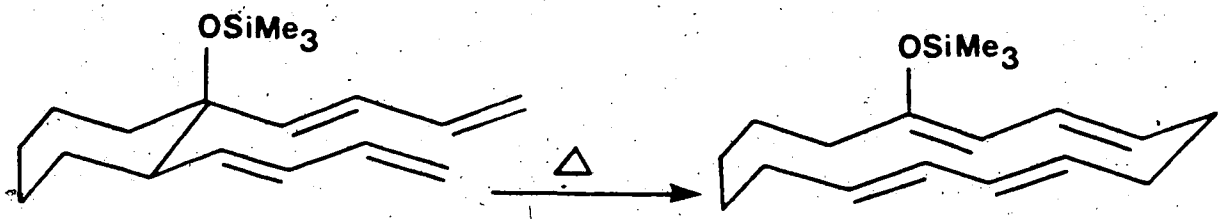


93 **99** (80)

The silyl ethers rearranged smoothly on heating under argon in a sealed ampoule at 200°C for 15 minutes. Thermolysis of **95** gave silyl enol ether **96** (88%) (eq. 82).



94 **102** (81)

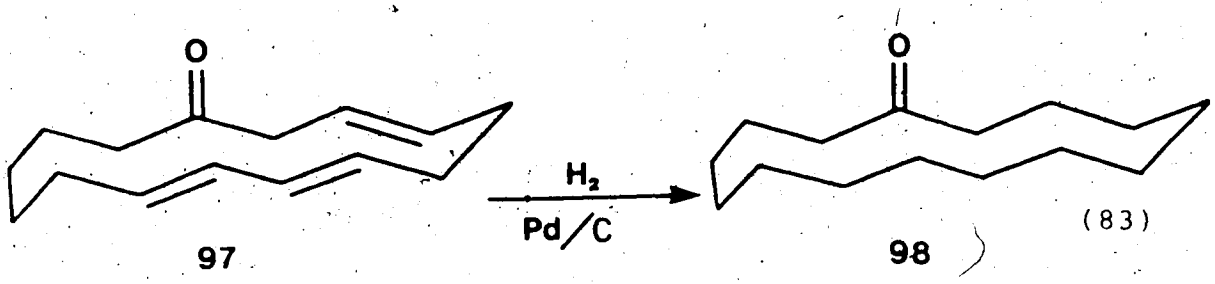


95 **96** (82)

The material contained 8% (^{1}H NMR integration) of residual **95**.* An attempt to convert **96** into its parent ketone by

*We did not establish whether this is the result of incomplete rearrangement or of an equilibrium.

treatment with tetrabutylammonium fluoride in THF gave a very complex mixture (tlc) and we resorted to the unconventional process of treating the compound with methyllithium in ether in the presence of tetramethylethylenediamine. Aqueous workup gave (85%) the non-conjugated ketone **97** as a single isomer (^{13}C NMR) and on hydrogenation it afforded cyclopentadecanone (Exaltone)[106] **98** in 95% yield (eq. 83).

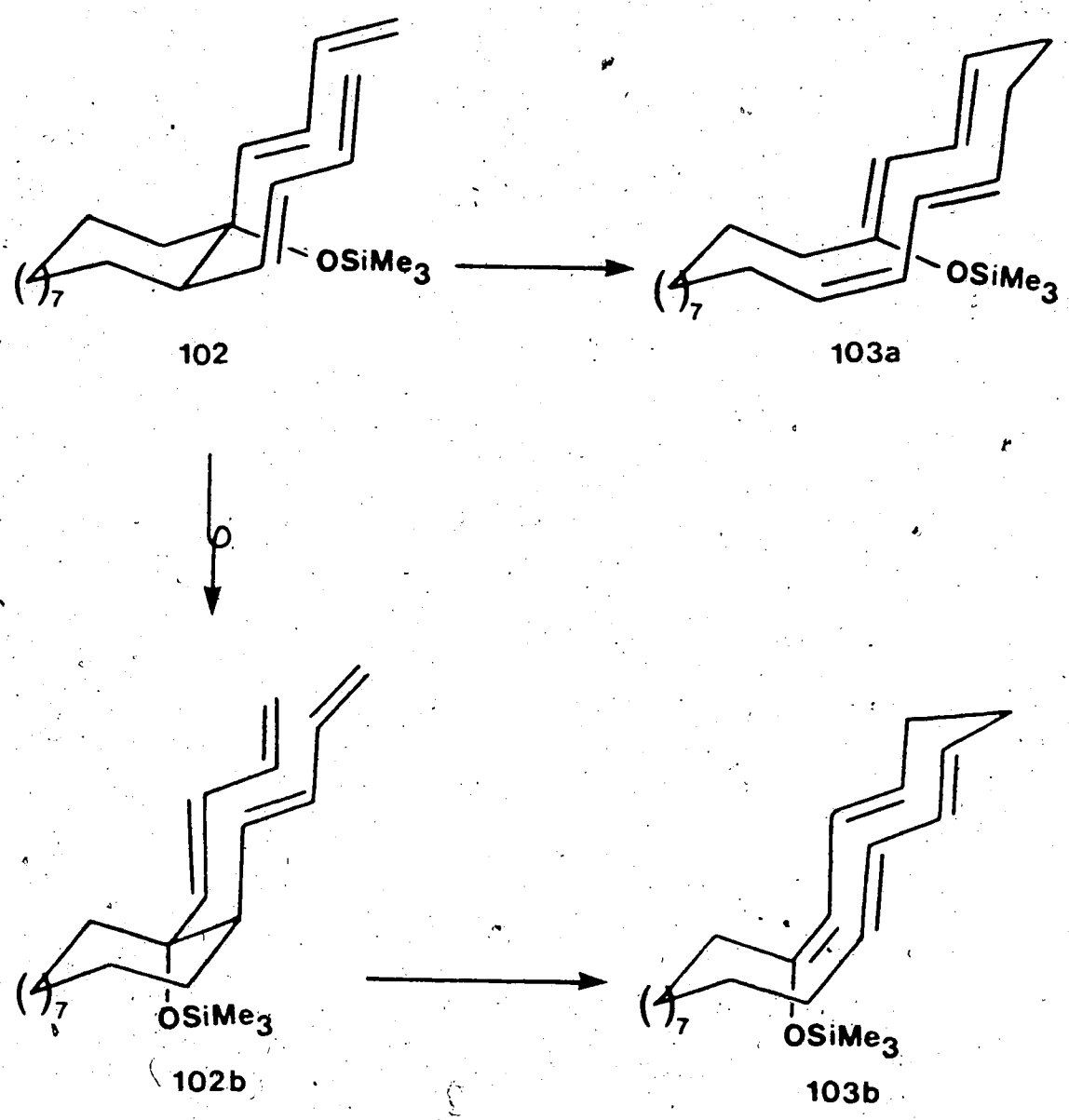


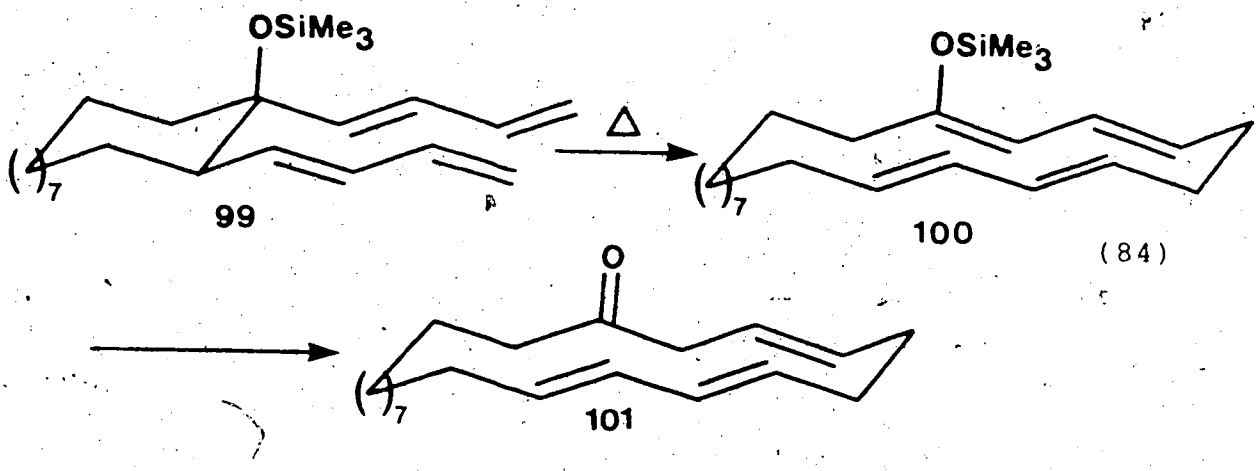
97 **98** (83)

Silyl ether **99** gave, on thermolysis, silyl enol ether **100** in 95% yield. It was a single product, as judged by ^{13}C NMR and was converted (79%) into the non-conjugated ketone **101** by the action of methyllithium and tetramethylethylenediamine followed by acetic acid (eq. 84).

Thermolysis of **102** gave, in 91% yield, two isomeric silyl enol ethers which we consider to have structures **103a** and **103b** as shown in Scheme 10.

Scheme 10





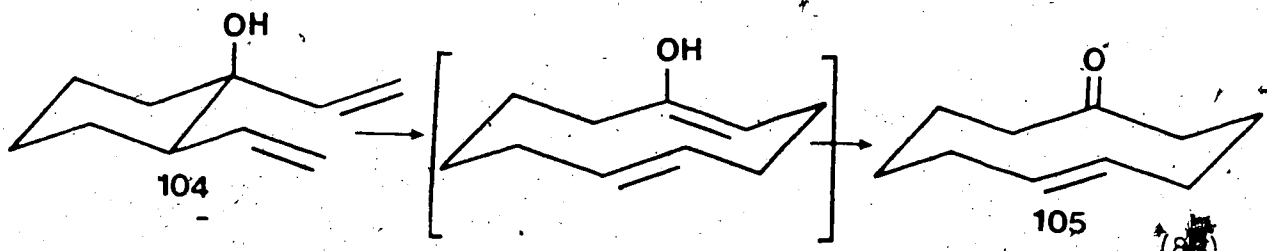
(84)

Our structural assignments to **92**, **93**, **94**, **95**, **96**, **99**, **100**. **102**, **103a**, and **103b** rest on the following considerations:

In the case of the bis(butadienyl)-compounds **92**, **93**, and **94**, the mode of formation defines the gross structure but not the relative stereochemistry at the two asymmetric centres. Some guidance in assigning stereochemistry was provided by a line of argument used[51] in the following context.

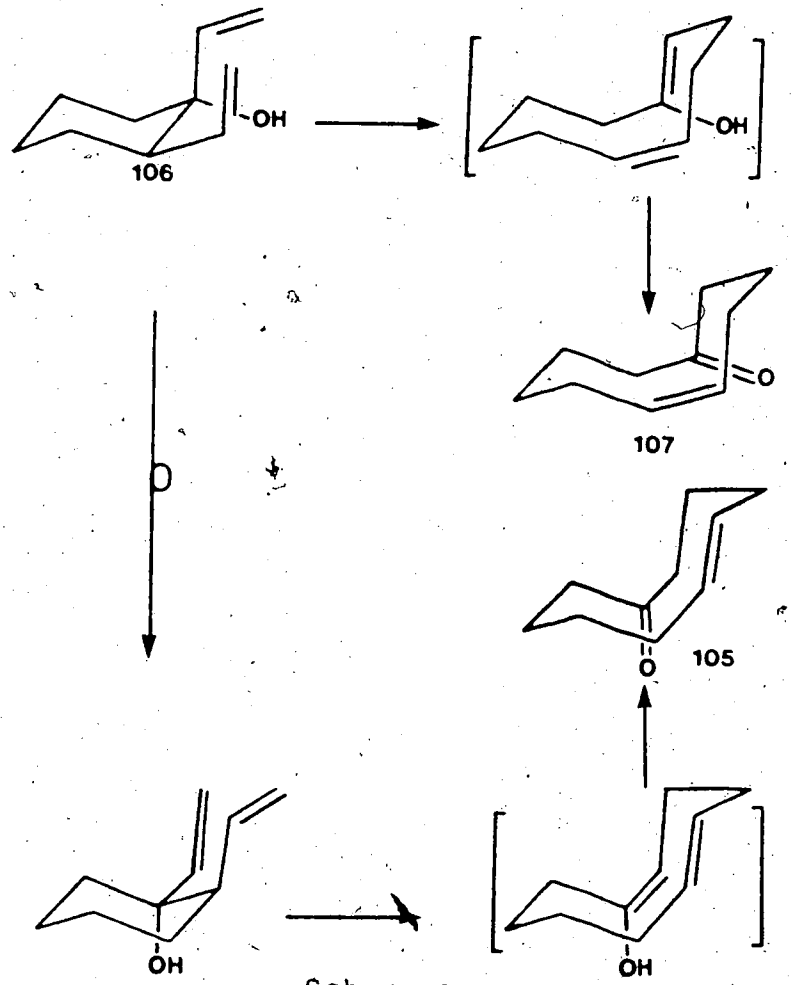
A divinylcyclohexanol, assigned stereochemistry **104**, underwent thermal isomerization to ketone **105** (IR 1709, 987 cm^{-1}), whereas the isomeric alcohol **106**, gave a mixture of **107** (IR 1706, 703 cm^{-1}) and **105** (see Scheme 11). The ketones were fully characterized.

If one makes the reasonable assumption that the oxy-Cope rearrangement involves a concerted process via a



(8

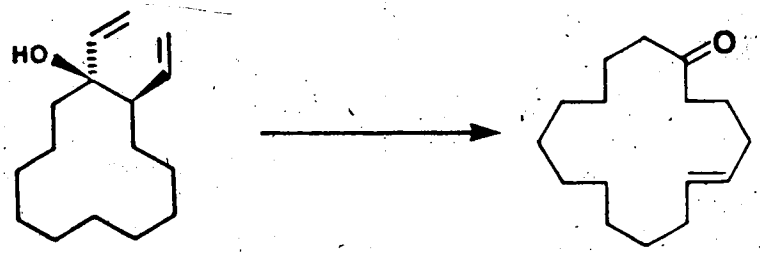
chair transition state, then the stereochemical assignments to the two alcohols **104** and **106** allow the



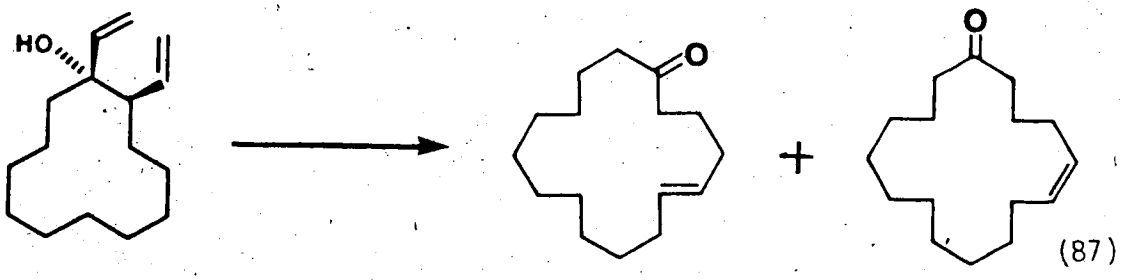
Scheme 11

stereochemistries for **105** and **107** to be rationalized. An exactly similar argument was used[79] to accommodate the observations summarized in eqs. 86 and 87.

When these lines of reasoning, and assumptions about the conformation in the oxy-Cope rearrangement, are applied to our compounds then the degree of stereochemical homogeneity of the thermolysis products is readily understood. If the divinyl alcohol in the cycloheptanone



(86)



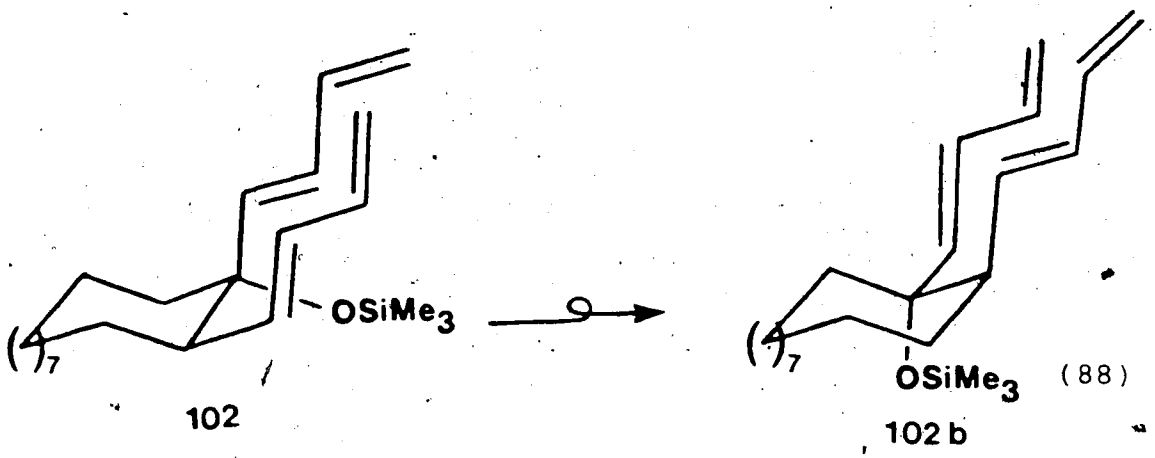
(87)

case (i.e. compound **92**) has the stereochemistry shown it would be predicted to afford (after silylation, thermolysis, and desilylation) a single ketone rather than a pair of geometric isomers. That ketone is expected to have the (3E,7E,9E) geometry and this geometry is, accordingly assigned to the one ketone **97** that is actually produced.

The major bis(butadienyl)alcohol in the cyclododecanone series (i.e. **93**) must, similarly, have the assigned stereochemistry. It too gives a single thermolysis product. Correspondingly, the other isomeric alcohol should lead to two products when the derived silyl ether **102** is heated. It is not unreasonable to expect **102** to exist in two conformations, each having one large group axial (see eq. 88). Conformation **102** leads to **103a** and conformation **102b** leads to **103b**.

It is surprising that the reported[67] macroexpansion (eq. 72) gave a single product. We suspect that the instrumentation used in that work was not sensitive enough to detect the minor isomer.

We have not addressed the question of the mechanism of the macroexpansion. Our observations are consistent with two [3,3] shifts or a single [5,5] rearrangement.



(88)

Conclusion

In the first section of this chapter we have developed a repetitive four-carbon ring expansion procedure that makes use of (phénylseleno)acétaldehyde and the siloxy-Cope rearrangement. The sequence was carried out over two cycles of expansion and we were able to overcome the problem of regiochemical scrambling of enolates that occurs during anionic oxy-Cope

rearrangement.

We have found, in the second part, a synthetic equivalent for the butadienyl carbonium ion. It can be used to make terminal dienes with (E)-geometry and it also provides a route to α-butadienyl ketones, which are useful for macroexpansion. Macroexpansion by anionic oxy-Cope rearrangement is not a general reaction and the silylation route developed here merits consideration when the ionic pathway is unsuccessful.

EXPERIMENTAL

Unless otherwise stated the following particulars apply. Experiments were carried out under argon that was purified by passage through a column (3.5 × 42 cm) of R-311 catalyst[107] and then through a similar column of Drierite.

Glassware was dried in an oven for at least 3 h (130°C), cooled in a dessicator, quickly assembled, and sealed with rubber septa (when applicable). Inlet and exit needles for argon were passed through a septum on the apparatus and argon was purged through the system. The exit needle was removed and the apparatus was kept under a slight static pressure of argon (provided no gas was to be generated in the reaction). Stirring was effected by using a dry, Teflon-coated magnetic stirring bar.

Materials were weighed quickly into dry flasks which were then sealed with rubber septa and purged with argon. Transfer of moisture- and/or air-sensitive materials was accomplished using dry, well-greased syringes whenever possible, solids being dissolved in a suitable solvent prior to transfer. Solvents were distilled before use for chromatography or extractions. When required, solvents and reagents were dried with appropriate drying agents and distilled under argon. Dry ether, tetrahydrofuran (THF), and benzene were distilled

from sodium-benzophenone ketyl; dichloromethane, chloroform, carbon tetrachloride, 1,2-dichloroethane, toluene, hexane, pyridine, triethylamine, diisopropylamine, acetonitrile, dimethylsulfoxide (DMSO), and hexamethylphosphoric triamide (HMPA) were distilled from calcium hydride [the latter two under reduced pressure (ca. 10 mm)]. N,N,N',N'-Tetramethylethylenediamine was distilled first from sodium hydroxide and then from calcium hydride, methanol was distilled from magnesium methoxide; U.S.P. absolute ethanol[108] and hexamethyldisilazane (HMDS) were used without further drying. The commercial solutions (Aldrich) of methyllithium in ether, n-butyllithium in hexane, and vinyllithium (Lachat) in THF were titrated before use by the diphenylacetic acid method.[109] Sodium iodide and paraformaldehyde were dried in vacuo for at least 12 h. Magnesium turnings for Grignard reactions were stored at 130°C. Benzeneselenenyl chloride, pyridinium chlorochromate, diphenyldiselenide, manganese(IV)oxide and methyltriphenylphosphonium bromide (all Aldrich materials) were used as received. Azobisisobutyronitrile (AIBN) from Eastman was used without further purification and stored at 0°C.

Products were isolated from solution by concentration under water pump vacuum at 30°C using a rotary

evaporator. Where compounds were isolated by simple evaporation of their solutions, the residues were kept under vacuum (<0.1 mm) until of constant weight. Melting points were measured using a Kofler block melting point apparatus. Boiling points quoted for products distilled in a Kugelrohr apparatus refer to the oven temperature.

Commercial silica (Merck 60F-254) thin-layer chromatography (TLC) plates were used. Silica gel for flash column chromatography was Merck type 60 (230-400 mesh). TLC plates were examined under uv radiation (254 nm), treated with iodine vapour, and charred on a hot plate after being sprayed with sulfuric acid (6 N in methanol).

Vapour phase chromatography was performed using a Hewlett-Packard 5830A gas chromatograph equipped with an FID detector. A Hewlett-Packard stainless steel prepacked column (1/8" OD × 6 ft; 10% QF-1 on Chromosorb W, 80-100 mesh) was used.

Spinning band distillations were carried out on a Perkin-Elmer 151 annular still. Combustion elemental analyses were performed in the microanalytical laboratories of the University of Alberta or by Butterworth Laboratories Ltd. in England. Infrared spectra were recorded on a Perkin-Elmer 297 spectrophotometer or a Nicolet 7000 FT-IR model. Liquids were run as neat films

on potassium chloride plates and solids were run as solutions in the specified solvent, using 0.5 mm potassium chloride cells. Proton NMR spectra were recorded on Bruker WP-80 (at 80 MHz), Bruker WH-200 (at 200 MHz) or Bruker WH-400 (at 400 MHz) spectrometers, in the specified deuterated solvent with tetramethylsilane (TMS) as an internal standard. ^{13}C NMR spectra were recorded on Bruker HFX-90 (at 22.6 MHz), Bruker WH-200 (at 50.3 MHz) or Bruker WH-400 (at 100.6 MHz) spectrometers in deuterated chloroform with TMS as an internal standard. The following abbreviations are used in the text: s, singlet; d, doublet; t, triplet; q, quartet; q', quintet; m, multiplet; s', sextet; J, coupling constant; δ, chemical shift. Mass spectra were recorded on an A.E.I. MS50 mass spectrometer at an ionizing voltage of 70 EV.

General procedure for the preparation of trimethylsilyl enol ethers: The literature[110] procedure was followed: Sodium iodide (0.13 mol) in dry acetonitrile (125 mL) was added dropwise under argon to a mixture of the corresponding ketone (0.1 mol), triethylamine (0.12 mol) and chlorotrimethylsilane (0.12 mol). The resulting suspension was stirred at room temperature for 12 h and the solvent was evaporated. The precipitate was filtered

off and washed well with dry hexane. Evaporation of the solvent (Büchi; $CaSO_4$ tube in line to waterpump) and spinning-band distillation of the resulting oil gave the corresponding silylenol ethers.

(Cyclohexen-1-yloxy)trimethylsilane **69**:[82] IR (neat) 1662, 1250, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 0.2 (s, 9H), 1.4 — 1.8 (m, 4H), 1.95 — 2.35 (m, 4H), 4.9 (t, J = 7 Hz, 1H); bp 88-89°C (20 mm) [lit bp 75 — 80°C (20 mm)].

(Cyclohepten-1-yloxy)trimethylsilane **73**:[111] IR (neat) 1660, 1250, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.22 (s, 9H), 1.52 (m, 4H), 1.7 (m, 2H), 2.0 (m, 2H), 2.21 (m, 2H), 5.0 (t, J = 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 0.2, 25.2, 25.3, 27.8, 31.5, 35.5, 108.5, 156.0; exact mass, m/z 184.2301 (calcd for $C_{10}H_{20}OSi$, 184.2364); bp 105-106°C (20 mm).

(Cyclododecen-1-yloxy)trimethylsilane **77**:[111] IR (neat) 1665, 1250, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ 0.2 (s, 9H), 1.1 — 1.5 (m, 16H), 1.8 — 2.1 (m, 4H), 4.5 (t, J = 7 Hz, 1H); bp 97-98°C (0.55 mm).

(Cyclotridecen-1-yloxy)trimethylsilane **81**:[112] IR (neat)

1665, 1250, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.2 (2 s, 9H), 1.1 — 1.7 (m, 18H), 1.9 — 2.1 (m, 4H), 4.4 (t, J = 7.2 Hz, 0.6H), 4.45 (t, J = 7.2 Hz, 0.4H); ^{13}C NMR ($CDCl_3$, 22.6 MHz) δ 0.02, 0.5, 24.2, 24.4, 24.6, 25.3, 26.4, 26.8, 27.1, 27.6, 27.9, 28.3, 28.8, 29.0, 35.6, 108.8, 110.2, 132.5, 149.8, 151.1; exact mass, m/z 268.3213 (calcd for $C_{16}H_{32}OSi$, 268.3300). Anal. calcd for $C_{16}H_{32}OSi$: C, 71.55; H, 12.02. Found: C, 71.83; H, 11.91; bp 85-85°C (0.1 mm).

2-[1-Hydroxy-2-(phenylseleno)ethyl]cyclododecanone **12**: Methyllithium, (1.91 M in ether, 8.2 mL, 15.6 mmol) was injected by syringe pump over *ca.* 5 min at room temperature into a stirred mixture of silyl enol ether **77** (4.0 g, 15.6 mmol) in dry DME (15 mL). The resulting solution was stirred for 1 h and was then cooled in an ice-water bath. Anhydrous zinc chloride[76] (0.69 M in ether, 11.5 mL, 7.90 mmol) was added dropwise over a period of 10 min. Stirring at 0°C was continued for a further 10 min. Phenylselenoacetaldehyde[69] (3.12 g, 15.8 mmol) in DME (3 mL + 1 mL rinse) was injected rapidly over *ca.* 3 sec. The reaction mixture was stirred for 20 min and was then partitioned between ether (50 mL) and saturated aqueous ammonium chloride (50 mL). The organic layer was

separated and the aqueous phase was extracted with ether (2 × 15 mL). The combined ether extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 × 15 cm) with 15% ethyl acetate gave hydroxyselenide **12** (5.23 g, 88%) as a pure (TLC, silica, 20% ethyl acetate — hexane) mixture of diastereoisomers: IR (CCl_4) 3500, 1705 cm^{-1}; ($CDCl_3$, 200 MHz) δ 1.0 — 1.9 (m, 19H), 2.34 (m, 1H), 1.6 — 1.8 (m, 2H), 1.95 (m, 2H), 3.1 (m, 1H), 3.8 (m, 1H), 7.2 (m, 3H), 7.4 (m, 2H); exact mass, m/z 382.1401 (calcd for $C_{20}H_{30}A_2Se$, 382.1403). Anal. calcd for $C_{20}H_{30}O_2Se$: C, 62.98; H, 7.92; O, 8.38. Found: C, 63.03; H, 8.09; O, 8.69.

2-Ethenylcyclododecanone **13**: Triethylamine (3.8 mL, 27.0 mmol) was injected into a stirred solution of hydroxyselenide **12** (2.1 g, 5.5 mmol) in dichloromethane (20 mL) and methanesulfonyl chloride (1.28 mL, 16.5 mmol) in dichloromethane (10 mL + 1 mL rinse) was injected at room temperature over a period of 2 h (syringe pump). The mixture was stirred for a further arbitrary period of 20 min and was then poured into hexane (30 mL) and ether (30 mL). The precipitate was filtered off and the solvent was evaporated. Flash chromatography of the residue over

silica gel (3 × 25 cm) first with hexane (to elute diphenyldiselenide), and then with 1% ethyl acetate — hexane followed by Kugelrohr distillation [bp 55-60°C (0.004 mm)] gave olefin **13** (917 mg, 80%) as a pure (TLC, 5% ethyl acetate — hexane), colorless oil: IR (neat) 1705, 1636, 1470, 1450, 920 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.1 — 1.55 (m, 16H), 1.8 (m, 1H), 1.95 (m, 1H), 2.4 (m, 1H), 2.6 (m, 1H), 5.1 (dd, J = 10, 1.5 Hz, 1H), 5.2 (dd, J = 17, 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 22.1, 22.2, 23.1, 24.1, 24.4, 24.5, 24.8, 25.3, 30.1, 38.1, 57.7, 116.6, 136.8, 212.1; exact mass, m/z 208.1827 (calcd for $C_{14}H_{24}O$, 208.1821).

(1R*,2S*)- and (1R*,2R*)-1,2-Diethenylcyclododecanol **14** and **15**[79]: Ketone **13** (1.47 g, 7.0 mmol) in THF (20 mL + 2 mL rinse) was added dropwise at -55°C into a stirred solution of vinyllithium (0.56 M in THF, 16.4 mL, 9.2 mmol). The mixture was stirred for 30 min and saturated aqueous ammonium chloride (20 mL) was added. The organic layer was separated and the aqueous layer was extracted with ether (2 × 15 mL). The combined organic extracts were washed with brine, dried, and evaporated. Column chromatography of the residue over 10% silver nitrate silica gel (5 × 30 cm) with 50% ethyl acetate — hexane

gave the individual isomers which were each dissolved in ether and extracted with brine (to remove traces of Ag^+). Evaporation of the solvent gave two apparently homogeneous (TLC, silica gel, 10% ethyl acetate — hexane) alcohols of combined weights (1.57 g, 94%). The material of higher R_f **15** (475 mg, 28.3%) was an oil: bp 102°C (0.2 mm) [lit.[79] bp 122-3°C (0.7 mm)]; IR (neat) 3540, 1640, 998, 920 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.1 — 1.9 (21H), 2.3 (t, J = 10 Hz, 1H), 5.0 — 5.2 (m, 4H), 5.35 — 5.60 (m, 1H), 5.95 (dd, J = 17, 10 Hz, 1H); ^{13}C ($CDCl_3$, 50.3 MHz) δ 18.4, 22.1, 22.4, 22.5, 22.7, 24.3, 26.1, 26.2, 26.3, 34.6, 48.5, 75.7, 112.3, 119.7, 139.1, 142.4; exact mass, m/z 236.2131 (calcd for $C_{16}H_{28}O$, 236.2133).

The material of lower R_f **14** (1.09 g, 65.7%) was a white crystalline solid: mp 50-52°C (lit.[79] mp 51-62°C); IR (neat) 3450, 1638, 998, 920 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.1 — 2.0 (m, 21H), 2.25 (t, J = 10 Hz, 1H), 4.9 — 5.3 (m, 4H), 5.5 — 5.7 (m, 1H), 5.9 (dd, J = 18, 10 Hz, 1H); ^{13}C ($CDCl_3$, 50.3 MHz) δ 20.3, 22.0, 22.7, 22.8, 23.0, 24.1, 26.2, 26.6, 38.0, 45.9, 76.9, 111.0, 116.0, 138.8, 144.7; exact mass, m/z 236.2130 (calcd for $C_{16}H_{28}O$, 236.2133).

(1R*,2S*)-[(1,2-Diethenylcyclododecyl)oxy]trimethylsilane **17**: Chlorotrimethylsilane (1.55 mL, 12.2 mmol) was injected at room temperature into a stirred solution of alcohol **14** (1.93 g, 8.16 mmol) and hexamethyldisilazane (2.1 mL, 9.7 mmol) in dry DMSO (15 mL). Stirring was continued for an additional 30 min and pentane (50 mL) was added. The mixture was shaken with water (20 mL) and the organic layer was washed successively with 5% aqueous sulfuric acid, saturated aqueous sodium bicarbonate, and brine. The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 × 15 cm) with hexane gave **17** (2.31 g, 91.6%) as a pure (TLC, silica, hexane) oil: IR (neat) 1640, 1250, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.25 (s, 9H), 1.0 — 1.9 (m, 19H), 2.02 (t, J = 10 Hz, 2H), 4.8 — 5.15 (m, 4H), 5.6 (m, 1H), 5.8 (dd, J = 16, 9 Hz, 1H); ^{13}C ($CDCl_3$, 22.6 MHz) δ 2.9, 20.9, 22.2, 22.7, 23.0, 23.8, 24.4, 26.4, 26.9, 37.0, 47.2, 81.0, 111.5, 114.7, 140.6, 143.9; exact mass, m/z 308.2530 (calcd for $C_{19}H_{36}OSi$, 308.2533). Anal. calcd for $C_{19}H_{36}OSi$: C, 74.03; H, 11.67. Found: C, 74.28; H, 11.94.

(1R*,2R*)-[1,2-Diethenylcyclododecyl)oxy]trimethylsilane **18**: Chlorotrimethylsilane (0.11 mL, 0.84 mmol) was

injected at room temperature into a stirred solution of alcohol **15** (135 mg, 0.56 mmol) and hexamethyldisilazane (0.11 mL, 0.67 mmol) in dry DMSO (2 mL). Stirring was continued for an additional 0.5 h and pentane (10 mL) was added. The mixture was shaken with water (20 mL) and the organic layer was washed successively with 5% aqueous sulfuric acid, saturated aqueous sodium bicarbonate, and brine. The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with hexane gave **18** (161 mg, 93%) as a pure (TLC, silica, hexane) oil: IR (neat) 1640, 1250, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.20 (s, 9H), 1.0 — 1.7 (m, 19H), 1.85 (m, 1H), 2.42 (t, J = 10 Hz, 1H), 4.8 — 5.2 (m, 4H), 5.7 (m, 1H), 6.02 (dd, J = 17, 10 Hz, 1H); exact mass m/z 308.2530 (calcd for $C_{19}H_{36}OSi$, 308.2533). Anal. calcd for $C_{19}H_{36}OSi$: C, 73.95; H, 11.75. Found: C, 74.00; H, 11.86.

1(Z),5(E)-(1,5-Cyclohexadecadien-1-yloxy)trimethylsilane **19**: Silyl ether **17** (500 mg, 1.62 mmol) was sealed in an ampoule under argon and immersed for 15 min in a preheated oil bath at 200°C. Kugelrohr distillation of the resulting oil gave silyl enol ether **19** (490 mg, 98%) as a pure (TLC, silica, hexane) oil: bp 95-100°C (0.05

mm); IR (neat) 1670, 1250, 970, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.2 (s, 9H), 1.2 — 1.65 (m, 16H), 2.1 (m, 8H), 4.52 (m, 1H), 5.4 (m, 2H); ^{13}C ($CDCl_3$, 100.6 MHz) δ 0.7, 24.0, 25.3, 26.1, 26.3, 26.5, 26.9, 28.4, 31.8, 32.2, 35.2, 107.7, 130.7, 130.9, 150.0; exact mass, m/z 308.2533 (calcd for $C_{19}H_{36}OSi$, 308.3612). Anal. calcd for $C_{19}H_{36}OSi$: C, 73.95; H, 11.75. Found: C, 74.04; H, 11.83.

(E)-5-Cyclohexadecen-1-one **21**:[79] Tetrabutylammonium fluoride (1 M in THF, 2 drops) was added to a stirred solution of silyl enol ether **19** (17 mg, 0.05 mmol) in THF (1 mL). The resulting mixture was stirred at room temperature for 30 min and water (5 mL) was added. The aqueous phase was extracted with ether, and the combined organic extracts were dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 5% ethyl acetate — hexane gave ketone **21** (11.7 mg, 90%) as a pure (TLC, silica, 5% ethyl acetate — hexane) oil: IR (neat) 1710, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.1 — 1.4 (m, 14H), 1.5 — 1.8 (m, 4H), 2.08 (m, 4H), 2.2 — 2.4 (m, 4H), 5.20 — 5.45 (m, 2H).

1(Z),5(Z)- and 1(E),5(E)-(1,5-Cyclohexadecadien-1-yloxy)-trimethylsilanes **20a** and **20b**: The silyl enol ether **18** (250 mg, 0.81 mmol) was sealed in an ampoule under argon and immersed for 15 min in a preheated oil bath at 200°C. Kugelrohr distillation of the resulting oil gave silyl enol ethers **20a** and **20b** (246 mg, 98%) as a pure mixture of isomers: bp 95-100°C (0.05 mm); IR (neat) 1665, 1250, 970, 850, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.22 (2 s, 9H), 1.1 — 1.6 (m, 16H), 2.1 (m, 8H), 4.2 — 5.6 (m, 1H), 6.4 (m, 2H); ^{13}C ($CDCl_3$, 50.3 MHz) δ 0.4, 0.6, 24.9, 25.1, 25.8, 26.1, 26.2, 26.5, 26.7, 26.8, 26.9, 27.0, 27.1, 27.2, 27.3, 27.5, 27.6, 28.1, 28.3, 30.8, 31.6, 33.4, 335.5, 107.0, 108.1, 129.8, 130.4, 130.6, 150.0, 156.1; exact mass, m/z 308.2537 (calcd for $C_{19}H_{36}OSi$, 308.2612). Anal. calcd for $C_{19}H_{36}OSi$: C, 73.95; H, 11.75. Found: C, 74.04; H, 11.83.

(E)- and (Z)-5-Cyclohexadecen-1-one **21** and **22**:[79] Tetrabutylammonium fluoride (1 M in THF, 0.5 mL, 0.51 mmol) was added to a stirred solution of silyl enol ethers **20a,b** (160 mg, 0.51 mmol) in THF (2 mL). The reaction mixture was stirred at room temperature for 30 min and water (10 mL) was added. The mixture was extracted with ether (2 × 10 mL) and the organic layer washed with brine, dried

($MgSO_4$), and evaporated. Chromatography of the residue over 10% silver nitrate silica gel (2 × 20 cm) with 2% ethyl acetate — hexane gave (E)-isomer **21** (50 mg, 40.7%) and (Z)-isomer **22** (60 mg, 49%). Both samples were pure by TLC (silica, 5% ethyl acetate — hexane). (E)-Isomer **21** had: IR (neat) 1710, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.1 — 1.4 (m, 14H), 1.5 — 1.8 (m, 4H), 2.08 (m, 4H), 2.2 — 2.4 (m, 4H), 5.20 — 5.45 (m, 2H).

The (Z)-isomer **22** had: IR (neat) 1710, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.1 — 1.42 (m, 14H), 1.5 — 1.8 (m, 4H), 2.01 (m, 4H), 2.4 (2 t, J = 8 Hz, 4H), 5.34 (m, 2H).

(Z)-(1-Cyclohexadecen-1-yloxy)trimethylsilane **23**: Silyl enol ether **19** (100 mg, 0.32 mmol) in degassed benzene (2 mL + 1 mL rinse) was injected into a stirred solution of Wilkinson's catalyst (66 mg, 0.071 mmol) in degassed benzene (2 mL) that had been presaturated with hydrogen for 1 h. The reaction mixture was stirred at room temperature for 12 h under hydrogen (10 psi). The solvent was evaporated and the mixture was filtered through a small pad of Florisil (1 × 2 cm) using 10% ethyl acetate — hexane as a rinse. Evaporation of the solvent and Kugelrohr distillation of the resulting oil gave silyl enol ether **23** as a pure (v.p.c. 10% QF-1) colorless oil

(109 mg, 96.6%): bp 90-95°C (0.07 mm); IR (neat) 1665, 1250, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.22 (s, 9H), 1.0 — 1.6 (m, 24H), 1.98 (m, 4H), 4.42 (t, J = 11 Hz, 1H), (small t, δ 4.62 corresponding to (E)-isomer); exact mass, m/z 310.2682 (calcd for $C_{19}H_{38}OSi$, 310.3768). Anal. calcd for $C_{19}H_{38}OSi$: C, 73.47; H, 12.33. Found: C, 73.21; H, 12.26.

(E)- and (Z)-(1-Cyclohexadecen-1-yloxy)trimethylsilanes **24**: The procedure employed for **23** was followed using silyl enol ether **20a,b** (204 mg, 0.66 mmol) in degassed benzene (2 mL + 1 mL rinse) and Wilkinson's catalyst (127 mg, 0.13 mmol) in degassed benzene (5 mL). The reaction mixture was stirred at room temperature for 12 h under hydrogen (10 psi) and worked up. Evaporation of the solvent and Kugelrohr distillation of the residue gave the silyl enol ethers **24** as two apparently homogeneous (v.p.c. 10% QF-1) isomers (190 mg, 92.5%): bp 70-75°C (0.003 mm); IR (neat) 1670, 1250, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.22 (s, 9H), 1.1 — 1.8 (m, 24H), 1.9 — 2.1 (m, 4H), 4.42 (t, J = 11 Hz, 0.6H), 4.63 (t, J = 11 Hz, 0.4H); exact mass, m/z 310.2687 (calcd for $C_{19}H_{38}OSi$, 310.2682). Anal. calcd for $C_{19}H_{38}OSi$: C, 73.47; H, 12.33. Found: C, 73.30; H, 12.14.

Aldol condensation of silyl enol ether **23**; 2-[1-Hydroxy-2-(phenylseleno)ethyl]cyclohexadecanone **25**: Titanium tetrachloride (0.05 mL, 0.47 mmol) was injected at -78°C into a stirred solution of phenylselenoacetaldehyde[69] (76.6 mg, 0.387 mmol) in dry dichloromethane (2 mL) containing molecular sieves 3A (ca. 200 mg). The solution was stirred for 10 min and silyl enol ether **23** (120 mg, 0.387 mmol) in dry dichloromethane (2 mL + 1 mL rinse) was added dropwise over a period of 10 min (syringe pump). The resulting mixture was stirred at -78°C for 1 h and water (10 mL) was added. The aqueous layer was separated and extracted with ether (2 × 15 mL). The combined organic layers were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 15 cm) with 15% ethyl acetate — hexane gave hydroxyselenides **25** (136 mg, 80%) as a pure (TLC, silica, 20% ethyl acetate — hexane) mixture of diastereoisomers: IR (CCl_4) 3500, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.0 — 1.9 (m, 26H), 2.2 — 2.60 (m, 2H), 2.7 — 3.2 (m, 4H), 3.8 (m, 1H), 7.25 (m, 3H), 7.5 (m, 2H); ^{13}C ($CDCl_3$, 50.3 MHz) δ 21.7, 21.9, 26.2, 26.4, 26.5, 26.9, 27.0, 27.5, 27.6, 27.9, 28.0, 29.0, 33.7, 34.6, 43.6, 43.7, 55.5, 55.7, 70.2, 71.6, 127.3, 127.4, 129.0, 129.2, 132.8, 133.0, 214.5, 214.6; exact mass, m/z

438.2044 (calcd for $C_{24}H_{38}O_2Se$, 438.2045). Anal. calcd for $C_{24}H_{38}O_2Se$: C, 65.89; H, 8.75; O, 7.31. Found: C, 66.06; H, 8.57; O, 7.23.

