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FREE RADICAL SYNTHETIC METHODOLOGY:- CLOSURE OF DOUBLE RADICAL PRECURSORS AND SEQUENTIAL PAUSON-KHAND REACTION--RADICAL CYCLIZATION

by

DEREK C. COLE

A THESIS

SUBMITTED TO THE FACULTY OF GRADUATE STUDIES AND RESEARCH IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

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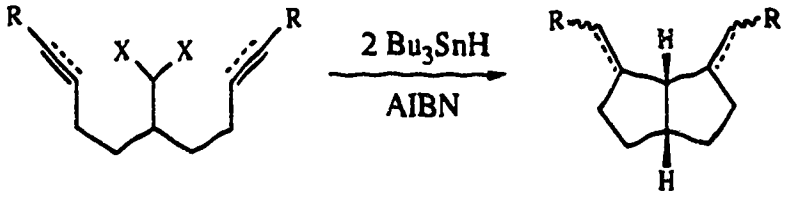
To my family and friends

ABSTRACT

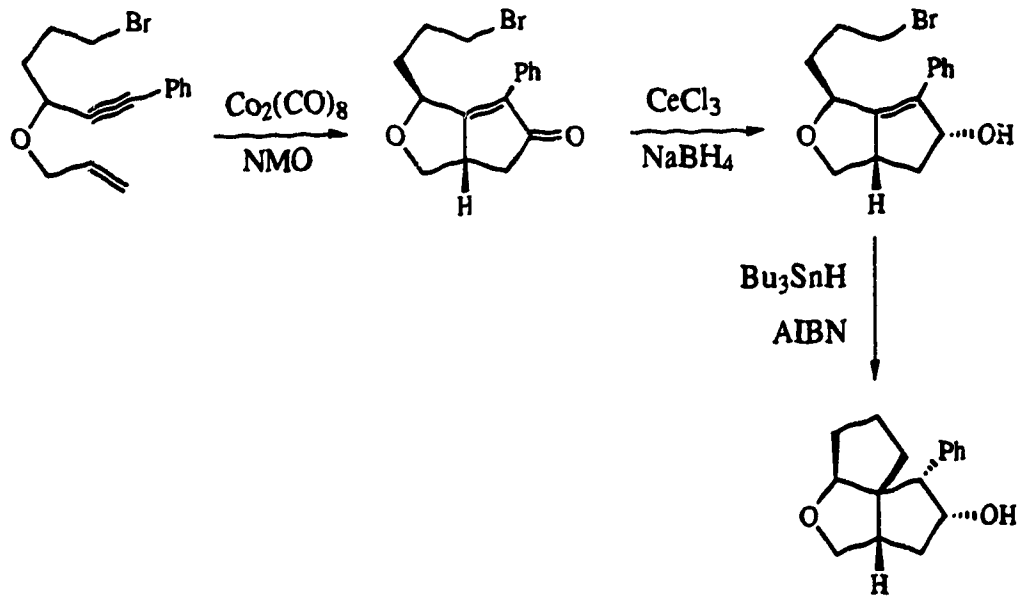
This thesis describes the formation of polycyclic structures, by two different strategies, from non-cyclic compounds.

The first strategy makes use of compounds which contain a central carbon atom bearing two homolyzable groups X, which can be cleaved to produce radicals. To this central carbon are attached two pendants containing suitably located radical acceptors. On treatment with a trialkyltin hydride two radicals are sequentially generated and undergo 5-*exo* closure to give polycyclic structures (Scheme A).



Scheme A

The second strategy involves the use of the Pauson-Khand reaction in conjunction with radical cyclization. The Pauson-Khand reaction of an enyne, to which a chain carrying a homolyzable group is attached, produces bicyclic enones. Following reduction of the enone to the corresponding alcohol, radical cyclization gives angularly fused polyquinanes (Scheme B).



Scheme B

ACKNOWLEDGEMENTS

I would like to express my gratitude to Professor D. L. J. Clive for his advice and encouragement during the course of my studies, and for his assistance in the preparation of this thesis.

The help of the technical staff of the Chemistry Department is appreciated, in particular the NMR technical staff provided considerable assistance and training on the high-field NMR spectrometers.

I would like to thank my friends and co-workers, namely Antonio C. Joussef, Keshava K. S. Murthy, Hartford W. Manning, Dorit Kellner, Craig J. Railton, Dênis P. DeLima and Steve R Magnuson for frequent helpful discussions and constant support.

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LIST OF ABBREVIATIONS

AIBN	azoisobutyronitrile
CAN	ceric ammonium nitrate
DEAD	diethylazodicarboxylate
DIBAl	diisobutylaluminum hydride
DMAP	4-(*N*,*N*-dimethylamino)pyridine
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
HMPA	hexamethylphosphoramide
Imid	imidazole
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
MCPBA	*m*-chloroperbenzoic acid
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NMO	4-methylmorpholine *N*-oxide
P-K	Pauson-Khand
PCC	pyridiniumchlorochromate
Ph	phenyl
PPTS	pyridinium *para*-toluenesulfonate
PTSA	*para*-toluenesulfonic acid
pyr	pyridine
t-Bu	tertiary butyl

TBS	*t*-butyldimethylsilyl
TMANO	trimethylamine-*N*-oxide
TMS	trimethylsilyl
tol	toluene
U.S.	ultrasound
U.V.	ultraviolet

INTRODUCTION

In the late 1960's Julia[1] carried out pioneering work in the area of free radical cyclization chemistry. Since the early 1980's free radical chain reactions have attracted wide interest from synthetic organic chemists. This interest is due to the discovery of a variety of techniques for the generation of free radicals, the mild reaction conditions which avoid the need for protecting groups, and the high levels of chemo-, regio- and, often, stereoselectivity. For thorough discussions several current reviews are available.[2]

This review will deal with the basic principles involved in free radical chain reactions, the behavior of radicals on carbon atoms which have a homolyzable group attached and, finally, some of the methodology used to assemble radical precursors.

Principles of Radical Cyclization

Free radical chain processes can be divided into three stages. In the initiation step radicals are formed either thermally or photochemically. These radicals, which are frequently stannyl centered, react by abstraction of an atom or group from a neutral molecule, to produce a carbon radical. The most commonly abstracted groups are halogens, sulfides and selenides.

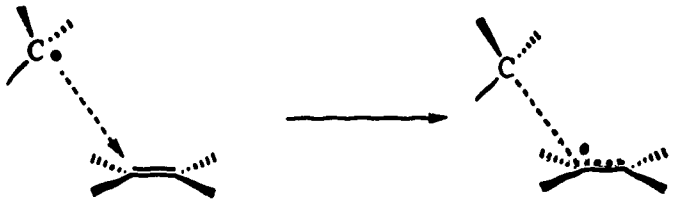
The second phase of the process is then reaction of these--usually carbon centered--radicals. The most synthetically useful reactions are additions to carbon-carbon multiple bonds. Addition to carbon-nitrogen and carbon-oxygen bonds may also be useful in intramolecular cases.

Finally, the chain process is ended by recombination of two radicals or by disproportionation. Both of these reactions occur at diffusion controlled

rates, so maintenance of low concentration of radical species during the reaction is necessary. Free radical additions will be discussed as two groups, inter- and intramolecular reactions.

Intermolecular Additions

Additions of alkyl radicals to alkenes are exothermic since a σ bond is formed at the expense of a π bond.[3] Thus, according to the Hammond postulate,[4] the reaction has an early transition state and the stabilities of the products are not important. Calculations have shown that maximum overlap between the reacting orbitals is possible if the radical approaches as shown in Scheme 1 to produce an unsymmetrical obtuse triangle-shaped transition state with unequal distances between the attacking radical and the two vinylic carbon atoms.[5]



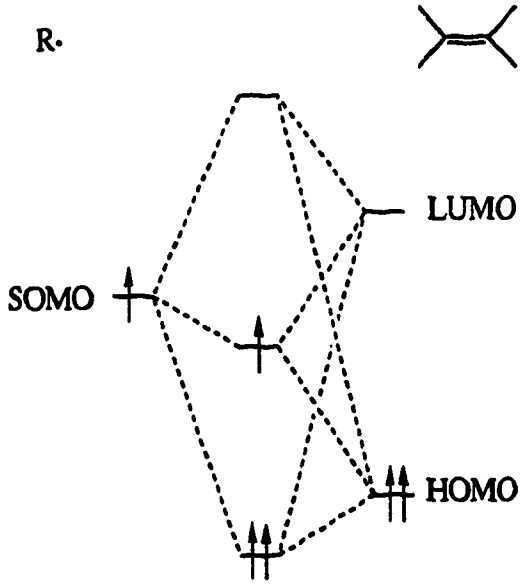
Scheme 1

The existence of early transition states allows the polar substituent effects to be described in terms of frontier orbital theory.[3] This theory states that the interaction between the free radical singly occupied molecular orbital (SOMO) and the lowest unoccupied or the highest occupied molecular orbital (LUMO or HOMO) will determine the addition rates (Scheme 2).

Electron-withdrawing groups on the alkene lower its LUMO, thus decreasing the SOMO-LUMO energy difference, and increasing the rate of

addition of free radicals. The reactivity of nucleophilic radicals increases with incorporation of electron donating substituents, since this increases the SOMO energy of the radical and also decreases the SOMO-LUMO difference.

Strongly electron-withdrawing substituents on the radical decrease the SOMO energy level to such an extent that the SOMO-HOMO interaction becomes dominant. The radical thus loses its nucleophilic character and becomes electrophilic, and so the reaction rate is increased by electron donating substituents on the olefin.

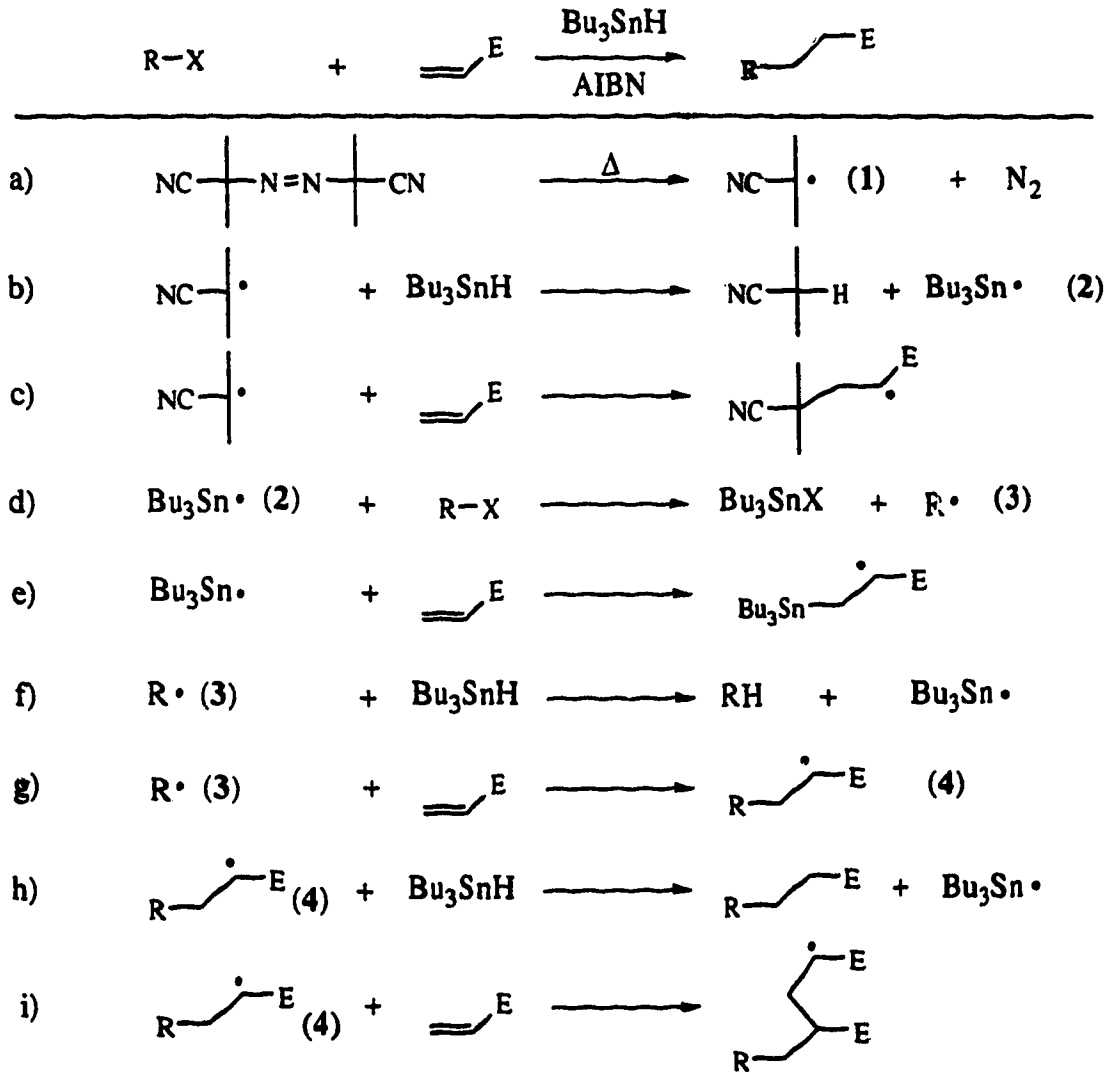


Scheme 2

For alkynes, the LUMO is higher, and the HOMO lower in energy, than for alkenes. Thus the interaction with the SOMO of the attacking radical is less and the rates are lower than for double bonds.

The unsymmetrical transition state makes the α steric effect much more pronounced than the β-effect. Free radicals preferentially attack the unsubstituted terminus of terminal olefins or the less substituted carbon of

unsymmetrically substituted olefins. In isosteric situations the regiochemistry is controlled by polarity.



Scheme 3

Trialkyltin hydrides are commonly used as the chain transfer reagent in free radical reactions. Scheme 3 presents the possible steps that must be considered in a tin hydride mediated intermolecular addition sequence.

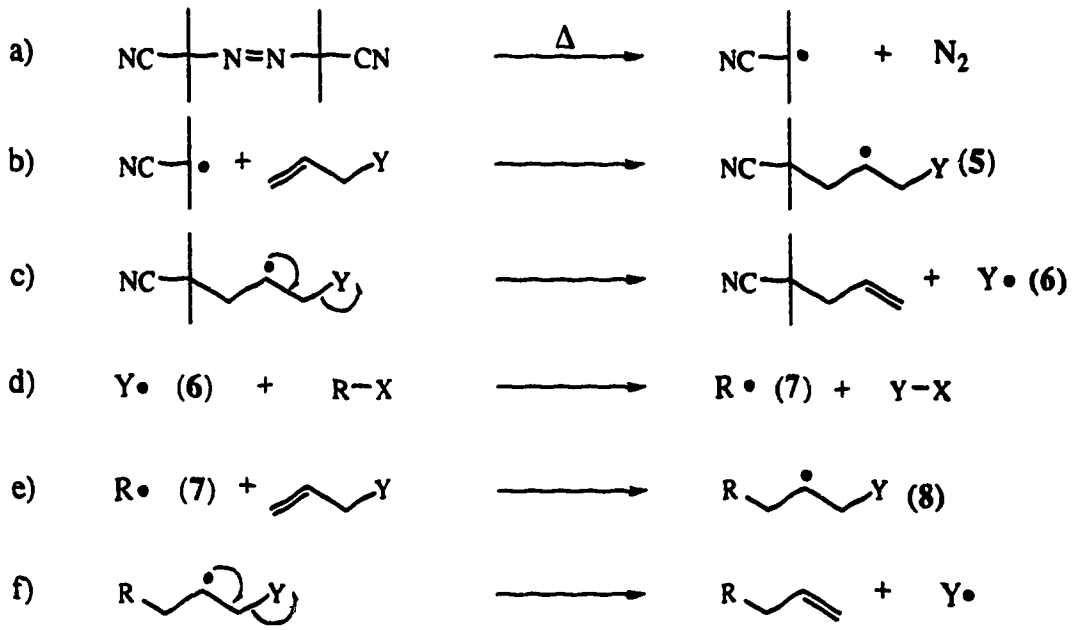
When azobisisobutyronitrile is heated it undergoes fragmentation to liberate molecular nitrogen and two 2-cyanopropyl radicals. If **E** is an electron

withdrawing group, then the addition of the electrophilic 2-cyanopropyl radical 1 to the olefin (path *c*), will not compete with path *b*, the abstraction of hydrogen from tin hydride to produce stannyl radicals.

The stannyl radical produced may either abstract X (path *d*) or add to the olefin (path *e*). This addition is reversible due to the weak tin-carbon bond, and so stannyl addition only competes when X abstraction is slow, *i.e.* X = chloride or sulfide.[6] Therefore radical 3 is produced preferentially. If 3 is nucleophilic and if the tributyltin hydride is used in low concentration, then addition (path *g*) to produce 4 should prevail. This new radical is electrophilic and does not react with the electron poor olefin. Therefore it is reduced by the tin hydride, and polymerization (path *i*) is prevented.

The disadvantage of the tin hydride method for radical propagation is the reduction of intermediates--if their lifetimes are not short enough. Use of a fragmentation reaction for chain-transfer (rather than H abstraction in the case of tin hydride) is a powerful alternative.[7] Scheme 4 illustrates the steps involved in this process.

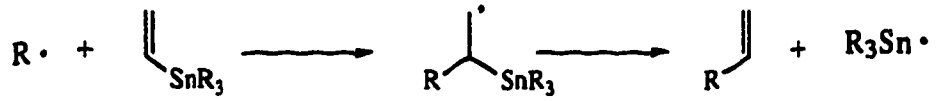
The 2-cyanopropyl radical adds to the olefin to form intermediate 5, which has a sufficiently weak C-Y bond such that rapid fragmentation occurs, to produce the chain transfer agent 6. Abstraction of X leads to a new carbon radical 7, and addition of 7 to the radical acceptor produces a new intermediate 8. This is prone to the same fragmentation as 5. The net result is allylation of the radical precursor.



Scheme 4

Allyl trialkyltins are found to be the compounds of choice for these reactions. Cleavage of carbon-silicon and carbon-germanium bonds is too slow to allow use of allylgermanes or allylsilanes, however allylplumbanes have been used.[8]

Vinyltins may also be used (Scheme 5); however this process requires an activating group to direct the addition of the radical to the carbon bearing the tin group.[9]

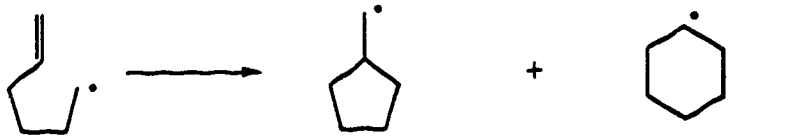


Scheme 5

Intramolecular Additions

Intramolecular addition reactions are useful for the construction of rings. Since a large number of naturally occurring compounds contain cyclic

units this process has received much attention. The fundamental ring closure is that of the 5-hexenyl radical,[10] shown in Scheme 6.



9 (5-exo) **10** (6-endo)

50 : 1

Scheme 6

There are two possible modes of cyclization, 5-*exo* and 6-*endo*, both of which are allowed by Baldwin's rules.[11] The orbital interactions discussed for intermolecular additions are best accommodated if attack occurs in an *exo* mode[12] (path *a* in figure 1). This preferred mode of reaction--5-*exo* closure--produces the primary radical **9**, while 6-*endo* closure produces the thermodynamically more stable secondary radical **10** (Scheme 6).

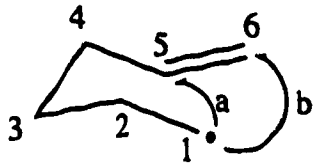


Figure 1

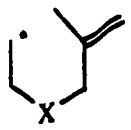
Substitution at positions 1 and 6 has little effect on the rate or regiochemistry of cyclization, however substituents at C-5 lower the rate of 5-*exo* closure, and the 6-*endo* pathway may then predominate.[13] Substituents at the 2, 3 or 4 positions enhance the rate of cyclization. For example, the 2,2-dimethyl hexenyl radical **11** (Scheme 7) cyclizes 10 times faster than the

unsubstituted system.[13] The Thorpe-Ingold effect[14] has been invoked to explain this observation.

11

Scheme 7

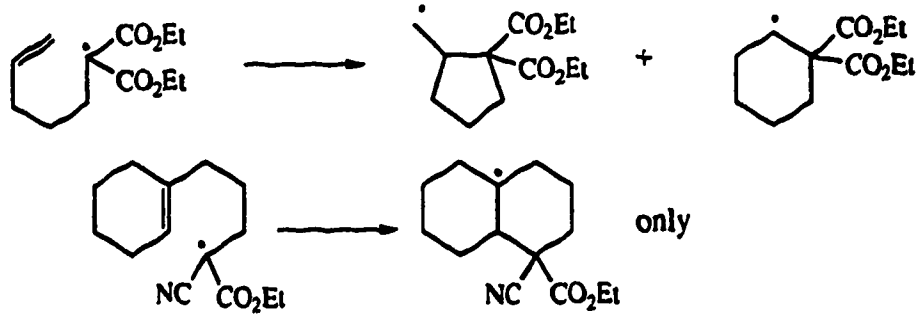
When the ring contains a first-row heteroatom, the decreased bond angle C-X-C and the shorter C-X bonds allow the radical to accommodate the triangular transition state, leading to 5-*exo* closure, more easily. For example, the 5-substituted hexenyl radical reverts to the *exo* mode of closure when X = oxygen[13] (Scheme 8).



X	k exo / k endo
CH_2	0.55
O	38.6

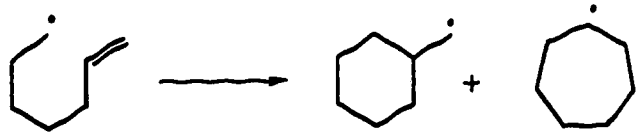
Scheme 8

Closures of stabilized radicals are reversible; therefore, the thermodynamically more stable product may predominate[15] (Scheme 9).



Scheme 9

3-Butenyl radicals close in a 3-*exo* fashion, but the products are subject to rapid reopening due to ring strain.[16] In general, 4-pentenyl radicals do not cyclize.[13] *Exo* closure would give thermodynamically disfavored cyclobutenyl carbinyl radicals, and the stereoelectronic requirements for *endo* closure cannot be accommodated easily.



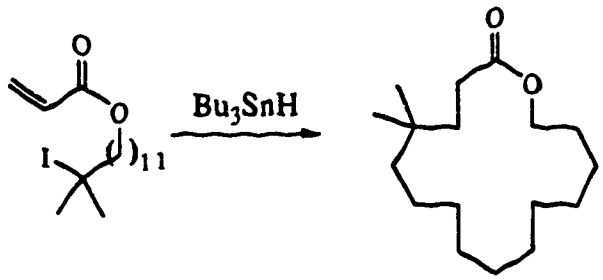
88 : 12

12

Scheme 10

Ring closure of 6-heptenyl radicals is sometimes used in organic synthesis (scheme 10). However due to the chain length, the system has more flexibility than in the hexenyl case, so that *exo* and *endo* transition states are possible, resulting in a loss of selectivity.[13] In addition, 1,5 hydrogen abstraction[17] gives a stable allylic radical **12**, which terminates the cyclization pathway and produces reduction products after workup.

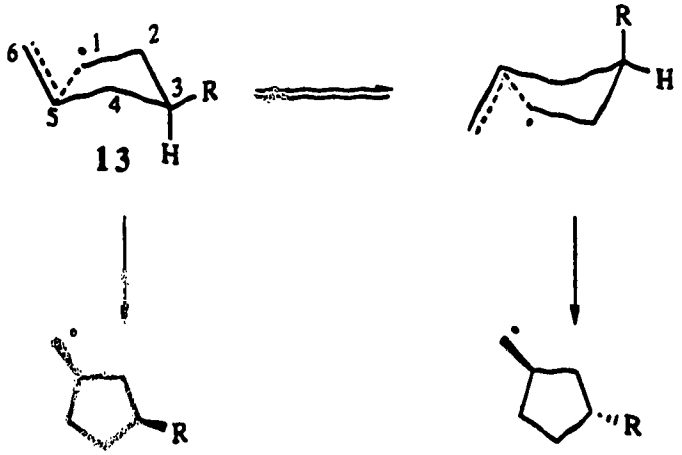
Formation of 7-10 membered rings by radical cyclization reactions is plagued by a lack of selectivity and also by low rates of closure, allowing reduction of radical intermediates to predominate. Closures forming macrolides of 11-20 atoms are known[18] and the reactions behave like intermolecular closures, being controlled by steric and polar effects (Scheme 11).



Scheme 11

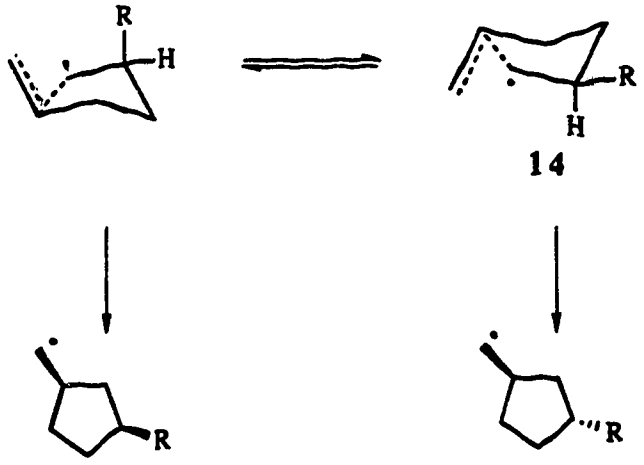
The stereochemistry of radical cyclizations of 5-hexenyl radicals has been studied extensively by Beckwith.[19] 5-*Exo* closures of hexenyl systems monosubstituted at C-1, C-2, C-3, or C-4 (see Scheme 12) gave rise to mixtures of cis and trans-disubstituted products. Conformational effects in the cyclic transition states were used to explain this product distribution.

Theoretical calculations suggest that the transition state for closure of the 5-hexenyl radical resembles the chair form of cyclohexane (Scheme 12). Therefore, there will be two possible conformations of the transition state. The one with the substituent in the pseudo-equatorial position will have the lower energy. Thus, the more stable conformation of the transition state for a 1- or 3-substituted radical is **13**, and this leads to cis-products.[13]



Scheme 12

The transition state which places the 2- or 4- substituents pseudo-equatorially, **14**, produces trans-products[13] (Scheme 13).

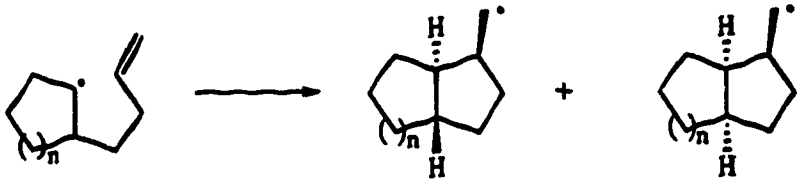


14

Scheme 13

Formation of Bicyclic Compounds

The above guidelines cannot be fully applied to radical cyclizations which produce bicyclic compounds. However, the outcome of such processes is consistent with the steric and stereoelectronic considerations on which the guidelines are based.[13, 20]



15 **16** **17**

n	
1	a
2	b

Scheme 14

Butenyl cycloalkyl radicals **15a** and **15b** may be regarded as 1,2-substituted hexenyl systems with the expected major products being **16a** and **16b** in which the carbinyl radical is cis to the 1-substituent and trans to the 2-substituent. The actual major products are **17a** and **17b** in which all substituents are cis. Inspection of models shows that the most efficient overlap between the SOMO and π^* orbital is attained when reaction occurs through a conformer which puts the substituent in a pseudo axial position.

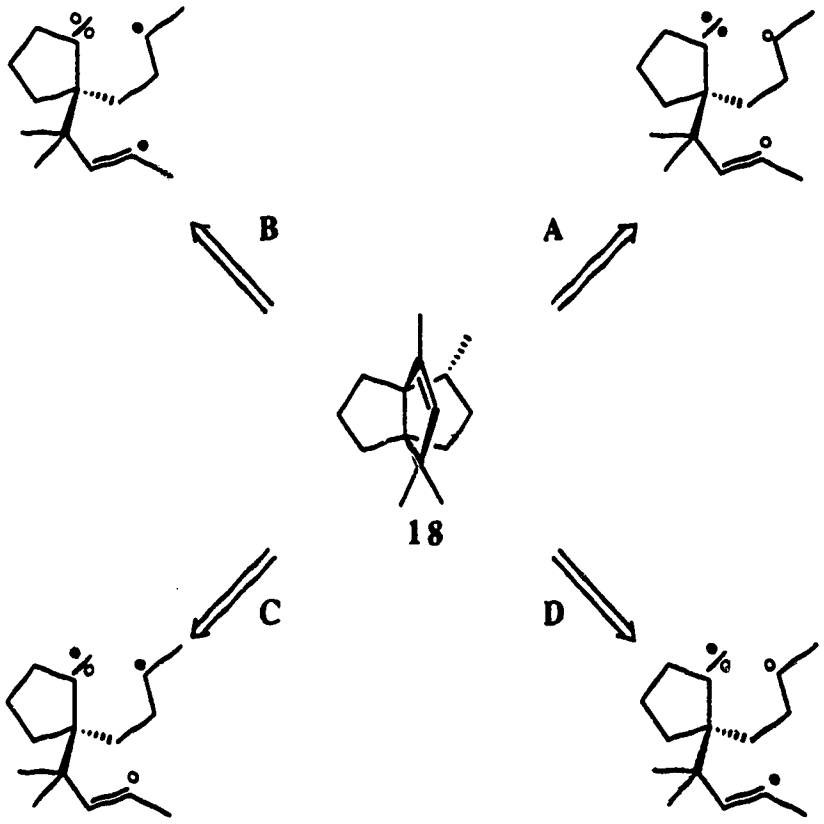
Double Radical Cyclization

Simple radical cyclization and more complex tandem polycyclizations have been used for the synthesis of polycyclic products.[21] However, it is only in recent literature that the concept of double radical addition based on a bifurcating, rather than tandem, pathway has been considered.

In Curran's synthesis[22] of modhephene **18** (Scheme 15) it was not possible to use a tandem radical cyclization sequence, because of the architecture of the propellane system, and so two separate radical cyclizations were necessary. Curran analysed the problem in the context of a new retrosynthetic notation for radical reactions (Scheme 15). In this notation, (•) represents a site of radical generation, while (◦) represents a radical acceptor.

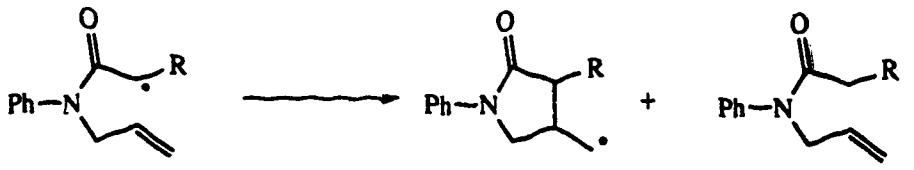
In path **A** two radicals are independently generated at one center and cyclized onto the two pendants, while in path **B** both radicals are generated on the chains and cyclized onto the ring. Paths **C** and **D** represent criss-cross routes with one radical cyclizing from the ring to the chain, and one from the chain to the ring. Curran went on to use paths **B** and **D** for the synthesis of desmethylmodhephene and modhephene itself.

In this section of the review, a process will be discussed that corresponds to Curran's path A, in which two radicals are independently generated at the same carbon in consecutive events. Special attention will be paid to the behavior of radicals on carbons which also contain a homolyzable group.



Scheme 15

It is known that the behavior and reactivity of a radical is influenced both electronically and sterically by the remaining substituents attached to that carbon. This change in reactivity of radicals is evident in a series of cyclizations carried out by Sato et al.[23] (Scheme 16).



R	cyclized	reduced	
SMe	--	--	
SPh	--	--	
Cl	85	11	
Me	74	12	
Ph	94	--	
OMe	63	--	21[a]
OAc	95[b]	--	
H	12	65	
SO_2Ph	--	34	29[a]

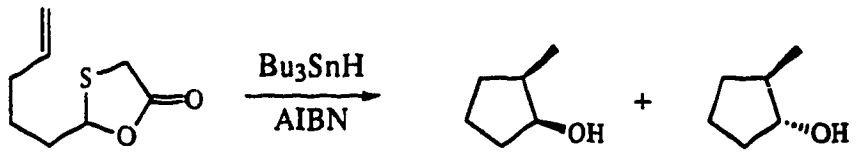
a) recovered starting material

b) including 28% hydrolized mateial

Scheme 16

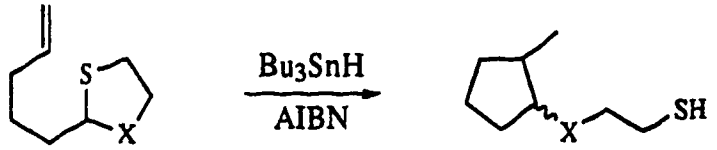
Radicals substituted with SMe, SPh, Cl, Me, Ph, OMe, or OAc undergo cyclization preferentially or exclusively, as opposed to reduction. When R is hydrogen the reduced product predominates (12% cyclization), whereas substitution with the electron withdrawing group SO_2Ph completely suppressed cyclization.

Fallis[24] has shown that cyclizations of 5-hexenyl derivatives substituted with sulfur and oxygen undergo efficient closure. It is interesting to note that the stereoselectivity (cis-trans ratio) depends on the substitution at the radical center (Scheme 17).



3 : 2

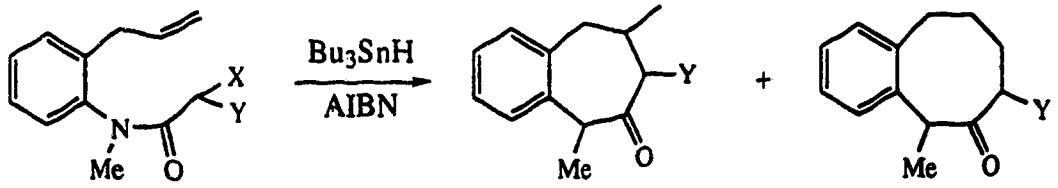
74% after hydrolysis



X		cis	:	trans
S	60%	2	:	1
O	60%	0	:	100

Scheme 17

The regiochemistry of radical cyclization can also be influenced by the substitution at the radical center,[25] as shown in Scheme 18.



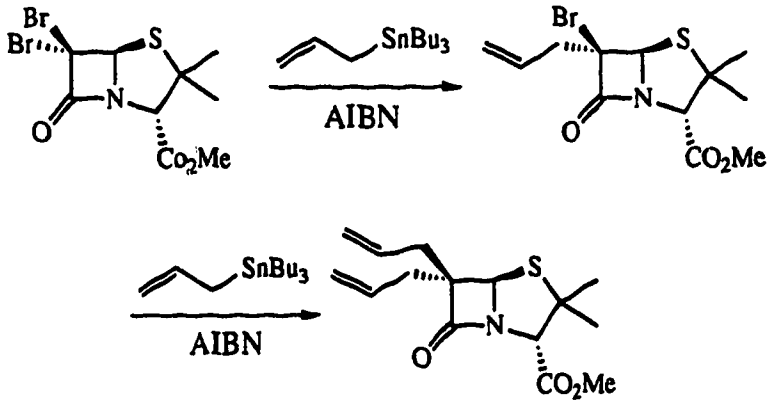
X	Y	7-exo	8-endo
Cl	Cl	49	--
SPh	SPh	--	47[a]
Cl	H	38	44
Cl	Me	58	36
Cl	Ph	23	63

a) 9% reduced material (i.e. no cyclization) was also isolated

Scheme 18

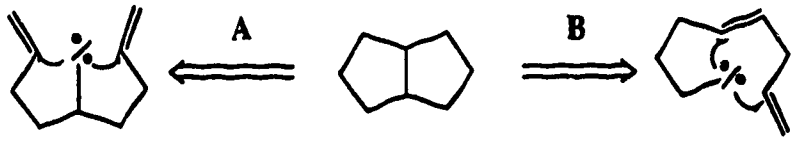
By changing the substituent Y the ratio of 7-*exo* to 8-*endo* cyclization could be altered. When Y was a chlorine atom, 7-*exo* closure was predominant, while 8-*endo* closure was the exclusive reaction path when Y was a phenylthio group.

Hanessian[26] has shown that radicals on carbons bearing a homolyzable atom or group are also capable of undergoing intermolecular additions (Scheme 19). Reaction with allyltins can lead either to the mono- or diaddition product, depending on the stoicheometry used. Addition is always from the less hindered *exo*-face of the penicillin molecule.

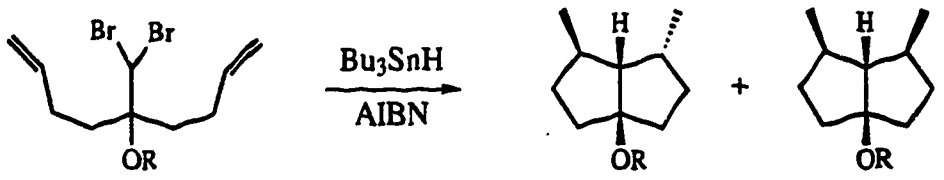


Scheme 19

The only example of intramolecular double-radical cyclization based on a bifurcating pathway was published by Wilcox[27] during the course of this work. He described two possible methods for construction of bicyclo[3.3.0]octanes from acyclic substrates (Scheme 20).

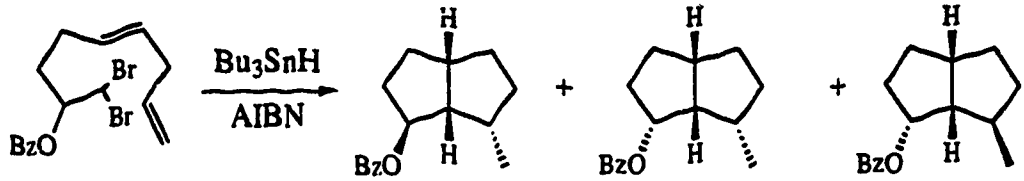


Scheme 20



R				
H	45%	84	:	16[a]
MOM	64%	80	:	20[a]

a) Ratio determined by capillary GC analysis.



75% 45 : 20 : 35

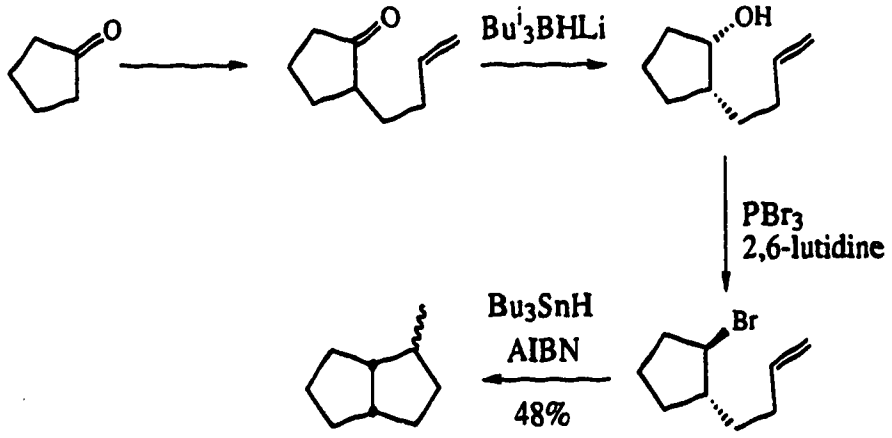
Scheme 21

The radical precursors were generated by reaction of dibromomethyllithium with the appropriate ketone or aldehyde, and subsequent protection of the hydroxy group. Treatment with two equivalents of tin reagent resulted in sequential generation of two radicals at the same carbon, and each radical cyclized in a 5-*exo* fashion, to provide the bicyclic products.

STRATEGIES FOR PREPARATION OF RADICAL PRECURSORS

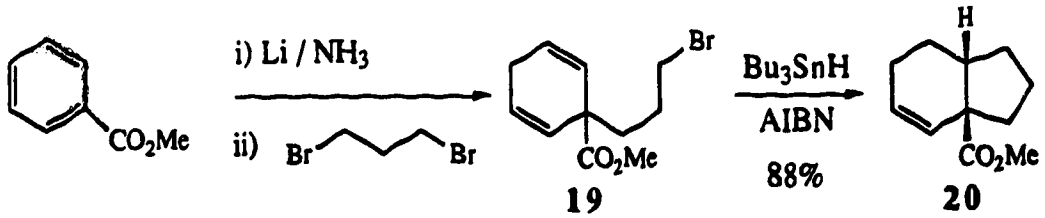
The synthetic utility of radical cyclization depends on the efficient construction of radical precursors. In this section of the review radical cyclizations will be grouped according to some common feature used in the construction of the radical precursor.

First, radical precursors which are generated by alkylation of carbonyl compounds will be discussed. Alkylation with butenyl or butynyl units, followed by generation of a radical at the carbonyl carbon, and 5-*exo* closure, is a convenient method for annulation of five membered rings[28] (Scheme 22).



Scheme 22

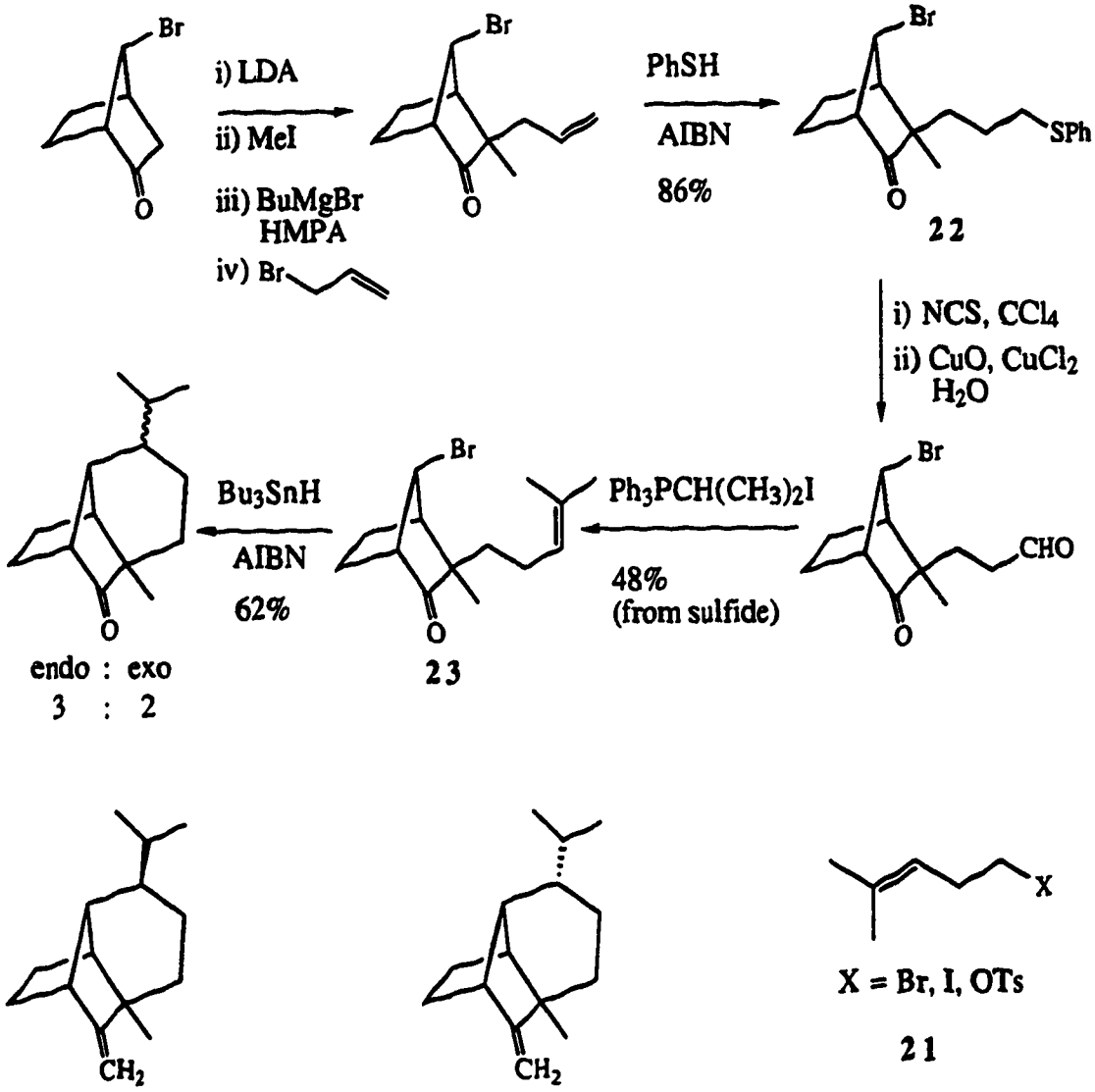
Beckwith[29] alkylated the anion produced by Birch reduction of methyl benzoate with 1,3 dibromopropane (Scheme 23).



Scheme 23

This reaction gave compound **19** which, on treatment with tributyltin hydride, produced the cis fused hydrindane **20**.

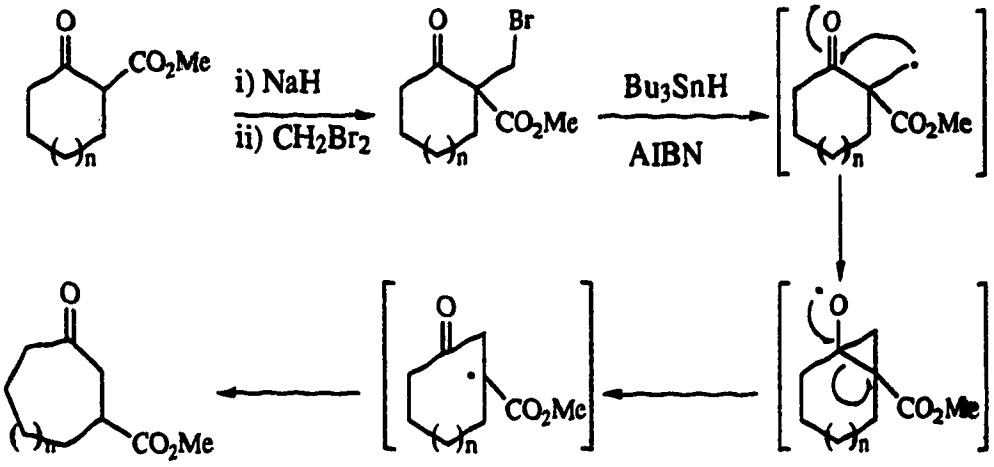
In the total synthesis of the tricyclic sesquiterpenes, sativene and copacamphene[30] (Scheme 24), ketone alkylation was also used to prepare the precursor.



Scheme 24

Syn-7-bromonorbornanone was alkylated under conditions developed by House.[31] Unfortunately alkylation with **21** (Scheme 24) failed, and so a longer route involving alkylation with allyl bromide, conversion to the sulfide **22**, oxidation and Wittig reaction, were necessary to produce the radical precursor **23**. Radical cyclization provided the tricyclic ketone as a diastereomeric mixture with the isopropyl group disposed either *exo* or *endo*. The isomers were separated and converted into the racemic forms of the natural materials.

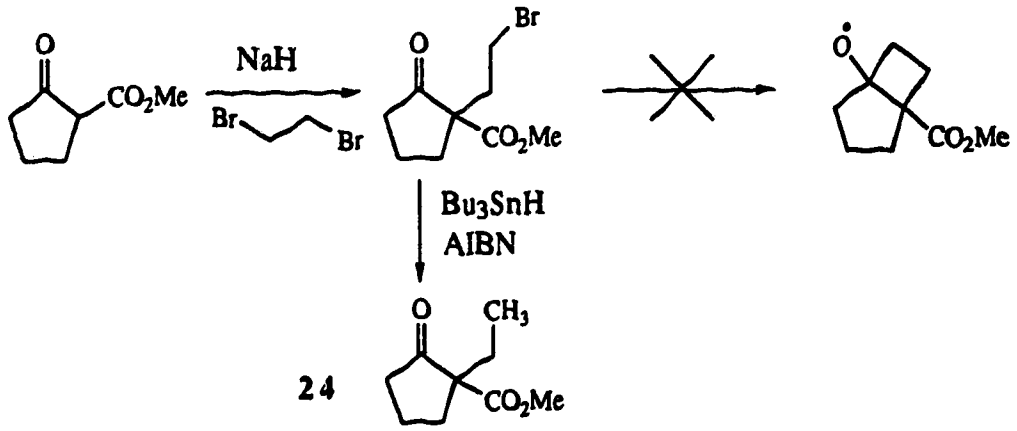
Dowd[32] has shown that cyclic β-ketoesters can be expanded by one, three or four carbons. The β-ketoesters were first alkylated to produce the corresponding bromomethyl, bromopropyl or bromobutyl derivatives; then radical cyclization onto the carbonyl followed by fragmentation, produced the ring expanded products. Scheme 25 shows the mechanism of a one-carbon expansion. The three- and four-carbon reactions are expected to follow analogous paths.



Scheme 25

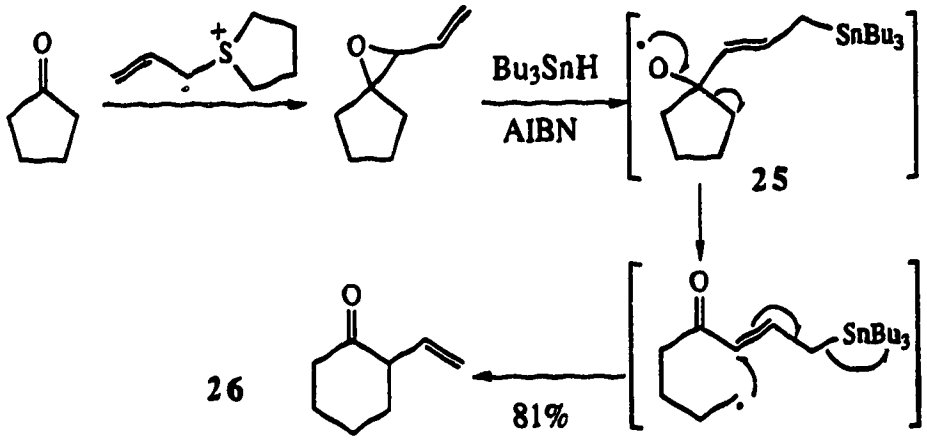
When a two-carbon bromoethyl unit was attached, ring expansion would require formation of a four membered ring oxy radical, a process

which would not be expected to compete with reduction. In fact the only product isolated was the reduction product 24[33] (Scheme 26).



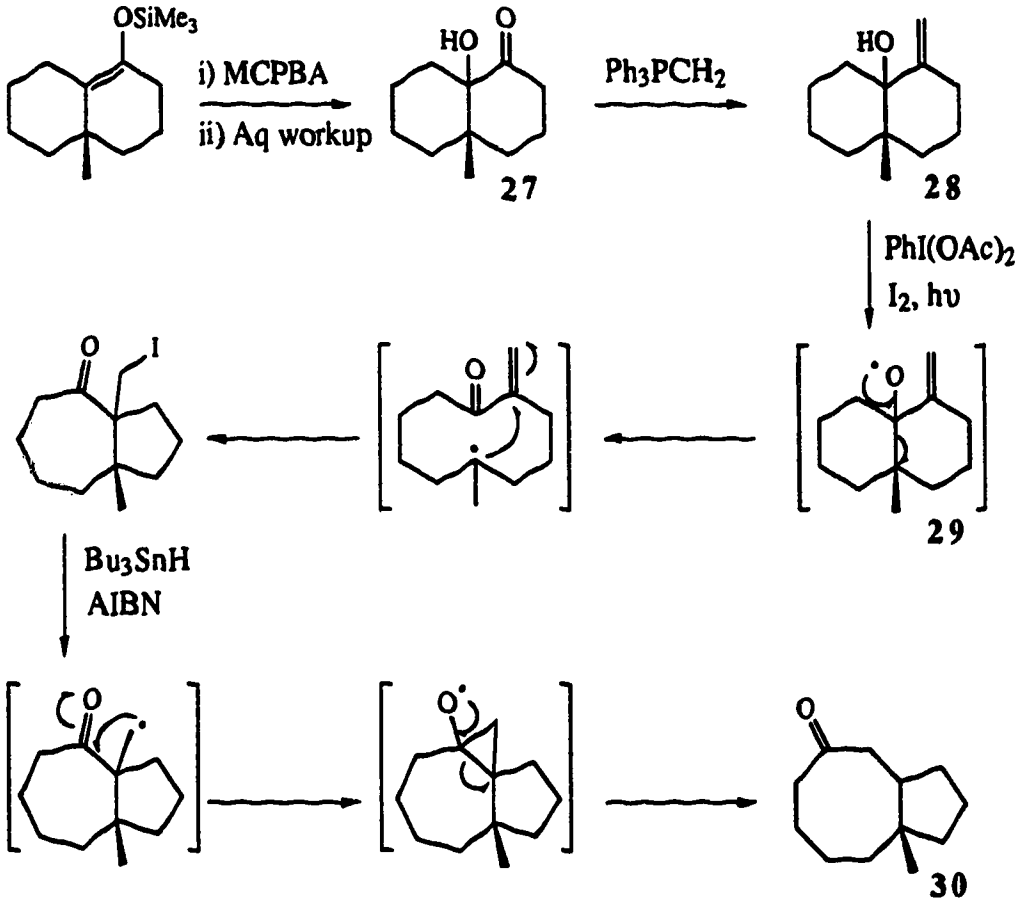
Scheme 26

Kim[34] has described a conceptually new ring expansion which proceeds via a radical chain process. Vinyl epoxides were prepared by reaction of cycloalkanones with allyl sulfurylides (Scheme 27). Addition of tributyltin radical to the vinyl epoxide, followed by epoxide fragmentation, yielded the alkoxy radical **25**. β-Cleavage then produced a primary carbon radical which cyclized in a 6-*exo* fashion, to produce a one-carbon expanded β-enone **26**.



Scheme 27

Ring expanded compounds have also been produced by Pattenden[35] (Scheme 28). Oxidation followed by in situ cleavage of the intermediate epoxy silyl ether led to the hydroxy ketone 27. Wittig reaction then afforded the α-methylene substituted decanol. Irradiation in the presence of iodosylbenzene diacetate and iodine generated the oxy radical 29, which rearranged to give the corresponding iodomethyl hydroazulenone.

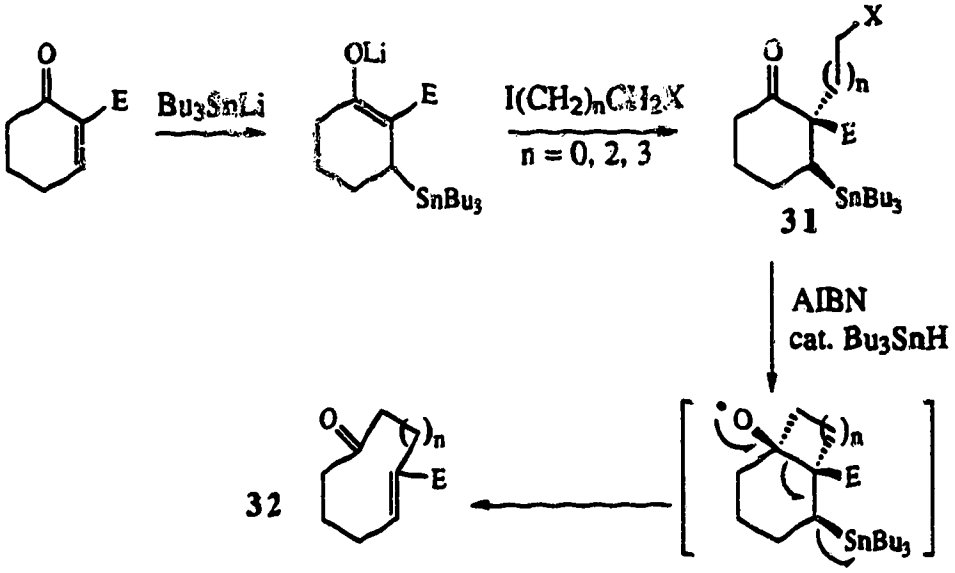


Scheme 28

Subsequent treatment with tributyltin hydride under high dilution conditions, led to the bicyclo[6.3.0]undecane 30.