Aldol condensation of silyl enol ethers **24**; 2-[1-Hydroxy-2-(phenylseleno)ethyl)]cyclohexadecanone **25**: The procedure employed for **23→25** was followed using titanium tetrachloride (0.31 mL, 0.28 mmol), phenylselenoacetaldehyde (56.6 mg, 0.28 mmol), powdered molecular sieves 3Å (ca. 200 mg) in dry dichloromethane (2 mL), and silyl enol ether **24** (88 mg, 0.28 mmol) in dichloromethane (2 mL + 1 mL rinse). The reaction mixture was stirred at -78°C for 1 h and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 15 cm) with 15% ethyl acetate — hexane gave hydroxyselenide **25** (94 mg, 76%) as a pure (TLC, silica, 20% ethyl acetate — hexane) mixture of diastereoisomers: IR (CCl_4) 3500, 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.10 — 1.95 (m, 27H), 4.4 (m, 2H), 2.8 — 3.2 (m, 3H), 3.8 (m, 1H), 7.3 (m, 3H), 7.5 (m, 2H); exact mass, m/z 438.2034 (calcd for $C_{24}H_{38}O_2Se$, 438.2027).

2-Ethenylcyclohexadecanone **26**: Triethylamine (0.19 mL, 1.39 mmol) was injected into a stirred solution of

hydroxyselenide **25** (122 mg, 0.27 mmol) in dry dichloromethane (2 mL), and methanesulfonyl chloride (0.06 mL, 0.87 mmol) in dichloromethane (1 mL + 1 mL rinse) was injected at room temperature over a period of 1 h (syringe pump). The mixture was stirred for a further arbitrary period of 20 min and was then poured into hexane (10 mL) and ether (10 mL). The precipitate was filtered off and the solvent was evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) first with hexane (to elute diphenyldiselenide) and then with 1% ethyl acetate — hexane, followed by Kugelrohr distillation, gave olefin **26** (59 mg, 80.8%) as a pure (TLC, silica, 5% ethyl acetate — hexane) colorless oil: bp 65-70°C (0.001 mm); IR (neat) 1715, 1640, 1000, 928 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.0 — 1.95 (m, 26H), 2.4 (m, 2H), 3.2 (m, 1H), 5.1 (ddd, J = 16, 8, 1.5 Hz, 2H), 5.72 (m, 1H); ^{13}C ($CDCl_3$, 50.3 MHz) δ 22.8, 26.1, 26.4, 26.5, 26.9, 27.2, 27.6, 27.7, 31.2, 36.2, 40.8, 57.1, 116.7, 136.9, 211.8; exact mass, m/z 264.2450 (calcd for $C_{18}H_{32}O$, 264.2445). Anal. calcd for $C_{18}H_{32}O$: C, 81.75; H, 12.2. Found: C, 81.37; H, 11.98.

1,2-Diethenylcyclohexadecanols **27**: Ketone **26** (314 mg, 1.18 mmol) in THF (3 mL + 1 mL rinse) was injected dropwise at -55°C into a stirred solution of vinyllithium

(1.22 M in THF, 2.5 mL, 2.96 mmol). The reaction mixture was stirred at -55°C for 20 min and was then poured into saturated aqueous ammonium chloride. The aqueous layer was extracted with ether and the combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 2% ethyl acetate — hexane gave alcohols **27** (295 mg, 85%) as a pure (TLC, silica, 5% ethyl acetate — hexane) mixture of isomers: IR (neat) 3480, 1640, 1000, 920 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.0 — 1.95 (m, 29H), 2.2 (t, J = 8 Hz, 1H), 4.95 — 5.25 (m, 4H), 5.65 (m, 1H), 5.95 (dd, J = 17, 10 Hz, 1H), (small peaks at δ 2.3, 5.5 and 5.9 corresponding to isomer); ^{13}C ($CDCl_3$, 22.6 MHz) δ 22.6, 25.4, 25.7, 26.0, 26.3, 26.8, 27.07, 27.3, 27.7, 28.2, 39.7, 49.3, 76.6, 111.7, 116.8, 138.5, 144.6; exact mass, m/z 292.2763 (calcd for $C_{20}H_{36}O$, 292.2757). Anal. calcd for $C_{20}H_{36}O$: C, 82.12; H, 12.41. Found: C, 82.48; H, 12.37.

5(Z),5(E)-Cycloeicosen-1-one **28**: Potassium hydride (24.01% w/w in oil, 26.5 mg, 0.158 mmol) was washed in a septum-covered flask with dry hexane (2 × 3 mL). Residual solvent was evaporated by a stream of dry nitrogen and dry 1,2-dimethoxyethane (DME) (5 mL) was injected into the

flask. Alcohols **27** (31 mg, 0.106 mmol) in DME (1 mL + 1 mL rinse) were injected and the mixture was stirred at room temperature for 15 min and then refluxed for 15 min. Aqueous ammonium chloride (10% w/w, 10 mL) was added and the aqueous phase was extracted with ether (2 × 10 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 2% ethyl acetate — hexane and Kugelrohr distillation gave ketones **28** (24.2 mg, 78%) as a pure (v.p.c., 10% QF-1) mixture of isomers: bp 68 — 72°C (0.003 mm); IR (neat) 1715, 975, 738 cm^{-1} ^1H NMR ($CDCl_3$, 200 MHz) δ 1.1 — 1.4 (m, 22H), 1.62 (m, 4H), 2.0 (m, 4H), 2.35 (m, 4H), 5.32 (m, 2H); ^{13}C ($CDCl_3$, 50.3 MHz) δ 23.4, 23.5, 23.6, 26.6, 27.0, 27.2, 27.4, 27.5, 27.7, 27.8, 28.1, 28.3, 28.4, 28.6, 28.9, 29.3, 29.7, 31.7, 32.2, 41.4, 41.9, 42.5, 76.3, 128.9, 129.5, 131.0, 131.9, 211.3, 211.7; exact mass, m/z 292.2765 (calcd for $C_{20}H_{36}O$, 292.2757). Anal. calcd for $C_{20}H_{36}O$: C, 82.12; H, 12.40. Found: C, 82.31; H, 12.42.

(E)-2-[1-Hydroxy-2-(phenylseleno)ethyl]-5-cyclohexadecen-1-one **29**: Methyllithium (1.53 M in ether, 0.86 mL, 1.32 mmol) was injected at room temperature into a stirred

solution of silyl enol ether **19** (410 mg, 1.32 mmol) and tetramethylethylenediamine (0.2 mL, 1.32 mmol) in ether (8 mL). The resulting mixture was stirred for 1 h and was then cooled in an ice-water bath. Anhydrous zinc chloride (0.69 M n ether, 0.96 mL, 0.66 mmol) was added dropwise and the mixture was stirred for a further 10 min. Phenylselenoacetaldehyde (278 mg, 1.38 mmol) in ether (3 mL + 1 mL rinse) was injected rapidly over ca. 3 sec. Stirring at 0°C was continued for a further 20 min and the mixture was then partitioned between ether (15 mL) and saturated aqueous ammonium chloride (15 mL). The organic layer was separated and the aqueous phase was extracted with ether (2 × 15 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm) with 15% ethyl acetate — hexane gave hydroxyselenides **29** (540 mg, 93%) as a pure (TLC, silica, 20% ethyl acetate — hexane) mixture of diastereoisomers: IR (neat) 3450, 1705, 1585, 750, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.2 — 1.45 (m, 13H), 1.56 (m, 4H), 1.8 (m, 1H), 2.0 (m, 4H), 2.2 — 2.55 (m, 2H), 2.8 (d, J = 4 Hz, 0.5H), 2.9 — 3.10 (m, 3H), 3.45 (d, J = 8 Hz, 0.43 H), 3.8 (m, 1H), 5.35 (m, 2H), 7.2 (m, 3H), 7.5 (m, 2H); ^{13}C ($CDCl_3$, 50.3 MHz) δ 22.0, 22.3, 25.5, 25.8, 25.9, 26.0, 26.2, 26.2, 26.5, 26.8, 27.1,

27.9, 29.5, 30.1, 31.6, 33.6, 34.0, 42.7, 43.0, 52.5, 53.7, 70.4, 70.9, 127.3, 129.1, 129.2, 129.4, 132.0, 132.4, 132.9, 214.3, 216.4; exact mass, m/z 436.1877 (calcd for $C_{24}H_{36}O_2Se$, 436.1871). Anal. calcd for $C_{24}H_{36}O_2Se$: C, 66.189; H, 8.33; O, 7.34. Found: C, 66.12; H, 8.22; O, 7.70.

(E)- and (Z)-2-[1-Hydroxy-2-(phenylseleno)ethyl]-5-cyclohexadecen-1-one **30**: The procedure employed for **29** was followed using methyllithium (1.53 M in ether, 0.13 mL, 0.18 mmol), silyl enol ether **20a,b** (56 mg, 0.18 mmol), TMEDA (0.03 mL, 0.18 mmol) in ether (2 mL), anhydrous zinc chloride (0.69 M in ether, 0.13 mL, 0.09 mmol), and phenylselenoacetaldehyde (38.7 mg, 0.19 mmol) in ether (1 mL + 1 mL rinse). The reaction mixture was stirred at 0°C for 20 min and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 15 cm) with 15% ethyl acetate — hexane gave hydroxyselenide **30** (73.1 mg, 92%) as a pure (TLC, silica, 20% ethyl acetate — hexane) mixture of isomers: IR (CCl_4) 3500, 1710, 1480, 1440, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.1 — 1.4 (m, 15H), 1.55 (m, 2H), 1.75 (m, 1H), 2.0 (m, 4H), 2.5 (m, 2H), 2.8 — 3.1 (m, 3H), 3.8 (m, 1H), 5.35 (m, 2H), 7.25 (m, 3H), 7.5 (m, 2H); exact mass, m/z

436.1881 (calcd for $C_{24}H_{36}O_2Se$, 436.1871). Anal. calcd for $C_{24}H_{36}O_2Se$: C, 66.18; H, 8.33. Found: C, 65.89; H, 8.28.

(E)-2-Ethenyl-5-cyclohexadecen-1-one **31**: The procedure employed for **26** was followed using triethylamine (0.49 mL, 3.5 mmol), hydroxyselenides **29** (307 mg, 0.705 mmol) in dry dichloromethane (3 mL), and methanesulfonyl chloride (0.16 mL, 2.11 mmol) in dichloromethane (3 mL + 1 mL rinse). The reaction mixture was stirred for 30 min at room temperature and was worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm) first with hexane (to elute diphenyldiselenide) and then with 1% ethyl acetate — hexane gave olefin **31** (153 mg, 82.7%) as a pure (TLC, silica, 5% ethyl acetate — hexane) colorless oil: IR (neat) 1710, 135, 970, 920 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.3 (m, 14H), 1.52 (m, 3H), 1.72 (m, 1H), 1.95 (m, 4H), 2.1 — 2.55 (m, 2H), 3.21 (m, 1H), 5.1 (dd, J = 16, 9 Hz, 2H), 5.35 (m, 2H), 5.67 (dt, J = 16, 9 Hz, 1H); ^{13}C ($CDCl_3$, 50.3 MHz) δ 23.1, 25.8, 26.1, 26.4, 27.0, 27.1, 28.3, 29.1, 30.0, 31.8, 40.9, 54.8, 117.9, 129.7, 132.1, 136.6, 212.1; exact mass, m/z 262.2295 (calcd for $C_{18}H_{30}O$, 262.2291).

(E)- and (Z)-2-Ethenyl-5-cyclohexadecen-1-one **32**: The procedure employed for **26** was followed using triethylamine (0.25 mL, 1.79 mmol), hydroxyselenide **30** (156 mg, 0.358 mmol) in dry dichloromethane (2 mL), and methanesulfonyl chloride (0.83 mL, 1.07 mmol) in dichloromethane (1 mL + 1 mL rinse). The reaction mixture was stirred at room temperature for 30 min and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm) first with hexane (to elute diphenyldiselenide) and then with 2% ethyl acetate — hexane gave olefin **32** (80 mg, 85%) as a pure (TLC, silica, 5% ethyl acetate — hexane) mixture of isomers: IR (neat) 1711, 1635, 970, 920, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.0 — 2.15 (m, 22H), 2.35 (m, 1H), 2.55 (m, 1H), 3.3 (m, 1H), 5.15 (m, 2H), 5.4 (m, 2H), 5.73 (m, 1H); ^{13}C ($CDCl_3$, 50.3 MHz) δ 22.6, 22.7, 25.0, 25.6, 25.9, 26.1, 26.4, 26.6, 26.7, 26.8, 26.9, 27.2, 27.6, 28.0, 28.8, 29.8, 31.5, 40.5, 41.0, 54.5, 56.6, 116.8, 117.5, 128.6, 129.4, 130.4, 131.7, 136.4, 136.5, 210.9, 211.3; exact mass, m/z 262.2291 (calcd for $C_{18}H_{30}O$, 262.2291).

(E)-1,2-Diethenyl-5-cyclohexadecen-1-ol **33**: Ketone **31** (85 mg, 0.32 mmol) in THF (3 mL + 1 mL rinse) was injected dropwise at -78°C into a stirred solution of vinyllithium

(1.63 M, in THF, 0.595 mL, 0.96 mmol). The mixture was stirred for 30 min and glacial acetic acid (0.037 mL, 0.64 mmol) was added. The reaction mixture was poured into saturated aqueous ammonium chloride and extracted with ether (2 × 10 mL). The organic extracts were washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 2% ethyl acetate — hexane gave alcohols **33** (84 mg, 89%) as a pure (TLC, 5% ethyl acetate — hexane) mixture of isomers: IR (neat) 3500, 1640, 970, 920 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.0 — 2.1 (m, 25H), 2.35 (m, 1H), 5.0 — 5.6 (m, 7H), 5.95 (dd, J = 17, 1 Hz, 1H); ^{13}C ($CDCl_3$, 50.3 MHz) δ 21.1, 21.4, 25.5, 25.8, 26.5, 26.6, 26.8, 26.9, 27.1, 27.3, 27.4, 27.7, 27.8, 28.2, 28.7, 29.3, 29.5, 29.8, 31.8, 32.2, 38.2, 39.2, 47.6, 50.0, 112.0, 113.0, 117.1, 119.6, 129.8, 130.5, 131.7, 138.4, 142.3, 143.7; exact mass, m/z 290.2610 (calcd for $C_{20}H_{34}O$, 290.2601). Anal. calcd for $C_{20}H_{34}O$: C, 82.59; H, 11.95. Found: C, 82.69; H, 11.79.

(Z)- and (E)-1,2-Diethenyl-5-cyclohexadecen-1-ols **34**: The procedure employed for **33** was followed using ketone **32** (142 mg, 0.54 mmol) in THF (3 mL + 1 mL rinse) and vinyllithium (1.63 M in THF, 0.99 mL, 1.62 mmol). The reaction mixture was stirred at -78°C for 30 min and glacial acetic

acid (0.062 mL, 1.08 mmol) was added. Workup and flash chromatography of the residue over silica gel (1 × 15 cm) with 3% ethyl acetate — hexane gave alcohol **34** (133 mg, 85%) as a pure (TLC, silica, 5% ethyl acetate — hexane) mixture of isomers: IR (neat) 3500, 1640, 970, 920, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.1 — 2.2 (m, 25H), 2.4 (m, 1H), 5.02 — 5.3 (m, 4H), 5.35 — 5.75 (m, 3H), 6.01 (m, 1H); ^{13}C ($CDCl_3$, 50.3 MHz), δ (vinylic signals) 111.9, 112.0, 112.9, 113.0, 117.3, 118.9, 119.6, 128.5, 129.8, 129.9, 130.5, 131.7, 138.2, 138.4, 138.6, 143.7, 144.6, 192.3, 235.3, 235.5; exact mass, m/z 290.2610 (calcd for $C_{20}H_{34}O$, 290.2601). Anal. calcd for $C_{20}H_{34}O$: C, 82.69; H, 11.79. Found: C, 82.67; H, 11.77.

(E)-[(1,2-Diethenyl-5-cyclohexadecen-1-yl)oxy]trimethylsilanes **35**: The procedure employed for **17** was followed using chlorotrimethylsilane (0.082 mL, 0.64 mmol), alcohol **33** (124 mg, 0.429 mmol), and hexamethyldisilazane (0.11 mL, 0.51 mmol) in dry DMSO (2 mL). The reaction mixture was stirred at room temperature for 30 min and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 15 cm) with 5% ethyl acetate — hexane gave silyl ethers **35** (149 mg, 95%) as a pure (TLC, silica, 5% ethyl acetate —

hexane) mixture of isomers: IR (neat) 1640, 1250, 970, 920, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.1H (s, 9H), 1.0 — 2.1 (m, 24H), 2.34 (t, J = 12 Hz, 1H), 4.9 — 5.2 (m, 4H), 5.4 (m, 3H), 5.95 (m, 1H); exact mass, m/z 362.3006 (calcd for $C_{23}H_{42}OSi$, 362.4080).

(1,5,9-Cycloeicosatrien-1-yloxy)trimethylsilane **36**: Silyl ethers **35** (80 mg, 0.22 mmol) were sealed in an ampoule under argon and immersed for 15 min in a preheated oil bath at 200°C. Kugelrohr distillation of the resulting oil gave silyl enol ethers **36** (76.5 mg, 95.6%) as a pure (TLC, silica, hexane) mixture of isomers: bp 90 — 95°C (0.002 mm); IR (neat) 1670, 1250, 970, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.15 (s, 9H), 1.1 — 1.4 (m, 17H), 1.9 — 2.1 (m, 12H), 4.4 (m, 1H), 5.32 (m, 4H); ^{13}C ($CDCl_3$, 50.3 MHz) δ 0.4, 0.6, 25.2, 25.6, 26.3, 26.5, 27.3, 27.5, 27.6, 27.8, 27.9, 28.1, 28.4, 28.6, 28.7, 28.8, 31.7, 32.0, 32.7, 32.9, 33.1, 36.0, 108.7, 130.0, 130.3, 130.5, 130.7, 130.9, 149.5; exact mass, m/z 362.3004 (calcd for $C_{23}H_{42}OSi$, 362.4004). Anal. calcd for $C_{23}H_{42}OSi$: C, 76.18; H, 11.67. Found: C, 76.12; H, 11.47.

5,9-Cycloeicosadien-1-one **37**: Tetrabutylammonium fluoride (1 M IN THF, 0.1 mL, 0.10 mmol) was added to a stirred

solution of silyl enol ethers **36** (35 mg, 0.096 mmol) in THF (2 mL). The resulting mixture was stirred at room temperature for 30 min and water (5 mL) was added. The aqueous phase was extracted with ether and the combined organic extracts were dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 2% ethyl acetate — hexane gave ketones **37** (26.8 mg, 96%) as a pure (TLC, silica, 5% ethyl acetate — hexane) mixture of isomers: IR (neat) 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.1 — 1.45 (m, 14H), 1.6 (m, 4H), 2.01 (m, 8H), 2.4 (m, 4H), 5.4 (m, 4H); exact mass, m/z, 290.2612 (calcd for $C_{20}H_{34}O$, 290.2601).

(E)- and (Z)-[(1,2-diethenyl-5-cyclohexadecen-1-yl)oxy]-trimethylsilanes **38**: The procedure employed for **17** was followed using chlorotrimethylsilane (0.087 mL, 0.68 mmol), alcohol **34** (133 mg, 0.457 mmol), and hexamethyldisilazane (0.12 mL, 0.54 mmol) in dry DMSO (2 mL). The reaction mixture was stirred at room temperature for 30 min and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 15 cm) with 4% ethyl acetate — hexane gave silyl ethers **38** (153 mg, 92%) as a pure (TLC, silica, 5% ethyl acetate — hexane) mixture of isomers: IR (neat) 1640,

1250, 970, 920, 850, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.15 (4 s, 9H), 1.1 — 2.3 (m, 25H), 4.9 — 5.2 (m, 4H), 5.25 — 5.5 (m, 2H), 5.62 (m, 1H), 5.95 (m, 1H); exact mass, m/z 362.3004 (calcd for $C_{23}H_{42}OSi$, 362.4004). Anal. calcd for $C_{23}H_{42}OSi$: C, 76.18; H, 11.67. Found: C, 76.17; H, 11.77.

(1,5,9-Cycloeicosatrien-1-yloxy)trimethylsilanes **39**: Silyl ethers **38** (109 mg, 0.3 mmol) were sealed in an ampoule under argon and immersed for 15 min in a preheated oil bath at 200°C. Kugelrohr distillation of the resulting oil gave silyl enol ethers **39** (102 mg, 92%) as a pure (TLC, silica, hexane) mixture of isomers: bp 80 — 90°C (0.001 mm); IR (neat) 1670, 1250, 970, 850, 720 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.8 (s, 9H), 1.1 — 1.6 (m, 16H), 2.0 (m, 12H), 4.45 (m, 0.6H), 4.72 (m, 0.4H), 5.4 (m, 4H); exact mass, m/z 362.3004 (calcd for $C_{23}H_{42}OSi$, 362.4004). Anal. calcd for $C_{23}H_{42}OSi$: C, 76.18; H, 11.67. Found: C, 76.34; H, 11.83.

5,9-Cycloeicosadien-1-one **40**: The procedure employed for **37** was followed using TBAF (1 M in THF, 0.13 mL, 0.13 mmol) and silyl enol ethers **39** (48 mg, 0.13 mmol) in THF (2 mL). The reaction mixture was stirred at room

temperature for 30 min and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 15 cm) with 3% ethyl acetate — hexane gave ketones **40** (37 mg, 97%) as a pure (TLC, silica, 5% ethyl acetate — hexane) mixture of isomers: IR (neat) 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.1 — 1.4 (m, 14H), 1.6 (m, 4H), 2.02 (m, 8H), 2.4 (m, 4H), 5.4 (m, 4H); exact mass, m/z 290.2612 (calcd for $C_{20}H_{34}O$, 290.2601).

Catalytic hydrogenation of (E)-hydroxyselenides **29** with Wilkinson's catalyst; 2-[1-Hydroxy-2-(phenylseleno)ethyl]-cyclohexadecanone **25**: The procedure employed for **23** was followed using hydroxyselenide **29** (60 mg, 0.137 mmol) in degassed benzene (1 mL + 1 mL rinse) and Wilkinson's catalyst (30 mg, 0.03 mmol) in degassed benzene (2 mL). The reaction mixture was stirred at room temperature for 12 h under hydrogen (10 psi). As the reaction was judged incomplete (TLC, silica, 15% ethyl acetate — hexane), a second portion of catalyst (30 mg) in degassed benzene (1 mL + 1 mL rinse) was added and the mixture was stirred for a further 13 h and worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel gave hydroxyselenides **25** (49 mg, 80%) as a pure (TLC,

silica, 15% ethyl acetate — hexane) crystalline solid that was identical [IR, ^{1}H NMR (200 MHz) and mass spectrum] to a sample prepared by the titanium tetrachloride induced aldol condensation.

Catalytic hydrogenation of (E) and (Z)-hydroxy-selenides **30** with Wilkinson's catalyst; 2-[1-hydroxy-2-(phenylseleno)ethyl]cyclohexadecanone **25**: Hydroxyselenides **30** (177 mg, 0.406 mmol) in degassed benzene (2 mL + 1 mL rinse) were injected into a stirred solution of Wilkinson's catalyst (77 mg, 0.083 mmol) in degassed benzene (3 mL) that had been presaturated with hydrogen for 1 h. The reaction mixture was stirred at room temperature for 12 h under hydrogen (10 psi). As the reaction was judged to be incomplete (TLC, silica, 15% ethyl acetate — hexane), a second portion of catalyst (33 mg) in degassed benzene (1 mL + 1 mL rinse) was added and the mixture was stirred for a further 10 h at room temperature. The solvent was evaporated and the mixture was filtered through a small pad of Florisil (1 × 2 cm) using 15% ethyl acetate — hexane as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel gave hydroxyselenide **25** (143 mg, 80.8%) that was identical [IR, ^{1}H NMR (200 MHz) and mass

spectrum] with a sample prepared by the titanium tetrachloride induced aldol condensation.

(E)-4-(Phenylseleno)but-2-enal **44**: Phenylselenenyl chloride (3.1 g, 16.1 mmol) in ether (40 mL + 2 mL rinse) was injected over 2.5 h (syringe pump) into a stirred solution of silyl enol ether **43**[85] (2.5 g, 15.8 mmol) in ether (25 mL) at -78°C. The reaction mixture was stirred for 30 min more and was then poured into 10% aqueous sodium bicarbonate (30 mL). The organic phase was separated and the aqueous layer was extracted with ether (2 × 30 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (5 × 15 cm) first with hexane (to elute diphenyldiselenide) and then with 15% ethyl acetate — hexane gave aldehyde **44** (3.2 g, 91.1%) as a homogeneous (TLC, silica, 15% ethyl acetate — hexane), pale yellow oil: IR (neat) 1680, 1620, 1575, 740, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.70 (d, J = 8.4 Hz, 2H), 5.8 (dd, J = 16, 8 Hz, 1H), 6.89 (dt, J = 16, 8 Hz, 1H), 9.5 (d, J = 8 Hz, 1H); exact mass, m/z 225.9892 (calcd for $C_{10}H_{10}OSe$, 225.9894).

2-[(E)-1-Hydroxy-4-(phenylseleno)but-2-enyl)cyclohexanone **45**: Methyllithium (1.52 M in ether, 0.46 mL,

0.69 mmol) was injected dropwise over 10 min at room temperature into a stirred solution of silyl enol ether **69** (119 mg, 0.69 mmol) in ether (4 mL). The reaction mixture was stirred for 20 min and was then cooled in an ice-water bath. Anhydrous zinc chloride[76] (0.69 M in ether, 0.5 mL, 0.34 mmol) was added dropwise and stirring at 0°C was continued for a further 10 min. Aldehyde **44** (172 mg, 0.76 mmol) in ether (2 mL + 1 mL rinse) was injected rapidly over ca. 3 sec. The reaction mixture was stirred for 10 min at 0°C and was then partitioned between ether (10 mL) and saturated aqueous ammonium chloride (10 mL). The organic phase was separated and the aqueous layer was extracted with ether (2 × 15 mL). The combined ether extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm) with 15% ethyl acetate — hexane afforded hydroxyselenide **45** as a pure (TLC, silica, 20% ethyl acetate — hexane) mixture of isomers (185 mg, 82.3%): IR (neat) 3450, 1705, 1560, 965, 740, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.9 — 2.4 (m, 6H), 2.5 — 3.0 (m, 4H), 3.8 (m, 2H), 4.3 (m, 1H), 5.3 (m, 1H), 5.60 (m, 1H), 7.1 (m, 3H), 7.2 (m, 2H); exact mass, m/z 323.2817 (calcd for $C_{16}H_{20}O_2Se$, 323.2802).

Treatment of hydroxyselenide **45** with triethylamine and methanesulfonyl chloride: Triethylamine (0.135 mL, 0.968 mmol) was injected into a stirred solution of **45** (63 mg, 0.194 mmol) in dichloromethane (2 mL) and methanesulfonyl chloride (0.04 mL, 0.586 mmol) in dichloromethane (2 mL + 1 mL rinse) was injected over a period of 1 h (syringe pump). The mixture was stirred for a further arbitrary period of 15 min and then poured into hexane (10 mL) and ether (10 mL). The precipitate was filtered off and the solvent was evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) first with hexane (to elute diphenyldiselenide), and then with 10% ethyl acetate — hexane gave a pale yellow oil (31 mg) corresponding (IR and ^{1}H NMR) to **46**, which decomposed upon standing at room temperature.

Trimethyl-2-propynylsilane **59**:[97] The literature procedure[97] was followed: Propargyl bromide (2.0 g, 16.8 mmol) was added at room temperature to a mechanically stirred suspension of magnesium (5.0 g, 0.20 mol) and mercuric chloride (150 mg, 0.55 mmol) in dry ether (30 mL). An exothermic reaction occurred immediately. Ether (30 mL) was added rapidly and the flask was immersed in a bath at -20°C. Propargyl bromide (22.0 g, 0.184 mol) in

ether (50 mL) was then added dropwise over a period of 1 h with sufficient cooling to maintain the temperature at -20°C. The mixture was stirred for an additional 30 min and then chlorotrimethylsilane (25.6 mL, 0.20 mmol) in ether (50 mL) was added over 1 h. The flask was allowed to warm up to room temperature over 1 h. The precipitate was filtered off and the filtrate was poured into saturated aqueous ammonium chloride (100 mL). The organic layer was washed with water (50 mL) and brine (50 mL), and dried ($MgSO_4$). The solvent was removed at 1 atmosphere by spinning-band distillation and the product was distilled (bp 89 — 91°C) (lit.[97] 90°C) to give a clear liquid (18 g, 80%). The material was 90% pure by VPC (10% QF-1) and had IR (neat) 3300, 2120, 1250, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.1 (s, 1H), 1.45 (d, J = 2.9 Hz, 2H), 1.80 (t, J = 3 Hz, 1H).

4-(Trimethylsilyl)-2-butyn-1-ol **60**: The silyl acetylene **59** (4.9 g, 43.6 mmol) in dry ether (40 mL) was injected at room temperature over a period of 1 h (syringe pump) into a stirred solution of n-butyllithium (1.5 M in hexane, 29.0 mL, 43.6 mmol). Stirring was continued for a further 0.5 h and dry paraformaldehyde (1.70 g, 56.6 mmol) was added in small portions from a side-arm addition tube.

Stirring was continued for 12 h and the mixture was then quenched with saturated aqueous ammonium chloride (40 mL). The organic layer was separated and the aqueous phase was extracted with ether (20 mL). The combined extracts were dried ($MgSO_4$) and evaporated. Kugelrohr distillation gave alcohol **60** (4.89 g, 79%) as a homogeneous (TLC, silica, 20% ethylacetate — hexane), colorless oil which had: bp 88 — 92°C, (11 mm); IR (neat) 3300, 2220, 1250, 850 cm^{-1}; ^1H NMR (DMSO, 80 MHz) δ 0.01 (s, 9H), 1.52 (t, J = 2.4 Hz, 2H), 4.1 (dt, J = 4.4, 2.4 Hz, 2H), 4.80 (t, J = 6 Hz, 1H).

Preparation of 4-(trimethylsilyl)2-butynal **58**: This aldehyde is sensitive and is best made and used within 24 h. Pyridinium chlorochromate[100] (11.89 g, 56.0 mmol) was added in small portions at 0°C to a stirred solution of the alcohol **60** (1.91 g, 14.0 mmol) in dry dichloromethane (70 mL). The cold bath was removed and stirring was continued for a further 1 h during which time the mixture warmed to room temperature. The reaction was judged to be complete (TLC, silica, 20% ethyl acetate — hexane) at this stage and the dark brown mixture was poured into ice-cold hexane (100 mL) and stirred vigorously for 15 min. The brown suspension was then filtered through Celite (2.5 ×

10 cm), using hexane (100 mL) for washings. The combined filtrates were dried ($MgSO_4$), concentrated to ca. 10 mL under waterpump vacuum, and kept over 3Å molecular sieves (500 mg) at 0°C.

[3-(Trimethylsilyl)-1-propynyl]benzenepropanol **62**: A solution of aldehyde **58** (3-fold excess, see preparation) in dry hexane (10 mL) was added dropwise at 0°C to a stirred solution of Grignard reagent **61** (1.41 M in ether, 1.42 mL, 2.0 mmol). The cold bath was removed and the mixture was stirred for 15 min. Saturated aqueous ammonium chloride (10 mL) was added and the aqueous layer was extracted with ether (10 mL). The combined organic layers were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm) with 12% ethyl acetate — hexane gave hydroxysilane **62** as a clear, homogeneous (TLC, silica, 20% ethyl acetate — hexane) oil (390 mg, 79%): IR (neat) 3335, 2200, 1600, 1250, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.10 (s, 9H), 1.50 (d, J = 2 Hz, 2H), 1.70 (d, J = 8 Hz, 1H), 1.98 (m, 2H), 2.76 (t, J = 10.4 Hz, 2H), 4.34 (m, 1H), 7.23 (m, 5H); exact mass, m/z 246.1440 (calcd. for $C_{15}H_{22}OSi$, 246.4101.

(Z)-[3-(Trimethylsilyl)-1-propenyl]benzenepropanol **63**: A mixture of acetylene **62** (160 mg, 0.651 mmol), Lindlar catalyst[101] (40 mg), and dry hexane (3 mL) was stirred at room temperature under hydrogen (50 psi) for 12 h. The catalyst was removed by filtration through a pad of Celite (1 × 2 cm) using ether (15 mL) as a rinse. The solvent was evaporated and flash chromatography of the residue over silica gel (1 × 15 cm) with 12% ethyl acetate — hexane gave the olefin **63** (153 mg, 95%) as a pure (TLC, silica, 20% ethyl acetate — hexane) oil: IR (neat) 3335, 1640, 1600, 1250, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.08 (s, 9H), 1.31 (broad s, 1H), 1.53 (d, J = 8 Hz, 2H), 1.65 — 2.0 (m, 2H), 2.72 (m, 2H), 4.4 (m, 1H), 5.5 [m, incorporating a J = 8.5 Hz (observed by decoupling experiments), 2H], 7.25 (m, 5H); exact mass, m/z ($M^+ - H_2O$) 230.1487 (calcd for $C_{15}H_{24}OSi$, 248.1410).

(E)-3,5-Hexadienylbenzene **64**:[113] Potassium hydride (24.01% w/w in oil, 200 mg, 1.2 mmol) was washed in a septum-covered flask with dry hexane (2 × 5 mL). Residual solvent was evaporated by a stream of dry nitrogen and THF (7 mL) was added to the flask. The hydroxysilane **63** (100 mg, 0.402 mmol) in THF (3 mL + 1 mL rinse) was then injected dropwise and the mixture was stirred at room

temperature for 1 h. Aqueous ammonium chloride (10% w/w, 50 mL) was added and the aqueous layer was extracted with ether (2 × 25 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) with 1% ethyl acetate in hexane yielded the diene **64** (47 mg, 74%) as a homogeneous (TLC, silica, 2% ethyl acetate — hexane), colorless oil which had: IR (neat) 1650, 1600, 1000, 900 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.35 (dt, J = 12, 8 Hz, 2H), 2.7 (t, J = 8 Hz, 2H), 4.95 (dd, J = 10.1, 1.4 Hz, 1H), 5.10 (dd, J = 16.7, 1.4 Hz, 1H), 5.7 (dt, J = 14.9, 6.5 Hz, 1H), 6.1 (dd, J = 14.9, 10.2 Hz, 1H), 6.3 (dt, J = 16.7, 10.2 Hz, 1H), 7.2 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 343.3, 35.68, 115.1, 125.8, 128.3, 128.4, 131.5, 134.1, 137.1, 141.7; exact mass, m/z 158.1098 (calcd for $C_{12}H_{14}$, 158.1091).

5-Methyl-1-(trimethylsilyl)-2-pentadecyn-4-ol **66**: The procedure employed for **62** was followed using aldehyde **58** (3-fold excess) and Grignard reagent **65** (0.27 M, in ether, 7.4 mL, 1.99 mmol). The reaction mixture was stirred for 0.5 h and then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 15 cm) with 5% ethyl acetate — hexane gave **66** (370 mg,

60%) as a colorless, homogeneous (TLC, silica, 10% ethyl acetate — hexane) oil: IR (neat) 3350, 2200, 1250, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.10 (s, 9H), 0.7 — 1.0 (m, 6H), 1.1 — 4.0 (m, 16H), 1.45 — 1.80 (m, 4H), 4.25 (m, 1H); exact mass, m/z 310.2680 (calcd for $C_{19}H_{38}OSi$, 310.5826).

(Z)-5-Methyl-1-(trimethylsilyl)-2-pentadecen-4-ol **67**: The procedure employed for **63** was followed using acetylene **66** (180 mg, 0.58 mmol) and Lindlar catalyst[101] (50 mg) in dry hexane (3 mL). The reaction mixture was stirred at room temperature under hydrogen (50 psi) for 12 h and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm) with 5% ethyl acetate — hexane gave olefin **67** (173 mg, 95.5%) as a pure (TLC, silica, 10% ethyl acetate — hexane) colorless oil: IR (neat) 3335, 1645, 1250, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.05 (s, 9H), 0.9 (m, 6H), 1.10 — 1.70 (m, 22H), 4.19 (m, 1H), 5.25 — 5.70 (m, 2H); exact mass, m/z ($M^+ - H_2O$) 294.2742 (calcd for $C_{19}H_{20}OSi$, 312.3924).

(E)-5-Methyl-1,3-pentadecadiene **68**: The procedure employed for **64** was followed using potassium hydride (24.01% w/w in oil, 160 mg, 0.96 mmol) in THF (7 mL) and

hydroxysilane **67** (100 mg, 0.32 mmol) in THF (3 ML + 1 mL rinse). The reaction mixture was stirred at room temperature for 1 h and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 15 cm) with 1% ethyl acetate — hexane gave diene **68** (60 mg, 84.3%) as a pure (TLC, silica, 2% ethyl acetate — hexane) colorless oil which had: IR (neat) 1640, 1600, 1000, 895 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.85 (t, J = 6 Hz, 3H), 0.98 (d, J = 7.2 Hz, 3H), 1.15 (m, 18H), 4.95 (d, J = 17 Hz, 1H), 5.10 (d, J = 10 Hz, 1H), 5.6 (dd, J = 14.4, 7.2 Hz, 1H), 6.0 (dd, J = 14.4, 9.7 Hz, 1H); 6.3 (dt, J = 17.2, 10 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 14.0, 20.4, 22.7, 27.7, 29.3, 29.6, 29.7, 29.8, 31.9, 36.7, 37.0, 114.5, 129.1, 137.5, 141.5; exact mass, m/z 222.2347 (calcd for $C_{16}H_{30}$, 222.2319). Anal. calcd for $C_{16}H_{30}$: C, 86.39; H, 13.60. Found: C, 86.56; H, 13.56.

2-[1-Hydroxy-4-(trimethylsilyl)-2-butynyl]cyclohexanone **70**: (Note: It is convenient to prepare the enolate of **69** during the preparation of aldehyde **58**.) Methyllithium (1.56 M in ether, 3.0 mL, 4.7 mmol) was injected by syringe pump over ca. 5 min at room temperature into a stirred mixture of silyl enol ether **69** (800 mg, 4.7 mmol)

and anhydrous tetramethylethylenediamine (0.7 mL, 4.7 mmol) in dry ether (15 mL). The resulting solution was stirred for 1 h and was then cooled in an ice-water bath. Anhydrous zinc chloride[76] (0.69 M in ether, 3.4 mL, 2.35 mmol) was added dropwise over a period of 10 min and stirring at 0°C was continue for a further 10 min. The aldehyde **58** (ca. 3-fold excess is used) in ether (10 mL) was injected rapidly over ca. 3 sec. The reaction mixture was stirred for 20 min and was then partitioned between ether (30 mL) and aqueous saturated ammonium chloride (30 mL). The organic layer was separated and the aqueous layer was extracted with ether (2 × 15 mL). The combined ether extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm) with 15% ethyl acetate — hexane afforded hydroxylsilane **70** as a pure (TLC, silica, 20% ethyl acetate — hexane) mixture of diastereoisomers (825 mg, 76%): IR (neat) 3450, 2230, 1705, 1250, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.01 (2 s, 9H), 1.30 — 1.80 (m, 5H), 1.85 (m, 1H), 2.0 (m, 1H), 2.01 — 2.37 (m, 3H), 2.48 (m, 1H), 3:1 (d, J = 7.2 Hz, 0.44H), 3.3 (d, J = 4 Hz, 0.56 H), 4.48 (m, 0.56H), 4.58 (m, 0.44H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 02.1, 7.0, 7.1, 24.4, 24.5, 26.8, 27.6, 27.8, 30.4, 42.0, 42.2, 55.6, 56.7, 62.1, 63.0, 77.5, 77.7,

83.7, 84.2, 212.4, 213.1; exact mass, m/z 238.1374 (calcd for $C_{13}H_{22}O_2Si$, 238.2469). Anal. calcd for $C_{13}H_{22}O_2Si$: C, 65.47; H, 9.30. Found: C, 65.70; H, 9.34.

2-[1-Hydroxy-4-(trimethylsilyl)-2-butynyl]cycloheptanone **74**: The procedure employed for **70** was followed using methyl lithium (1.56 M in ether, 3.2 mL, 5.0 mmol), silyenol ether **73** (921 mg, 5.0 mmol), anhydrous tetramethylethylenediamine (0.75 mL, 5.0 mmol) in ether (20 mL), anhydrous zinc chloride (0.69 M in ether, 3.6 mL, 2.5 mmol), and aldehyde **58** (ca. 3-fold excess) in ether (10 mL). The reaction mixture was stirred at 0°C for 45 min and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 15 cm) with 15% ethyl acetate — hexane gave hydroxysilane **74** as a pure (TLC, silica, 20% ethyl acetate — hexane) mixture of diastereoisomers (1.08 g, 85.6%): IR (neat) 3450, 2220, 1695, 1250, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.05 (2 s, 9H), 1.10 — 1.70 (m, 7H), 1.75 — 2.10 (m, 3H), 2.45 (m, 2H), 2.75 (m, 1H), 3.0 (d, J = 7.2 Hz, 0.5H), 3.15 (d, J = 7.2 Hz, 0.5H), 4.5 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -2.0, 7.1, 7.1, 23.4, 24.0, 26.4, 28.1, 28.9, 29.0, 29.3, 30.0, 44.0, 44.2, 57.4, 58.0, 64.2, 64.3, 78.0, 78.1, 83.8, 84.2, 94.7, 185.6, 215.7,

216.6; exact mass, m/z 252.1535 (calcd for $C_{14}H_{24}O_2Si$, 252.2551). Anal. calcd for $C_{14}H_{24}O_2Si$: C, 66.59; H, 9.58. Found: C, 66.88; H, 9.53.