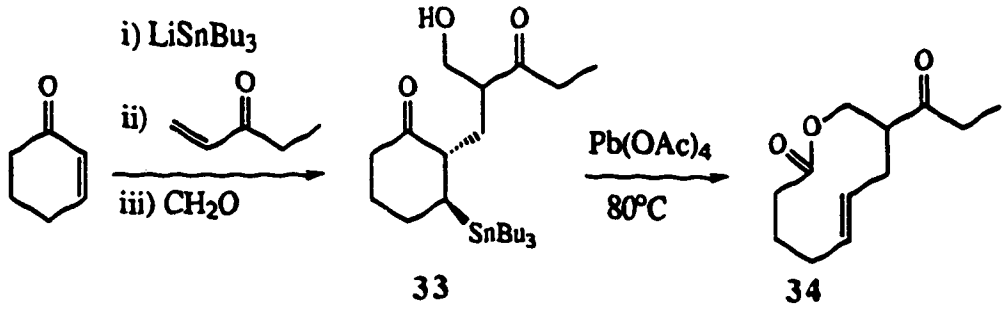
Michael addition to enones has also been used to set up the necessary framework for radical cyclizations. 1,4-Addition of tributyltin anion, followed

by trapping of the resulting anion using dihaloalkanes, produced radical precursors of the type 31[36] (Scheme 29). Treatment with tributyltin hydride provided the ring expanded product 32. If the carbonyl α-carbon bears a hydrogen, (i.e. Scheme 29, E = hydrogen) then intramolecular abstraction of that hydrogen and reduction becomes competitive with cyclization for the case of n = 3.



Scheme 29

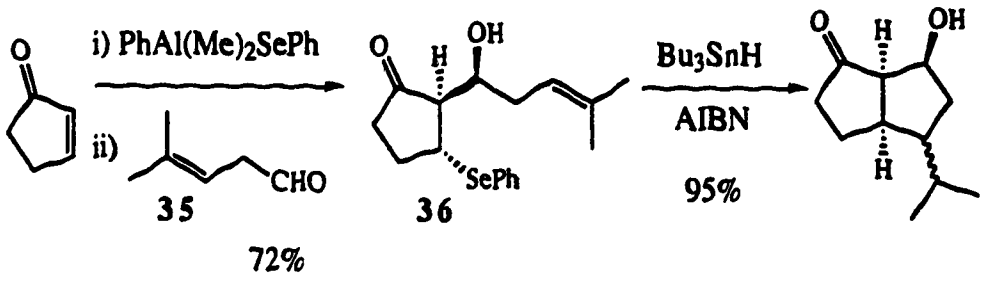
Posner[37] has used a similar strategy to generate 9-, 10- and 11-membered macrolides, as shown in Scheme 30. The anion produced by Michael addition of the tin anion was trapped by an enone, to produce a second enolate, which was then trapped by formaldehyde, thus forming the diketo alcohol 33. Treatment with lead acetate generated an oxy radical which closed onto the ketone. Fragmentation of the resulting bicyclic intermediates and loss of tributyltin radical then provided the macrolide 34.



33 34

Scheme 30

Enones were also used by Livinghouse[38] to annulate a five membered ring (Scheme 31). Michael addition of phenylselenide to the enone, followed by trapping, using aldehyde 35, furnished the radical precursor 36, with a suitably located radical acceptor. Treatment with tributyltin hydride formed the corresponding bicyclic hydroxy ketone.

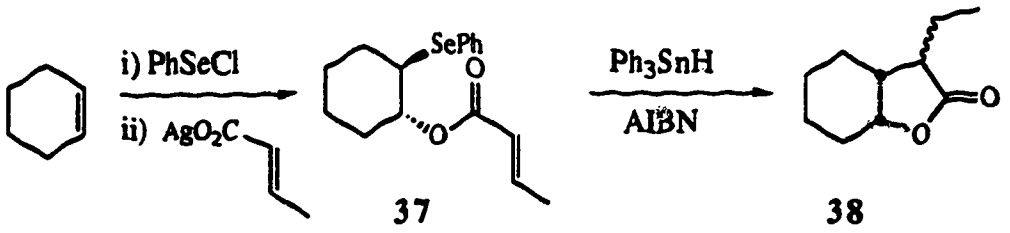


35 36

72%

Scheme 31

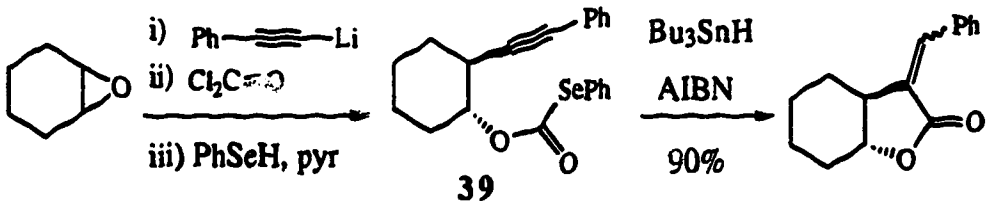
Unconjugated double bonds have been used as starting points for generation of radical precursors. In a method developed by Clive,[39] treatment of an isolated olefin with phenylselenenyl chloride followed by silver crotonate gave the trans 2-(phenylseleno)cyclohexyl crotonate 37 (Scheme 32). Homolysis of the carbon selenium bond generated a radical which closed in a 5-*exo* fashion to give the fused lactones 38.



37 38

Scheme 32

A complementary approach has been developed by Bachi,[40] and is illustrated in Scheme 33. In this method the olefin was epoxidized and then converted to the homopropargylic selenocarbonate **39**. Radical cyclization then produced the methylene lactone with trans ring fusion.

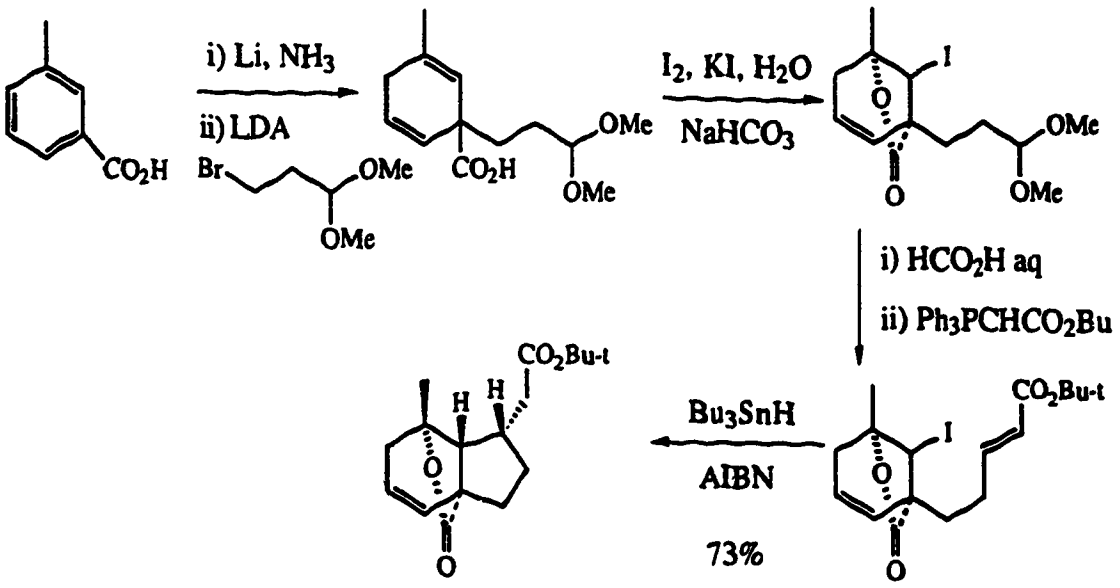


39

Scheme 33

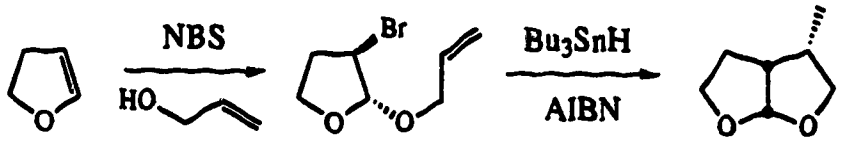
Other groups have used similar strategies to introduce radical acceptors and sources, via reaction with carbon-carbon double bonds.[41]

Hart[42] has used an iodolactonization of a double bond to install the radical source (Scheme 34). The radical acceptor was attached by alkylation of an anion formed by Birch reduction. The interesting feature about this example is that the radical cyclization proceeded to give the trans perhydroindane ring junction, due to the preference of the oxabicyclo[3.3.0]octane substructure for a cis geometry.



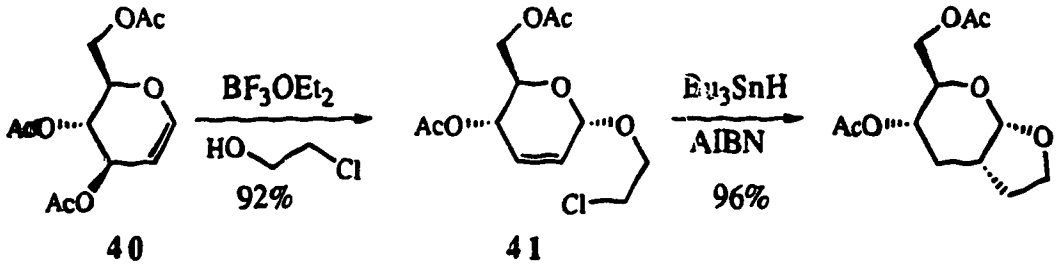
Scheme 34

Vinyl ethers[43] can also serve as starting points for making radical precursors. Treatment with electrophilic reagents such as *N*-halosuccinimides, followed by an alcohol containing a radical acceptor, results in formation of unsaturated α-halogeno acetals (Scheme 35). Radical cyclization then gives a bicyclic acetal.[44]



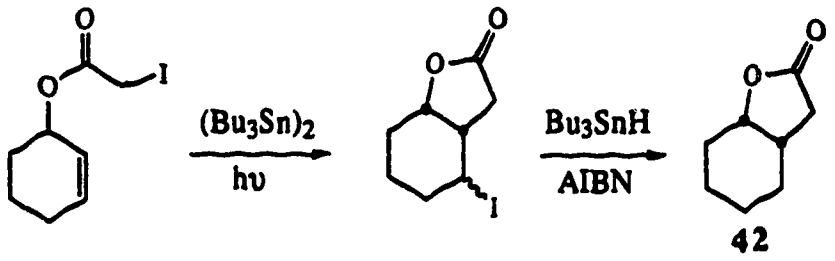
Scheme 35

Another efficient route to bicyclic acetals is via Ferrier reaction[45] - radical cyclization.[46] Treatment of the glucal 40 with chloroethanol in the presence of boron trifluoride diethyl ether provided the 2-chloroethyl glycoside 41, with a high degree of stereoselectivity. Radical cyclization then lead to the bicyclic acetal shown (Scheme 36).



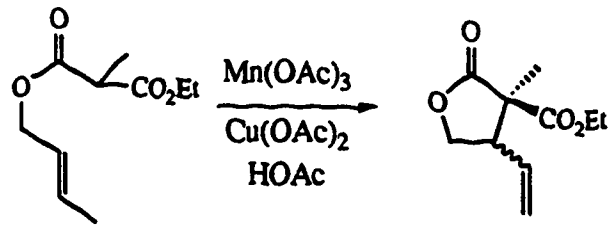
Scheme 36

There is a vast number of syntheses of lactones by radical cyclization, and for the purposes of this review they can be divided into two main groups. The first strategy involves generation of an α-ester radical, and closure onto a radical acceptor.[47] An example from Curran's group is illustrative[48] (Scheme 37). The ester was produced by reaction of the allylic alcohol with iodoacetyl chloride. Atom transfer radical cyclization, followed by reduction with tributyltin hydride gave the bicyclic lactone 42. The slow closure of these α-halo allyl esters prohibits the use of a tin hydride as the radical mediator, since only reduced materials are then isolated.[48]



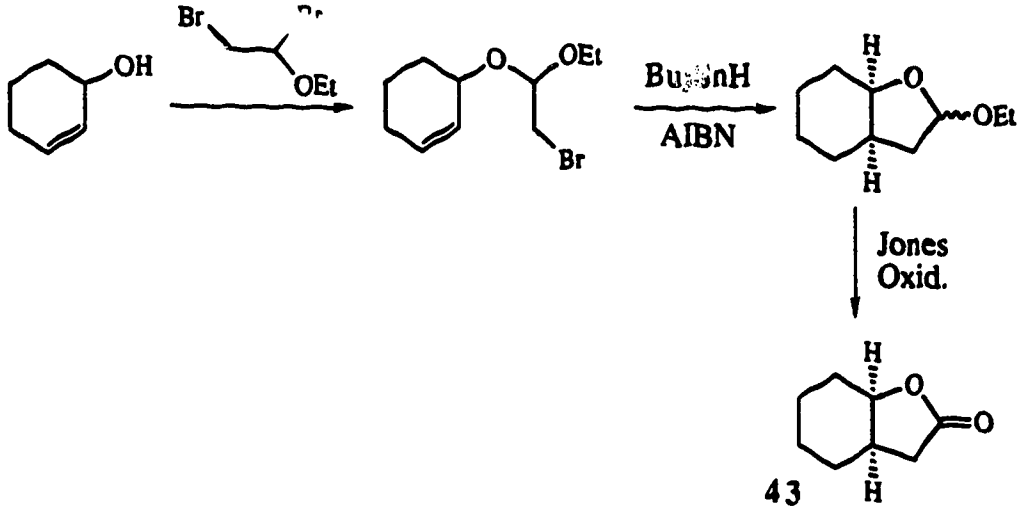
Scheme 37

Bertrand[49] reported the oxidative cyclization of unsaturated β-diesters to produce lactones, as shown in Scheme 38. The mechanism of this type of reaction has been studied by Fristad[50] and Snider.[51]



Scheme 38

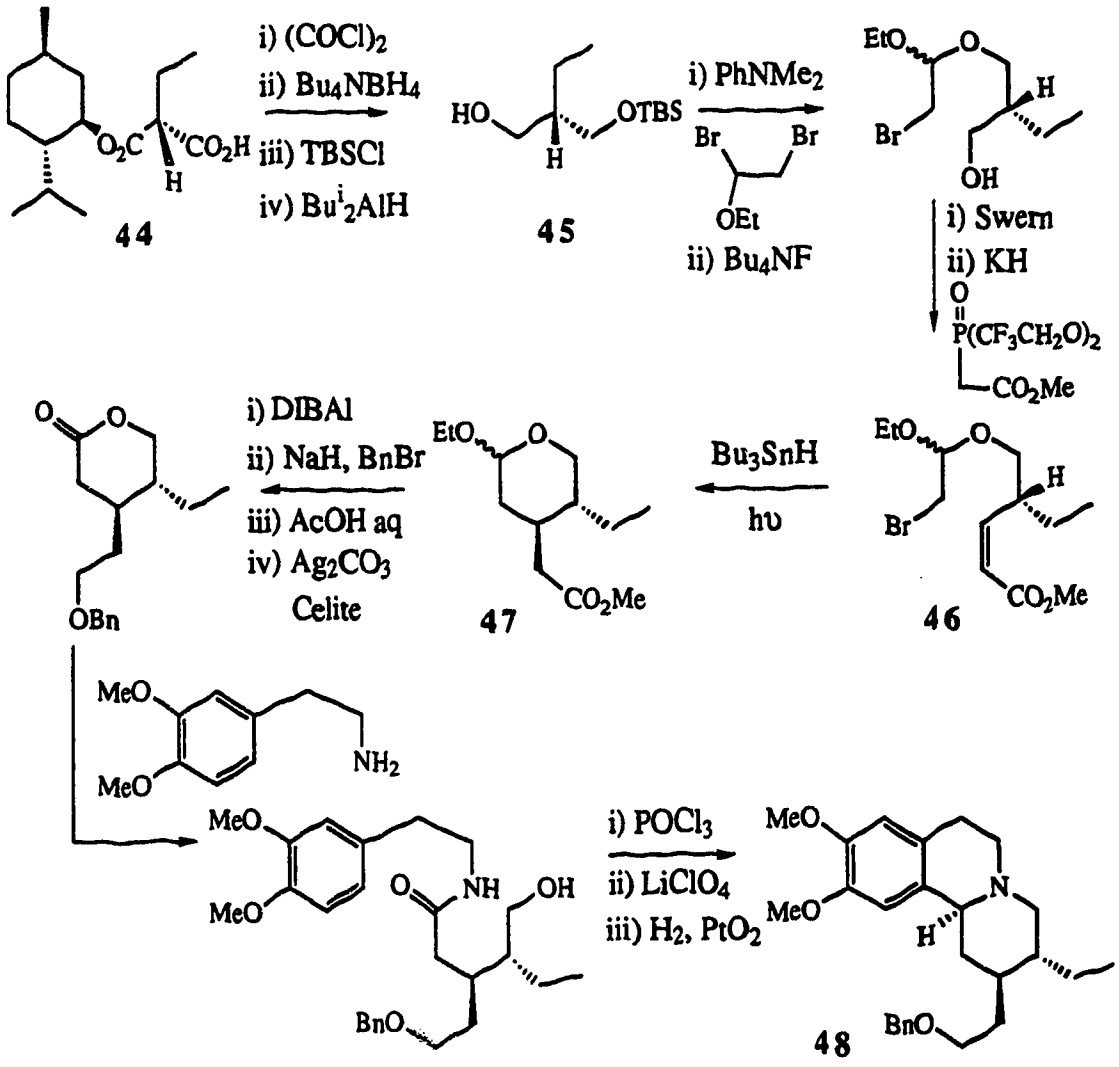
The second general strategy for lactone synthesis was developed independently by Stork[52] and Ueno.[53] It involves tributyltin hydride mediated radical cyclization of unsaturated halo acetals, followed by Jones oxidation to the lactone. In the example from Stork's group, described in Scheme 39, 2-cyclohexenol was converted to the mixed acetal. Subsequent treatment with tributyltin hydride gave the bicyclic lactol as a mixture of isomers, which was converted to the lactone **43** by Jones oxidation.



Scheme 39

This strategy is the most common for lactone synthesis, and has been used by a number of groups.[54] Of note is a total synthesis of protoenentinol **48**, which used a **6-*exo*** radical cyclization of a bromoacetal to set the stereochemistry[55] (Scheme 40). The monoprotected diol **45**, derived from the

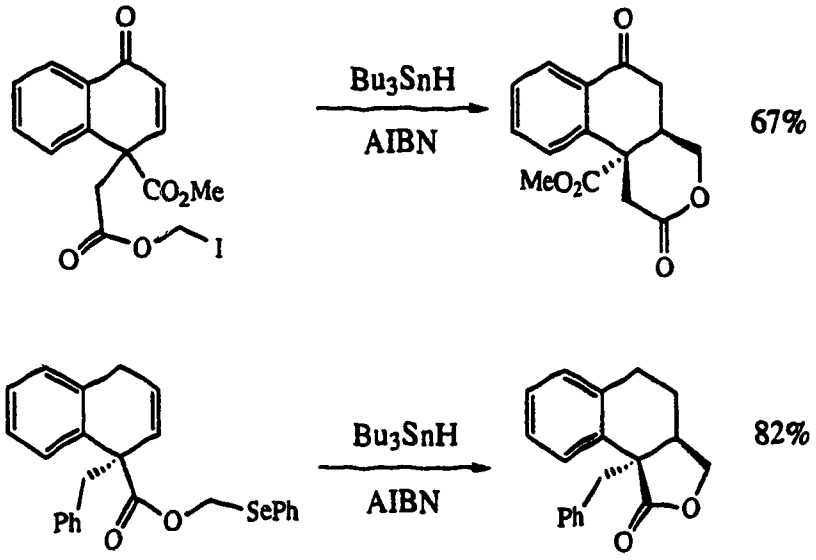
half ester **44**, was converted into the bromoacetal. Following removal of the silyl protecting group, the alcohol was elaborated into the unsaturated ester **46**. 6-*Exo* radical closure then proceeded to give compounds **47**, with the pendants trans to each other. Jones oxidation gave the lactone, and this in turn was converted into the natural product.



Scheme 40

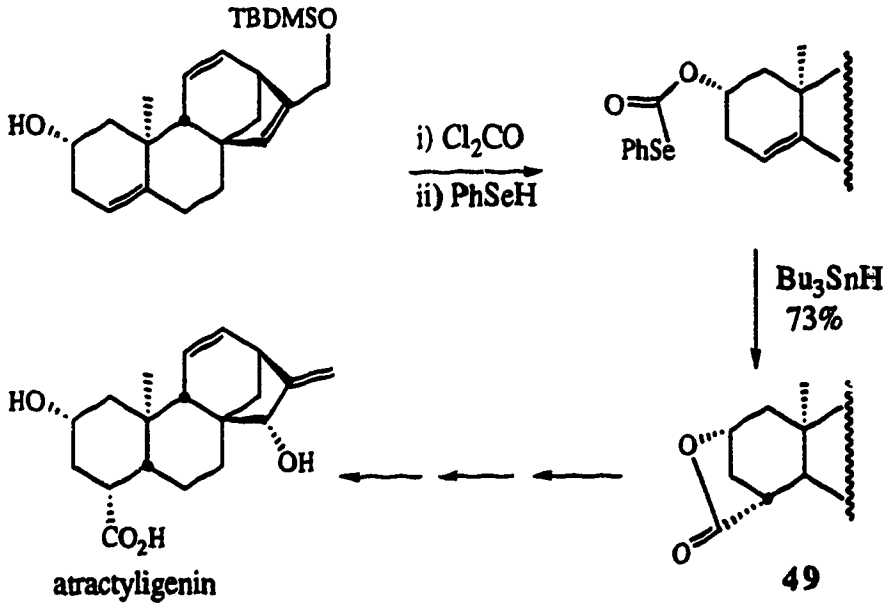
Beckwith[56] used a completely different approach to synthesize lactones, as shown in Scheme 41. Unsaturated acids were converted into esters

containing a homolyzable group. Subsequent treatment with tributyltin hydride then produced γ- and δ-lactones.



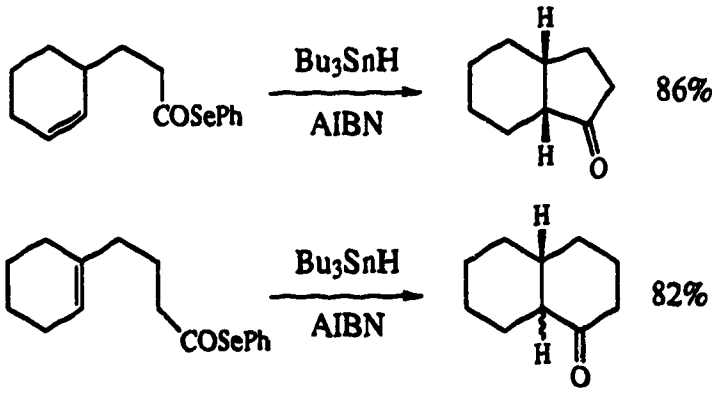
Scheme 41

In Corey's total synthesis of atractyligenin[57] (Scheme 42) lactone **49** was formed by radical cyclization of an acyl radical, generated from the corresponding selenocarbonate. The alcohol was converted into the selenocarbonate by sequential reaction with phosgene and benzeneselenol. Treatment with tributylin hydride produced the acyl radical which closed in a 5-*exo* fashion, to give a single diastereomer, setting the necessary stereochemistry for the natural compound.



Scheme 42

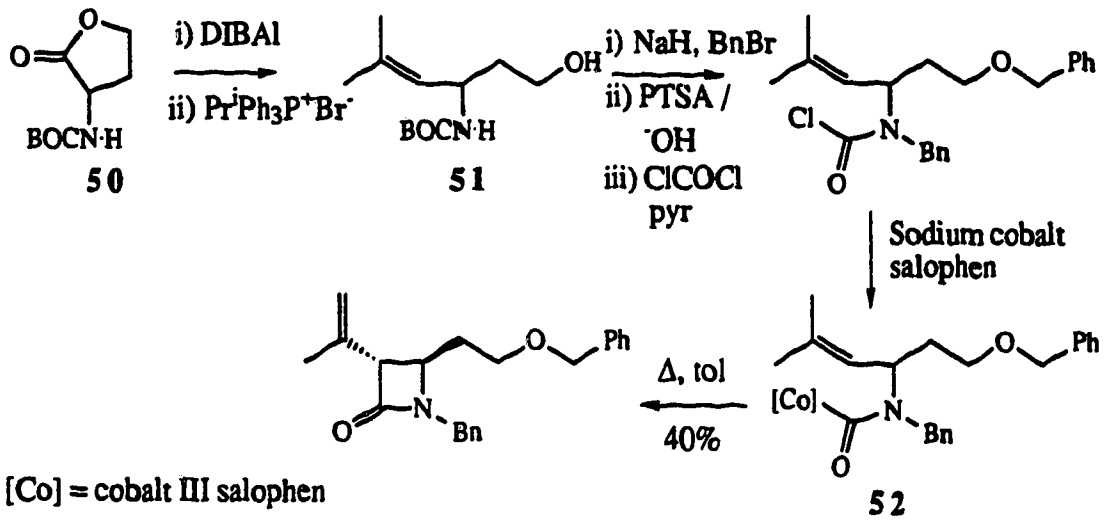
Acyl radicals have also been used by Boger to prepare five and six membered ketones[58] (Scheme 43). The seleno esters, readily available from the corresponding acids, undergo cyclization at rates competitive with intermolecular reduction and decarbonylation.



Scheme 43

Radical cyclization reactions are useful for the synthesis of amides and amines. 4-*Exo* closure of carbamoyl radicals was used by Pattenden[59] in his synthesis of the β-lactam portion of penicillin (Scheme 44). Reduction of

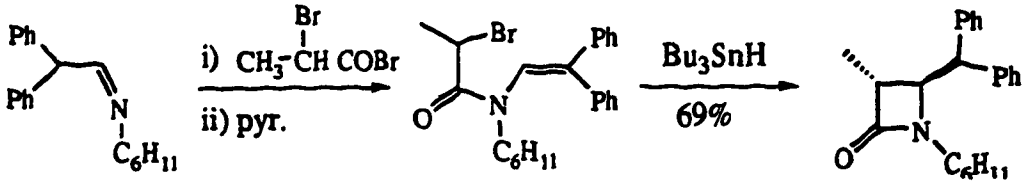
lactone **50** to the corresponding lactol, followed by Wittig reaction provided **51**, which was protected as the bisbenzyl derivative. Deprotection of the amine and reaction with phosgene gave the carbamoyl chloride, which was converted to the carbamoylcobalt salophen **52**. On heating, homolytic cleavage of the carbon-cobalt bond gave the carbamoyl radical and this underwent 4-*exo* closure. Finally dehydrocobaltation generated the propenyl side chain.



Scheme 44

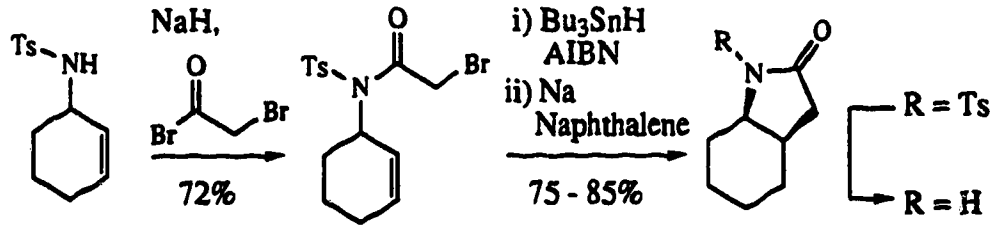
A more common method for construction of amides, which is analogous to the previously discussed synthesis of lactones,[47] is the condensation of an amine containing a suitably located unsaturation, with an α-halo acid halide, followed by radical cyclization. In this way 4-, 5-, 6-, 7- and 8-membered lactams have been produced.

In Scheme 45, the imine was treated with the α-bromo acid bromide in the presence of pyridine, to produce the radical precursor.[60] Treatment with tributyltin hydride resulted in efficient β-lactam formation.



Scheme 45

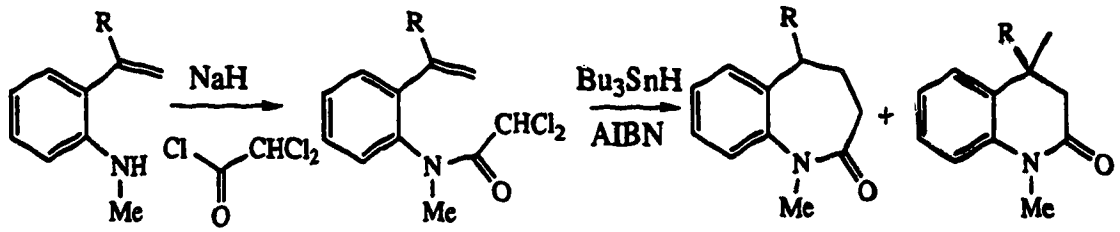
Synthesis of 5-membered lactams is a more common operation. The example below is illustrative.[61] Treatment of the allyl amine with bromoacetyl bromide afforded the α-bromo acetamide. Radical cyclization, followed by tosyl group removal, then gave the deprotected lactam. The corresponding iodoacetamides gave similar results, while chlorides failed to react completely.



Scheme 46

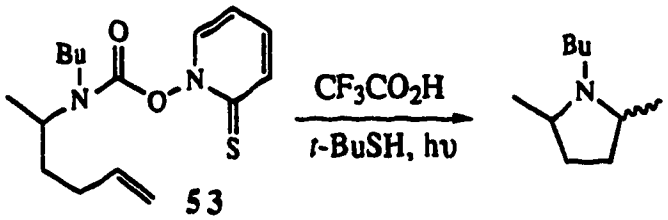
Ikeda[62] studied the regiochemistry of 6-*exo* versus 7-*endo* and of 7-*exo* versus 8-*endo* cyclizations, with *N*-(*o*-alkenylphenyl)acetamides containing homolyzable groups (Cl or SPh) α to the carbonyl. The radical precursors were prepared by reaction of amines with the appropriately substituted acid chloride (Scheme 47). Radical cyclization of *N*-[*o*-(alk-1-enyl)phenyl]-2,2-dichloroacetamides gave quinolin-2(1H)-one (6-*exo* closure) and/or 2H-1-benzazepin-2-one (7-*endo* closure), with 6-*exo* cyclization being favored, unless a large group was present in the 1-position of the alkene (Scheme 47,

entry b). *N*-[*o*-(Prop-2-enyl)phenyl]acetamide derivatives gave mixtures of 7-*exo* and 8-*endo* cyclization products.

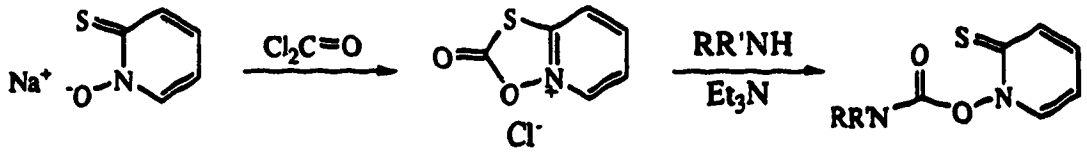


Scheme 47

Cyclization of 1-, 2-, 3- and 4-aza-5-hexenyl radicals has been used for the formation of pyrrolidines. Newcomb[63] (Scheme 48) and others[64] have studied the cyclization of 1-aza-5-hexenyl radicals. The aminyl radical, produced by irradiation of the *N*-hydroxypyridine-2-thione carbamate **53**, cyclized in a 5-*exo* fashion to give a carbon radical, which was reduced by hydrogen abstraction from *t*-butyl thiol. The radical precursors are easily prepared[65] as shown in Scheme 49.

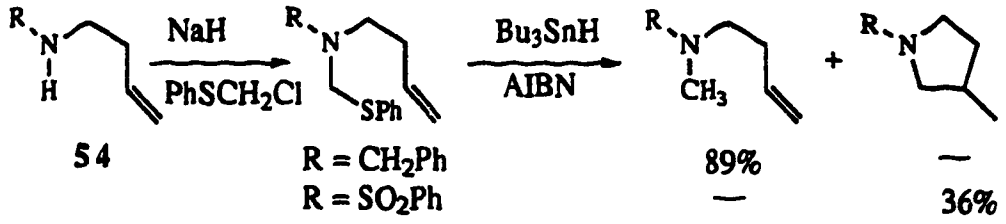


Scheme 48



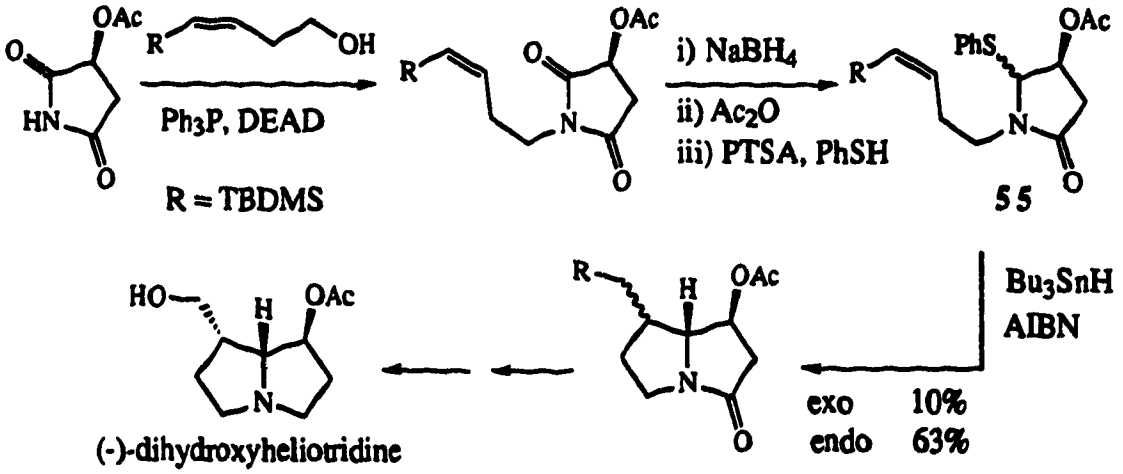
Scheme 49

Synthesis of pyrrolidines by radical cyclization of 2-aza-5-hexenyl radicals has been studied by Padwa[66] (Scheme 50). The radical precursors were easily prepared from the secondary amine **54** and chloromethyl phenyl sulfide. It was necessary to place an electron withdrawing group (e.g. SO_2Ph) on the nitrogen, in order to inhibit resonance stabilization of the radical center; such stabilization would retard cyclization.



Scheme 50

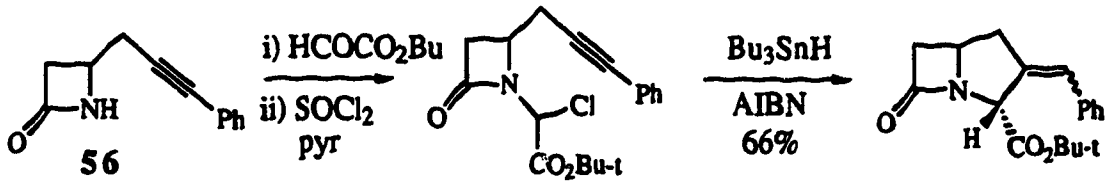
N-Butenyl succinimide derivatives have also been used to annulate pyrrolidine rings.[67] Scheme 51 shows Hart's synthesis[68] of the pyrrolizidine alkaloid, dihydroxyheliotridine. The *N*-substituted succinimide, prepared under Mitsunobu conditions, was transformed into **55** using standard reactions.



Scheme 51

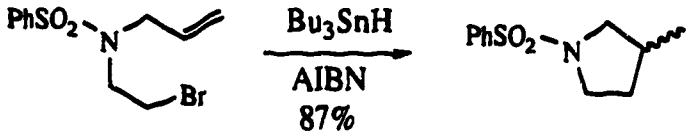
Radical cyclization proceeded smoothly, since the nitrogen is part of an amide, and the radical is not appreciably stabilized by the nitrogen. The diastereomers were separated by column chromatography and the major product, the *endo* isomer, was converted into the natural compound.

Bachi[69] has also used 2-azahexenyl radicals to annulate pyrrolidine rings onto β-lactams (Scheme 52). The *N*-unsubstituted β-lactam **56** was converted into the radical precursor by reaction with *t*-butyl glyoxalate. Radical cyclization produced a mixture of *t*-butyl 2-benzylidene-1-carbapenam-3-carboxylates, along with a small amount (10%) of reduced (non-cyclized) material.



Scheme 52

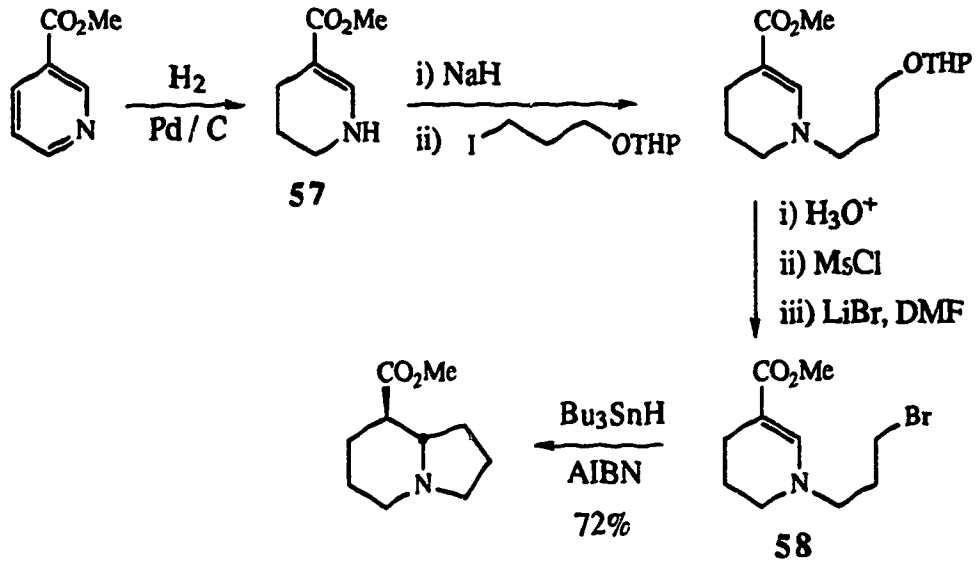
3-Aza-5-hexenyl radicals are not stabilized by the nitrogen, an effect which prevents cyclization of 2-aza-5-hexenyl radicals, and a number of groups[70] have reported pyrrolidine ring annulation using 3-aza-5-hexenyl radicals. The example below (Scheme 53) is from Padwa's group.[71]



Scheme 53

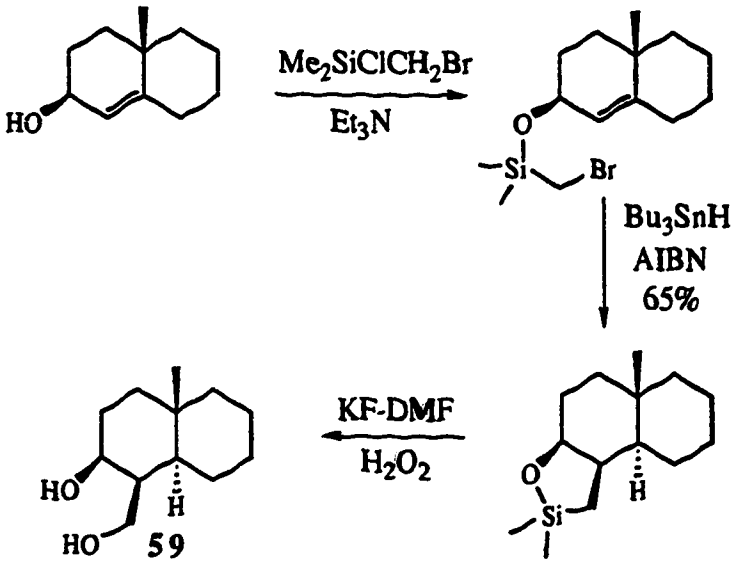
Finally, Beckwith[72] has described the use of 4-aza-5-hexenyl radicals for the preparation of pyrrolidine units (Scheme 54). Hydrogenation of methyl

nicotinate gave the tetrahydropyridine **57**. Alkylation with a primary alkyl iodide, and subsequent functional group manipulation, furnished the bromide **58**. Radical cyclization proceeded to give the 5-*exo* product.



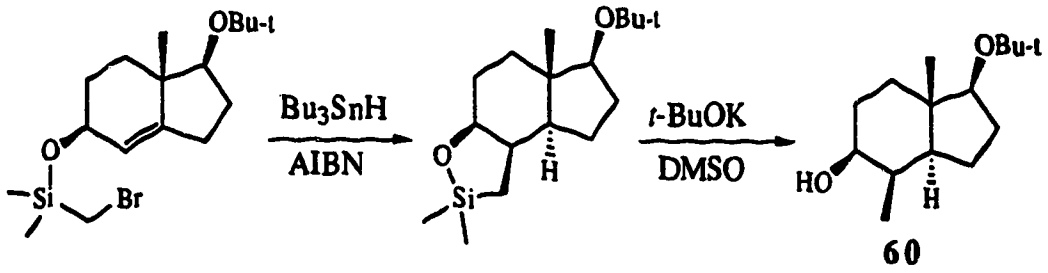
Scheme 54

In 1985 Stork[73] introduced the use of silylethers as tethers in intramolecular radical cyclizations (Scheme 55). The allyl alcohol was easily converted to the α-bromo silyl ether. Radical cyclization proceeded in a 5-*exo* fashion, to give a single cis fused cyclic siloxane. The silicon was then oxidatively removed to give the cis 1,3-diol **59**.



Scheme 55

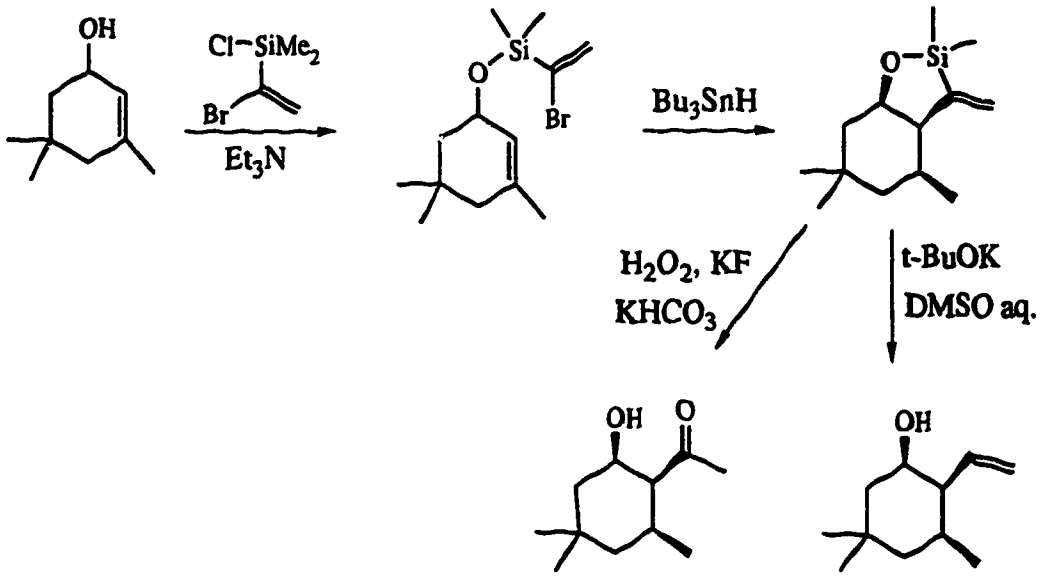
Alternatively, treatment of the cyclic siloxane with potassium *t*-butoxide in dimethyl sulfoxide produced the cis α-methyl alcohol **60**, in 60% yield from the silyl ether.[74] Thus the process can be used to introduce a hydroxy methyl or a methyl group regiospecifically next to the hydroxyl group, and stereospecifically cis to it.



Scheme 56

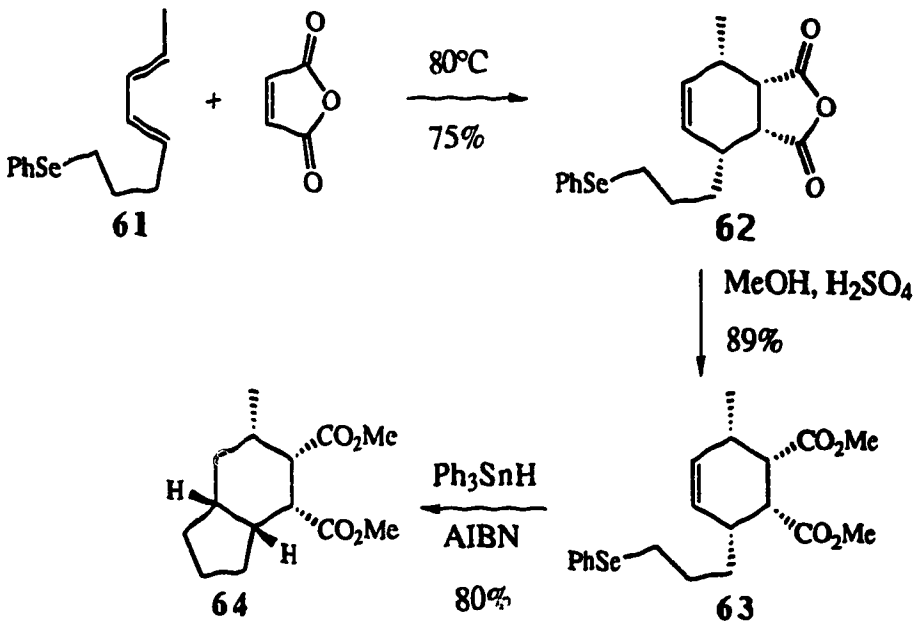
This technology has since been used in a number of other laboratories.[75] Tamao[76] has shown that, if the allyl alcohol is silylated with 1-(bromovinyl)dimethylsilyl chloride, then, after radical cyclization, the vinyl silane can be converted into an acyl or vinyl group (Scheme 57). Thus, the

overall process is a regio- and stereoselective hydroacylation or hydrovinylation of an allylic alcohol.



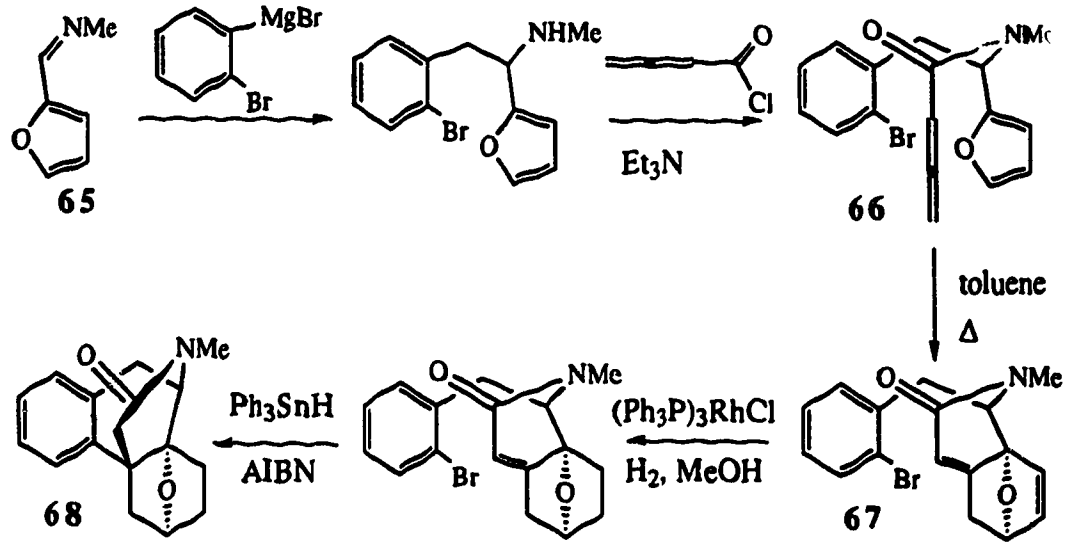
Scheme 57

The Diels-Alder reaction is a useful method for the preparation of radical precursors. Clive[77] used dienes and dienophiles containing a radical source (e.g. **61**, Scheme 58). The Diels-Alder product **62** was too rigid, and radical cyclization was not efficient. However, when the anhydride was converted to the diester **63**, radical cyclization proceeded smoothly to provide the hydrindane **64**, in which the relative stereochemistry of five centers was established in the two step sequence.



Scheme 58

Tandem Diels-Alder--radical cyclization was also used by Harwood[78] in a concise approach to the morphinan skeleton **68** (Scheme 59).

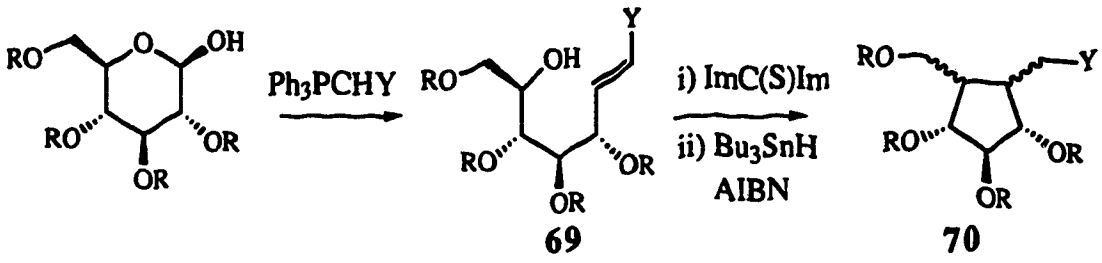


Scheme 59

o-Bromobenzylmagnesium bromide was added to *N*-methyl-2-furylimine **65**, and the resulting amine acylated with propa-2,3-dienoyl-

chloride to give **66**. Diels-Alder reaction afforded compound **67**, as a single diastereomer. Selective hydrogenation of the unwanted double bond and radical cyclization gave **68**, which has the morphinan structure.

Wittig reaction, with a variety of pyranose derivatives led to hex-5-enyl alcohols of the type **69** (Scheme 60). These serve as radical precursors to highly functionalized cyclopentane derivatives.[79] Conversion of the hydroxy group to a radical source, via, for example, the Barton procedure,[80] followed by radical cyclization onto the unsaturation, itself generated by the Wittig reaction, produced cyclopentanes of the type **70**.



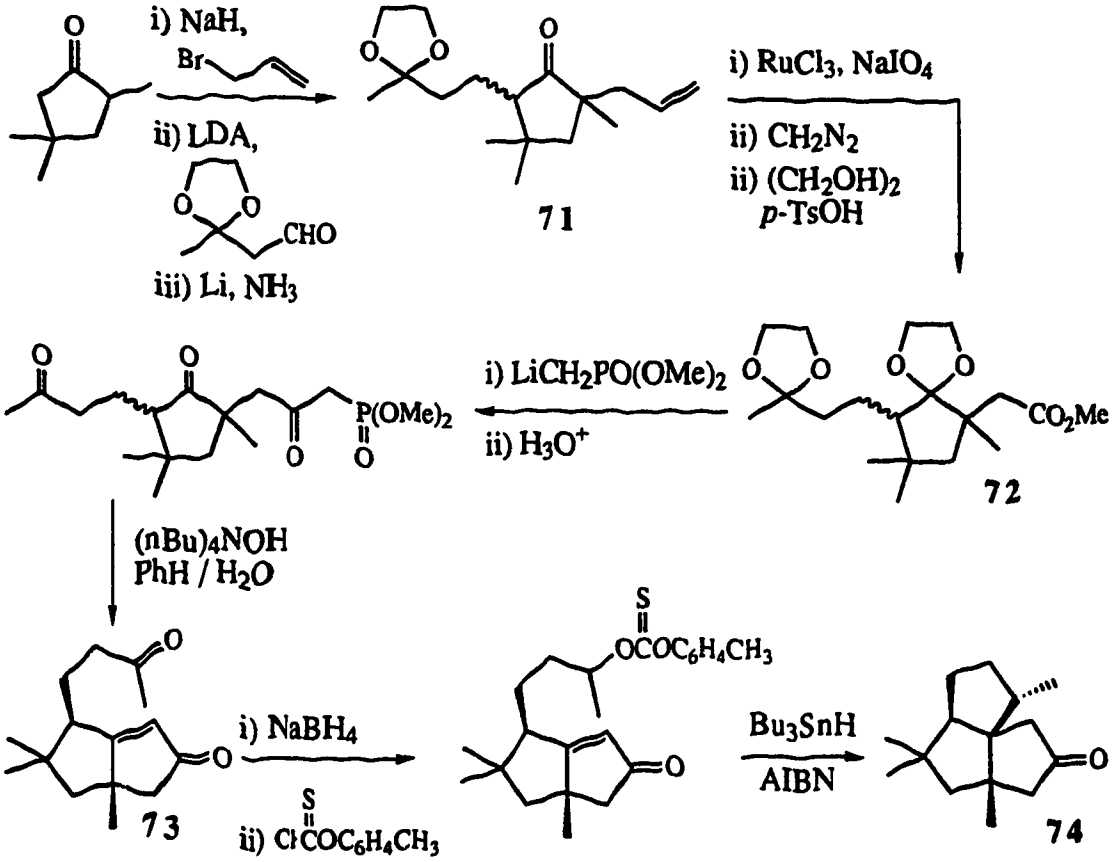
69 **70**

Scheme 60

RajanBabu has studied the stereochemical control of these reactions, and has developed a free radical route to the Corey lactone.[81]

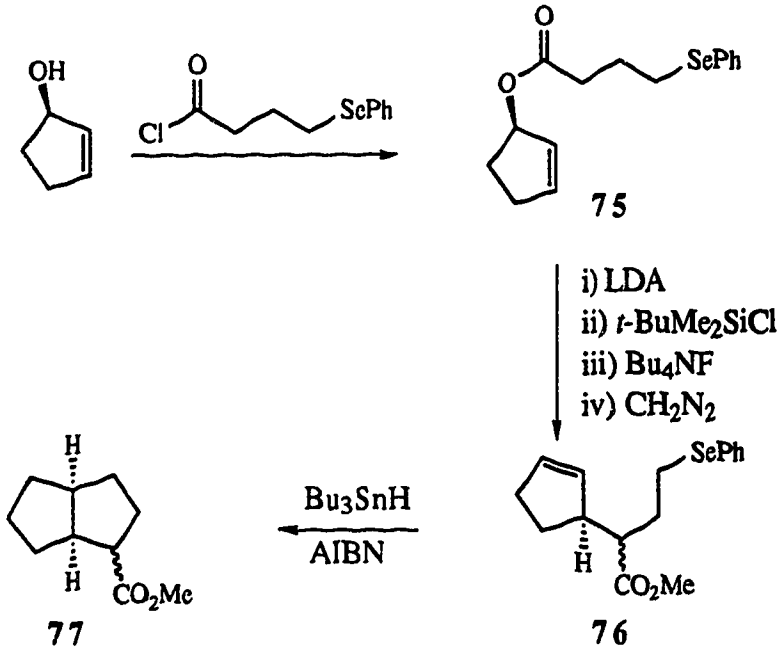
Nagarajan[82] also used a Wittig reaction to construct the olefin which would later be used as the radical acceptor in his synthesis of silphinene (Scheme 61). Ketones **71** were prepared from 2,4,4-trimethylcyclopentanone by two successive alkylations. They were then easily converted into the diketals **72**. The derived β-ketophosphonates were subjected to intramolecular Wittig-Horner conditions, to form **73**, with the correct relative stereochemistry. The saturated ketone was reduced and converted to the Barton radical precursor. Treatment with tributyltin hydride, generated a

radical which added in a stereoselective fashion to the double bond of the enone, giving the triquinane 74.