2[1-Hydroxy-4-(trimethylsilyl)-2-butynyl]-cyclododecanone **78**: The procedure employed for **70** was followed using methyllithium (1.56 M in ether, 3.0 mL, 4.7 mmol), silyl enol ether **77** (1.21 g, 4.7 mmol), anhydrous tetramethylethylenediamine (0.7 mL, 4.7 mmol) in ether (15 mL), anhydrous zinc chloride[76] (0.69 M in ether, 3.4 mL, 2.35 mmol), and aldehyde **58** (ca. 3-fold excess) in ether (10 mL). The reaction mixture was stirred at 0°C for 45 min and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 15 cm) with 15% ethyl acetate — hexane gave hydroxysilane **78** as a pure (TLC, silica, 20% ethyl acetate — hexane) mixture of isomers (1.19 g, 78%): IR (neat) 3400, 2200, 1702, 1250, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.10 (2 s, 9H), 1.1 — 2.0 (m, 20H), 2.1 — 3.95 (m, 4H), 4.53 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -2.1, -2.0, 21.4, 21.6, 22.0, 22.2, 23.1, 23.4, 23.6, 23.9, 24.1, 25.5, 25.8, 26.0, 26.2, 27.2, 39.2, 58.3, 58.6, 63.0, 63.4, 78.0, 84.5, 212.7, 213.6; exact mass, m/z 322.2324 (calcd for $C_{19}H_{34}O_2Si$, 322.3380). Anal. calcd for $C_{19}H_{34}O_2Si$: C,

70.73; H, 10.63. Found: C, 70.06; H, 10.57.

2-[1-Hydroxy-4-(trimethylsilyl)-2-butynyl]cyclotridecanone **82**: The procedure employed for **70** was followed using methyllithium (1.3 M in ether, 1.36 mL, 1.78 mmol), silyl enol ether **81** (479 mg, 1.78 mmol), anhydrous tetramethylethylenediamine (0.26 mL, 1.78 mmol) in ether (10 mL), anhydrous zinc chloride (0.69 M in ether, 1.28 mL, 0.89 mmol), and aldehyde **58** (ca. 3-fold excess) in ether (10 mL). The reaction mixture was stirred at 0°C for 20 min and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 15 cm) with 15% ethyl acetate — hexane gave hydroxysilane **82** as a pure (TLC, silica, 20% ethyl acetate — hexane) mixture of diastereoisomers (415 mg, 70%): IR (neat) 3400, 2220, 1705, 1200, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.10 (2 s, 9H), 1.10 — 2.0 (m, 23H), 2.3 — 2.60 (m, 2H), 2.65 — 2.90 (m, 2H), 4.50 (m, 1H); exact mass, m/z, 336.2486 (calcd for $C_{20}H_{36}O_2Si$, 336.5801).

(Z)-2-[1-Hydroxy-4-(trimethylsilyl)-2-butenyl]cyclohexanone **71**: A mixture of silyl acetylene **70** (590 mg, 2.47 mmol), 5% palladium on barium sulfate[102] (200 mg), and dry pyridine (12 mL) was stirred at room temperature

under hydrogen (10 psi) for 12 h. The catalyst was removed by filtration through a pad of Celite (1.5 × 2 cm) using ether (ca. 30 mL) as a rinse. The organic filtrate was extracted successively with ice-cold 1 M HCl (50 mL), saturated aqueous sodium bicarbonate (30 mL), and brine (30 mL). The ethereal layer was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm) with 16% ethyl acetate — hexane afforded **71** as a pure (TLC, silica, 20% ethyl acetate — hexane) mixture of diastereoisomers (572 mg, 96%): IR (neat) 3350, 1700, 1650, 1250, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.09 (2 s, 9H), 1.20 — 1.90 (m, 6H), 2.05 (m, 2H), 2.3 (m, 3H), 2.64 (d, J = 4 Hz, 0.4H), 3.36 (d, J = 2.4 Hz, 0.6H), 4.50 (dt, J = 16, 2.4 Hz, 0.6H), 4.75 (m, 0.4H), 5.2 (t, J = 10 Hz, 0.6H), 5.33 (t, 9.4 Hz, 0.4H), 5.5 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -1.9, 19.0, 19.1, 24.6, 24.7, 27.1, 27.2, 27.7, 30.5, 42.3, 42.5, 55.6, 56.3, 65.7, 67.1, 126.9, 127.1, 128.6, 129.8, 213.8, 214.8; exact mass, m/z 240.1544 (calcd for $C_{13}H_{24}O_2Si$, 240.2825). Anal. calcd for $C_{13}H_{24}O_2Si$: C, 64.92; H, 10.06. Found: C, 65.10; H, 10.04.

(Z)-2-[1-Hydroxy-4-(trimethylsilyl)-2-butenyl]cyclo-heptanone **75**: The procedure employed for **71** was followed

using silyl acetylene **74** (220 mg, 0.86 mmol) and 5% palladium on barium sulphate (50 mg) in dry pyridine (2 mL). The resulting mixture was stirred under hydrogen (10 psi) for 12 h and then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm) with 20% ethyl acetate — hexane afforded **75** as a pure (TLC, silica, 20% ethyl acetate — hexane) mixture of diastereoisomers (572 mg, 96%): IR (neat) 3450, 1690, 1250, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.09 (2 s, 9H), 1.10 — 2.0 (m, 11H), 2.30 — 2.78 (m, 3H), 2.81 (d, J = 4 Hz, 0.8H), 2.91 (d, J = 4 Hz, 0.2H), 4.55 (dt, J = 6, 4 Hz, 1H), 5.30 (m, 1H), 5.65 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -1.7, 19.3, 24.1, 25.5, 29.2, 29.6, 44.2, 57.1, 68.3, 127.2, 129.3, 217.7; exact mass, m/z 254.1696 (calcd for $C_{14}H_{26}O_2Si$, 254.2709). Anal. calcd for $C_{14}H_{26}O_2Si$: C, 66.07; H, 10.30. Found: C, 66.21; H, 10.28.

(Z)-2-[1-Hydroxy-4-(trimethylsilyl)-2-butenyl]cyclodecanone **79**: The procedure employed for **71** was followed using silyl acetylene **78** (890 mg, 2.76 mmol) and 5% palladium on barium sulphate (200 mg) in dry pyridine (12 mL). The resulting mixture was stirred under hydrogen (10 psi) for 12.5 h and then worked up. Evaporation of the

solvent and flash chromatography of the residue over silica gel (3 × 15 cm) with 15% ethyl acetate — hexane afforded **79** as a pure (TLC, silica, 20% ethyl acetate — hexane) mixture of diastereoisomers (880 mg, 96%): IR (neat) 3400, 1700, 1650, 1600, 1250, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz), 0.08 (2 s, 9H), 1.10 — 2.90 (m, 21H), 2.30 — 2.90 (m, 3H), 4.53 (m, 1H), 5.3 (m, 1H), 5.6 (m, 1H); exact mass, m/z 324.2496 (calcd for $C_{19}H_{36}O_2Si$, 324.3531). Anal. calcd for $C_{19}H_{36}O_2Si$: C, 70.29; H, 11.18. Found: C, 70.41; H, 11.24.

(Z)-2-[1-Hydroxy-4-(trimethylsilyl)-2-butenyl]cyclotridecanone **83**: The procedure employed for **71** was followed using silyl acetylene **82** (190 mg, 0.56 mmol) and 5% palladium on barium sulphate (50 mg) in dry pyridine (2 mL). The resulting mixture was stirred under hydrogen (10 psi) for 12 h and then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm) with 15% ethyl acetate — hexane afforded **83** as a pure (TLC, silica, 20% ethyl acetate — hexane) mixture of diastereoisomers (180 mg, 95%): IR (neat) 3350, 1705, 1250, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.02 (2 s, 9H), 1.0 — 2.0 (m, 23H), 2.2 — 2.8 (m, 3H), 4.45 (m, 1H), 5.2 — 5.64 (m, 2H); exact mass, m/z 338.5312

(calcd for $C_{20}H_{36}O_2Si$, 338.5956).

(E)-2-(1,3-Butadienyl)cyclohexanone **72**: A solution of tin(IV)chloride (0.38 mL, 3.32 mmol) in dry dichloromethane (2 mL + 1 mL rinse) was injected dropwise at -20°C into a stirred solution of hydroxysilane **71** (400 mg, 1.66 mmol) in dichloromethane (20 mL). The resulting mixture was stirred at -20°C for 10 min and water (15 mL) was added. The aqueous layer was extracted with ether (25 mL). The combined organic layers were washed successively with saturated aqueous sodium bicarbonate and brine, and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 15 cm) with 8% ethyl acetate — hexane gave **72** as a pure (TLC, silica, 5% ethyl acetate — hexane) oil (172 mg, 69%): IR (neat) 1705, 1600, 1010, 900 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.70 (m, 3H), 1.85 (m, 1H), 2.05 (m, 2H), 2.30 (m, 1H), 2.43 (m, 1H), 3.08 (m, 1H), 5. (dd, J = 10.1, 1.3 Hz, 1H), 5.15 (dd, J = 17.4, 1.3 Hz, 1H), 5.88 (dd, J = 15.4, 7.2 Hz, 1H), 6.05 (dd, J = 15.4, 10.0 Hz, 1H), 6.35 (dt, J = 17.4, 10.0 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 24.0, 27.2, 33.8, 41.3, 53.2, 115.9, 131.3, 132.0, 136.6, 210.1; exact mass, m/z 150.1044 (calcd for $C_{10}H_{14}O$, 150.1041). Anal. calcd for $C_{10}H_{14}O$: C, 80.01; H, 9.39. Found: C,

79.80; H, 9.33.

(E)-2-(1,3-Butadienyl)cycloheptanone **76**: The procedure employed for **72** was followed using tin tetrachloride (0.76 mL, 6.48 mmol) in dichloromethane (4 mL) and hydroxysilane **75** (825 mg, 3.24 mmol) in dichloromethane (30 mL). The mixture was stirred at -20°C for 10 min and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 15 cm) with 5% ethyl acetate — hexane gave **76** as a pure (TLC, silica, 10% ethyl acetate — hexane) colorless oil (430 mg, 80.8%): IR (neat) 1704, 1000, 900 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.20 — 2.0 (m, 8H), 2.45 (m, 2H), 3.20 (m, 1H), 5.10 (dd, J = 10.1, 1.3 Hz, 1H), 5.15 (dd, J = 16.5, 1.3 Hz, 1H), 5.79 (dd, J = 15.1, 7.6 Hz, 1H), 6.05 (dd, J = 5.19, 10 Hz, 1H), 6.30 (dt, J = 16.5, 10.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 24.7, 27.8, 29.6, 31.2, 42.3, 55.8, 116.5, 131.8, 132.5, 136.7, 213.4; exact mass, m/z 164.1180 (calcd for $C_{11}H_{16}O$, 164.1180). Anal. calcd for $C_{11}H_{16}O$: C, 80.42; H, 9.82. Found: C, 79.05; H, 9.60.

(E)-2-(1,3-Butadienyl)cyclododecanone **80**: The procedure employed for **72** was followed using tin tetrachloride (0.74 mL, 6.34 mmol) in dichloromethane (2 mL) and hydroxysilane

79 (1.03 g, 3.17 mmol) in dichloromethane (20 mL). The mixture was stirred at -20°C for 5 min and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 15 cm) with 2% ethyl acetate — hexane gave **80** as a pure (TLC, silica, 5% ethyl acetate — hexane) colorless oil (580 mg, 78%): IR (neat) 1705, 1645, 1600, 1005, 905 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.0 — 2.0 (m, 18H), 2.3 — 2.60 (m, 2H), 3.3 (m, 1H), 5.05 (dd, J = 9.6, 1.8 Hz, 1H), 5.15 (dd, J = 16.5, 1.8 Hz, 1H), 5.60 (dd, J = 15.3, 8.7 Hz, 1H), 6.08 (dd, J = 15.3, 9.6 Hz, 1H), 6.25 (dt, J = 16.5, 9.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 22.26, 22.24, 23.3, 24.3, 24.6, 24.7, 25.0, 25.5, 30.5, 38.5, 54.6, 116.7, 132.3, 132.7, 136.5, 211.7; exact mass, m/z 234.1983 (calcd for $C_{16}H_{26}O$, 234.1960). Anal. calcd for $C_{16}H_{26}O$: C, 81.98; H, 11.18. Found: C, 81.74; H, 11.19.

(E)-2-(1,3-Butadienyl)cyclotridecanone **84**: The procedure employed for **72** was followed using tin tetrachloride (0.025 mL, 0.22 mmol) in dichloromethane (1 mL) and hydroxysilane **83** (38 mg, 0.11 mmol) in dichloromethane (3 mL). The mixture was stirred at -20°C for 5 min and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 15 cm)

with 1% ethyl acetate — hexane gave **84** as a pure (TLC, silica, 5% ethyl acetate — hexane) colorless oil (20 mg, 73.2%): IR (neat) 1705, 1650, 1600, 1005, 901 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.0 — 1.98 (m, 20H), 2.2 — 2.75 (m, 2H), 3.25 (dt, J = 9.5, 4.0 Hz, 1H), 5.05 (dd, J = 9.5, 1.8 Hz, 1H), 5.15 (dd, J = 16.4, 1.8 Hz, 1H), 5.65 (dd, J = 15.1, 8.6 Hz, 1H), 6.09 (dd, J = 15.1, 9.5 Hz, 1H), 6.25 (dt, J = 16.4, 9.4 Hz, 1H); exact mass, m/z 248.2141 (calcd for $C_{17}H_{28}O$, 248.2110).

(E)- and (Z)-3-(Tri-n-butylstannyl)-2-propen-1-ol **85**:[105]

The literature procedure[105] was followed: A mixture of 2-propyn-1-ol (4.0 g, 7.14 mmol), tri-n-butyltin hydride (25.0 mL, 9.28 mmol), and AIBN (60 mg, 0.36 mmol) was heated under argon at 80°C for 2 h. Distillation of the resulting solution afforded alcohol **88** (20.0 g, 80.6%) as a mixture of (Z) and (E) isomers: bp 110 — 115°C (0.1 mm) [lit.[67] bp 120 — 125°C (0.25 mm)]; IR (neat) 3350, 1600, 1160, 990, 960 cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.8 — 0.99 (m, 10H), 1.5 — 1.9 (m, 18H), 4.20 (m, 2H), 6.20 (m, 2H).

(E)- and (Z)-3-(Tri-n-butylstannyl)-2-propen-1-al **89**:[67]

Manganese(IV)oxide (8.87 g, 100 mmol) was added at room temperature to a solution of alcohol **88** (3.53 g, 10.1

mmol) in dichloromethane (50 mL). The reaction mixture was stirred for 15 h and was then filtered through Celite (4 × 6 cm) using ether as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (5 × 15 cm) with 2% ethyl acetate — hexane gave aldehyde **89** [1.40 g, 74%, based on recovered starting material (1.6 g)]: IR (neat) 1690, 1460 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.81 — 1.60 (m, 27H), 6.60 (dd, J = 19.7, 7.8 Hz, 1H), 7.5 (d, J = 19.7 Hz, 1H), 9.38 (d, J = 7.8 Hz, 1H).

(E)-1,3-Butadienyltributylstannane **90**:[67] The literature procedure[67] was followed: n-Butyllithium (13.8 mL, 22.0 mmol) was injected dropwise at 0°C into a stirred suspension of methyltriphenylphosphonium bromide (14.2 g, 40.2 mmol) in THF (125 mL). The cooling bath was removed and stirring was continued for 2 h. Aldehyde **89** (6.98 g, 20.2 mmol) in THF (10 mL + 2 mL rinse) was added dropwise over a period of 15 min and the reaction mixture was stirred at room temperature for 2 h more. Saturated aqueous ammonium chloride (100 mL) was added and the aqueous phase was extracted with ether (2 × 50 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over

silica gel (5 × 15 cm) with hexane gave stannane **90** (5.8 g, 83.7%) as a pure (TLC, silica, hexane), colorless oil: IR (neat) 1560, 1010, 905 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.95 (m, 14H), 1.34 (m, 6H), 1.52 (m, 7H), 5.02 — 5.3 (m, 2H), 6.15 — 6.61 (m, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 9.5, 13.6, 27.2, 29.1, 15.6, 134.6, 140.2, 147.5.

[1α,1(E),2β(E)]-1,2-di-1,3-Butadienylcycloheptanol **92**: n-Butyllithium (1.6 M in hexane, 1.37 mL, 2.2 mmol) was injected dropwise at -78°C into a stirred solution of stannane **90** (1.12 g, 3.3 mmol) in THF (25 mL). The mixture was stirred for an additional 15 min and ketone **76** (180 mg, 1.1 mmol) in THF (2 mL + 1 mL rinse) was then added dropwise over several minutes. Stirring at -78°C was continued for 30 min. Saturated aqueous ammonium chloride (15 mL) was added and the aqueous phase was extracted with ether (2 × 15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm) with 5% ethyl acetate — hexane gave an inseparable mixture consisting of alcohol **91** and ketone **76**. The mixture was used directly for the next step.

[1α,1(E),2α(E)]- and [1α,1(E),2β(E)]-1,2-di-1,3-butadienylcyclododecanol **93** and **94**: The procedure employed for **91** was followed using n-butyllithium (1.6 M in hexane, 0.47 mL, 0.76 mmol), stannane **90** (514 mg, 1.5 mmol) in THF (15 mL), and ketone **80** (120 mg, 0.51 mmol) in THF (2 mL + 1 mL rinse). The reaction mixture was stirred at -78°C for 30 min and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 15 cm) with 5% ethyl acetate — hexane gave **94** (27 mg, 18.3%) as a pure (TLC, silica, 10% ethyl acetate — hexane), colorless oil and the other diastereoisomer **93** (83 mg, 56.5%) as a pure (TLC, silica, 10% ethyl acetate — hexane), crystalline solid. Compound **94** had: IR (neat) 3540, 1650, 1600, 1000, 950, 900 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.05 — 1.64 (m, 19H), 1.79 (m, involving a singlet, 2H), 2.41 (t, J = 8.8 Hz, 1H), 5.03 (ddd, J = 9.7, 4.4, 1.4 Hz, 2H), 5.18 (ddd, J = 16, 7.6, 1.4 Hz, 2H), 5.35 (dd, J = 15.2, 9.7 Hz, 1H), 5.8 (d, J = 15.2 Hz, 1H), 6.10 — 6.40 (m, 4H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.5, 22.1, 22.5, 22.7, 26.2, 26.3, 27.4, 29.6, 34.9, 47.7, 76.0, 116.4, 128.9, 134.6, 136.0, 136.4, 136.6, 138.5; exact mass, 288.2313 (calcd for $C_{20}H_{32}O$, 288.2430). Anal. calcd for $C_{20}H_{32}O$: C, 83.26; H, 11.18. Found: C, 83.19; H, 11.25.

Isomer **93** had: IR (CCl_4) 3610, 1800, 1640, 1600, 1000, 950, 900 cm^{-1}; ^1H NMR (($CDCl_3$, 200 MHz) δ 1/1 — 1.60 (m, 19H), 1.80 (m, 1H), 2.01 (m, 1H), 2.30 (t, J = 8.5 Hz, 1H), 4.9 — 5.3 (m, 4H), 5.53 (dd, J = 15.6, 8.4 Hz, 1H), 5.78 (d, J = 15 Hz, 1H), 6.0 (dd, J = 15.6, 10.8 Hz, 1H), 6.10 — 6.42 (m, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.5, 22.1, 22.7, 22.8, 23.1, 23.6, 24.2, 26.3, 26.6, 38.2, 45.3, 77.0, 115.1, 116.2, 127.9, 132.6, 135.2, 136.8, 137.2, 140.5; exact mass, m/z 288.2462 (calcd for $C_{20}H_{32}O$, 288.2430). Anal. calcd for $C_{20}H_{32}O$: C, 83.26; H, 11.18. Found: C, 83.07; H, 11.18.

Attempted rearrangement of **92** with potassium hydride; 1,3,7,9-cyclopentadecatetraen-1-ol, potassium salt **92a**: Potassium hydride (24.01% w/w in oil, 103 mg, 0.60 mmol) was washed in a septum-covered flask with dry hexane (2 × 3 mL). Residual solvent was evaporated by a stream of dry nitrogen and THF (5 mL) was added to the flask. Alcohol **92** (50 mg, 0.23 mmol) in THF (1 mL + 1 mL rinse) was added dropwise and the mixture was stirred at room temperature for 1 h. Aqueous ammonium chloride (10% w/w, 5 mL) was added and the aqueous layer was then extracted with ether. The combined organic extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent

yielded a residue that was a complex mixture by TLC (silica, 5% ethyl acetate — hexane).

Attempted rearrangement of **93** with potassium hydride; 1,3,7,9-Cycloeicosatetraen-1-ol, potassium salt **93a**: The procedure employed for **92a** was followed using potassium hydride (24.01% w/w in oil, 48 mg, 0.29 mmol) in THF (3 mL) and alcohol **93** (28 mg, 0.097 mmol) in THF (1 mL + 1 mL rinse). The reaction mixture was stirred at room temperature for 2 h and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 15 cm) with 2% ethyl acetate — hexane gave an oil (21 mg): IR (neat) 1705, 990, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.1 — 2.80 (m, 25H), 4.89 — 6.4 (m, 7 vinyl H); exact mass, m/z 288.2430 (calcd for $C_{20}H_{32}O$, 288.2430.

[1α,1(E),2β(E)],[(1,2-di-1,3-Butadienylcycloheptyl)-oxy]trimethylsilane **95**: Chlorotrimethylsilane (0.14 mL, 1.09 mmol) was injected at room temperature into a stirred solution of alcohol **92** (160 mg, 0.733 mmol) and hexamethyldisilazane (HMDS) (0.185 mL, 0.87 mmol) in dry DMSO (5 mL). Stirring was continued for an additional 30 min and pentane (20 mL) was added. The mixture was shaken

with water (10 mL) and the organic layer was washed successively with 5% aqueous sulfuric acid, saturated aqueous sodium bicarbonate, and brine. The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with hexane gave **95** as a pure (TLC, silica, hexane), colorless oil (170 mg, 53% based on ketone **76**): IR (neat) 1645, 1600, 1250, 1000, 900, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.05 (s, 9H), 1.2 — 1.60 (m, 4H), 1.65 — 1.85 (m, 5H), 2.0 (m, 2H), 4.92 (dd, J = 10, 1.7 Hz, 1H), 5.01 (dd, J = 9.5, 1.7 Hz, 1H), 5.09 (dd, J = 16.9, 1.8 Hz), 5.17 (dd, J = 16.5, 1.7 Hz, 1H), 5.85 (m, 3H), 5.98 (dd, J = 15.4, 10 Hz, 1H), 6.30 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 2.4, 21.8, 27.9, 29.0, 29.2, 39.4, 54.6, 78.9, 114.2, 116.4, 127.6, 130.1, 137.2, 137.7, 138.3, 141.8; exact mass, m/z 290.2070 (calcd for $C_{18}H_{30}OSi$, 290.3478). Anal. calcd for $C_{18}H_{20}OSi$: C, 74.39; H, 10.41. Found: C, 75.25; H, 10.55.

1(E),3(E),7(E),9(E)-(1,3,7,9-Cyclopentadecatetraen-1-yloxy)trimethylsilane **96**: The silyl ether **95** (100 mg, 0.37 mmol) was sealed in an ampoule under argon and immersed for 15 min in a preheated oil bath at 200°C. Kugelrohr distillation of the resulting oil gave silyl

enol ether **96** (97 mg, 88%) as a colorless oil: bp 80 — 85°C (0.04 mm); IR (neat) 1652, 1600m, 1250, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.10 (s, 9H), 1.15 — 1.60 (m, 6H), 2.0 (m, 4H), 2.18 (m, 4H), 5.0 — 5.20 (m, 3H), 5.40 (dt, J = 16, 6.4 Hz, 1H), 5.68 (dd, J = 16, 8 Hz, 1H), 5.9 (m, 2H), (small peaks at δ 1.8, 4.9, 6.08, and 6.3 corresponding to starting material **95**); exact mass, m/z 290.2071 (calcd for $C_{18}H_{30}OSi$, 290.3478).

3(E),7(E),9(E)-3,7,9-Cyclopentadecatrien-1-one **97**:

Methyllithium (1.56 M in ether, 0.32 mL, 0.49 mmol) was injected dropwise at room temperature into a stirred solution of silyl enol ether **96** (130 mg, 0.447 mmol) and tetramethylethylenediamine (0.067 mL, 0.447 mmol) in dry ether (5 mL). The mixture was stirred for 45 min and was then poured into dilute acetic acid (1 M, 5 mL). The aqueous phase was extracted with ether (2 × 10 mL) and the combined organic extracts were washed with saturated aqueous sodium bicarbonate and brine, and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 15 cm) with 5% ethyl acetate — hexane afforded ketone **97** as a pure (TLC, silica, 10% ethyl acetate — hexane) oil (83 mg, 85%): IR (neat) 1705, 990, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ

1.10 — 1.70 (m, 6H), 2.0 — 2.30 (m, 6H), 2.35 (t, J = 7 Hz, 2H), 3.0 (d, J = 5.5 Hz, 2H), 5.15 — 5.61 (m, 4H), 5.72 — 6.04 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 22.8, 26.4, 27.4, 31.2, 31.8, 32.3, 41.5, 47.2, 124.2, 130.7, 131.3, 132.1, 132.4, 133.8, 209.4; exact mass, 218.1669 (calcd for $C_{15}H_{22}O$, 218.1665). Anal. calcd for $C_{15}H_{22}O$: C, 82.50; H, 10.16. Found: C, 82.45; H, 10.23.

Cyclopentadecanone **98**:[106] A mixture of olefin **97** (54 mg, 0.247 mmol) and 5% palladium on carbon (10 mg) in dry ethyl acetate (5 mL) was stirred at room temperature under hydrogen (10 psi) for 2 h. The catalyst was removed by filtration through a pad of Celite (1 × 2 cm) using ether (10 mL) as a rinse. Evaporation of the solvent gave Exaltone **98**[106] (53 mg, 95%) as a pure (TLC, silica, 5% ethyl acetate — hexane and V.P.C.; 10% QF-1) white, crystalline solid: IR (CCl_4) 1705 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 3.34 (m, 20H), 1.67 (m, 4H), 2.42 (t, J = 6.6 Hz, 4H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 23.4, 26.4, 26.5, 26.8, 26.9, 27.6, 42.0, 212.1; exact mass, m/z 224.2141 (calcd for $C_{15}H_{28}O$, 224.2133).

[1α,1(E),2α(E)],[1,2-di-1,3-butadienyl-1-cyclododecyl)-oxy]trimethylsilane **99**: The procedure employed for **95** was

followed using chlorotrimethylsilane (0.10 mL, 0.81 mmol), alcohol **93** (158 mg, 0.54 mmol), and hexamethyldisilazane (0.138 mL, 0.648 mmol) in dry DMSO (5 mL). The reaction mixture was stirred at room temperature for 30 min and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 15 cm) with hexane gave **99** (194 mg, 98%) as a pure (TLC, silica, hexane), colorless oil: IR (neat) 1600, 1250, 1000, 970, 900, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.15 (s, 9H), 1.0 — 1.70 (m, 18H), 2.2 (m, 3H), 4.95 (dd, J = 9.9, 1.8 Hz, 1H), 5.0 (dd, J = 9.9, 1.8 Hz, 1H), 5.05 (dd, J = 16.5, 1.8 Hz, 1H), 5.15 (dd, J = 16.5, 1.8 Hz, 1H), 5.52 (dd, J = 15.4, 8.8 Hz, 1H), 5.70 (d, J = 4.8 Hz, 1H), 6.05 — 6.41 (m, 4H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 2.8, 15.2, 21.0, 22.4, 22.8, 23.0, 23.1, 24.0, 24.9, 26.4, 26.9, 37.1, 46.4, 65.8, 80.5, 114.1, 115.7, 128.6, 131.8, 137.0, 137.1, 137.5, 139.9; exact mass, m/z 260.3920 (calcd for $C_{23}H_{40}OSi$, 360.3810). Anal. calcd for $C_{23}H_{40}OSi$: C, 76.58; H, 11.18. Found: C, 76.74; H, 11.15.

1(Z),3(E),7(E),9(E)-1,3,7,9-Cycloeicosatetraen-1-yloxy)-trimethylsilane **100**: The silyl ether **99** (125 mg, 0.346 mmol) was sealed in an ampoule under argon and immersed

for 15 min in a preheated oil bath at 200°C. Kugelrohr distillation of the resulting oil gave silyl enol ether **100** (120 mg, 96%) as a pure (TLC, silica hexane), colorless oil: bp 105 — 110°C (0.04 mm); IR (neat) 1655, 16, 1250, 850 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.3 (s, 1H), 1.1 — 1.70 (m, 16H), 2.0 — 2.4 (m, 8H), 5.10 — 5.60 (m, 4H), 5.8 — 6.3 (m, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 0.7, 25.8, 27.2, 27.7, 28.3, 28.4, 28.5, 28.6, 28.7, 31.8, 32.1, 32.2, 35.9, 104.7, 110.6, 125.5, 128.6, 131.2, 131.3, 131.5, 131.9, 149.9; exact mass, m/z 360.2845 (calcd for $C_{23}H_{40}OSi$, 360.3920).

3(E),7(E),9(E)-3,7,9-Cycloeicosatrien-1-one **101**: The procedure employed for **97** was followed using methyllithium (1.56 M in ether, 0.24 mL, 0.374 mmol), silyl enol ether **100** (125 mg, 0.346 mmol), and tetramethylethylenediamine (0.052 mL, 0.346 mmol) in ether (5 mL). The reaction mixture was stirred at room temperature for 45 min and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm) with 5% ethyl acetate — hexane afforded **101** as a pure (TLC, silica, 10% ethyl acetate — hexane) colorless oil (79 mg, 79%): IR (neat) 1708, 989, 970 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.10 — 1.65 (m, 16H), 2.0 — 2.29 (m,

6H), 2.42 (t, J = 7.5 Hz, 2H), 3.05 (m, 2H), 5.48 (m, 4H), 5.98 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 23.5, 26.4, 27.0, 27.3, 27.5, 28.0, 28.5, 31.0, 31.2, 31.7, 41.7, 47.0, 123.3, 130.6, 130.8, 131.3, 132.0, 134.2, 209.6; exact mass, m/z 288.2453 (calcd for $C_{20}H_{32}O$, 288.2430). Anal. calcd for $C_{20}H_{32}O$: C, 83.26; H, 11.18. Found: C, 83.43; H, 11.26.

[1α,1(E),2β(E)],[1,2-di-1,3-Butadienylcyclododecyl)oxy]-trimethylsilane **102**: The procedure employed for **95** was followed using chlorotrimethylsilane (0.013 mL, 0.10 mmol), alcohol **94** (20 mg, 0.069 mmol), and hexamethyldisilazane (0.02 mL, 0.09 mmol) in DMSO (2 mL). The reaction mixture was stirred at room temperature for 20 min and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 15 cm) with hexane gave **102** (24 mg, 96%) as a pure (TLC, silica, hexane), colorless oil: IR (neat) 1650, 1600, 1005, 965, 905 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.01 (s, 9H), 1.0 — 1.61 (m, 19H), 1.85 (m, 1H), 2.5 (broad t, J = 8.8 Hz, 1H), 4.95 (dd, J = 9.8, 1.8 Hz, 1H), 5.01 (dd, J = 16.3, 1.8 Hz, 1H), 5.02 (dd, J = 9.8, 1.8 Hz, 1H), 5.20 (dd, J = 16.3, 1.8 Hz, 1H), 5.60 (dd, J = 15.5, 8.1 Hz, 1H), 5.79 (d, J = 15.5 Hz, 1H), 6.05 (m, 2H), 6.3 (m, 2H);

exact mass, m/z 360.3819 (calcd for $C_{23}H_{40}OSi$, 360.3920).

1,3,7,9-Cycloeicosatetraen-1-yloxy)trimethylsilane **103a,b**: The silyl ether **102** (22 mg, 0.06 mmol) was sealed in an ampoule under argon and immersed for 15 min in a preheated oil bath at 200°C. Kugelrohr distillation of the resulting oil gave silyl enol ethers **103a** and **103b** (20 mg, 91%) as a pure (TLC, silica, hexane) oil: bp 100 — 115°C (0.06 mm); IR (neat) 1660, 1620, 1250, 850 cm^{-1} ^1H NMR ($CDCl_3$, 400 MHz) δ 0.09 (2s, 9H), 1.09 — 1.54 (m, 16H), 2.0 — 2.25 (m, 8H), 5.10 — 5.70 (m, 4H), 5.95 (m, 2H), 6.21 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ (olefinic signals) 109.7, 110.5, 125.4, 127.0, 127.2, 127.3, 128.4, 129.1, 129.9, 130.7, 131.1, 131.6, 133.0, 149.9, 153.7; exact mass, m/z 360.2829 (calcd for $C_{23}H_{40}OSi$, 360.3920).

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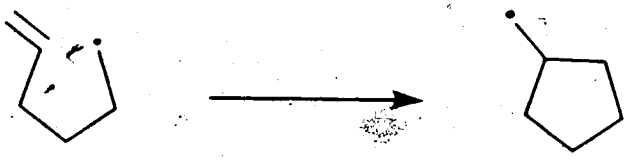
CHAPTER 2

RADICAL ANNULATIONS AND CYCLIZATIONS

Synthetic Methodology Based on Radical Cyclization

Of the four mechanistic domains of chemistry based on carbonium ions, carbanions, concerted processes, and free radicals, the latter has been neglected by synthetic chemists — apart from those involved in the preparation of polymers — as a way of making carbon — carbon bonds. This state of affairs is surprising because there is a huge literature on free radical chemistry and the cyclization process depicted in eq. 1 has been studied extensively by mechanistic chemists so that the subject of radical ring closure has hardly been an obscure one. Moreover, free



(1)

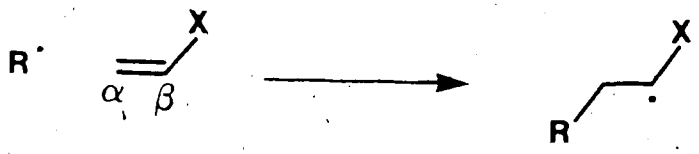
radical chemistry has a number of obvious advantages and features that could be put to good use in the area of synthesis. These are: (1) It represents a type of method that operates often under mild and neutral conditions which are very different from those used in most existing approaches to the formation of carbon — carbon bonds. In this regard free radical methods generate opportunities for avoiding masking of certain functional groups, that in conventional methodology would need protection — deprotection sequences, and for handling compounds with structural features that render standard methods inapplicable. (2) The stereochemical and/or regiochemical consequenes of ring-forming reactions based on radicals are likely to differ in some respects from those that characterize ionic reactions. In this way, radical-based chemistry could provide solutions to specific problems of stereochemical or regiochemical control. Intramolecular radical reactions appear to be less subject to interference from steric effects than ionic processes.

Although the emphasis of our research is on radical cyclizations, ordinary intermolecular radical processes are also involved and a review of that portion of the literature is appropriate.

Intermolecular Processes

Intermolecular radical additions to π-systems are, of course, part of industrial polymerization processes. Mechanistic studies and synthetic applications (outside the area of polymer science) in which one carbon — carbon bond is formed have been the subject of recent pioneering work and detailed review.[1] The main points relevant to our own research are as follow:[1]

(1) For the process shown in eq. 2, in which R• is an alkyl radical and X is an electron-withdrawing group,



(2)

more than 98% of the attack occurs at the α-position and the relative rates vary[1] in the order listed in Table 1. Alkyl radicals are nucleophilic as shown by the rate increase as X (eq. 2) becomes more electron-withdrawing.

(2) (E)-Alkenes react faster with the cyclohexyl radical than do (Z)-alkenes. For the sequence of eq. 3, for example, k_E/k_Z is 1.4 if Y is methyl, and 5.0 if Y is

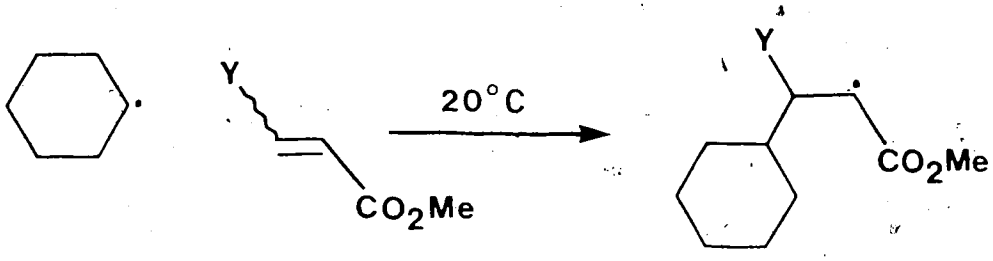
TABLE 1

Relative Rate of Addition to $H_2C=CHX$[a]

X	CHO	CN	COMe	COOH	COOMe	$CONH_2$
Rel. Rate	34	24	13	--	6.7	1.1
X	Ph	Cl	$OCOCH_3$	H	Bu	OEt
Rel. Rate	1	.12	.016	0.15	0.004	-

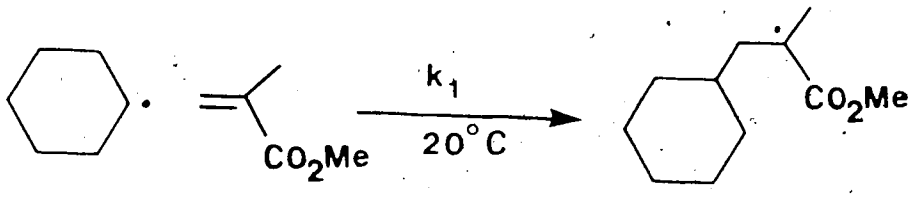
[a]Reactions at 20°C using $C_6H_{11}^{\bullet}$.

phenyl.

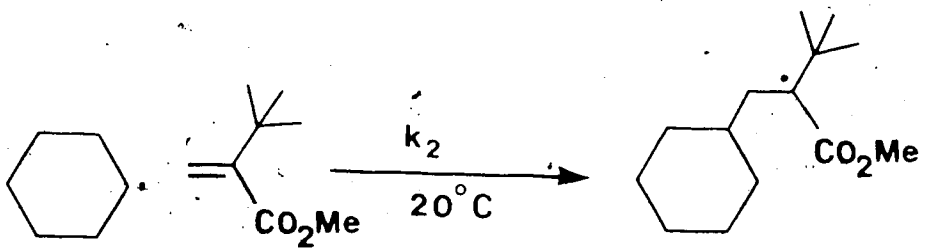


(3)

(3) Bulky substituents in the β-position have little influence on the rate: For the reactions summarized by eq. 4 and eq. 5, k_1/k_2 is only 2.95.

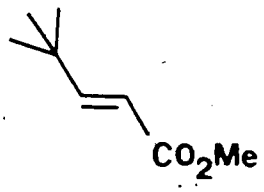


(4)



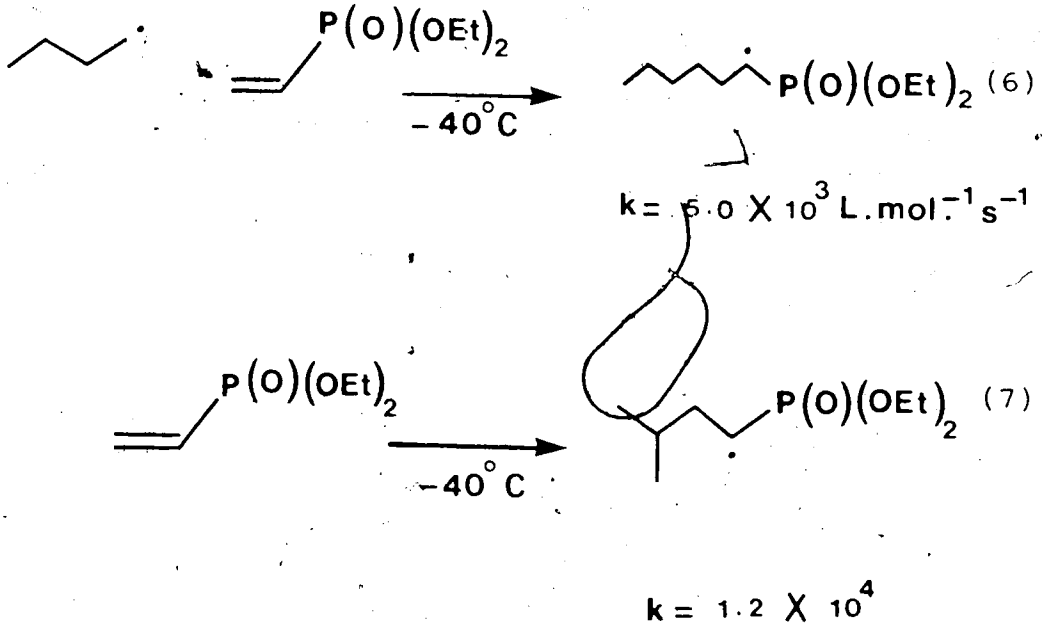
(5)

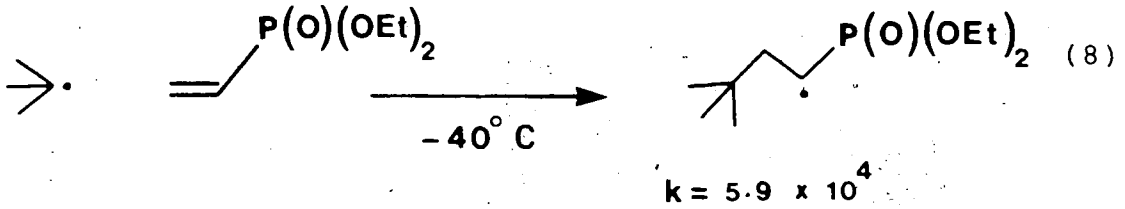
By contrast, bulky substituents at the α-position have an enormous retarding effect. Attack of cyclohexyl radicals on **1** is 2×10^4 times slower at 20°C than on methyl acrylate.



1

(4) Electron-releasing groups attached to a radical site increase the rate of attack on an electron-deficient olefin (cf. eqs. 6 — 8).