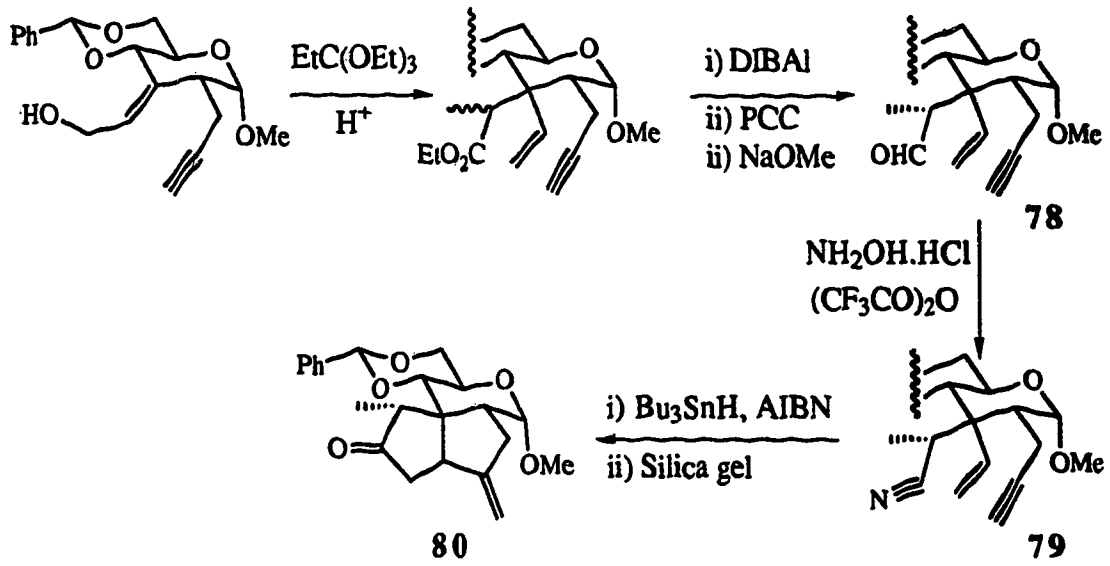
Scheme 61

The ester enolate rearrangement of an ester of type 75 (Scheme 62), was used by Clive[83] to prepare precursors for radical cyclization. Reaction of an allylic alcohol with an acid chloride containing a radical source provided the necessary ester 75. Following ester enolate rearrangement, the silyl esters were converted into the methyl esters 76. Radical cyclization then gave a mixture of bicyclic esters 77, with cis fusion.



Scheme 62

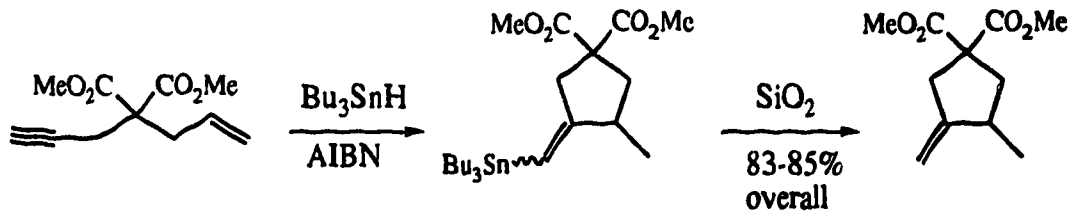
A related rearrangement has been used by Fraser-Ried[84] in his synthesis of the pyranoside diquinane **80** (Scheme 63). The allyl alcohol was converted into a mixture of esters by ester enolate rearrangement. The esters, in turn, were converted into the corresponding aldehydes by reduction and oxidation. The minor isomer of **78** could be converted into the major isomer, by treatment with sodium methoxide in methanol. The aldehyde was elaborated to the corresponding nitrile **79**.



Scheme 63

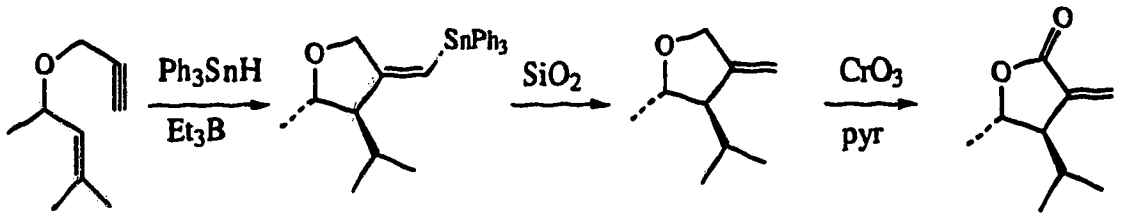
On treatment with tributyltin hydride and AIBN, the tin radical added to the terminus of the alkyne, to produce a vinyl radical. 5-*Exo* closure onto the olefin produced a second carbon radical, which underwent 5-*exo* closure onto the nitrile. Protodestannylation on silica gel afforded the methylene diquinane **80**.

The addition of tributyltin radicals to triple bonds to produce a vinyl radical, which then undergoes cyclization, has been used by a number of groups[85] to prepare methylene cyclopentanes from heptenynes, as shown in Scheme 64.



Scheme 64

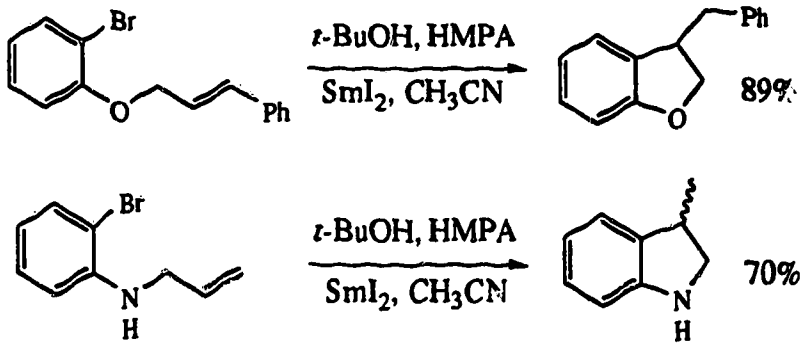
Nozaki[86] employed this strategy to prepare α-methylene butyrolactones (Scheme 65). Reaction of the 4-oxahept-1-en-6-yne **81**, with triphenyltin radical produced the vinyl radical. This then cyclized in a 5-*exo* fashion, to give a product with the pendants trans to each other. Protodestannylation gave compound **82**, which was oxidized to the butyrolactone **83**.



81 **82** **83**

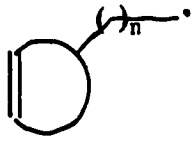
Scheme 65

Intramolecular radical cyclization of *o*-allyloxy- or *o*-allylamino-aryl radicals can lead to a variety of aryl fused heterocycles (Scheme 66). The radical precursors were easily prepared from *o*-bromophenol and allylic alcohols under Mitsunobu conditions, from *o*-bromoaniline and allylic halides in the presence of a base.[87] The carbon-bromine bonds were cleaved by a samarium diiodide promoted electron transfer process. The resulting aryl radicals closed in a 5-*exo* fashion. The second example is noteworthy for the presence of NH; this functionality is usually unacceptable in reactions done with stannanes, because the stannanes decompose in the presence of primary and secondary amines.



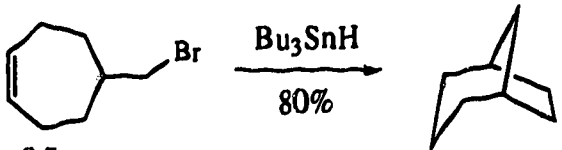
Scheme 66

Transannular additions, i.e. additions of a radical across a ring, to an unsaturation have been used to construct polycyclic systems from larger rings. Radical addition to a ring double bond as in structure **84**, requires that the molecule have enough flexibility such that the correct conformation can be adopted, and the radical can approach the radical acceptor from the required direction. Normally the chain must be at least two carbons long (**84**; n > 0) for cyclization to occur.[88]



84

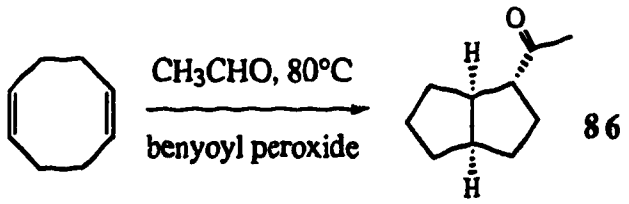
Two radicals of type **84**, cyclohept-4-enylmethyl (Scheme 67), and cyclooct-4-enylmethyl, in which the chain is only one carbon long, undergo transannular cyclization.[88]



85

Scheme 67

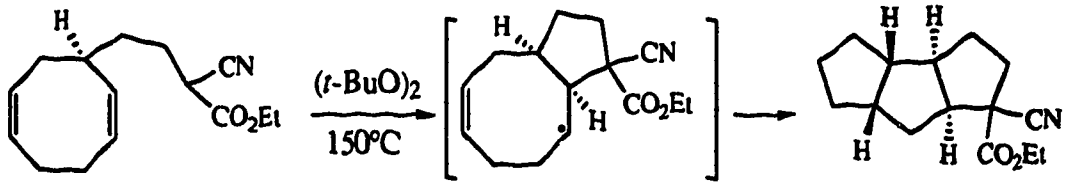
Dowbenko[89a] and Friedman[89b] independently reported that addition of exogenous radicals to 1,5-cyclooctadiene produced *exo* substituted cis fused bicyclo[3.3.0]octanes (i.e. **86**, Scheme 68).



86

Scheme 68

Winkler[90] used an intramolecular version of the above reaction to synthesize linearly fused cyclopentanoids (Scheme 69). Reaction of **87** with di-*t*-butyl peroxide in cyclohexane at 150°C led to 45% of the (cis-anti-cis) tricyclic product **88**, by a sequence of two 5-*exo* radical closures.



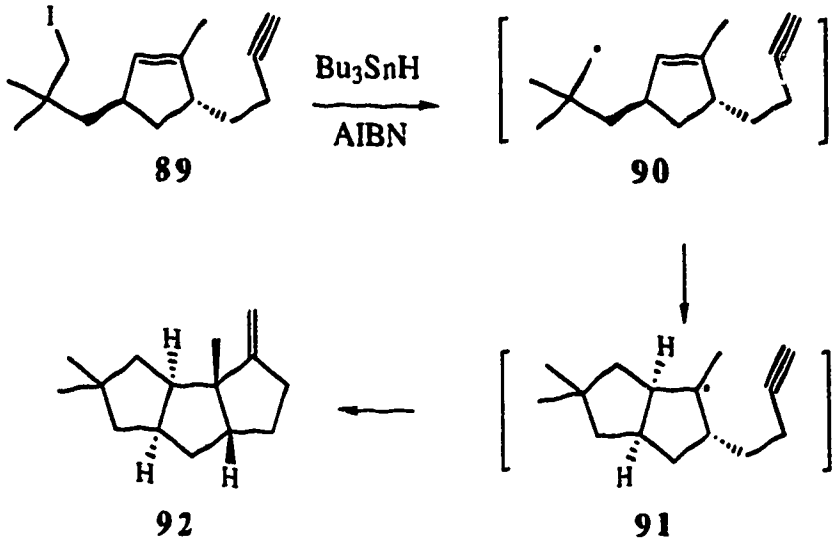
87 **88**

Scheme 69

In recent years, tandem radical cyclizations (as in Scheme 69) have received increased attention. An initial radical undergoes an intramolecular cyclization to produce an intermediate radical which can undergo a second closure onto a nearby unsaturation. In this way complex polycyclic compounds can be built up in a single step.

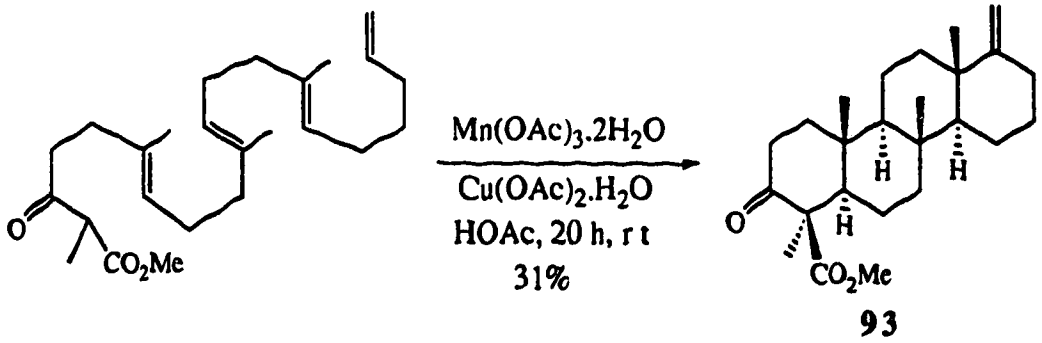
Curran[91] has studied tandem cyclizations extensively. Shown below (Scheme 70) is his synthesis of hirsutene **92**. Treatment of **89** with tributyltin

radical generated **90**, which underwent two successive 5-*exo* closures with controlled stereochemistry. Reduction of the intermediate vinyl radical by tributyltin hydride produced the natural compound **92**.



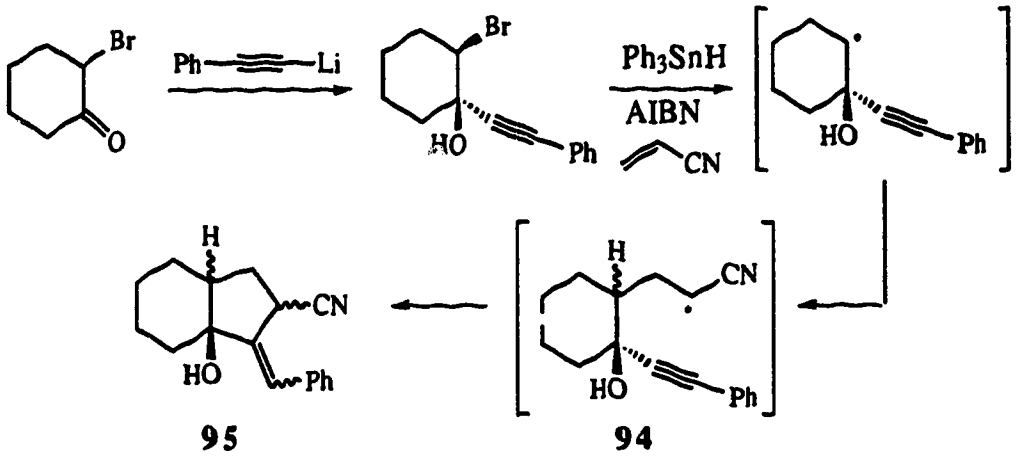
Scheme 70

Many other groups have also become involved in the area of tandem radical cyclization.[21] Of special note is an oxidative free radical cyclization by Zoretic[92] (Scheme 71), in which four consecutive cyclizations produced the tetracyclic D-homo-5a-androstane-3-one **93**. Seven asymmetric centers were established in a specific relative configuration.



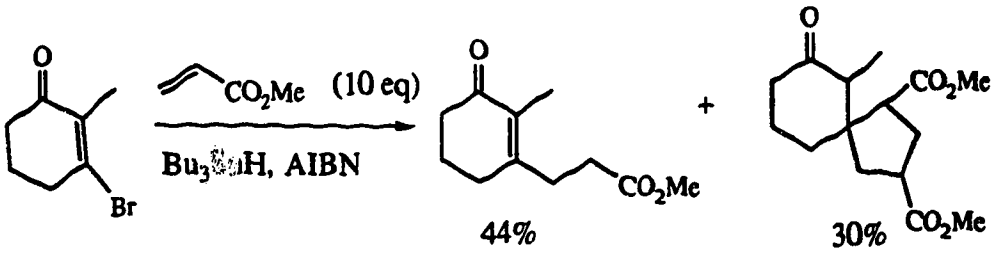
Scheme 71

A sequence of tandem inter- and intramolecular radical additions can also be used for ring annulation. For example Clive[93] combined Giese's intermolecular radical conjugate addition with intramolecular 5-hexenyl radical cyclization in sequence, to close a cyclopentane ring from two unsaturated molecules (Scheme 72). The reaction of triphenyltin radical with the alkynyl halide produced a homopropargyl radical which, in the presence of an excess of the radical acceptor, underwent an intermolecular conjugate addition, generating radical **94**. This radical is much less nucleophilic, because of the adjacent nitrile, and even in the presence of an excess of acrylonitrile underwent a 5-*exo* intramolecular closure to produce **95**, after abstraction of hydrogen from the triphenyltin hydride.



Scheme 72

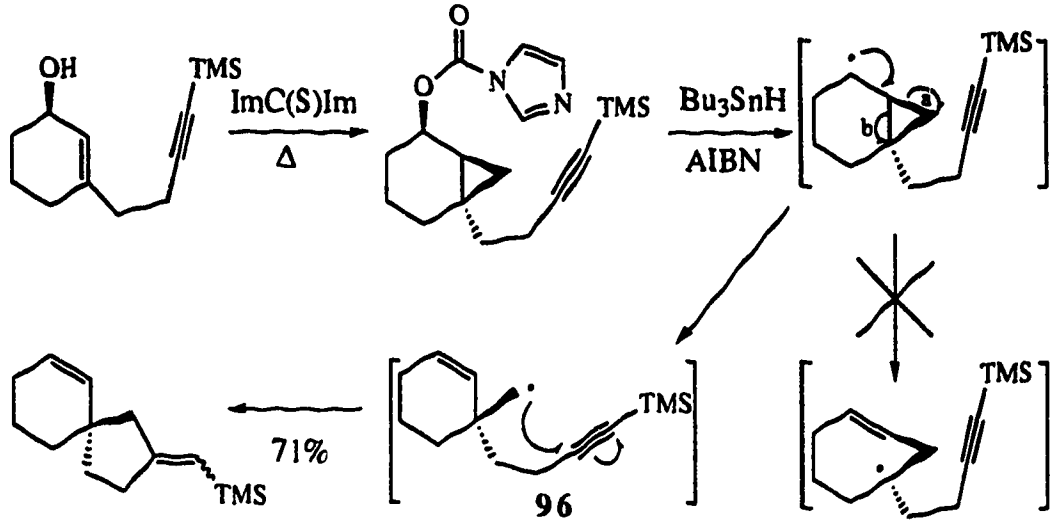
Lee[94] has used a sequence of two inter- and intramolecular additions in his spiroannulation onto 3-bromo enones (Scheme 73). Moderate yields of the spiroannulated product were obtained in these [2 + 2 + 1] triple radical Michael reactions.



Scheme 73

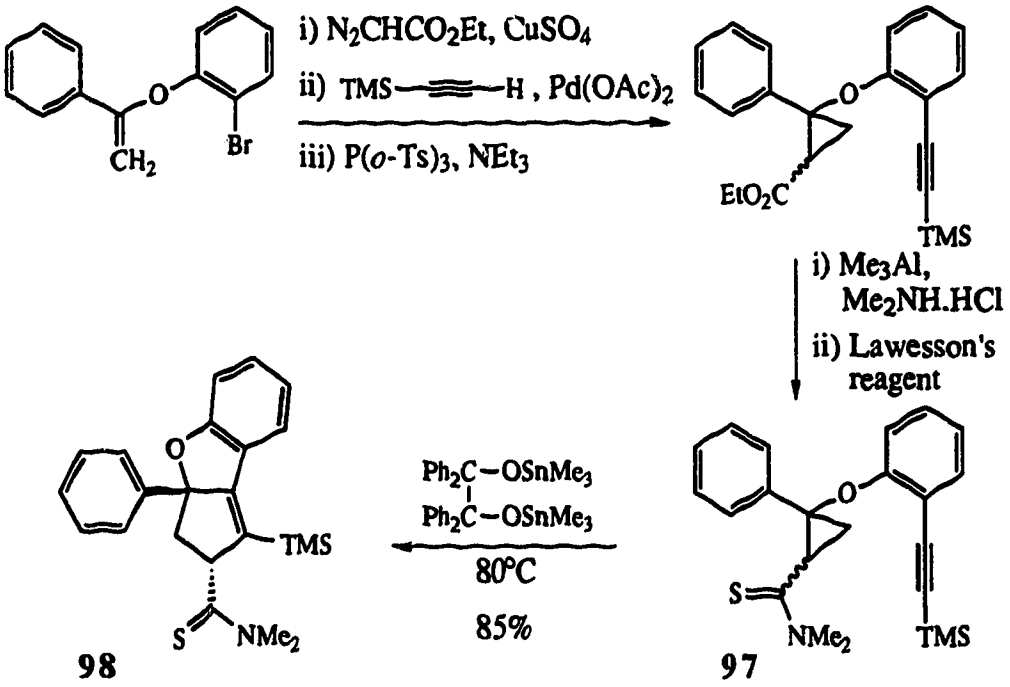
Although tandem radical additions are now receiving significant attention, tandem sequences involving rearrangement of an intermediate free radical as part of a chain are much less common, particularly in all-carbon systems.

In the example shown (Scheme 74) from Motherwell's[95] group, the radical was generated adjacent to a cyclopropane ring. Rearrangement via a stereoelectronically controlled cleavage of bond (a) produced the higher energy primary radical **96**. 5-*Exo* closure, then gave the spiro-fused *exo*-methylene cyclopentane.



Scheme 74

Feldman[96] used an intermediate radical rearrangement in a sequence with two 5-*exo* intramolecular additions to generate the cyclopentabenzofuran ring system **98** of the natural compound, racoglamide (Scheme 75). The radical precursor **97** was synthesized by a sequence of standard steps. Treatment of the diastereomeric mixture with trimethyltin radical, generated by thermolysis of bis(trimethylstannyl)benzopinacolate, gave the desired product **98**, as a single isomer, in high yield.

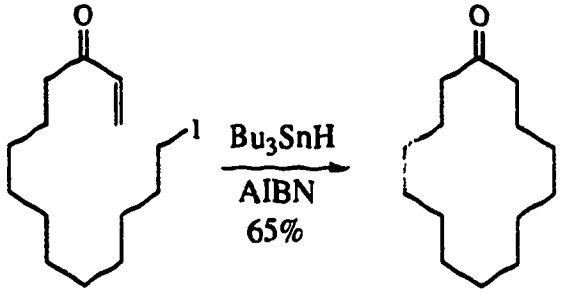


Scheme 75

In all the examples discussed so far the use of radical cyclization has been limited primarily to the construction of five- and six- membered rings, and not larger ring systems. The reason for this is that the rate of closure decreases rapidly from 5-*exo*, to 6-*exo*, to 7-*exo*, etc. In fact, for larger ring construction, the intramolecular cyclization becomes more like an

intermolecular addition, with steric and polar effects becoming more important.

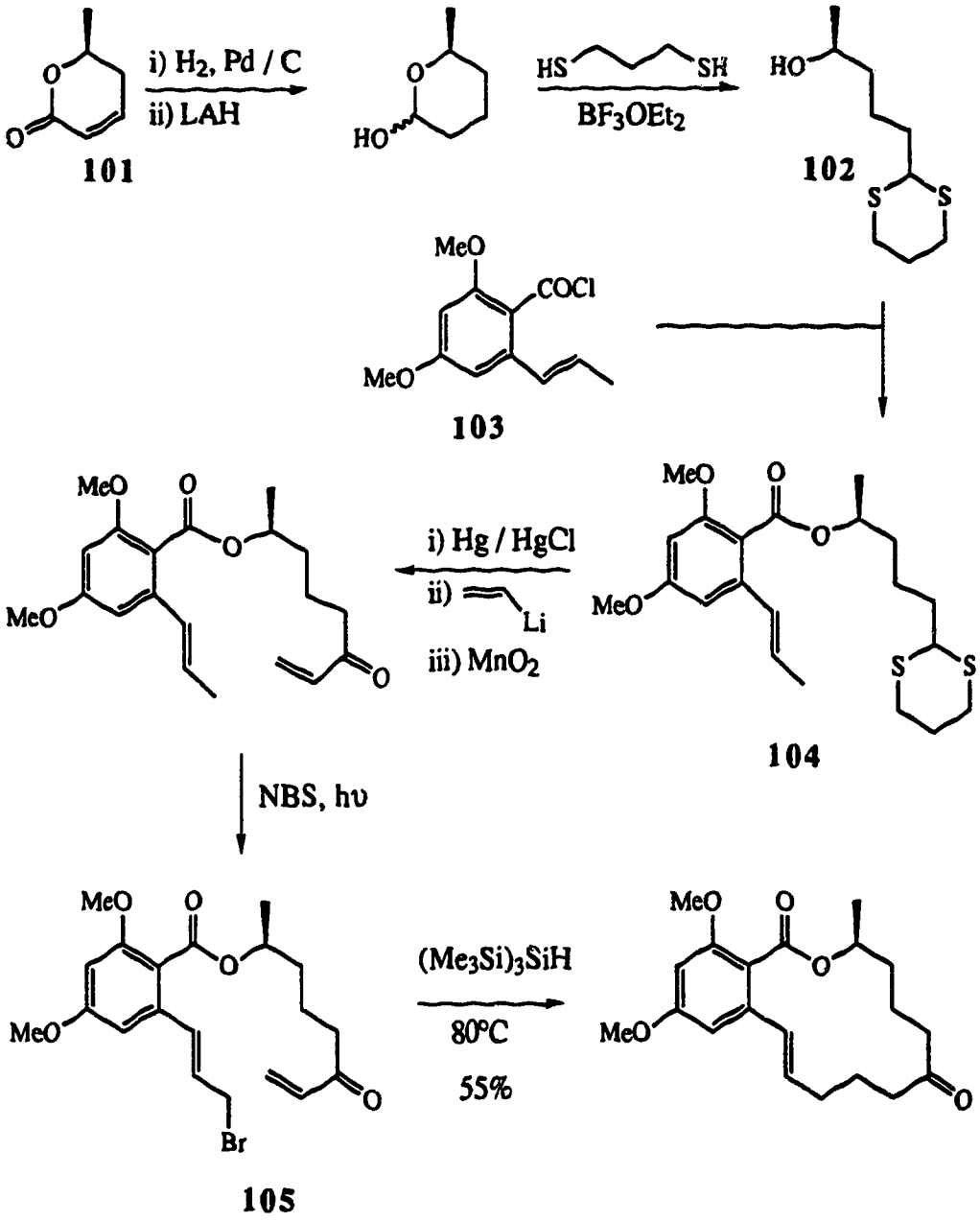
Porter[97] has extensively studied radical cyclizations which produce large rings. An example of his work is shown in Scheme 76. Treatment of the alkyl iodide **99** with tributyltin radical, produced a primary alkyl radical which underwent a 14-*endo* closure onto the enone, to produce the cyclic ketone **100**. Yields as high as 90% have been obtained for macrocyclizations of secondary or tertiary radicals onto electron deficient alkenes



99 **100**

Scheme 76

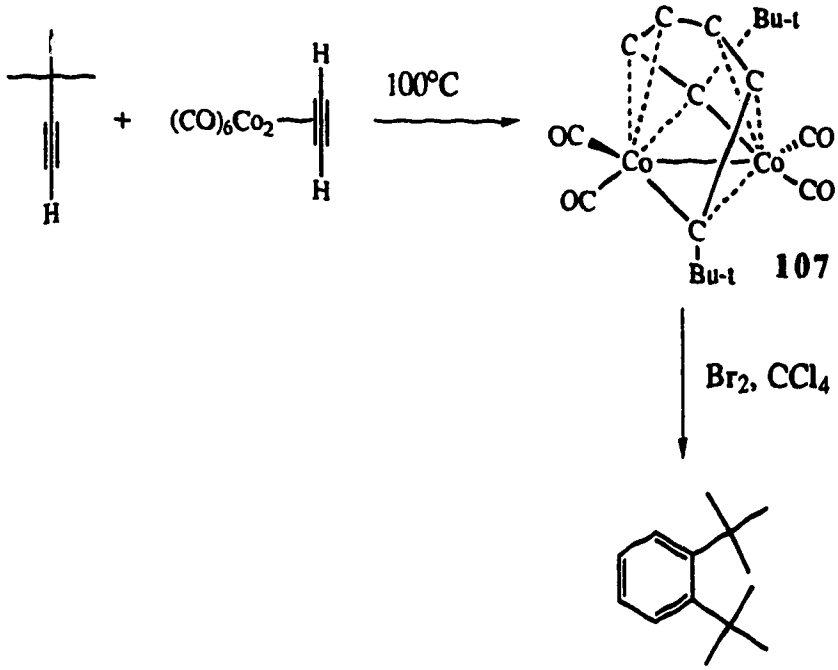
Pattenden[98] also used a 14-*endo* trigonal macrocyclization in the synthesis of optically active zearalenone **106** (Scheme 77). Treatment of the chiral alcohol **102**, derived from the naturally occurring parasorbic acid **101**, with the acid chloride **103**, derived from resorcinol, produced the ester **104**. Deprotection of the thioketal, addition of vinyllithium and oxidation gave the enone. Reaction with *N*-bromosuccinimide in the presence of ultraviolet light, gave exclusively the *E*-cinnamyl bromide **105**. 14-*Endo* trigonal closure then led to the natural compound **106** in 55% yield.


i) H2, Pd / C
ii) LAH
HS
SH
BF3OEt2
HO
101
102
MeO
COCl
MeO
103
MeO
O
MeO
i) Hg / HgCl
ii)
Li
iii) MnO2
MeO
O
MeO
104
NBS, hυ
MeO
O
MeO
Br
105
(Me3Si)3SiH
80°C
55%
MeO
O
MeO

Scheme 77

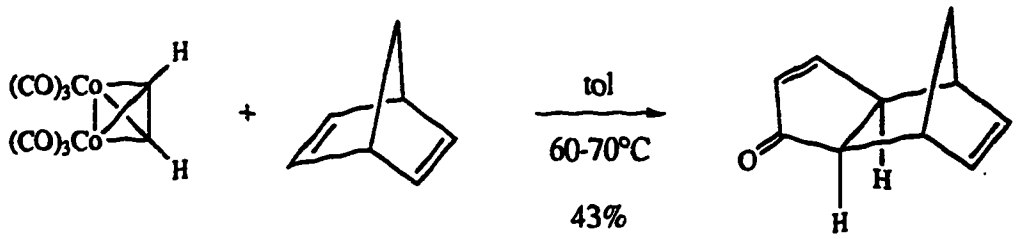
THE PAUSON-KHAND CYCLOPENTENE SYNTHESIS

In 1961 Kruerke[99] reported the oxidative decomposition of the organometalic complex $Co_2(CO)_4(t\text{-}BuC_2H)_3$ to produce the first ortho-substituted *t*-butylbenzene. Mills and Robinson[100] later obtained the crystal structure of the so called 'flyover' complex $Co_2(CO)_4(t\text{-}BuC_2H)_2\text{-}(C_2H_2)$ **107**, formed by reaction of cobalt complexed acetylene with *t*-butyl acetylene. Oxidative decomposition led to the related 1,2 di-*t*-butylbenzene.



Scheme 78

While investigating a possible analogous insertion of norbornadiene, Khand and Pauson[101, 102] isolated a cyclopentenone derived by a [2 + 2 + 1] cycloaddition of the alkyne, alkene and carbon monoxide.



Scheme 79

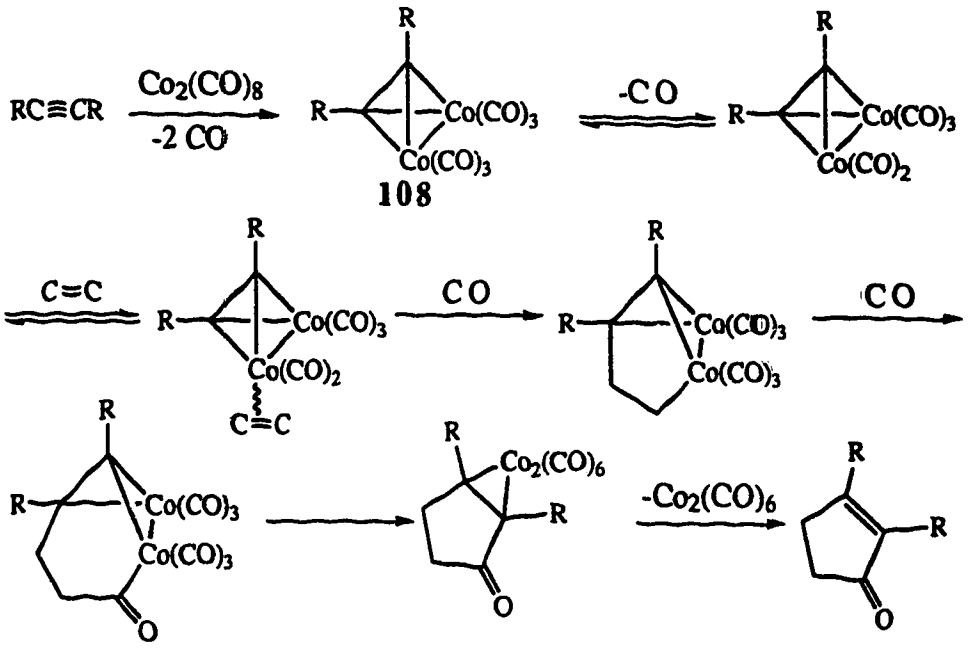
During early work the Pauson-Khand reaction typically was carried out by heating a mixture of cobalt complexed alkyne with the alkene in a hydrocarbon or ethereal solvent. Yields in the 40-60% range could be expected.

Development of the reaction has resulted in a number of milder experimental conditions, such that the reaction is compatible with a wide variety of functionalities and can be carried out with a high degree of stereo- and regioselectivity.

This section of the review will discuss the scope and generality of the reaction, as well as the recent modifications to reaction conditions. Excellent reviews have been published.[103-107]

Mechanism

The only direct evidence for the mechanism of the Pauson-Khand reaction is the observation that the alkyne complex $Co_2(CO)_6$.R'CCR' (**108**) is formed in the first stage of the process.[107] Other mechanistic understanding must account for the regio- and stereochemical information of a large number of examples.[108-110]



Scheme 80

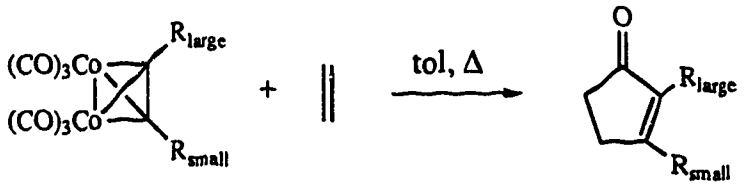
The initial loss of CO is thought to be reversible, and is followed by complexation of the alkene. The irreversible insertion of the complexed alkene π bond into one of the cobalt-carbon bonds is both the rate determining and product determining step and involves the most sterically accessible alkyne and alkene carbons. Carbon monoxide migration, addition of a ligand, and reductive elimination, close the five membered ring. Cleavage of the cobalt cyclopropane produces the enone and dicobalt hexacarbonyl capable of forming a new cobalt-alkyne complex.

Intermolecular Cycloadditions

For intermolecular cycloadditions the most satisfactory alkynes are acetylene and terminal alkynes. Internal alkynes usually give lower yields of cyclopentenone. The range of applicable alkenes is a much more serious limitation. Strained alkenes such as norbornadiene, norbornene and

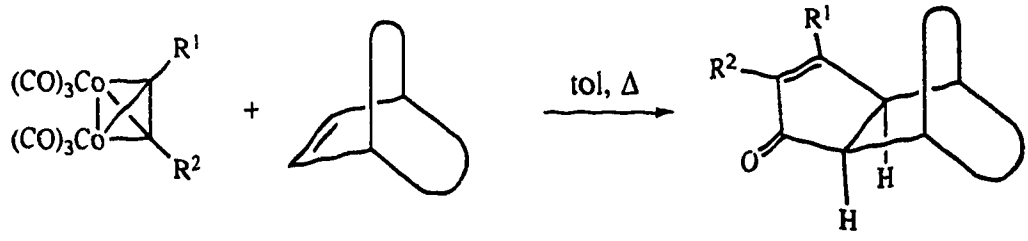
cyclobutenes are reactive under mild conditions, with yields in excess of 50% being obtained. Cyclopentenes, cyclohexenes and acyclic alkenes are less reactive and require considerably higher temperatures. Tri- and tetrasubstituted alkenes suffer from steric hindrance, which reduces the ability of the alkene to compete with additional molecules of alkyne for reaction with the alkyne cobalt complex. Thus, side reactions such as alkyne trimerization, and cycloadditions involving the alkyne and carbon monoxide, predominate.[111]

A high degree of regiocontrol can be expected with respect to the alkyne.[112] Thus, terminal alkynes afford 2-substituted cyclopentenones exclusively, while disubstituted alkynes usually react to produce cyclopentenones with the larger group adjacent to the ketone[113] (Scheme 81).



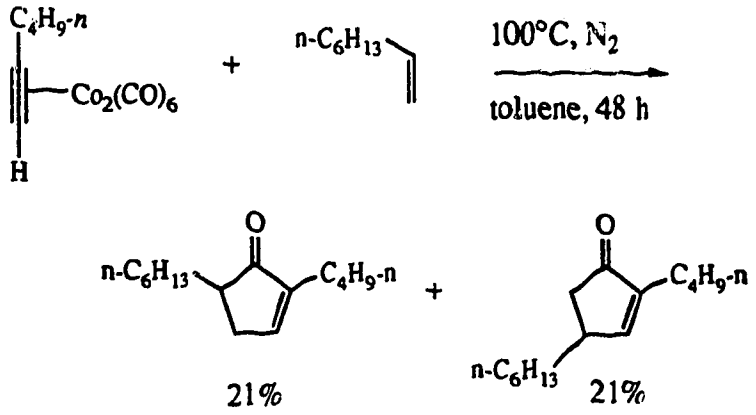
Scheme 81

Cycloaddition of norbornene, norbornadiene and similar bicyclic alkenes occurs exclusively from the less sterically crowded *exo* face[101, 102, 114] (Scheme 82).



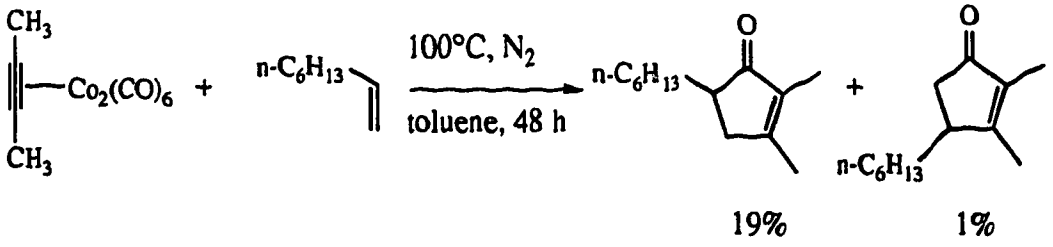
Scheme 82

There is, however, a lack of regiocontrol in incorporation of simple acyclic alkenes, as shown in Scheme 83, where a 1:1 mixture of isomers was obtained.[110]



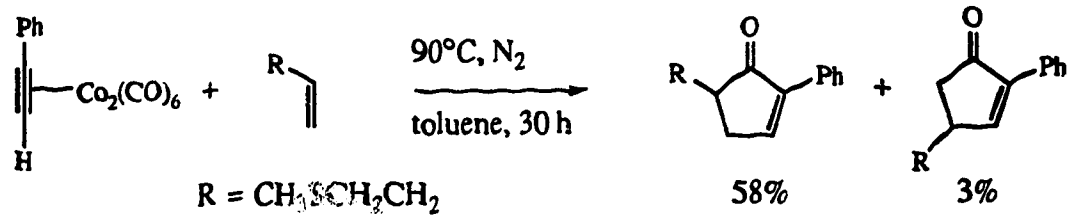
Scheme 83

Increased regioselectivity, but reduced yields, are observed in reactions with internal alkynes[110] (Scheme 84).



Scheme 84

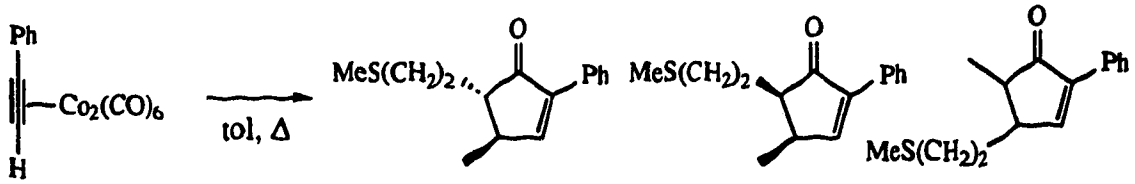
Alkenes with heteroatoms in the allylic position frequently give higher yields and very high regioselectivity.[109, 115]



Scheme 85

It is thought that the heteroatom coordinates to the cobalt prior to insertion, thus fixing the coordination so as to produce the 5-substituted product.[109, 116]

Krafft has shown that the stereochemistry of the alkene is not maintained during the P-K reaction.[109, 116] Reaction of either methyl *cis*-3-pentenyl sulfide or methyl *trans*-3-pentenyl sulfide with phenylacetylene-cobalt complex yielded the trans 2,3,5-trisubstituted cyclopentenone as the major product (Scheme 86).



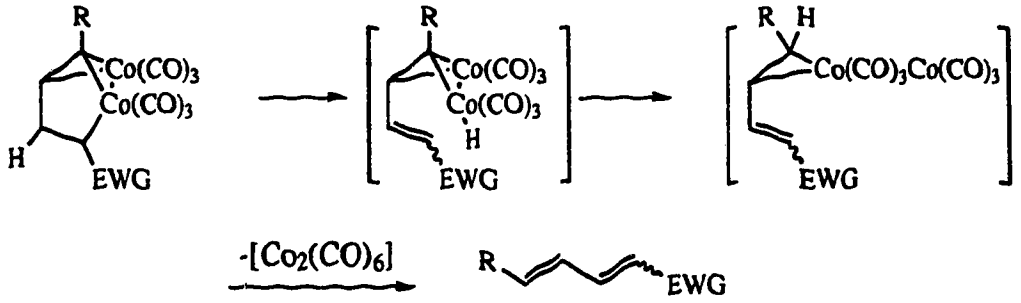
Alkene	Yield					
	73%	38	:	2	:	<1
	40%	12	:	1	:	2

Scheme 86

Certain functionalized alkynes such as 4-pentyn-1-ol give low yields, possibly due to competing alkyne trimerization. Schore has been able to suppress these side reactions by covalent attachment of the alkyne to an inert

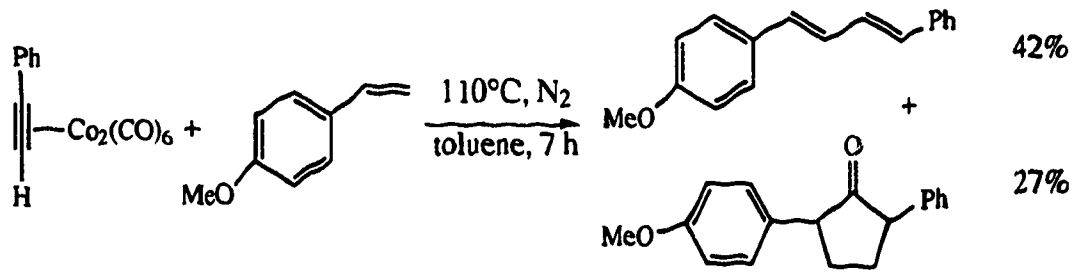
polymer support. Following the P-K reaction, cleavage of the polymer-bound alkyne affords excellent yields of the cyclopentene product.[117]

Electronic effects may also be observed in the Pauson-Khand reaction. Alkynes conjugated with electron withdrawing groups are not reactive. Electron poor alkenes give 1,3-dienes, with the new carbon-carbon bond being formed between the less hindered carbon of the alkene and alkyne.[118, 119] It is presumed that the initial alkene complexation proceeds as normal, but the electron withdrawing group (EWG) makes the β-hydrogen elimination-reduction sequence more favorable, than carbon monoxide insertion.



Scheme 87

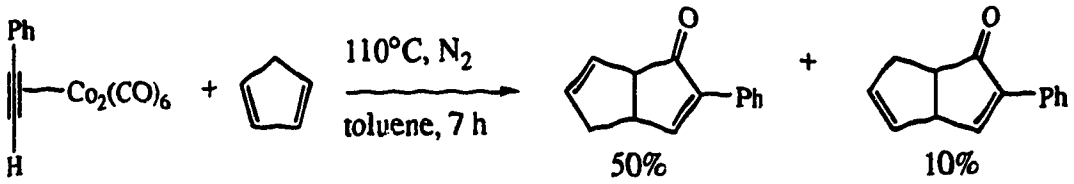
Conjugated acyclic dienes also give linear polyene products.[103] Aryl alkenes occupy an intermediate position, giving both dienes and 5-arylcyclopentenones, each with a high degree of regioselectivity[112, 120, 121] (Scheme 88).



Scheme 88

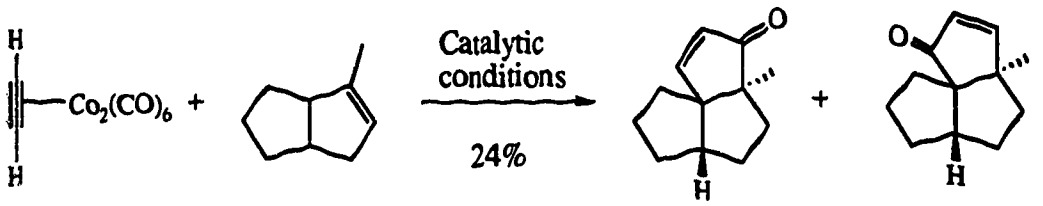
Cyclopentene derivatives react with terminal alkynes to give 30-70% of bicyclic enones,[112, 122-124] while cyclohexene, cycloheptane, and cyclooctene are poor Pauson-Khand substrates. To date, cyclopropenes and cyclobutenes have not been studied.

In contrast to acyclic dienes, cyclopentadienes and fulvenes give bicyclo[3.3.0]octenones in moderate yields[125] (Scheme 89).



Scheme 89

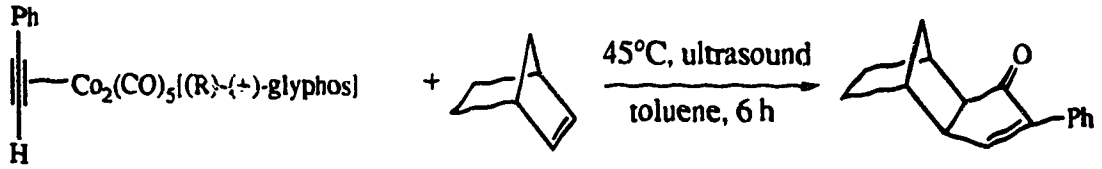
Bicyclo[3.3.0]oct-2-enes undergo isomerization of the double bond, to bicyclo[3.3.0]oct-1-enes prior to cycloaddition. Thus an angular fused triquinane is produced[126] (Scheme 90). The example shown is the only case of a Pauson-Khand reaction involving a tetrasubstituted alkene.[124]



Scheme 90

The first example of optical induction in the Pauson-Khand reaction was described in 1988.[127] Reaction of phenylacetylene-$Co_2(CO)_6$ with optically active (R)-(+)-2,3-O-isopropylideneglycerine-1-diphenylphosphine [(R)-(+)-glyphos] gave two separable diastereomers of phenylacetylene-$Co_2(CO)_5$-(R)-(+)-glyphos.

Since the reaction with norbornene is face selective,[114] then reaction at exclusively one of the two diastereotopic cobalt atoms, probably the $Co(CO)_3$ rather than the $Co(CO)_2$-(R)-(+)-glyphos, produces enantiomerically pure enone (Scheme 19).

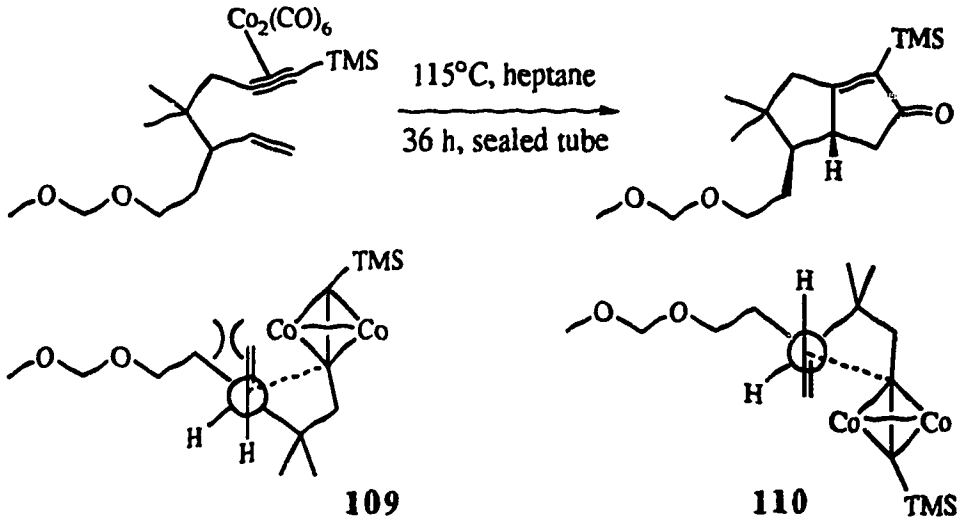


Scheme 91

Intramolecular Additions

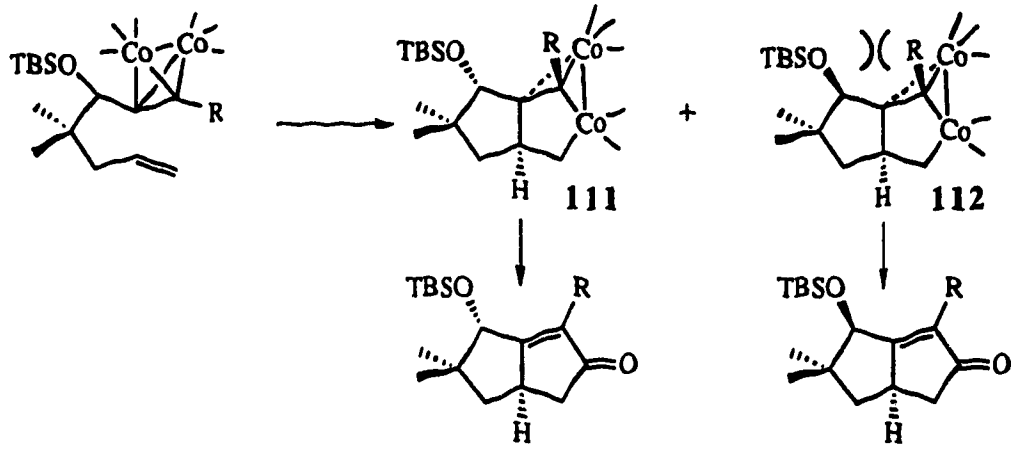
Intramolecular Pauson-Khand reactions have been carried out on enyne systems where the alkene and alkyne are joined by a three or four atom chain. Cobalt octacarbonyl is added to the enyne to form the cobalt complex and subsequent heating produces the bicyclic enone. Intramolecularity relaxes the steric requirements of the alkene, although reaction of trisubstituted alkenes is limited to terminal alkynes.

Substitution effects in cycloadditions of heptenynes have been well studied by Magnus et al.[128] There is a stereochemical preference for substituents at the allylic and propargylic positions to be on the *exo* face of the bicyclic product.



Scheme 92

Scheme 92 shows the two possible conformers for the cyclization of the allylic (C-3) substituted heptenyne. The dashed lines represent the ring fusion which would form on alkene insertion. In conformer **109** the double bond is adjacent to the medium size group, and thus suffers from a pseudo 1,3-diaxial interaction, which is not present in **110** where the double bond is next to the hydrogen. Conformer **110** leads to the observed product with the substituent on the *exo* face.

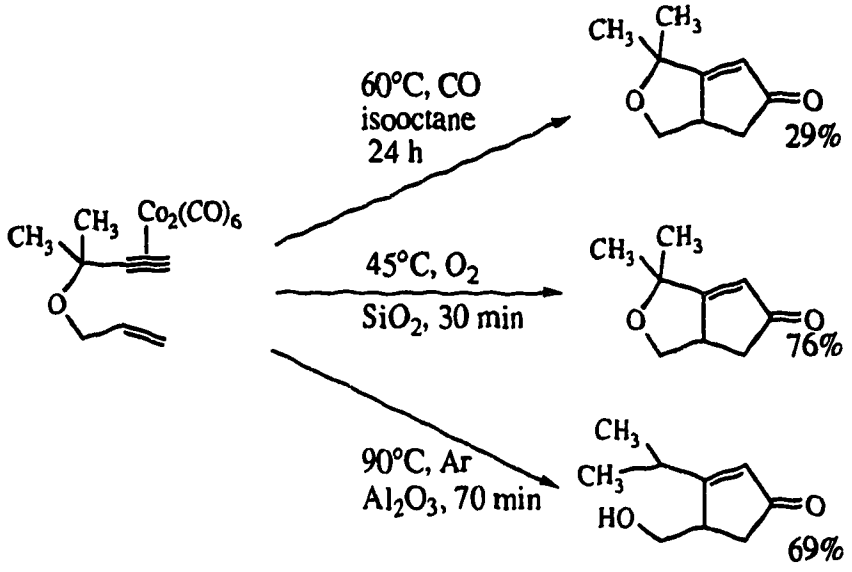


R = TMS 26 : 1
Me 3 : 1

Scheme 93

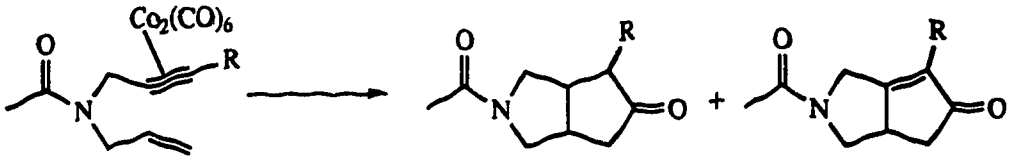
For propargylic (C-5) substituted enyne systems steric interactions between the propargylic and the alkyne substituent are responsible for the stereoselectivity. Scheme 93 shows the two possible metalocycles formed by insertion of the alkene into the carbon-cobalt bond. Assuming that the metalocycles are cis fused, then metalocycle **112** suffers from severe steric interactions which are not present in **111**. Cyclization through **111** leads to the bicyclic product with the (C-5) substituent on the *exo* face. The selectivity is enhanced by more bulky substituents on the alkyne terminus. Substituents at C-4 of the enone have no stereochemical consequences but may improve the yields[129] by the Thorpe-Ingold effect.[130]

Enynes which contain a heteroatom in the chain connecting the alkene and alkyne have also been studied as Pauson-Khand substrates. Allyl propargyl ethers give only moderate yields under standard solution conditions.[131] However, Smit and Caple[132-134] have had good success with these cycloadditions under dry conditions (Scheme 94).



Scheme 94

Pauson et al.[135] have recently described the intramolecular cycloaddition of *N*-acylhept- and *N*-acyloctenynes (Scheme 95). In the heptenyne series, with terminal alkynes, unsaturated ketones were obtained in all cases, except under UV irradiation in chlorocarbon solvents. When the alkyne hydrogen was replaced by a alkyl group, good yields of the enone were isolated.

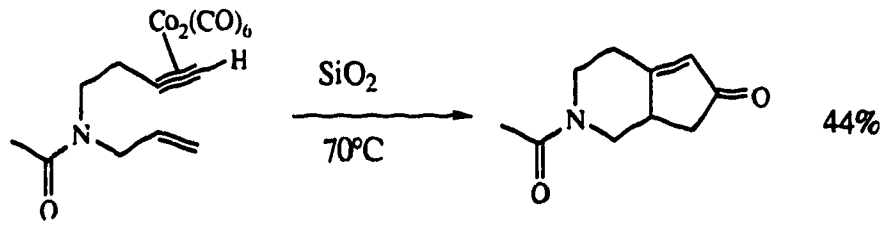


	Reaction Conditons[a]	Yield	
R = H	Isooctane, 100°C	5%	0%
	Isooctane, U.V., 50°C	33%	0%
	CCl_4, U.V., 50°C	0%	38%
	Isooctane, U.S., 60°C	36%	0%
	SiO_2	67%	0%
R = Et	Isooctane, 110°C	--	57%
	Isooctane, U.V., 50°C	--	52%
	Isooctane, U.S., 60°C	--	47%
	SiO_2	--	75%

a) U.S. = ultrasound

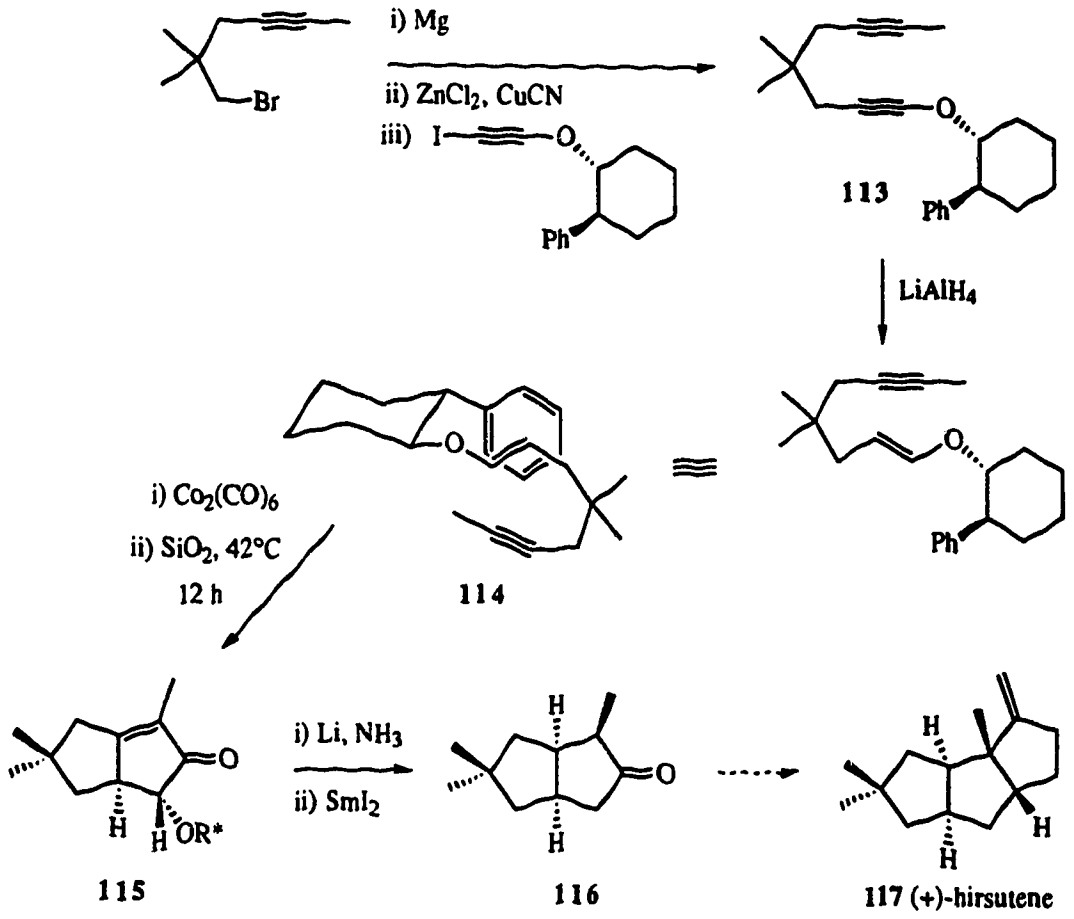
Scheme 95

In the case of the octenyl series, unsaturated enones were obtained, even when the alkyne was terminal[135] (Scheme 96).



Scheme 96

The first asymmetric Pauson-Khand reaction was recently reported by Greene.[136] The potential use of this approach was illustrated by an enantioselective formal total synthesis of hirsutene **117** (Scheme 97).



Scheme 97

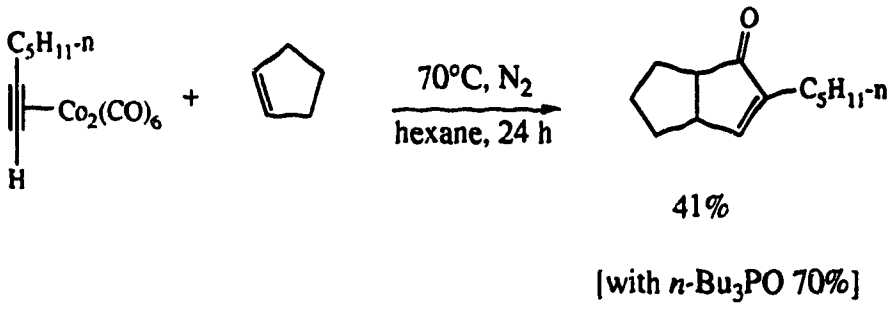
Diyne **113** was prepared by a copper mediated coupling procedure, and converted to the corresponding *E*-enol ether by reduction with lithium aluminum hydride. The Pauson-Khand reaction was carried out by adsorbing the dicobalt hexacarbonyl complex onto silica gel and heating. It is assumed that the complex adopted the conformation shown (**114**, Scheme 97), such that the chiral auxiliary forced π-face discrimination. Enone **115** was obtained in 55% yield with an induction level of 5-6:1. Birch reduction and removal of

the chiral auxiliary gave **116**. This bicyclic ketone, in racemic form, had previously been converted into (±)-hirsutene (**117**).

Experimental Conditions

The Pauson-Khand reaction is most frequently carried out under stoichiometric conditions. The alkyne is treated with commercially available $Co_2(CO)_8$ at room temperature for 2-4 hours in a hydrocarbon, ether or chlorinated solvent. The thermally stable, readily characterized $Co_2(CO)_6$-RCCR complex is thus formed.[137] This complex is then heated with the alkene in a high boiling solvent (60-120°C) usually in an argon or nitrogen, but occasionally, carbon monoxide atmosphere, to produce the cyclopentenone product.[125, 138] Improved yields are occasionally realized if the reaction is carried out in a lower boiling solvent in a sealed tube.

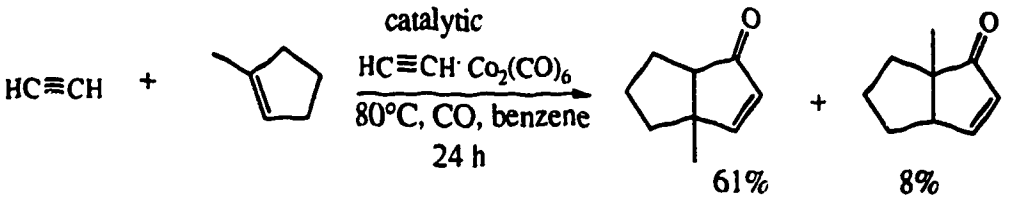
Pauson has found that addition of one equivalent of tri-*n*-butylphosphine oxide often improves the yields of intermolecular reactions, perhaps by facilitating loss of carbon monoxide.[135] To date no significant yield enhancement in intramolecular reactions have been observed when tri-*n*-butylphosphine is added.



Scheme 98

Pauson et al. have also studied the effects of ultrasound irradiation. They conclude that reaction proceeds faster and at lower temperatures but yields are not significantly changed.[135, 139] They have also shown that UV radiation can be used as an alternative source of energy.[139]

With gaseous alkynes improved yields are often obtained under 'catalytic' conditions.[124] A benzene solution of the alkene is heated in the presence of ca. 10-20 mol % $Co_2(CO)_8$ and a 1:1 mixture of the alkyne and carbon monoxide, to produce the cyclopentenone and $Co_2(CO)_6$. The latter then reacts with another acetylene molecule. Catalytic conditions were used in the reaction of the trisubstituted alkene, 1-methylcyclopentene, with acetylene to produce the cycloaddition product in excellent yields (Scheme 99).

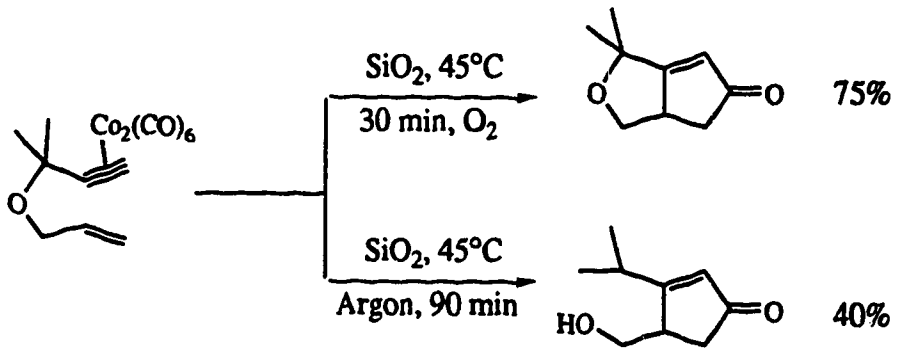


Scheme 99

In 1985 Smit made the remarkable discovery that adsorption of the cobalt-complexed enyne onto silica gel caused dramatic acceleration of the reaction[132]. Reaction times drop from days to hours, reaction temperatures are reduced and improved yields are observed for both inter- and intramolecular cycloadditions.

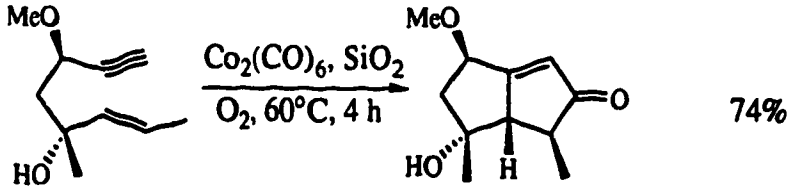
The cobalt-complexed enyne, or a mixture of alkene and cobalt-complexed alkyne, was applied to the adsorbent, the solvent was removed by evaporation, and the solid was warmed until the color of the complex faded. Cycloadditions of allyl propargyl ethers are best done on silica gel under oxygen to suppress hydrogenolysis of the propargylic carbon-oxygen bond

(Scheme 100). It is assumed that the oxygen scavenges reducing species such as cobalt hydrides.



Scheme 100

The technique is also applicable to ordinary enynes if they possess appropriately positioned polar groups for silica adsorption[132, 140] (Scheme 101).

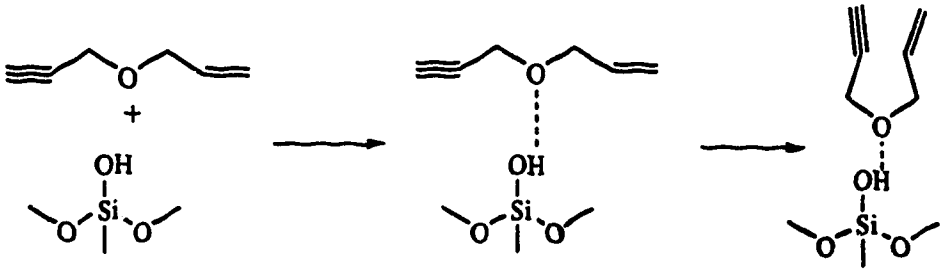


Scheme 101

For other substrates a variety of absorbants including alumina and zeolites, and an inert atmosphere may be used.[133]

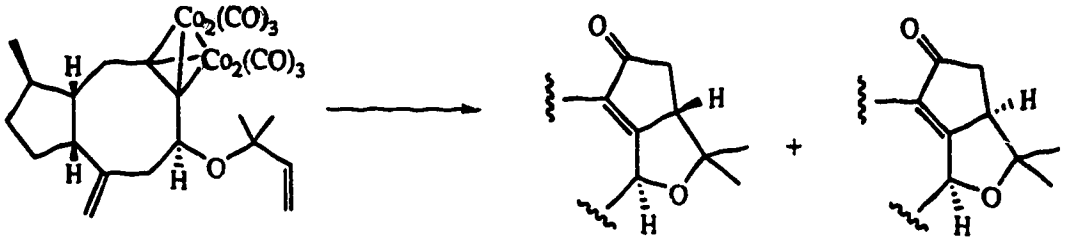
Recent studies of cyclizations to produce 3-oxabicyclo[3.3.0]octenes reveal that reaction rates are significantly increased by forcing the alkene and alkyne ends closer together. Adsorption of the enyne onto silica gel, via the ether center, results in repulsion of the low polarity hydrocarbon ends. Thus, the entropy barrier for formation of the cyclic transition state is decreased

(Scheme 102). Silica gel may also promote ligand exchange and decarbonylation, therefore facilitating alkene complexation.[133]



Scheme 102

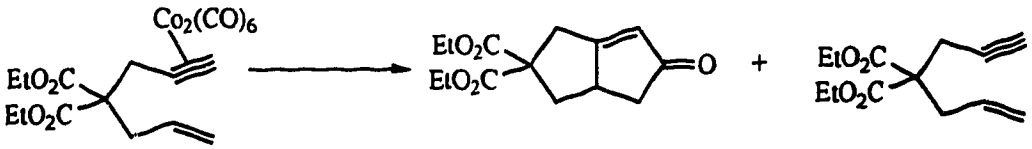
In 1990 Schreiber reported the use of trialkylamine-*N*-oxides to promote the Pauson-Khand cycloaddition.[141] The cobalt complexed enyne in dichloromethane is treated with a single portion of solid *N*-methylmorpholine-*N*-oxide (6 equivalents). The mixture is then stirred at room temperature under an inert atmosphere for 12-24 hours. The use of lower temperatures can often lead to higher yields or, as in the example below (Scheme 103), higher levels of stereoselectivity, compared to thermal or sonicated reactions.



Reaction Conditions	Yield	Selectivity
NMO, CH_2Cl_2, r.t.	68	11 : 1
CH_3CN, 82°C	75	4 : 1
CH_3CN, U.S., 45°C	45	3 : 1

Scheme 103

In independent work by Jeong and Chung,[142] trimethylamine-*N*-oxide (TMANO), *N*-methylmorpholine-*N*-oxide (NMO) and ceric ammonium nitrate (CAN) were screened as promoters of the reaction. Both TMANO and NMO were found to be useful additives, with TMANO being slightly more efficient (Scheme 104).

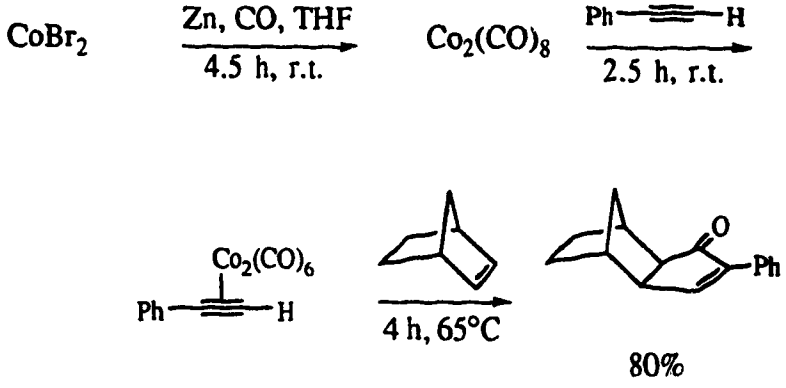


Conditions		
TMANO (3 eq), O_2, CH_2Cl_2, 3 h, r.t.	90%	0%
CAN (3 eq), CH_2Cl_2, 16 h, r.t.	32%	45%
CAN (3 eq), acetone, 3 h, r.t.	0%	80%
NMO (3 eq), CH_2Cl_2, 8 h, r.t.	87%	0%

Scheme 104

It is known that tertiary amine-*N*-oxides can remove carbon monoxide from transition metals oxidatively as carbon dioxide.[142] Thus, it seems likely that the mechanism involves initial oxidation of cobalt carbon monoxide ligand to carbon dioxide, thereby providing a vacancy for the incoming olefin. The *N*-oxide or the tertiary amine produced in the reaction, may also act as a ligand for one of the intermediates, thus diverting the steric and electronic course of the reaction from the classical thermal Pauson-Khand.

The octacarbonyldicobalt may also be generated in situ as shown by Devasagauari[143] (Scheme 105). Anhydrous cobalt dibromide is treated with zinc dust in the presence of carbon monoxide. If the alkyne is then added, the complexed alkyne $RCCR.Co_2(CO)_6$ can be isolated, while addition of the alkene and heating produces the cyclopentene.


CoBr2
Zn, CO, THF
4.5 h, r.t.
Co2(CO)8
Ph
H
2.5 h, r.t.
Co2(CO)6
Ph
H
4 h, 65°C
O
Ph
80%

Scheme 105

RESULTS AND DISCUSSION

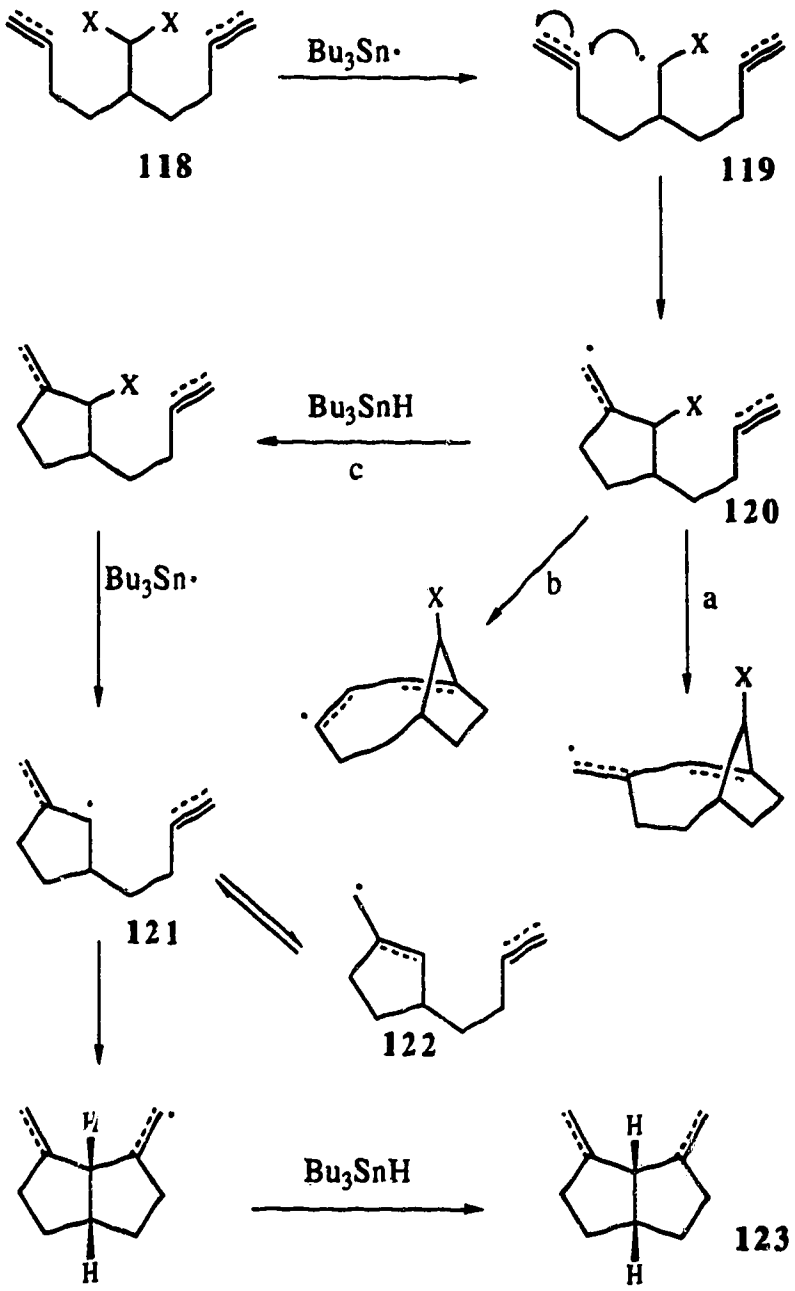
DOUBLE RADICAL CYCLIZATION

5-*Exo* closure of 5-hexenyl radicals is now a well established method for construction of 5-membered rings, and recent literature[144] has seen this process extended to tandem tri- and tetra- sequential closures. A number of groups[145] have reported cyclization reactions of radicals, which are located on carbon atoms, and which contain a homolyzable substituent.

When we began this work there were no examples reported in the literature in which two homolyzable substituents, located on the same central carbon atom, were sequentially cleaved and the radicals so produced used to undergo consecutive 5-*exo* closures.

In order to test the feasibility of such a reaction, a molecule of type **118** (Scheme 106) would be necessary. A pair of homolyzable groups X, are located on the same central carbon, to which two unsaturated pendants are attached. On treatment with a trialkyltin hydride, one of the carbon-X bonds would be homolytically cleaved to produce radical **119**. 5-*Exo* closure of this radical would give a vinyl radical **120** (primary radical in the case of addition to an olefin). This radical could then undergo a number of reactions, namely 7-*exo* (path a), 8-*endo* (path b) closure, or reduction by trialkyltin hydride (path c). Since both 7-*exo* and 8-*endo* cyclizations are known to be slow reactions,[146] and the products (of path a) are not allowed by Bredt rule,[147] they are not expected to compete with abstraction of hydrogen from the tin hydride under the reaction conditions. Cleavage of the second carbon-X bond and 5-*exo* closure would then produce a bicyclic structure **123**, which has, therefore, been generated in a single step from a non cyclic system.

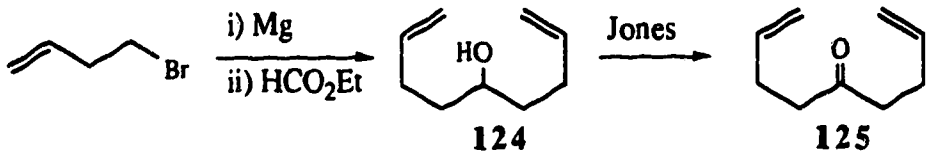
In the case where alkynes are used as radical acceptors, the second radical generated (**121**) is an allylic radical,[148] for which two resonance structures can be drawn (**121** and **122**). However, since 5-*exo* closure is much faster than either the 7-*exo* or 8-*endo* modes,[149] reaction is expected to occur through conical form **121**.



Scheme 106

In order to test this theory we had to prepare a system of type **118** and, after some preliminary experiments, we made a study of the reactions shown in Schemes 107 and 108.

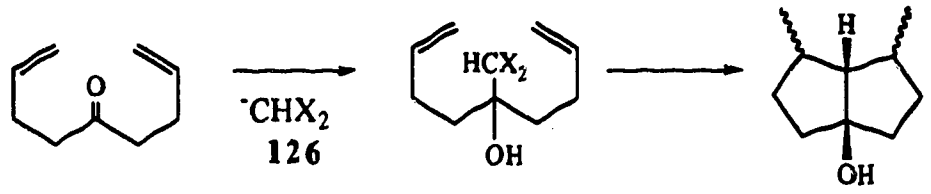
Allen and Converse[150] reported that ketones of type **125** could be constructed easily by Jones oxidation[151] of an alcohol such as **124**, itself prepared by reaction of two equivalents of Grignard reagent with ethyl formate.



124 **125**

Scheme 107

We hoped that reaction of ketone **125** with an anion of the type **126** would produce alcohol **127** (Scheme 108). The X groups would be chosen such that the carbon-X bond can be cleaved homolytically to produce a pair of radicals. Compound **127** also contains two unsaturations suitably located for 5-*exo* closure of the radicals formed by C-X homolysis.

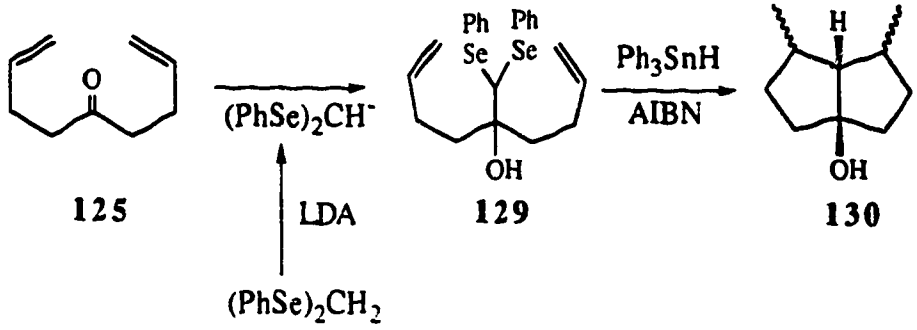


125 **127** **128**

Scheme 108

Thus, we expected that, on treatment with a trialkyltin hydride, two consecutive 5-*exo* closures would afford the bicyclo[3.3.0]octane system **128** (Scheme 108).

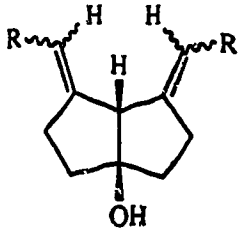
The double Grignard reaction proceeded smoothly to produce alcohol **124**, which was oxidized to ketone **125** (Scheme 107). Reaction of this ketone with bis(phenylseleno)methyl lithium, generated by LDA deprotonation[152] of bis(phenylseleno)methane,[153] afforded alcohol **129** (Scheme 109).



Scheme 109

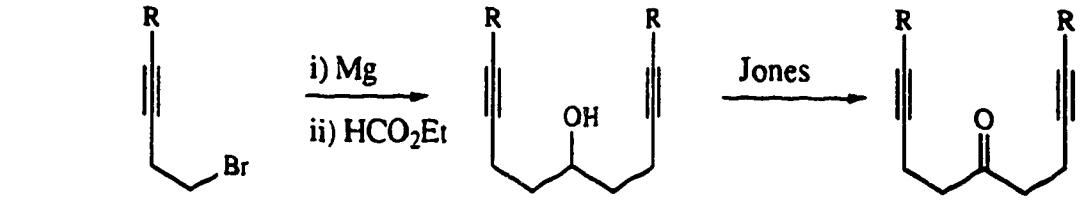
Reaction of **129** with triphenyltin hydride and AIBN under high dilution conditions, in refluxing benzene, produced a complex mixture. NMR analysis of this material showed a series of methyl doublets; however, due to the volatility of the material it was impossible to purify the components.

We therefore turned our attention to systems which would give bicyclic compounds of higher molecular weight and we also decided to use carbon-carbon triple bonds as radical acceptors, since the products from radical cyclization (i.e. **131**) would contain olefinic hydrogens readily detectable (NMR) in crude mixtures.



131

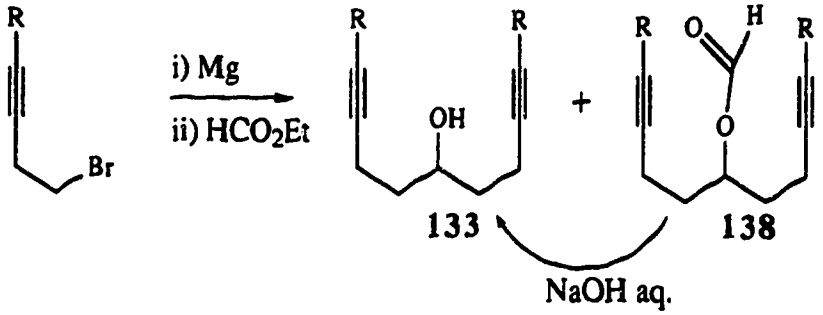
Ketones **134** and **137** (Scheme 110) were prepared by the same strategy used for **125**.[150]



R = $SiMe_3$ **132** **133** **134**
R = $SiMePh_2$ **135** **136** **137**

Scheme 110

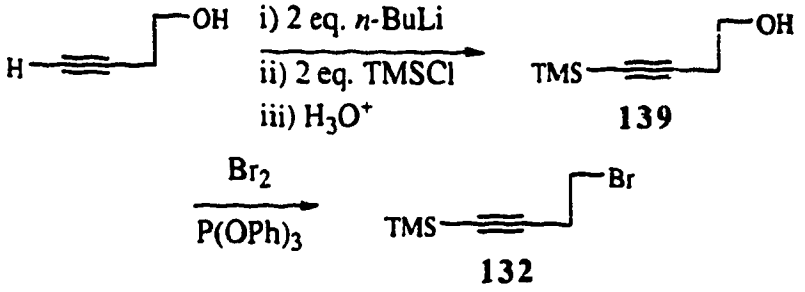
Substantial quantities of the formate ester **138** (Scheme 111) were also produced during the double Grignard reaction with ethyl formate. Therefore the reaction mixture was treated with dilute sodium hydroxide, to hydrolyze the formate ester to the desired alcohol **133**.



Scheme 111

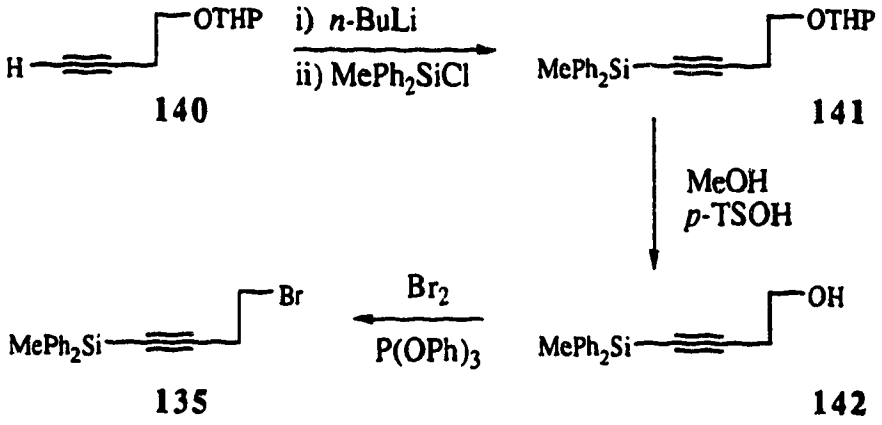
The Grignard reagents needed for the above sequence were made as follows:- (4-Bromobut-1-ynyl)trimethylsilane[154] **132** was prepared from the corresponding alcohol **139** (Scheme 112). Alcohol **139**,[155] in turn, was made from 3-butynol by double deprotonation and trapping with trimethylsilyl

chloride, to produce the bis-trimethylsilyl protected butynol. Acid hydrolysis cleaved the trimethylsilyl ether selectively, affording the desired alcohol **139**.



Scheme 112

(Methyldiphenylsilyl)butynyl bromide **135** was prepared as shown in Scheme 113.

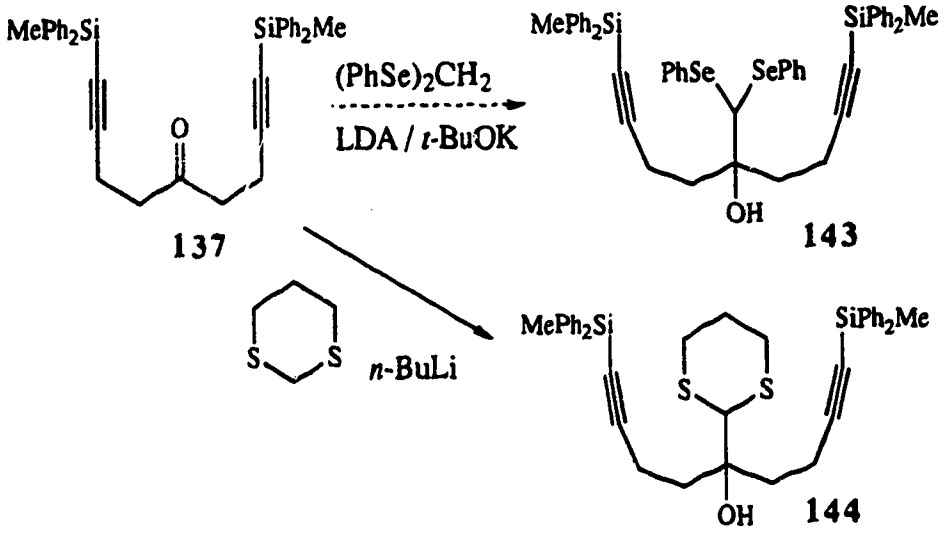


Scheme 113

2-(3-Butynyloxy)tetrahydro-2*H*-pyran[156] **140** was converted to the silyl compound **141** by reaction with butyllithium and methyldiphenylsilyl chloride. The tetrahydropyran protecting group was then removed,[157] and the alcohol was converted into the bromide **135**.

We next turned to the potential use of benzeneseleno groups as radical precursors. Condensation between ketone **137** (Scheme 114) and

bis(phenylseleno)methyl lithium failed to give the alcohol **143**. Raucher[158] reported that deprotonation of selenoacetals with potassium diisopropylamide/lithium *t*-butoxide produced an anion which is more nucleophilic; however, even this anion did not afford the desired bis(phenylseleno) alcohol **143**.



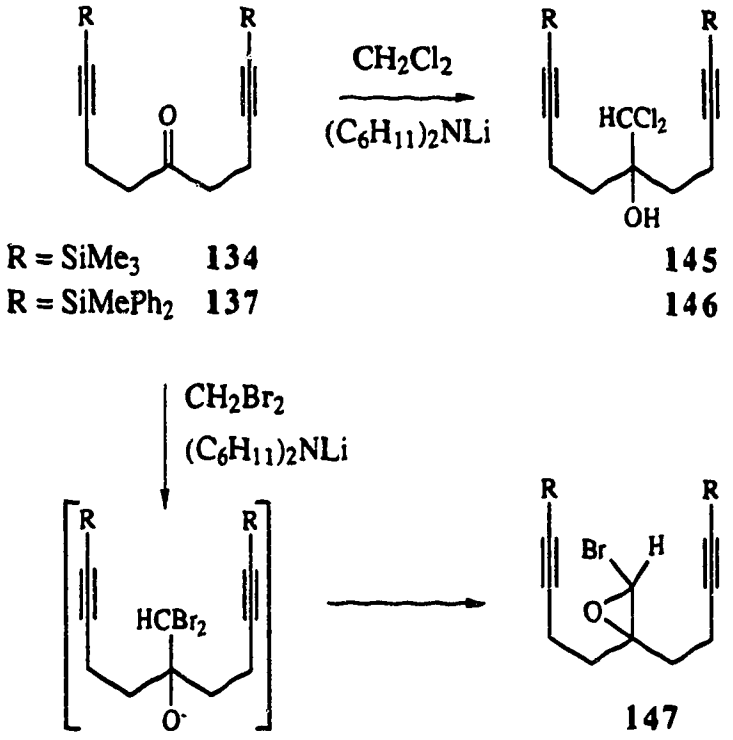
Scheme 114

Since the bis(phenylseleno) radical precursor could not be prepared, it was decided to use instead the corresponding dithio compound **144**. Deprotonation of 1,3-dithiane with *n*-butyllithium and trapping with ketone **137** afforded **144** in high yield.[159]

Attempted radical cyclization of **144** under high dilution conditions in benzene (80°C) or in toluene (110°C) resulted only in recovery of the starting material. When the reaction was carried out in xylene (140°C) a complex mixture which contained no olefinic hydrogens (as judged by NMR analysis) was produced.

Nozaki[160] reported the reaction of dibromo- and dichloromethyllithium with ketones to produce β,β-dihalo alcohols, and we

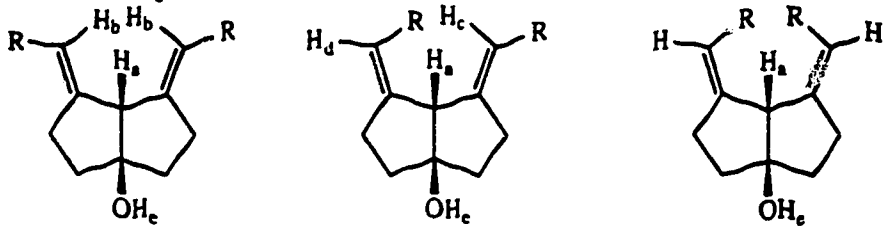
examined this possibility next. Deprotonation with lithium dicyclohexylamine was said to produce an anion which did not undergo elimination to the corresponding carbene. Reaction of ketones **134, 137** (Scheme 115) with dichloromethyllithium proceeded efficiently. However, when the ketones were treated with dibromomethyllithium,[160] only the bromoepoxide was isolated, even when the reaction was carried out and quenched at low (-78°C) temperature.



Scheme 115

Having the dichloroalcohols **145** and **146** in hand, the radical cyclizations were carried out under high dilution conditions, by slow addition (over 8 h) of benzene solutions of tributyltin hydride and AIBN to a refluxing solution of the substrate in benzene.

In each case there are three possible isomeric structures to be considered for the product of double radical closure.



a **b** **c**

$R = SiMe_3$ = **148**

$R = SiMePh_2$ = **149**

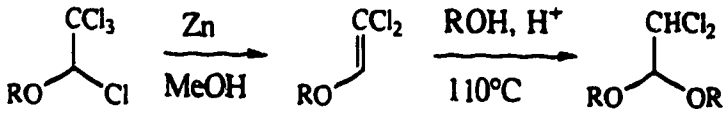
The symmetrical *Z,Z* isomers (**148c** and **149c**) suffer from severe steric crowding between the two vinyl silane groups, and was not expected to be formed. In both cases only two isomers of the product were actually isolated (in approximately equal amounts). One of these was symmetrical and one unsymmetrical. The symmetrical compounds (**148a** and **149a**) were shown to have *E,E* geometry by measurement of NOE's between the central bis-allylic hydrogens (H_a) and the vinyl hydrogens (H_b).

The unsymmetrical (**148b** and **149b**) products showed an NOE between the central hydrogens (H_a) and only one of the vinyl hydrogens (H_c). A small NOE effect between the allylic hydrogen (H_a) and the hydroxy hydrogen (H_e) also proves the cis fusion for **149**. This ring fusion geometry was taken for granted[161] for **148**. In both experiments the products were isolated by flash chromatography and the isomers separated from each other by preparative HPLC.

For **148** the *E,Z* to *E,E* ratio was 45:55, with the total yield being 46%. The cyclization to **149** proceeded much more efficiently (80% yield). The reason for the difference in yields between the two compounds is unclear, since the products are very similar and both are non-volatile.

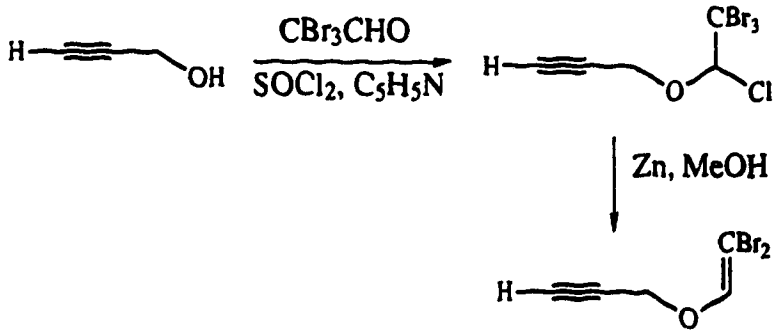
Having shown that radicals could be generated sequentially at a single carbon and used to undergo 5-*exo* closures, we set about defining the scope of the reaction.

Atavin[162] reported the synthesis of β,β-dichlorovinyl ethers of unsaturated alcohols by elimination of two chlorine atoms from the corresponding α,β,β,β-tetrachloroethyl ethers with zinc dust.



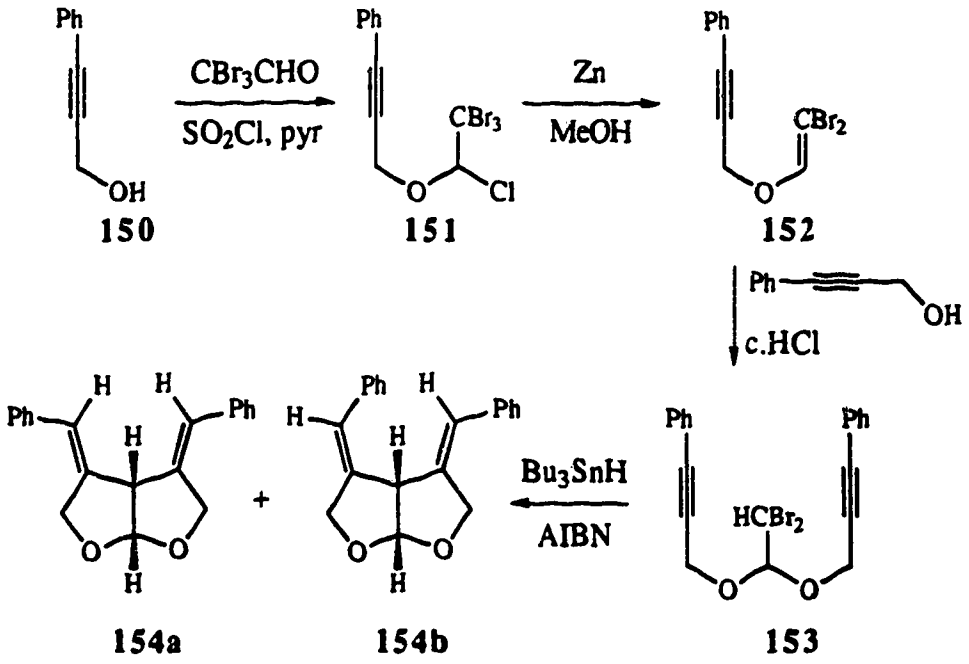
Scheme 116

On treatment with an alcohol under the harsh conditions indicated (Scheme 116), dichloroacetals could be formed. Atavin also reported the preparation of β,β-dibromovinyl ethers by a similar route (Scheme 117), although no mention of further conversion to acetals was made.



Scheme 117

We used the above strategy for the synthesis of our next double radical substrate, dibromoacetal **153**. (Scheme 118)

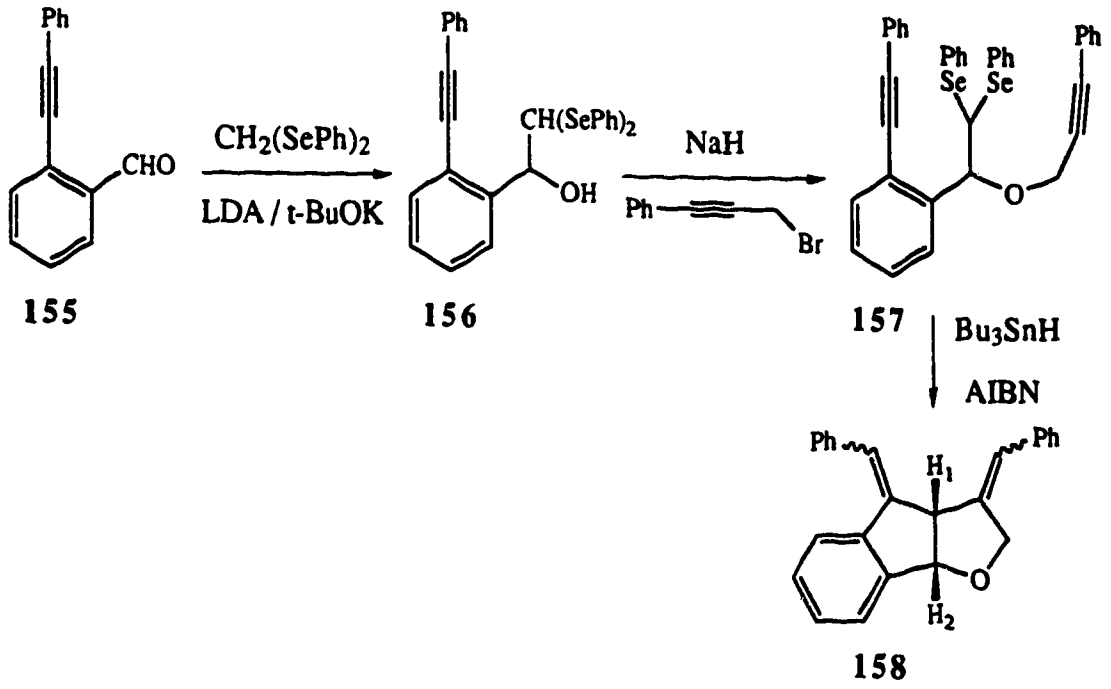


Scheme 118

Reaction of phenylprop-2-ynyl alcohol with bromal[163] in the presence of thionyl chloride and pyridine provided the chloro ether **151**. Partial dehalogenation with zinc dust gave the dibromovinyl ether **152**, and the acetal-forming reaction was then attempted under a variety of conditions. When the dibromovinyl ether was treated with phenylprop-2-ynyl alcohol benzene with trifluoroacetic acid, the acetal (**153**) was obtained in 35% y However, better results (51%) were obtained under the drastic conditions u by Atavin,[162] i.e. stirring the vinyl ether in neat alcohol with a few drops c concentrated hydrochloric acid at 110°C for 4 h.

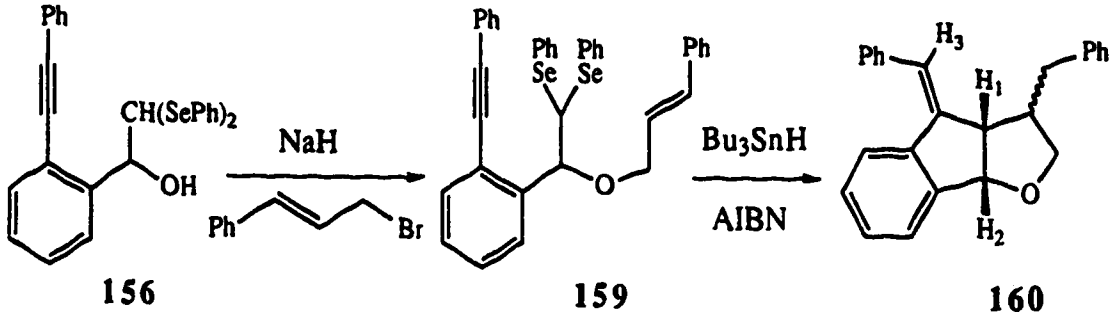
The double radical cyclization was carried out under standard high dilution conditions. Compound **154** was formed as a mixture of *Z,Z* (**154a**) and *Z,E* (**154b**) isomers (Scheme 118). The geometry of the double bonds and the cis fusion were established by NOE measurements.

The remaining two precursors, **157** and **159**, were assembled in two steps from the known aldehyde **155**[164] (Schemes 119 and 120).



155 **156** **157** **158**

Scheme 119



156 **159** **160**

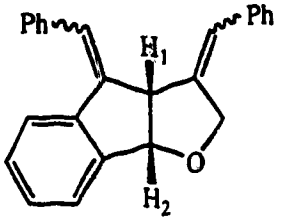
Scheme 120

The anion of bis(phenylseleno)methane, produced by reaction with potassium diisopropylamide/lithium *t*-butoxide[158] afforded the bis(phenylseleno) alcohol in high (81%) yield. When LDA was used as the base, much lower yields (<10%) were obtained.[152] Alcohol **156** was alkylated

with phenylprop-2-ynyl bromide and cinnamyl bromide in the presence of sodium hydride, thus producing **157** and **159**, respectively.

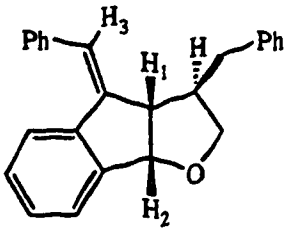
Best results were obtained when the double radical closure reactions of these bis(phenylseleno)acetals were conducted at room temperature using triethylboron and oxygen as radical initiator.[165] The reactions were carried out in flasks protected from the atmosphere by a drying tube filled with Drierite. The tricyclic products of these reactions, **158** and **160**, were obtained as mixtures of isomers which were separated by preparative HPLC.

For compound **158** three isomers were isolated in 3 : 3 : 4 ratio. Saturation of the NMR signal of the bis-allylic hydrogen (H_1) showed NOE enhancements of the benzylic hydrogen (H_2) signals, in all three cases, establishing the cis fusion of the rings. Isomer **A** (least polar, Z,Z geometry) also showed enhancements of both olefinic hydrogen signals. There was no enhancement of the olefinic signals for isomers **B** or **C**. A more comprehensive discussion of the stereochemical assignments is given in the experimental section.

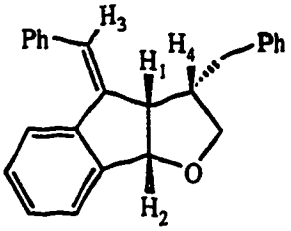


158

Two isomers of compound **160** were isolated, and the structures determined by NOE measurements. Saturation of the signal for the allylic hydrogens (H_1) produced signal enhancements for the benzylic (H_2) and olefinic hydrogens (H_3) in both cases, and for hydrogen (H_4) in the more polar isomer **160b**.

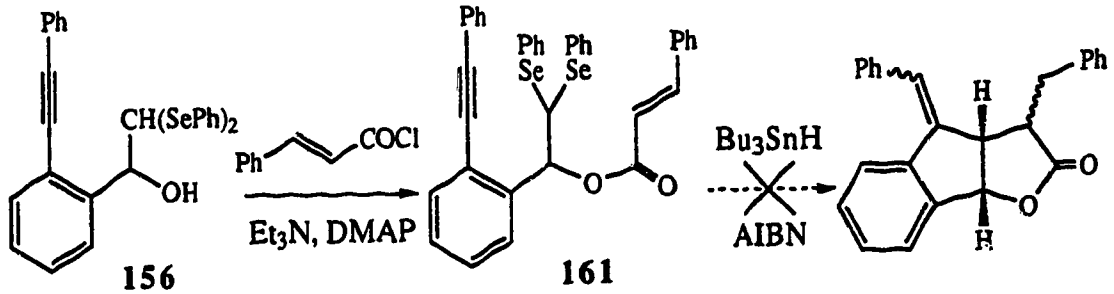


160a



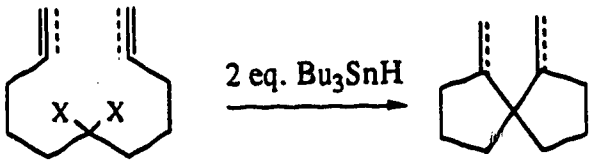
160b

We next tried to extend this double radical cyclization reaction to the synthesis of γ-lactones. The necessary precursor (**161**) was easily prepared from alcohol **156**, by reaction with cinnamoyl chloride in the presence of triethylamine and DMAP[166] (Scheme 121). Various conditions were used for the radical cyclization of compound **161**; however no cyclized product was detected.



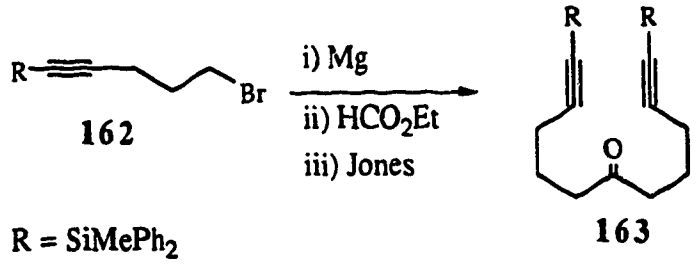
Scheme 121

At this point we turned out attention to the synthesis of spiro bicyclic compounds (Scheme 122) using double radical cyclization technology.



Scheme 122

Compound **163** was prepared by the reaction sequence previously used for the synthesis of symmetrical ketones[150] (e.g. compound **137**).

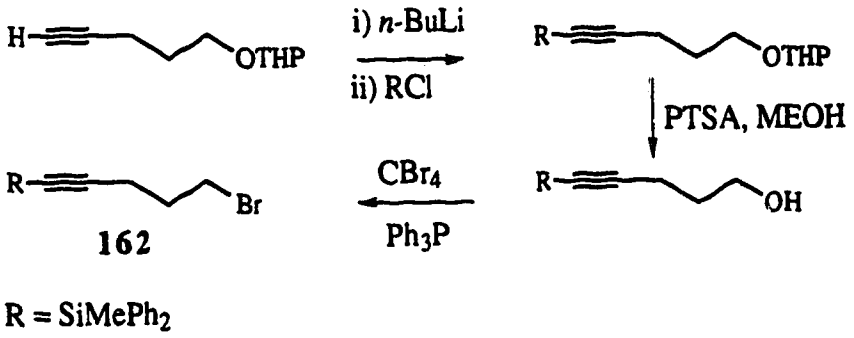


162 **163**

R = $SiMePh_2$

Scheme 123

The required bromide **162** was also synthesized by a previously employed sequence (Scheme 124).



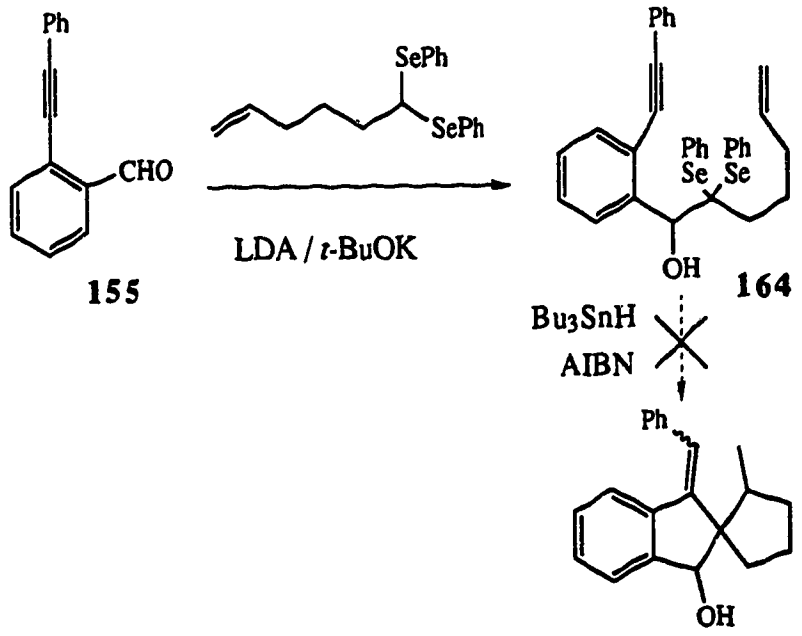
162

R = $SiMePh_2$

Scheme 124

Reaction of ketone **163** with benzeneselenol in the presence of an acid catalyst should produce the corresponding bis(phenylseleno)acetal, which would serve as the precursor for the double radical cyclization. However, reaction with two equivalents of benzeneselenol in the presence of concentrated sulfuric acid,[167, 168] boron trifluoride etherate, hydrogen chloride gas,[169] or zinc chloride[168] failed to give the acetal.

A similar radical precursor **164** was prepared, however, in a single step from aldehyde **155**, which we already had in hand (Scheme 125).

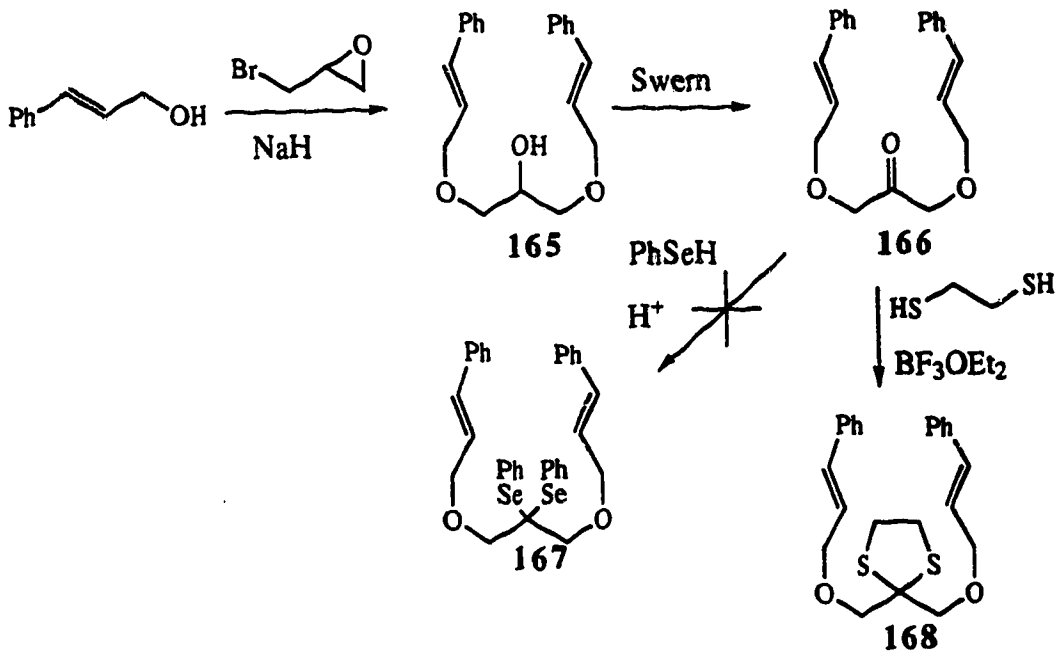


Scheme 125

1,1-Bis(phenylseleno)hex-5-ene[170] was deprotonated by potassium diisopropylamide/lithium *t*-butoxide,[158] and the anion produced reacted with aldehyde **155** to afford alcohol **164** without incident. However, attempts at radical cyclization failed to give the desired cyclized products.

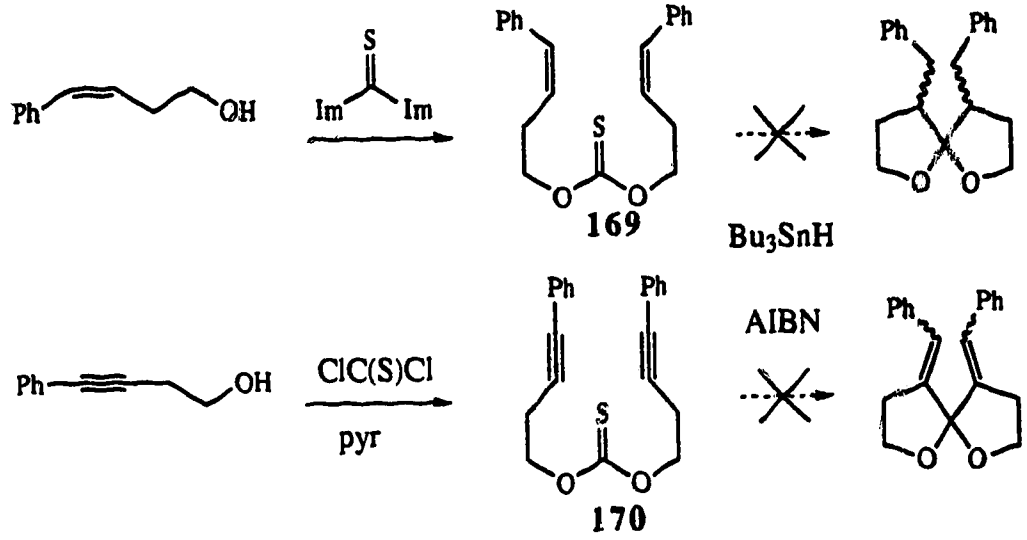
Other potential precursors to spiro compounds were also synthesized, but, despite repeated attempts under a variety of radical cyclization conditions, we were unable to isolate any spirocyclic products. The synthesis of these radical precursors will be described in this part of the discussion.