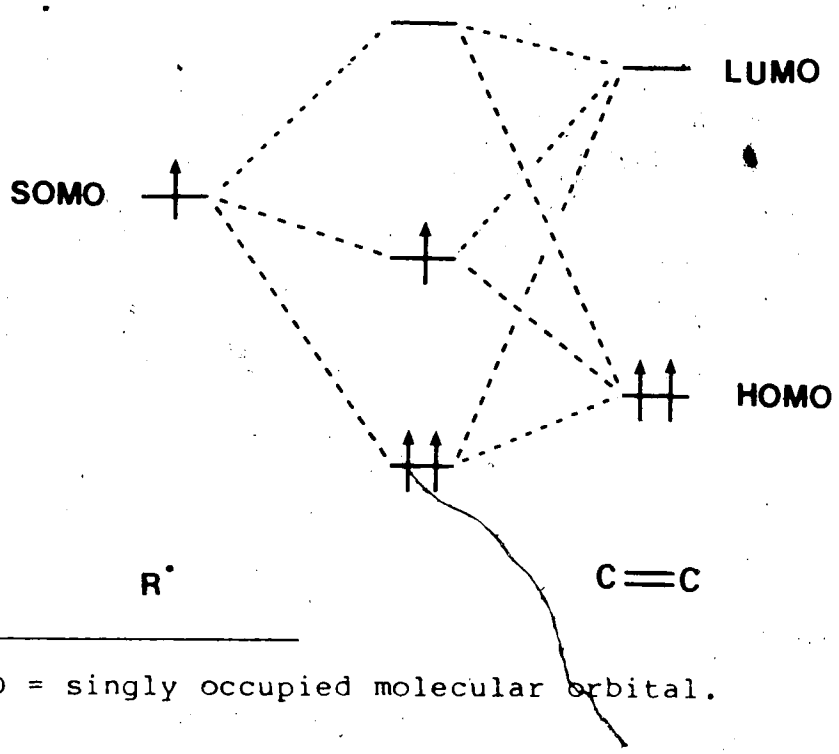




(8)

(5) Large (isopropyl, tert-butyl) alkyl substituents at a radical site decrease the rate of addition by exerting a steric effect.

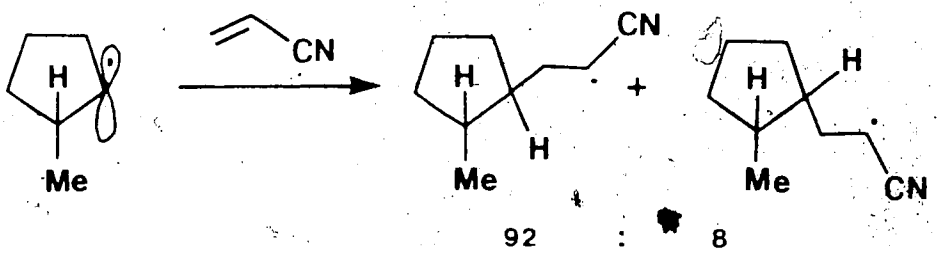
(6) Radicals react faster with alkenes than with alkynes. The SOMO* of the radical interacts with the LUMO of the alkene:



*SOMO = singly occupied molecular orbital.

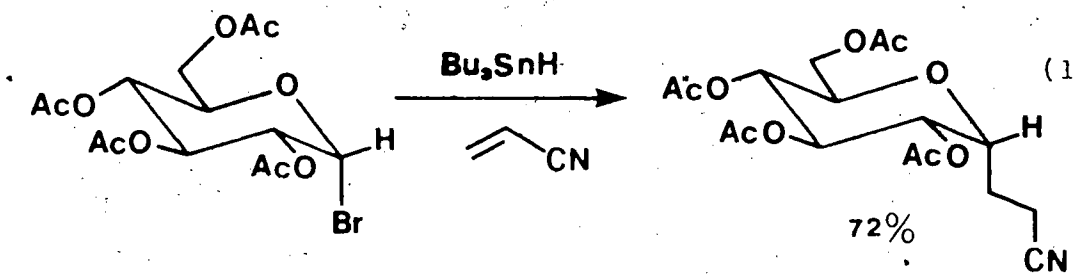
The LUMO of C≡C is higher, and the HOMO lower than for alkenes. Hence, the interaction SOMO — LUMO is less favourable in the case of a triple bond and radicals react faster with alkenes than with alkynes, though the rate ratio is small (ca. 2.5).

(7) Steric effects can exert control over stereoselectivity as in the example shown[1] in eq. 9



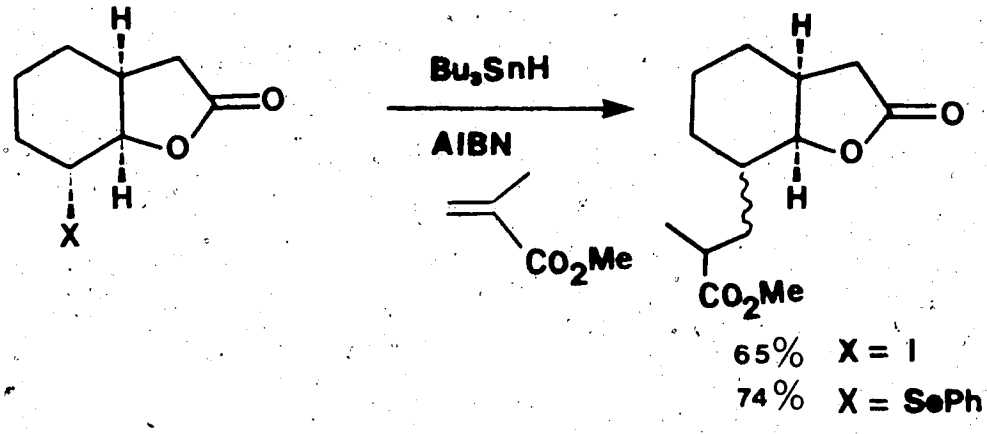
(9)

(8) Stereoelectronic effects also determine stereochemistry as illustrated by eq. 10.[2]



(10)

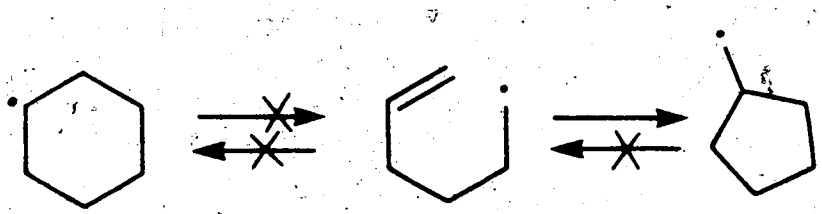
A number of synthetic applications of intermolecular radical reactions have been published;[3] that shown in eq. 11[3d] will serve as an example as it is representative of all the published work, and it is relevant to our own studies.



(11)

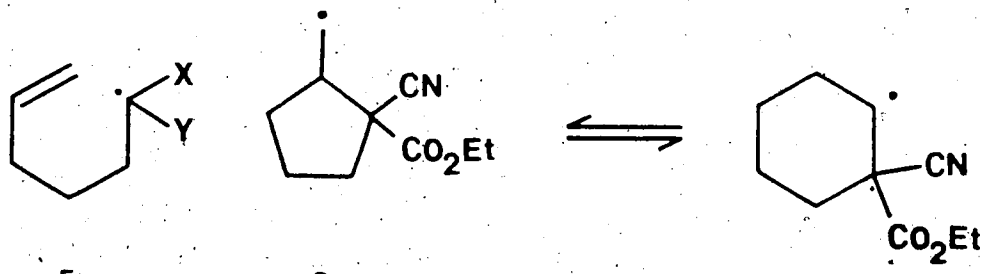
Intramolecular Processes[4]

Reactions of the 5-hexenyl radical **2** have attracted considerable attention over many years from mechanistic



4 **2** **3**

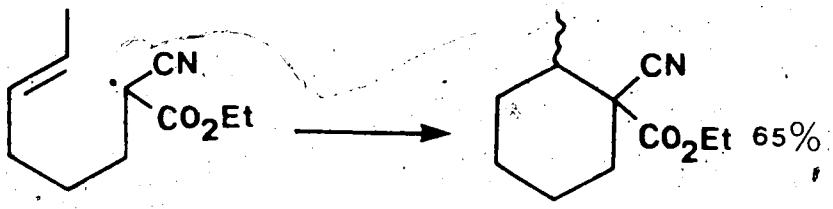
chemists.[5] They concerned themselves with establishing the true identity of the initial product as the primary radical **3**, and then with explaining the production of **3** rather than the thermodynamically more stable **4**. Species **4** would be the result of attack at the less hindered terminus of the double bond and factors of ring strain would also favour production of **4**. Nevertheless, it is not formed, except in special cases (see below). The possible intervention of equilibria, e.g. **4** ⇌ **2** ⇌ **3** was also examined in detail.[6] In this regard it was found[7] that radicals of type **5** (X,Y = elecron-withdrawing groups) undergo reversible cyclization. Thus, radicals **6** and **7**,



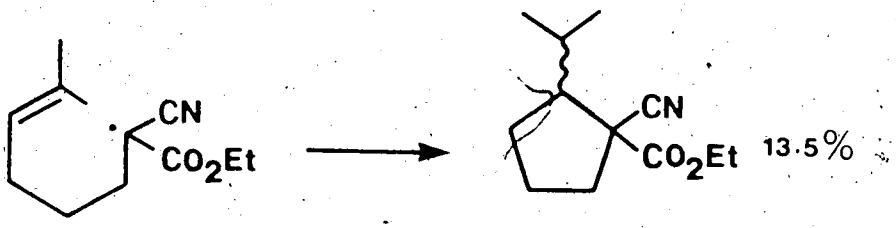
5 **6** **7**

when prepared independently, gave the same equilibrium mixture of methylcyclopentyl- and cyclohexyl-products, and the ratio was identical to that obtained by closure of the

acyclic radical 5. Some significant results bearing on this subject are collected in Table 2.[6a,8] These results are understandable in terms of kinetic 5-exo closure for X = Y = H and, if the closure is made reversible by suitable adjustment of X and Y, then the thermodynamic products, i.e. those resulting from 6-endo cyclization, are formed. The extent of endo closure is sensitive to steric factors as the following results[8] show (eq. 12 and eq. 13):



(12)

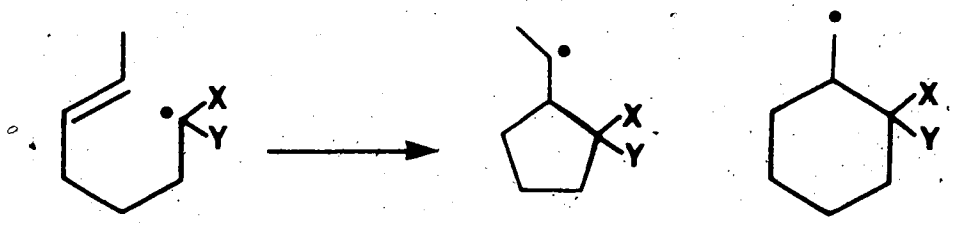


(13)

Cyclization of well-stabilized radicals, as the data of Table 2 show, is often not highly regioselective. In

TABLE 2

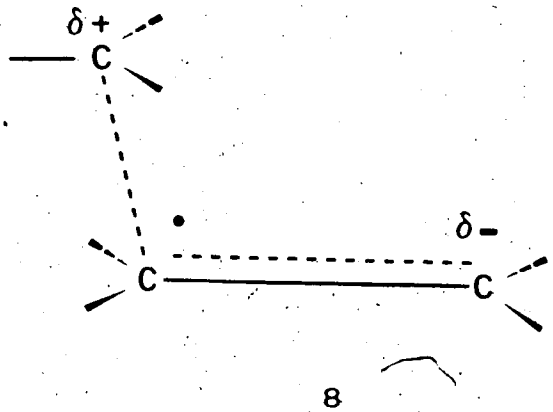
Cyclization of the 5-hexenyl radical.



X	Y	Relative Yields (%)	
H	H	100	0
Ph	H	90	10
COOEt	COOEt	70	30
COOEt	CN	16	84
=O		0	100

our research we are concerned with non-stabilized radicals.

By the mid-nineteen-seventies it was recognized that the initially puzzling results with the 5-hexenyl radical are accommodated by ideas of stereoelectronic control. The structure of the transition state for alkyl radical additions to double bonds is believed[9] to have the geometry shown in 8.

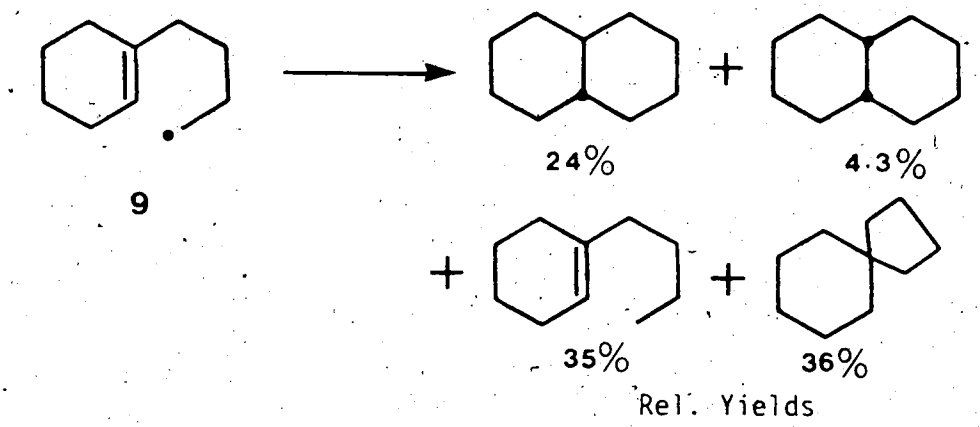


8

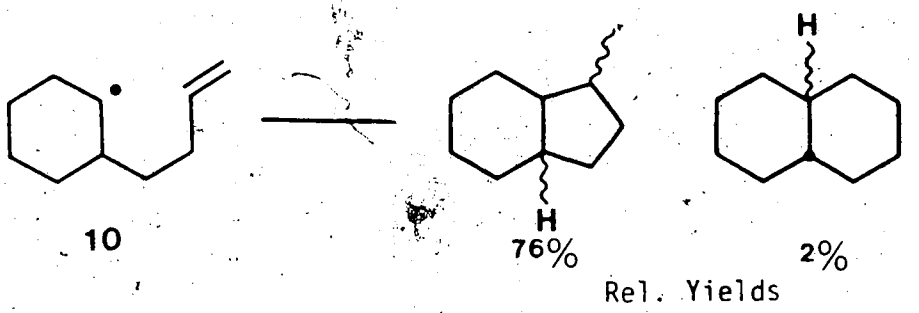
The initial interaction occurs between the singly occupied 2p orbital of the radical and one lobe of the π* orbital of the olefin.

In the cyclization of 5-hexenyl radicals the extent of 5-exo and 6-endo closure, is determined by the relative ease of accommodating the transition state **8**, and an inspection of molecular models suggests that the planar array shown in **8** is more easily accommodated for the

process of 5-exo closure than it is for the 6-endo pathway. For example, the reactions of radicals **9**[10] and **10**[11] (see eqs. 14 and 15) are considered to be under (kinetic) stereoelectronic control.

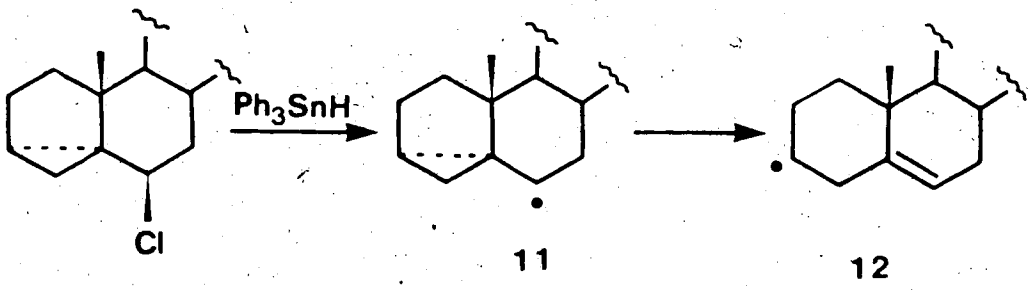


(14)

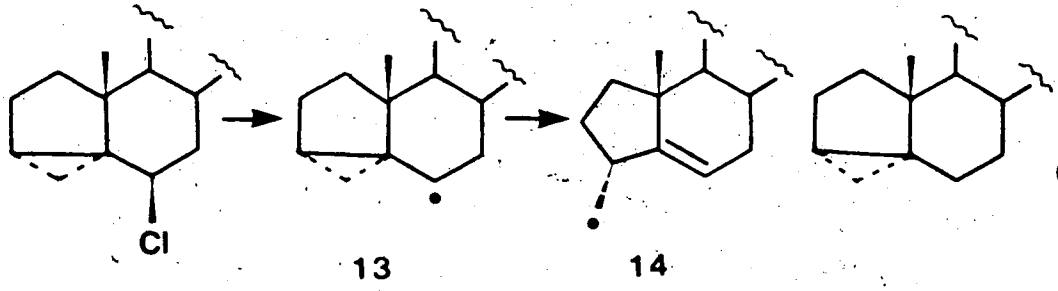


(15)

The operation of stereoelectronic control is clearly demonstrated by the results[12] shown in eqs. 16 and 17. Dreiding molecular models show that the bonds broken in the transformations **11**→**12** and **13**→**14** are those most nearly colinear with the singly occupied p-orbital.

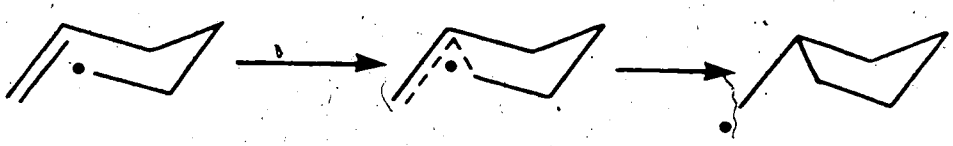


(16)



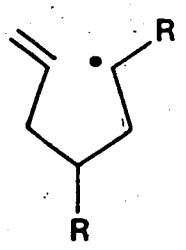
(17)

5-Hexenyl radicals are regarded[13] as preferentially undergoing cyclization via a conformation similar to a cyclohexane chair (eq. 18).

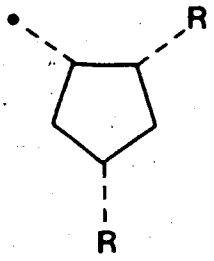


(18)

Consequently, the stereochemical result when substituents are present may be predicted by assigning, as far as is possible, to each substituent in the transition state, an equatorial conformation. Thus, cyclization of **15** is predicted[14] to give **16** and this is understandable in

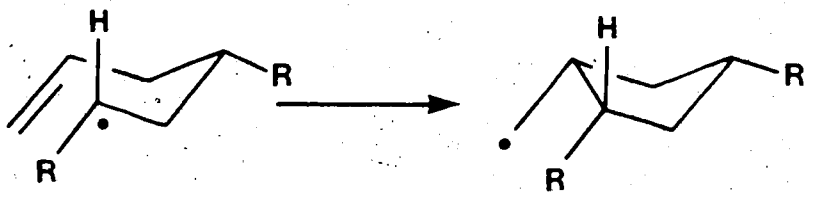


15



16

terms of the conformational diagrams of eq. 19.

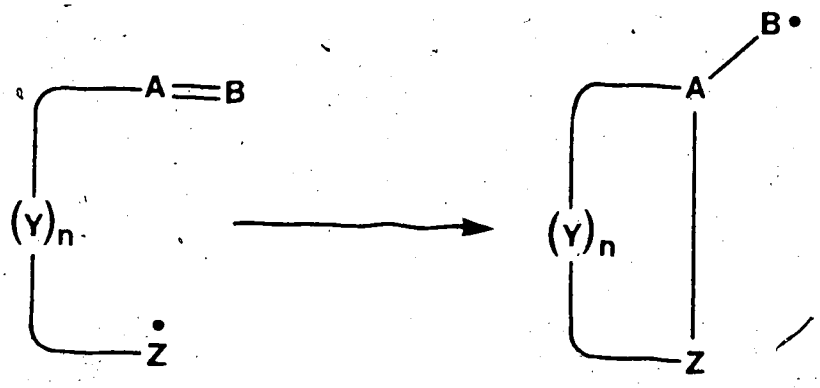


(19)

A set of guidelines is available[14] to help predict the outcome of radical cyclizations:

(1) Radical cyclizations onto C=C and C≡C bonds

under kinetic control occur preferentially in the exo mode (eq. 20) for $3 < n < 5$. For $n > 5$, the flexibility of the chain allows endo closure and this pathway, which involves attack at the less substituted terminus of the



(20)

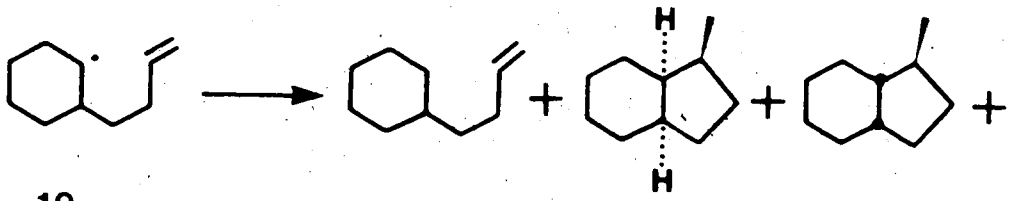
π-system (cf. intermolecular additions), can become the preferred pathway. Also, for systems under thermodynamic control endo cyclization products are isolated.

(2) Substituents on a double bond retard the rate of attack at that position and can even lead to total reversal of the usual regioselectivity.

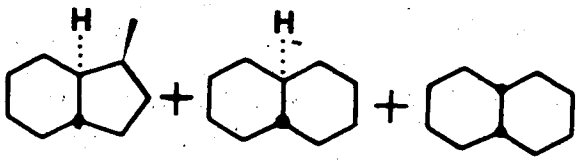
(3) Substituted 5-hexenyl radicals undergo stereoselective ring closure. Systems substituted at C-1 or C-3 give mainly cis products; systems substituted at C-2 or C-4 give mainly trans products.

The above guidelines apply to cyclization of acyclic species. If a ring is already present, then these simple guidelines are not absolutely followed. For example,

radical **10** (eq. 21) is formally a 1,2-substituted 5-hexenyl radical. The guidelines suggest that **20** where the methyl group is cis to the C-1 "substituent" and trans to the C-2 "substituent" should be the favoured product. In fact, the main product is **18**, and its formation is evidently due to the steric constraints imposed by the six-membered ring. Dreiding models of **23** and **24** show clearly that when the pendant is in an axial conformation,



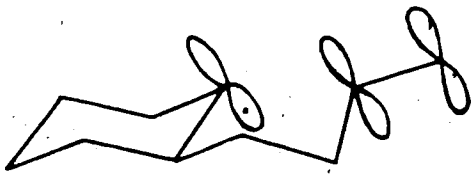
10 **17** 21.1% **18** 56.3% **19** 15.9% (21)



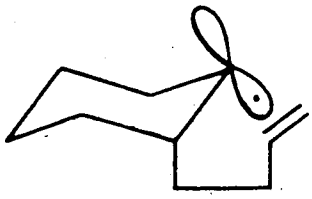
20 3.7% **21** 1.3% **22** 0.7%

as in **24**, the preferred planar arrangement of radical and π-system (see **8**) is much more easily accommodated than when the pendant is equatorial (as in **23**). Hence cis ring-fusion is expected. The major product actually

observed is **18**, but the reason for the preference of **18** over **19** is not obvious from an inspection of Dreiding models. The 6-endo pathway (see **21** and **22**) is followed to a small extent.

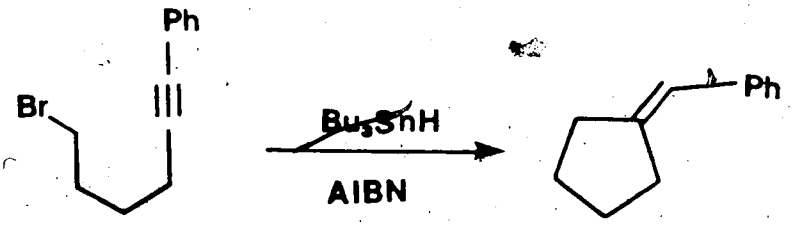


23

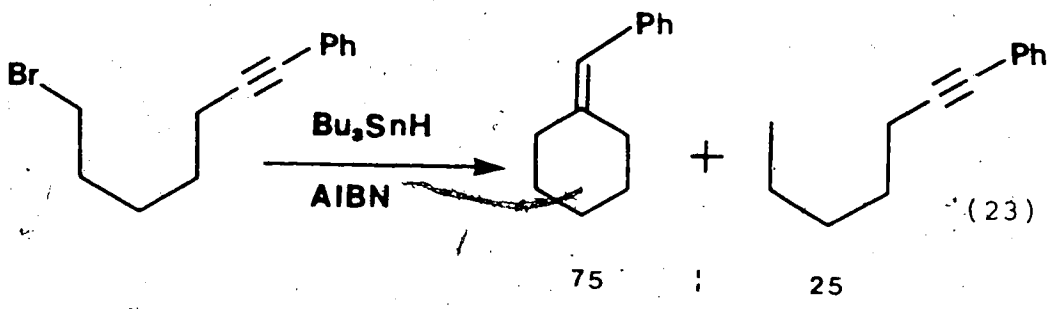


24

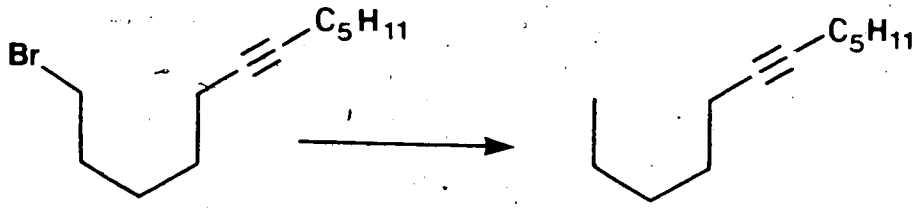
Radical cyclizations onto triple bonds have received less attention from mechanistic chemists. Exo cyclization leading to 5- and 6-membered rings is kinetically preferred over the endo mode. The reactions shown in eqs. 22 — 24 are from a detailed study[15] of regiochemistry.



(22)

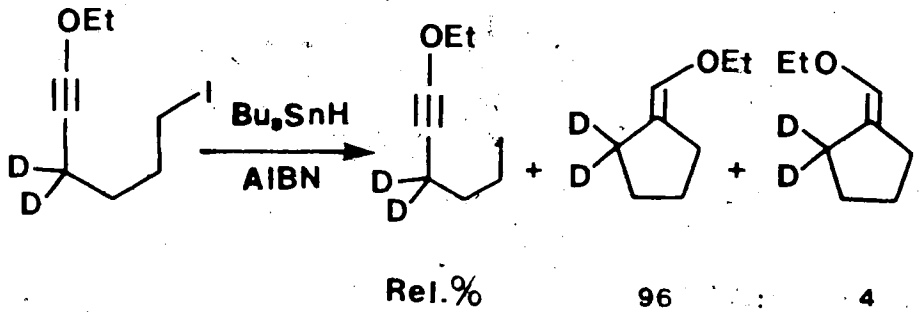


(23)

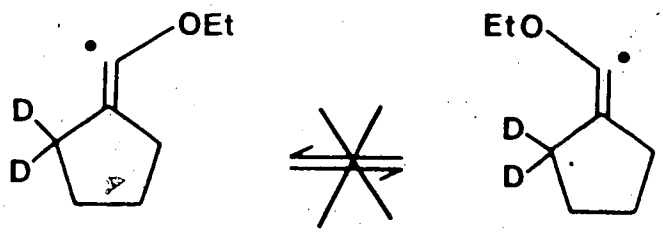


(24)

Cyclization takes place in a stereoselective fashion (eq. 25)[16]. Evidently in this case, the cyclized radical 25 does not undergo rapid isomerization.

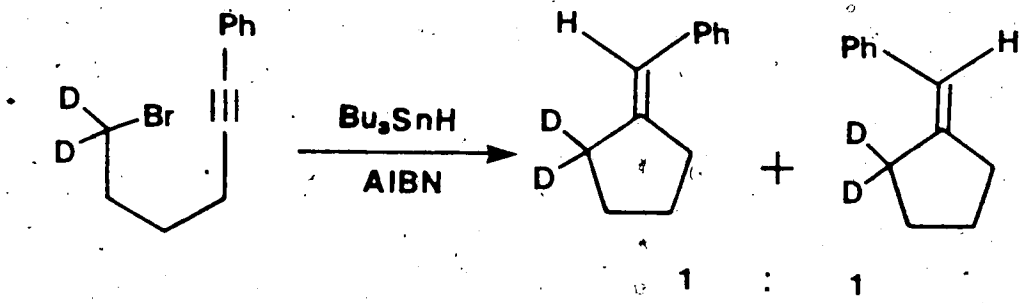


(25)



25

In the case of a phenyl-substituted alkyne, where delocalization of the unpaired electron into the benzene ring can occur, there is no[17] stereoselectivity (eq. 26).



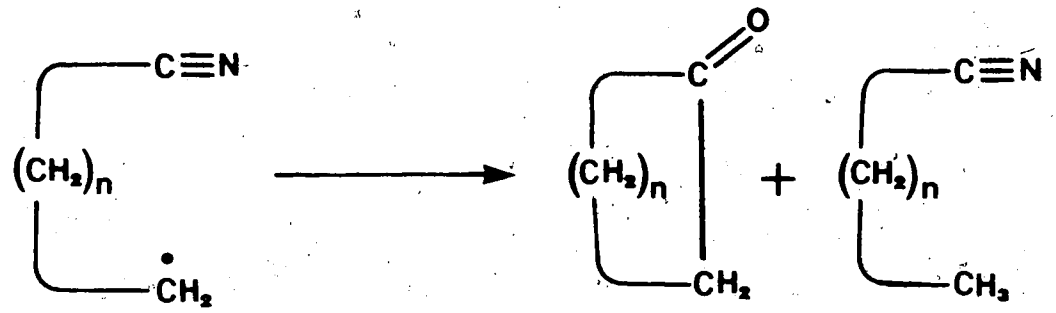
(26)

Carbon radicals also undergo 5-exo closure onto the triple bond of nitrile groups as the data[18] in Table 3 establish.

The relative rates of 5-exo cyclization onto double and triple bonds are collected in Table 4.[19,20] The value

TABLE 3[a]

Cyclization onto the triple of nitrile groups.

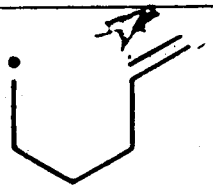
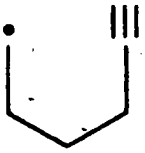
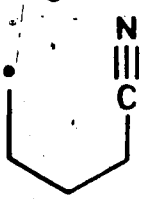


	Relative Yields (%)	
n = 2	0	100
n = 3	94	6
n = 4	29	71
n = 5	3	97

[a]Absolute yields are 65-75%. The radicals were generated from carboxylic acids.

TABLE 4

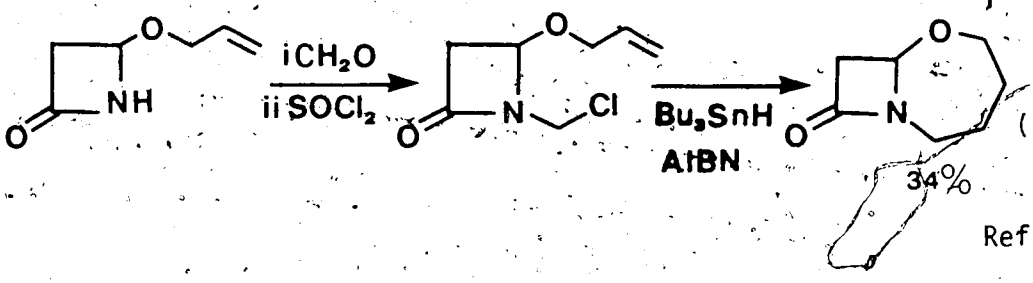
Relative rates of 5-exo cyclization onto double and triple bonds.

(i)		5.3×10^5 sec^{-1} at 80°C
(ii)		1.2×10^5 "
(iii)		-----
(iv)		4.0×10^4 "

for the phenyl-substituted acetylene (entry iii) is higher[20] than 1.2×10^5 sec^{-1}.

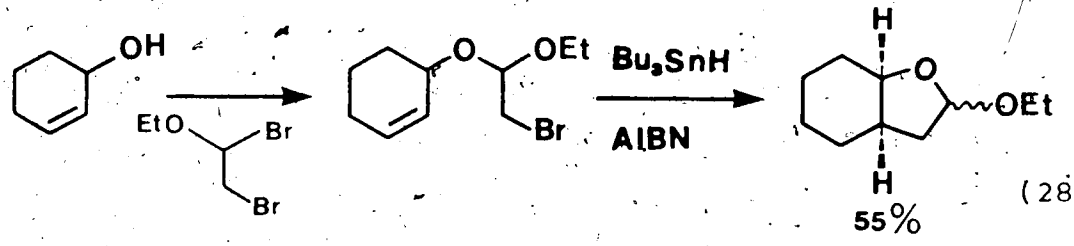
Synthetic Applications of Radical Cyclization

Until three or four years ago the utility of intramolecular radical cyclizations did not seem to have been recognized by synthetic organic chemists.[4] This situation has now changed and a growing number of heterocycles has been made by radical ring closure onto double bonds. Representative examples from the main laboratories involved in such work are summarized in eq. 27 — 34.



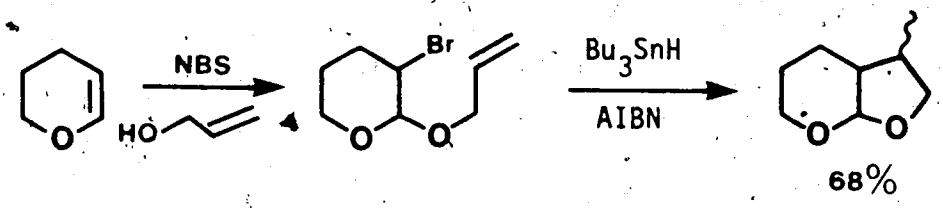
(27)

Ref. 21



(28)

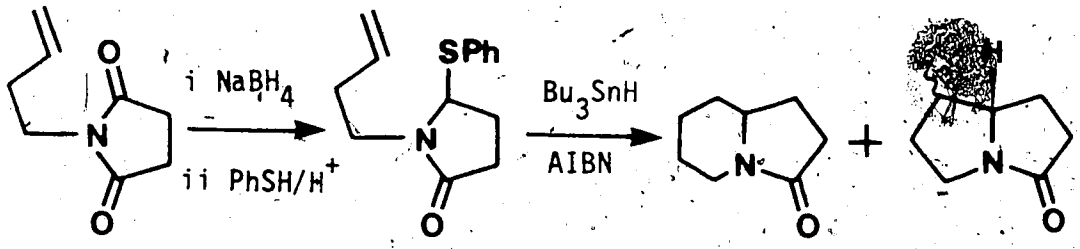
Ref. 22



68%

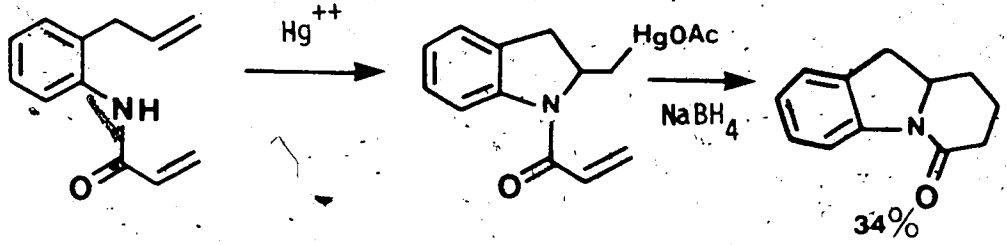
(29)

Ref. 23



22% 48% (30)

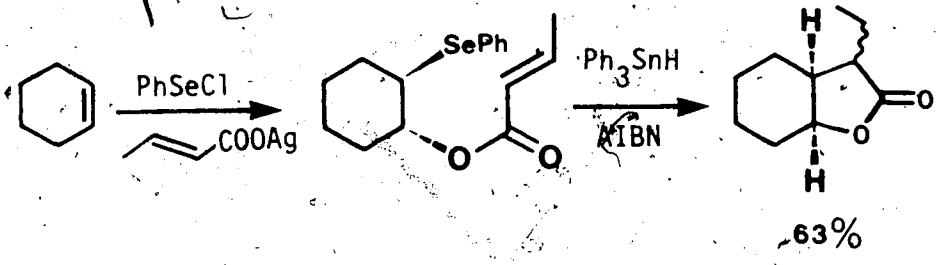
Ref. 24



34%

(31)

Ref. 25



63%

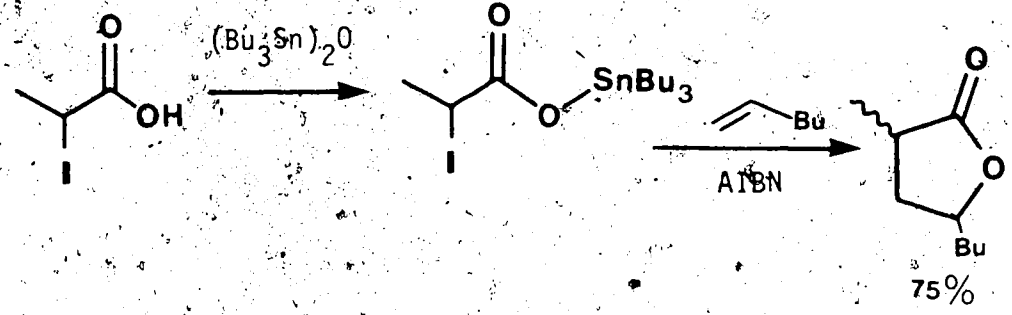
(32)

Ref. 26

The last entry is from earlier work in this laboratory[26] and will be used to illustrate some important features of this type of radical reaction. First of all, the reason why formation of heterocycles by radical chemistry has been studied is that the starting materials necessary for the ring closure are, in general, much more readily accessible than corresponding all carbon systems. For example, in the context of eq. 32, addition of a benzeneseleno-group and a carboxylate across a double bond is an easy and well-known[27] reaction; however, addition of a benzeneseleno-group and a carbon chain to the termini of a double bond is more difficult,[28] and has not been achieved in an intermolecular case.[29]

The stereochemical outcome of eq. 32 is of theoretical interest as there is evidently a stereoelectronic factor that results in 5-exo closure[30] rather than 6-endo. It was also established that ring closure is not reversible.

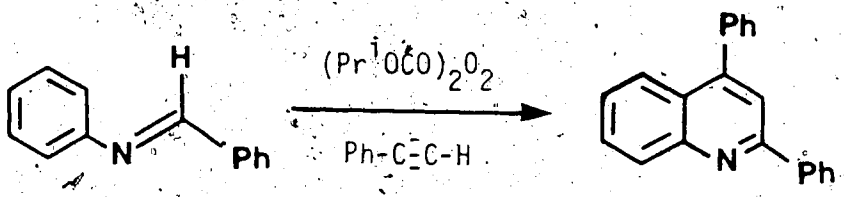
Very recently two methods, involving again formation of heterocycles, but using an intermolecular process as the first stage, have been reported (eqs. 33, 34).



(33)

Ref. 31

75%

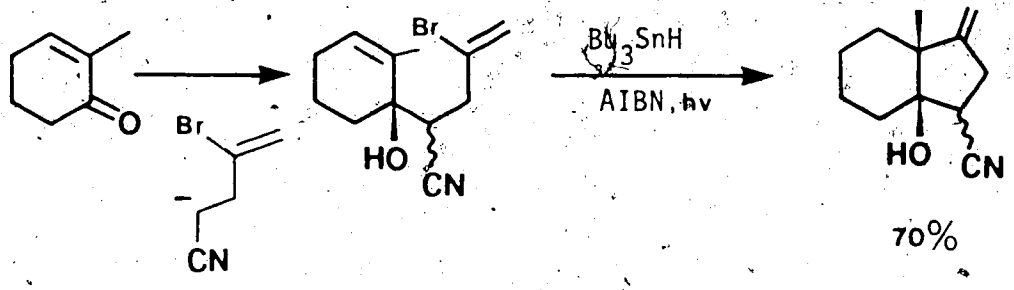


(34)

75%

Ref. 32

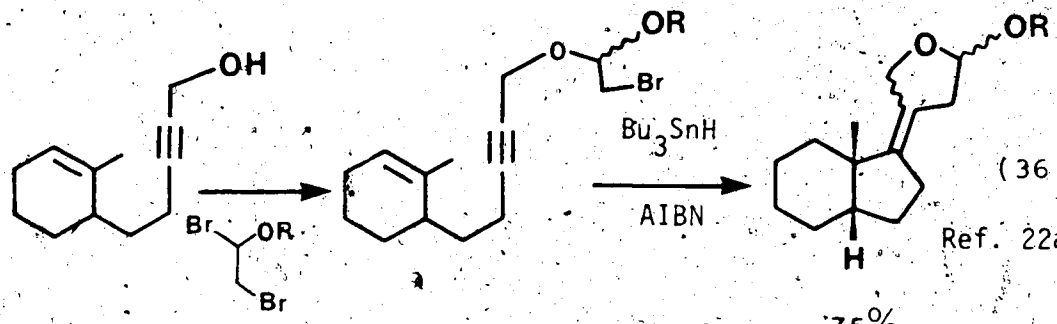
Although access, from readily available starting materials, to appropriate ω-olefinic radicals is generally difficult, a few cases are known in which ω-olefinic radicals have been used to make carbocycles, and representative examples are summarized in eqs. 35 — 40.