Ketone **166** was prepared in two steps as shown in Scheme 126. Reaction of epibromohydrin with excess cinnamyl alcohol in the presence of sodium hydride gave **165** in moderate (51%) yield. Swern oxidation then produced the ketone. Conversion to the selenoacetal **167** under the conditions tried with ketone **163**, were equally unsuccessful in this case; however, the thioacetal **168** could be made.[171]



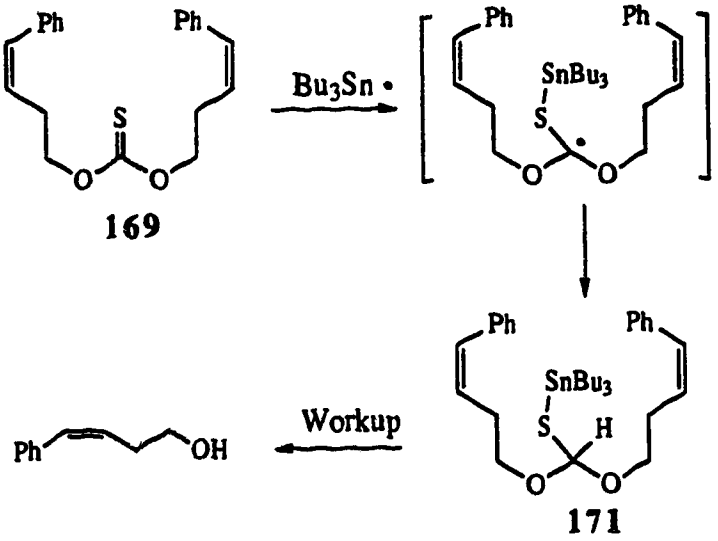
Scheme 126

Thiocarbonates **169** and **270** were prepared in a single step from the corresponding alcohols and either thiocarbonyldiimidazole or thiophosgene.



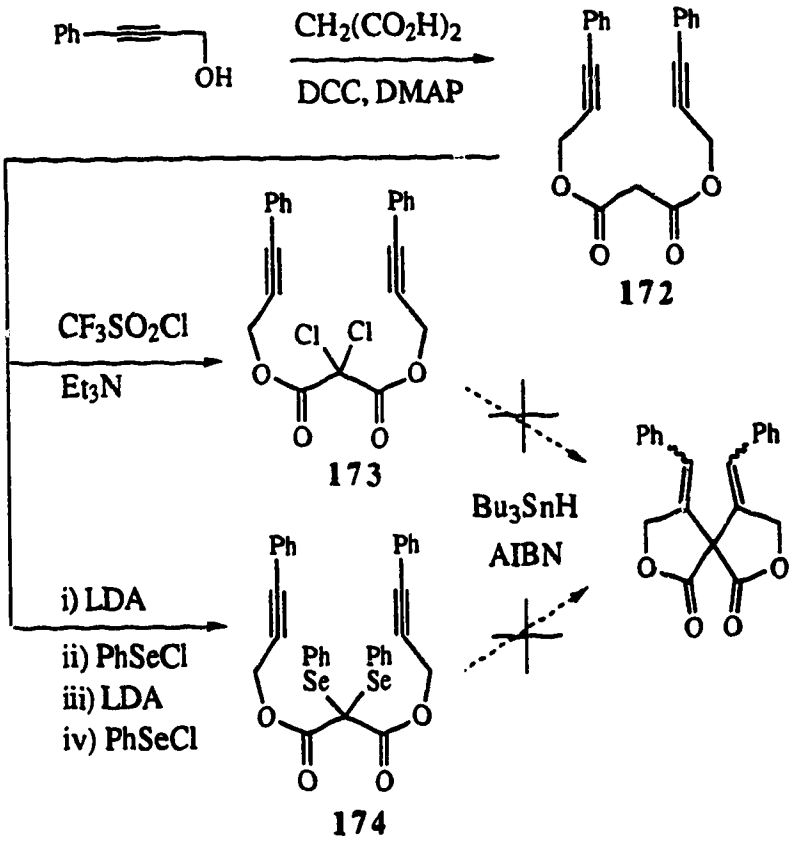
Scheme 127

Treatment of 169 or 170 under radical cyclization conditions failed to give cyclized products. In the case of the reaction of tributyltin hydride and AIBN with 169, the only isolated product was the original alcohol (57%), possibly formed by hydrolysis of an orthoester of type 171 (Scheme 128).



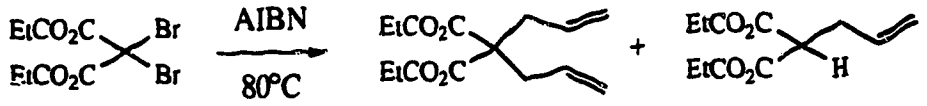
Scheme 128

Finally, we synthesized dichloro- and diseleno-derivatives of malonate ester 172, as shown in Scheme 129. Diester 172 was prepared from malonic acid under Mitsunobu conditions.[172] This compound could then be converted into dichloride 173 by reaction with trifluoromethanesulfonyl chloride and triethylamine.[173] Alternatively, two sequential deprotonations and trapping with phenylselenenyl chloride could be used to convert 172 into the bis(phenylseleno) compound 174. Neither 173 nor 174 gave spiro dilactones on treatment with stannane and an initiator.



Scheme 129

We concluded our investigation of double radical additions with a brief examination of the corresponding intermolecular processes. Allyltributyltin was chosen as the radical acceptor as it has been shown to be quite efficient.[7] AIBN was added to a refluxing benzene solution of the substrate and an excess of allyltributyltin. The double addition product **175** was obtained in moderate yield. However, even when a large excess of allyltributyltin was used, the mono addition product **176** was also formed.



175 **176**

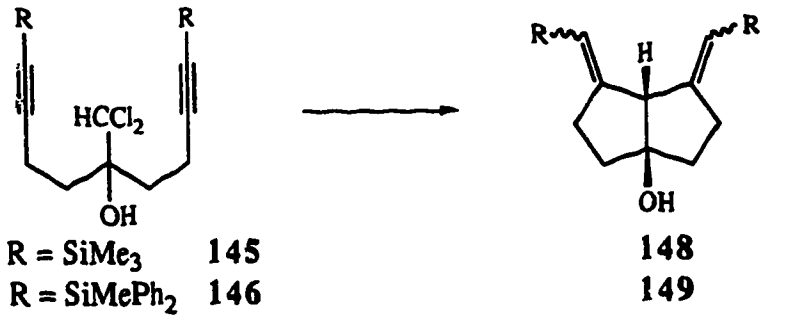
SnBu3	temp (°C)	yield (%)	
5 eq.	80	31	21
10 eq.	80	49	27
10 eq.	110	28	24

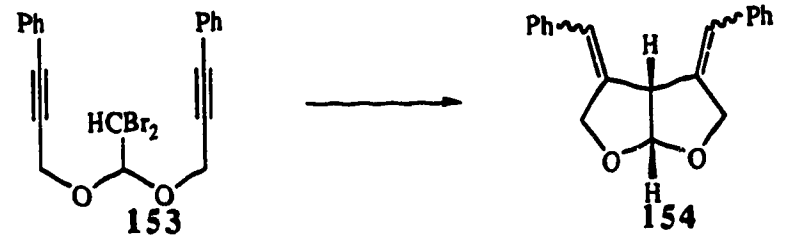
Scheme 130

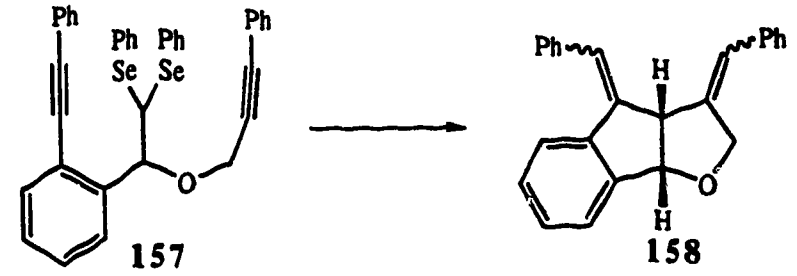
CONCLUSION

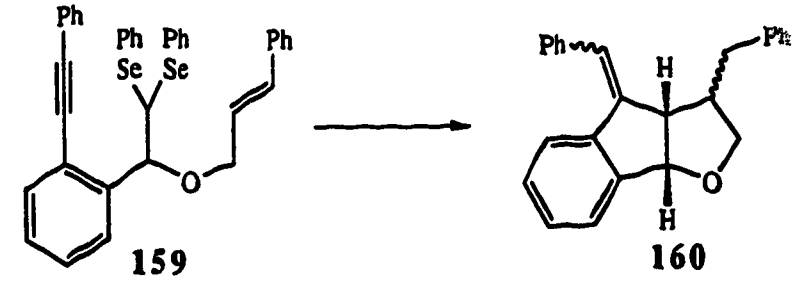
In summary, the double radical closures shown in Table I were carried out, but, our experience shows that making the required precursors can sometimes be difficult.

Table I





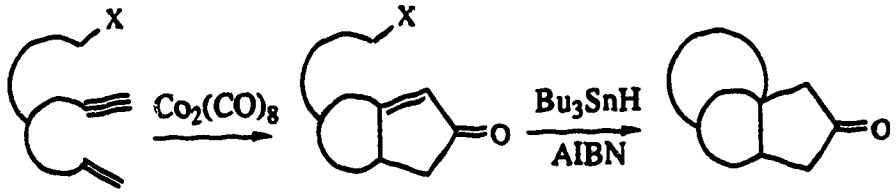




PAUSON-KHAND / RADICAL CYCLIZATION

In the introduction section of this thesis radical cyclizations were discussed with emphasis on the method used for preparation of the precursors. This section deals with our investigation into the use of the Pauson-Khand (P-K) reaction as a method for making radical cyclization substrates.

In the P-K reaction an enyne is treated with octacarbonyldicobalt to produce a cyclopentenone **178** (Scheme 131). An inherent feature of the process is formation of a double bond, which may act as a radical acceptor. This fact makes the P-K reaction suitable for combination with radical cyclization chemistry.



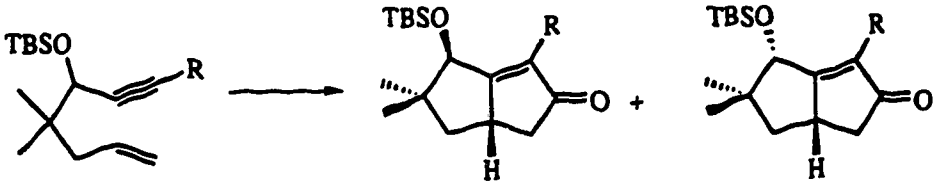
177 **178** **179**

Scheme 131

We hoped to carry out this reaction on an enyne **177**, to which a 'tail' carrying a homolyzable group had been attached. Then, following the P-K reaction, cleavage of the carbon-X bond would produce a radical which, on closure onto the olefin, would provide access to tricyclic alkanones of type **179**, in two steps from the corresponding acyclic enyne **177**.

Both heptenyne and octenyne systems have been used as substrates for the P-K reaction.[174] However, in general the heptenyne substrates appear to undergo P-K reaction more efficiently.[175]

Inspection of the literature told us that if the 'tail' carrying the homolyzable group were placed in the propargylic position of the enyne, then a high degree of stereoselectivity could be expected.[128] For example the enyne shown in Scheme 132, produced the enone with the C-5 pendant on the *exo*-face preferentially, especially when the alkyne substituent was large (e.g. R = TMS).

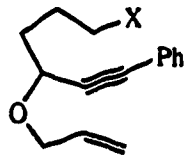


R = TMS	26	:	1
R = Me	3	:	1

Scheme 132

Smit[176] has shown that enynes in which the alkene and alkyne units are joined by an oxygen are excellent substrates for P-K cycloaddition on silica gel.

Considering the above information, it was decided that compounds **180** would be appropriate substrates, for the P-K / radical cyclization sequence.



180

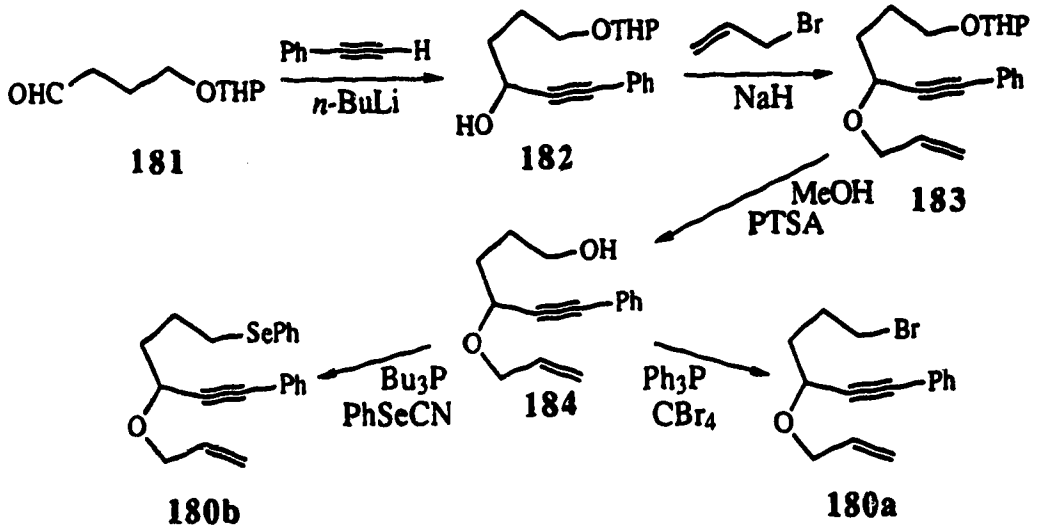
	X
a	Br
b	SePh

It was decided that the 'tail' carrying the homolyzable group should be three atoms in length, so that radical closure would be a 5-*exo* process -- a type known to be efficient. At this time there was no record of the P-K reaction

being carried out on substrates which contained homolyzable groups, and it was not clear if these groups would withstand the reaction conditions.[177] Both the bromide (**180a**) and the corresponding phenyl selenide (**180b**) were prepared, in an effort to determine which was most suitable.

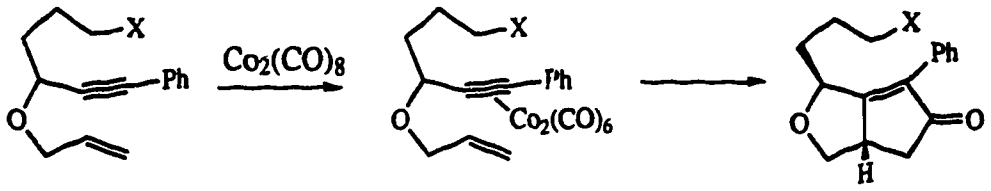
A phenyl group was placed on the 7-position of the enyne, since Magnus[128] had shown that a large group in this position was necessary to provide stereocontrol at the 5-position, during the P-K reaction. On the practical side, the phenyl group also made the compounds visible on TLC plates examined under a U.V. lamp, facilitating convenient analysis by thin layer chromatography.

The synthesis of the P-K precursors **180a** and **180b** is shown in Scheme 133. Both compounds were readily accessible from the corresponding alcohol **184** which, in turn, was available by removal of the protecting group[166] from compound **183**. The latter was prepared from aldehyde **181** by reaction with phenylacetylide followed by 3-bromopropene.



Scheme 133

When the individual enynes were stirred with octacarbonyldicobalt the cobalt complexes **185** (Scheme 134) were formed quickly (2-3 h at room temperature). They could be purified by flash chromatography, but we preferred to treat the crude material directly under cycloaddition conditions.



180 **185** **186**

	X
a	Br
b	SePh

Scheme 134

There are a variety of conditions under which the P-K reaction can be done (see Introduction Section). We investigated a number of these methods in order to determine which was most suited for our enynes, and the results of these studies are shown in Table 2.

The first attempt at the P-K reaction was conducted by heating the cobalt complexed alkyne **185a**, in the high boiling *t*-butylbenzene (entry *a*).[178] The bromine functionality survived these harsh conditions and the cycloaddition product was obtained in moderate yield, as a single isomer, which was assumed to have the pendant on the *exo*-face, by analogy with Magnus' work.[128]

Table 2

Entry	Compound **185** X =	Conditions	Yield (%)
a	Br	CO, *tert*-butylbenzene 170°C, 3h	26
b	Br	SiO_2 <5% H_2O 45°C, O_2	11
c	Br	SiO_2 10% H_2O 45°C, O_2	33
d	Br	SiO_2 20% H_2O 45°C, O_2	41
e	Br	Alumina 45°C Argon	0
f	Br	NMO, r.t.	47
g	SePh	SiO_2 20% H_2O 45°C, O_2	53
h	SePh	NMO, r.t.	59

The Smit[133] technology for P-K reaction, which involves adsorbing the cobalt complexed alkyne onto silica gel and heating in an oxygen environment, was investigated in an attempt to improve the yields. Initially commercial grade silica gel was used as purchased and again a single isomer was in obtained, but in very poor yield (entry *b*). Smit[133] noted that silica gels containing <5% water were inactive as P-K supports, as were those containing more than 30%. Therefore the P-K reaction on silica gel was repeated, using silica gel to which water had been added (10% w/w in entry *c*, and 20% w/w in entry *d*). Smit stated that equal success could be expected with other supports; however, in our hands, alumina (CAMAG, Aluminium Oxide for chromatography, 507-C, neutral) (entry *e*) was inactive.

The silica gel containing 20% water was found to be the support of choice. In some cases difficulties in reproducing experimental yields were experienced, especially when the scale of the reaction was increased. This may have been due to inefficient mixing of the dry reaction mixture.

Schreiber[141] reported the use of 4-methylmorpholine *N*-oxide (NMO) in promoting the P-K reaction. In our hands this method (entry *f*) was also very successful. Consistently reasonable yields were obtained even on larger scale reactions. It is important that the NMO be completely dry, and so it was sublimed and stored under argon prior to use.

The corresponding phenylseleno complex **185b** was subjected to P-K reaction conditions both on silica gel (entry *g*) and with NMO (entry *h*). The cycloadditions were equally or slightly more efficient than with the bromide. Also, as with the bromide, only one isomer of the product **186** was obtained.

The stage was now set for the 5-*exo* radical cyclization. The enones **186a** and **186b** were treated with tributyltin hydride and AIBN; however, in both cases substantial amounts of the reduction product **188** was isolated (Scheme 135).*

It appeared that radical **187** was being reduced before it had time to undergo 5-*exo* closure onto the double bond. We speculated that abstraction of hydrogen (H_a) would produce radical **189a**, in which the radical is highly stabilized, since it is adjacent to an oxygen, and conjugated with an aromatic

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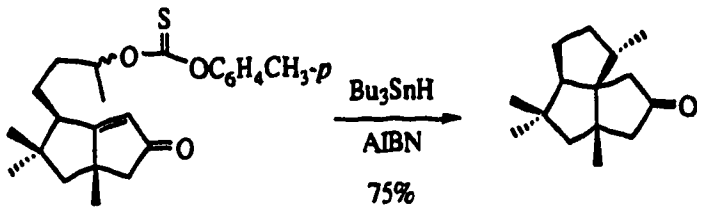
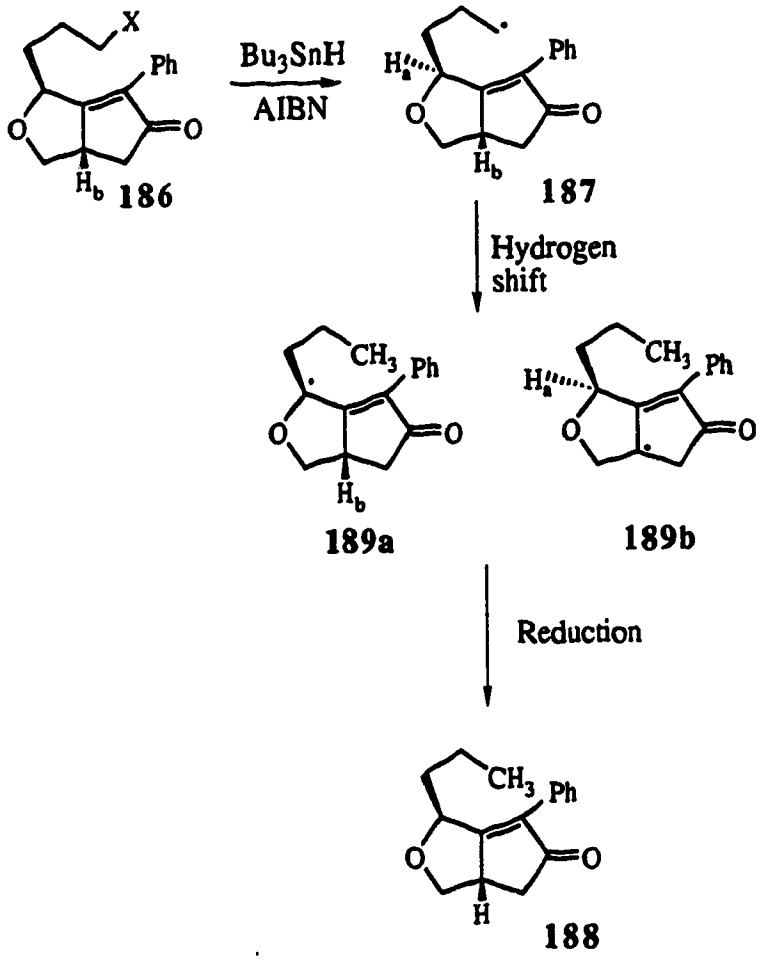
* Rao reported the radical cyclization of a similar compound in his synthesis of silphinene.[179]



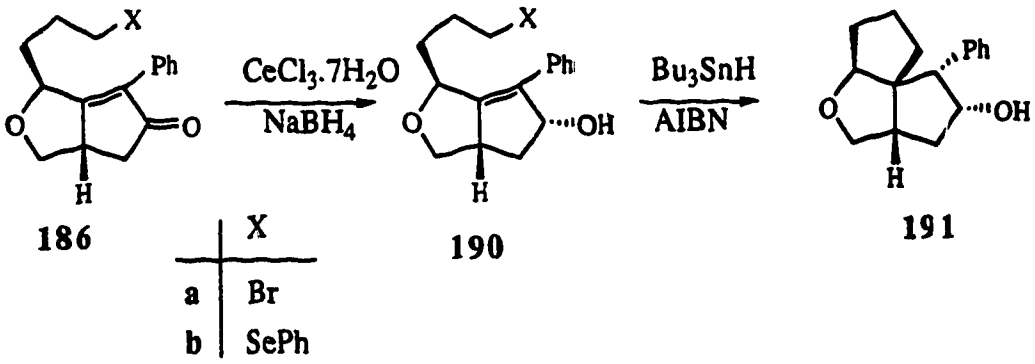
ring and a ketone. This abstraction in probably intermolecular, since intramolecular 1,4-hydrogen abstractions are rare.[180] Similarly, abstraction of (H_b) would produce a radical conjugated with the aromatic ring and ketone. Inspection of models suggest that abstraction of (H_b) is feasible and probably involves an intramolecular 1,6-hydrogen shift.[181]



Scheme 135

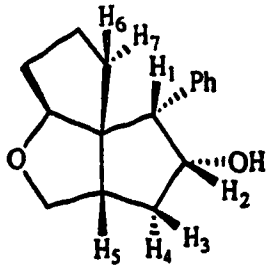
In order to obtain efficient radical cyclization it appeared necessary to destabilize radicals **189a** and **189b**. To this end the enones **186** were reduced to the corresponding allyl alcohols **190** (Scheme 136).[182] This reduction proceeded in a stereoselective manner to produce only one isomeric product,

which we assumed was that formed by reduction from the *exo*-face. This stereochemical result was confirmed at a later stage.



Scheme 136

The radical cyclization of compounds **190a** and **190b** proceeded smoothly. In each case the angularly-fused triquinane **191** was obtained as a single isomer, and its stereochemistry was established by a detailed ^1H NMR analysis.

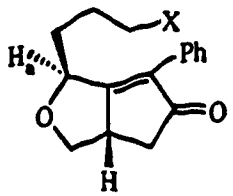


191

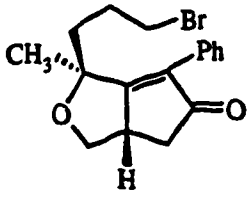
A large coupling between H_1 and H_2, H_2 and H_3, and between H_3 and H_5 indicated that these three hydrogens are on the same face of the cyclopentane ring. H_4 had a large coupling with H_3, but only small couplings with either H_2 or H_5. When H_1 was irradiated an NOE effect was seen for H_2, H_3, H_5, H_6 and H_7, proving that the hydroxyl and phenyl groups were cis, and

on the *endo* face of the cyclopentane ring. A more comprehensive discussion of the stereochemical assignment is given in the experimental section.

In the next example the hydrogen H_a (in **186**), which we suspected might be responsible for premature reduction in the previous examples, was replaced by a methyl group (as in **192**).

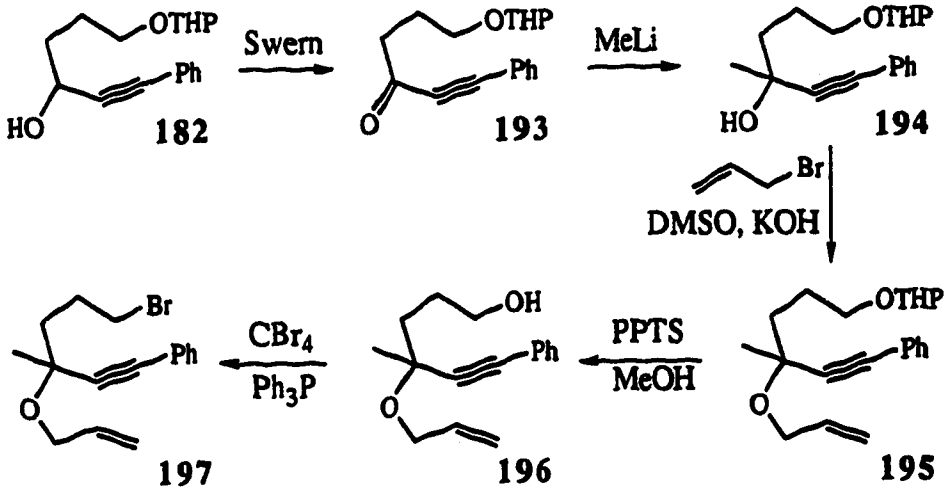


186



192

The key precursor (**197**) leading to **192** was synthesized by a similar route to that used in the previous example.

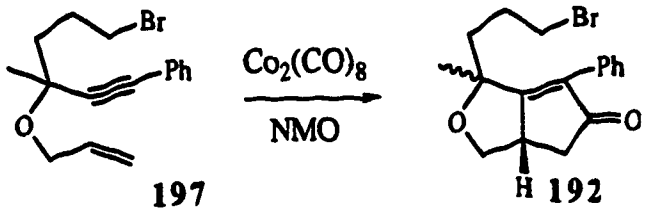


Scheme 137

Alcohol **182** was oxidized under Swern conditions to ketone **193** which, on reaction with methyllithium, afforded the tertiary alcohol **194**. Reaction of this alcohol with 3-bromopropene in the presence of sodium hydride (as used for the preparation of compound **183**) failed to give the O-alkylated product

195. However, when freshly crushed potassium hydroxide was used as the base, and DMSO as the solvent, the alkylation proceeded to give **195** in high (70%) yield.[183] The tetrahydropyranyl protecting group could be removed by refluxing a methanol solution of **195** in the presence of PTTS,[184] and then alcohol **196** was converted into bromide **197**.

The P-K reaction, carried out using NMO, gave a 1:1 (as judged by ^1H NMR) inseparable mixture of two diastereomers in excellent yield (74%). In this case there is little difference in the steric bulk of the 5-methyl and 5-bromopropyl substituents, and hence equal amounts of the two possible diastereomers were produced.[128]



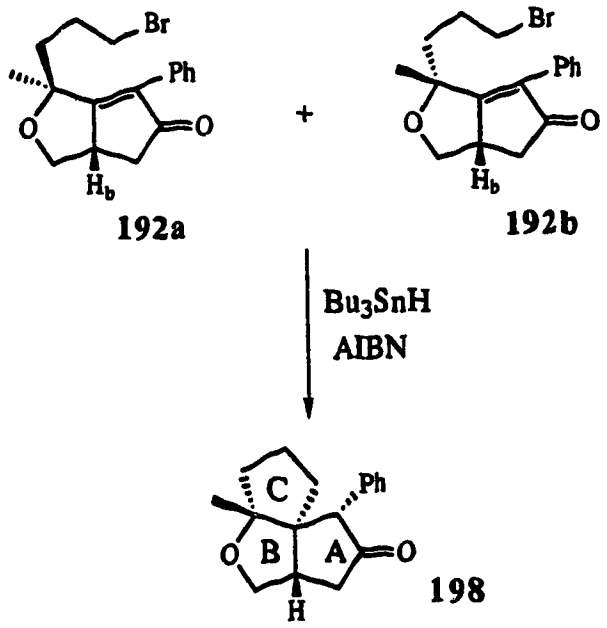
197 **192**

Scheme 138

The mixture of **192a** and **192b** (Scheme 139) was treated under radical cyclization conditions, but gave a rather complex mixture* . However, it was possible to isolate the tricyclic ketone **198**, in good yield (74%, assuming a 1:1 ratio of starting materials). No product from **192a** was isolated. The fact that **192a** did not undergo efficient closure supports the theory that the radical is being reduced by a 1,6-hydrogen abstraction of (H_b). In compound **192b**, the radical is generated on the opposite face of the molecule, and this abstraction is not possible. Closure of **192b** in a 5-*exo* fashion produces a cis fused B-C ring system, however in doing so the A-B system is forced to be trans fused.

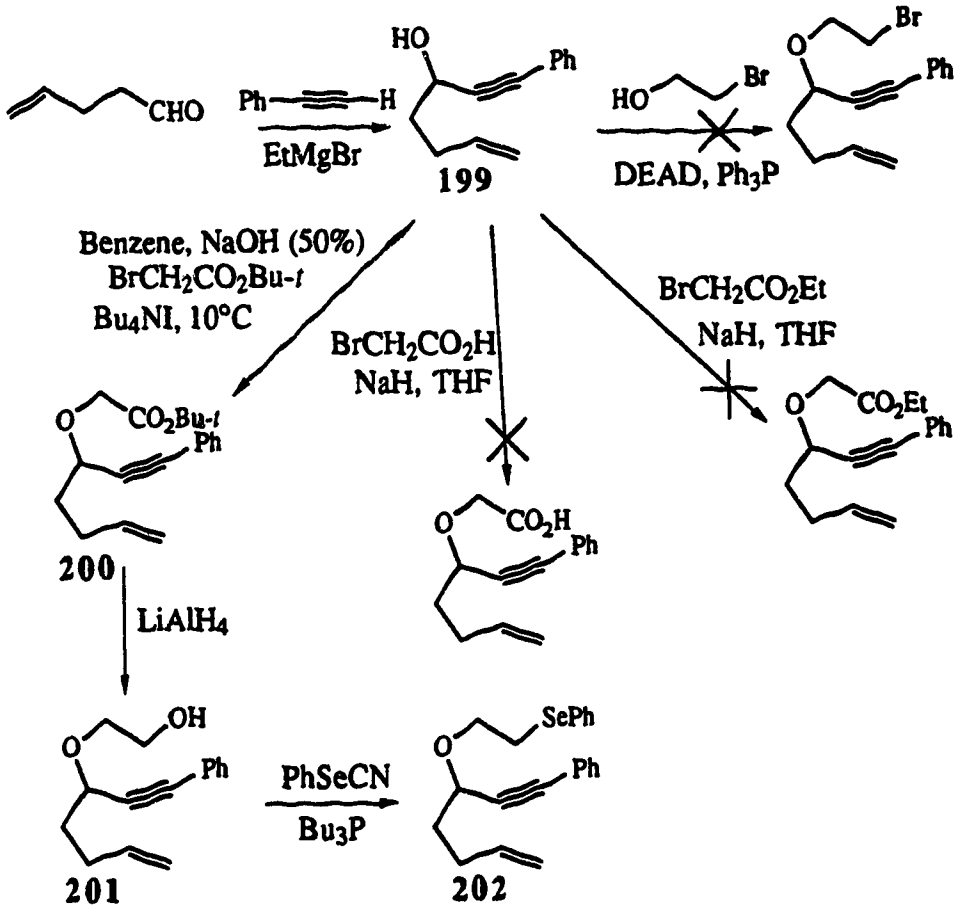
* Radical cyclization of the corresponding selenides gave a more complex reaction mixture containing substantial quantities of the starting material.

Thus there is considerable steric strain in **198**. A complete discussion of the stereochemical assignment of **198** is given in the experimental section.



Scheme 139

Smit has shown that all-carbon enynes (i.e. no heteroatom is present in the chain) with polar substituents adsorb onto silica gel and undergo efficient P-K reaction (see Scheme 101).[132,140] The next substrate synthesized was made up of an all-carbon heptenyne unit, with a polar ether chain containing the homolyzable group (**202** in Scheme 140).

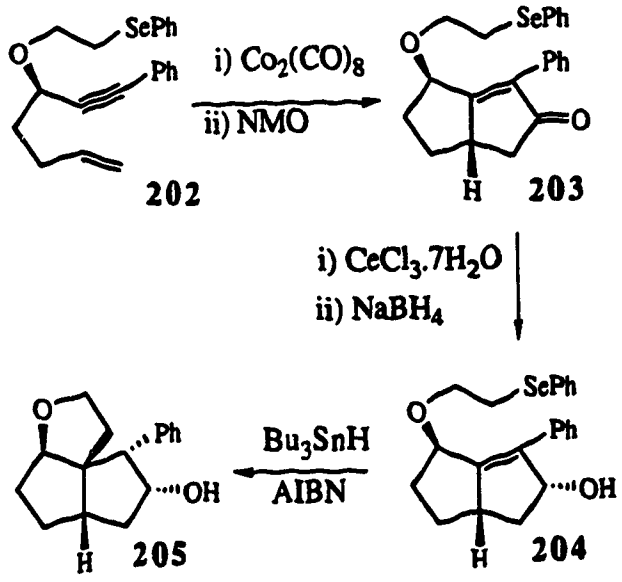


Scheme 140

Alcohol **199** was obtained by condensation of phenylacetylide and 4-pentenal. Various attempts were made to alkylate this alcohol with a two carbon unit, including reaction with 2-bromoethanol under Mitsunobu conditions,[172] reaction with bromoacetic acid, and ethyl bromoacetate in the presence of sodium hydride. Finally, it was found that reaction with *t*-butyl bromoacetate under phase-transfer conditions[185] gave access to the corresponding *t*-butyl ester **200**. Reduction to alcohol **201** with lithium aluminum hydride and conversion to the selenide proceeded without incident.

The P-K reaction with substrate **202** was carried out using NMO as reaction promoter and proceeded smoothly, producing **203** in 75% yield, as a

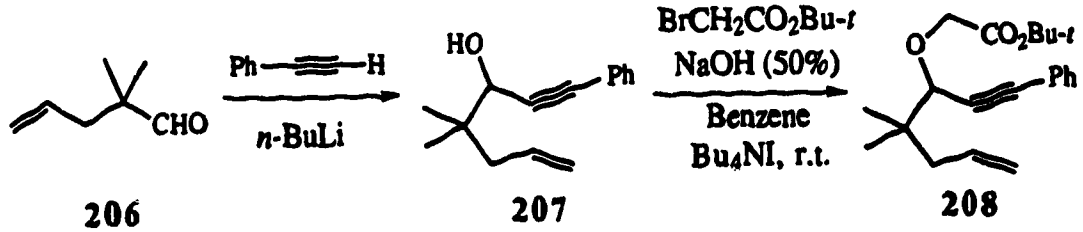
single isomer. The enone was reduced stereoselectively[182] to **204**, and radical cyclization gave a single isomer of the tricyclic product.



Scheme 141

The relative stereochemistry of the final product (**205**) was determined by NMR decoupling and NOE experiments. A comprehensive discussion is given in the experimental section.

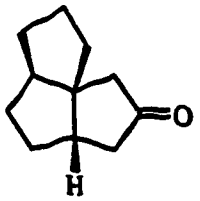
Substituents at the 4-position of an enyne have been shown to improve the yields of the P-K reaction in certain cases,[129] by the Thorpe-Ingold effect.[130] We decided, therefore, to prepare an analog of **202**, which contained a gem-dimethyl group at the 4-position, to take advantage of this phenomenon.



Scheme 142

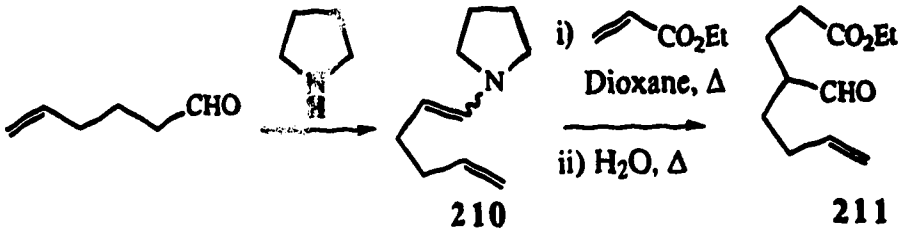
2,2-Dimethyl-4-pentenal was made by a literature procedure,[186] and converted to enyne **207** by reaction with phenylacetylide. Unfortunately the neopentyl alcohol was quite unreactive and attempts to alkylate it were not very promising. The phase-transfer conditions[185] used for the corresponding 4-unsubstituted example were only moderately successful (20%) and the route was abandoned.

The examples described so far had an oxygen in one of the rings formed during the P-K / radical cyclization sequence, and we decided to investigate next the potential of the sequence for preparing all carbon triquinanes (i.e. **209**).[187]



209

The synthesis of the P-K substrate is shown in Schemes 143-145. The pyrrolidine enamine of 5-hexenal (**210**) was treated with ethyl acrylate, and the product hydrolyzed to give ester aldehyde **211**.[188]

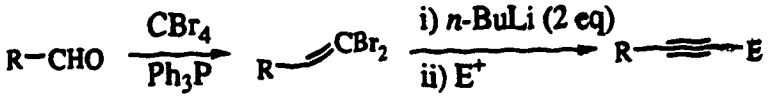


210 **211**

Scheme 143

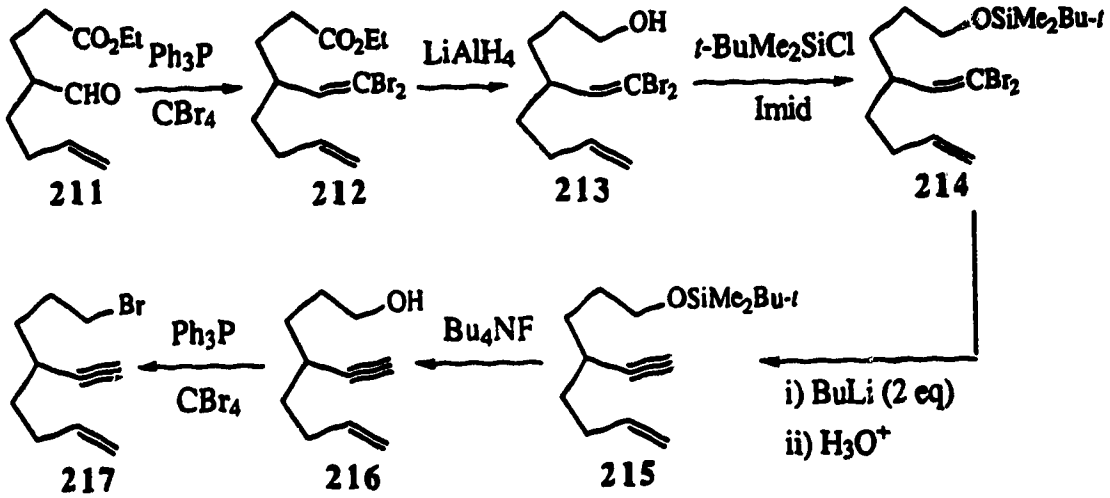
The ester would be reduced to the corresponding alcohol and subsequently converted into the bromide, while the aldehyde functionality

would serve to generate the alkyne, by a strategy developed by Corey[189] (Scheme 144). Reaction of an aldehyde with carbon tetrabromide and triphenylphosphine gives the corresponding dibromoalkene. Treatment with two equivalents of *n*-butyllithium then results in elimination of hydrogen bromide followed by lithium-bromine exchange to furnish the acetylide, which may be trapped by an electrophile.



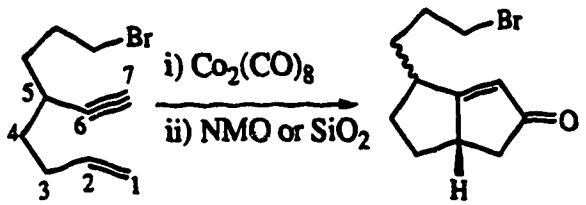
Scheme 144

Reaction of aldehyde **211** with carbon tetrabromide and triphenylphosphine gave the dibromoalkene **212**, in high yield. The ester was then reduced and protected as the silyl ether. Reaction of the dibromoalkene **214** with *n*-butyllithium (2 equivalents) and trapping with water afforded the terminal alkyne **215**. The silyl protecting group was removed and the alcohol converted to the bromide without any difficulty.



Scheme 145

The P-K reaction was carried out with NMO and with silica gel (20% water), and the pentalenones **218** were produced in yields of 40 and 31%, respectively.

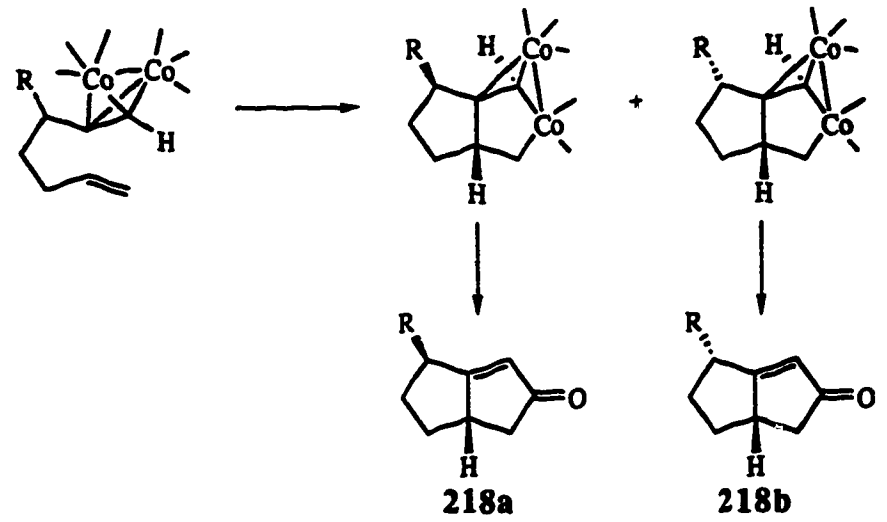


217 **218**

Scheme 146

A 31% yield when silica gel was used as support is significant, since it was previously believed that the enyne molecule must contain a polar group to enable it to bind with the silica gel.[107]

With both NMO and silica gel the enone was obtained as mixture of two diastereomers. Since the C-7 substituent is a hydrogen, there is an absence of large steric interactions between the C-5 and C-7 substituents in the metalocycle intermediates (Scheme 147). Thus, both bicyclic enones, **218a** and **218b**, are possible.[128]

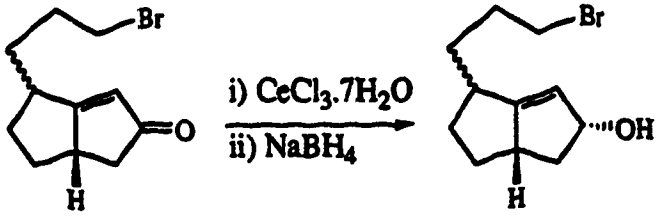


218a **218b**

Scheme 147

When the mixture of enones **218** was treated under radical cyclization conditions, a complex mixture was produced and, because of the low polarity of the products, the components could not be separated.

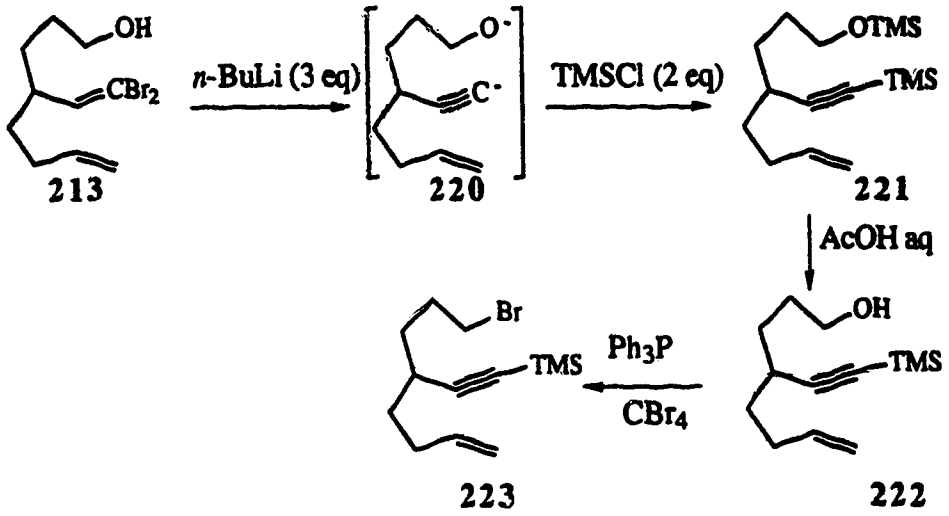
The enone mixture **218** was therefore reduced to the allylic alcohols (**219**, Scheme 148) in an effort to increase the polarity. However, the allylic alcohols were inseparable, as were the derived radical cyclization products.



218 **219**

Scheme 148

At this point we decided to repeat this example with a larger group on the C-7 position of the enyne, in order to increase the stereoselectivity of the P-K reaction. The corresponding enyne with a trimethylsilyl group on the alkyne terminus was therefore prepared.



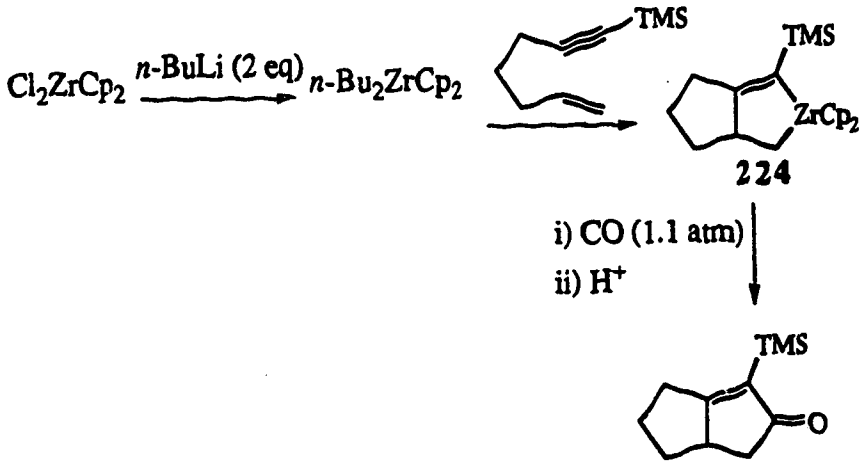
Scheme 149

Bromide **223** was available from alcohol **222**, which, in turn, was prepared from the dibromoalkene **213** without isolation of intermediates.[189] Reaction of **213** with *n*-butyllithium (3 equivalents) gave the dianion **220** as shown in Scheme 149. Trapping with trimethylsilyl chloride (2 equivalents) and subsequent hydrolysis of the silyl ether afforded **222**. The P-K reaction of **223** on both silica gel (20% water) and with NMO, failed to produce any of the desired product.

Trimethylsubstituted alkynes have been reported to give higher yields than the corresponding unsubstituted compounds in some cases.[190] However, there are also reports of low yields and failures, especially when the 5-position is heavily substituted.[178, 191]

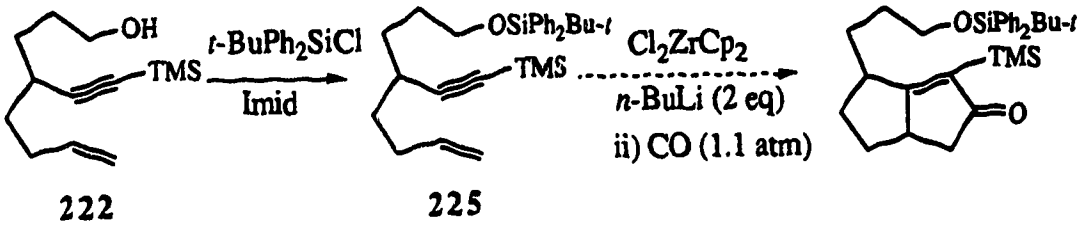
Negishi[192] has reported the use of a zirconocene equivalent in zirconium-promoted cyclization of enynes (Scheme 150). Reaction of zirconocene dichloride with alkyllithiums is a convenient method for generating these zirconocene equivalents. The zirconocene then reacts with

enynes to produce the zirconobicyclic product **224**, which can be carbonylated to give the bicyclic enone.



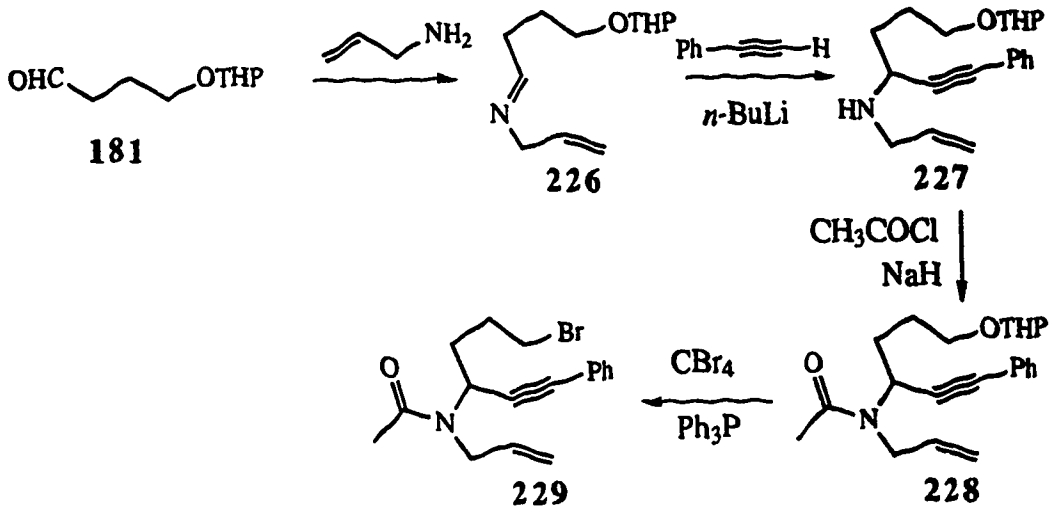
Scheme 150

In the light of this information we converted alcohol **222** into a protected form **225** (Scheme 151), and subjected this to the Negishi conditions;[192] however, no bicyclootenone was formed.



Scheme 151

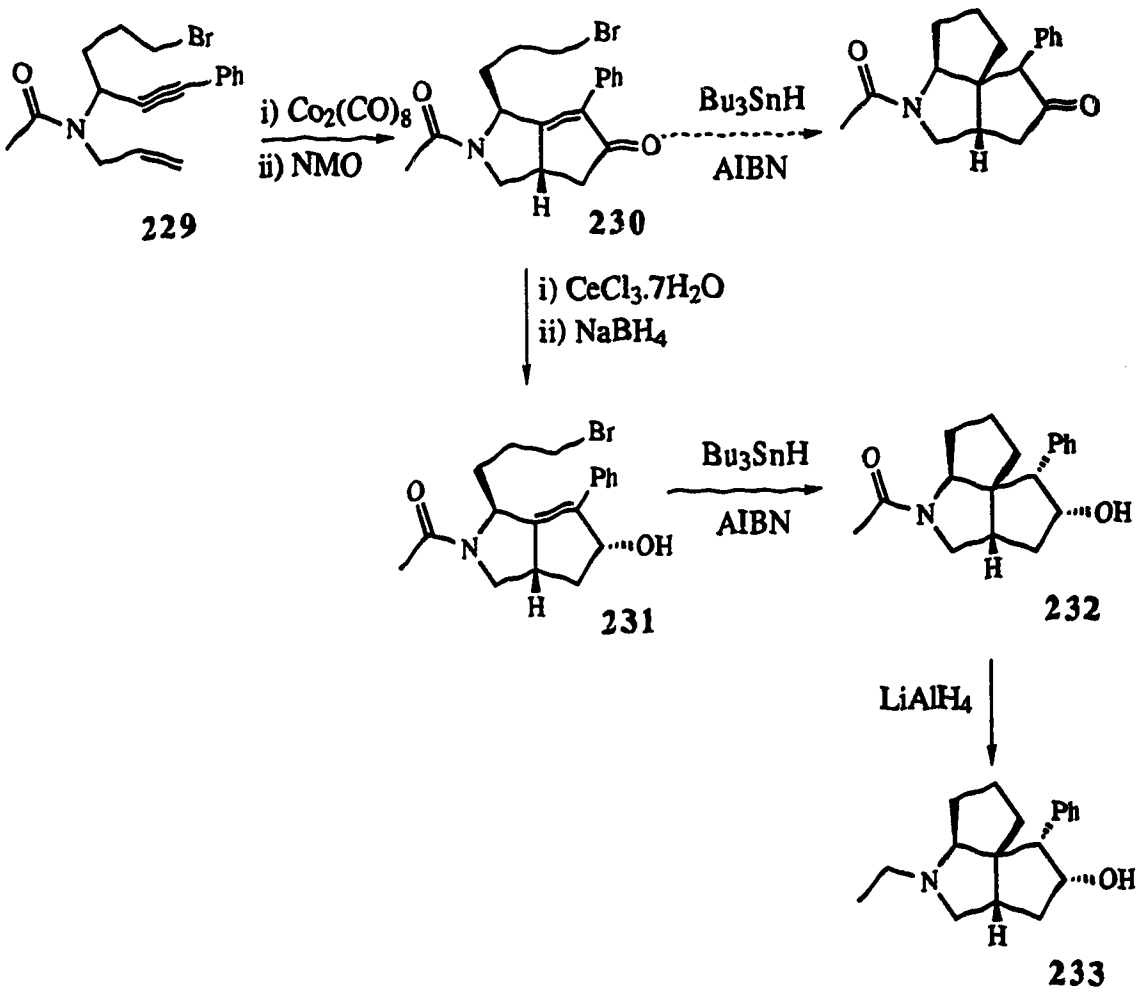
We next turned our attention to the synthesis of nitrogen substituted triquinanes. The precursor **229** was synthesized according to Scheme 152.



Scheme 152

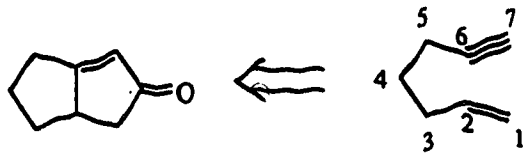
Aldehyde **181** was converted to the imine, which, on reaction with phenylacetylide,[193] gave the amine **227**. This was then converted into the corresponding amide.[194] The tetrahydropyranyl group was then removed and the alcohol converted in a single step[195] into bromide **229**.

The P-K reaction was carried out with NMO as promoter, affording the product **230** as a single isomer in 64% yield. Treatment of **230** under radical cyclization conditions produced a complex mixture from which no identifiable product could be isolated. However, after the enone was reduced to the allyl alcohol **231**, radical cyclization proceeded smoothly to give an inseparable mixture of two products **232**, (2:1 as judged by NMR at 25°C). Decoupling and NOE experiments showed that the hydroxyl and phenyl groups were cis, and on the β-face in both structures. Thus, **232** was determined to be a mixture of N-C(O) rotamers.[196] This was confirmed by efficient conversion of both rotamers to a single amine **233**. A full account of the NMR assignments of the amide rotamers is given in the experimental section.



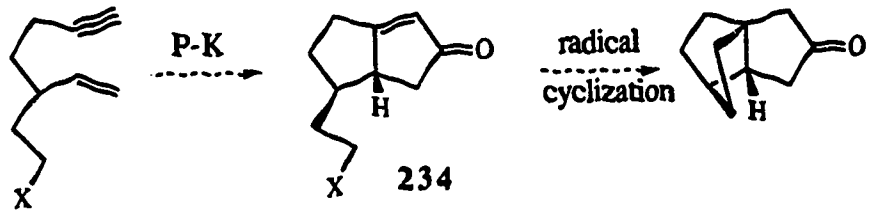
Scheme 153

All the examples discussed so far were similar in that the pendants carrying the homolyzable group were attached to the propargylic C-5 position (of the enyne). We now inspected the general structure of the P-K bicyclic system to determine which other positions would be suitable for attachment of the chain carrying the radical precursor.



Scheme 154

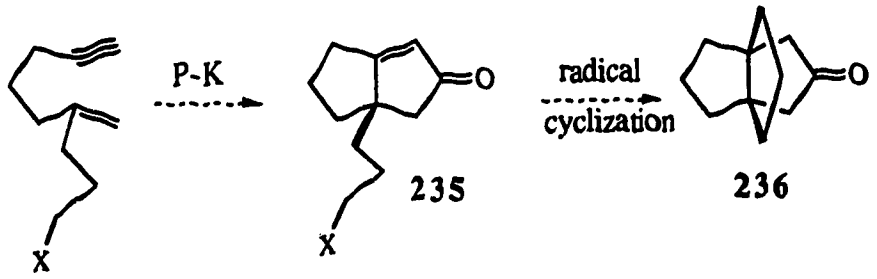
Substituents at C-4 are known to improve yields, however there is a lack of steric control.[128, 197] Allylic C-3 substituents exert stereochemical control and reside on the *exo*-face in the major product.[127, 198] In order for 5-*exo* closure to be possible a two atom chain would be needed on C-3, as in compound **234** (Scheme 155), but inspection of models of **234** indicates that the radical center would be very distant from the radical acceptor, and so radical cyclization was expected to be inefficient.



234

Scheme 155

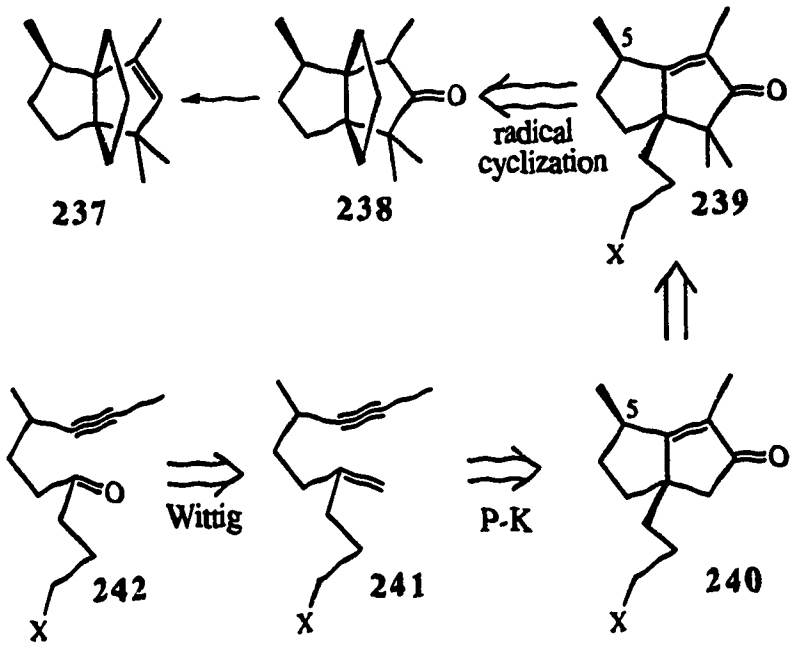
Only one stereoisomer is possible from the P-K reaction of enynes substituted at the C-2 position.[132] If the substituent were a three atom chain carrying a homolyzable group X (as in **235**, Scheme 156) then 5-*exo* radical cyclization would provide access to propellane **236**.



235 **236**

Scheme 156

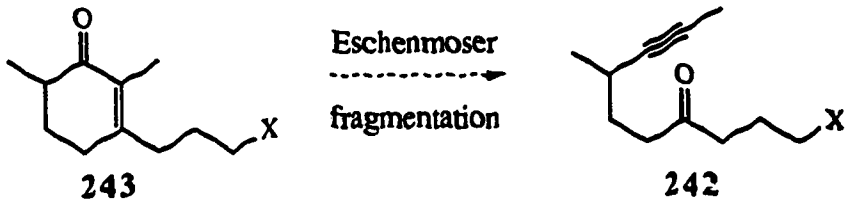
At this point we noticed that this reaction would be well suited to the preparation of the naturally occurring triquinane modhephene **237**,[194] since this compound had been shown to be accessible from tricyclic ketone **238**.[200]



Scheme 157

It appeared that **238** would be available by 5-*exo* closure of **239**, which, in turn, would be made from **240** by two sequential kinetic deprotonations and trapping with methyl iodide. Compound **240** should be the major product from the P-K reaction of enyne **241**, i.e. the C-5 methyl would be expected to be on the *exo*-face.[128] [Also, if a mixture were produced it should be possible to epimerize the C-5 methyl in compound **239**.] We expected **241** to be available from **242** by Wittig reaction.[201]

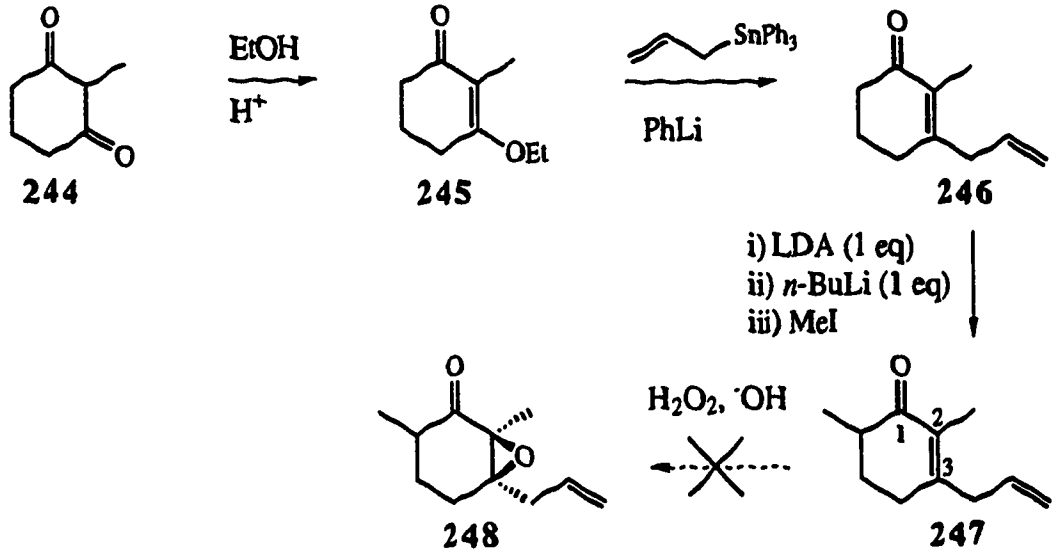
Our first strategy for the preparation of **242** was to use an Eschenmoser fragmentation (Scheme 158).



243 242

Scheme 158

We selected 248 as the Eschenmoser substrate. The terminal olefin would later be hydroborated and converted to the X group.



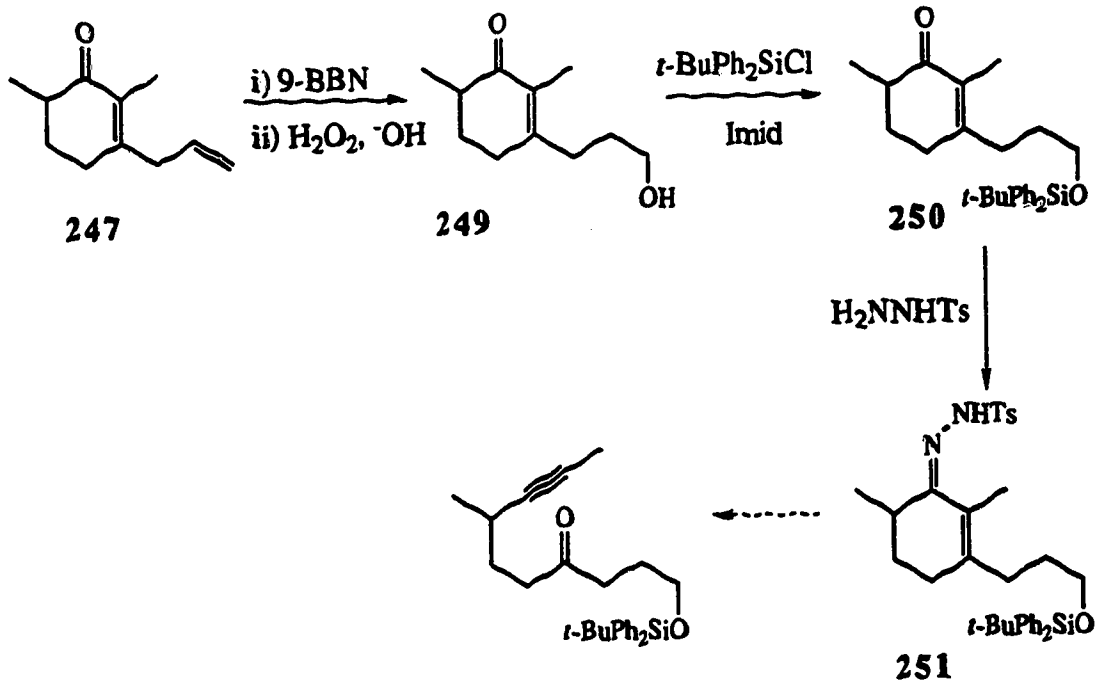
244 245 246 248 247

Scheme 159

The diketone 244 was converted into 245 by a literature procedure.[202] This compound was treated with allyllithium[203] to furnish the allyl enone 246.[204] A double deprotonation and trapping with methyl iodide then gave 247. However, epoxide 248 could not be prepared from 247,[205] probably due to steric crowding at C-3.

In cases where direct epoxidation of the enone is difficult, the problem may be circumvented by reversing the order of the two steps in the

Eschenmoser fragmentation sequence.[206, 207] In order to test this technology, compound **247** had to be converted to the corresponding hydrazone.

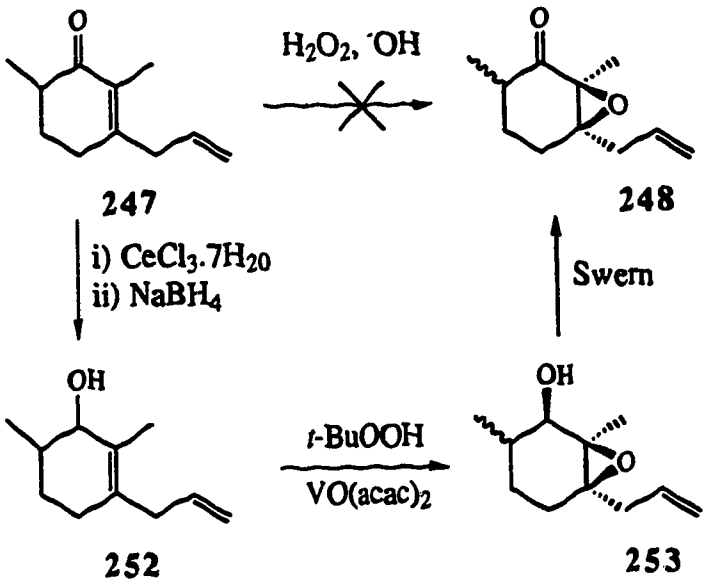


Scheme 160

To this end compound **247** was selectively hydroborated[208] at the terminal alkene, and oxidized to the primary alcohol, which was then protected as the silyl ether **250**. Reaction with *p*-toluenesulfonyl hydrazine[209] gave the tosyl hydrazone **251**. However, only small quantities (14%) of the product could be obtained, probably due to the steric crowding about the carbonyl. In any case, efforts to carry out the fragmentation by epoxidation[206] and by treatment with NBS in ethylene glycol[207] failed.

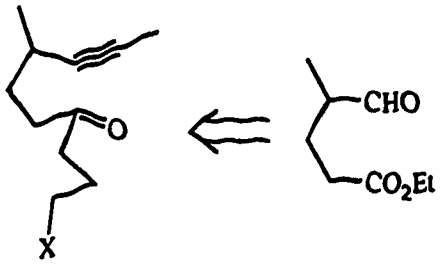
We then decided to prepare the epoxyketone **248** in a round-about manner. Compound **247** was reduced[182] to the allylic alcohol **252**, and then directed epoxidation[210] followed by oxidation afforded **248**. However,

reaction with *p*-toluenesulfonyl hydrazine failed to give any Eschenmoser fragmentation product.[211]



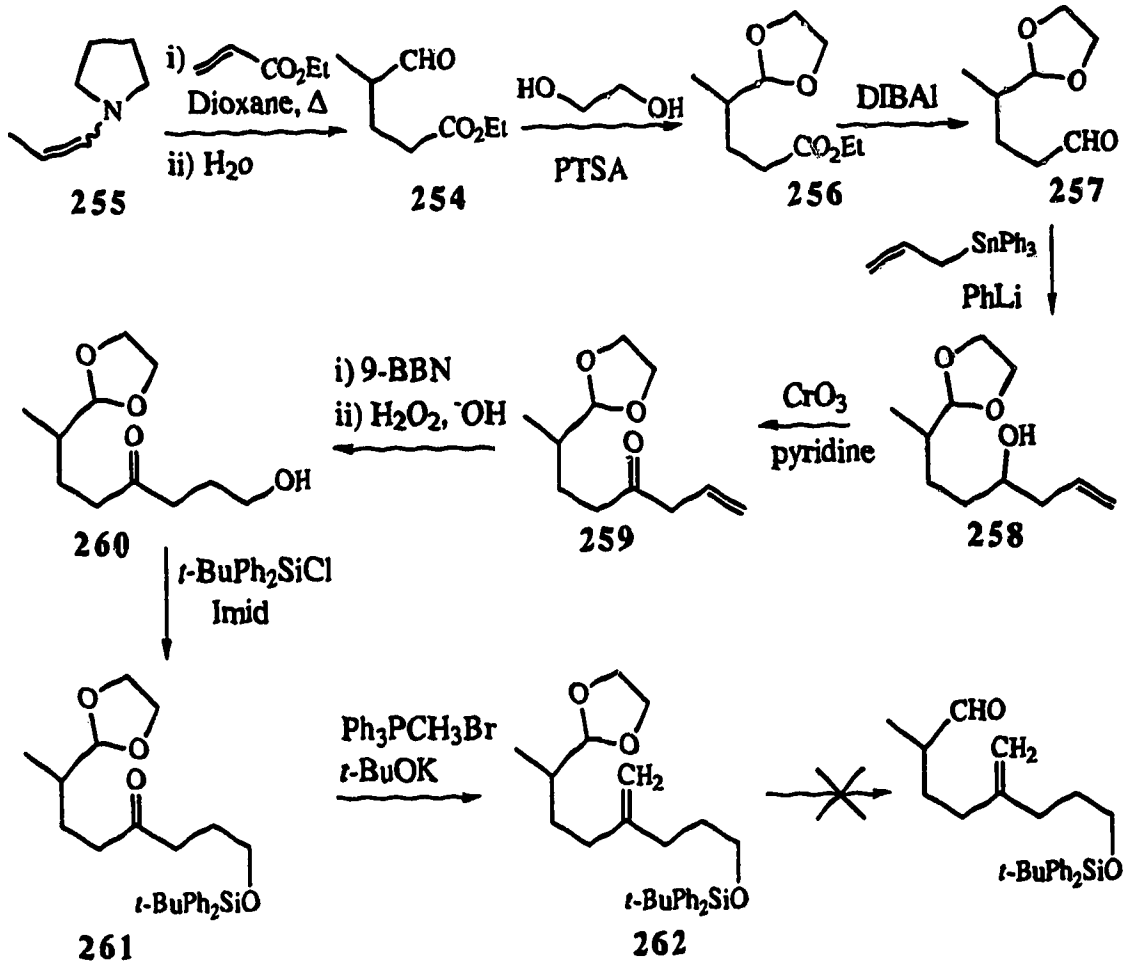
Scheme 161

We therefore returned to out original target **242**, and used a different approach, as shown in Scheme 162. We envisaged the alkyne unit being derived from the aldehyde, by the Corey dibromoalkene strategy used previously,[189] while the ester functionality would be converted to the ketone side chain carrying the X group.



Scheme 162

The synthesis is shown in Scheme 163. Michael addition of enamine 255 to ethyl acrylate gave aldehyde ester 254.[188] The aldehyde was then protected as the dioxolane.[212] Reduction of ester 256 with DIBAL afforded aldehyde 257, which was reacted with allyllithium to produce the alcohols 258. Oxidation to 259 had to be carried out under mild non-acidic conditions to avoid migration of the double bond into the conjugated position. Collins reagent was quite effective.[213] Hydroboration-oxidation[208] and protection of the alcohol as a silyl ether proceeded efficiently. Ketone 261 was then converted to the alkene 262 by Wittig reaction.[201]



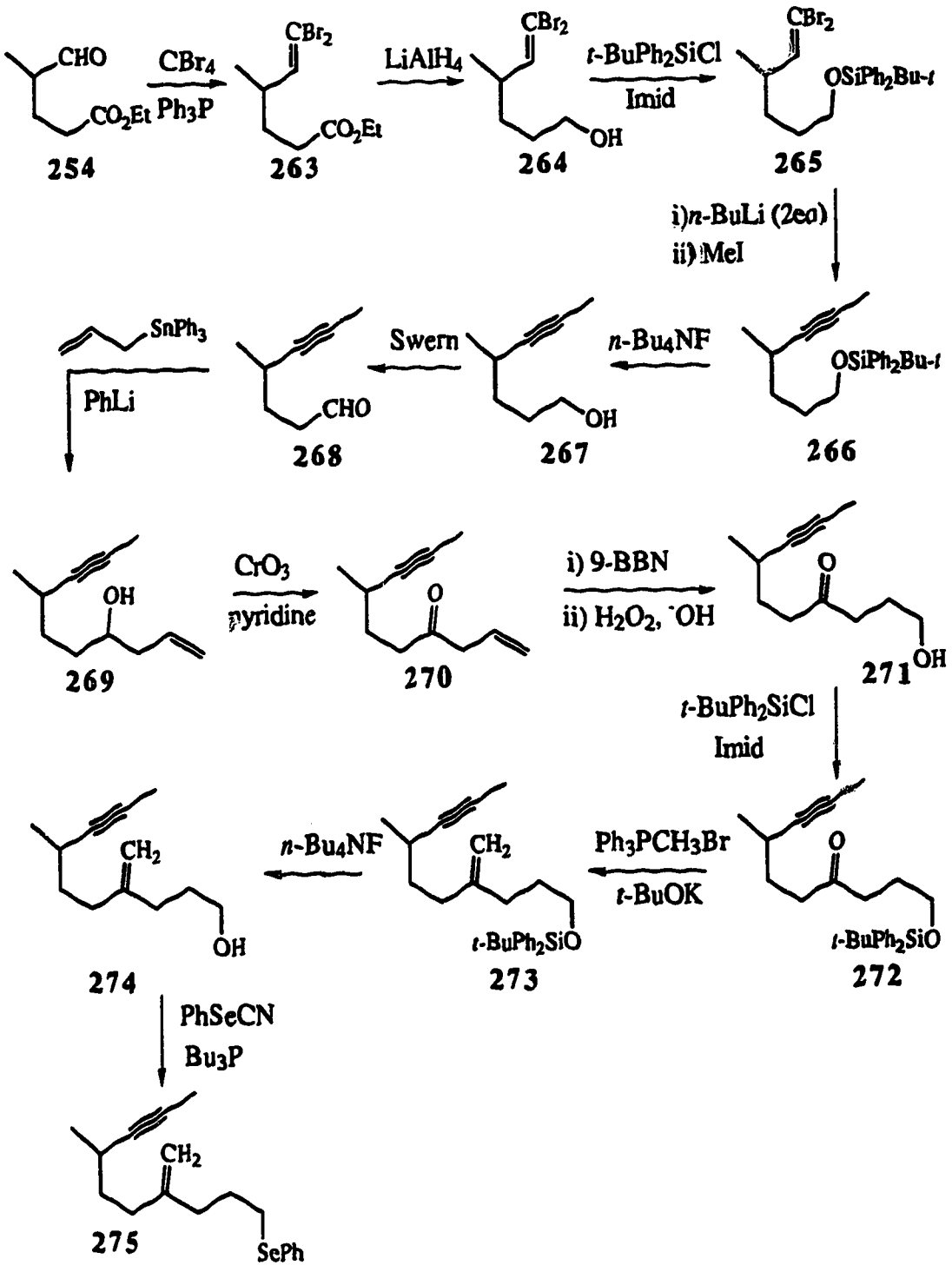
Scheme 163

Removal of the dioxolane protecting group proved to be problematic. Many methods were tried, resulting in either recovery of starting material or decomposition. The methods examined included 2.5% aqueous hydrochloric acid in acetone,[214] PPTS in aqueous acetone,[215] oxalic acid in aqueous methanol,[216] 10% aqueous hydrochloric acid in acetone, trimethylsilyl iodide in acetonitrile,[217] dimethylboron bromide in dichloromethane,[218] 80% acetic acid at 65°C,[216] perchloric acid,[219] boron tribromide in dichloromethane, aqueous DMSO at 120°C,[220] aqueous hydrochloric acid in acetic acid/THF mixture,[221] and *N*-bromosuccinimide and barium carbonate in carbon tetrachloride, followed by lithium tetrafluoroborate in acetonitrile.[222]

Due to our inability to cleave the dioxolane, the order of the reaction sequence had to be changed, as shown in Scheme 164.

Aldehyde ester **254** was treated under Corey's conditions[189] to give the dibromoalkene **263**. The ester was then reduced, and the alcohol protected. At this stage the dibromoalkene was converted into the alkyne **266** by trapping the acetylide anion with methyl iodide. The alcohol was deprotected and oxidized to **268**. Reaction with allyllithium, Collins oxidation and protection of alcohol **271** furnished **272** without any problems. Following the Wittig reaction (**272**→**273**) the alcohol was deprotected and converted into the corresponding phenyl selenide **275**.

With enyne **275** in hand we were now in a position to carry out the P-K / radical cyclization sequence. Unfortunately, attempts to carry out the P-K using either NMO or silica gel (20% water) failed. When carried out under standard conditions only starting material was recovered, and when these reactions were conducted under more forcing conditions, i.e. silica gel 20% water 45°C for 24 h, NMO 2 days at room temperature or NMO at 85°C, decomposition occurred.

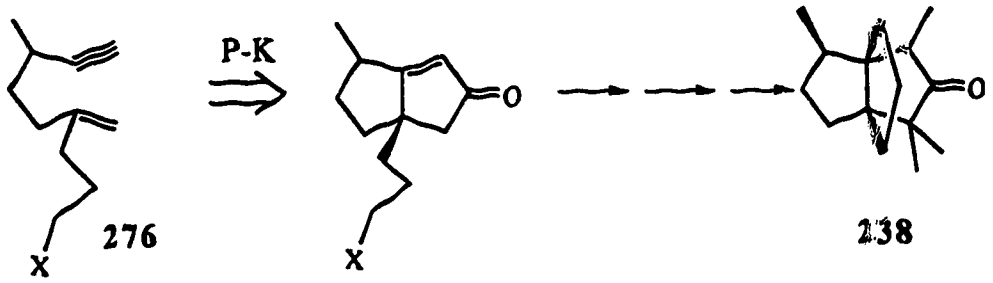


Scheme 164

We subjected the silylether 273 to similar conditions, hoping that it would be more robust, and also that the polar group might help adsorbtion

onto the silica gel[107] but these experiments were equally unsuccessful. Thin layer chromatographic inspection of the reaction mixtures indicated that the cobalt-complexed alkyne formed rapidly, as usual; however, the disubstituted alkene appears to be too hindered to permit insertion into the cobalt complex.

It is known that terminal alkynes are less selective with respect to alkene substitution.[110] Thus it may still be possible to synthesize modhephene by P-K / radical cyclization technology with compound **276** (Scheme 165), but we have not yet pursued this possibility.

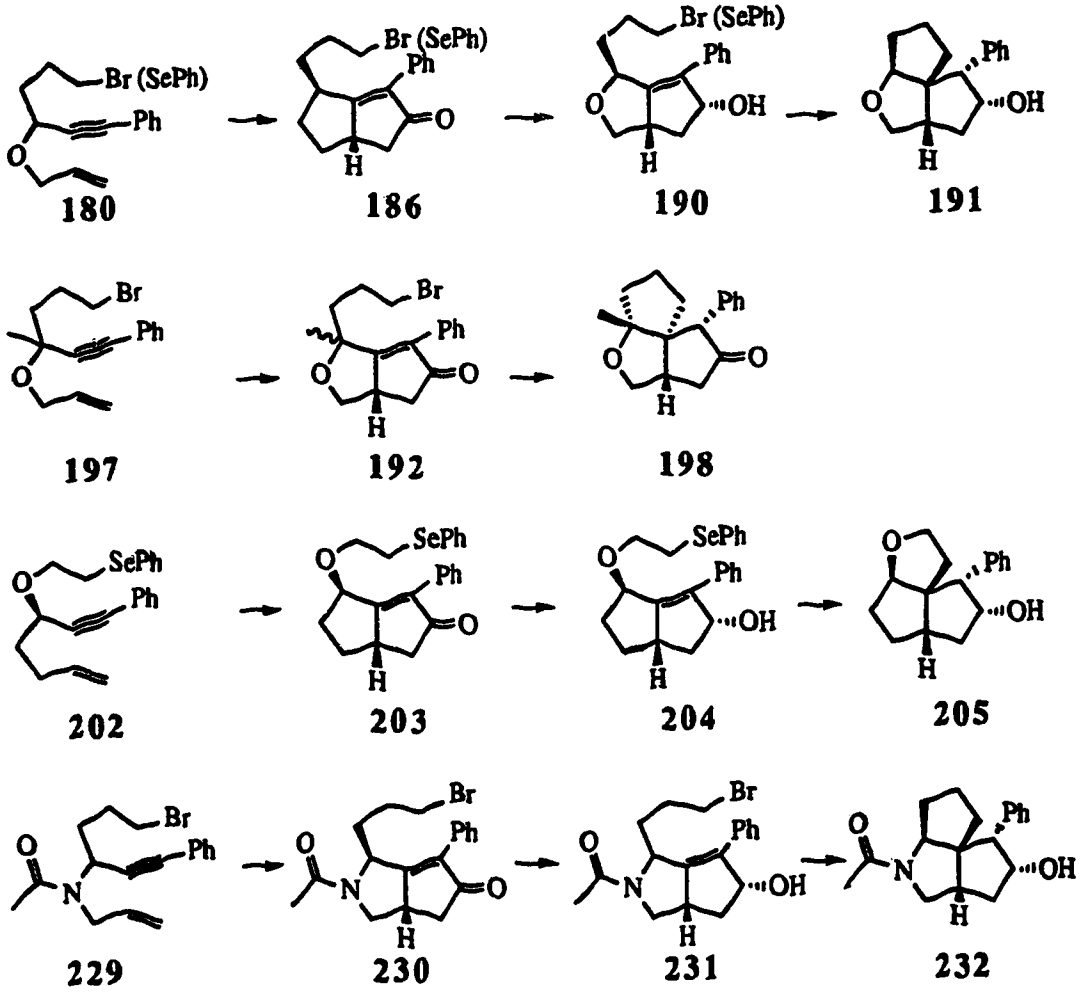


Scheme 165

CONCLUSION

The Pauson-Khand reaction was found to be compatible with radical cyclization chemistry, and the homolyzable groups necessary for generation of radicals (PhSe and Br) were stable enough to withstand the Pauson-Khand conditions. Complex tricyclic molecules could be synthesized easily by the two-step sequence, and our results are summarized in Table 3. Clearly, the P-K / radical sequence is a convenient route to complex polyquinane structures.

Table 3


Br (SePh)
Ph
O
180
Br (SePh)
Ph
O
H
186
Br (SePh)
Ph
O
OH
H
190
Ph
O
OH
H
191
Br
Ph
O
197
Br
Ph
O
O
H
192
Ph
O
O
H
198
SePh
O
Ph
202
SePh
O
Ph
O
H
203
SePh
O
Ph
OH
H
204
O
Ph
OH
H
205
Br
O
Ph
N
229
Br
O
Ph
N
O
H
230
Br
O
Ph
N
OH
H
231
O
Ph
N
OH
H
232

EXPERIMENTAL

GENERAL. Argon was purified by passage through a column (3.5 x 42 cm) of R-311 catalyst[223] and then through a similar column of Drierite. Glassware was dried in an oven for at least 3 h before use (120 °C) and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of argon. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Solvents for chromatography and extractions were distilled before use. Petroleum ether refers to the fraction bp 35-60°C.

Products were isolated from solution by evaporation under water-aspirator vacuum at, or below, 30 °C using a rotary evaporator. HPLC separations were carried out using a Hewlett-Packard 1082B instrument fitted with a Whatman 22 mm (i.d.) x 25 cm Partisil silica column.

Melting points were determined on a Kofler block melting point apparatus.

Commercial thin layer chromatography (TLC) plates (silica gel, Merck 60F–254) were used. Spots were detected by spraying the plate with a solution of phosphomolybdic acid,[224] followed by charring on a hot plate, or by examination under UV light. Silica gel for flash chromatography was Merck type 60 (230-400 mesh).

Dry solvents were prepared under an inert atmosphere and transferred by oven-dried syringes. Dry tetrahydrofuran (THF) and diethyl ether (ether) were distilled from sodium and benzophenone ketyl. Dry benzene was distilled from sodium. Dry diisopropylamine, triethylamine, dichloromethane, methanol, pyridine, and *N*,*N*-dimethylformamide (DMF) were distilled from calcium hydride, the last solvent being distilled under

water-aspirator vacuum. Commercial (Aldrich) solutions of *n*-butyllithium and methyllithium (both in hexanes) were assumed to have the stated molarity.

Infrared spectra were recorded on a Nicolet 7000 FT-IR model. Measurements were made as casts from the specified solvent using potassium bromide plates.

Proton nuclear magnetic resonance spectra were recorded with Bruker WP-200 (at 200 MHz), Bruker AM-300 (at 300 MHz), or Bruker AM-400 (at 400 MHz) spectrometers in the specified deuterated solvent with tetramethylsilane as an internal standard. ^{13}C N.M.R. spectra were recorded with Bruker WP-200 (at 50.3 MHz), Bruker AM-300 (at 75.5 MHz), or Bruker AM-400 (at 100.6 MHz) spectrometers using deuterochloroform as an internal standard. The symbols s', d', t', and q' used for ^{13}C NMR signals in APT (Attached Proton Technique) spectra indicate 0, 1, 2, or 3 attached hydrogens, respectively.

Mass spectra were recorded with an AEI Model MS-12 or MS-50 mass spectrometer at an ionizing voltage of 70eV.

Microanalyses were performed by the microanalytical laboratory of this Department.

General Procedure for Radical Cyclization. The substrate was placed in a round bottomed flask equipped with a Teflon-coated stirring bar and a reflux condenser that was sealed with a rubber septum. The system was flushed with argon for 5-10 min and benzene was injected into the flask. The flask was placed in an oil bath preheated to 85°C, and solutions of tributyltin hydride and AIBN in benzene were injected simultaneously via syringe

the addition was complete. The reaction mixture was cooled and the solvent was evaporated to give a residue which was processed as described for the individual experiments.

General Procedure for Pauson-Khand Reaction on Silica Gel.[132] The substrate was placed in a round bottomed flask that was then flushed with argon for 5-10 min. The indicated solvent was injected, followed by octacarbonyldicobalt. The resulting brown solution was stirred for 2-3 h at room temperature. This solution was then poured onto silica gel which had been covered with ether. [Commercial flash chromatography silica gel (Merck type 60, 230-400 mesh) was used. The indicated amount of water was added and the mixture stirred for 30 min, then stored in a sealed container.] The solvent was removed at <25°C. The flask was then flushed with oxygen for 5-10 min and heated under a slight static pressure of oxygen. On cooling, the silica gel was extracted with ether (4 x 20 mL) and the extract was evaporated to give a residue which was purified as described in the individual experiments.

General Procedure for Pauson-Khand Reaction Using 4-Methylmorpholine *N*-oxide (NMO).[141] The octacarbonyldicobalt-alkyne complex was prepared as for the silica gel method. The brown solution was cooled to 0°C and NMO [which was sublimed and stored under argon prior to use] was added. The cooling bath was removed and the mixture was stirred at room temperature. The solvent was evaporated and the residue was processed as described in each experiment.

1,8-Nonadien-5-ol (124).[225]

124

A solution of 4-bromobutene (6.65 g, 49.0 mmol) in THF (20 mL) was added over 15 min to a mixture of magnesium (1.145 g, 47.0 mmol, activated by heating and cooling under argon and addition of 1,2-dibromoethane)[226] in THF (20 mL). The mixture was then refluxed for 1 h and cooled to 0°C. Ethyl formate (1.58 g, 21.3 mmol) in THF (5 mL) was added. The cooling bath was removed and stirring was continued for 30 min. Saturated aqueous ammonium chloride (10 mL) was added and the layers were separated. The organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 20 cm), using 10% ethyl acetate-petroleum ether, gave alcohol **124** (2.33 g, 76%) as a homogeneous [^{1}H NMR (80 MHz)] colorless oil: ^{1}H NMR ($CDCl_3$, 80 MHz) δ 1.45-1.60 (m, 4 H), 1.60-2.45 (m, 5 H), 3.40-3.85 (m, 1 H), 4.76-5.30 (m, 4 H), 5.65-6.35 (m, 2 H).

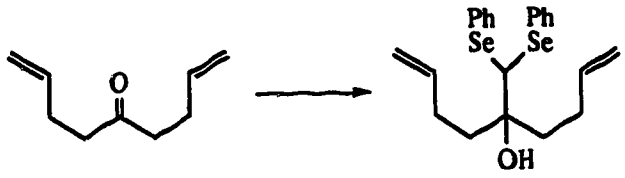
1,8-Nonadien-5-one (125).[225]

124 **125**

The procedure for the preparation of **133** was followed, using alcohol **124**[225] (2.33 g, 16.6 mmol) in acetone (10 mL). Flash chromatography of the residue over silica gel (4 x 18 cm), using 1% ethyl acetate--hexane, gave ketone **125** (0.8 g, 35%) as a homogeneous [^{1}H NMR (300 MHz)] colorless oil: FT-IR ($CHCl_3$ cast) 2929, 1714 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.33 (br q, J = 7.0 Hz,

4 H), 2.51 (t, J = 7.3 Hz, 4 H), 4.94-5.07 (m, 4 H), 5.80 (ddt, J = 16.8, 10.3, 6.5 Hz, 2 H), ^{13}C NMR (APT) ($CDCl_3$, 75.5 MHz) δ 27.68 (t'), 41.82 (t'), 115.16 (t'), 137.07 (d'), 209.21 (s'); exact mass, m/z calcd for $C_9H_{14}O$ 138.1045, found 138.1044.

5-[Bis(phenylseleno)methyl]-1,8-nonadien-5-ol (129).



125 129

LDA [prepared from n-butyllithium (0.475 mL, 1.6, M in hexanes, 0.76 mmol) and diisopropylamine (0.106 mL, 0.76 mmol) in THF (3 mL)] was injected over 10 min to a stirred solution of bis(phenylseleno)methane[153] (236 mg, 0.72 mmol) in THF (10 mL) at -78°C. After 1 h, ketone **125** (100 mg, 0.72 mmol) in THF (2 mL) was added over 10 min. Stirring at -78°C was continued for 1 h, then saturated aqueous ammonium chloride (2 mL) was added and the cooling bath was removed. When the mixture reached room temperature the layers were separated and the organic layer was washed with water (5 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 2% ethyl acetate--hexane, gave **129** (216.8 mg, 64%) as a homogeneous [^{1}H NMR (300 MHz)], pale yellow oil: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.79-1.93 (m, 4 H), 2.04-2.20 (m, 4 H), 2.65 (s, 1 H), 4.60 (s, 1 H), 4.90-5.04 (m, 4 H), 5.78 (ddt, J = 17.0, 10.2, 6.5 Hz, 2 H), 7.12-7.31 (m, 6 H), 7.37-7.47 (m, 4 H); ^{13}C NMR (APT) ($CDCl_3$, 75.5 MHz) δ 27.73 (t'), 37.07 (t'), 62.50 (d'), 76.96 (s'), 114.71 (t'), 128.71 (d'), 129.18 (d'), 131.01 (s'), 134.72 (d'), 138.39 (d'); exact mass, m/z calcd for $C_{22}H_{26}OSe_2$ 466.0314, found 466.0323.

(4-Bromo-1-butynyl)trimethylsilane (132).[154]

132

Bromine (6.20 g, 38.79 mmol) was added to a stirred solution of triphenyl phosphite (13.10 g, 42.20 mmol) in ether (40 mL). The mixture was cooled to 0°C and a solution of 4-(trimethylsilyl)-3-butyn-1-ol[154] (5.00 g, 35.21 mmol) and pyridine (2.79 g, 35.21 mmol) in ether (20 mL) was added over 10 min. Stirring at room temperature was continued for 8 h and the mixture was poured into water (100 mL). The layers were separated and the aqueous layer was extracted with ether (1 x 20 mL). The combined ether layers were dried ($MgSO_4$) and evaporated. Kugelrohr distillation (110°C, 30 mm Hg) of the residue, gave **132** (4.5 g, 63%) as a homogeneous [^{1}H NMR (200 MHz)] colorless oil: FT-IR ($CDCl_3$ cast) 1645, 1506 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.12 (s, 9 H), 2.72 (t, J = 7.5 Hz, 2 H), 3.37 (t, J = 7.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -0.07, 24.27, 28.98, 86.83, 103.13; exact mass, m/z calcd for $C_7H_{13}{}^{79}BrSi$ 203.9970, found 203.9954.

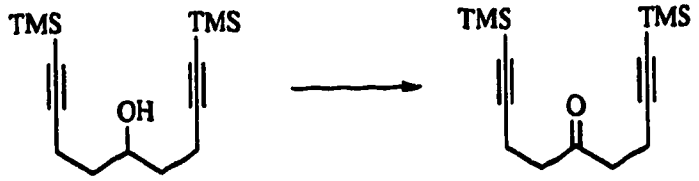
1,9-Bis(trimethylsilyl)nona-1,8-diyn-5-ol (133).

132 **133**

A general procedure[150] was followed. Magnesium turnings (0.35 g,

14.40 mmol), contained in a round-bottomed flask, were activated by heating and cooling under argon, by crushing of a few turnings with a spatula, and by addition of several drops of 1,2-dibromoethane.[226] THF (1 mL) was then added, followed by (4-bromo-1-butynyl)trimethylsilane (2.50 g, 12.19 mmol) in THF (5 mL), which was introduced dropwise at a rate to maintain a modest exotherm. The mixture was refluxed for 1 h and then cooled in an ice bath. Ethyl formate (0.54 mL, 6.68 mmol) in THF (5 mL) was added dropwise with stirring over 20 min, the ice bath was removed and stirring was continued for 30 min. Aqueous 3 N sodium hydroxide (20 mL) was added and the mixture was stirred for 10 h. The organic layer was separated and washed with saturated aqueous sodium bicarbonate solution (1 x 10 mL) and water (1 x 10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm), using 10% ethyl acetate--hexane, gave **133** (616 mg, 36%) as a homogeneous [^{1}H NMR (300 MHz)] colorless oil: FT-IR ($CDCl_3$ cast) 3120-3560, 2958, 2175, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.14 (s, 18 H), 1.58-1.77 (m, 4 H), 2.19 (d, J = 4.4 Hz, 1 H), 2.37 (t, J = 7 Hz, 4 H), 3.61-3.92 (m, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 75.5 MHz) δ 0.15 (q'), 16.49 (t'), 17.84 (t'), 70.51 (d'), 85.39 (s'), 106.92 (s'); mass (CI), m/z calcd for $C_{15}H_{28}OSi_2$ 280, found 298 (M + 18)$^+$. Anal. Calcd for $C_{15}H_{28}OSi_2$: C,64.22; H, 10.06. Found: C, 64.66; H, 10.28.

1,9-Bis(trimethylsilyl)nona-1,8-diyn-5-one (134).



133 **134**

Jones reagent[151] was added dropwise with stirring to a solution of **133**

(408 mg, 1.454 mmol) in acetone (5 mL) until the orange color of the reagent persisted for 30 min. Propan-2-ol was then added until the green color returned. The solvent was evaporated and the residue was extracted with ether (1 x 10 mL) and washed with water (1 x 10 mL). The aqueous phase was re-extracted with ether (1 x 10 mL), and the combined organic phases were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica (2 x 18 cm), using 5% ethyl acetate--hexane, gave **134** (361 mg, 89%) as a homogeneous [^{1}H NMR (300 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 2959, 2178, 1719, 1250 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.15 (s, 18 H), 2.45-2.52 (m, 4 H), 2.64-2.71 (m, 4 H); ^{13}C NMR (APT) ($CDCl_3$, 75.5 MHz) δ 0.07 (q'), 14.49 (t'), 41.75 (t'), 85.33 (s'), 105.47 (s'), 206.64 (s'); mass (CI), *m/z* calcd for $C_{15}H_{26}OSi_2$ 278, found 296 $(M + 18)^+$. Anal. Calcd for $C_{15}H_{26}OSi_2$: C, 64.68; H, 9.41. Found: C, 64.53; H, 9.66.

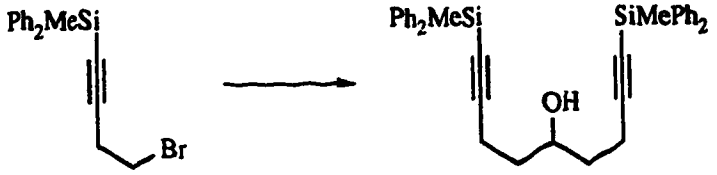
(4-Bromo-1-butynyl)methyldiphenylsilane (135).

142 **135**

The procedure for the preparation of **132** was followed, using bromine (4.34 g, 27.14 mmol), triphenyl phosphite (9.12 g, 28.82 mmol) in ether (30 mL), and 4-(methyldiphenylsilyl)-3-butyn-1-ol (6.50 g, 24.40 mmol) and pyridine (2.0 mL, 25.80 mmol) in ether (15 mL). Flash chromatography of the crude product over silica gel (5 x 18 cm), using 10% ethyl acetate--hexane, gave **135** (7.22 g, 90%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR ($CDCl_3$ cast) 3059, 2179, 1429, 1115 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.76 (s, 3 H), 2.94 (t, *J* = 7.2 Hz, 2 H), 3.54 (t, *J* = 7.2 Hz, 2 H), 7.39-7.50 (m, 6 H), 7.68-7.76

(m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -1.98, 24.48, 29.10, 83.51, 106.73, 127.96, 129.70, 134.50, 135.28; exact mass, *m/z* calcd for $C_{17}H_{17}{}^{79}BrSi$ 328.0283, found 328.0260. Anal. Calcd for $C_{17}H_{17}BrSi$: C, 62.00; H, 5.20, Br, 24.26. Found: C, 61.98; H 5.32; Br, 24.35.

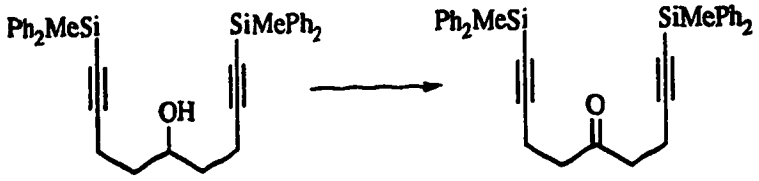
1,9-Bis(methyldiphenylsilyl)-1,8-nonadiyn-5-ol (136).



135 **136**

The procedure for the preparation of **133** was followed, using **135** (7.22 g, 21.94 mmol) in THF (20 mL), magnesium turnings (0.64 g, 26.34 mmol), and ethyl formate (0.89 g, 12.07 mmol) in THF (5 mL). Flash chromatography of the crude product over silica gel (4 x 18 cm), using 10% ethyl acetate–hexane, gave **136** as a homogeneous [^1H NMR (300 MHz)] oil: FT-IR ($CDCl_3$ cast) 3200-3640, 2800-3080, 2173, 1428 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.58 (s, 6 H), 0.97-1.18 (m, 4 H), 1.49 (d, *J* = 4.7 Hz, 1 H), 1.79 (td, *J* = 7.0, 3.0 Hz, 4 H), 3.14-3.26 (m, 1 H), 6.61-6.76 (m, 12 H), 6.90-7.02 (m, 8 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ -1.88 (q'), 14.92 (t'), 40.13 (t'), 72.05 (d'), 81.50 (s'), 110.87 (s'), 127.91 (d'), 129.58 (d'), 134.45 (d'), 135.58 (s'); exact mass, *m/z* calcd for $C_{35}H_{36}OSi_2$ 528.2305, found 528.2288

1,9-Bis(methyldiphenylsilyl)-1,8-nonadiyn-5-one (137).



136 137

The procedure for the preparation of **134** was followed, using **136** (3.83 g, 7.25 mmol) in acetone (10 mL). Flash chromatography of the crude product over silica gel (3 x 18 cm), using 10% ethyl acetate--hexane, gave **137** (3.40 g, 89%) as a homogeneous [^{1}H NMR (400 MHz)] white powder: mp 92-95°C; FT-IR ($CDCl_3$ cast) 2176, 1720, 1428, 1114 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.65 (s, 6 H), 2.55 (br t, J = 6.8 Hz, 4 H), 2.64 (br t, J = 6.8 Hz, 4 H), 7.26-7.41 (m, 12 H), 7.53-7.69 (m, 8 H); ^{13}C NMR (APT) ($CDCl_3$, 75.5 MHz) δ -1.91 (q'), 14.65 (t'), 41.55 (t'), 81.74 (s'), 109.04 (s'), 127.92 (d'), 129.61 (d'), 134.45 (d'), 135.55 (s'), 206.07 (s'); mass (CI), *m/z* calcd for $C_{35}H_{34}OSi_2$ 526, found 544 $(M + 18)^+$. Anal. Calcd for $C_{35}H_{34}OSi_2$: C,79.80; H, 6.51. Found: C,79.52; H, 6.55.

4-Trimethylsilyl-3-butyn-1-ol (139).[155]

139

Methyllithium (214 mL, 1.4, M in hexanes, 0.299 mol) was injected over 30 min to a stirred solution of 3-butyn-1-ol (10 g, 0.142 mol) in ether (40 mL) and THF (60 mL) at -78°C. After 1 h, chlorotrimethylsilane (2.55 g, 0.299 mol) was added over 20 min. After a further 1 h, the cooling bath was removed and stirring was continued for 2 h. Aqueous acetic acid (100 mL, 1 M) was added and the mixture was stirred for 10 h. The organic layer was separated

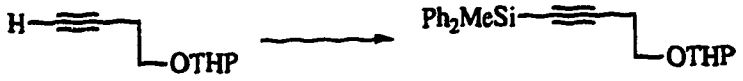
and washed with saturated aqueous sodium bicarbonate (50 mL) and water (50 mL), dried ($MgSO_4$) and evaporated. Distillation of the residue gave **139** (19.7 g, 97%) as a colorless oil: bp 81-84°C (20 mm Hg); FT-IR (CH_2Cl_2 cast) 3600-3100, 2959, 2177 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.12 (s, 9 H), 2.39-2.48 (m, 1 H), 2.45 (t, J = 6.4 Hz, 2 H), 3.63-3.70 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 0.03, 24.16, 60.85, 86.74, 103.45; exact mass, m/z calcd for $C_6H_{11}OSi$ $(M - CH_3)^+$ 127.0579, found 127.0580.

2-(3-Butynyloxy)tetrahydro-2*H*-pyran (140).[156]

140

3,4-Dihydro-2*H*-pyran (12.954 g, 154 mmol) and phosphorus oxychloride (60 mL) were added to a stirred and cooled (0°C) solution of 3-butyn-1-ol (10.787 g, 154 mmol). The ice bath was removed and, after 2 h, 1 N aqueous potassium hydroxide (5 mL) was added. The mixture was extracted with ether (2 x 20 mL) and the combined extracts were dried ($MgSO_4$) and evaporated. Distillation of the residue gave 2-(3-butynyloxy)tetrahydro-2*H*-pyran (20.6 g, 87%) as a homogeneous [^1H NMR (400 MHz)] colorless oil: bp 53-57°C (0.8 mm Hg) [lit.[156] 51°C (2 mm Hg)]; FT-IR (neat) 3285, 2940, 1120, 1094 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.44-1.90 (m, 6 H), 1.99 (br t, J = 2.6 Hz, 1 H), 2.49 (br t, 7.0, 2.8 Hz, 2 H), 3.46-3.52 (m, 2 H), 3.77-3.94 (m, 2 H), 4.65 (t, J = 3.3 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.06, 19.65, 25.18, 30.24, 61.72, 65.22, 69.15, 81.08, 98.35; exact mass, m/z calcd for $C_9H_{13}O_2$ $(M - H)^+$ 153.0916, found 153.0915.

Methyldiphenyl[4-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-butynyl]silane (141).



140 **141**

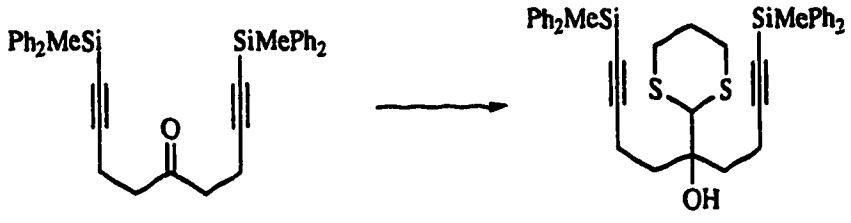
Methyllithium (1.4 M, in ether, 20.4 mL, 28.5 mmol) was added dropwise over 10 min to a stirred and cooled (-78°C) solution of 2-(3-butynyloxy)tetrahydro-2*H*-pyran (3.67 g, 23.9 mmol) in a mixture of ether (20 mL) and THF (10 mL). Stirring was continued for 1.5 h and then chloromethyldiphenylsilane (6.09 g, 26.18 mmol) was added over 20 min (syringe pump). Stirring at -78°C was continued for a further 1 h, the cooling bath was removed and, after a further 3 h, water (10 mL) was added. The organic layer was separated and the aqueous phase was extracted with ether (2 x 20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 18 cm), using 10% ethyl acetate–hexane, gave **141** (6.42 g, 77%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (film) 2840-3080, 2165, 1430 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.67 (s, 3 H), 1.42-1.91 (m, 6 H), 2.65 (t, J = 7 Hz, 2 H), 3.45-3.52 (m, 1 H), 3.62 (dt, J = 9.4, 7 Hz, 1 H), 3.85-3.93 (m, 2 H), 4.68 (t, J = 3.5 Hz, 1 H), 7.32-7.42 (m, 6 H), 7.61-7.67 (m, 4 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ -1.5 (q'), 19.61 (t'), 22.04 (t'), 25.82 (t'), 30.92 (t'), 62.34 (t'), 65.84 (t'), 82.32 (s'), 99.01 (d'), 106.17 (s'), 128.24 (d'), 129.92 (d'), 134.85 (d'), 136.06 (s'); exact mass, *m/z* calcd for $C_{22}H_{26}O_2Si$ 350.1702, found 350.1693.

4-(Methyldiphenylsilyl)-3-butyn-1-ol (142).

141 **142**

A catalytic amount of *p*-toluenesulfonic acid monohydrate was added to a solution of **141** (6.41 g, 18.29 mmol) in methanol (50 mL). The mixture was stirred and refluxed for 24 h, and the methanol was then evaporated. The residue was dissolved in ether (20 mL) and the solution was washed with saturated aqueous sodium bicarbonate (1 x 10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3.5 x 18 cm), using 20% ethyl acetate–hexane, gave **142** (3.90 g, 80%) as a homogeneous [^1H NMR (400 MHz)] colorless oil: FT-IR (neat) 3120-3600, 2840-2940, 2176, 1576, 1429, 1115, 792, 727, 698 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.80 (s, 3 H), 2.42 (t, *J* = 5.5 Hz, 1 H), 2.65 (t, *J* = 6.5 Hz, 2 H), 3.80 (dt, *J* = 6.5, 5.5 Hz, 2 H), 7.41-7.51 (m, 6 H), 7.73-7.89 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ -1.94, 24.35, 60.81, 83.05, 107.21, 127.92, 129.63, 134.40, 135.40; exact mass, *m*/z calcd for $C_{17}H_{18}SiO$ 266.1127, found 266.1123.

5-(1,3-Dithian-2-yl)-1,9-bis(methyldiphenylsilyl)-1,8-nonadiyn-5-ol (144).

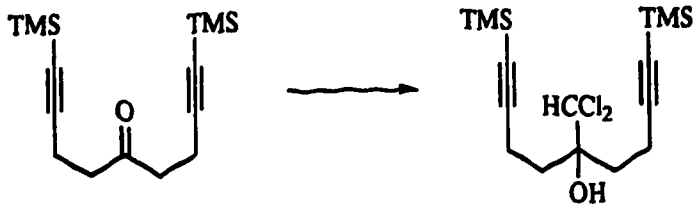


137 **144**

n-Butyllithium (0.3 mL, 1.6 M, in hexanes, 0.48 mmol) was injected over 2 min to a stirred solution of 1,3-dithian (freshly sublimed, 57 mg, 0.475

mmol) in THF (20 mL) at -23°C. After 1.5 h, ketone **137** (125 mg, 0.24 mmol) in THF (5 mL) was added over 5 min. The cooling bath was replaced with an ice/water (0°C) bath and stirring was continued for 3 h. Water (5 mL) was added and the layers were separated. The organic layer was washed with water (5 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm), using 10% ethyl acetate--hexane, gave **144** [116 mg, 84% (based on 12 mg recovered starting material)] as a homogeneous [^1H NMR (300 MHz)] colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 0.71 (s, 6 H), 1.95-2.21 (m, 6 H), 2.75 (t, *J* = 7.7 Hz, 4 H), 2.68 (br s, 1 H), 2.75-2.96 (m, 4 H), 4.33 (s, 1 H), 7.31-7.50 (m, 12 H), 7.60-7.77 (m, 8 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ -1.86 (q'), 14.45 (t'), 25.77 (t'), 31.08 (t'), 35.41 (t'), 58.17 (d'), 74.83 (s'), 81.52 (s'), 110.42 (s'), 127.87 (d'), 129.53 (d'), 134.47 (d'), 135.59(s'); mass (CI) calcd for $C_{39}H_{42}OSi_2S_2$ 647, found 647.

5-(Dichloromethyl)-1,9-bis(trimethylsilyl)nona-1,8-diyn-5-ol (145).