(35)

Ref. 33

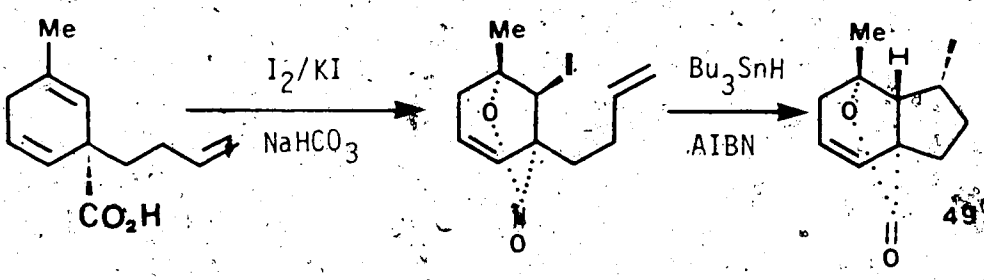
70%



(36)

Ref. 22a, 34

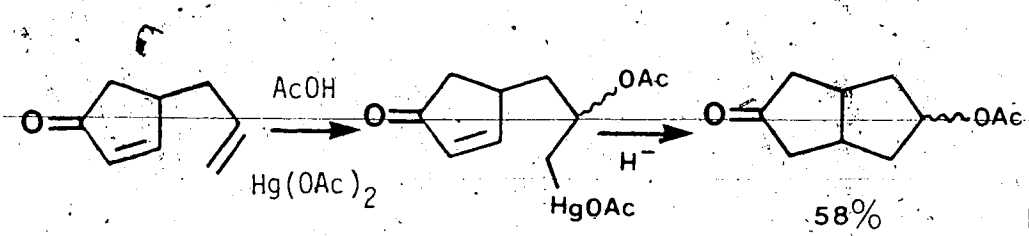
75%



(37)

Ref. 35,36

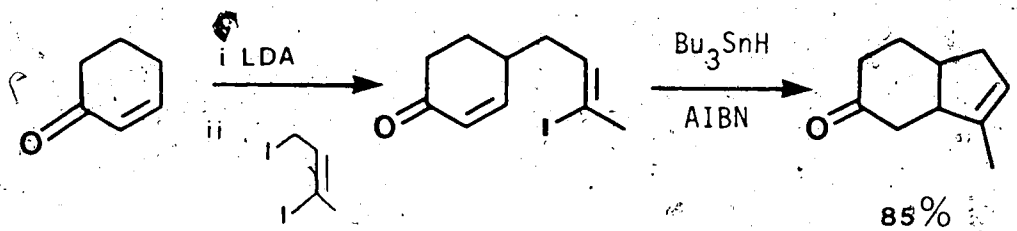
49%



(38)

58%

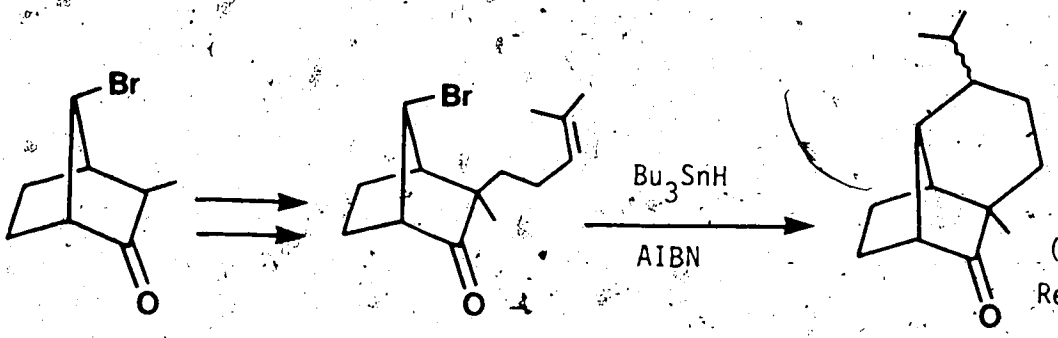
Ref. 37



(39)

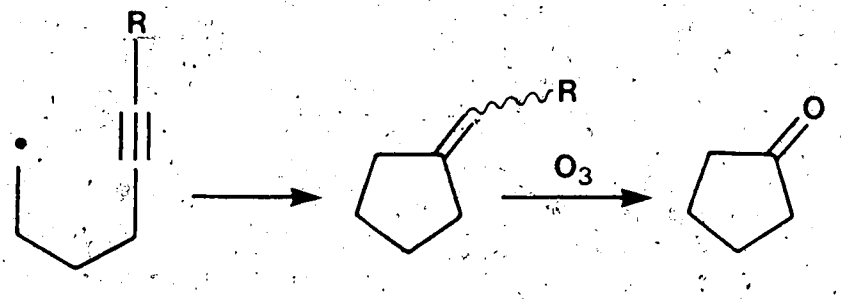
Ref. 38

85%



(40)
Ref. 39

It should be noted that in all of these reactions (eqs. 35 — 40) functionality is lost in progressing from the olefinic radical to the ring-closed product. Such is not the case in the cyclization of acetylenes because the product contains a double bond and ozonolysis leads to a ketone (eqn. 41) — a compound class that offers many opportunities for further manipulation.

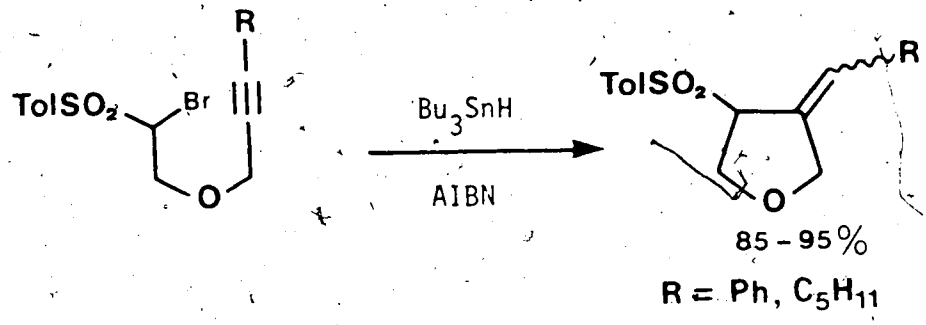


(41)

26 **27**

A few mechanistic studies have been reported for the transformation **26**→**27**.[15,16,17,20] Exclusive 5-exo closure was observed for **26** (R = Ph) and the process is 39 times faster than the case in which R = Bu.[20] The number of

synthetic applications is very small. Again, more cases are known for heterocycle formation, the main examples being those represented by eqs. 42 — 46.

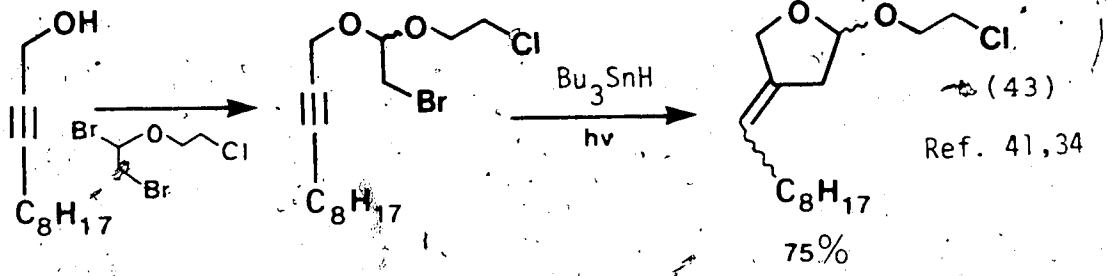


85 - 95%

R = Ph, C_5H_{11}

(42)

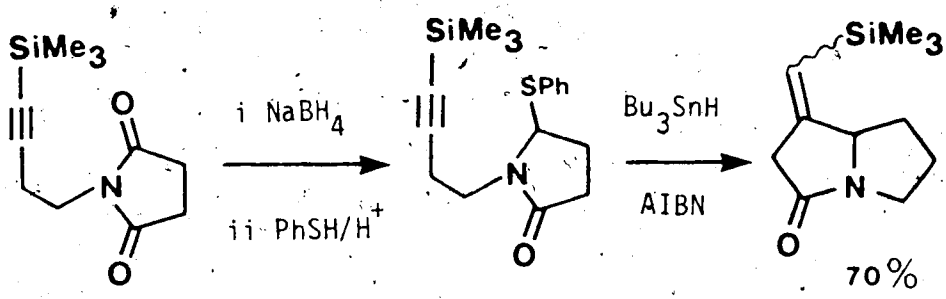
Ref. 40



(43)

Ref. 41,34

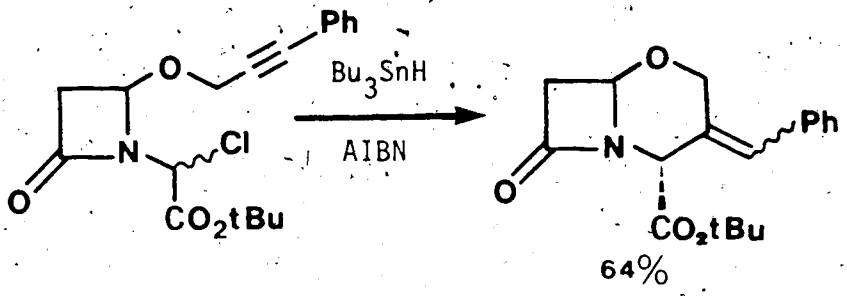
75%



(44)

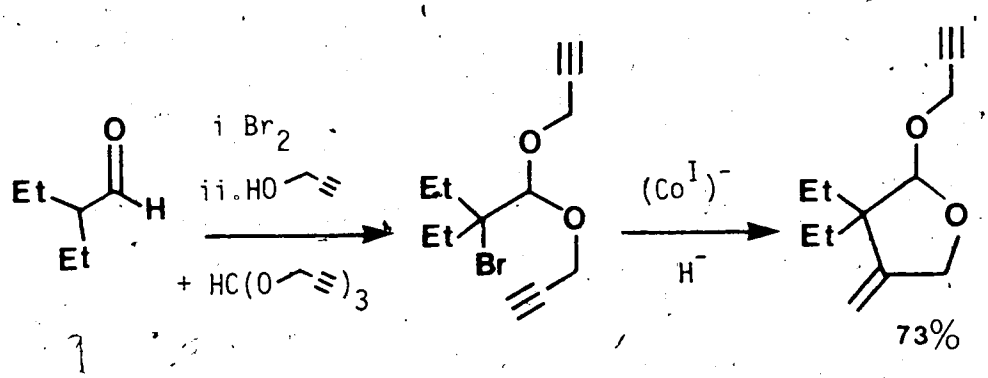
Ref. 42

70%



(45)

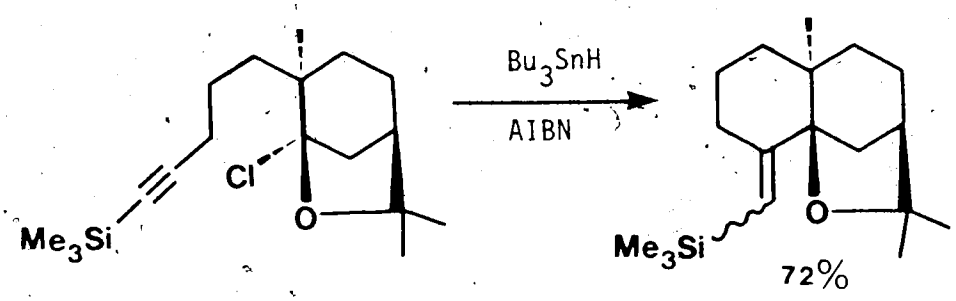
Ref. 21



(46)

Ref. 43,44

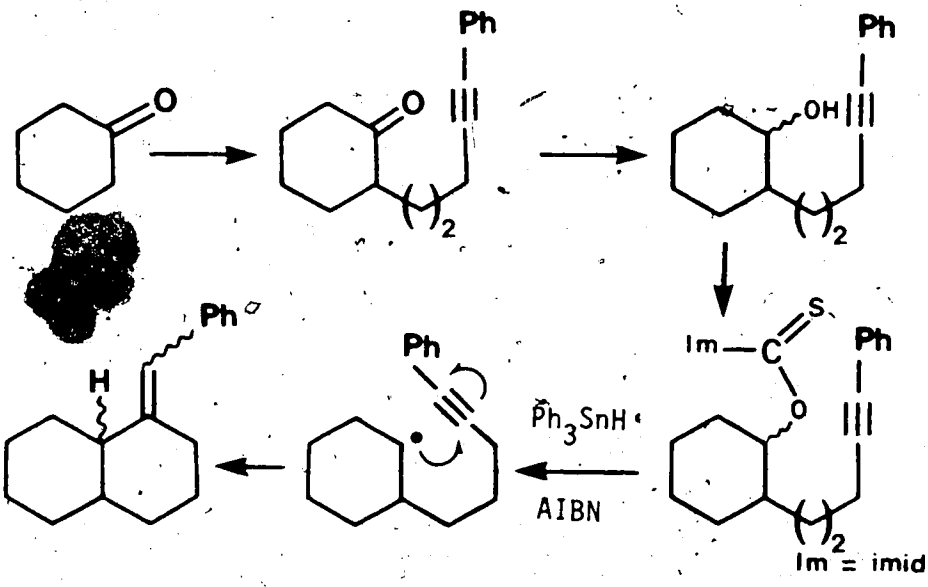
In the case of carbocycles, besides work in this laboratory (see eqs. 48 — 50), the main example is that shown in eq. 47.



(47)

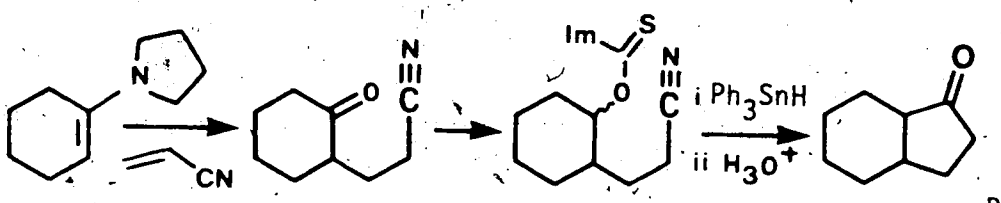
Ref. 45, 46

It would appear that the potential utility of ω-acetylenic radicals for making carbocycles has not been properly recognized, and hardly any attempt has been made to devise useful general solutions to the problem of gaining easy access to suitable starting materials. These subjects are being deliberately tackled in this laboratory and routes have been found (see eqs. 48 — 50) for adapting ketones and olefins for radical cyclization onto sp-hybridized carbon.



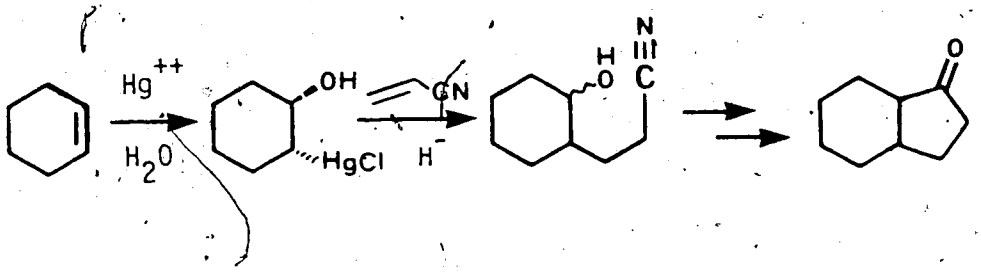
(48)

Ref. 47



(49)

Ref. 47



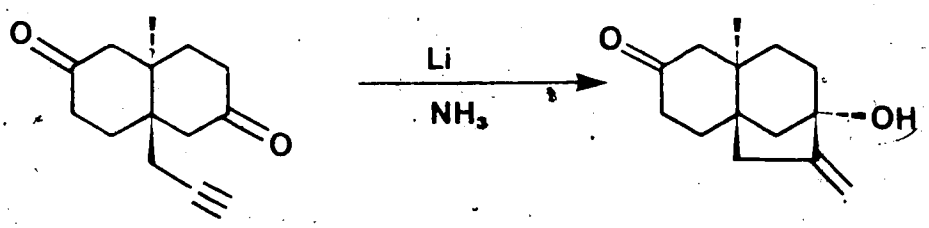
(50)

Ref. 47

The yields in the cyclization step are usually in the range 65 — 79%.[47] The now classical enamine chemistry[48] and the more recently developed deoxygenation process[49] were crucial to the development of the reaction schemes shown in eqs. 48 — 50.

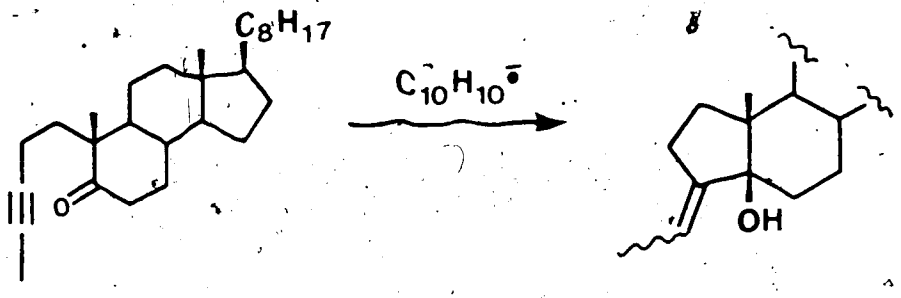
Anionic Radical Closures

A number of processes, believed to proceed via radical anions, are related to the radical cyclizations already discussed. Equations 51 — 53 show these types.



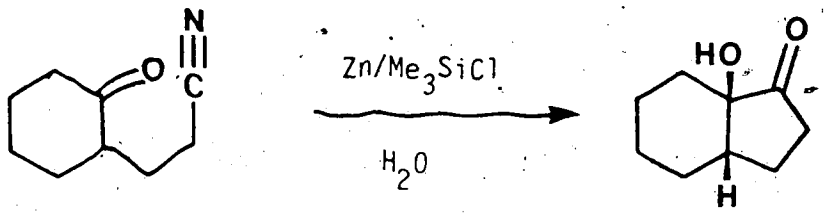
(51)

Ref. 50



(52)

Ref. 51



(53)

Ref. 52

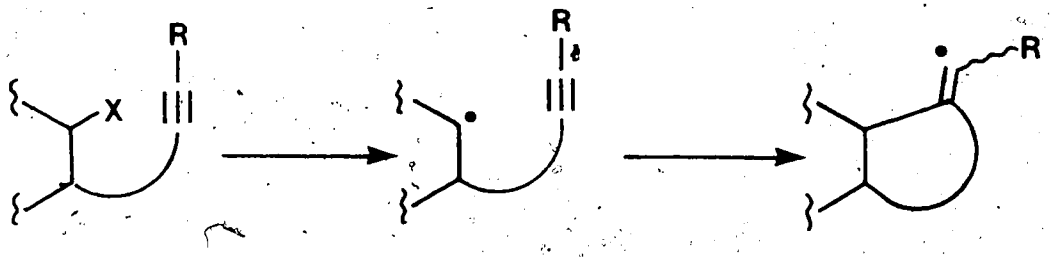
It should be noted that, at least for the last example, it is not yet proven that the species $\dot{C}$-OSiMe$_3$ is involved, rather than $\bar{C}$-OSiMe$_3$.

In summary, the use of free radicals to make carbocycles is a very promising technique but widespread adoption of cyclizations based on ω-acetylenic radicals will depend on (1) the development of simple and general methods of access to such species and (2) an exploration of the versatility of these and related radicals.

RESULTS AND DISCUSSION

As explained in the previous section, cyclization methods based on radical ring closures are potentially useful in the field of organic synthesis and we decided to continue some studies in this area that had already been initiated[26,47] in our laboratory.

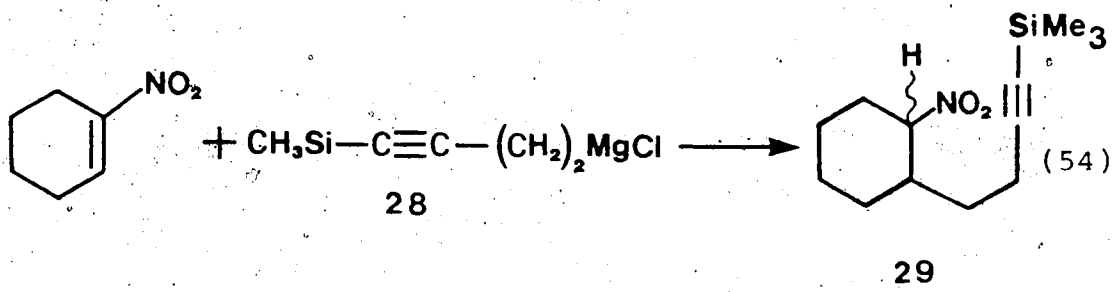
A main problem to be overcome was the development of a method for converting readily accessible compounds into materials that were properly constituted to undergo radical ring closure. A straightforward synthesis was needed of a class of compounds in which were present a pendant acetylenic group and a suitable functionality that could be used to generate a carbon radical. The latter has to be in an appropriate position to undergo ring closure onto the triple bond (Scheme 1).



Scheme 1

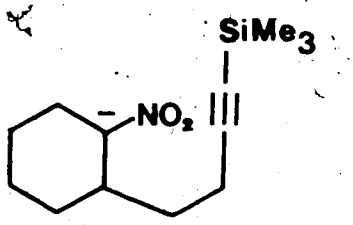
We tried several possibilities, which are described briefly below, before finding a system that warranted extensive investigation.

Our initial plan was to use α,β-unsaturated nitro-compounds, which can be made easily from olefins.[53] Such nitro-compounds are known[53] to undergo Michael addition with organometallic species. However, with 1-nitrocyclohexene as a test case, we were not successful in obtaining a satisfactory yield of Michael adduct using the acetylenic Grignard reagent **28** (eq. 54). Our best yield



was 48%. Moreover, the product **29** is not yet properly constructed for the generation of radicals because it is known[54] that only tertiary nitro-compounds, apart from those bearing an α-activating group, undergo homolysis of the carbon — nitrogen bond. It was necessary, therefore, to trap the initial conjugate addition product, i.e. **30**, but we were unable to do this even using the very reactive

electrophile, benzyl bromide. Examination of the



30

literature[55,56] showed that, indeed, alkylation on carbon of secondary nitro-compounds is generally not a high-yield process. When we treated compound **29** with LDA and benzeneselenenyl chloride the desired product **31*** was not obtained, only starting material **29** was recovered. This observation stands in contrast to the reported[57] phenylselenation of primary nitro-compounds.

We next tried to carry out corresponding experiments with the α,β-unsaturated sulfone **32**.[58] Notwithstanding a number of examples[59] of conjugate addition to sulfones, we found that this substance does not react with Grignard reagent **28** in the presence of copper(I) iodide (eq. 56).

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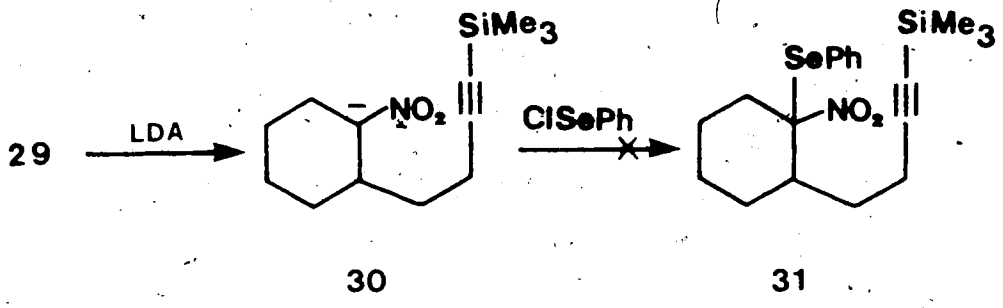
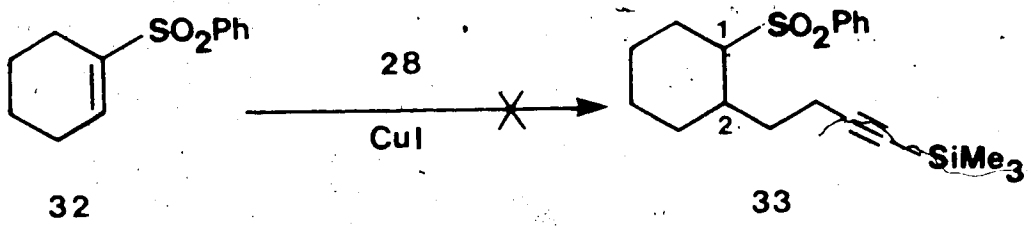
*We believe that either the C — SePh or the C — NO_2 bond in **31** could be homolyzed in the presence of $Ph_3Sn^{\bullet}$ but we do not know which would be preferred.



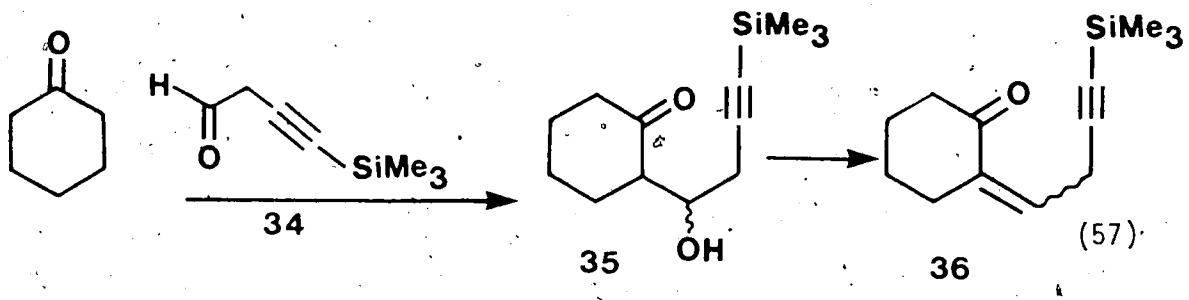
30 31 (55)



32 33 (56)

[We had planned to trap the intermediate anion with benzeneselenenyl chloride in order to place a PhSe-group at C(1,) in 33. This would be necessary in order to be able to generate a radical at C(1) since we had found in an independent experiment that cyclohexyl phenyl sulfone is not homolyzed by treatment with triphenyltin hydride in the presence of AIBN. In the event, the failure of the conjugate addition prevented us from exploring the phenylselenation of 33.]

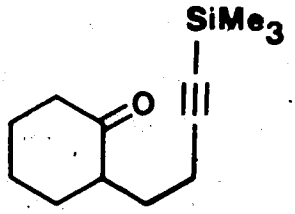
The next approach that we tested was based on aldol condensation of cyclohexanone with aldehyde **34** (eq. 57).



(57)

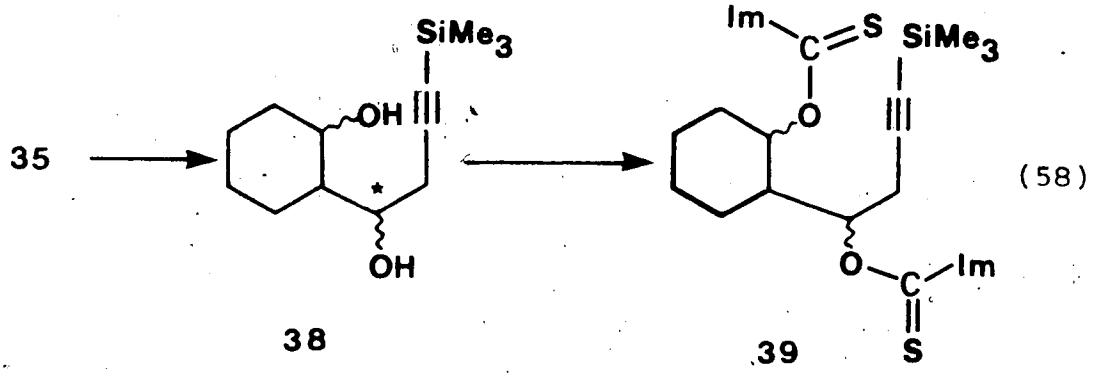
When the resulting aldol **35**, which was isolated in 63% yield, was exposed to the action of methanesulfonyl chloride and triethylamine it was possible to obtain the corresponding dehydration product **36** (as a mixture of isomers) in 86% yield. Unfortunately, we were unable to hydrogenate the double bond selectively. We had hoped that the bulk of the trimethylsilyl group would protect the triple bond, but catalytic hydrogenation over palladium on carbon did not give the desired substance as shown by IR and NMR measurements on the total reaction product. Use of lithium in liquid ammonia did produce ketone **37**, but only in 58% yield.

With the aldol **35** available we did, of course, examine the possibility of carrying out a radical ring



37

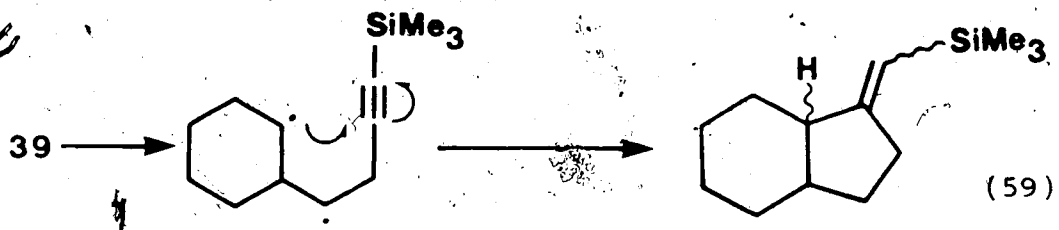
closure with simultaneous removal of the unwanted hydroxyl (see **38**, starred position). Reduction of **35** with lithium aluminum hydride gave the diol **38** in near quantitative yield and we examined the possibility of acylating both of the hydroxyl groups <u>individually</u> with thiocarbonyldiimidazole (**38**→**39**; eq. 58). If each hydroxyl could be protected independently as in **39** then treatment with a stannane might serve to generate the diradical **40**, which



(58)

could undergo, among other processes, the desired ring

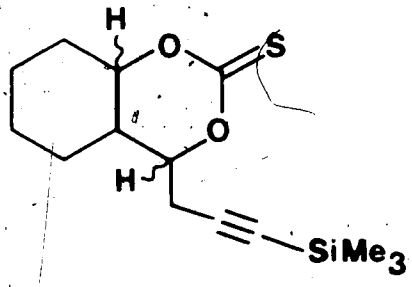
closure, followed by hydrogen abstraction* (**40**→**41**) (eq. 59).



(59)

40 **41**

In the event, treatment of the diol **38** with an excess of thiocarbonyldiimidazole served only to produce the cyclic thionocarbonate **42**.



42

*The individual radical centres shown in **40** could, of course, be generated (and could react) sequentially.

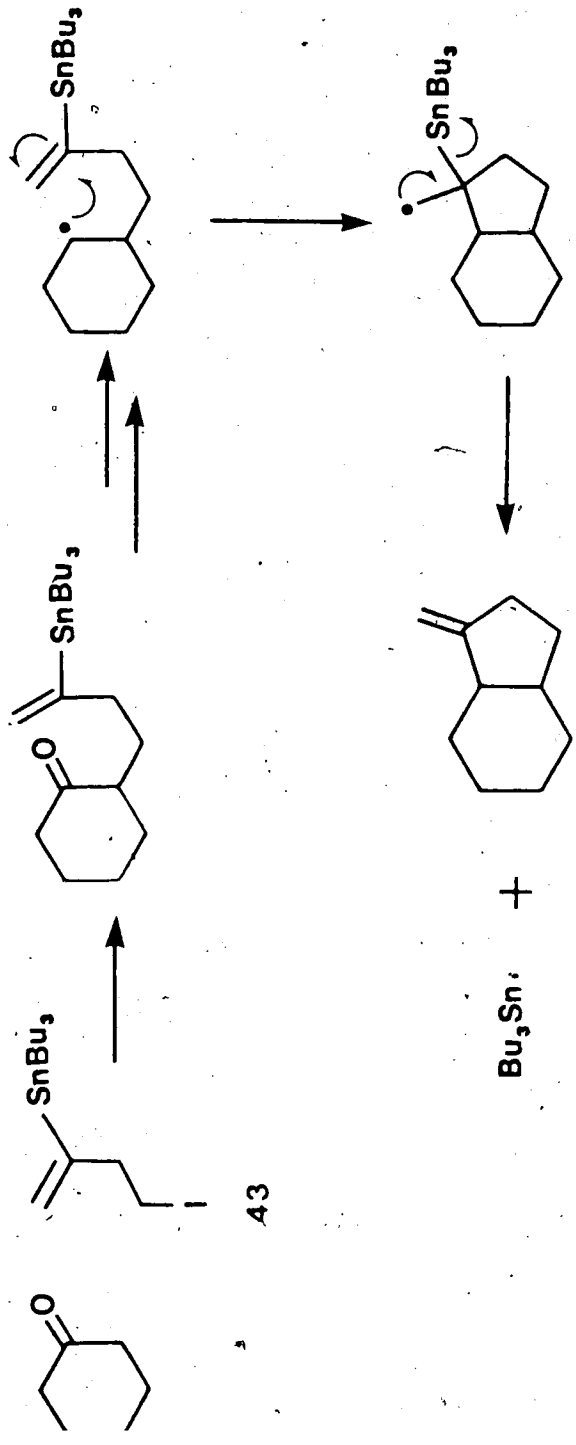
Likewise, when diol **38** was treated successively with butyllithium, carbon disulfide, and methyl iodide, the same product **42** was formed.

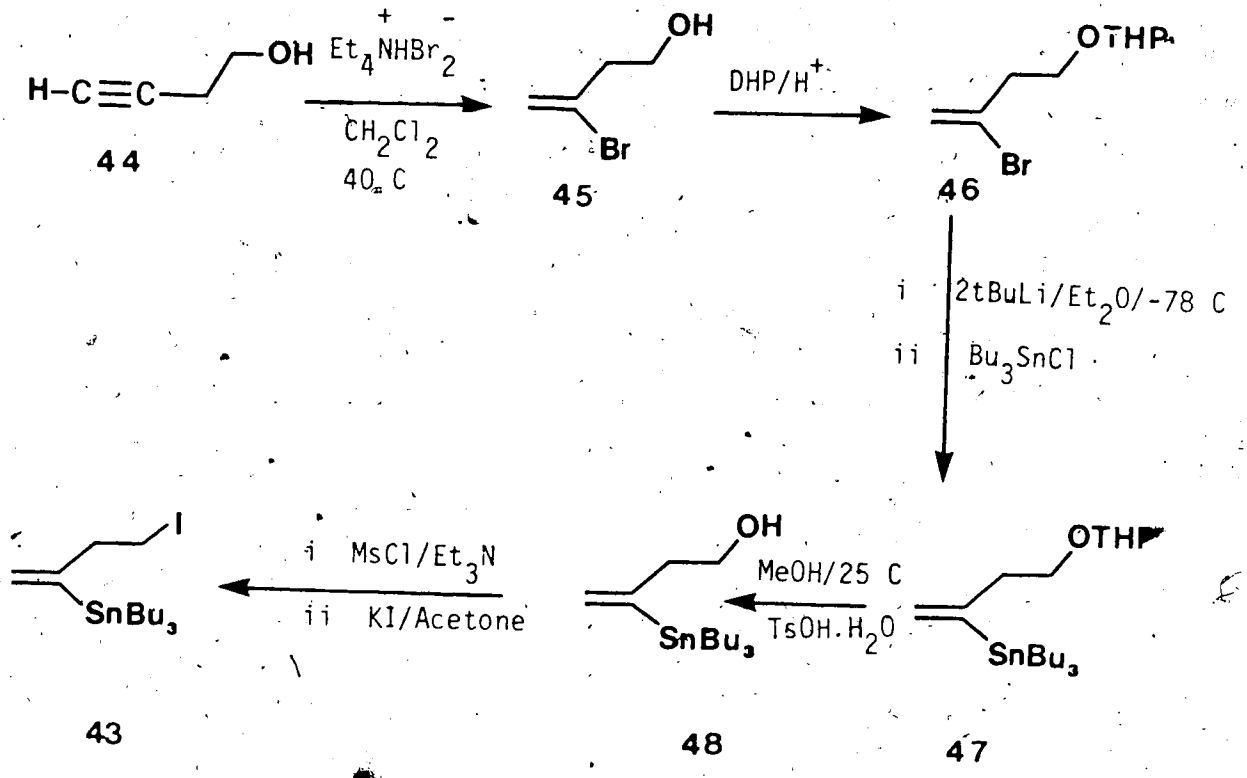
At this stage we turned to previous work in this laboratory[60] in which it had been shown that use of homoallylic halides to alkylate ketone enolates proceeds in fairly good yields (72%). By contrast, corresponding work with homopropargylic halides resulted mainly in dehydrohalogenation of the alkylating agent. On this basis, the homoallylic halide **43** (see Scheme 2) could offer the benefits of the allylic series in the alkylation step and, at the same time, provide, on cyclization, a double bond. This latter possibility arises in the fashion summarized in Scheme **2**, for which there exists precedent.[3e]

The required tin compound **43** was made, eventually, in a fairly straightforward manner that is summarized in Scheme 3. Alcohol **48** was made from hydroxybromide **45**, which is a known[61] compound. The yield of **48** was 83% (from **45**). Preparation of the iodide (**48**→**43**) proceeded in 63% yield.

As anticipated, the anion of N-cyclohexylidenecyclohexanamine reacted smoothly (79%) with iodide **43** (eq. 60).

Scheme 2

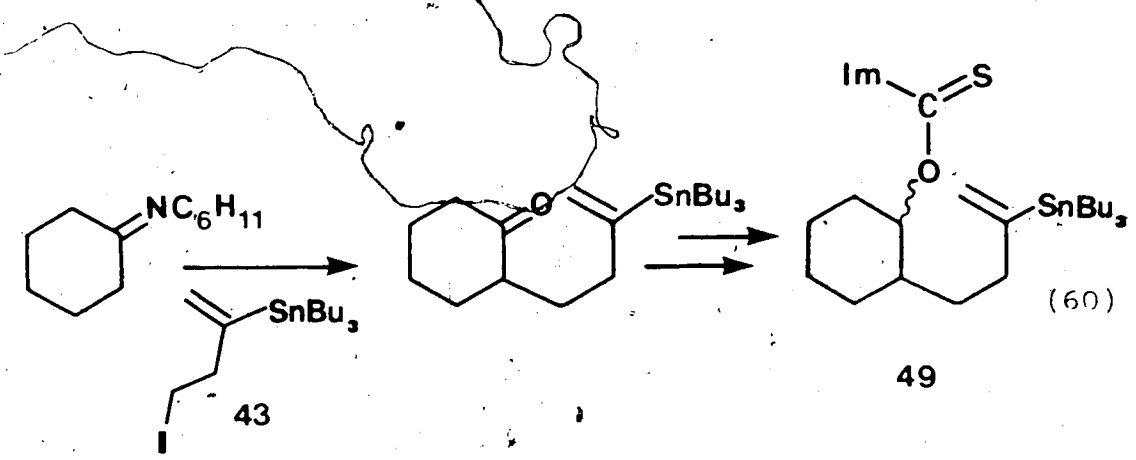




Scheme 3

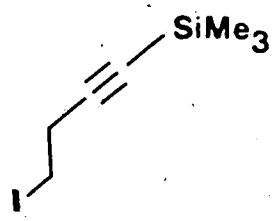
Reduction to the alcohol and derivatization with thiocarbonyldiimidazole were also efficient (97% and 89% yields, respectively) (eq. 60). When the final product **49** was treated under standard conditions[47] for deoxygenation we did not observe any ring-closed product and, in fact,

obtained a complex mixture.



Im = imidazoyl

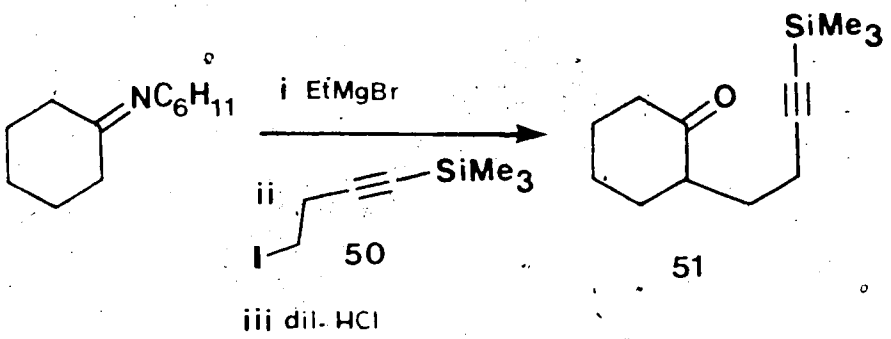
Finally, we prepared iodide 50 because a current report[62] in the literature showed that it could be used to alkylate anions derived from amides and in very high yields.



50

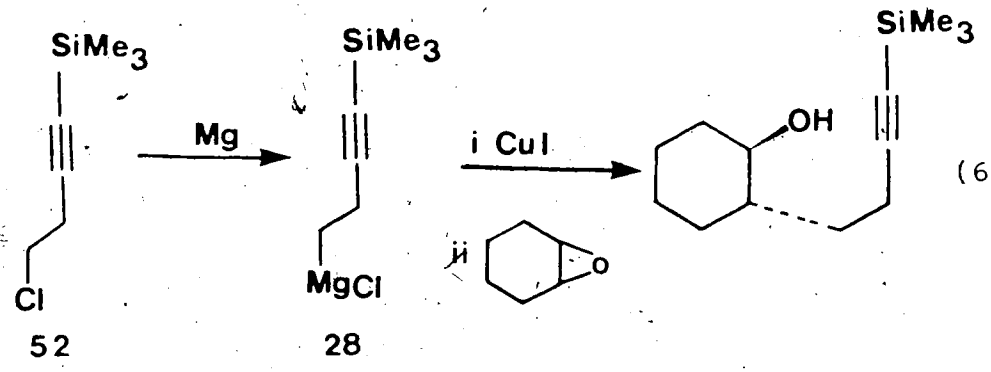
Why this iodide should not suffer dehydroiodination is not clear but, of course, the basicity and nucleophilicity of a carbanion stabilized by an amide carbonyl are different from those of a ketone- or imine-stabilized carbanion.

Nonetheless, the favourable report in the amide alkylation prompted us to try the same iodide in our own work, and indeed we were able to obtain the desired product **51** in 64% yield (eq. 61). However, we did not feel that this represented an adequately efficient process to merit detailed study. Instead we took the corresponding chloride **52**, from which the iodide is actually made, and prepared again the Grignard reagent **28**. This reagent, in the presence of a catalytic amount of copper(I)iodide,



(61)

reacted with cyclohexene oxide to give the ring-opened product in 55% yield (eq. 62). This yield again was not satisfactory for our purposes, but the experiment had the important role of drawing our attention to the opening of epoxides by organometallic reagents and it so happened that there were two reports[63,64] in the current literature

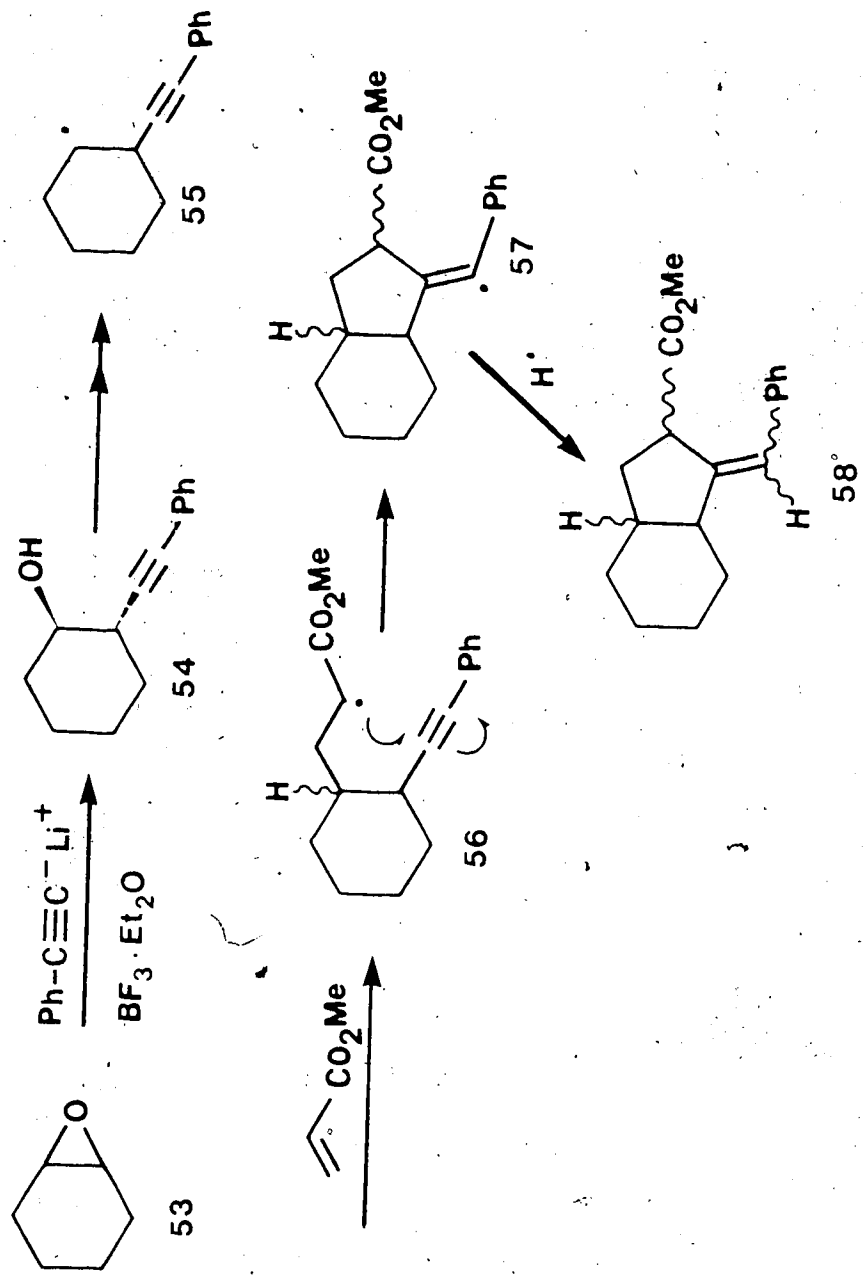


(62)

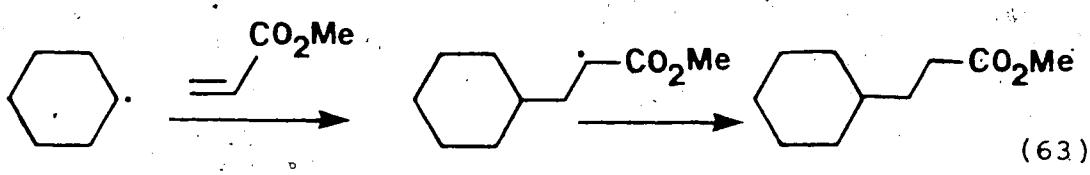
on the reaction of acetylenic carbanions with epoxides. It occurred to us that this reaction could be put to good use in the following sense.

If an epoxide were opened with the anion from phenylacetylene (**53**→**54**; Scheme 4) then the resulting hydroxyl group (see **54**) could serve as a precursor of the carbon radical **55**. We planned to generate that radical in the presence of a Michael acceptor, such as methyl acrylate. It is known from extensive mechanistic studies[1] that, for example, cyclohexyl radicals, add to methyl acrylate in the required manner (eq. 63). Applying this process to the case in hand, we hoped to trap the initial adduct **56** by an intramolecular ring closure (**56**→**57**), a process for which there was precedent.[15,47] The resulting species (**57**) would abstract hydrogen from triphenyltin

Scheme 4

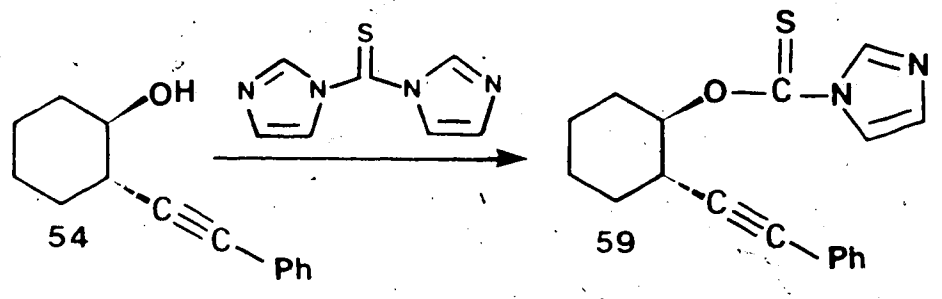

Ph
55
CO2Me
Ph
57
H
H·
CO2Me
Ph
58
H
OH
Ph
54
CO2Me
Ph
56
H
Ph-C≡C⁻ Li⁺
BF3·Et2O
O
53
CO2Me

hydride (57→58).



(63)

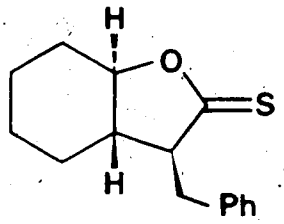
It was a simple matter to test this idea: Cyclohexene oxide was added, according to the literature procedure,[64] to a mixture of lithium phenylacetylide and boron trifluoride etherate in THF at -78°C. The resulting trans-alcohol **54** (92%) was easily derivatized (eq. 64) by heating in dichloroethane with thiocarbonyldiimidazole to give the thiocarbamate **59** in 80% yield. Treatment of this



(64)

compound in refluxing benzene with triphenyltin hydride in

the presence of a fifteen-fold excess of methylacrylate and a trace of AIBN gave an unstable product. It quickly became obvious that the material was not the desired substance. First of all it was unstable — a property not expected of ester **58** (see Scheme 4). Secondly, the IR spectrum did not show carbonyl absorption. An accurate mass measurement suggested the molecular formula $C_{15}H_{18}OS$ and examination of the ^1H NMR spectrum suggested structure 60.

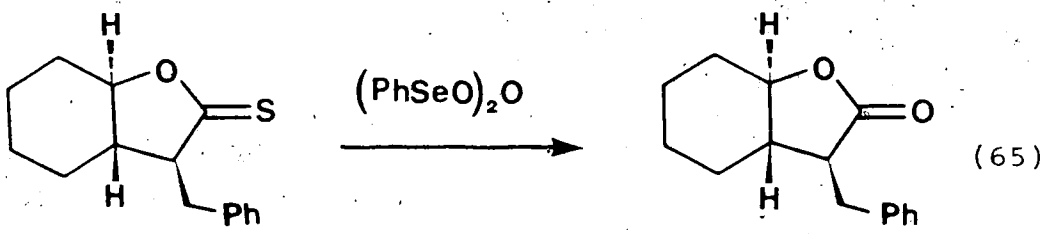


$C_{15}H_{18}OS$

60

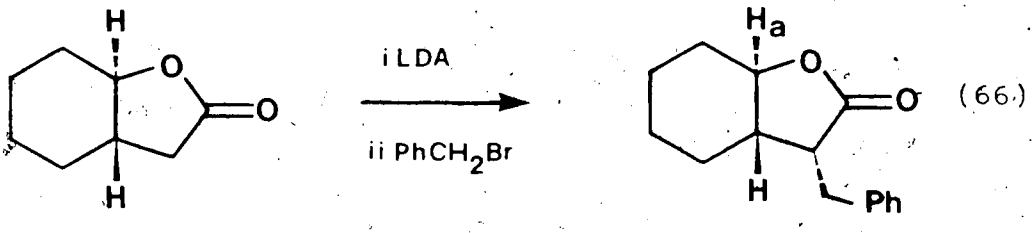
We were able to prove this structure and to define the stereochemistry shown. As expected on the basis of structure **60**, the same product is formed if the original experiment is repeated (i.e. treatment of **59** with triphenyltin hydride) but in the absence of methyl acrylate.

In order to establish the structure of **60**, we treated our product with benzeneselenenic anhydride[65] and obtained the γ-lactone **61** with IR carbonyl absorption at 1775 cm^{-1}.



60 61 (65)

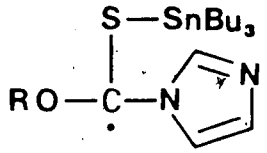
We then took a sample of the known[66] bicyclic lactone **62**, deprotonated it with LDA according to a published method[67] and treated the carbanion with benzyl bromide (eq. 66). The resulting substance was different from our original lactone **61**, but could be converted into it by deprotonation with LDA, followed by reprotonation. On the basis of analogy[68,69] we considered that the initial benzylation product has the stereochemistry shown in **63**, which is the result of electrophilic attack from the same face as H_a (see **63**). In the deprotonation — reprotonation



62 63 (66)

sequence the proton has also approached from that face. These considerations define the stereochemistry of our thionolactone as that given in **60**, with the proviso that our stereochemical assignment to **63** is based on analogy; attempts to gain confirmatory evidence by NOE experiments were not definitive.

During our triphenyltin hydride reduction of **59** it is evident that the initially-formed radical **64** is captured intramolecularly at a higher rate than it decomposes to **55** (see Scheme 5). Radical species of general type **65** have

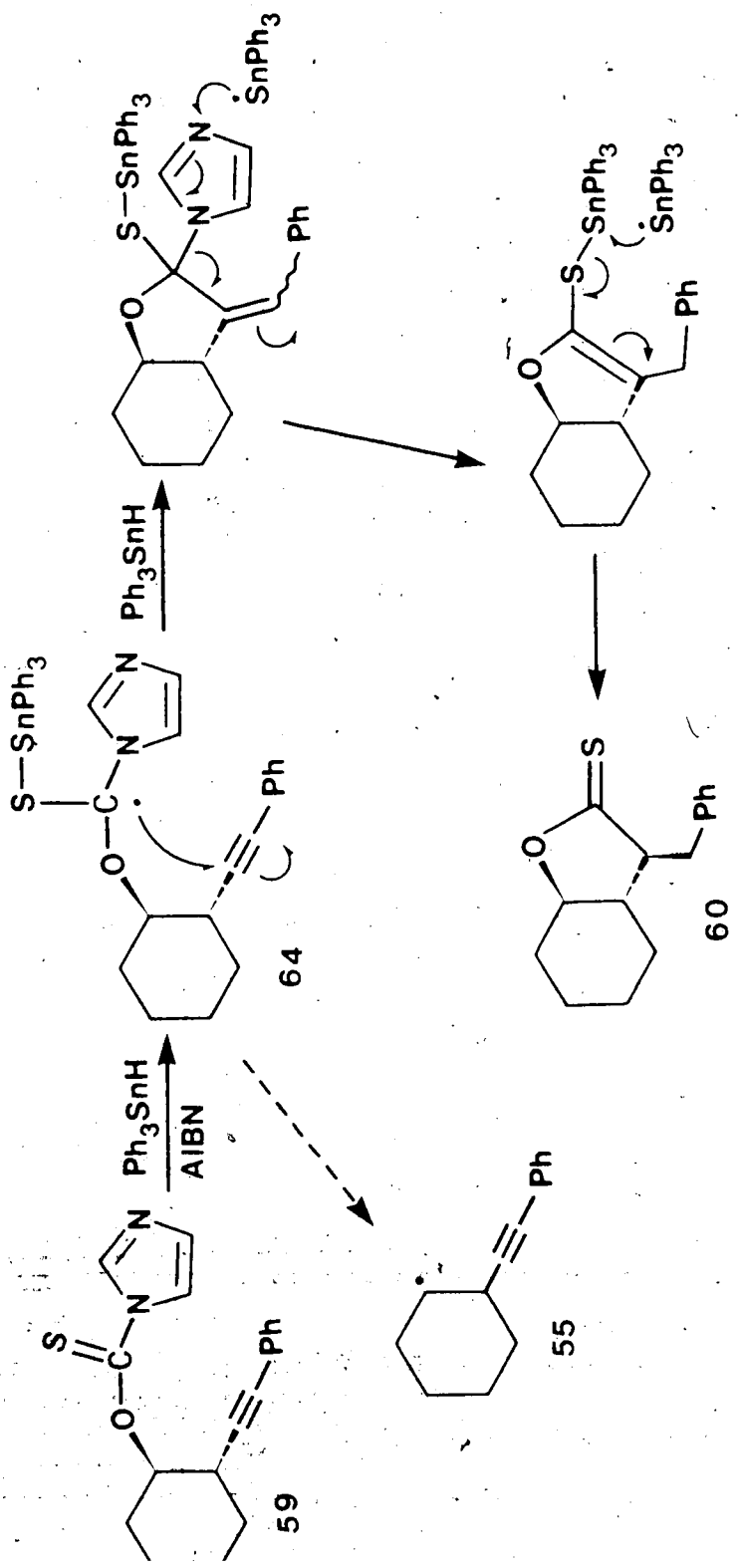


65

been trapped by hydrogen abstraction[70] and have been detected spectroscopically.[71] The present case (Scheme 5) is the first one to our knowledge in which trapping by carbon has been found; the mechanistic proposal for the conversion of **64** into **60** is speculative.

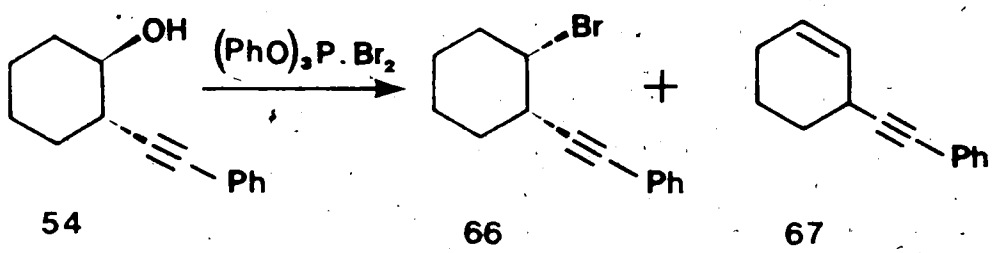
It is clear from our observations that, at least for the cyclohexyl system (cf. p. 225), the hydroxyl group is

Scheme 5


SnPh3
S—SnPh3
Ph
O
N
Ph3SnH
S—SnPh3
Ph
64
Ph3SnH
AIBN
59
55
60
S
Ph

not a suitable precursor to radical **55** and so we replaced the hydroxyl by halogen.

Treatment of acetylenic alcohol **54** with triphenylphosphite-bromine complex[72] gave the desired bromide **66** in which the cis stereochemistry was clear from the ^3J values. The yield of bromide was only 50%, the byproduct being the olefin **67** (eq. 67).



54 **66** **67** (67)

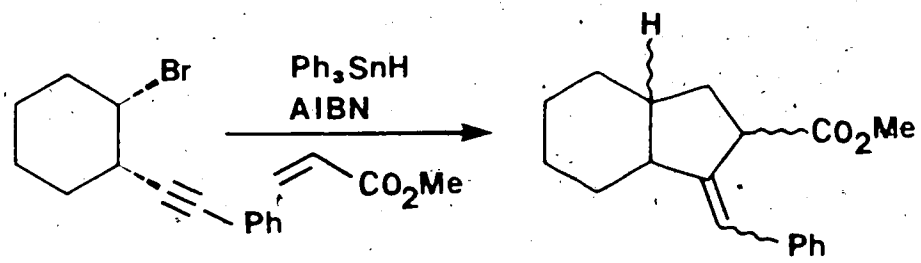
We examined a number of other halogenating agents,*, but noe was more successful, and we decided to accept the result with the triphenylphosphite-bromine complex.

With the bromide in hand, we repeated our initial experiment, that is to say, we mixed the bromide with a fifteen-fold excess of methyl acrylate in refluxing

---

*$(C_6H_5)_3P/DEAD/ZnCl_2$,[73] PPSE/NaI,[74] Ph_3P/CCl_4,[75] $Me_3SiCl/LiBr$.[76]

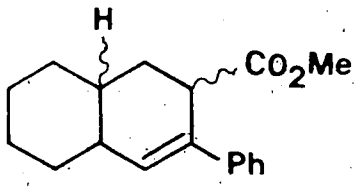
benzene and we added slowly to this mixture two dilute solutions: one of triphenyltin hydride in benzene and the other a very small amount of AIBN in the same solvent. At the end of the experiment it was possible to isolate the desired bicyclic compound **58** (eq. 68) in 38% yield.



(68)

66 **58**

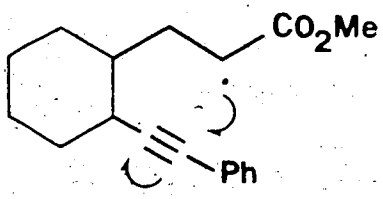
The elemental composition of our product was defined by the mass spectrum and the gross structure was shown to be **58** or **68** by the ^1H NMR spectrum.



68

The product was clearly a mixture of isomers, as

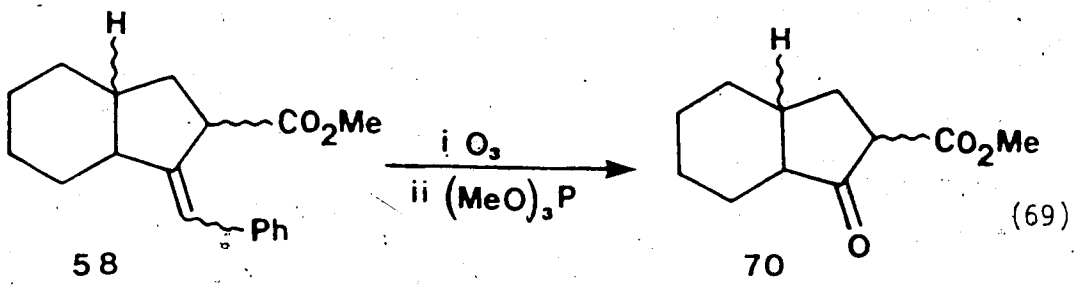
expected. This was obvious, not only from the ^{1}H NMR spectrum but also from the ^{13}C spectrum. Product 58 is the result of a 5-exo closure (see 56 in Scheme 4) while 68 is the product of 6-endo closure (see 69).



69

There exists carefully obtained mechanistic evidence[15] as well as examples from heterocycle synthesis[4b,34] to support the belief that δ-acetylenic radicals would undergo exclusively 5-exo closure and we were able to prove structure 58 by ozonolysis. This experiment gave a mixture of cyclopentanones[70] in 77% yield* (eq. 69).

*Admittedly, our material could have contained 23% of 68, but this is unlikely from evidence with other compounds given later.

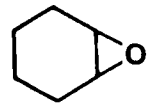
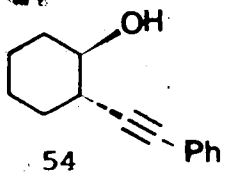
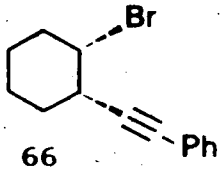
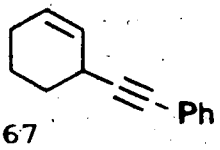
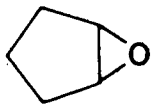
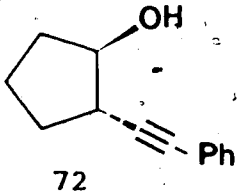
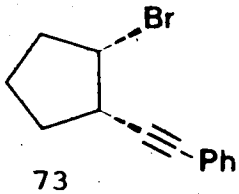
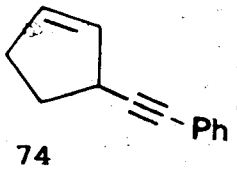
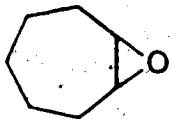
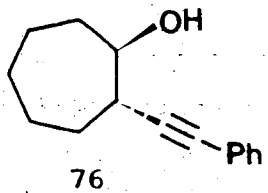
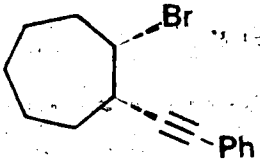
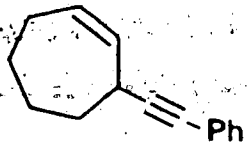
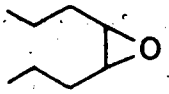
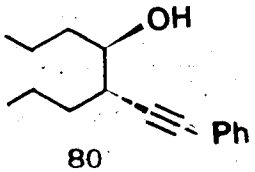
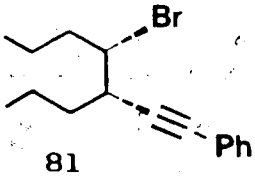
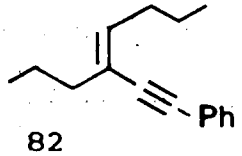
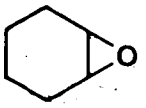
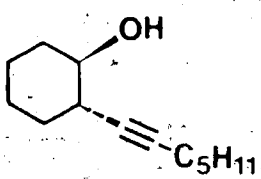
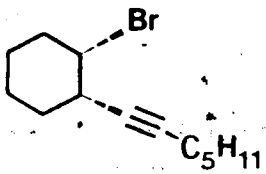
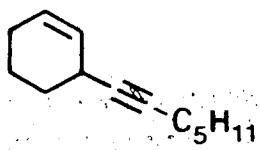


58 70 (69)

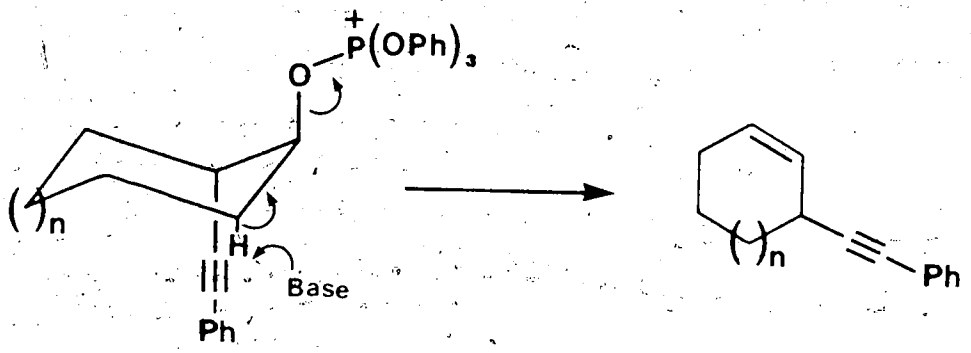
Although the yield in our radical annulation **66→58** is only 38%, it should be pointed out that <u>two</u> carbon — carbon bonds are formed in a single stage. We took the transformations as validating our initial idea shown in Scheme 4 and we regarded them as providing a prototype for an interesting method of forming carbocycles. Accordingly, we decided to investigate the process further. Our finding is that the method is a general one and it is convenient to describe our observations in a retrospective fashion as they can be dealt with more economically by this means.

The procedures used with cyclohexene oxide were applied with equal success to the compounds listed in Table 5. Each alcohol was converted into its bromide using triphenylphosphite and bromine.[72] As can be seen, the yields are in the range 41% to 61% and, obviously, some alternative method will have to be found in the future to improve these yields. In each case the major

TABLE 5

ENTRY	EPOXIDES	ALCOHOLS	BROMIDES	OLEFINS
1				
	53	54	66	67
		92%	50%	35%
2				
	71	72	73	74
		96%	44%	30%
3				
	75	76	77	78
		81%	61%	12%
4				
	79	80	81	82
		87%	60%	26%
5				
	53	83	84	85
		69%	41%	57%

byproduct was the non-conjugated olefin that would arise from the intermediate phosphonium salt as shown in eq. 70.

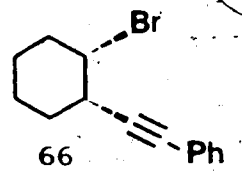
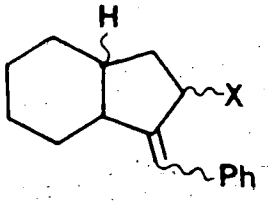
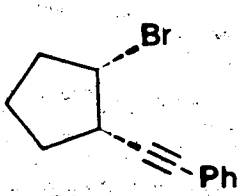
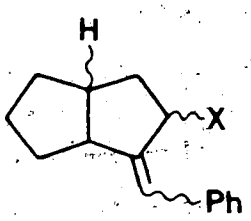
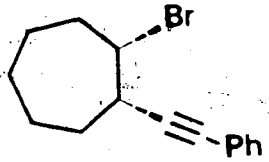
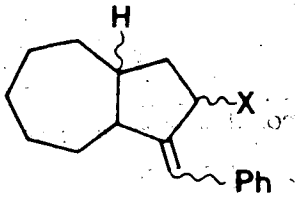
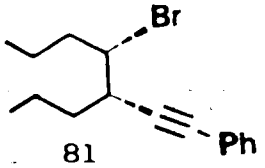
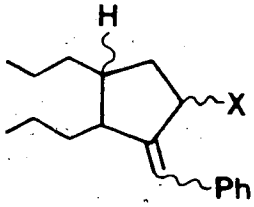
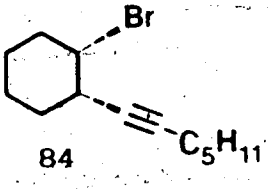
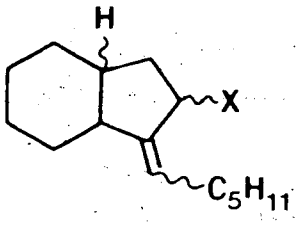


70

The only exception, understandably, was in the transformation 80→81, in which the conjugated enyne 82 was formed.

Each bromide listed in Table 5 was treated, under the conditions used previously; with triphenyltin hydride and a trace of AIBN. This was done in the presence of a ten- to fifteen-fold excess of a Michael acceptor. Three acceptors were studied: methyl acrylate, acrylonitrile, and phenyl vinyl sulfone. The last one was chosen because a sulfone group is readily removable once it has served its purpose. It will be recalled that the aim of the experiments was not to make benzylidene derivatives but to regard those derivatives as masked ketones. In each experiment we obtained a mixture of isomers (see Table 6)

TABLE 6

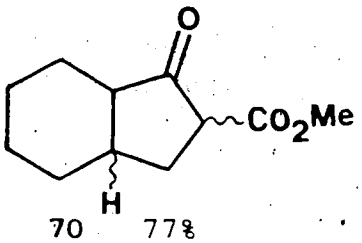
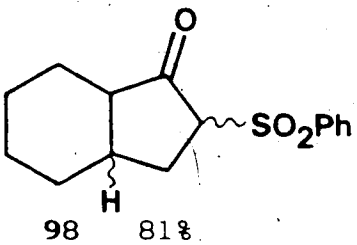
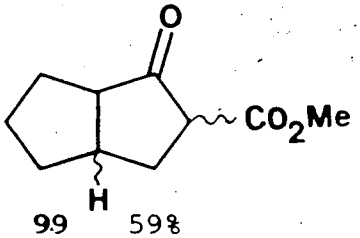
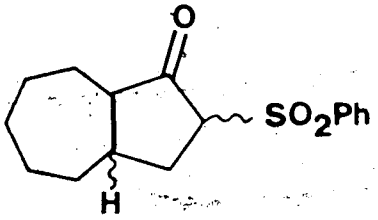
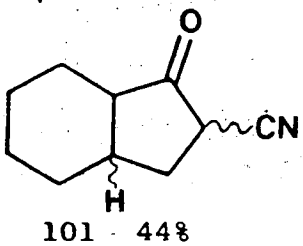
ENTRY	BROMIDES	PRODUCTS	X		
			COOMe	CN	SO_2Ph
1	 66		58 38%	86 57%	87 52%
2	 73		88 31%	89 38%	90 28%
3	 77		91 44%	92 54%	93 38%
4	 81		94 40%	95 46%	96 20%
5	 84			97 34%	

that we could not separate by TLC or HPLC. The materials gave what we take to be molecular ion peaks at a m/z ratios corresponding to the indicated structures and the ^1H NMR spectra were consistent with those assignments. The vinyl region usually showed 5 to 7 peaks (a maximum of 8 isomers is expected for 5-exo closure). In the case of the esters **58**, **88**, **91**, and **94**, several methoxy signals were also detected. The ^{13}C NMR spectra in all cases were extremely complicated because of the number of isomers present.

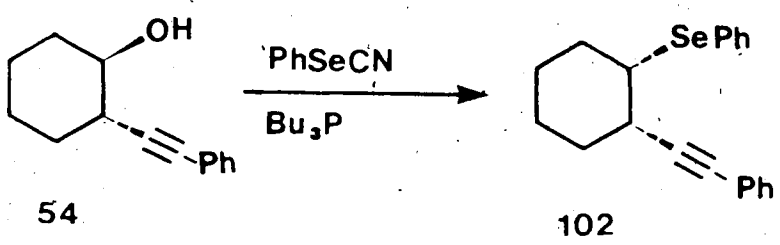
In the case of compounds **58**, **87**, **88**, **93**, and **97** (see Table 6) we carried out ozonolysis experiments and obtained the anticipated five-membered ketones in yields listed in Table 7. The compounds all showed IR absorbtion at 1740 cm^{-1}. In the specific cases of **98**, **99**, and **100** we examined the crude ozonolysis mixture by ^1H NMR at 400 MHz and could detect only the aldehyde signal attributable to benzaldehyde. [Any annulation product resulting from 6-endo closure (cf. **68**) would give a formyl signal split into a doublet; the signal of benzaldehyde is a singlet.]

Because of the poor yields in the conversion of alcohol to bromide (see Table 5) we decided to investigate alternative radical precursors. We converted hydroxy-acetylene **54** into the corresponding selenide **102** by

TABLE 7

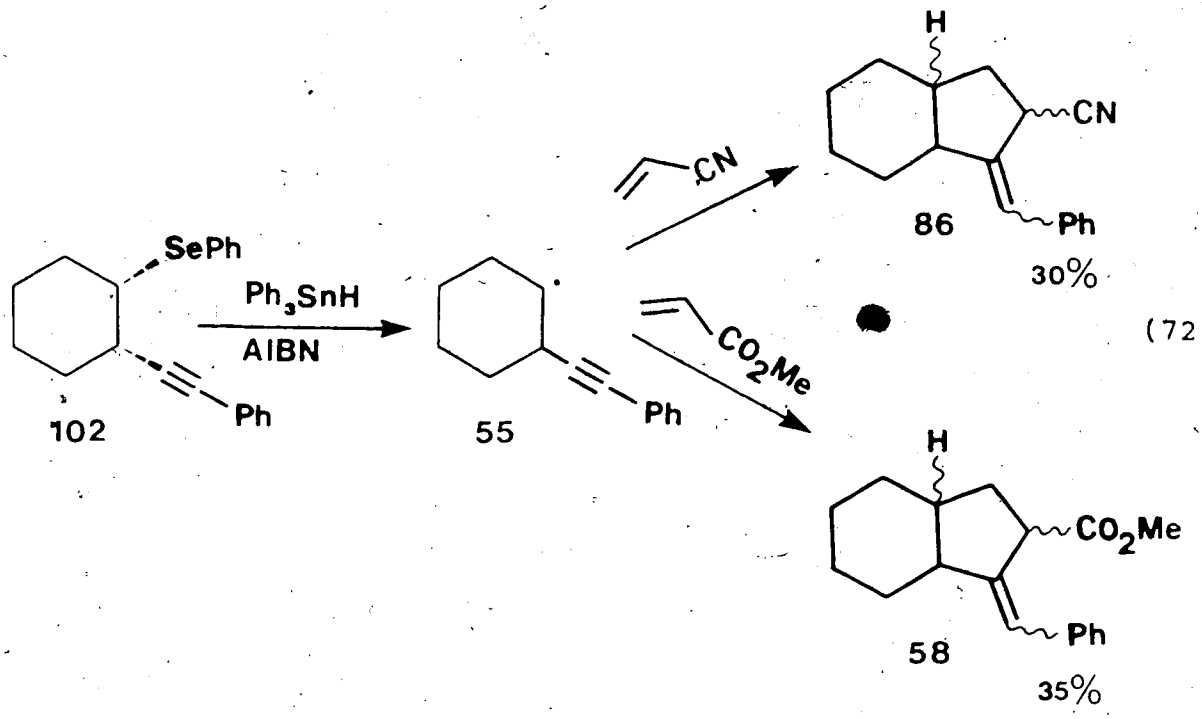
ENTRY	OLEFINS	CYCLOPENTANONES
1	58	 70 77%
2	87	 98 81%
3	88	 99 59%
4	93	 100 84%
5	97	 101 44%

treatment with phenylselenocyanate and tributylphosphine (eq. 71).[77] The reaction proceeded slowly but, after 3 days, the desired selenide **102** could be isolated in 76% yield. [When corrected for recovered alcohol **54**, the yield was quantitative.]



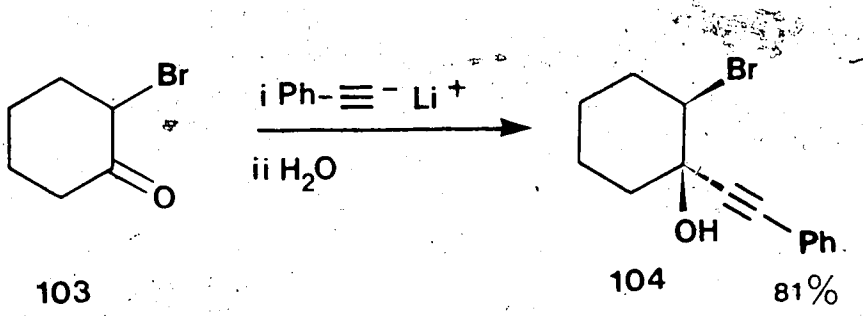
54 **102** (71)

Selenide **102** also serves as a precursor to radical **55** but the yields of annulation products were lower than with the corresponding bromide (eq. 72).



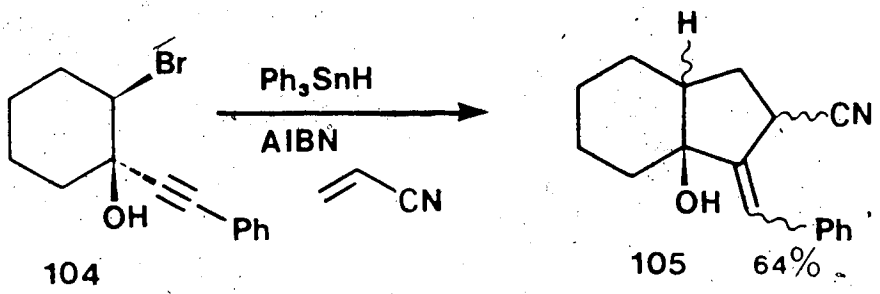
102 **55** **86** 30% **58** 35% (72)

Our next approach was to take α-bromocyclohexanone **103** and treat it with lithium phenylacetylide to generate bromohydrin **104*** (eq. 73).



103 **104** 81% (73)

Bromohydrin **104** underwent the radical annulation (eq. 74) in 64% yield with acrylonitrile as the Michael acceptor.



104 **105** 64% (74)

It should be noted that the presence of the hydroxyl group will facilitate production of the required radical and may alter its reactivity.[79]

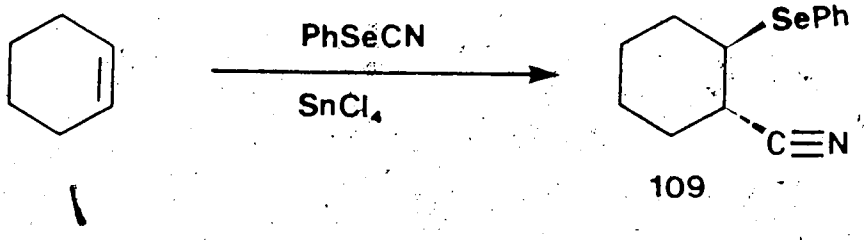
It will be recalled that in an earlier experiment the hydroxyl group in the simple cyclohexyl case (**54**) was

---

*The stereochemistry is assigned on the basis of literature[78] precedent.

found not to be a suitable precursor for the radical **55** (see p. 212). We investigated the cyclopentyl system (see **72**→**88**; Scheme 6) in the expectation that geometrical factors would inhibit closure of **107** onto the triple bond and render formation of **108**, and hence, of **88** the favoured pathway. In the event, treatment of alcohol **72** with thiocarbonyldiimidazole gave thiocarbamate **106** (90%) and, when this was subjected to the usual radical annulation conditions, in the presence of a fifteen-fold excess of acrylonitrile, benzylidenes **88** were isolated in 26% yield. These observations suggest that where appropriate factors* (in this example they are geometrical) operate, then direct use of alcohols in our annulation sequence is possible.

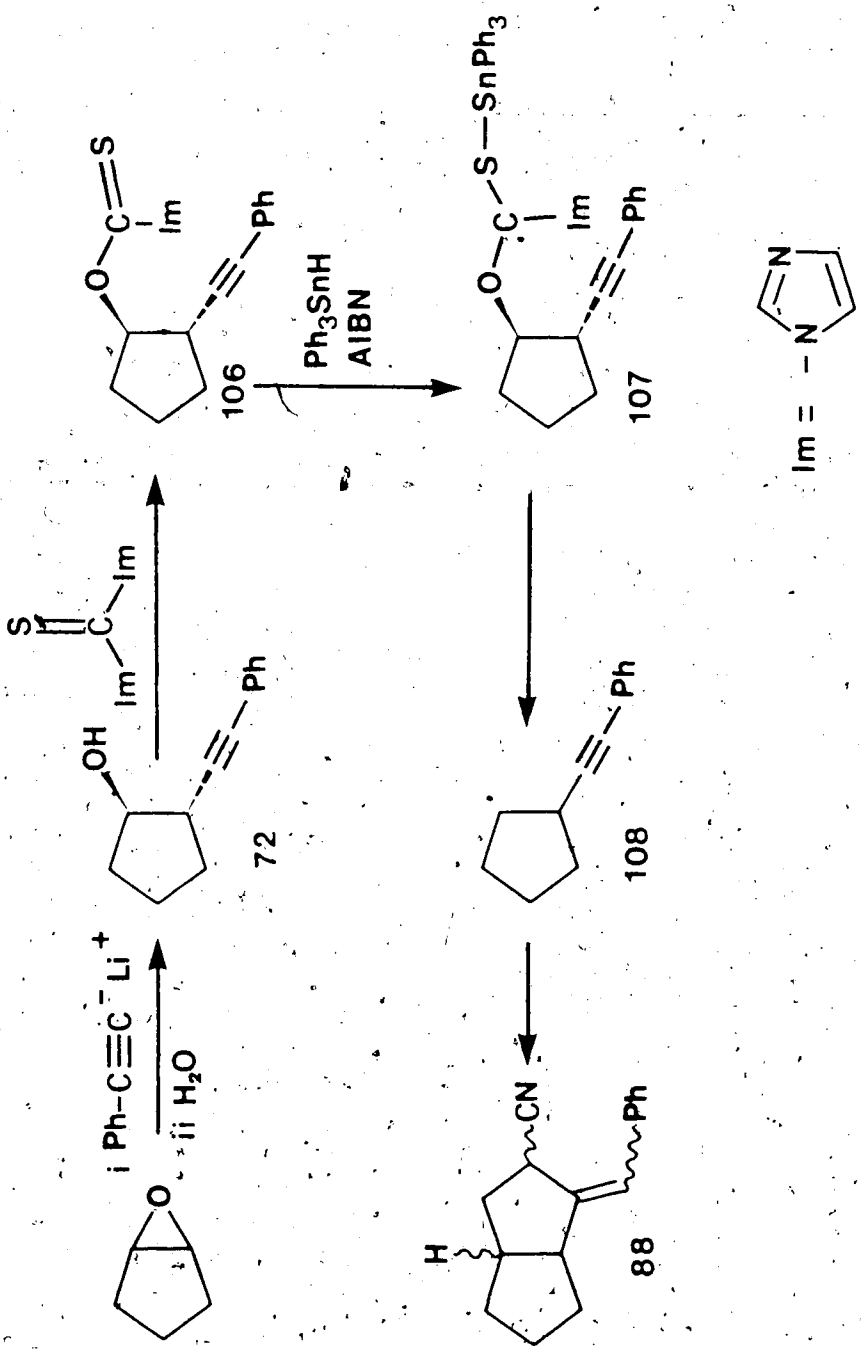
Finally, we decided to determine whether we could take advantage of the reaction reported in the literature[80] and summarized in eq. 75.



109 (75)

*The presence of a β-oxygen function[79] may also facilitate collapse of the radical intermediate and this possibility is under investigation.

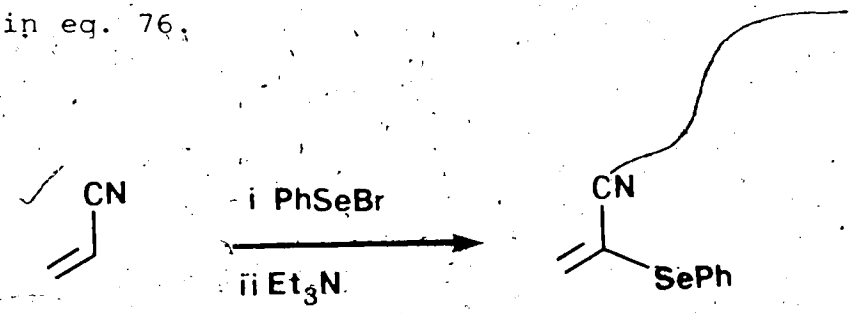
Scheme 6


Ph3SnH
AIBN
106
107
108
72
88
i Ph–C≡C⁻ Li⁺
ii H2O
Im = N N
Ph
OH
CN
H
O
S
Im

In this process, a benzeneseleno-group and a carbon unit in the form of a nitrile are added in high yield (90%) to the termini of a double bond. However, when we treated **109** under the usual annulation conditions in the presence of methyl acrylate we did not detect any characterizable products.

While the experiments on radical annulation were being carried out, we gave further thought to the general problem of devising easy routes to compounds that can undergo radical cyclization and we describe below a straightforward general synthesis that requires simple starting materials, provides exactly the class of compounds needed, and works efficiently.

Our plan was to start with the known[81] 2-phenylselenoacrylonitrile **110**, which is easily made by the route shown in eq. 76.