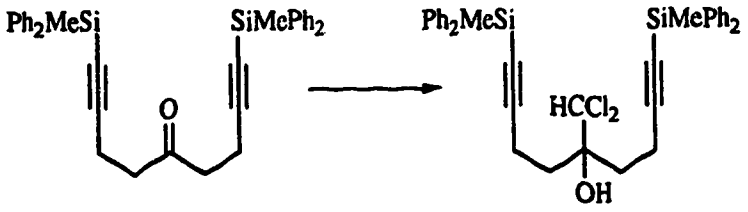


134 **145**

Following a literature procedure,[160] a solution of lithium dicyclohexylamide [prepared by addition of *n*-butyllithium (1.6 M, 0.429 mL, 0.686 mmol) to a stirred and cooled (0°C) solution of dicyclohexylamine (0.137 mL, 0.69 mmol) in THF (3 mL)] was added by syringe over 20 min to a stirred and cooled (-78°C) solution of **134** (95.6 mg, 0.343 mmol) in dichloromethane (3 mL). The mixture was stirred at -78°C for 2 h, quenched by addition of saturated aqueous ammonium chloride solution (10 mL), allowed warm to

room temperature, and then extracted with ether (2 x 20 mL). The ether extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (1.5 x 18 cm), using 2% ethyl acetate--hexane, gave **145** (92.5 mg, 74 %) as a homogeneous [TLC, silica, 5% ethyl acetate-petroleum ether] colorless oil: FT-IR ($CHCl_3$ cast) 3360-3600, 2958, 2177, 1250 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.15 (s, 18 H), 2.01 (dt, *J* = 14.0, 7.5 Hz, 2 H), 2.09 (dt, *J* = 14.0, 7.5 Hz, 2 H), 2.41 (t, *J* = 7.5 Hz, 4 H), 2.73 (s, 1 H), 5.96 (s, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 75.5 MHz) δ 0.02 (q'), 14.08 (t'), 33.29 (t'), 77.28 (s'), 78.61 (d'), 86.10 (s'), 106.24 (s'); mass (CI), *m/z* calcd for $C_{16}H_{28}Cl_2OSi_2$ 363, found 381 (M + 18)$^+$. Anal. Calcd for $C_{16}H_{28}Cl_2OSi_2$: C, 52.87; H, 7.76. Found: C, 53.54; H, 7.69.

5-(Dichloromethyl)-1,9-bis(methyldiphenylsilyl)-1,8-nonadiyn-5-ol (146).

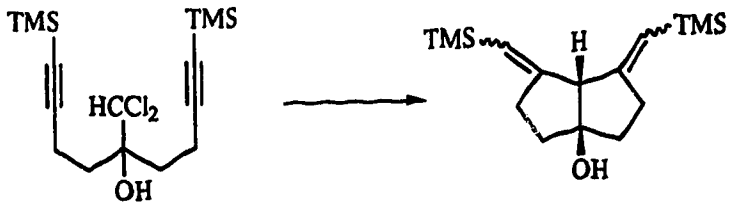


137 **146**

The procedure for the preparation of **145** was followed, using **137** (187 mg, 0.355 mmol) in dichloromethane (5 mL), and dicyclohexylamine (0.14 mL, 0.70 mmol) and *n*-butyllithium (0.42 mL, 1.6 M, in hexane, 0.67 mmol) in THF (5 mL). Flash chromatography of the crude product over alumina (2 x 18 cm), using 10% ethyl acetate--hexane, gave **146** (165 mg, 76%) as a homogeneous [^1H NMR (200 MHz)] colorless oil: FT-IR ($CHCl_3$ cast) 3440-3600, 2840-3360, 2175, 1429 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.72 (s, 6 H), 2.02-2.28 (m, 4 H), 2.53 (t, *J* = 7.5 Hz, 4 H), 2.65 (s, 1 H), 5.99 (s, 1 H), 7.33-7.50 (m, 12 H), 7.61-7.74 (m, 8 H); ^{13}C NMR (APT) ($CDCl_3$, 75.5 MHz) δ -1.93 (q'), 14.30 (t'),

33.25 (t'), 77.13 (s'), 78.57 (d'), 82.44 (s'), 109.63 (s'), 127.98 (d'), 129.69 (d'), 134.50 (d'), 135.39 (s'); exact mass, *m/z* calcd for $C_{36}H_{36}Cl_2OSi_2$ 610.168174, found 610.168181. Anal. Calcd for $C_{36}H_{36}Cl_2OSi_2$: C, 70.68; H, 5.93; Cl, 11.59. Found: C, 70.07; H, 6.17; Cl, 11.74.

cis-Hexahydro-1,6-bis(trimethylsilylmethylene)-3a(1*H*)-pentalenol (148).



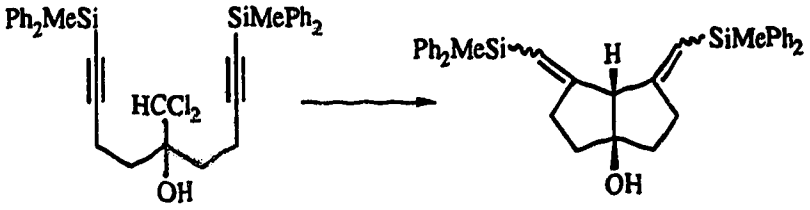
145 **148**

The general procedure for radical cyclization was followed, using dichloride **145** (61.4 mg, 0.169 mmol) in benzene (20 mL), tributyltin hydride (0.135 mL, 0.507 mmol) in benzene (5 mL), and AIBN (5.5 mg, 0.034 mmol) in benzene (5 mL). Flash chromatography of the residue over silica gel (2 x 18 cm), using 5% ethyl acetate--hexane, gave **148** (23 mg, 46%) as a mixture of two isomers [55:45::(*E*,*E*):(*Z*,*E*)]. The isomers were separated by HPLC (refractive index detector; 50% ether--hexane at a flow rate of 3.0 mL/min). The *E*,*E* isomer had: FT-IR ($CHCl_3$ cast) 3040-3340, 2953, 1635, 1248 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.10 (s, 18 H), 1.62 (br s, 1 H), 1.79-1.91 (m, 4 H), 2.30-2.68 (m, 4 H), 2.95 (br s, 1 H), 5.43 (q, *J* = 2.2 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ -0.20, 31.23, 37.37, 68.30, 88.39, 121.87, 160.95; exact mass, *m/z* calcd for $C_{16}H_{30}OSi_2$ 294.1835, found 294.1840. Saturation of the signal at δ 2.95 (bis-allylic) in the ^1H NMR spectrum produced enhancements of 17% and 6% in the signals at δ 5.43 (olefinic) and δ 1.6 (hydroxy), respectively.

The *Z*,*E* isomer had: FT-IR ($CDCl_3$ cast) 3040-3400, 2760-3000, 1530, 1245 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.08 (s, 9 H), 0.10 (s, 9 H), 1.55 (br s, 1 H),

1.64-1.86 (m, 2 H), 1.96 (t, J = 7.8 Hz, 2 H), 2.39-2.51 (m, 3 H), 2.57-2.68 (m, 1 H), 3.10 (br s, 1 H), 5.39 (q, J = 2.3 Hz, 1 H), 5.48-5.51 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ -0.39, 0.24, 31.06, 35.30, 36.93, 37.18, 64.49, 89.37, 121.84, 123.15, 159.76, 160.39; exact mass, m/z calcd for $C_{16}H_{30}OSi_2$ 294.1835, found 294.1840. Saturation of the signal at δ 3.10 (bis-allylic) in the ^1H NMR spectrum produced enhancements of 6% and 5% in the signals at δ 5.39 (olefinic) and δ 1.5 (hydroxy), respectively.

***cis*-Hexahydro-1,6-bis[(methyldiphenylsilyl)methylene]-3a(1*H*)-pentalenol (149).**



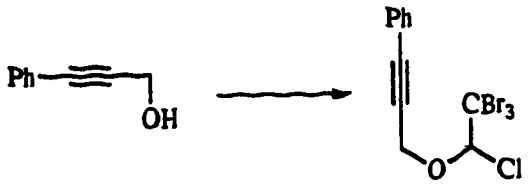
146 **149**

The general procedure for radical cyclization was followed using dichloride **146** (92.5 mg, 0.152 mmol) in benzene (20 mL), tributyltin hydride (132 mg, 0.453 mmol) in benzene (5 mL), and AIBN (5.0 mg, 0.030 mmol) in benzene (5 mL). Flash chromatography of the crude product over silica gel (2 x 18 cm), using 10% ethyl acetate--hexane, gave **149** (65.5 mg, 80%) as a mixture of two isomers [^1H NMR (200 MHz)] which were partially separated during the flash chromatography. The (*E*,*E*) isomer had: FT-IR ($CDCl_3$ cast) 3200-3520, 2800-3080, 1626, 1427 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 0.67 (s, 6 H), 1.58 (br s, 1 H), 1.74 (t, J = 7.7 Hz, 4 H), 2.07-2.47 (m, 4 H), 3.20 (br s, 1 H), 5.93 (q, J = 2.0 Hz, 2 H), 7.23-7.43 (m, 12 H), 7.47-7.67 (m, 8 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ -2.40, 32.00, 37.62, 68.75, 88.37, 117.92, 127.90, 129.12, 134.63, 134.68, 137.45, 137.56, 164.98; exact mass, m/z calcd for $C_{36}H_{38}OSi_2$, 542.2461, found 542.2451. Saturation of the signal at δ 3.20 (bis-allylic) in the ^1H NMR

spectrum produced an enhancement of 16% in the signal at δ 5.93 (olefinic).

The (*Z*,*E*) isomer had: FT-IR ($CDCl_3$ cast) 3160-3600, 2800-3080, 1630, 1427 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.50 (s, 3 H), 0.67 (s, 3 H), 1.55 (br s, 1 H), 1.70-1.85 (m, 4 H), 2.05-2.27 (m, 2 H), 2.58-2.65 (m, 2 H), 3.02 (br s, 1 H), 5.67 (q, *J* = 2.3 Hz, 1 H), 5.94 (q, *J* = 1.0 Hz, 1 H), 7.22-7.46 (m, 16 H), 7.50-7.60 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ -2.43, -2.02, 31.60, 35.66, 37.06, 64.93, 89.30, 117.97, 119.37, 127.85, 129.13, 129.55, 134.66, 134.98, 137.36, 137.96, 163.21, 164.05; exact mass, *m/z* calcd for $C_{36}H_{38}OSi_2$, 542.2461, found 542.2453.

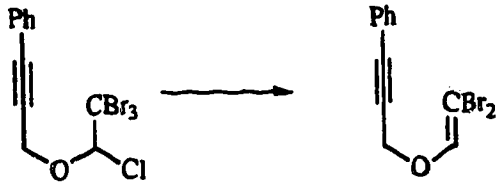
3-(2,2,2-Tribromo-1-chloroethoxy)-1-phenyl-1-propyne (151).



150 **151**

Bromal[163] (2.0 g, 7.12 mmol), phenylprop-2-ynyl alcohol (0.94 g, 7.12 mmol), thionyl chloride (0.35 mL, 0.57 g, 4.80 mmol), and pyridine (0.88 mL, 10.88 mmol) were dissolved in ether (6 mL) and the mixture was stirred at room temperature for 3 h. The ether layer was decanted, washed with water (1 x 10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3.5 x 18 cm), using 2% ethyl acetate--hexane, gave **151** (1.72 g, 56%) as a homogeneous [^1H NMR (400 MHz)] oil: FT-IR ($CHCl_3$ cast) 2090-2335, 1490, 1109 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.77 (d, *J* = 16.0 Hz, 1 H), 4.86 (d, *J* = 16.0 Hz, 1 H), 6.10 (s, 1 H), 7.29-7.51 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 42.91, 58.88, 81.20, 89.62, 99.06, 121.66, 128.50, 129.21, 131.94; mass (CI), *m/z* calcd for $C_{11}H_8{}^{81}Br_2{}^{79}Br^{35}ClO$ 432, found 450 $(M + 18)^+$. Anal. Calcd for $C_{11}H_8Br_3ClO$: C, 30.43; H, 1.85. Found: C, 30.43; H, 1.92.

3-[(2,2-Dibromoethenyl)oxy]-1-phenyl-1-propyne (152).



151 152

Zinc dust (0.31 g, 4.74 mmol) was added to a solution of **151** (1.72 g, 3.99 mmol) in methanol (4 mL), and the suspension was stirred at 50-60°C for 4 h. The mixture was cooled to room temperature and filtered through a pad (1 x 2 cm) of Celite. Evaporation of the filtrate and flash chromatography of the residue over silica gel (2.2 x 18 cm), using 5% ethyl acetate--hexane, gave **152** (0.95 g, 75%) as a homogeneous [^{1}H NMR (400 MHz)] oil: FT-IR (CH_2Cl_2 cast) 2400-3600, 1736 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.71 (s, 2 H), 7.04 (s, 1 H), 7.26-7.37 (m, 3 H), 7.41-7.47 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 60.55, 72.99, 82.52, 88.62, 121.62, 128.36, 129.04, 131.87, 146.24; mass (CI), *m/z* calcd for $C_{11}H_8{}^{81}Br^{79}BrO$ 318, found 334 $(M + 18)^+$. Anal. Calcd for $C_{11}H_8Br_2O$: C, 41.81; H, 2.55. Found: C, 41.38; H,2.63.

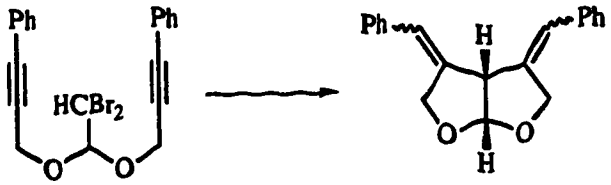
1,1-Dibromo-2,2-di[(3-phenylprop-2-ynyl)oxy]ethane (153).

152 153

Vinyl ether **152** (1.006 g, 3.19 mmol), phenylprop-2-ynyl alcohol (1.0 g, 7.58 mmol), and concentrated hydrochloric acid (3 drops) were mixed and stirred at 110°C for 4 h. The mixture was cooled, and flash chromatography of

the material over alumina (3.5 x 18 cm), using 5% ethyl acetate--hexane, gave **153** (728 mg, 51%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR ($CHCl_3$ cast) 2318, 1490, 1103, 1069, 1045 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.68 (d, J = 16 Hz, 2 H), 4.75 (d, J = 16 H, 2 H), 5.22 (d, J = 4 Hz, 1 H), 5.74 (d, J = 4 Hz, 1 H), 7.24-7.47 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz), δ 44.10, 57.11, 83.68, 87.73, 100.61, 122.07, 128.34, 128.77, 131.86; mass (CI), m/z calcd for $C_{20}H_{16}{}^{81}Br^{79}BrO_2$ 448, found 466 $(M + 18)^+$.

***cis*-3,4-Bis(phenylmethylene)hexahydrofuro[2,3-b]furan (154).**



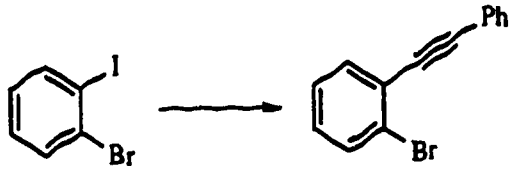
153 **154**

The general procedure for radical cyclization was followed using dibromide **153** (223 mg, 0.50 mmol) in benzene (40 mL), tributyltin hydride (320 mg, 1.10 mmol) in benzene (5 mL), and AIBN (16.4 mg, 0.10 mmol) in benzene (5 mL). Flash chromatography of the crude product over silica gel (2 x 18 cm), using 10% ethyl acetate--hexane, gave **154** as a mixture of two isomers [^{1}H NMR (200 MHz)] (77.07 mg, 53%). The compounds were separated by HPLC (U.V. detector; 20% ether--hexane at a flow rate of 4.5 mL/min). The (Z,Z)-isomer had: FT-IR ($CDCl_3$ cast) 2820-3300, 1495, 1450, 1025 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.95-4.00 (m, 1 H), 4.77 (dd, J = 13.8, 2.2 Hz, 2 H), 4.86 (dt, J = 13.8, 2.2 Hz, 2 H), 5.90 (d, J = 4.5 Hz, 1 H), 6.60 (q, J = 2.0 Hz, 2 H), 7.12-7.18 (m, 4 H), 7.22-7.30 (m, 2 H), 7.33-7.40 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.07, 69.55, 106.77, 123.38, 127.25, 128.28, 128.64, 141.35; exact mass, m/z calcd for $C_{20}H_{18}O_2$ 290.1307, found 290.1314. Saturation of the

signal at δ 4.0 (bis-allylic) in the ^{1}H NMR spectrum produced enhancements of 21% and 27% in the signals at δ 6.60 (olefinic) and δ 5.90 (O-C<u>H</u>-O), respectively.

The (*Z*,*E*)-isomer had: FT-IR ($CDCl_3$ cast) 2820-3080, 1026 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.45 [dd, *J* = 12.0, 1.5 Hz (including br s, (1 H), at δ 4.44), 2 H], 4.69 (dt, *J* = 12.0, 1.5 Hz, 1 H), 4.90 (q, *J* = 1.4 Hz, 2 H), 5.85 (d, *J* = 4.5 Hz, 1 H), 6.38 (q, *J* = 2.3 Hz, 1 H), 6.50 (d, *J* = 1.0 Hz, 1 H), 7.02-7.52 (m, 10 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.07, 50.99, 70.78, 72.03, 108.71, 122.84, 124.08, 127.27, 127.61, 128.32, 128.57, 128.89, 139.59, 140.04; exact mass, *m/z* calcd for $C_{20}H_{18}O_2$ 290.1307, found 290.1316. Saturation of the signal at δ 4.45 (bis-allylic) in the ^{1}H NMR spectrum produced an enhancements of 12% in the signal at δ 7.5 (*aromatic* hydrogen), and an enhancement of 15% in the signal at δ 5.85 (O-C<u>H</u>-O).

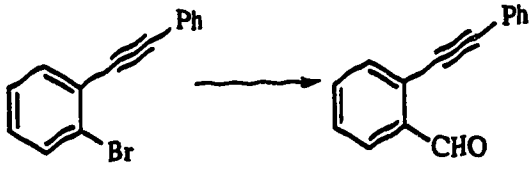
1-Bromo-2-(phenylethynyl)benzene.[227]



Copper(I) phenylacetylide (1.29 g, 7.84 mmol) was stirred in pyridine (50 mL) for 20 min (argon atmosphere). 1-Bromo-2-iodobenzene (1.85 g, 6.55 mmol) was added, and the mixture was refluxed for 10 h, cooled and poured into ether (100 mL). The solution was washed with 10% aqueous hydrochloric acid (2 x 20 mL), saturated aqueous cupric sulfate (2 x 20 mL), and water (1 x 20 mL), and the organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 18 cm), using 2% ethyl acetate--hexane, gave 1-bromo-2-(phenylethynyl)benzene (1.41 g, 84%) as a

homogeneous [^{1}H NMR (200 MHz)] colorless oil: bp. 160-165°C (0.22 mm Hg) [lit.[227] 155-160 (0.7 mm Hg)]; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.04-7.63 (m, 9 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 88.07 (s'), 93.97 (s'), 122.94 (s'), 125.43 (s'), 125.66 (s'), 127.03 (d'), 128.39 (d'), 128.65 (d'), 129.37 (d'), 131.71 (d'), 132.46 (d'), 133.23 (d').

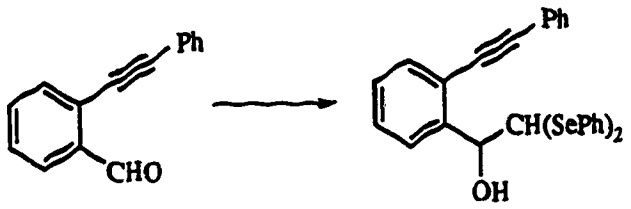
2-(Phenylethynyl)benzaldehyde (155).[164]



155

n-Butyllithium (20 mL, 1.6 M, in hexanes, 32.4 mmol) was added over 20 min to a stirred and cooled (-30°C) solution of 1-bromo-2-(phenylethynyl)benzene (3.96 g, 15.4 mmol) in ether (50 mL). After 45 min the cold bath was replaced by an ice bath and, after a further 1 h, DMF (2.80 mL, 38.3 mmol) was added. The mixture was stirred at room temperature for 10 h and then diluted with water (20 mL). The ether layer was separated and the aqueous layer was extracted with ether (1 x 20 mL). The combined ether layers were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 18 cm), using 2% ethyl acetate–hexane, gave **155** (2.82 g, 88%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR ($CDCl_3$ cast) 1690 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.1-8.0 (m, 9 H), 10.64 (s, 1 H).

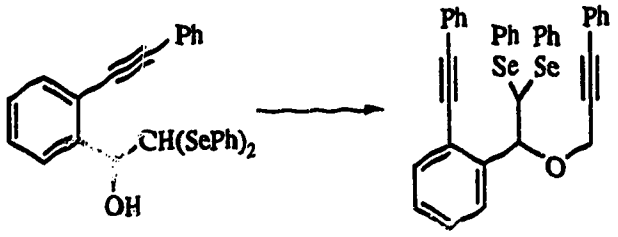
1-[(2-Phenylethynyl)phenyl]-2,2-bis(phenylseleno)ethanol (156).



155 156

Bis(phenylseleno)methane[153] (529.7 mg, 1.69 mmol) in THF (2 mL) was added over 10 min to a stirred and cooled (-78°C) solution of potassium diisopropylamide [prepared by addition at of *n*-butyllithium (1.05 mL, 1.6 M, in hexanes, 1.69 mmol) to a stirred and cooled (-78°C) solution of potassium *t*-butoxide (218.5 mg, 1.95 mmol) and diisopropylamine (0.272 mL, 1.95 mmol) in THF (5 mL)]. Stirring at -78°C was continued for a further 10 min, and **155** (263 mg, 1.28 mmol) in THF (3 mL) was added over 2 min. After 2 h at -78°C the mixture was quenched with saturated aqueous ammonium chloride (10 mL) and the cooling bath was removed. The mixture was extracted with ether (2 x 20 mL), and the combined ether extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 18 cm), using 10% ethyl acetate--hexane, gave **156** (550 mg, 81%) as a homogeneous [^{1}H NMR (400 MHz)], pale yellow oil: FT-IR (CH_2Cl_2 cast) 3440, 3057, 1577, 1492, 1475, 1437 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.37 (d, J = 4.2 Hz, 1 H), 5.23 (d, J = 3.8 Hz, 1 H), 5.50 (t, J = 3.7 Hz, 1 H), 6.93-7.38 (m, 16 H), 7.45-7.52 (m, 2 H), 7.66-7.73 (m, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 53.29 (d'), 73.22 (d'), 86.86 (s'), 94.85 (s'), 122.70 (s'), 127.03 (d'), 127.42 (d'), 127.58 (d'), 128.10 (d'), 128.23 (d'), 128.41 (d'), 128.48 (d'), 128.69 (d'), 128.94 (d'), 129.73 (s'), 12980 (s'), 131.56 (d'), 132.17(d'), 134.14 (d'), 134.96 (d'), 136.90 (d'), 142.20 (s'); exact mass, m/z calcd for $C_{28}H_{22}OSe_2$ 534.0001, found 534.0007. Anal. Calcd for $C_{28}H_{22}OSe_2$: C, 63.17; H, 4.16. Found: C, 62.93; H, 4.48.

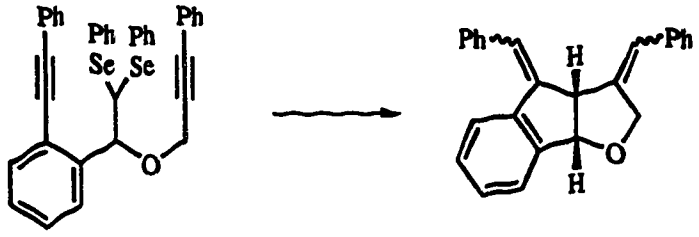
1-[1-[2-(Phenylethynyl)phenyl]-2,2-bis(phenylseleno)ethoxy]-3-phenyl-2-propyne (157).



156 157

Sodium hydride (60% dispersion in oil, 66 mg, 1.65 mmol) was added to a stirred solution of **156** (615 mg, 1.16 mmol) and 3-bromo-1-phenyl-1-propyne (676 mg, 3.48 mmol) in THF (20 mL). The mixture was refluxed for 1 h, cooled to room temperature, quenched with saturated aqueous ammonium chloride (20 mL), and extracted with ether (2 x 20 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 18 cm), using 5% ethyl acetate--hexane, gave **157** (569 mg, 76%) as a homogeneous [^1H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3175-3010, 1488, 1478, 1440 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.30 (d, J = 16.0 Hz, 1 H), 4.57 (d, J = 16.0 Hz, 1 H), 4.96 (d, J = 3.5 Hz, 1 H), 5.99 (d, J = 3.5 Hz, 1 H), 6.91 (d, J = 4.4 Hz, 4 H), 6.94-7.48 (m, 19 H), 7.72 (d, J = 8 Hz, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 51.97 (d'), 57.40 (t'), 80.96 (d'), 84.84 (s'), 86.76 (s'), 87.32 (s'), 95.30 (s'), 122.22 (s'), 122.59 (s'), 122.75 (s'), 127.17 (d'), 127.66 (d'), 127.71 (d'), 127,79 (d'), 128.12 (d'), 128.16 (d'), 128.27 (d'), 128.42 (d'), 128.71 (d'), 130.51 (s'), 131.07 (s'), 131.68 (d'), 131.74 (d'), 132,00 (d'), 134.20 (d'), 134.91 (d'), 140.60 (s'); exact mass, m/z calcd for $C_{27}H_{28}OSe_2$ 648.0471, found 648.0464.

cis-3,4-Bis(phenylmethylene)-3,3a,4,8b-tetrahydro-2*H*-indeno[1,2-b]furan (158).



157 158

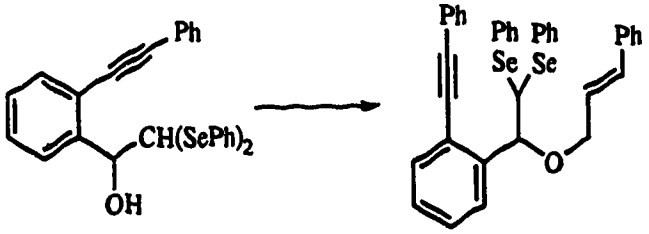
Tributyltin hydride (496 mg, 1.70 mmol) and triethylborane (1.7 mL, 1.0 M solution in hexanes, 1.70 mmol) were added to a solution of **157** (501 mg, 0.775 mmol) in hexane (40 mL) and benzene (10 mL). The mixture was stirred for 10 h with protection from the atmosphere by a drying tube packed with Drierite, and the solvent was then evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm), using 10% ethyl acetate--hexane, gave **158**. The material was obtained as two fractions. The first (less polar) was a 1:1 mixture of two isomers **A** and **B** (64 mg, 20.8%) and the second contained only a third isomer **C** (45 mg, 17%). Isomers **A** and **B** were separated by HPLC (U.V. detector; 10% ethyl acetate--hexane at a flow rate of 4.0 mL/min). Isomer **A** (less polar, Z,Z geometry) had: FT-IR ($CDCl_3$ cast) 2800-3120, 1492, 1061 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.14 (dd, *J* = 7.4, 1.5 Hz, 1 H), 4.43 (dt, *J* = 13.5, 2.2 Hz, 1 H), 4.77 (dd, *J* = 13.5, 2.0 Hz, 1 H), 5.67 (d, *J* = 6.6 Hz, 1 H), 6.71 (q, *J* = 2.0 Hz, 1 H), 6.86 (s, 1 H), 7.02-7.70 (m, 14 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 56.00, 69.20, 83.09, 122.65, 124.52, 125.82, 126.87, 127.25, 128.52, 128.55, 128.58, 129.08, 137.35, 137.70, 138.34, 142.66, 144.00, 145.50; exact mass, *m/z* calcd for $C_{25}H_{20}O$ 336.1514, found 336.1512. Saturation of the signal at δ 4.14 (bis-allylic) in the ^1H NMR spectrum produced enhancements of 6%, 12%, and 24% in the signals at δ 6.71 (olefinic), δ 6.86 (olefinic), and δ 5.67 (Ar-CH-O), respectively.

Isomer **B** (geometry not determined) had: FT-IR ($CDCl_3$ cast) 2800-3120,

1493, 1063 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 4.51 (dt, *J* = 13.6, 2.1 Hz, 1 H), 4.79 (d, *J* = 6.8 Hz, 1 H), 4.90 (dq, *J* = 13.6, 1.0 Hz, 1 H), 5.73 (d, *J* = 6.8 Hz, 1 H), 6.41 (q, *J* = 2.3 Hz, 1 H), 6.96 (d, *J* = 7.2 Hz, 1 H), 7.10-7.70 (m, 14 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 51.87, 70.02, 84.56, 120.61, 121.75, 123.30, 125.62, 126.83, 127.35, 128.29, 128.33, 128.39, 128.93, 137.03, 137.19, 141.29, 141.43, 141.94, 142.91; exact mass, *m/z* calcd for $C_{25}H_{20}O$ 336.1514, found 336.1512. Saturation of the signal at δ 4.79 (bis-allylic) in the ^1H NMR spectrum produced enhancements of *ca.* 12%, and *ca.* 15% in the signals at δ 7.68 (*aromatic*) and δ 5.73 (Ar-C<u>H</u>-O) respectively.

Isomer C (geometry not determined) had: FT-IR ($CDCl_3$ cast) 7280-3100, 1475, 1060 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.71 (dq, *J* = 6.6, 1.8 Hz, 1 H), 4.28 (dd, *J* = 13.6, 1.8 Hz, 1 H), 4.83 (dd, *J* = 13.6, 1.2 Hz, 1 H), 5.80 (d, *J* = 6.6 Hz, 1 H), 7.00-7.68 (m, 16 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 49.10, 72.56, 86.13, 119.07, 121.21, 125.55, 126.20, 126.27, 127.17, 128.24, 129.22, 129.58, 130.28, 131.54, 136.88, 139.65, 140.65, 140.75, 142.00, 145.01; exact mass, *m/z* calcd for $C_{25}H_{20}O$ 336.1514, found 336.1499. Saturation of the signal at δ 3.71 (bis-allylic) in the ^1H NMR spectrum did not produce an enhancement of any olefinic or aromatic signals, but did produce an enhancement of 26% in the signal at δ 5.80 (Ar-C<u>H</u>-O).

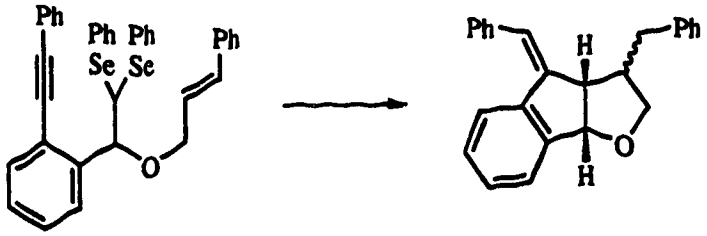
(*E*)-1-[1-[2-(Phenylethynyl)phenyl]-2,2-bis(phenylseleno)ethoxy]-3-phenyl-2-propene (159).



156 **159**

Sodium hydride (63 mg, 60% dispersion in oil, 1.58 mmol) was added to a stirred solution of **156** (844 mg, 1.58 mmol) and cinnamyl bromide (320 mg, 1.58 mmol) in THF (20 mL). The mixture was refluxed for 2 h, cooled to room temperature, quenched with saturated aqueous ammonium chloride (10 mL), and extracted with ether (2 x 20 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 18 cm), using 5% ethyl acetate--hexane, gave **159** (682 mg, 66%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR ($CDCl_3$ cast) 3080-3000, 1494, 1475, 1440 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.03 (ddd, *J* = 12.8, 6.9, 1.4 Hz, 1 H), 4.31 (ddd, *J* = 12.8, 6.9, 1.4, 1 H), 4.94 (d, *J* = 3.5 Hz, 1 H), 5.62 (d, *J* = 3.5 Hz, 1 H), 6.35 (ddd, *J* = 16.0, 6.8, 5.6 Hz, 1 H), 6.60 (d, *J* = 16.0 Hz, 1 H), 6.90-7.44 (m, 23 H), 7.73 (d, *J* = 7.5 Hz, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 52.34 (d'), 70.33 (t'), 81.83 (d'), 87.02 (s'), 95.40 (s'), 122.27 (s'), 123.02 (s'), 125.91 (d'), 126.91 (d'), 127.49 (d'), 127.93 (d'), 127.98 (d'), 128.51 (d'), 128.60 (d'), 129.03 (d'), 130.92 (s'),131.34 (s'), 131.94 (d'), 132.34 (d'), 133.23 (d'), 134.42 (d'), 136.99 (s'), 141.54 (s'); exact mass, *m/z* calcd for $C_{37}H_{30}OSe_2$ 650.0627, found 650.0596.

(Z)-3α,3aα,8bα- and (Z)-3α,3aβ,8bβ-3-(Phenylmethyl)-4-(phenylmethylene)-3,3a,4,8b-tetrahydro-2*H*-indeno[1,2-b]furan (160).



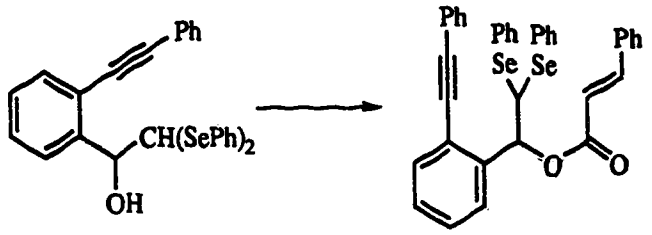
159 **160**

The procedure for the preparation of **158** was followed, using

diselenide **159** (670 mg, 1.03 mmol) in hexane (40 mL) and benzene (10 mL), triethylborane (1 M in hexane, 2.3 mL, 2.27 mmol), and tributyltin hydride (0.61 mL, 2.27 mmol). Flash chromatography of the crude product over silica gel (3 x 18 cm), using 5% ethyl acetate--hexane, gave **160** (167 mg, 47%) as a mixture of two isomers,[228] which were separated by HPLC (U.V. detector; 7% ethyl acetate--hexane at a flow rate of 4.0 mL/min). The less polar isomer [(Z)-3α,3aα,8bα stereochemistry] had: FT-IR ($CHCl_3$ cast) 3140-2830, 1494 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.32 (dt, *J* = 11.0, 4.2 Hz, 1 H), 2.71 (dd, *J* = 13.0, 11.0 Hz, 1 H, 2.92 (dd, *J* = 13.0, 4.0 Hz, 1 H), 3.13 (ddd, *J* = 9.0, 4.4, 1.2, 1 H), 3.50 (d, *J* = 9.0, 1 H), 3.84 (br d, *J* = 6.5 Hz, 1 H), 5.70 (d, *J* = 6.9 Hz, 1 H), 6.97-7.60 (m, 15 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 40.13, 47.63, 52.04, 68.19, 84.04, 119.53, 121.01, 126.19, 126.37, 127.01, 128.43, 128.61, 128.79, 129.17, 137.22, 140.47, 142.54, 142.96, 143.92; exact mass, *m/z* calcd for $C_{25}H_{22}O$ 338.1670, found 338.1669. Irradiation of the signal at δ 3.84 (allylic) in the ^1H NMR spectrum produced enhancements of 18% and 20% in the signals at δ 7.54 (olefinic) and δ 5.70 (Ar-C<u>H</u>-O), respectively.

The more polar isomer [(Z)-3α,3aβ,8bβ stereochemistry] had: FT-IR ($CDCl_3$ cast) 3120-2810, 1494 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.05 (t, *J* = 13.0 Hz, 1 H), 2.78 (dd, *J* = 13.6, 3.4 Hz, 1 H), 2.83-2.98 (m, 1 H), 3.47 (dd, *J* = 8.8, 5.5 Hz, 1 H), 3.85 (dd, *J* = 9.0, 6.0 Hz, 1 H), 4.15-4.28 (m, 1 H), 5.65 (d, *J* = 7.0 Hz, 1 H), 6.86-7.70 (m, 15 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 35.12, 44.64, 49.94, 73.01, 86.36, 119.80, 122.30, 125.54, 125.94, 127.19, 128.37, 128.70, 128.84, 129.03, 129.10, 137.45, 140.46, 142.96, 143.26; exact mass, *m/z* calcd for $C_{25}H_{22}O$ 338.1670, found 338.1667. Saturation of the signal at δ 4.20 (allylic) in the ^1H NMR spectrum produced enhancements of 18%, 25%, and 18% in the signals at δ 7.64 (olefinic), δ 5.65 (Ar-C<u>H</u>-O), and δ 2.83-2.98 (Ar-CH_2-C<u>H</u>), respectively.

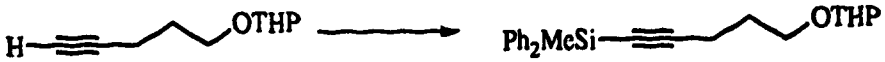
(*E*)-1-[1-[2-(Phenylethynyl)phenyl]-2,2-bis(phenylseleno)ethyl] 3-phenyl-2-propenoate (161).



156 **161**

Triethylamine (1.6 mL, 11.4 mmol) and DMAP (110 mg) were added to a solution of alcohol **156** (607 mg, 1.14 mmol) and cinnamoyl chloride (1.9 g, 11.4 mmol) in ether (40 mL), and the mixture was stirred for 10 h. Water (10 mL) was added and the layers were separated. The aqueous layer was extracted with ether (20 mL), and the combined ether layers were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 18 cm), using 5% ethyl acetate--hexane, gave **161** (526 mg, 69%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 1718, 1154 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.23 (d, *J* = 4.2 Hz, 1 H), 6.46 (d, *J* = 16.0 Hz, 1 H), 6.90 (d, *J* = 4.2 Hz, 1 H), 6.97-7.59 (m, 24 H), 7.72 (d, *J* = 16.0 Hz, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 48.93 (d'), 76.75 (d'), 86.69 (s'), 95.35 (s'), 117.19 (d'), 121.08 (s'), 122.68 (s'), 126.90 (d'), 127.59 (d'), 127.84 (d'), 128.12 (d'), 128.25 (d'), 128.45 (d'), 128.64 (d'), 128.77 (d'), 128.80 (d'), 129.57 (s'), 131.62 (d'), 132.28 (d'), 134.04 (s'), 134.22 (d'), 135.18 (d'), 140.11 (s'), 145.74 (d'), 165.18 (s').

Methyldiphenyl[5-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-pentynyl]silane.



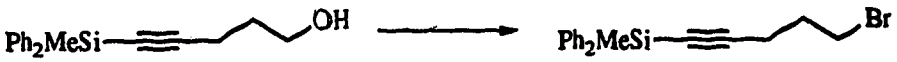
n-Butyllithium (20.4 mL, 1.6 M, in hexane, 32.8 mmol) was added to a stirred solution of 2-(4-pentynyloxy)tetrahydro-2*H*-pyran[229] (5.0 g, 29.8 mmol) in ether (20 mL) and THF (5 mL) at -78°C. After 1 h, *t*-butylchlorodiphenylsilane (6.9 mL, 32.8 mmol) was added over 20 min, and after a further 1 h, the cooling bath was removed and stirring was continued for 10 h. Water (10 mL) was added, the layers were separated and the organic layer was dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (8 x 20 cm), using 10% ethyl acetate--hexane, gave methyldiphenyl[5-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-pentynyl]silane (9.5 g, 87%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.67 (s, 3 H), 1.44-1.95 [m (including quintet J = 7.3 Hz, (2 H), at δ 1.88), 8 H], 3.41-3.57 (m, 2 H), 3.81-3.93 (m, 2 H), 4.59 (t, J = 3.5 Hz, 1 H), 7.30-7.43 (m, 6 H), 7.59-7.70 (m, 4 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ -1.78 (q'), 17.04 (t'), 19.52 (t'), 25.50 (t'), 28.80 (t'), 36.69 (t'), 62.16 (t'), 65.82 (t'), 81.06 (s'), 98.82 (d'), 110.53 (s'), 127.88 (d'), 129.52 (d'), 134.49 (d'), 135.90 (s').

5-(Methyldiphenylsilyl)-4-pentyn-1-ol.

A solution of methyldiphenyl[5-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-pentynyl]silane (9.2 g, 25.3 mmol) and *p*-toluenesulfonic acid monohydrate (0.2 g, 1.05 mmol) in methanol (60 mL) was refluxed for 20 h, cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (4 x 20 cm), using 20% ethyl acetate--hexane, gave 5-(methyldiphenylsilyl)-4-pentyn-1-ol (5.8 g, 83%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR ($CDCl_3$ cast) 3600-3100, 3100-2800, 2174 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400

MHz) δ 0.76 (s, 3 H), 1.87 (quintet, J = 6.6 Hz, 2 H), 12.96-2.21 (m, 1 H), 2.50 (t, J = 7.1 Hz, 2 H), 3.80 (t, J = 5.8 Hz, 2 H), 7.36-7.50 (m, 6 H), 7.65-7.77 (m, 4 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ -1.75 (q'), 16.74 (t'), 31.26 (t'), 61.61 (t'), 81.52 (s'), 110.42 (s'), 127.99 (d'), 129.66 (d'), 134.51 (d'), 135.78 (s'); exact mass, *m/z* calcd for $C_{18}H_{20}OSi$ 280.1283, found 280.1281. Anal. Calcd for $C_{18}H_{20}OSi$: C, 77.09; H, 7.19. Found: C, 76.75; H, 7.31.

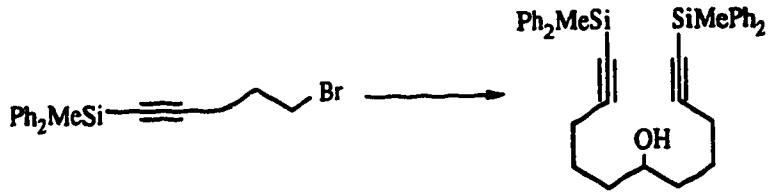
(5-Bromo-1-pentynyl)methyldiphenylsilane (162).



162

Carbon tetrabromide (2.73 g, 8.2 mmol) and triphenylphosphine (2.69 g, 10.3 mmol) were added to a solution of 5-(methyldiphenylsilyl)-4-pentyn-1-ol (1.92 g, 6.86 mmol) in dichloromethane (20 mL), and the resulting solution was stirred at room temperature for 2 h. The mixture was then filtered through silica gel (2 x 2 cm) with dichloromethane (50 mL). The filtrate was evaporated and flash chromatography of the residue over silica gel (3 x 20 cm), using 1% ethyl acetate--hexane, gave bromide **162** (1.75 g, 74%) as a homogeneous [^1H NMR (400 MHz)] colorless oil: FT-IR (film) 3100-2880, 2175 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.67 (s, 3 H), 2.05 (quintet, J = 6.6 Hz, 2 H), 2.49 (t, J = 6.8 Hz, 2 H), 3.50 (t, J = 6.5 Hz, 2 H), 7.30-7.41 (m, 6 H), 7.60-7.68 (m, 4 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ -1.85 (q'), 18.80 (t'), 31.28 (t'), 32.19 (t'), 82.22 (s'), 108.66 (s'), 127.93 (d'), 129.61 (d'), 134.42 (d'), 135.58 (s'); exact mass, *m/z* calcd for $C_{18}H_{19}{}^{81}BrSi$ 344.0419, found 344.0420. Anal. Calcd for $C_{18}H_{19}{}^{81}BrSi$: C, 62.97; H, 5.58. Found: C, 62.91; H, 5.37.

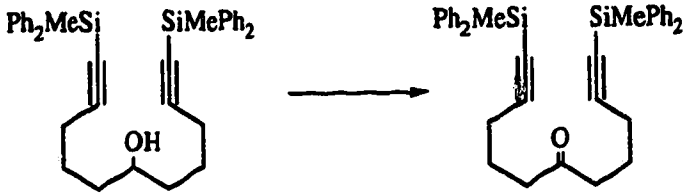
1,11-Bis(methyldiphenylsilyl)-1,10-undecadiyn-6-ol.



162

The procedure for the preparation of **133** was followed, using **162** (1.61 g, 4.69 mmol) in THF (20 mL), magnesium (0.14 g, 5.62 mmol) in THF (20 mL), and ethyl formate (0.21 mL, 2.58 mmol) in THF (5 mL). Flash chromatography of the crude product over silica gel (3 x 20 cm), using 20% ethyl acetate--hexane, gave 1,11-bis(methyldiphenylsilyl)-1,10-undecadiyn-6-ol (0.44 g, 46%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.67 (s, 6 H), 1.42 (d, *J* = 7.2 Hz, 1 H), 1.46-1.79 (m, 8 H), 2.33 (t, *J* = 7.2 Hz, 4 H), 3.60-3.70 (m, 1 H), 7.29-7.40 (m, 12 H), 7.59-7.67 (m, 8 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ -1.81 (q'), 20.05 (t'), 24.59 (t'), 36.56 (t'), 70.78 (d'), 81.23 (s'), 110.87 (s'), 127.88 (d'), 129.54 (d'), 134.44 (d'), 135.82 (s').

1,11-Bis(methyldiphenylsilyl)-1,10-undecadiyn-6-one (163).



163

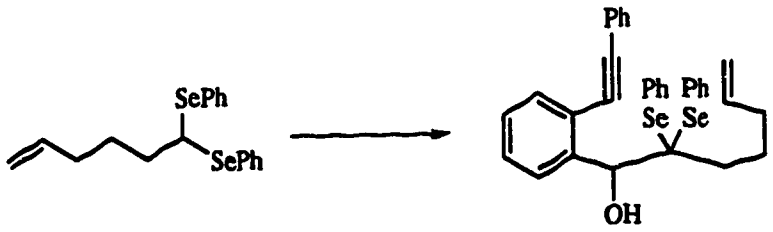
The procedure for the preparation of **134** was followed, using 1,11-bis(methyldiphenylsilyl)-1,10-undecadiyn-6-ol (0.44 g, 1.09 mmol) in acetone (10 mL). Flash chromatography of the crude product over silica gel (3 x 20 cm), using 5% ethyl acetate--hexane, gave ketone **163** (369 mg, 90%) as a

homogeneous [^{1}H NMR (400 MHz)] colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.66 (s, 6 H), 1.80 (quintet, J = 7.1 Hz, 4 H), 2.32 (t, J = 6.9 Hz, 4 H), 2.50 (t, J = 7.3 Hz, 4 H), 7.29-7.39 (m, 12 H), 7.59-7.68 (m, 8 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ -1.89 (q'), 19.34 (t'), 22.30 (t'), 41.21 (t'), 81.77 (s'), 109.96 (s'), 127.86 (d'), 129.53 (d'), 134.37 (d'), 135.64 (s'), 209.36 (s').

1,1-Bis(phenylseleno)-5-hexene.[170]

Tris(phenylseleno)borane[230] (0.683 g, 1.43 mmol) and trifluoroacetic acid (17 mL, 0.22 mmol) were added to a solution of 5-hexenal (210 mg, 2.14 mmol) in chloroform (2 mL). The mixture was stirred at room temperature for 8 h, then washed with saturated aqueous sodium bicarbonate (2 mL), and water (2 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm), using first hexane and then 1% ethyl acetate--hexane, gave 1,1-bis(phenylseleno)-5-hexene (350 mg, 42%) as a homogeneous [^{1}H NMR (200 MHz)], pale yellow oil: FT-IR (CH_2Cl_2 cast) 3070, 2990, 1578, 1475, 1438 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.58-1.74 (m, 2 H), 1.86-2.06 (m, 4 H), 4.48 (t, J = 6.5 Hz, 1 H), 4.85-5.00 (m, 2 H), 5.70 (ddt, J = 17.0, 10.2, 6.5 Hz, 1 H), 7.19-7.34 (m, 6 H), 7.50-7.63 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 27.57, 32.93, 36.61, 114.90, 127.97, 129.02, 130.41, 134.72, 138.11; exact mass, m/z calcd for $C_{18}H_{20}Se_2$ 395.9895, found 395.9819.

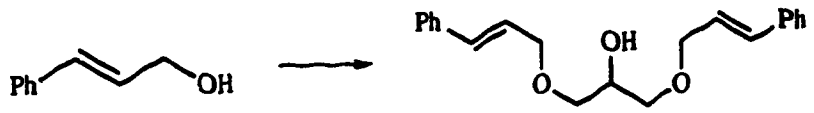
1-[2-(Phenylethynyl)phenyl]-2,2-bis(phenylseleno)hept-6-en-1-ol (164).



164

1,1-Bis(phenylseleno)-5-hexene[170] (250 mg, 0.634 mmol) in THF (2 mL) was added to a stirred and cooled (-78°C) solution of potassium diisopropylamide, generated as described for the preparation of **155**, using *n*-butyllithium (0.43 mL, 1.6 M, in hexanes, 0.688 mmol), and potassium *t*-butoxide (89 mg, 0.792 mmol) and diisopropylamine (0.11 mL, 0.792 mmol) in THF (5 mL). The mixture was stirred for 10 min at -78°C, and **156** (109 mg, 0.528 mmol) in THF (4 mL) was added over 1 min. Stirring was continued for 1 h, and the mixture was then quenched with water (5 mL), allowed to attain room temperature, and extracted with ether (2 x 10 mL). The combined ether extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 18) with 10% ethyl acetate--hexane, gave **164** (137 mg, 43%) as a homogeneous [^{1}H NMR (200 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3459, 3057, 2940, 1492, 1475, 1436 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.48-2.16 (m, 6 H), 3.80 (d, *J* = 1.6 Hz, 1 H), 4.66-4.83 (m, 2 H), 5.30 (d, *J* = 1.6 Hz, 1 H), 5.51 (ddt, *J* = 17.0, 10.0, 3.2 Hz, 1 H), 6.95-7.63 (m, 18 H), 8.19 (br d, *J* = 8 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 26.66, 33.56, 36.02, 70.62, 74.87, 87.81, 93.89, 114.60, 122.86, 123.59, 126.93, 127.88, 128.05, 128.18, 128.612, 128.96, 129.04, 129.22, 130.08, 131.48, 131.48, 132.27, 137.22, 137.98, 138.18, 139.92; exact mass, *m/z* calcd for $C_{27}H_{25}OSe$ (M - PhSe)$^+$ 445.1071, found 445.1073.

1,3-Bis[(*E*-3-phenylprop-2-enyl)oxy]-2-propanol (165).



165

Sodium hydride (0.9 g, 60% dispersion in oil, 22.5 mmol) was added to a solution of cinnamyl alcohol (5.0 g, 37.3 mmol) and 1-bromo-2,3-epoxypropane (1.02 g, 7.47 mmol) in DME (20 mL), and the mixture was heated at 85°C for 4 h. Sodium hydride (0.5 g, 12.5 mmol) was added and heating was continued for a further 2 h. The mixture was cooled, ether (50 mL) was added and the mixture was poured into saturated aqueous sodium bicarbonate (10 mL). The layers were separated and the organic layer was washed with water (2 x 10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (6 x 20 cm), using % ethyl acetate--hexane, gave alcohol **165** (1.24 g, 51%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.71 (d, *J* = 4.4 Hz, 1 H), 3.52 (dd, *J* = 9.8, 6.3 Hz, 2 H), 3.58 (dd, *J* = 9.8, 4.4 Hz, 2 H), 3.99-4.08 (m, 1 H), 4.18 (dd, *J* = 6.0, 1.7 Hz, 4 H), 6.27 (dt, *J* = 16.0, 6.0 Hz, 2 H), 6.57 (d, *J* = 16.0 Hz, 2 H), 7.13-7.42 (m, 10 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 69.62 (d'), 71.36 (t'), 71.99 (t'), 125.72 (d'), 126.49 (d'), 127.72 (d'), 128.54 (d'), 132.62 (d'), 136.58 (s').

1,3-Bis[(*E*-3-phenylprop-2-enyl)oxy]-2-propanone (166).

165 **166**

DMSO (0.61 mL, 8.7 mmol) was added over 10 min to a stirred and

cooled (-78°C) solution of oxalyl chloride (0.38 mL, 4.35 mmol) in dichloromethane (50 mL). Alcohol **165** (0.70 g, 2.16 mmol) in dichloromethane (5 mL) was then injected over 30 min. After 1 h triethylamine (1.8 mL, 12.96 mmol) was added and the cooling bath was removed. After a further 1 h the solvent was evaporated and flash chromatography of the residue over silica gel (2 x 20 cm), using 20% ethyl acetate–hexane, gave ketone **166** (519 mg, 74%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (film) 3027, 2898, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.14 (dd, J = 6.1, 1.4 Hz, 4 H), 4.24 (s, 4 H), 6.23 (dt, J = 15.8, 6.1 Hz, 2 H), 6.57 (d, J = 15.8 Hz, 2 H), 7.22-7.44 (m, 10 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 71.60 (t'), 73.03 (t'), 124.55 (d'), 126.16 (d'), 127.51 (d'), 128.20 (d'), 132.91 (d'), 135.92 (s'), 205.33 (s'); exact mass, *m/z* calcd for $C_{21}H_{22}O_3$ 322.1569, found 322.1568.

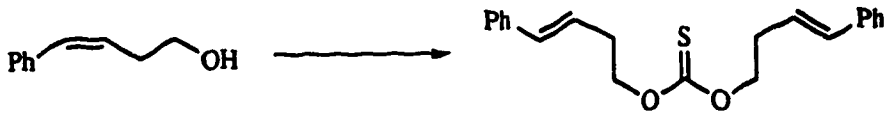
2,2-Bis[(*E*)-3-phenylprop-2-enyl)oxy]methyl-1,3-dithiane (168).

166 **168**

Following a literature procedure,[171] boron trifluoride etherate (0.1 mL, 0.81 mmol) was added to a stirred solution of ketone **166** (94 mg, 0.29 mmol) and 1,2-ethanedithiol (0.029 mL, 0.35 mmol) in chloroform (2 mL) at 0°C. After 2 h, water (5 mL) was added and the cooling bath was removed. Dichloromethane (10 mL) was added and the layers were separated. The organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 10% ethyl acetate–hexane, gave thioketal **168** (30 mg, 25%) as a homogeneous [^{1}H NMR (400 MHz)] colorless

oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.26 (s, 4 H), 3.80 (s, 4 H), 4.25 (dd, *J* = 6.0, 1.7 Hz, 4 H), 6.26 (dt, *J* = 16.0, 6.0 Hz, 2 H), 6.80 (d, *J* = 16.1 Hz, 2 H), 7.18-7.38 (m, 10 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 38.68 (t'), 68.87 (s'), 72.14 (t'), 74.43 (t'), 126.11 (d'), 126.55 (d'), 127.66 (d'), 128.56 (d'), 132.27 (d'), 136.77 (s').

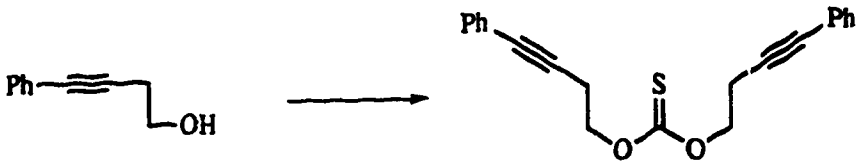
Bis-*O*-[(Z)-4-phenyl-3-butenyl] thiocarbonate (169).



169

A solution of (Z)-4-phenyl-3-buten-1-ol[231] (0.448 g, 3.03 mmol) and 1,1'-thiocarbonyldiimidazole (0.270 g, 1.51 mmol) in 1,2-dichloroethane (5 mL) was refluxed for 2 h. The solvent was evaporated, and flash chromatography of the residue over silica gel (2 x 18 cm), using 5% ethyl acetate--hexane, gave **17** (182 mg, 35%) as a homogeneous [^{1}H NMR (400 MHz)], pale yellow oil: FT-IR ($CDCl_3$ cast) 1307, 1286, 1298 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.75 (qd, *J* = 7.0, 1.8 Hz, 4 H), 4.58 (t, *J* = 6.7 Hz, 4 H), 5.64 (dt, *J* = 11.5, 7.2 Hz, 1 H), 6.54 (d, *J* = 11.5 Hz, 1 H), 7.17-7.36 (m, 10 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 27.80 (t'), 72.37 (t'), 126.59 (d'), 127.00 (d'), 128.32 (d'), 128.71 (d'), 131.88 (d'), 137.01 (s'), 195.53 (s'); exact mass, *m/z* calcd for $C_{21}H_{22}O_2S$ 338.1342, found 338.1324. Anal. Calcd for $C_{21}H_{22}O_2S$: C, 74.52; H, 6.55; S, 9.47. Found: C, 74.27; H, 6.68; S, 9.21.

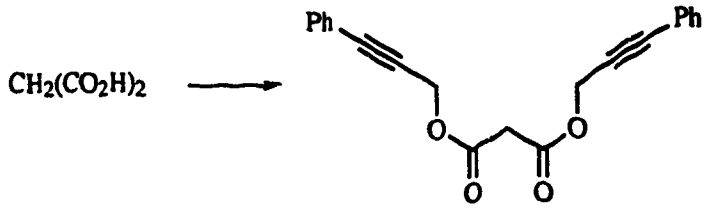
Bis-*O*-[(*Z*)-4-phenyl-3-butynyl] thiocarbonate (170).