(76)

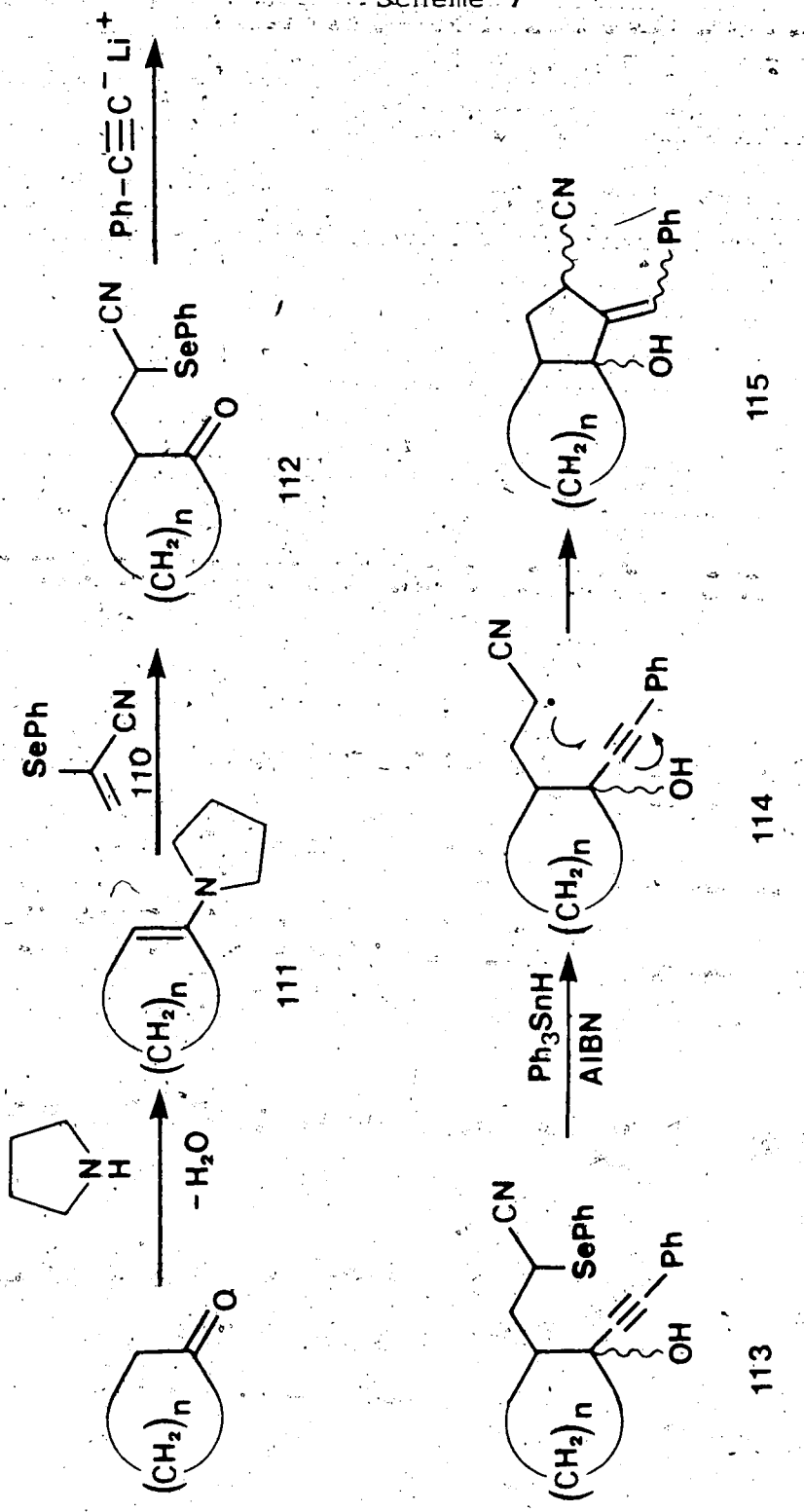
110

Compound **110** was expected to react with enamines **111** in a Michael fashion[48] (see Scheme 7) to give ketonitriles **112**. It was anticipated that treatment of these ketonitriles with lithium phenylacetylide would generate hydroxyselenides **113**, which are properly constituted to undergo the radical ring closure to benzylidenes **115**.

This sequence, as applied to cyclohexanone is shown in Scheme 8. Michael addition of cyclohexanone pyrrolidine enamine **116** to 2-phenylselenoacrylonitrile **110** in THF at room temperature for 3 h gave ketonitrile **117** (91%) as a mixture of two isomers, which on treatment with phenylacetylide, afforded alcohols **118** in 93% yield. Radical **119** was generated in the usual manner and it underwent ring closure in excellent (94%) yield. On the basis of prior analogy we assign the structure as **105**. We have carried out a number of experiments along the above lines and our results are summarized in Table 8. The data show that cycloalkanones are easily transformed in high yields into substrates **113**, and that, in all cases studied, ring closure occurred in good yields.

The above preliminary experiments show that 2-phenylselenoacrylonitrile **110** is a suitable reagent for

Scheme 7


Ph–C≡C⁻ Li⁺
CN
SePh
O
(CH₂)n
112
SePh
CN
110
N
111
N
H
-H₂O
O
113
Ph₃SnH
AIBN
CN
Ph
OH
114
CN
Ph
OH
115

Scheme 8

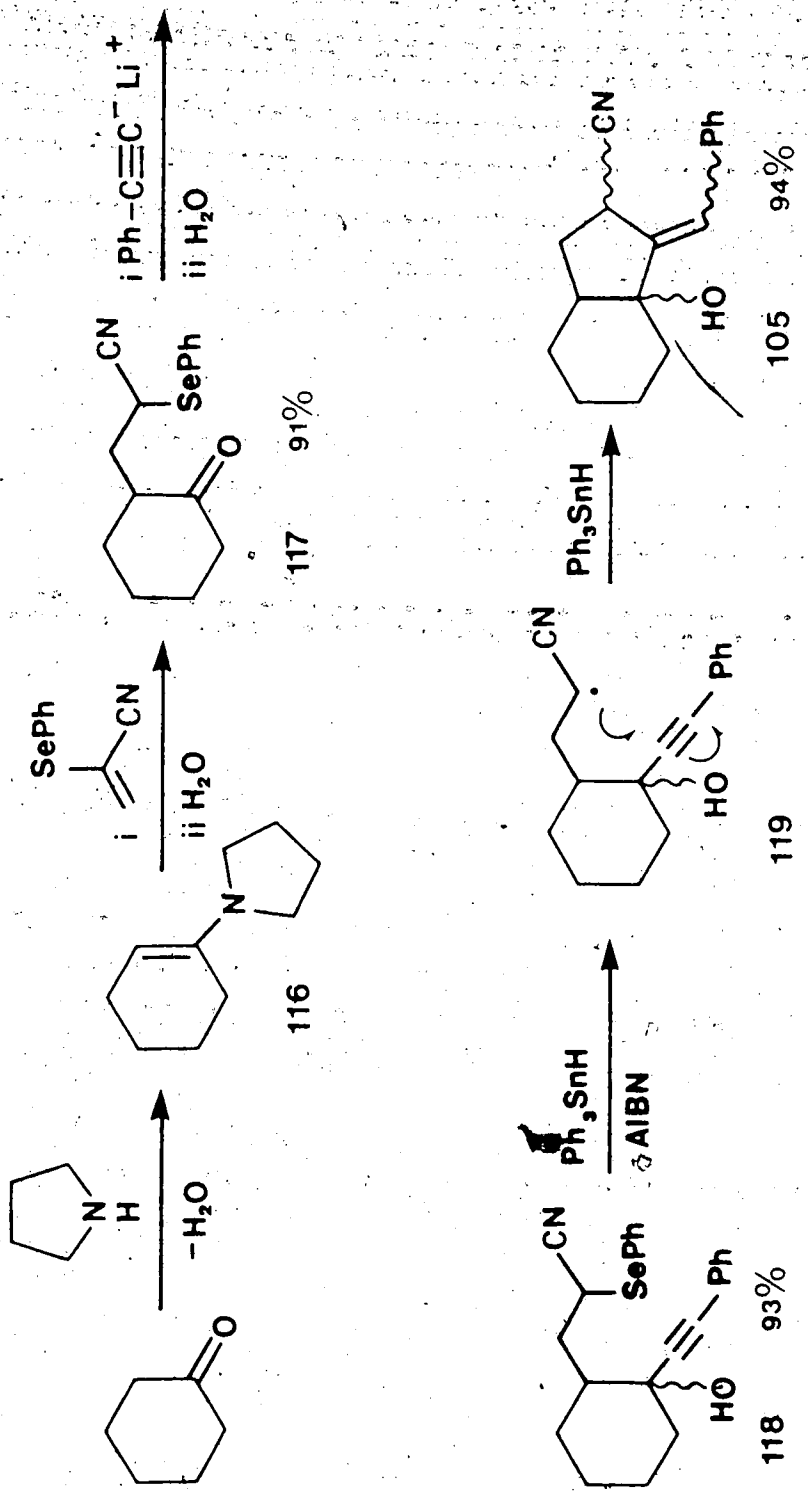
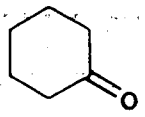
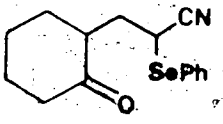
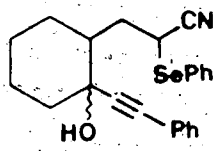
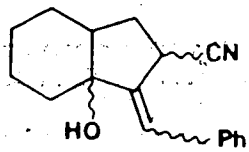
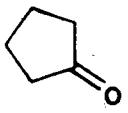
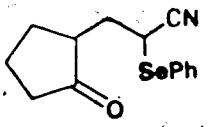
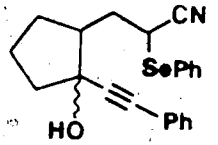
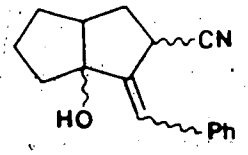
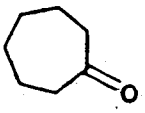
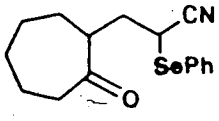
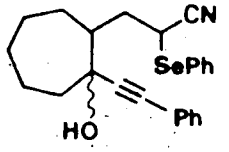
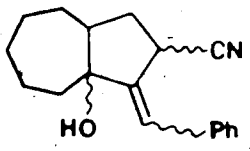
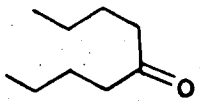
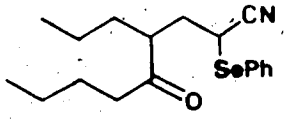
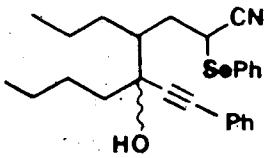
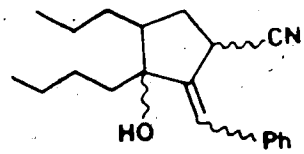

i Ph–C≡C⁻ Li⁺
ii H₂O
CN
SePh
O
117
91%
SePh
CN
i
ii H₂O
N
116
–H₂O
N
H
O
Ph₃SnH
CN
Ph
HO
105
94%
CN
Ph
HO
119
Ph₃SnH
AIBN
CN
SePh
Ph
HO
118
93%

TABLE 8

STARTING MATERIALS %	KETO-NITRILES[a] (%)[b]	ALCOHOLS (%)	BENZYLIDENES (%)
			
	117 (91%)	**118** (93%)	**105** (94%)
			
	120 (94%)[c]	**121** (68%)[d]	**122** (89%)
			
	123 (75%)	**124** (94%)	**125** (91%)
			
	126 (77%)[e]	**127** (80%)	**128** (79%)

[a]Prepared via the pyrrolidine enamine.
[b]Yield based on enamine.
[c]The material was not pure.
[d]Overall from enamine.
[e]Prepared via the morpholine enamine.

Michael acceptor-radical cyclization. Further experiments are underway to verify the structure of products **105**, **122**, **125**, and **128**. Of course, other Michael acceptors will also be evaluated.

Conclusion

The experiments described in this section support the view that methodology based on radical cyclization is a synthetically promising approach to carbocycles.

The present work, together with independent and prior contributions in the literature, suggests that the subject is likely to develop in the near future and to acquire a significant place in general organic synthesis.

EXPERIMENTAL

General Techniques

See Chapter 1, experimental section (p. 85).

trans-2-(Phenylethynyl)cyclohexanol **54**:[64] The literature procedure,[64] was followed: A solution of n-butyllithium in hexane (1.5 M, 40.7 mL, 61.0 mmol) was added to phenylacetylene (6.24 g, 61.1 mmol) in THF (60 mL) at -78°C and the mixture was stirred for 15 min. Boron trifluoride etherate (6.26 mL, 50.9 mmol) was added dropwise to the solution and stirring was continued for 10 min at -78°C. Then 7-oxabicyclo[4.1.0]heptane (4.0 g, 407 mmol) in THF (10 mL + 2 mL rinse) was added dropwise and, after stirring for 30 min more at -78°C, the reaction was quenched by addition of aqueous saturated ammonium chloride (50 mL). The organic layer was separated and the aqueous phase was extracted with ethyl acetate (2 × 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 × 15 cm) with 15% ethyl acetate — hexane yielded the pure (TLC, silica, 20% ethyl acetate — hexane) alcohol **54** (7.84 g, 96%): IR (neat) 3400, 2230, 1600,

1570, 760, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.10 — 1.55 (m, 4H), 1.75 (m, 2H), 2.05 (m, 2H), 2.45 (m, 1H), 2.55 (s, 1H), 3.55 (m, 1H), 7.26 (m, 3H), 7.40 (m, 2H).

1H-Imidazole-1-carbothioate **59**, O-2-(Phenylethynyl)cyclohexyl **59**: Alcohol **54** (0.740 g, 3.7 mmol) and 1,1'-carbonothioylbis-1H-imidazole[82] (1.6 g, 9.0 mmol) were placed in a flask and covered with dry 1,2-dichloroethane (13 mL). The resulting solution was refluxed under argon for 20 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 15 cm) with 20% ethyl acetate — hexane gave pure (TLC, silica, 30% ethyl acetate — hexane) **59** [800 mg, 80.6% corrected for on recovered starting material (100 mg)]: IR (neat) 1600, 1530, 760, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.30 — 1.95 (m, 6H), 2.15 (m, 1H), 2.35 (m, 1H), 3.05 (m, 1H), 5.60 (dt, 16, 4 Hz, 1H), 7.05 (s, 1H), 7.30 (m, 5H), 7.70 (broad s, 1H), 8.4 (s, 1H); exact mass, m/z 310.1147 (calcd for $C_{18}H_{18}N_2OS$, 310.2087). Anal. calcd for $C_{18}H_{18}N_2OS$: C, 69.63; H, 5.84. Found: C, 69.62; H, 5.82.

General procedure for radical annulations: [Oven-dried apparatus and anhydrous solvents were used. AIBN (Eastman

material) was used without purification.] The substrate (0.5 — 1.0 mmol) and the Michael acceptor (a 15-fold molar excess) were placed in a 100 mL round-bottomed flask containing a Teflon-coated magnetic stirring bar and equipped with a reflux condenser closed by a rubber septum. The system was purged with argon for 5 min. Benzene (30 — 40 mL) was injected into the flask which was then immersed in an oil bath preheated to 80°C. Benzene solutions of triphenyltin hydride (1.2 — 1.5 mmol per mmol substrate, 0.07 — 0.1 M) and of AIBN (0.05 — 0.1 mmol per mmol substrate, 0.008 M) were added simultaneously over 10 h by means of a double syringe pump. Refluxing under argon was continued throughout the addition and for a further arbitrary period of 2 h. The mixture was then cooled and evaporated under water pump vacuum. The residue was processed as described for the individual examples.

Attempted annulation of alkoxythiocarbonylimidazole **59** with acrylonitrile; (3β,3aβ,7aα)-Hexahydro-3-(phenylmethyl)-2(3H)-benzofuranthione **60**: The general procedure for radical annulation was followed using alkoxythiocarbonylimidazole **59** (166 mg, 0.535 mmol) and freshly distilled methyl acrylate (690 mg, 8.02 mmol) in benzene

(30 mL), triphenyltin hydride (280 mg, 0.80 mmol) in benzene (10 mL), and AIBN (15 mg, 0.097 mmol) in benzene (10 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 15 cm) with 5% ethyl acetate — hexane gave pure (TLC, silica, 5% ethyl acetate — hexane) **60** (40 mg, 30%): IR (neat) 1600, 1495, 1445 1250, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.96 (dq, J = 9.6, 4 Hz, 1H), 1.10 (tq, J = 9.6, 4 Hz, 1H), 1.3 (m, 2H), 1.55 (m, 3H), 1.88 (m, 1H), 2.28 (dq, J = 11, 3.6 Hz, 1H), 2.75 (m, 2H), 3.66 (m, 1H), 3.97 (dt, 10.4, 3.6 Hz, 1H), 7.23 (m, 5H); exact mass, m/z 246.1070 (calcd for $C_{15}H_{18}OS$, 246.1953).

Reduction of alkoxythiocarbonylimidazole **59**; (3β,3aβ,7aα)-Hexahydro-3-(phenylmethyl)-2(3H)-benzofuranthione **60**:

Triphenyltin hydride (422 mg, 1.2 mmol) in benzene (10 mL) and AIBN (16 mg, 0.097 mmol) in benzene (10 mL) were injected simultaneously (double syringe pump) over 10 h into a refluxing solution of alkoxythiocarbonylimidazole **59** (325 mg, 1.04 mmol) in benzene (10 mL). Refluxing was continued for a further arbitrary period of 2 h. The mixture was then cooled and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 5% ethyl acetate — hexane gave pure (TLC, silica, 10%

ethyl acetate — hexane) **60** (140 mg, 55%) which was identical [IR, ^{1}H NMR (400 MHz), mass spectrum] with a sample isolated from the attempted radical annulation of **59**.

(3β,3aβ,7aα)-Hexahydro-3-(phenylmethyl)-2(3H)-benzofuranon **61**: Thiolactone **60** (53 mg, 0.215 mmol) and benzeneseleninic anhydride[65] (77 mg, 0.215 mmol) were placed in a flask and covered with THF (5 mL). The resulting solution was stirred under argon at room temperature for 0.5 h. Water (10 mL) was added and the mixture was extracted with ether (2 × 10 mL). The organic phase was washed with brine, dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1 × 15 cm) first with hexane (to elute diphenyldiselenide) and then with 10% ethyl acetate — hexane yielded the pure (TLC, silica, 10% ethylacetate — hexane) lactone **61** (40 mg, 80%) as a pale yellow oil: IR (neat) 1780, 1600, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.95 — 1.67 (m, 7H), 1.80 (m, 1H), 2.13 (m, 1H), 2.53 (ddd, J = 12.2, 7.4, 4.9 Hz, 1H), 2.75 (dd, J = 13.6, 8 Hz, 1H), 3.2 (dd, J = 13.6, 4.4 Hz, 1H), 3.65 (dt, J = 11.5, 10.8, 4 Hz, 1H), 7.5 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 23.7, 24.9, 27.6, 29.9, 34.3, 47.5, 49.4, 82.5,

126.3, 128.3, 128.8, 138.3, 177.6; exact mass, m/z 230.1307 (calcd for $C_{15}H_{18}O_2$, 230.1302). Anal. calcd for $C_{15}H_{18}O_2$: C, 78.21; H, 7.88. Found: C, 78.31; H, 7.73.

(3α,3aβ,7aα)-Hexahydro-3-(phenylmethyl)-2(3H)-benzofuranone **63**: n-Butyllithium (1.33 M, hexane solution, 1.65 mL, 2.2 mmol) was injected dropwise at 0°C into a stirred solution of diisopropylamine (0.42 mL, 3.0 mmol) in THF (8 mL). After being stirred for 15 min at 0°C, the solution was cooled to -78°C and lactone **62**[66] (280 mg, 2.0 mmol) in THF (4 mL + 1 mL rinse) was added over a period of 1 h. Stirring was continued for 30 min. Benzyl bromide (376 mg, 2.2 mmol) and hexamethylphosphortriamide (HMPA) (0.38 mL, 2.2 mmol) in THF (4 mL + 1 mL rinse) were added dropwise. The temperature was raised to ca. -40°C and stirring was continued for 2 h. The reaction mixture was quenched by addition of 10% HCl (20 mL) and extracted with ether (2 × 20 mL). The combined extracts were washed with aqueous saturated sodium bicarbonate and brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 × 15 cm) with 10% ethyl acetate — hexane gave the pure (TLC, silica, 15% ethylacetate — hexane) lactone **63** [230 mg, 73.6%, based on recovered starting material (90 mg)] as a white

crystalline solid: IR (neat) 1785, 1600, 1500, 1450 cm^{-1}; ^{1}HNMR ($CDCl_3$, 200 MHz) δ 1.0 — 2.35 (m, 9H), 2.95 (m, 3H), 4.0 (dt, J = 11.1, 3.8 Hz, 1H), 7.26 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 23.7, 25.2, 25.3, 30.6, 31.3, 45.0, 47.6, 81.8, 126.3, 128.2, 128.3, 138.2, 178.1; exact mass, m/z 230.1307 (calcd for $C_{15}H_{18}O_2$, 230.1302).

Isomerization of lactone **63**; (3β,3aβ,7aα)-Hexahydro-3-(phenylmethyl)-2(3H)-benzofuranone **61**: LDA was prepared as in the synthesis of **63** using n-butyllithium (1.33 M, hexane solution, 0.489 mL, 0.651 mmol) and diisopropylamine (0.12 mL, 0.868 mmol) in THF (5 mL). The solution was cooled to -78°C and lactone **63** (100 mg, 0.434 mmol) in THF (2 mL + 1 mL rinse) was injected over 1 h. The solution was stirred at -78°C for 30 min and poured into aqueous saturated ammonium chloride (10 mL). The mixture was extracted with ether (2 × 10 mL), washed with brine, and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 15 cm) with 10% ethylacetate — hexane gave lactone **61** (92 mg, 92%) as a colorless, homogeneous (TLC, silica, 15% ethyl acetate — hexane) oil: IR (neat) 1780 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.95 — 1.67 (m, 7H), 1.80 (m, 1H), 2.13 (m, 1H), 2.53 (ddd, J = 12.2, 7.49, 4.9 Hz, 1H), 2.75 (dd,

J = 13.6, 8 Hz, 1H), 3.20 (dd, J = 13.6, 4.4 Hz, 1H), 3.65 (dt, J = 11.5, 10.8, 4 Hz, 1H), 7.23 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 23.7, 24.9, 27.6, 29.9, 34.3, 47.5, 49.4, 82.5, 126.3, 128.3, 128.8, 138.3, 177.6.

cis-1-Bromo-2-(phenylethynyl)cyclohexane **66**: Bromine (2.0 mL, 38.9 mmol) was added dropwise to a stirred solution of triphenyl phosphite (14.5 g, 46.7 mmol) in dry ether (100 mL) at 0°C. A mixture of alcohol **54** (7.8 g, 38.9 mmol) and dry pyridine (3.1 mL, 38.9 mmol) in ether (15 mL) was added dropwise and the resulting white slurry was stirred for 15 h at room temperature. The mixture was poured into water (50 mL) and extracted with ether (2 × 30 mL). The combined extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (4 × 20 cm) with hexane gave pure (TLC, silica, hexane) bromide **66** (4.5 g, 50%) and pure (TLC, silica, hexane) 3-(phenylethynyl)cyclohexene **67**[83] (2.23 g, 35.5%). Bromide **66** had: IR (neat) 2230, 1595, 1485, 1440, 760, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.60 (m, 2H), 1.99 (m, 3H), 2.21 (m, 2H), 2.42 (m, 1H), 3.33 (m, 1H), 4.55 (dt, J = 8.7, 3.5 Hz, 1H), 7.25 (m, 3H), 7.40 (m, 2H): ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 22.2, 24.5, 30.6, 33.9, 37.6, 55.0, 83.7, 89.9, 123.7, 127.7, 128.1, 131.7;

exact mass, m/z 264.0340 (calcd for $C_{14}H_{15}{}^{81}Br$, 264.0241). Anal. calcd for $C_{14}H_{14}Br$: C, 63.87; H, 5.74. Found: C, 63.76; H, 5.78.

Olefin **67** had: IR (neat) 2220, 1598, 1487, 1440, 756, 721, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.50 — 2.20 (m, 6H), 3.33 (m, 1H), 5.80 (m, 2H), 7.25 (m, 3H), 7.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.6, 20.7, 24.6, 28.0, 29.4, 80.3, 92.7, 124.0, 127.1, 127.3, 127.8, 128.0, 131.5; exact mass, m/z 182.1094 (calcd for $C_{14}H_{14}$, 182.1092). Anal. calcd for $C_{14}H_{14}$: C, 92.25; H, 7.74. Found: C, 92.19; H, 7.86.

Annulation of bromide **66** with methyl acrylate; Methyl octahydro-1-(phenylmethylene)-1H-indene-2-carboxylate **58**: The general procedure for radical annulation was followed using bromide **66** (0.200 g, 0.76 mmol), freshly distilled methyl acrylate (1.47 g, 17.1 mmol) in benzene (40 mL), triphenyltin hydride (0.400 g, 1.14 mmol) in benzene (10 mL), and AIBN (16 mg, 0.097 mmol) in benzene (10 mL). After evaporation of the solvent the residue was dissolved in ether (25 mL) and stirred vigorously at room temperature for 15 min with a solution of potassium fluoride (0.50 g, 8.61 mmol) in water (20 mL). The precipitate (triphenyltin fluoride) was filtered off and

washed well with ether. The combined filtrates were separated and the ether layer was washed with brine, dried ($MgSO_4$), and evaporated. The residue was dissolved in chloroform (5 mL) and silica gel (ca. 2.5 g) was added. The solvent was then evaporated at room temperature and the resulting mixture was loaded onto a flash chromatography column [silica gel, (2 × 15 cm)] that had a sufficient head of solvent to cover the added material. Elution with 5% ethyl acetate — hexane gave **58** (70 mg, 35%), as a mixture of isomers, and (cyclohexylethynyl)benzene **84** (10 mg, 7%). Each sample was homogeneous by TLC (silica, 5% ethylacetate — hexane). Mixture **58** had: IR (neat) 1725, 1430, 730, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.95 — 2.30 (m, 12H), 3.30 — 3.88 (5 s, 4H), 6.20 — 6.72 (6 broad s, 1H), 7.15 — 7.40 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ (carbonyl signals) 174.8, 174.9, 175.0, 175.2, 176.4, 177.0; exact mass, m/z 270.1619 (calcd for $C_{18}H_{22}O_2$, 270.1619). Anal. calcd for $C_{18}H_{22}O_2$: C, 79.95; H, 8.20. Found: C, 80.21; H, 8.23.

Ozonolysis of olefins **58**; Methyl octahydro-1-oxo-1H-indene-2-carboxylate **70**: An ozone — oxygen stream was bubbled through a solution of olefins **58** (80 mg, 0.291 mmol) in dry methanol (5 mL) at -78°C until the starting

material had just disappeared [5 min, TLC (silica, 10% ethyl acetate — hexane)]. Argon was passed through the solution for 5 min to remove the excess of ozone, and trimethyl phosphite (0.05 mL, 0.40 mmol) was injected. The cold bath was removed and the solution was stirred for 12 h (during which time it attained room temperature). Evaporation of the solvent, followed by flash chromatography of the residue over silica gel (1 × 15 cm) with 10% ethyl acetate — hexane gave **70** (43 mg, 77%) as a mixture of isomers that was homogeneous by TLC (silica, 10% ethyl acetate — hexane): IR (neat) 1750, 1720 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.95 — 2.60 (m, 12H), 3.05 — 3.50 (m, 1H), 3.75 (2s, 3H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ (carbonyl signals) 169.9, 170.1, 170.3, 209.8, 209.9, 211.6; exact mass, m/z 196.1106 (calcd for $C_{11}H_{16}O_3$, 196.1095).

trans-2-(Phenylethynyl)cyclopentanol **72**: The procedure employed for **54** was followed using n-butyllithium in hexane (1.5 M, 14.0 mL, 21.6 mmol), phenylacetylene (2.20 g, 21.6 mmol) in THF (30 mL), boron trifluoride etherate (2.2 mL, 17.7 mmol), and 6-oxabicyclo[3.1.0]hexane (1.21 g, 14.4 mmol) in THF (5 mL + 1 mL rinse). Workup and flash chromatography of the residue over silica gel (4 × 15 cm) with 17% ethyl acetate — hexane gave pure (TLC,

silica, 20% ethyl acetate — hexane) alcohol **72** (2.64 g, 98%): IR (neat) 3350, 2220, 1600, 1490, 1442, 760, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.5 — 2.3 (m, 7H), 1.8 (m, 1H), 4.3 (q, J = 6 Hz, 1H), 7.2 — 7.6 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.8, 31.0, 33.5, 40.2, 79.2, 81.8, 91.7, 123.7, 127.5, 128.0, 131.4; exact mass, m/z 186.1038 (calcd for $C_{13}H_{14}O$, 186.1041). Anal. calcd for $C_{13}H_{14}O$: C, 83.82; H, 7.58. Found: C, 83.88; H, 7.52.

cis-1-Bromo-2-(phenylethynyl)cyclopentane **73**: The procedure employed for **66** was followed using bromine (1.27 mL, 24.9 mmol), triphenyl phosphite (8.45 g, 27.2 mmol), in ether (125 mL), alcohol **72** (4.24 g, 22.7 mmol), and pyridine (1.83 mL, 22.7 mmol) in ether (15 mL). The reaction mixture was stirred for 12 h and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (6 × 20 cm) first with hexane (to elute the olefinic acetylene) and then with 5% ethyl acetate — hexane gave pure (TLC, silica, 5% ethyl acetate — hexane) bromide **73** (2.5 g, 44.2%) and 3-(phenylethynyl)cyclopentene **74** (1.15 g, 30%). Bromide **73** had: IR (neat) 2230, 1600, 1570, 1490, 1443, 760, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.50 — 2.40 (m, 6H), 3.0 (dt, J = 8.3, 4.3 Hz, 1H), 4.50 (m, 1H), 7.25 (m, 3H), 7.42 (m,

2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.5, 30.1, 36.1, 39.2, 57.0, 83.0, 89.9, 123.5, 127.6, 128.0, 131.4; exact mass, m/z 250.0180 (calcd for $C_{13}H_{13}{}^{81}Br$, 250.0160). Anal. calcd for $C_{13}H_{13}Br$: C, 62.64; H, 5.26. Found: C, 62.09; H, 5.17.

Olefin **74** had: IR (neat) 2220, 1598, 760, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.80 — 2.80 (m, 4H), 3.75 (m, 1H), 5.70 — 6.0 (m, 2H), 7.30 (m, 3H), 7.45 (m, 2H); exact mass, m/z 168.0931 (calcd for $C_{13}H_{12}$, 168.0936).

trans-2-(Phenylethynyl)cycloheptanol **76**: The procedure employed for **54** was followed using n-butyllithium in hexane (1.6 M, 31.7 mL, 50.8 mmol), phenylacetylene (5.19 g, 50.8 mmol) in THF (50 mL), boron trifluoride etherate (4.58 mL, 37.3 mmol) and 8-oxabicyclo[5.1.0]octane (3.80 g, 33.9 mmol) in THF (10 mL + 1 mL rinse). Workup and flash chromatography of the residue over silica gel (5 × 20 cm) with 10% ethylacetate — hexane gave pure (TLC, silica, 20% ethyl acetate — hexane) alcohol **76** (5.9 g, 81%): IR (neat) 3390, 2220, 1598, 1488, 755, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40 — 1.85 (m, 8H), 2.00 (m, 2H), 2.35 (s, 1H), 2.70 (m, 1H), 3.75 (m, 1H), 7.28 (m, 3H), 7.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.7, 25.2, 27.0, 29.6, 34.4, 41.2, 75.5, 82.8, 91.9, 123.3, 127.6,

128.0, 131.4; exact mass, m/z 214.1363 (calcd for $C_{15}H_{18}O$, 214.1353). Anal. calcd for $C_{15}H_{18}O$: C, 84.06; H, 8.47. Found: C, 84.36; H, 8.45.

cis-1-Bromo-2-(phenylethynyl)cycloheptane **77**: The procedure employed for **66** was followed using bromine (0.89 mL, 17.38 mmol), triphenyl phosphite (6.86 g, 22.0 mmol) in ether (125 mL), alcohol **76** (3.4 g, 15.8 mmol), and pyridine (1.3 mL, 15.8 mmol) in ether (15 mL). The mixture was stirred for 15 h and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (6 × 25 cm) first with hexane (to elute the olefinic acetylene) and then with 5% ethyl acetate — hexane gave pure (TLC, silica, 5% ethyl acetate — hexane) bromide **77** (2.7 g, 61.6%) and 3-(phenylethynyl)cycloheptene **78**[85] (380 mg, 12.2%). Bromide **77** had: IR (neat) 1595, 1485, 1438, 752, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40 — 1.90 (m, 7H), 2.0 (m, 1H), 2.10 — 2.42 (m, 2H), 3.38 (m, 1H), 4.30 (dq, J = 9.4, 4.0, 3.4 Hz, 1H), 7.5 (m, 3H), 7.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 24.3, 25.2, 25.9, 31.6, 37.0, 40.9, 57.5, 84.1, 89.3, 123.6, 127.6, 128.0, 131.5; exact mass, m/z 278.0489 (calcd for $C_{15}H_{17}{}^{81}Br$, 278.0366). Anal. calcd for $C_{15}H_{17}Br$: C, 64.97; H, 6.18. Found: C, 65.13; H,

6.23.

Olefin **78** had: IR (neat) 2220, 1598, 1488, 1440, 751, 689 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.40 — 1.83 (m, 4H), 1.92 (m, 1H), 2.08 (m, 2H), 2.25 (m, 1H), 3.47 (d, 8.8 Hz, 1H), 5.83 (m, 2H), 7.23 (m, 3H), 7.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.6, 28.2, 29.4, 32.4, 35.5, 80.6, 92.8, 123.9, 127.3, 128.0, 131.4, 132.4, 133.2; exact mass, m/z 196.1255 (calcd for $C_{15}H_{16}$, 196.1248).

(±)-(3R*,4R*)-1-Phenyl-3-propylhept-1-yne-4-ol **80**: The procedure employed for **54** was followed using n-butyllithium in hexane (1.5 M, 2.81 mL, 42.2 mmol), phenylacetylene (6.24 g, 61.1 mmol) in THF (60 mL), boron trifluoride etherate (4.46 mL, 35.29 mmol), and (Z)-4,5-epoxyoctane[86] (4.0 g, 40.7 mmol) in THF (10 mL + 2 mL rinse). Workup and flash chromatography of the residue over silica gel (5 × 15 cm) with 10% ethyl acetate — hexane gave pure (TLC, silica, 15% ethyl acetate — hexane) alcohol **80** (5.64 g, 87%): IR (neat) 3400, 2230, 1598, 1480, 755, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.97 (m, 6H), 1.30 — 1.80 (m, 9H), 2.65 (m, 1H), 3.58 (m, 1H), 7.28 (m, 3H), 7.40 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.8, 13.9, 19.0, 20.8, 33.9, 37.8, 39.6, 73.0, 94.3, 89.4, 123.5, 127.5, 128.1, 131.6; exact mass, m/z 230.1665

(calcd for $C_{16}H_{22}O$, 230.1665). Anal. calcd for $C_{16}H_{22}O$: C, 83.41; H, 9.63. Found: C, 83.65; H, 9.65.

(±)-(3R*,4S*)-4-Bromo-1-phenyl-3-propylhept-1-yne **81**:

The procedure employed for **66** was followed using bromine (1.2 mL, 23.4 mmol), triphenyl phosphite (7.93 g, 28.5 mmol) in ether (125 mL), alcohol **80** (4.9 g, 21.3 mmol), and pyridine (1.72 mL, 21.3 mmol) in ether (15 mL). The reaction mixture was stirred for 12 h and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (6 × 20 cm) with hexane gave pure (TLC, silica, hexane) bromide **81** (3.3 g, 60%) and (Z)-1-phenyl-3-propylhept-3-ene-1-yne **82** (1.20 g, 26.5%). Bromide **81** had: IR (neat) 1598, 1488, 755, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.95 (m, 6H), 1.30 — 1.88 (m, 6H), 2.0 (m, 2H), 2.95 (m, 1H), 4.09 (m, 1H), 7.30 (m, 3H), 7.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.3, 13.8, 20.4, 20.8, 35.4, 38.3, 40.7, 59.2, 84.1, 89.6, 123.6, 127.8, 128.1, 131.6; exact mass, m/z 294.0811 (calcd for $C_{16}H_{21}{}^{81}Br$, 294.0678). Anal. calcd for $C_{16}H_{21}Br$: C, 65.51; H, 7.22. Found: C, 65.91; H, 7.22.

Olefin **82** had: IR (neat) 1590, 1483, 750, 689 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.95 (m, 6H), 1.52 (ds', J = 8.8 Hz, 1H), 2.18 (t, J = 6 Hz, 2H), 2.32 (q, J = 8.4 Hz, 2H),

5.75 (t, 8 Hz, 1H), 7.34 (m, 3H), 7.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.36, 13.7, 21.7, 22.4, 32.6, 39.1, 88.4, 93.2, 123.4, 124.0, 127.6, 128.1, 131.3, 137.7; exact mass, m/z 212.1561 (calcd for $C_{16}H_{20}$, 212.1560).

trans-2-(1-Heptynyl)-cyclohexanol **83**: The procedure employed for **54** was followed using n-butyllithium in hexane (1.55 M, 40.1 mL, 61.0 mmol), 1-heptyne (5.87 g, 61.0 mmol) in THF (50 mL), boron trifluoride etherate (4.1 mL, 33.5 mmol), and cyclohexene oxide (3.0 g, 30.5 mmol) in THF (10 mL + 1 mL rinse). Workup and flash chromatography of the residue over silica gel (5 × 15 cm) with 10% ethyl acetate — hexane yielded the pure (TLC, silica, 15% ethyl acetate — hexane) alcohol **83** (4.1 g, 69%): IR (neat) 3400, 1450, 1068; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.88 (m, 3H), 1.00 — 2.25 (m, 17H), 2.38 (s, 1H), 3.4 (m, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.8, 18.6, 22.2, 24.8, 28.6, 30.9, 31.3, 32.9, 39.0, 73.7, 81.1, 82.6; exact mass, m/z 194.1665 (calcd for $C_{13}H_{22}O$, 194.1665). Anal. calcd for $C_{13}H_{22}O$: C, 80.34; H, 1.41. Found: C, 80.51; H, 11.35.

cis-1-Bromo-2-(1-heptynyl)cyclohexane **84**: The procedure employed for **66** was followed using bromine (0.83 mL, 16.4 mmol), triphenyl phosphite (6.95 g, 22.4 mmol) in ether

(100 mL), alcohol **83** (2.90 g, 14.9 mmol), and pyridine (1.2 mL, 14.9 mmol) in ether (15 mL). The reaction mixture was stirred for 12 h and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (5 × 20 cm) with hexane gave pure (TLC, silica, hexane) bromide **84** (1.6 g, 41.7%) and 3-(1-heptynyl)cyclohexene[85] (1.5 g, 57%). Bromide **84** had: IR (neat) 1440, 1250, 1188, 980, 720 cm^{-1}, ^1H NMR ($CDCl_3$, 200 MHz) δ 0.89 (m, 3H), 1.20 — 2.0 (m, 13H), 3.0 — 3.30 (m, 3H), 3.88 (m, 1H), 4.30 (dt, J = 8.5, 3.2, 3.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.9, 18.7, 22.1, 24.5, 28.6, 30.9, 33.7, 37.0, 55.9, 80.0, 83.6; exact mass, m/z 258.0787 (calcd for $C_{13}H_{21}{}^{81}Br$, 258.0678). Anal. calcd for $C_{13}H_{21}Br$: C, 60.69; H, 8.28. Found: C, 60.99; H, 8.09.

Olefin **85** had: IR (neat) 1450, 725 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.85 (m, 3H), 1.10 — 2.20 (m, 14H), 3.0 (m, 1H), 5.68 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.8, 18.7, 20.6, 22.1, 24.6, 27.4, 28.8, 29.8, 31.0, 80.0, 82.9, 127.1, 128.1; exact mass, m/z 176.1565 (calcd for $C_{13}H_{20}$, 176.1560). Anal. calcd for $C_{13}H_{20}$: C, 88.55; H, 11.44. Found: C, 88.15; H, 11.49.

Annulation of bromide **66** with acrylonitrile; Octahydro-1-(phenylmethylene)-1H-indene-2-carbonitrile **86**: The general procedure for radical annulation was followed using bromide **66** (0.200 g, 0.76 mmol), freshly distilled acrylonitrile (0.604 g, 11.4 mmol) in benzene (40 mL), triphenyltin hydride (0.400 g, 1.14 mmol) in benzene (10 mL), and AIBN (16 mg, 0.097 mmol) in benzene (10 mL). After evaporation of the solvent the residue was worked up as described for **58**. Flash chromatography, in the manner indicated, using 5% ethyl acetate — hexane gave **86** (100 mg, 56.8%), as a mixture of isomers, and (cyclohexylethynyl)benzene[84] (5 mg, 3.5%). Each sample was homogeneous by TLC (silica, 5% ethyl acetate — hexane). Mixture **86** had: IR (neat) 2235, 1446, 795 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.55 — 2.70 (m, 12H), 3.40 — 3.90 (m, 1H), 6.28 — 6.82 (7 broad t, J = 2.9 Hz, 1H), 7.30 (m, 5H); exact mass, m/z 237.1516 (calcd for $C_{17}H_{19}N$, 237.1549). Anal. calcd for $C_{17}H_{19}N$: C, 86.01; H, 8.07. Found: C, 86.18; H, 8.00.

Annulation of bromide **66** with (ethenylsulfonyl)benzene;[87] Octahydro-1-(phenylmethylene)-2-(phenylsulfonyl)-1H-indene **87**: The general procedure for radical annulation was followed using bromide **66** (205 mg, 0.77 mmol),

(ethenylsulfonyl)benzene (1.96 g, 11.6 mmol) in benzene (30 mL), triphenyltin hydride (314 mg, 0.89 mmol) in benzene (10 mL), and AIBN (20 mg, 0.12 mmol) in benzene (10 mL). After evaporation of the solvent, the residue was worked up as described for **58**. Flash chromatography, in the manner indicated, using 20% ethyl acetate — hexane gave **87** (145 mg, 52%) as a mixture of isomers that was homogeneous by TLC (silica, 30% ethyl acetate — hexane): IR (neat) 1585, 1300, 1145, 744, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.40 — 2.50 (m, 12H), 4.15 (m, 1H), 6.0 — 6.70 (5 broad d, J = 2.4 Hz, 1H), 7.10 — 8.95 (m, 10H); exact mass, m/z ($M^+ - SO_2C_6H_5$) 211.1488 (calcd for $C_{16}H_{19}$, 211.1482). Anal. calcd for $C_{22}H_{24}O_2S$,: C, 74.94; H, 6.86; S, 9.10. Found: C, 73.57; H, 6.64; S, 9.17.

Annulation of bromide **73** with methyl acrylate; Methyl octahydro-1-(phenylmethylene)pentalene-2-carboxylate **88**: The general procedure for radical annulation was followed using bromide **73** (249 mg, 1.0 mmol), freshly distilled methyl acrylate (1.29 g, 1.50 mmol) in benzene (30 mL), triphenyltin hydride (526 mg, 1.5 mmol) in benzene (10 mL), and AIBN (20 mg, 0.12 mmol) in benzene (10 mL). After evaporation of the solvent, the residue was worked up as described for **58**. Flash chromatography, in the manner indicated, using 2% ethyl acetate — hexane gave **88**

(80 mg, 31%), as a mixture of isomers. The sample was homogeneous by TLC (silica, 5% ethyl acetate — hexane). Mixture **88** had: IR (neat) 1730, 1600, 1492, 758, 700 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80 — 2.75 (m, 10H), 3.25 — 4.20 (7 s, 4H), 6.20 — 6.60 (6m, 1H), 7.25 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ (carbonyl signals) 174.4, 174.5, 174.7, 174.73, 174.75, 174.87; exact mass, 256.1455 (calcd for $C_{17}H_{20}O_2$, 256.1458). Anal. calcd for $C_{17}H_{20}O_2$: C, 79.64, H, 7.86. Found: C, 79.70; H, 7.86.

Annulation of bromide **73** with acrylonitrile; Octahydro-1-(phenylmethylene)pentalene-2-carbonitrile **89**: The general procedure for radical annulation was followed using bromide **73** (249 mg, 1.0 mmol), freshly distilled acrylonitrile (795 mg, 15.0 mmol) in benzene (30 mL), triphenyltin hydride (526 mg, 1.5 mmol) in benzene (10 mL), and AIBN (20 mg, 0.12 mmol) in benzene (10 mL). After evaporation of the solvent the residue was worked up as described for **58**. Flash chromatography, in the manner indicated, using 6% ethyl acetate — hexane gave **89** (85 mg, 38%), as a mixture of isomers. The sample was homogeneous by TLC (silica, 5% ethyl acetate — hexane). Mixture **89** had: IR (neat) 2230, 1600, 1495, 1440, 758, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.70 — 2.95 (m, 10H), 3.20 — 3.90 (m, 1H), 6.31 — 6.75 (5 m, 1H), 7.29 (m, 5H); exact mass,

m/z 223.1361 (calcd for $C_{16}H_{17}N$, 223.1393). Anal. calcd for $C_{16}H_{17}N$: C, 86.04; H, 7.67. Found: C, 85.69; H, 7.73.

Annulation of bromide **73** with (ethenylsulfonyl)benzene; Octahydro-1-(phenylmethylene)-2-(phenylsulfonylpentalene **90**: The general procedure for radical annulation was followed using bromide **73** (249 mg, 1.0 mmol), (ethenylsulfonyl)benzene (2.01 g, 12.0 mmol) in benzene (30 mL), triphenyltin hydride (526 mg, 1.5 mmol) in benzene (10 mL), and AIBN (20 mg, 0.12 mmol) in benzene (10 mL). After evaporation of the solvent the residue was worked up as described for **58**. Flash chromatography in the manner indicated, using 15% ethyl acetate — hexane, gave **90** (95 mg, 28%) as a mixture of isomers that was homogeneous by TLC (silica, 20% ethyl acetate — hexane): IR (neat) 1590, 1445, 1302, 1145, 735, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.59 — 2.50 (m, 10H), 4.30 — 4.60 (m, 1H), 6.05 — 6.80 (4 d, J = 3.2 Hz, 1H), 7.0 — 8.10 (m, 10H); exact mass, m/z 338.1292 (calcd for $C_{21}H_{22}O_2S$, 338.2214). Anal. calcd for $C_{21}H_{22}O_2S$: C, 74.50; H, 6.55; S, 9.478. Found: C, 74.67; H, 6.43; S, 9.32.

Annulation of bromide **77** with methyl acrylate; Methyl decahydro-1-(phenylmethylene)azulene-2-carboxylate **91**: The general procedure for radical annulation was followed using bromide **77** (277 mg, 1.0 mmol), freshly distilled methyl acrylate (1.30 g, 15.0 mmol) in benzene (30 mL), triphenyltin hydride (386 mg, 1.10 mmol) in benzene (10 mL), and AIBN (20 mg, 0.12 mmol) in benzene (10 mL). After evaporation of the solvent the residue was worked up as described for **58**. Flash chromatography, in the manner indicated, using 3% ethyl acetate — hexane gave **91** (125 mg, 44%) as a mixture of isomers that was homogeneous by TLC (silica, 5% ethyl acetate — hexane): IR (CCl_4) 1735, 1600, 1490, 750, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.10 — 2.60 (m, 14H), 3.30 — 3.95 (6 s, 4H), 6.30 — 6.60 (6 m, 1H), 7.30 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ (carbonyl signals) 17.2, 175.3, 175.9, 176.0, 176.5; exact mass, m/z 284.1773 (calcd for $C_{19}H_{24}O_2$, 284.1770). Anal. calcd for $C_{19}H_{24}O_2$: C, 80.23, H, 8.51. Found: C, 80.37; H, 8.46.

Annulation of bromide **77** with acrylonitrile; Decahydro-1-(phenylmethylene)azulene-2-carbonitrile **92**: The general procedure for radical annulation was followed using bromide **77** (277 mg, 1.0 mmol), freshly distilled acrylonitrile (795 mg, 15.0 mmol) in benzene (30 mL),

triphenyltin hydride (403 mg, 1.15 mmol) in benzene (10 mL), and AIBN (20 mg, 0.12 mmol) in benzene (10 mL). After evaporation of the solvent the residue was worked up as described for **58**. Flash chromatography, in the manner indicated, using 5% ethyl acetate — hexane gave **92** (135 mg, 53.7%), as a mixture of isomers, and (cycloheptylethynyl)benzene (13 mg, 6.5%). Each sample was homogeneous by TLC (silica, 5% ethyl acetate — hexane). The acetylene had: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.83 — 2.0 (m, 12H), 2.80 (m, 1H), 7.23 m, 3H), 7.35 (m, 2H); exact mass, m/z 198.1409 (calcd for $C_{15}H_{18}$, 198.1404).

Mixture **92** had: IR (CCl_4) 2230, 1600, 1490, 1449, 755, 695 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.10 — 2.50 (m, 14H), 3.65 (m, 1H), 6.38 — 6.70 (4 m, 1H), 7.30 (m, 5H); exact mass, m/z 251.1673 (calcd for $C_{18}H_{21}N$, 251.1705). Anal. calcd for $C_{18}H_{21}N$: C, 85.99; H, 8.42. Found: C, 86.27; H, 8.39.

Annulation of bromide **77** with (ethenylsulfonyl)benzene;[87] Decahydro-1-(phenylmethylene)-2-(phenylsulfonyl)azulene **93**: The general procedure for radical annulation was followed using bromide **77** (277 mg, 1.0 mmol), (ethenylsulfonyl)-benzene[87] (2.52 g, 15.0 mmol) in benzene (30 mL), triphenyltin hydride (403 mg, 1.15 mmol) in benzene (10 mL), and AIBN (20 mg, 0.12 mmol) in benzene (10 mL).

After evaporation of the solvent the residue was worked up as described for **58**. Flash chromatography, in the manner indicated, using 20% ethyl acetate — hexane gave **93** (140 mg, 38%) as a mixture of isomers that was homogeneous by TLC (silica, 25% ethyl acetate — hexane): IR (CCl_4) 1445, 1301, 1145, 760, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.95 — 3.10 (m, 14H), 3.9 — 4.5 (m, 1H), 5.8 — 6.8 (7 broad s, 1H), 7.0 — 8.0 (m, 10H); exact mass, m/z (M^+ — $SO_2C_6H_5$) 225.1649 (calcd for $C_{17}H_{21}$, 225.1638). Anal. calcd for $C_{23}H_{26}O_2S$: C, 75.35; H, 7.15; S, 8.75. Found: C, 73.99; H, 6.96; S, 8.97.

Annulation of bromide **81** with methyl acrylate; Methyl-2-(phenylmethylene)-3,4-dipropylcyclopentane-1-carboxylate **94**: The general procedure for radical annulation was followed using bromide **81** (250 mg, 0.853 mmol), freshly distilled methyl acrylate (1.46 g, 17.1 mmol) in benzene (30 mL), triphenyltin hydride (450 mg, 1.27 mmol) in benzene (10 mL), and AIBN (18 mg, 0.11 mmol) in benzene (10 mL). After evaporation of the solvent the residue was worked up as described for **58**. Flash chromatography, in the manner indicated, using 3% ethyl acetate — hexane gave **94** (100 mg, 40%) as a mixture of isomers, and 1-phenyl-2-propyl-1-heptyne (47 mg, 25.7%). Each sample was homogeneous by TLC (silica, 5% ethyl acetate — hexane).

Mixture **94** had: IR (neat) 1730, 1600, 1490, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.70 — 2.40 (m, 18H), 3.20 — 3.80 (6 s, 4H), 6.20 — 6.60 (5 broad s, 1H), 7.28 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ (carbonyl signals) 174.3, 174.9, 175.0, 175.2, 175.3, 175.4; exact mass, m/z 300.2090 (calcd for $C_{20}H_{28}O_2$, 300.2082). Anal. calcd for $C_{20}H_{28}O_2$: C, 79.94; H, 9.39. Found: C, 79.91; H, 9.22.

Annulation of bromide **81** with acrylonitrile; 2-(Phenylmethylene)-3,4-(dipropyl)cyclopentanecarbonitrile **95**: The general procedure for radical annulation was followed using bromide **81** (240 mg, 0.81 mmol), freshly distilled acrylonitrile (651 mg, 12.1 mmol) in benzene (30 mL), triphenyltin hydride (0.343 g, 0.977 mmol) in benzene (10 mL), and AIBN (18 mg, 0.11 mmol) in benzene (10 mL). After evaporation of the solvent the residue was worked up as described for **58**. Flash chromatography, in the manner indicated, with 5% ethyl acetate — hexane gave **95** (100 mg, 46.2%) as a mixture of isomers, and 1-phenyl-3-propyl-1-heptyne (45.5 mg, 26%). Each sample was homogeneous by TLC (silica, 5% ethyl acetate — hexane). The acetylene had: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.0 (m, 6H), 1.10 — 1.80 (m, 10H), 2.58 (m, 1H), 7.29 (m, 3H), 7.46 (m, 2H); exact mass, m/z 214.1723 (calcd for $C_{16}H_{22}$, 214.1716).

Mixture **95** had: IR (neat) 2230, 1450, 750, 695 cm^{-1};

^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.80 — 2.60 (m, 17H), 3.70 (m, 1H), 6.40 — 6.80 (5 broad s, 1H), 7.30 (m, 5H); exact mass, m/z 267.1990 (calcd for $C_{19}H_{25}N$, 267.2017). Anal. calcd for $C_{19}H_{25}N$: C, 85.32; H, 9.42. Found: C, 85.63; H, 9.44.

Annulation of bromide **81** with (ethenylsulfonyl)benzene;[37] 2-(Phenylmethylene)-1-(phenylsulfonyl)-3,4-dipropylcyclopentane **96**: The general procedure for radical annulation was followed using bromide **81** (250 mg, 0.853 mmol), (ethenylsulfonyl)benzene (1.72 g, 10.2 mmol) in benzene (30 mL), triphenyltin hydride (0.449 g, 1.27 mmol) in benzene (10 mL), and AIBN (18 mg, 0.11 mmol) in benzene (10 mL). After evaporation of the solvent the residue was worked up as described for **58**. Flash chromatography, in the manner indicated, using 14% ethyl acetate — hexane gave **96** (63 mg, 20%), as a mixture of isomers, and 1-phenyl-3-propyl-1-heptyne (140 mg, 76%). Each sample was homogeneous by TLC (silica, 5% ethyl acetate — hexane). Mixture **96** had: IR (neat) 1302, 1144, 730, 698 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.55 — 3.10 (m, 18H), 4.20 (m, 1H), 6.0 — 7.0 (6 m, 1H), 7.0 — 8.20 (m, 10H); exact mass, m/z($M^+ - SO_2C_6H_5$) 241.1959 (calcd for $C_{18}H_{25}$, 241.1950). Anal. calcd for $C_{24}H_{30}O_2S$: C, 75.33; H, 7.90; S, 8.38. Found: C, 75.61; H, 7.63; S, 8.53.

Annulation of bromide **84** with acrylonitrile; Octahydro-1-hexylidene-1H-indene-2-carbonitrile **97**: The general procedure for radical annulation was followed using bromide **84** (257 mg, 1.0 mmol), freshly distilled acrylonitrile (795 mg, 15.0 mmol) in benzene (10 mL), triphenyltin hydride (526 mg, 1.50 mmol) in benzene (10 mL), and AIBN (20 mg, 0.12 mmol) in benzene (10 mL). After evaporation of the solvent, the residue was worked up as described for **58**. Flash chromatography, in the manner indicated, using 3% ethyl acetate — hexane gave **97** (79 mg, 34%) as a mixture of isomers that was homogeneous by TLC (silica, 5% ethyl acetate — hexane): IR (neat) 2235, 1448, 1380 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.60 — 2.80 (m, 23H), 3.20 — 3.60 (m, 1H), 5.20 — 5.70 (m, 1H); exact mass, m/z 231.1991 (calcd for $C_{16}H_{25}N$, 231.2017). Anal. calcd for $C_{16}H_{25}N$: C, 83.04; H, 10.89. Found: C, 83.08; H, 10.69.

Ozonolysis of olefins **87**; Octahydro-1-oxo-2-(phenylsulfonyl)-1H-indene **90**: The procedure employed for **70** was followed using olefins **87** (157 mg, 0.445 mmol) in dry methanol (8 mL) and trimethyl phosphite (0.073 mL, 0.623 mmol). Evaporation of the solvent, followed by flash

chromatography of the residue over silica gel (1 × 15 cm) with 30% ethyl acetate — hexane gave ketones **98** (100 mg, 81%), as a mixture of isomers that was homogeneous by TLC (silica, 30% ethyl acetate — hexane): IR (CCl_4) 1748, 1449, 1309, 1149, 735, 688 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ1.0 — 2.60 (m, 12H), 3.80 (m, 1H), 7.65 (m, 3H), 7.90 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ (carbonyl signals) 204.4, 205.2; exact mass, m/z 278.0945 (calcd for $C_{15}H_{18}O_3S$, 278.1851).

Ozonolysis of olefins **93**; Decahydro-1-oxo-2-(phenylsulfonyl)azulene **100**: The procedure employed for **70** was followed using olefins **93** (75 mg, 0.20 mmol) in dry methanol (5 mL) and trimethyl phosphite (0.033 mL, 0.28 mmol). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 15 cm) with 30% ethyl acetate — hexane gave ketones **100** (48.1 mg, 83%), as a mixture of isomers that was homogeneous by TLC (silica, 30% ethyl acetate — hexane): IR (CCl_4) 1740, 1445, 1320, 1150 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ1.0 — 2.8 (m, 14H), 3.68 — 4.1 (m, 1H), 7.1 — 7.95 (m, 5H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ (carbonyl signals) 207.4, 209.2, 209.3, 214.3; exact mass, m/z 292.1137 (calcd for $C_{16}H_{20}O_3S$, 292.2007).

Ozonolysis of olefins **97**; Octahydro-1-oxo-1H-indene-2-carbonitrile **101**: The procedure employed for **70** was followed using olefins **97** (57 mg, 0.24 mmol) in dry dichloromethane (5 mL) and trimethyl phosphite (0.04 mL, 0.34 mmol). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 × 15 cm) with 20% ethyl acetate — hexane gave ketones **101** (18 mg, 44.7%), as a pure (TLC, silica, 20% ethyl acetate — hexane) mixture of isomers: IR (CCl_4) 2240, 1752, 1440, 700 cm^{-1} ^1H NMR ($CDCl_3$, 200 MHz) δ0.8 — 2.7 (m, 12H), 2.95 — 3.5 (m, 1H); exact mass, m/z 163.1001 (calcd for $C_{10}H_{13}NO$, 163.1030).

cis-1-(Phenylethynyl)-2-(phenylseleno)cyclohexane **102**: A solution of phenyl selenocyanate[88] (688 mg, 3.78 mmol) in THF (3 mL + 1 mL rinse) was injected into a stirred solution of the alcohol **54** (630 mg, 3.15 mmol) and tri-n-butyl phosphine (0.94 mL, 3.78 mmol) in THF (15 mL). The mixture was stirred at room temperature for 72 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 15 cm) first with hexane (to elute diphenyldiselenide) and then with 10% ethyl acetate — hexane gave the selenide **102** [845 mg, 94%, based on recovered starting material (105 mg)]. Selenide **102**

had: IR (neat) 2230, 1600, 1580, 760, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.29 — 2.20 (m, 8H), 3.25 (m, 1H), 3.40 (dt, J = 10, 4 Hz, 1H), 7.30 (m, 6H), 7.5 (m, 2H), 7.65 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 21.7, 26.4, 30.8, 32.0, 35.0, 47.4, 83.9, 90.5, 123.8, 127.2, 127.5, 128.8, 130.0, 131.6, 134.4; exact mass, m/z 340.0719 (calcd for $C_{20}H_{20}Se$, 340.0705). Anal. calcd for $C_{20}H_{20}Se$: C, 70.57; H, 5.92. Found: C, 69.22; H, 5.77.

Annulation of selenide **102** with methyl acrylate; Methyl octahydro-1-(phenylmethylene)-1H-indene-2-carboxylate **58**:

The general procedure for radical annulation was followed using selenide **102** (155 mg, 0.457 mmol), freshly distilled methyl acrylate (472 mg, 5.48 mmol) in benzene (30 mL), triphenyltin hydride (240 mg, 0.685 mmol) in benzene (10 mL), and AIBN (20 mg, 0.12 mmol) in benzene (10 mL). After evaporation of the solvent, flash chromatography of the residue over silica gel (2 × 15 cm) with 5% ethyl acetate — hexane gave **58** (43 mg, 35.3%) as a mixture of isomers that was homogeneous by TLC (silica, 5% ethyl acetate — hexane): ^1H NMR ($CDCl_3$, 200 MHz) δ 0.95 — 2.30 (m, 12H), 3.30 — 3.88 (5 s, 4H), 6.20 — 6.72 (6 broad s, 1H), 7.15 — 7.40 (m, 5H).

Annulation of selenide **102** with acrylonitrile; Octahydro-1-(phenylmethylene)-1H-indene-2-carbonitrile **86:** The general procedure for radical annulation was followed using selenide **102** (330 mg, 0.97 mmol), freshly distilled acrylonitrile (939 mg, 17.7 mmol) in benzene (30 mL), triphenyltin hydride (500 mg, 1.42 mmol) in benzene (10 mL), and AIBN (20 mg, 0.12 mmol) in benzene (10 mL). After evaporation of the solvent, flash chromatography of the residue over silica gel (2 × 15 cm) with 5% ethyl acetate — hexane gave **86** (69 mg, 30%) as a mixture of isomers that was homogeneous by TLC (silica, 5% ethyl acetate — hexane): ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.55 — 2.70 (m, 12H), 3.40 — 3.90 (m, 1H), 6.28 — 6.82 (7 broad t, J = 2.9 Hz, 1H), 7.30 (m, 5H).

2-Bromo-1-(phenylethynyl)cyclohexanol **104:** n-Butyllithium in hexane (1.6 M, 3.53 mL, 5.65 mmol) was added to phenylacetylene (692 mg, 6.78 mmol) in THF (15 mL) at -78°C and the mixture was stirred for 15 min. 2-Bromocyclohexanone **103**[89] (1.0 g, 5.65 mmol) in THF (6 mL + 1 mL rinse) was added dropwise to the solution and, after stirring for 30 min more at -78°C, the reaction mixture was quenched by addition of saturated ammonium chloride (15 mL). The organic layer was separated and the aqueous phase was

extracted with ether (2 × 15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 × 15 cm) with 8% ethyl acetate — hexane) gave pure (TLC, silica, 10% ethyl acetate — hexane) alcohol **104** (1.28 g, 81.3%): IR (neat) 3460, 2230, 1600, 1490, 1445, 760, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.19 — 2.35 (m, 8H), 2.70 (s, 1H), 4.50 (dd, J = 8.8, 5.2 Hz, 1H), 7.35 (m, 3H), 7.51 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 20.7, 24.7, 32.6, 37.4, 63.1, 69.4, 84.2, 91.0, 122.2, 128.2, 128.3, 131.6; exact mass, m/z 280.0287 (calcd for $C_{14}H_{15}{}^{81}BrO$, 280.0159). Anal. calcd for $C_{15}H_{15}BrO$: C, 60.21; H, 5.41. Found: C, 60.38; H, 5.41.

Annulation of bromide **104** with acrylonitrile; Octahydro-7a-hydroxy-1-(phenylmethylene)-1-H-indene-2-carbonitrile **105**: The general procedure for radical annulation was followed using bromide **104** (279 mg, 1.0 mmol), freshly distilled acrylonitrile (795 mg, 15.0 mmol) in benzene (15 mL), triphenyltin hydride (421 mg, 1.2 mmol) in benzene (10 mL), and AIBN (20 mg, 0.12 mmol) in benzene (10 mL). After evaporation of the solvent the residue was worked up as described for **58**. Flash chromatography, in the manner indicated, using 16% ethyl acetate — hexane gave **104** (164

mg, 64.8%) as a mixture of isomers: IR (neat) 3480, 2220, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.79 — 2.88 (m, 12H), 2.40 — 2.85 (m, 1H), 6.50 — 6.90 (6 broad s, 1H), 7.33 (m, 5H); exact mass, m/z 253.1472 (calcd for $C_{17}H_{19}NO$, 253.1498).

1H-Imidazole-1-carbothioic acid, O-2-(phenylethynyl)-cyclopentyl ester **106**: Alcohol **72** (700 mg, 3.76 mmol) and 1,1'-carbonothioylbis-1H-imidazole[82] (1.6 g, 9.0 mmol) were placed in a flask and covered with dry 1,2-dichloroethane (15 mL). The resulting solution was refluxed under argon for 16 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 × 15 cm) with 25% ethyl acetate — hexane gave pure (TLC, silica, 25% ethyl acetate — hexane) **106** (1.01 g, 90.6%): IR (neat) 2220, 1598, 1530, 760, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.70 — 2.60 (m, 6H), 3.30 (m, 1H), 5.85 (dt, J = 6.4, 2.8 Hz, 1H), 7.05 (s, 1H), 7.30 (m, 3H), 7.43 (m, 2H), 7.63 (t, J = 2 Hz, 1H), 8.32 (s, 1H); exact mass, m/z 296.0977 (calcd for $C_{17}H_{16}OS$, 296.1931). Anal. calcd for $C_{17}H_{16}OS$: C, 68.87; H, 5.44. Found: C, 68.52; H, 5.41.

Annulation of alkoxythiocarbonylimidazole **106** with acrylonitrile; Octahydro-1-(phenylmethylene)pentalene-2-carbonitrile **88**: The general procedure for radical annulation was followed using alkoxythiocarbonylimidazole **106** (200 mg, 0.675 mmol) and freshly distilled acrylonitrile (537 mg, 10.1 mmol) in benzene (30 mL), triphenyltin hydride (355 mg, 1.01 mmol) in benzene (10 mL), and AIBN (16 mg, 0.097 mmol) in benzene (10 mL). After evaporation of the solvent, flash chromatography of the residue over silica gel (2 × 15 cm) with 6% ethyl acetate — hexane gave pure (TLC, silica, 10% ethyl acetate — hexane) **88** (40 mg, 26%) as a mixture of isomers: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.70 — 2.95 (m, 10H), 3.20 — 3.90 (m, 1H), 6.30 — 6.75 (5 m, 1H), 7.29 (m, 5H); exact mass, m/z 223.1361 (calcd for $C_{16}H_{17}N$, 223.1390).

2-(Phenylseleno)-2-propenenitrile **110**:[81] The literature procedure[81] was followed: 2-Propenenitrile (2.0 g, 38.0 mmol) in dry dichloromethane (12 mL) was added to a stirred solution of phenylselenenyl bromide[90] (8.12 g, 32.0 mmol) in dichloromethane (50 mL). The resulting mixture was refluxed under argon for 18 h and cooled to room temperature. Triethylamine (6.09 mL, 48.0 mmol) in dry benzene (100 mL) was then added and stirring at room temperature was continued for a further 15 h. The

suspension was filtered using hexane as a rinse. Evaporation of the solvent and flash chromatography of the residue over silica gel (4 × 15 cm) first with 1% hexane (to elute diphenyldiselenide) and then with 5% ethyl acetate — hexane gave **110** (2.0 g, 30%) as a pale yellow oil: IR (neat) 2220, 1690, 740, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 80 MHz) δ6.1 (s, 1H), 6.55 (s, 1H), 7.2 — 7.55 (m, 5H). The compound was used immediately for the next stage.

1-(1-Cyclohexen-1-yl)pyrrolidine **116**:[91] The literature procedure[91] was followed: A solution of cyclohexanone (23.4 g, 0.238 mol) and pyrrolidine (20 mL, 0.238 mol) in benzene (50 mL) was refluxed using a Dean-Stark trap. After 3 h no more water was produced. The solvent was evaporated and the residue was distilled to give the enamine **116** (31.6 g, 88%): bp 100 — 105°C (5 mm) [lit.[91] bp 64 — 65°C (0.5 mm)]. The compound was used immediately for the next stage.

2-(Oxocyclohexyl)-2-(phenylseleno)propanenitrile **117**: 2-Phenylseleno-2-propenenitrile **110** (275 mg, 1.31 mmol) in dry THF (2 mL + 1 mL rinse) was injected dropwise at room temperature into a stirred solution of enamine **116** (180 mg, 1.19 mmol) in THF (6 mL). The resulting mixture was stirred for 3 h, water (10 mL) was added, and stirring at

room temperature was continued for 30 min. The mixture was extracted with ether (2 × 15 mL) and the combined extracts were washed with brine and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm) with 20% ethyl acetate — hexane gave ketone **117** (335 mg, 91%) as a pure (TLC, silica, 20% ethyl acetate — hexane) mixture of isomers: IR (neat) 2220, 1705, 750, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ1.2 — 2.15 (m, 7H), 2.2 — 2.45 (m, 3H), 2.5 — 2.75 (m, 1H), 3.8 (dd, J = 8.8, 7.6 Hz, 0.5H), 3.98 (dd, J = 12, 6 Hz, 0.5H), 7.4 (m, 3H), 717 (m, 2H); exact mass, m/z 307.0463 (calcd for $C_{15}H_{17}NOSe$, 307.0507). The substance was too unstable for combustion analysis.

[2-Hydroxy-2-(phenylethynyl)cyclohexyl]-2-(phenylseleno)-propanenitrile **118**: n-Butyllithium (1.6 M in hexane, 0.86 mL, 1.39 mmol) was injected dropwise at -78°C into a solution of phenylacetylene (163 mg, 1.6 mmol) in THF (5 mL) and the mixture was stirred for 15 min. Ketone **117** (330 mg, 1.0 [illegible] in THF (3 mL + 1 mL rinse) was added dropwise over 10 min and the resulting solution was stirred at -78°C for 30 min. Saturated aqueous ammonium chloride was added and the mixture was extracted with ether (2 × 15 mL). The combined organic extracts were washed with brine, dried ($MgSO_4$), and evaporated. Flash

chromatography of the residue over silica gel (2 × 15 cm) with 20% ethyl acetate — hexane gave **118** (414 mg, 94.7%) as a pure (TLC, silica, 20% ethyl acetate — hexane) mixture of isomers: IR (neat) 3450, 2240, 1590, 1570, 745, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ1.2 — 2.15 (m, 11H), 2.2 — 2.6 (m, 1H), 3.8 — 4.2 (m, 1H), 7.3 (m, 8H), 7.7 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ (aromatic signals) 119.8, 120.1, 120.4, 120.6, 122.2, 122.3, 125.8, 126.0, 126.1, 128.0, 128.1, 128.18, 128.2, 128.3, 128.4, 129.2, 129.3, 129.33, 129.4, 131.5, 131.6, 136.1, 136.16, 136.3, 136.4; exact mass, m/z 409.0952 (calcd for $C_{23}H_{23}NSeO$, 409.0970); satisfactory C analysis could not be obtained. Anal. calcd for $C_{23}H_{23}NOSe$: C, 67.46; H, 5.66; N, 3.42. Found: C, 64.95; H, 5.41; N, 3.37.

General procedure for radical cyclizations: [Oven-dried apparatus and anhydrous solvents were used. AIBN (Eastman material) was used without purification.] The substrate (0.4 — 1.0 mmol) was placed in a 100 mL round-bottomed flask containing a Teflon-coated magnetic stirring bar and equipped with a reflux condenser closed by a rubber septum. The system was purged with argon for 5 min. Benzene (15 — 25 mL) was injected into the flask which was then immersed in an oil bath preheated to 80°C. Benzene solutions of triphenyltin hydride (1.2 equivalents, 0.05 —

0.07 M) and AIBN (0.1 equivalent, 0.01 M) were then injected simultaneously over 10 h by means of a double syringe pump. Refluxing under argon was continued throughout the addition and for a further arbitrary period of 2 h. The mixture was then cooled and evaporated under water pump vacuum. The residue was processed as described for the individual examples.

Cyclization of selenides **118**; Octahydro-7a-hydroxy-1-(phenylmethylene)-1H-indene-2-carbonitrile **105**: The general procedure for radical cyclization was followed using selenides **118** (180 mg, 0.44 mmol) in benzene (15 mL), triphenyltin hydride (175 mg, 0.50 mmol) in benzene (7 mL), and AIBN (20 mg, 0.11 mmol) in benzene (7 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm) with 20% ethyl acetate — hexane gave **105** (101 mg, 91%) as a pure (TLC, silica 20% ethyl acetate — hexane) mixture of isomers: IR (CCl_4) 3450, 2250, 1590, 1550, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ0.9 — 2.5 (m, 12H), 3.4 — 3.85 (m, 1H), 6.5 — 6.9 (5 broad s, 1H), 7.4 (m, 5H); exact mass, m/z 253.1473 (calcd for $C_{17}H_{19}NO$, 253.1498). Anal. calcd for $C_{17}H_{19}NO$: C, 80.58; H, 7.56; N, 5.53. Found: C, 79.58; H, 7.47; N, 5.42.

1(1-Cyclopenten-1-yl)pyrrolidine **129**:[48,60] The procedure employed for **116** was followed using cyclopentanone (5.2 g, 61.8 mmol) and pyrrolidine (5.66 mL, 67.9 mmol) in benzene (50 mL). The reaction mixture was refluxed for 4 h. Distillation of the residue gave enamine **130** (6.52 g, 77%): bp 90 — 95°C (11 mm) [lit.[48,60] bp 81 — 83°C (9 mm)]. The compound was used immediately for the next stage.

2-(Oxocyclopentyl)-2-(phenylseleno)propanenitrile **120**: The procedure employed for **117** was followed using 2-phenylseleno-2-propenenitrile **110** (325 mg, 1.56 mmol) in dry THF (2 mL + 1 mL rinse) and enamine **129** (178 mg, 1.3 mmol) in THF (8 mL). The reaction mixture was stirred at room temperature for 3 h and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm) with 20% ethyl acetate — hexane gave ketones **120** (360 mg, 94%) as a mixture of isomers. The sample contained trace impurities as judged by ^{1}H and ^{13}C NMR: IR (CCl_4) 2220, 1735, 1570, 740, 690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ1.5 (m, 1H), 1.8 (m, 2H), 2.0 — 2.50 (m, 6H), 3.93 (dd, J = 8, 6 Hz, 0.4H), 4.03 (dd, J = 9.6, 6.3 Hz, 0.6H), 7.43 (m, 3H), 7.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ20.2, 20.3, 23.5, 23.7,

23.8, 29.1, 29.5, 32.6, 33.2, 37.3, 46.5, 46.6, 47.2, 53.7, 129.2, 129.3, 129.35, 129.4, 129.5, 136.1, 135.6, 218.4, 218.7; exact mass, m/z 293.0320 (calcd for $C_{14}H_{15}NOSe$, 293.0351). The sample was too unstable for combustion analysis.

[2-Hydroxy-2-(phenylethynyl)cyclopentyl]-2-(phenylseleno)-propanenitrile **121**: The procedure employed for **118** was followed using n-butyllithium (1.6 M in hexane, 1.53 mL, 2.46 mmol), phenylacetylene (376 mg, 3.69 mmol) in THF (8 mL), and ketones **120** (360 mg, 1.23 mmol) in THF (3 mL + 1 mL rinse). The reaction mixture was stirred at -78°C for 1 h and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm) with 20% ethyl acetate — hexane gave alcohols **121** as a pure (TLC, silica, 20% ethyl acetate — hexane) mixture of isomers (350 mg, 68% overall from enamine **130**): IR (neat) 3520, 2225, 1600, 1570, 750, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ1.2 — 2.5 (m, 10H), 3.75 — 4.05 (m, 1H), 7.35 (m, 8H), 7.72 (m, 2H); exact mass, m/z 395.0792 (calcd for $C_{22}H_{21}NOSe$, 395.0819). Anal. calcd for $C_{22}H_{21}NOSe$: C, 66.98; H, 5.36; N, 3.55. Found: C, 65.65; H, 5.36; N, 3.59. Statisfactory C analysis could not be obtained. Anal. calcd for $C_{22}H_{21}NOSe$: C, 66.98; H, 5.39; N, 3.55. Found: C, 65.65; H, 5.49; N, 3.59.

Cyclization of selenides **121**; Octahydro-6a-hydroxy-1-(phenylmethylene)pentalene-2-carbonitrile **122**: The general procedure for radical cyclization was followed using selenides **121** (164 mg, 0.42 mmol) in benzene (15 mL), triphenyltin hydride (175 mg, 0.50 mmol) in benzene (7 mL), and AIBN (20 mg, 0.11 mmol) in benzene (7 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm) with 30% ethyl acetate — hexane gave pentalenes **122** (88 mg, 89%) as a pure (TLC, silica, 30% ethyl acetate — hexane) mixture of isomers: IR (neat) 3450, 2240, 1600, 760, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ1.0 — 2.8 (m, 10H), 3.5 — 4.95 (m, including broad t, J = 8 Hz, 1H), 6.7 — 6.93 (4 broad s, 1H), 7.10 — 7.80 (m, 5H); exact mass, m/z 239.1311 (calcd for $C_{16}H_{17}NO$, 239.1342). Anal. calcd for $C_{16}H_{17}NO$: C, 80.28; H, 7.16; N, 5.85. Found: C, 79.53; H, 7.09; N, 5.73.

1-(1-Cyclohepten-1-yl)pyrrolidine **130**:[60,92] The procedure employed for **116** was followed using cycloheptanone (7.12 g, 63.5 mmol) and pyrrolidine (5.0 g, 70.0 mmol) in benzene (50 mL). The mixture was refluxed for 4 h and the solvent was evaporated. Distillation of the residue afforded enamine **131** (8.1 g, 78%): bp 76 — 78°C (0.8 mm)

[lit.[60] bp 93 — 95°C (2.2 mm)]. The compound was used immediately for the next stage.

2-(Oxocycloheptyl)-2-(phenylseleno)propanenitrile **123**: The procedure employed for **117** was followed using 2-phenylseleno-2-propenenitrile **110** (278 mg, 1.33 mmol) in dry THF (2 mL + 1 mL rinse) and enamine **130** (200 mg, 1.21 mmol) in THF (8 mL). The reaction mixture was stirred at room temperature for 3 h and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm) with 15% ethyl acetate — hexane gave ketones **123** (291 mg, 75%) as a pure (TLC, silica, 20% ethyl acetate — hexane) mixture of isomers: IR (neat) 2230, 1698, 745, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ1.1 — 2.02 (m, 9H), 2.2 — 2.7 (m, 3H), 2.8 — 3.1 (m, 1H), 3.75 (m, 1H), 7.25 (m, 3H), 7.7 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ15.1, 23.3, 23.4, 23.5, 24.2, 28.6, 28.65, 28.7, 28.8, 31.1, 32.0, 34.2, 35.3, 43.1, 43.3, 48.8, 49.8, 65.6, 119.6, 119.8, 125.5, 125.7, 129.3, 129.4, 129.5, 136.1, 213.7, 213.8; exact mass, m/z 321.0638 (calcd for $C_{16}H_{19}NOSe$, 321.0663). The substance was too unstable for combustion analysis.

[1-Hydroxy-2-(phenylethynyl)cycloheptyl]-2-(phenylseleno)-propanenitrile **124**: The procedure employed for **118** was

followed using n-butyllithium (1.6 M in hexane, 1.36 mL, 2.19 mmol), phenylacetylene (298 mg, 2.92 mmol) in THF (10 mL), and ketones **123** (470 mg, 1.46 mmol) in THF (3 mL + 1 mL rinse). The reaction mixture was stirred at -78°C for 45 min and was worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm) with 15% ethyl acetate — hexane gave alcohols **124** (585 mg, 94.6%) as a pure (TLC, silica, 20% ethyl acetate — hexane mixture of isomers: IR (neat) 3450, 2230, 755, 740, 700 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ1.2 — 2.25 (m, 13H), 2.3 — 2.55 (m, 1H), 3.8 — 4.05 (m, 1H), 7.3 — 7.7 (m, 2H); exact mass, m/z 423.1100 (calcd for $C_{24}H_{25}NOSe$, 423.1131). Anal. calcd for $C_{24}H_{25}NOSe$: C, 68.06; H, 5.95; N, 3.31. Found: C, 68.07; H, 6.13; N, 3.44.

Cyclization of selenides **124**; Decahydro-8a-hydroxy-1-(phenylmethylene)azulene-2-carbonitrile **125**: The general procedure for radical cyclization was followed using selenides **124** (230 mg, 0.54 mmol) in benzene (20 mL), triphenyltin hydride (219 mg, 0.62 mmol) in benzene (7 mL), and AIBN (20 mg, 0.11 mmol) in benzene (7 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm) with 20% ethyl acetate — hexane gave **125** (152 mg, 91.7%) as a pure (TLC,

silica, 25% ethyl acetate — hexane) mixture of isomers: IR (CCl_4) 3460, 2230, 740, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ1.1 — 2.6 (m, 14H), 3.4 — 3.85 (m, 1H), 6.7 — 6.95 (5 s, 1H), 7.2 — 7.7 (m, 5H); exact mass, m/z 267.1628 (calcd for $C_{18}H_{21}NO$, 267.1654). Anal. calcd for $C_{18}H_{21}NO$: C, 80.84; H, 7.92; N, 5.24. Found: C, 80.44; H, 7.95; N, 5.23.

4-(1-Butyl-1-pentenyl)-(E)-morpholine **131**:[60] The literature procedure[60] was followed: 5-Nonanone (2.85 g, 0.02 mol) and morpholine (6.10 g, 0.07 mol) in dry benzene (30 mL) were cooled to 0°C under argon. Titanium tetrachloride (1.21 mL, 0.011 mol) in benzene (20 mL) was added dropwise over 20 min and the mixture was stirred for 15 h at room temperature. The resulting slurry was filtered by suction through a pad of Celite (2 × 4 cm) and the solvent was evaporated. Kugelrohr distillation of the residue afforded the enamine **132** (3.6 g, 85%): bp 90 — 95°C (0.7 mm) [lit.[60] bp 105 — 115°C (0.9 mm)]. The compound was used immediately for the next stage.

5-Oxo-2-(phenylseleno)-4-propylnonanenitrile **126**: The procedure employed for **117** was followed using 2-phenylseleno-2-propenenitrile **110** (325 mg, 1.56 mmol) in

THF (2 mL + 1 mL rinse) and enamine **131** (274 mg, 1.3 mmol) in THF (8 mL). The reaction mixture was stirred at room temperature for 3 h and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm) with 6% ethyl acetate — hexane gave ketones **126** (352 mg, 77%) as a pure (TLC, silica, 10% ethyl acetate — hexane) mixture of isomers: IR (CCl_4) 2225, 1709, 1580, 745, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ0.9 (m, 6H), 1.1 — 1.8 (m, 9H), 2.25 (m, 1H), 2.2 (m, 2H), 2.8 (m, 1H), 3.6 (m, 1H), 7.4 (m, 3H), 7.7 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ13.7, 13.8, 13.9, 19.8, 19.9, 22.1, 23.4, 24.2, 25.5, 32.7, 33.3, 34.0, 42.0, 42.1, 49.0, 49.9, 119.5, 119.6, 125.5, 125.7, 129.3, 129.4, 129.5, 136.1, 212.1, 212.4; exact mass, m/z 351.1109 (calcd for $C_{18}H_{23}NOSe$, 351.1131).

5-Hydroxy-2-(phenylseleno)-5-(phenylethynyl)-4-propyl-nonanenitrile, **127**: The procedure employed for **118** was followed using n-butyllithium (1.6 M in hexane, 1.19 mL, 1.91 mmol), phenylacetylene (293 mg, 2.86 mmol) in THF (8 mL), and ketones **126** (335 mg, 0.956 mmol) in THF (3 mL + 1 mL rinse). The reaction mixture was stirred at -78°C for 1 h and was then worked up. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm) with 10% ethyl acetate — hexane gave alcohols **127**

as a pure (TLC, silica, 15% ethyl acetate — hexane) mixture of isomers: IR (neat) 3450, 2230, 1580, 755, 740, 690 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ0.92 (m, 6H), 1.05 — 1.8 (m, 10H), 1.95 (m, 2H), 2.05 (m, 0.5H), 2.11 (s, 0.5H), 2.2 — 2.4 (m, 1H), 4.0 (m, 0.5H), 4.15 (m, 0.5H), 7.35 (m, 8H), 7.72 (m, 2H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ (aromatic signals) 120.2, 120.5, 122.2, 122.3, 126.2, 126.4, 128.2, 128.3, 128.4, 128.45, 128.5, 129.1, 129.2, 129.3, 129.4, 131.5, 131.6, 135.9, 136.0, 136.1, 136.2; exact mass, m/z 453.1581 (calcd for $C_{26}H_{31}NOSe$, 453.1599). Anal. calcd for $C_{26}H_{31}NOSe$: C, 68.85; H, 6.89; N, 3.09. Found: C, 69.13; H, 6.90; N, 3.10.

Cyclization of selenides **127**; 3-Butyl-3-hydroxy-2-(phenylmethylene)-4-propylcyclopentane-1-carbonitrile **128**: The general procedure for radical cyclization was followed using selenides **127** (145 mg, 0.32 mmol) in benzene (10 mL), triphenyltin hydride (134 mg, 0.38 mmol) in benzene (6 mL), and AIBN (16 mg, 0.097 mmol) in benzene (6 mL). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 × 15 cm) with 20% ethyl acetate — hexane gave **128** (75 mg, 79%) as a pure (TLC, silica, 20% ethyl acetate — hexane) mixture of isomers: IR (neat) 3460, 2240, 1690, 1595, 755, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ0.59 — 2.6 (m, 20H), 3.6 — 3.9 (m, 1H),

6.6 — 7.02 (4 d, J = 6 Hz, 1H), 7.15 — 7.55 (m, 5H); exact mass, m/z 297.2095 (calcd for $C_{20}H_{27}NO$, 297.2122). Anal. calcd for $C_{20}H_{27}NO$: C, 80.75; H, 9.15; N, 4.71. Found: C, 79.97; H, 9.19; N, 4.4.

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