170

Pyridine (0.55 mL, 6.8 mmol) and thiophosgene (0.047 mL, 0.62 mmol) were added to a stirred solution of 4-phenyl-3-butyn-1-ol (198 mg, 1.36 mmol) in dichloromethane (5 mL) at room temperature. After 2 h the solvent was evaporated and flash chromatography of the residue over silica gel (2 x 18 cm), using 10% ethyl acetate–hexane, gave **170** (44 mg, 21%) as homogeneous [^{1}H NMR (400 MHz)] white crystals: FT-IR ($CHCl_3$ cast) 1490, 1300, 1257, 1231 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.91 (t, J = 7.1 Hz, 4 H), 4.64 (t, J = 7.1 Hz, 4 H), 7.26-7.33 (m, 6 H), 7.39-7.47 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.55 (t'), 70.58 (t'), 82.41 (s'), 84.65 (s'), 123.22 (s'), 128.04 (d'), 128.25 (d'), 131.70 (d'), 194.96 (s'); exact mass, *m/z* calcd for $C_{21}H_{18}O_2S$ 334.1027, found 334.1024.

Bis(3-phenylprop-2-ynyl) malonate (172).

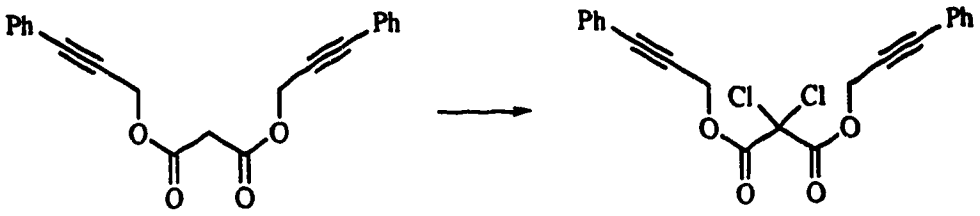


172

1,3-Dicyclohexylcarbodiimide (3.5 g, 17.0 mmol) and DMAP (0.19 g, 1.5 mmol) were added to a solution of phenylprop-2-ynyl alcohol (2.55 g, 19.3 mmol) and malonic acid (0.8 g, 7.7 mmol) in ether (30 mL) at 0°C. The resulting mixture was stirred at room temperature for 48 h, then diluted with

ether (50 mL), washed with water (20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 18 cm), using 10% ethyl acetate--hexane, gave **172** (1.98 g, 77%) as a homogeneous [^{1}H NMR (400 MHz)] yellow oil: FT-IR ($CHCl_3$ cast) 3100-2900, 2120, 1760, 1741, 1490 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 3.53 (s, 2 H), 4.97 (s, 4 H), 7.22-7.25 (m, 6 H), 7.40-7.48 (m, 4 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 40.94 (t'), 53.84 (t'), 82.15 (s'), 87.00 (s'), 121.86 (s'), 128.25 (d'), 128.81 (d'), 131.83 (d'), 165.44 (s'); exact mass, *m/z* calcd for $C_{21}H_{16}O_4$ 332.1049, found 332.1047. Anal. Calcd for $C_{21}H_{16}O_4$: C, 75.89; H, 4.85. Found: C, 75.86; H, 4.81.

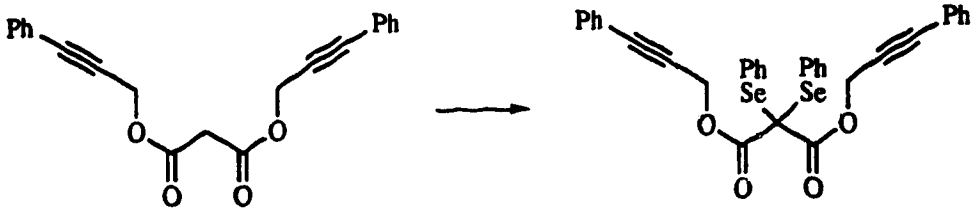
Bis(3-phenylprop-2-ynyl) 2,2-dichloromalonate (173).



172 **173**

Following a literature procedure,[173] triethylamine (0.245 mL, 1.76 mmol) and trifluoromethanesulfonyl chloride (0.188 mL, 1.76 mmol) were added to a stirred solution of **172** (293 mg, 0.882 mmol) in dichloromethane (10 mL). After 8 h water (10 mL) was added and the layers were separated. The organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm), using 10% ethyl acetate--hexane, gave **173** (326 mg, 96%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.12 (s, 4 H), 7.23-7.48 (m, 10 H); mass, *m/z* calcd for $C_{21}H_{14}Cl_2O_4$ 400, found 400. Anal. Calcd for $C_{21}H_{14}Cl_2O_4$: C, 62.86; H, 3.52; Cl, 17.67. Found: C, 62.55; H, 3.41; Cl, 17.73.

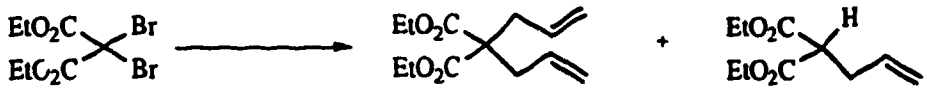
Bis(3-phenylprop-2-ynyl) 2,2-bis(phenylseleno)malonate (174).



172 174

LDA [prepared from *n*-butyllithium (4.0 mL, 1.6 M, in hexanes, 6.4 mmol) and diisopropylamine (0.98 mL, 7.05 mmol) in THF (5 mL)] was added to a stirred solution of **172** (1.95 g, 5.87 mmol) in THF (20 mL) at -78°C. After 10 min, benzeneselenol (1.23 g, 6.46 mmol) in THF (5 mL) was added, and stirring was continued for 30 min. LDA [prepared from *n*-butyllithium (4.0 mL, 1.6 M, in hexanes, 6.4 mmol) and diisopropylamine (0.98 mL, 7.05 mmol) in THF (5 mL)] was then added, followed, after 10 min, by benzeneselenol (1.23 g, 0.646 mmol). After a further 1 h at -78°C, water (5 mL) was added and the cooling bath was removed. The layers were separated and the organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 20 cm), using 2% ethyl acetate-15% dichloromethane--hexane, gave **174** (2.7 g) as a yellow solid, which was recrystallized from dichloromethane--hexane to give **174** (2.53 g, 67%) as a homogeneous [^{1}H NMR (400 MHz)], pale yellow solid: FT-IR ($CDCl_3$ cast) 1727, 1490, 1438, 1216 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 4.82 (s, 4 H), 7.22-7.50 (m, 16 H), 7.77-7.88 (m, 4 H); mass, (CI) calcd for $C_{33}H_{24}O_4Se$ 644, found 662 (M + 18)$^+$. Anal. Calcd for $C_{33}H_{24}O_4Se$: C, 61.69; H, 3.76; O, 9.96. Found: C, 61.52; H, 3.77; O, 10.02.

Diethyl 2,2-bis(prop-2-enyl)propanedioate (175) and Diethyl 2-(prop-2-enyl)propanedioate (176).

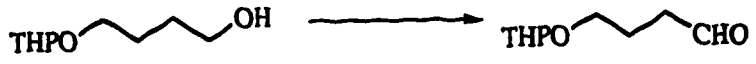


175 **176**

A solution of AIBN (10.2 mg, 0.062 mmol) in benzene (6 mL) was added over 8 h to a refluxing benzene (1.7 mL) solution of diethyl dibromomalonate (192 mg, 0.623 mmol) and allyltributyltin (2.05 g, 6.23 mmol). The solution was refluxed for an additional 4 h, cooled and evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm), using a 1:5:44 mixture of ethyl acetate, dichloromethane, and hexane, gave the double (**175**) and single (**176**) addition products in 49 and 27% yields, respectively, as homogeneous [^{1}H NMR (300 MHz)] oils. Compound **175** had: FT-IR ($CDCl_3$ cast) 2981, 1734, 1195 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.20 (t, *J* = 6.6 Hz, 6 H), 2.58 (br d, *J* = 14.8 Hz, 4 H), 4.12 (q, *J* = 7.0 Hz, 4 H), 5.00-5.10 (m, 4 H), 5.51-5.68 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 75.5 MHz) δ 14.03 (q'), 36.70 (t'), 57.17 (s'), 61.10 (t'), 118.99 (t'), 132.30 (d'), 170.62 (s'); exact mass, *m/z* calcd for $C_{13}H_{20}O_4$ 240.1361, found 240.1360. Anal. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39. Found: C, 65.09; H, 8.42.

Compound **176** had: FT-IR ($CDCl_3$ cast) 2970, 1750, 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (t, *J* = 7.1 Hz, 6 H), 2.65 (tt, *J* = 7.1, 1.3 Hz, 2 H), 3.42 (t, *J* = 7.5 Hz, 1 H), 4.20 (qd, *J* = 7.1, 0.6 Hz, 4 H), 5.03-5.17 (m, 2 H), 5.78 (ddt, *J* = 17.0, 10.0, 6.6 Hz, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 75.5 MHz) δ 14.08 (q'), 32.82 (t'), 51.68 (d'), 61.38 (t'), 117.49 (t'), 134.11 (d'), 168.92 (s'); exact mass, *m/z* calcd for $C_{10}H_{16}O_4$ 200.10649, found 200.1048. Anal. Calcd for $C_{10}H_{16}O_4$: C, 59.98; H, 8.05. Found: C 60.43; H, 8.21.

4-[(Tetrahydro-2*H*-pyran-2-yl)oxy]butanal (181).[232]



181

The procedure for the preparation of **166** was followed, using DMSO (7.8 mL, 0.11 mmol) and oxalyl chloride (5.05 mL, 0.058 mmol) in dichloromethane (50 mL), 4-[(tetrahydro-2*H*-pyran-2-yl)oxy]butanol[232] (9.6 g, 0.055 mol) in dichloromethane (10 mL) and triethylamine (20 mL, 0.143 mol). Flash chromatography of the residue over silica gel (6 x 20 cm), using 20% ethyl acetate--hexane, gave aldehyde **181** (6.4 g, 67%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 2942, 2870, 1725 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.44-1.87 (m, 6 H), 1.95 (dq, *J* = 6.0, 5.4 Hz, 2 H), 2.54 (tt, *J* = 7.2, 1.9 Hz, 2 H), 3.42 (dt, *J* = 10.0, 6.4 Hz, 2 H), 3.46-3.53 (m, 2 H), 4.57 (t, *J* = 3.7 Hz, 1 H), 9.79 (t, *J* = 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 19.36, 22.57, 25.33, 30.48, 40.97, 62.13, 66.27, 98.72, 202.09; exact mass, *m/z* calcd for $C_9H_{17}O_3$, 173.1177; found 173.1176.

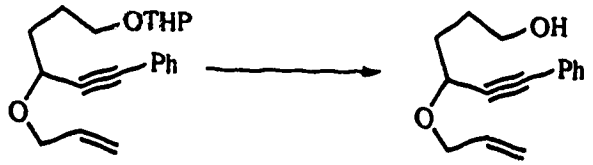
1-Phenyl-3-[(2-propenyl)oxy]-6-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-hexyne (183).

181 **183**

n-Butyllithium (10.4 mL, 1.6 M, in hexanes, 16.7 mmol) was added to a stirred and cooled (-78°C) solution of phenylacetylene (1.8 mL, 16.7 mmol) in THF (20 mL). After 10 min a solution of aldehyde **181**[232] (2.39 g, 13.9 mmol)

in THF (10 mL) was added over 10 min. Stirring at -78°C was continued for 1 h, and the mixture was then quenched with water (10 mL) and extracted with ether (2 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. The residue was dissolved in THF (20 mL) and sodium hydride (1.1 g, 60% dispersion in oil, 27.5 mmol), followed by 3-bromopropene (2.4 mL, 27.7 mmol), were added with stirring. The mixture was refluxed for 1 h, cooled, quenched with water (10 mL) and extracted with ether (2 x 30 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 20 cm), using 10% ethyl acetate--hexane, gave **183** (2.8 g, 64%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 2942 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43-1.63 (m, 4 H), 1.63-1.76 (m, 1 H), 1.76-2.01 (m, 5 H), 3.38-3.54 (m, 2 H), 3.74-3.91 (m, 2 H), 4.00-4.09 (m, 1 H), 4.28-4.39 (m, 2 H), 4.59 (br s, 1 H), 5.20 (d quintet, J = 10.5, 1.4 Hz, 1 H), 5.33 (d quintet, J = 17.4, 1.7 Hz, 1 H), 5.89-6.01 (m, 1 H), 7.23-7.33 (m, 3 H), 7.39-7.47 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 19.41 (t'), 25.38 (t'), 25.60 (t'), 30.59 (t'), 32.58 (t'), 62.01 (t'), 66.95 (t'), 69.01 (d'), 69.55 (d'), 85.72 (s'), 88.07 (s'), 98.57 (d'), 117.10 (s'), 122.68 (s'), 128.12 (d'), 131.60 (d'); exact mass, *m/z* calcd for $C_{20}H_{26}O_3$ 314.1882, found 314.1874.

6-Phenyl-4-[(2-propenyl)oxy]-5-hexyn-1-ol (184).

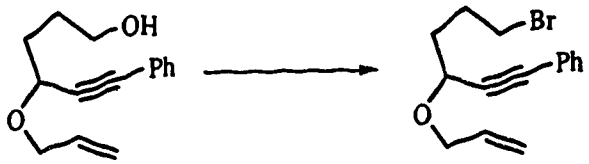


183 **184**

A solution of **183** (1.6 g, 5.09 mmol) and *p*-toluenesulfonic acid monohydrate (5 mg, 0.03 mmol) in methanol (20 mL) was refluxed for 10 h.

Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 20 cm), using 20% ethyl acetate--hexane, gave alcohol **184** (0.94 g, 80%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3120-3600, 2950 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.74-1.98 (m, 4 H), 2.31 (br s, 1 H), 3.69 (t, *J* = 6.3 Hz, 2 H), 4.05 (ddt, *J* = 12.2, 6.3, 1.3 Hz, 1 H), 4.34 (ddt, *J* = 12.8, 5.0, 3.0 Hz, 1 H), 4.37 (t, *J* = 6.1 Hz, 1 H), 5.22 (dq, *J* = 10.2, 4.2 Hz, 1 H), 5.33 (dq, *J* = 17.4, 4.8 Hz, 1 H), 5.90-6.00 (m, 1 H), 7.27-7.34 (m, 3 H), 7.40-7.47 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 28.64 (t'), 32.42 (t'), 62.45 (t'), 69.10 (t'), 69.76 (t'), 86.09 (s'), 87.74 (s'), 117.62 (t'), 122.61 (s'), 128.27 (d'), 128.36 (d'), 131.71 (d'), 134.23 (d'); exact mass, *m/z* calcd for $C_{15}H_{17}O_2$ $(M - H)^+$ 229.1228, found 229.1227.

6-Bromo-1-phenyl-3-[(2-propenyl)oxy]-1-hexyne (180a).

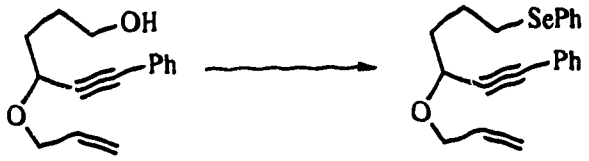


184 **180a**

Carbon tetrabromide (1.12 g, 3.37 mmol) and triphenylphosphine (0.88 g, 3.37 mmol) were added to a stirred and cooled (0°C) solution of alcohol **184** (0.648 g, 2.81 mmol) in dichloromethane (40 mL). The cooling bath was removed and stirring was continued for 30 min. The solution was then filtered through a pad of silica gel (2 x 2 cm) with 10% ethyl acetate--hexane (50 mL). The filtrate was evaporated and flash chromatography of the residue over silica gel (3 x 20 cm), using 20% ethyl acetate--hexane, gave bromide **180a** (0.70 g, 85%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 2800-3110, 1488 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.93-2.01 (m, 2

H), 2.08-2.17 (m, 2 H), 3.48 (t, J = 6.5 Hz, 2 H), 4.03 (ddt, J = 12.4, 6.2, 2.4 Hz, 2 H), 4.32 (ddt, J = 12.8, 5.0, 3.2 Hz, 1 H), 4.35 (t, J = 6.3 Hz, 1 H), 5.21 (dq, J = 10.2, 1.5 Hz, 1 H), 5.33 (dq, J = 17.0, 1.7 Hz, 1 H), 5.89-6.00 (m, 1 H), 7.27-7.34 (m, 3 H), 7.40-7.46 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 28.69 (t'), 33.55 (t'), 34.29 (t'), 68.38 (d'), 69.71 (t'), 86.18 (s'), 87.57 (s'), 117.46 (t'), 122.54 (s'), 128.30 (d'), 128.45 (d'), 131.75 (d'), 134.37 (d'); exact mass, m/z calcd for $C_{15}H_{17}{}^{81}BrO$ 294.0442, found 294.0419.

1-Phenyl-6-(phenylseleno)-3-[(2-propenyl)oxy]-1-hexyne (180b).



184 **180b**

Tributylphosphine (1.83 mL, 7.36 mmol) and phenylselenocyanate (1.07 mL, 7.36 mmol) were added to a stirred and cooled (0°C) solution of alcohol **184** (565 mg, 2.45 mmol) in THF (20 mL). After 1 h at 0°C, the mixture was diluted with ether (50 mL) and washed with water (1 x 10 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 10% ethyl acetate--hexane, gave selenide **180b** (884 mg, 97%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 2800-3040, 1480, 1477, 1437 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.88-2.02 (m, 4 H), 2.90-3.03 (m, 2 H), 4.01 (ddt, J = 12.2, 6.1, 1.2 Hz, 1 H), 4.27-4.36 (m, 2 H), 5.20 (dq, J = 10.2, 1.3 Hz, 1 H), 5.31 (dq, J = 17.2, 1.6 Hz, 1 H), 5.87-5.99 (m, 1 H), 7.17-7.25 (m, 3 H), 7.25-7.34 (m, 3 H), 7.34-7.42 (m, 2 H), 7.43-7.54 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 25.97 (t'), 27.56 (t'), 35.70 (t'), 68.74 (d'), 69.69 (t'), 86.07 (s'), 87.88 (s'), 117.32 (t'), 122.76 (s'), 126.71 (d'),

128.25 (d'), 128.35 (d'), 129.00 (d'), 130.32 (s'), 131.75 (d'), 132.62 (d'), 134.46 (d'); exact mass, *m/z* calcd for $C_{21}H_{22}OSe$ 370.0836, found 370.0823.

1α-(3-Bromopropyl)-3aα,4-dihydro-6-phenylcyclopenta[c]furan-5(3*H*)-one (186a).

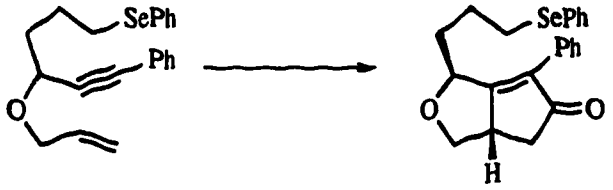
180a **186a**

(a) Silica Gel Method:- The general method for the P-K reaction with silica gel was followed, using **180a** (129 mg, 0.44 mmol) in benzene (10 mL), octacarbonyldicobalt (225 mg, 0.66 mmol), silica gel (5 g, containing 20% $^{w}/_{w}$ water). The mixture was heated for 3 h at 45°C. Flash chromatography of the crude product over silica gel (2 x 20 cm), using 20% ethyl acetate--hexane, gave enone **186a** (58.4 mg, 41%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3600-2800, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.86-1.99 (m, 1 H), 2.01-2.15 (m, 3 H), 2.30 (dd, *J* = 17.9, 1.7 Hz, 1 H), 2.82 (dd, *J* = 17.9, 6.1 Hz, 1 H), 3.24-3.39 (m, 3 H), 3.42-3.53 (m, 3 H), 4.37 (t, *J* = 6.2 Hz, 1 H), 4.77-4.85 (m, 1 H), 7.30-7.53 (m, 5 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 28.55 (t'), 33.29 (t'), 33.53 (t'), 39.73 (t'), 42.57 (d'), 71.33 (t'), 75.28 (d'), 128.28 (d'), 128.57 (d'), 130.69 (s'), 135.47 (s'), 178.68 (s'), 207.09 (s'); exact mass, *m/z* calcd for $C_{16}H_{17}O_2{}^{81}Br$ 322.0391, found 322.0390.

(b) 4-Methylmorpholine *N*-Oxide Method:- The general procedure for the P-K reaction with NMO was followed, using **180a** (102 mg, 0.348 mmol) in dichloromethane (5 mL), octacarbonyldicobalt (1.7 mL, 0.3 M solution in

dichloromethane, 0.52 mmol), and 4-methylmorpholine *N*-oxide (244 mg, 2.09 mmol). Flash chromatography of the crude product over silica gel (2 x 20 cm), using 20% ethyl acetate--hexane, gave enone **186a** (52.3 mg, 46.8%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil, which was identical with material obtained by the silica gel method.

3aα,4-Dihydro-1α-[3-(phenylseleno)propyl]-6-phenylcyclopenta[c]furan-5(3*H*)-one (186b).

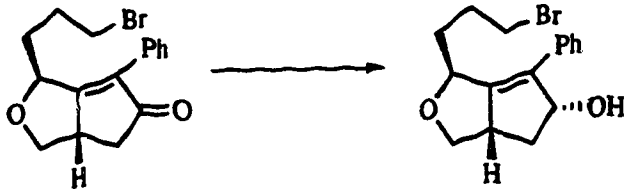


180b **186b**

(a) Silica Gel Method:- The general procedure for the P-K reaction with silica gel was followed, using **180b** (205 mg, 0.55 mmol) in benzene (10 mL), octacarbonyldicobalt (285 mg, 0.833 mmol), silica gel (5 g, 20% $^{w}/_{w}$ water). The mixture was heated for 3 h at 45°C. Flash chromatography of the residue over silica gel (2 x 20 cm), using 50% ethyl acetate--hexane, gave **186b** (116 mg, 53%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3120-2760, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.82-1.97 (m, 3 H), 1.97-2.11 (m, 1 H), 2.17 (dd, *J* = 17.7, 2.4 Hz, 1 H), 2.79 (dd, *J* = 17.8, 5.9 Hz, 1 H), 2.88-3.03 (m, 2 H), 3.28 (br d, *J* = 2.3 Hz, 2 H), 4.34 (t, *J* = 13.9 Hz, 1 H), 4.75-4.81 (m, 1 H), 7.20-7.30 (m, 3 H), 7.32-7.53 (m, 7 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 25.96 (t'), 27.64 (t'), 34.92 (t'), 39.76 (t'), 42.70 (d'), 71.32 (t'), 75.81 (d'), 126.95 (d'), 128.32 (d'), 128.52 (d'), 128.55 (d'), 129.07 (d'), 130.05 (s'), 130.87 (s'), 132.86 (t'), 135.35 (s'), 179.08 (s'), 207.07 (s'); exact mass, *m/z* calcd for $C_{22}H_{22}O_2Se$ 398.0785, found 398.0790.

(b) 4-Methylmorpholine *N*-Oxide Method:- The general procedure for the P-K reaction with NMO was followed, using **180b** (106 mg, 0.287 mmol) in dichloromethane (10 mL), octacarbonyldicobalt (1.4 mL, 0.3 M solution in dichloromethane, 0.43 mmol) and 4-Methylmorpholine *N*-oxide (201 mg, 1.72 mmol). Flash chromatography of the crude product over silica gel (2 x 20 cm), using 50% ethyl acetate--hexane, gave enone **186b** (68 mg, 59%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil, which was identical with that obtained by the silica gel method.

1β-(3-Bromopropyl)-1,3aβ,4,5–tetrahydro-6-phenyl-(3*H*)cyclopenta[c]furan-5α-ol (190a).

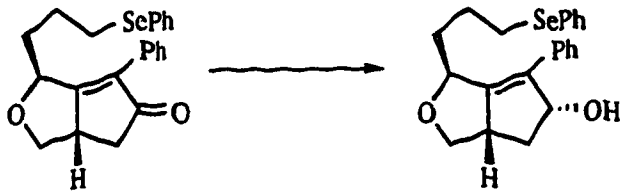


186a **190a**

A mixture of ketone **186a** (38 mg, 0.118 mmol) and cerium(III) chloride heptahydrate (48.5 mg, 0.130 mmol) in methanol (5 mL) was stirred at room temperature for 30 min and then cooled to -78°C. Sodium borohydride (5 mg, 0.130 mmol) was added, followed, after 1 h, by water (10 mL). The cooling bath was removed and, when the mixture had reached room temperature, it was extracted with ether (2 x 25 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 30% ethyl acetate--hexane, gave alcohol **190a** (34.5 mg, 90%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3600-3120, 2962, 2652 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47 (dt, J = 12.0, 8.5 Hz, 1 H), 1.55-1.65 (m, 1 H), 1.71-1.81 (m, 1 H), 1.83-1.93 (m, 2 H), 2.01 (br s, 1 H), 2.91

(dt, J = 12.4, 6.3 Hz, 1 H), 3.07-3.19 (m, 1 H), 33.1 (dd, J = 10.5, 8.6 Hz, 1 H), 3.36 (t, J = 6.5 Hz, 2 H), 4.18 (t, J = 7.5 Hz, 1 H), 4.87-4.94 (m, 1 H), 5.50-5.60 (m, 1 H), 7.21-7.30 (m, 1 H), 7.32-7.45 (m, 4 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 28.63 (t'), 32.10 (t'), 33.52 (t'), 38.60 (t'), 47.62 (d'), 72.35 (t'), 74.36 (d'), 83.57 (d'), 127.31 (d'), 127.51 (d'), 128.66 (d'), 133.98 (s'), 134.17 (s'), 148.45 (s'); exact mass m/z calcd for $C_{16}H_{19}O_2{}^{81}Br$ 324.0548, found 324.0549.

1α,3aβ,4,5β-tetrahydro-6-phenyl-1β-[3-(phenylseleno)propyl](3*H*) cyclopenta[c]furan-5α-ol (190b)

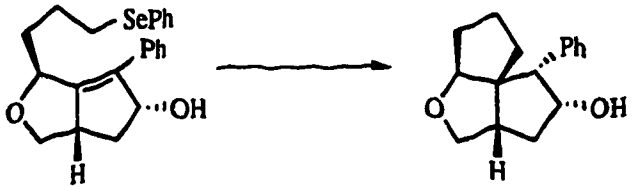


186b **190b**

The procedure for the preparation of bromide **190a** was followed, using ketone **186b** (63 mg, 0.158 mmol) in methanol (10 mL), cerium(III) chloride heptahydrate (65 mg, 0.175 mmol), and sodium borohydride (6.6 mg, 0.175 mmol). Flash chromatography of the crude product over silica gel (2 x 20 cm), using 50% ethyl acetate–hexane, gave alcohol **190b** (63.3 mg, 99%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3600-3080, 2963, 2933, 2856, 1477, 1437 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.40-1.50 (m, 1 H), 1.56-1.78 (m, 4 H), 1.94 (br s, 1 H), 2.67 (dt, J = 12.0, 6.3 Hz, 1 H), 2.83 (td, J = 6.9, 2.0 Hz, 2 H), 3.08 (br quintet, J = 8.4 Hz, 1 H), 3.29 (dd, J = 10.4, 8.0 Hz, 1 H), 4.16 (t, J = 7.6 Hz, 1 H), 4.85-4.92 (m, 1 H), 5.51 (br q, J = 6.4 Hz, 1 H), 7.16-7.30 (m, 4 H), 7.32-7.43 (m, 6 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 25.84 (t'), 27.75 (t'), 33.50 (t'), 38.77 (t'), 47.64 (d'), 72.29 (t'), 74.75 (d'), 83.54 (d'), 126.76 (d'), 127.23 (d'), 127.48 (d'), 128.62 (d'), 128.62 (d'), 130.22 (s'), 132.76 (d'), 133.66

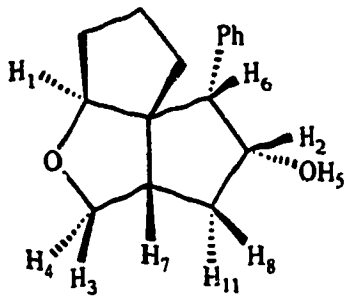
(s'), 134.23 (s'), 148.71 (s'); exact mass *m/z* calcd for $C_{22}H_{24}O_2Se$ 400.0942, found 400.0926.

***cis-cis*-(5*H*)-1,2,3,3a,5aα,6,7,8-Octahydro-8β-phenyldicyclopenta[b,*c*]furan-7α-ol (191).**



190b **191**

The general procedure for radical cyclization was followed using selenide **190b** (182 mg, 0.469 mmol) in benzene (20 mL), tributyltin hydride (0.15 mL, 0.563 mmol) in benzene (5 mL) and AIBN (5 mg, 0.030 mmol) in benzene (5 mL). Flash chromatography of the residue over silica gel (2 x 20 cm), using 20% ethyl acetate--hexane, gave alcohol **191** (87 mg, 78%) as a homogeneous [^{1}H NMR (400 MHz)] white solid: mp. 74-76°C; FT-IR (CH_2Cl_2 cast) 3600-3200, 2942, 2872 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.37-1.60 (m, 3 H), 1.63-1.68 (m, 1 H), 1.71 (d, *J* = 14.8 Hz, 1 H), 1.73-1.80 (m, 1 H), 1.83-1.89 (m, 1 H), 2.32 (ddd, *J* = 14.8, 10.2, 4.4 Hz, 1 H), 2.43 (dd, *J* = 10.1, 8.2 Hz, 1 H), 2.95 (d, *J* = 3.6 Hz, 1 H), 3.45 (d, *J* = 10.5 Hz, 1 H), 3.80 (dd, *J* = 9.2, 2.0 Hz, 1 H), 4.00 (dd, *J* = 9.4, 5.6 Hz, 1 H), 4.35 (dt, *J* = 10.5, 7.8 Hz, 1 H), 4.58-4.63 (m, 1 H), 7.20-7.34 (m, 3 H), 7.57-7.64 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 24.95 (t'), 33.29 (t'), 37.91 (t'), 42.36 (t'), 50.95 (d'), 57.12 (d'), 64.73 (s'), 75.38 (t'), 76.74 (d'), 84.57 (d'), 126.57 (d'), 127.95 (d'), 130.44 (d'), 139.31 (s'); exact mass, *m/z* calcd for $C_{16}H_{20}O_2$ 244.1463, found 244.1463.



Chemical Shift

H_1 = 4.58-4.63
H_2 = 4.35
H_3 = 4.00
H_4 = 3.80
H_5 = 3.45
H_6 = 2.95
H_7 = 2.43
H_8 = 2.32
H_{11} = 1.71

The stereochemistry of compound **197** was determined by decoupling and NOE enhancement NMR experiments.

H_5 was identified by its change in chemical shift in two spectra of samples of different concentrations.

Irradiation of H_5:- H_2 ⇒ triplet. Therefore H_2 is assigned. It has a large coupling with H_6 and H_8, and a negligible coupling with H_{11}.

Irradiation of H_2:- H_5 ⇒ singlet, H_6 ⇒ singlet, H_8 ⇒ doublet of doublets, no change in H_{11}. Therefore H_6 is assigned on the basis of its chemical shift and the fact that it is a doublet which collapses to a singlet on irradiation of H_2.

Irradiation of H_1:- The only changes occurred at high field (ca. 1.70 ppm) hence, on the basis of its chemical shift H_1 is assigned as shown.

Irradiation of H_3:- H_4 ⇒ singlet (with fine splitting), H_7 ⇒ broad doublet.

Irradiation of H_4:- H_7 ⇒ doublet of doublets, H_3 ⇒ doublet. Thus, on the basis of their chemical shifts and the fact that H_3 and H_4 have large and small couplings respectively, with H_7, they are assigned as shown.

Irradiation of H_6:- H_2 ⇒ doublet of doublets.

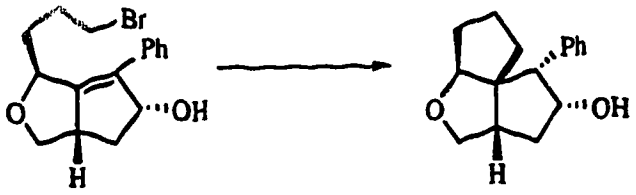
Irradiation of H_7:- H_3 ⇒ doublet, H_4 ⇒ doublet (with fine splitting), H_8 ⇒ simplified signal, no change in H_{11}. Therefore H_7 has a large coupling

with H_3 and H_8, and small or negligible coupling with H_4 and H_{11}.

Irradiation of H_8:- H_2 ⇒ broad doublet, H_7 ⇒ simplified signal, H_{11} ⇒ singlet (with fine splitting).

Inspection of models shows that the five membered rings are quite rigid, with the angle between cis hydrogens being 0-30°, and that between trans hydrogens being 70-100°. Therefore a larger coupling is expected between the cis hydrogens. Thus, the relatively large sizes of J (H_7-H_8), J (H_8-H_2) and J (H_2-H_6) and the almost negligible values of J (H_7-H_{11}) and J (H_2-H_{11}) indicate that the molecule has the stereochemistry shown. This assignment is supported by NOE measurements. Saturation of H_6 produces enhancements of 4% for H_2, 2% for H_7 and 4% for H_8.

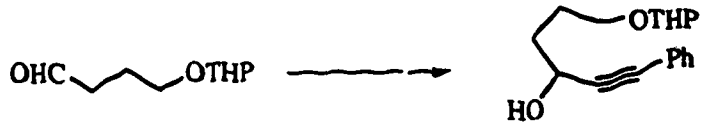
***cis-cis*-(5*H*)-1,2,3,3a,5aα,6,7,8-Octahydro-8β-phenyldicyclopenta[b,c]furan-7α-ol (191).**



190a **191**

The general procedure for radical cyclization was followed using bromide **190a** (93.5 mg, 0.289 mmol) in benzene (20 mL), tributyltin hydride (0.12 mL, 0.434 mmol) in benzene (5 mL), and AIBN (5 mg, 0.030 mmol) in benzene (5 mL). Flash chromatography of the crude product over silica gel (2 x 20 cm), using 20% ethyl acetate--hexane, gave alcohol **191** (47 mg, 66%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil, which was identical with material obtained by radical cyclization of the selenide **190b**.

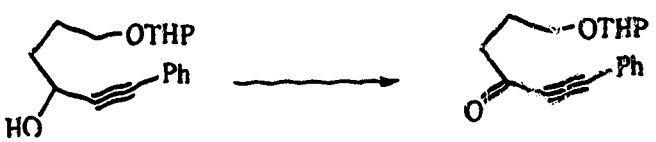
1-Phenyl-6-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-hexyn-3-ol (182).



181 **182**

Ethylmagnesium bromide (2.0 M in THF, 3.8 mL, 7.6 mmol) was added to a stirred and cooled (0°C) solution of phenylacetylene (0.84 mL, 7.67 mmol) in THF (20 mL). After 10 min a solution of aldehyde **181**[232] (1.1 g, 6.39 mmol) in THF (10 mL) was added over 5 min. The solution was stirred at 0°C for 1 h and then quenched by addition of water (10 mL). The layers were separated and the aqueous phase was washed with ether (2 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 20% ethyl acetate--hexane, gave alcohol **182** (1.12 g, 64%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3600-2960, 2945, 2889 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.46-2.00 (m, 10 H), 3.27 (br s, 1 H), 3.42-3.57 (m, 2 H), 3.77-3.91 (m, 2 H), 4.57-4.70 (m, 2 H), 7.25-7.32 (m, 3 H), 7.37-7.46 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 19.36 (t'), 25.34 (t'), 25.50 (t'), 25.56 (t'), 30.50 (t'), 30.52 (t'), 35.11 (t'), 62.14 (t'), 62.46 (t'), 67.11 (t'), 67 20 (t'), 84.57 (s'), 90.25 (s'), 98.60 (d'), 98.69 (d'), 112.76 (s'), 128.19 (d'), 131.60 (d'); exact mass, *m/z* calcd for $C_{17}H_{22}O_3$ 274.1569, found 274.1572.

1-Phenyl-6-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-hexyn-3-one (193).



182 **193**

The procedure for the preparation of **166** was followed, using **182** (6.50 g, 23.7 mmol) in dichloromethane (10 mL), oxalyl chloride (3.1 mL, 35.5 mmol) and DMSO (4.3 mL, 60.6 mmol) in dichloromethane (20 mL), and triethylamine (9.9 mL, 71.1 mmol). Flash chromatography of the crude product over silica gel (4 x 20 cm), using 10% ethyl acetate--hexane, gave ketone **193** (4.2 g, 65%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 2942, 2870, 2202, 1671 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43-1.63 (m, 4 H), 1.65-1.76 (m, 1 H), 1.76-1.90 (m 1 H), 2.03 (br quintet, J = 6.7 Hz, 2 H), 2.78 (td, J = 4.7, 1.7 Hz, 2 H), 3.40-3.54 (m, 2 H), 3.75-3.90 (m, 2 H), 4.58 (br t, J = 3.5 Hz, 1 H), 7.31-7.40 (m, 2 H), 7.40-7.48 (m, 1 H), 7.53-7.60 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 19.43 (t'), 24.31 (t'), 25.37 (t'), 30.55 (t'), 42.40 (t'), 62.16 (t'), 66.12 (t'), 87.78 (s'), 90.50 (s'), 96.74 (d'), 119.98 (s'), 128.53 (d'), 130.54 (d'), 132.89 (d'), 187.36 (s'); exact mass, *m/z* calcd for $C_{17}H_{20}O_3$ 272.1412, found 272.1404.

3-Methyl-1-phenyl-6-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-hexyn-3-ol (194).

193 **194**

Methyllithium, (3.6 mL, 1.4 M in ether, 5.0 mmol) was added to a stirred and cooled (-78°C) solution of ketone **193** (1.15 g, 4.22 mmol) in THF (20 mL). After 1 h at -78°C water (10 mL) was added, and the cooling bath was removed. The layers were separated and the aqueous phase was extracted with ether (1 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 20% ethyl acetate--hexane, gave alcohol **194** (0.678 g, 84%) as a

homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3600-3040, 2940 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.46-2.11 [m (including s, (3 H), at δ 1.60), 14 H], 3.41-3.60 (m, 2 H), 3.78-3.93 (m, 2 H), 4.66 (quintet, J = 3.6 Hz, 1 H), 7.26-7.35 (m, 3 H), 7.39-7.47 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 19.30, 19.39, 25.25, 25.38, 25.48, 30.18, 30.48, 41.25, 62.09, 62.16, 67.48, 67.55, 68.03, 68.11, 83.32, 83.39, 92.99, 93.03, 98.50, 98.63, 122.93, 128.13, 128.20, 131.62; exact mass, m/z calcd for $C_{18}H_{24}O_3$ 288.1725, found 288.1716.

3-Methyl-1-phenyl-3-[(2-propenyl)oxy]-6-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-hexyne (195).

194 **195**

3-Bromopropene (0.52 mL, 6.01 mmol) and potassium hydroxide (0.47 g, 8.37 mmol, freshly crushed) were added to a solution of alcohol **194** (0.601 g, 2.08 mmol) in DMSO (20 mL).[183] The mixture was stirred at 55°C for 30 min, then cooled and diluted with ether (30 mL). The solution was washed with saturated aqueous sodium bicarbonate (10 mL) and water (10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 10% ethyl acetate--hexane, gave **195** (479 mg, 70%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 2959, 1120, 1068, 1033 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45-1.64 [m (including s, (3 H), at δ 1.55), 7 H], 1.66-1.78 (m, 1 H), 1.78-1.98 (m, 5 H), 3.40-3.56 (m, 2 H), 3.76-3.93 (m, 2 H), 4.00-4.15 (m, 2 H), 4.59 (t, J = 3.6 Hz, 1 H), 5.14 (dq, J = 10.8, 1.6 Hz, 1 H), 5.31 (dq, J = 17.1, 1.7 Hz, 1 H), 5.98 (ddt, J = 17.1, 10.6, 5.4 Hz, 1 H), 7.27-7.34 (m, 3 H), 7.38-7.47 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 19.54 (t'),

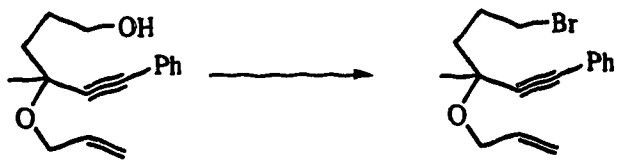
24.86 (t'), 25.44 (t'), 26.37 (q'), 30.69 (t'), 38.46 (t'), 62.15 (t'), 65.23 (t'), 67.48 (t'), 73.60 (s'), 85.37 (s'), 90.51 (s'), 98.64 (d'), 98.71 (d'), 115.87 (t'), 122.83 (s'), 128.11 (d'), 128.14 (d'), 131.60 (d'), 135.58 (d'); mass (CI), *m/z* calcd for $C_{21}H_{28}O_3$ 328, found 346 $(M + 18)^+$.

4-Methyl-6-phenyl-4-[(2-propenyl)oxy]-5-hexyn-1-ol (196).

195 **196**

A solution of enyne **195** (442 mg, 1.35 mmol) and pyridinium *p*-toluenesulfonate (10 mg, 0.04 mmol) in methanol (10 mL) was refluxed for 1.5 h, cooled, and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 30% ethyl acetate--hexane, gave alcohol **196** (317 mg, 96%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH[illegible] cast) 3600-2920, 2933, 1059 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.54 (s, 3 1.94 (m, 4 H), 2.34 (br s, 1 H), 3.69 (br t, *J* = 5.0 Hz, 2 H), 4.15 (ddt *J* Hz, 1 H), 4.23 (ddt, *J* = 12.1, 5.5, 1.5 Hz, 1 H), 5.31 (dq, *J* = 17.0, 1 (dq, *J* = 10.3, 1.5 Hz, 1 H), 5.97 (ddt, *J* = 17.2, 10.2, 5.6 Hz, 1 H), 7.. 7.40-7.46 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 26.48 38.66 (t'), 62.87 (t'), 65.49 (t'), 73.80 (s'), 85.75 (s'), 90.07 (s'), 116.60 (t'), [illegible] (s'), 128.30 (d'), 128.34 (d'), 131.70 (d'), 135.21 (d'); exact mass, *m/z* calcd for $C_{16}H_{20}O_2$ 244.1463, found 244.1436.

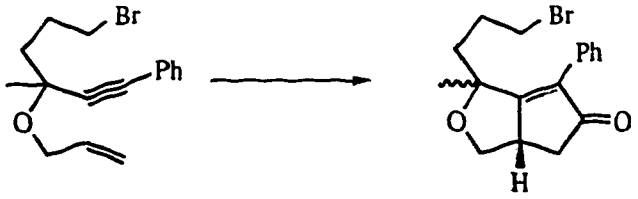
6-Bromo-3-methyl-1-phenyl-3-[(2-propenyl)oxy]-1-hexyne (197).



196 **197**

Carbon tetrabromide (1.74 mmol, 576 mg) and triphenylphosphine (1.74 mmol, 456 mg) were added to a solution of **196** (354 mg, 1.45 mmol) in dichloromethane (20 mL) at 0°C. The resulting mixture was stirred at room temperature for 2 h, and then filtered through silica gel (2 x 3 cm) with 10% ethyl acetate--hexane (50 mL). The filtrate was evaporated and flash chromatography of the residue over silica gel (2 x 20 cm), using 10% ethyl acetate--hexane, gave bromide **197** (372 mg, 83%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3120-2800, 1489, 1273 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.54 (s, 3 H), 1.87-1.97 (m, 2 H), 2.05-2.25 (m, 2 H), 3.42-3.54 (m, 2 H), 4.13 (ddt, *J* = 13.2, 5.6, 1.6 Hz, 1 H), 4.21 (ddt, *J* = 12.8, 5.2, 1.6 Hz, 1 H), 5.15 (dq, *J* = 10.6, 1.7 Hz, 1 H), 5.31 (dq, *J* = 17.1, 1.7 Hz, 1 H), 5.96 (ddt, *J* = 17.1, 10.2, 5.4 Hz, 1 H), 7.28-7.33 (m, 3 H), 7.40-7.46 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 26.57 (q'), 28.16 (t'), 34.12 (t'), 40.66 (t'), 65.41 (t'), 73.33 (s'), 85. 81 (s'), 90.00 (s'), 116.21 (t'), 122.67 (s'), 128.32 (d'), 128.39 (d'), 131.74 (d'), 135.45 (d'); exact mass, *m/z* calcd for $C_{15}H_{16}{}^{81}BrO$ $(M - CH_3)^+$ 293.0364, found 293.0361.

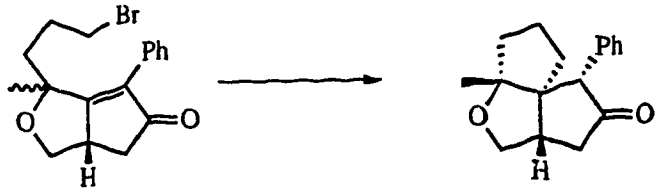
1-(3-Bromopropyl)-3a,4-dihydro-1-methyl-6-phenyl-cyclopenta[c]furan-5(3*H*)-one (192).



197 192

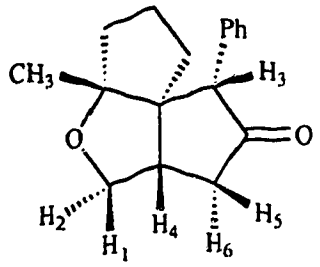
The general procedure for the P-K reaction with NMO was followed, using **197** (214 mg, 0.696 mmol) and octacarbonyldicobalt (3.5 mL, 0.3 M, in dichloromethane, 1.05 mmol) in dichloromethane (10 mL) for 2 h, and 4-methylmorpholine *N*-oxide (489 mg, 4.18 mmol) for 12 h. Flash chromatography of the residue over silica gel (3 x 20 cm), using 70% ethyl acetate--hexane, gave a mixture of isomers of **192** (1:1, 183 mg, 74%) as an otherwise homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3100-2800, 1711 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.09 (s, 3 x 0.5 H), 1.43-1.70 [m (including s, (3 x 0.5 H), at δ 1.60), 3 H], 1.71-1.87 (m, 0.5 H), 1.90-2.03 (m, 1 H), 2.03-2.36 (m, 2 H), 2.70-2.86 (m, 1 H), 2.97-3.07 (m, 1 H), 3.27-3.60 (m, 3 H), 4.26-4.40 (m, 1 H), 7.20-7.46 (m, 5 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 23.36 (q'), 27.39 (t'), 28.01 (t'), 28.55 (q'), 33.27 (t'), 33.85 (t'), 35.81 (t'), 39.35 (t'), 39.75 (t'), 40.75 (t'), 43.36 (d'), 45.52 (d'), 69.86 (t'), 71.38 (t'), 80.61 (s'), 81.47 (s'), 128.49 (d'), 128.55 (d'), 128.59 (d'), 128.74 (d'), 129.03 (d'), 129.07 (d'), 130.50 (s'), 130.72 (s'), 136.45 (s'), 137.44 (d'), 181.56 (s'), 183.31 (s'), 207.15 (s'), 207.23 (s'); exact mass, *m/z* calcd for $C_{17}H_{19}{}^{81}BrO_2$ 336.0548, found 336.0550. Anal. Calcd for $C_{17}H_{19}BrO_2$: C, 60.91; H, 5.71. Found: C, 60.82; H, 5.60.

cis-trans-1,2,3,3a,5aα,6,7,8-Octahydro-4aα-methyl-8β-phenyldicyclopenta [b,c]furan-7(5*H*)-one (198).



192 198

The general procedure for radical cyclization was followed, using **192** (83 mg, 0.247 mmol) in benzene (10 mL), tributyltin hydride (0.093 mL, 0.34 mmol) in benzene (5 mL) and AIBN (16 mg, 0.1 mmol) in benzene (5 mL). Flash chromatography of the residue over silica gel (2 x 20 cm), using 20 % ethyl acetate--hexane, gave ketone **198** (24.2 mg, 76% assuming a 1:1 mixture of starting materials) as a homogeneous [^{1}H NMR (400 MHz)] white solid: mp. 134-138°C; FT-IR (CH_2Cl_2 cast) 2982, 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.11-1.31 (m, 2 H), 1.42-1.72 [m, (including s, (3 H), at δ 1.49), 6 H], 1.89 (dd, *J* = 11.2, 4.8 Hz, 1 H), 2.32 (dd, *J* = 17.4, 14.2 Hz, 1 H), 2.55 (dd, *J* = 17.2, 6.9 Hz, 1 H), 2.71 (dddd, *J* = 13.2, 11.0, 6.8, 6.8 Hz, 1 H), 3.56 (s, 1 H), 3.63 (dd, *J* = 11.4, 7.8 Hz, 1 H), 4.08 (dd, *J* = 7 3, 7.3 Hz, 1 H), 7.08-7.15 (m, 2 H), 7.23-7.30 (m, 1 H), 7.30-7.38 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 21.54 (q'), 22.25 (t'), 26.21 (t'), 38.57 (t'), 40.50 (t'), 47.10 (d'), 63.02 (d'), 64.36 (s'), 67.25 (t'), 89.12 (s'), 127.31 (d'), 128.44 (d'), 130.31 (d'), 1135.48 (s'), 216.17 (s'); exact mass, *m/z* calcd for $C_{17}H_{20}O_2$ 256.1463, found 256.1461.



Chemical Shift

$H_1 = 4.08$
$H_2 = 3.63$
$H_3 = 3.56$
$H_4 = 2.71$
$H_5 = 2.5^{5}$
$H_6 = 2.5^{2}$

The stereochemistry of compound **198** has been tentatively determined by decoupling and NOE enhancement NMR experiments.

Irradiation of H_1:- $H_2 \Rightarrow$ doublet, H_4 changes. NOE enhancement:- 18% for H_2 and 5% for H_4.

Irradiation of H_2:- $H_1 \Rightarrow$ doublet, H_4 changes. On the basis of chemical shift H_1 and H_2 are assigned as being adjacent to the oxygen. They couple with each other and H_4, which was thus assigned as the ring fusion hydrogen. NOE enhancement between H_1 and H_4 indicates that they are cis.

Irradiation of H_3 produces NOE enhancement of 11% in the aromatic region, 10% for H_4, and 3% for the CH_3 group. On the basis of its chemical shift and the fact that it is a singlet, H_3 is assigned as shown.

Irradiation of H_4:- H_1 and $H_5 \Rightarrow$ doublets, H_2 and $H_6 \Rightarrow$ broad doublets (with fine splitting). NOE enhancement:- 8% for H_1, 10% for H_3, 4.5% for H_5 and 4.5% for the CH_3 group.

Irradiation of H_5:- $H_6 \Rightarrow$ doublet (with fine splitting), H_4 changes. NOE enhancement:- 2% for H_4 and 23% for H_6.

Irradiation of H_6:- $H_5 \Rightarrow$ doublet (with fine splitting), H_4 changes. NOE enhancement:- 23% for H_5. On the basis of mutual NOE enhancements H_1, H_4, H_5 and H_3 are assigned as being on the same face of the molecule.

Irradiation of the aromatic signal (7.20-7.30 ppm) produces NOE enhancements of 4.4% for H_3, and 3.6% for the CH_3 group.

Irradiation of the CH_3 group produces NOE enhancements of 5% for the aromatic signal, 2.4% for H_3, 3% for H_4.

Of the possible products of this reaction, only the structure shown fits the data completely: in particular the NOE enhancement between the CH_3 group and H_4, the fact that H_4 has a larger coupling with the hydrogens trans (i.e. H_2 and H_6) than with those cis to it (i.e. H_1 and H_5).

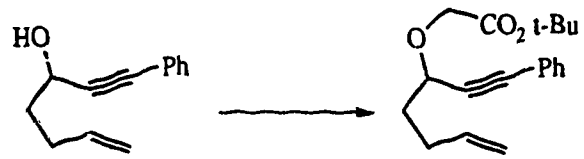
1-Phenyl-6-hepten-1-yn-3-ol (199).

199

Ethylmagnesium bromide (2.0 M solution in THF, 10 mL, 20 mmol) was added over 5 min to a stirred and cooled (0°C) solution of phenylacetylene (2.0 mL, 18.2 mmol) in THF (20 mL). After 30 min, 4-pentenal (3.2 g, 38.0 mmol) in THF (5 mL) was added over 5 min and the cooling bath was removed. After a further 1 h, water (10 mL) was added and the mixture was extracted with ether (2 x 25 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 20 cm), using 10% ethyl acetate--hexane, gave alcohol **199** (2.70 g, 80%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3600-3120, 1489 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.81-1.97 (m, 2 H), 2.27 (br q, J = 7.0 Hz, 2 H), 2.86 (br s, 1 H), 4.61 (q, J = 5.6 Hz, 1 H), 4.96-5.01 (m, 1 H), 5.07 (dq, J = 17.0, 1.6 Hz, 1 H), 5.83 (ddt, J = 17.0, 10.2, 6.7 Hz, 1 H), 7.20-7.30 (m, 3 H), 7.35-7.47 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 29.41 (t'), 36.76 (t'), 62.20 (d'), 84.95 (s'), 89.92 (s'), 115.20 (t'), 122.56 (s'), 128.18 (d'), 128.27 (d'), 131.59 (d'), 137.60 (d'); exact mass, m/z calcd for $C_{13}H_{13}O$ $(M - H)^+$ 185.0966,

found 185.0967. Anal. Calcd for $C_{13}H_{14}O$: C, 83.83; 7.58. Found: C, 83.09; H, 7.37.

t-Butyl 2-[(1-phenyl-6-hepten-1-yn-3-yl)oxy]acetate (200).



199 **200**

Tetrabutylammonium iodide (150 mg, 0.406 mmol) and *t*-butyl bromoacetate (0.20 mL, 1.24 mmol) were added to a stirred and cooled (10°C) mixture of **199** (150 mg, 0.805 mmol) in benzene (3 mL) and 50% $^{w}/_{v}$ aqueous sodium hydroxide (2.5 mL). After 3 h the mixture was diluted with ether (10 mL), and the organic layer was washed successively with 1 M hydrochloric acid (1 x 5 mL), saturated aqueous sodium bicarbonate (1 x 5 mL) and water (1 x 5 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 2% ethyl acetate--hexane, gave ester **200** (201 mg, 83%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: bp 150°C (0.5 mm Hg; Kugelrohr); FT-IR (CH_2Cl_2 cast) 1745, 1159, 1120 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.50 (s, 9 H), 1.88-2.06 (m, 2 H), 2.33 (br q, *J* = 7.3 Hz, 2 H), 4.17 (d, *J* = 11.0 Hz, 1 H), 4.21 (d, *J* = 11.0 Hz, 1 H), 4.50 (t, *J* = 7.5 Hz, 1 H), 5.00 (ddt, *J* = 10.2, 2.0, 2.0 Hz, 1 H), 5.09 (dq, *J* = 17.0, 1.7 Hz, 1 H), 5.88 (ddt, 17.0, 10.2, 7.5 Hz, 1 H), 7.28-7.36 (m, 3 H), 7.41-7.49 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 28.15 (q'), 29.47 (t'), 34.86 (t'), 66.07 (t'), 69.76 (d'), 81.63 (s'), 86.64 (s'), 87.09 (s'), 115.12 (t'), 122.54 (s'), 128.32 (d'), 128.50 (d'), 131.80 (d'), 137.76 (d'), 169.55 (s'); exact mass, *m/z* calcd for $C_{15}H_{15}O_3$ $(M - C_4H_9)^+$ 243.1021, found 243.1023.

2-[(1-Phenyl-6-hepten-1-yn-3-yl)oxy]ethanol (201).

200 **201**

Lithium aluminum hydride (27 mg, 0.711 mmol) was added to a stirred and cooled (0°C) solution of ester **200** (175 mg, 0.583 mmol) in ether (10 mL). The mixture was stirred at 0°C for 1 h and then water (5 mL) and 5% sodium hydroxide (5 mL) were added. The layers were separated and the aqueous phase was washed with ether (1 x 10 mL). The combined ether extracts were dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 20% ethyl acetate--hexane, gave alcohol **201** (131 mg, 97%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3600-3120, 2931, 1106 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.84-2.01 (m, 2 H), 2.92 (br q, *J* = 7.3 Hz, 2 H), 2.52 (br s, 1 H), 3.53-3.60 (m, 1 H), 3.77 (br s, 1 H), 3.88-3.94 (m, 2 H), 4.32 (t, *J* = 6.6 Hz, 1 H), 5.01 (dq, *J* = 10.2, 1.4 Hz, 1 H), 5.08 (dq, *J* = 17.0, 1.6 Hz, 1 H), 5.85 (ddt, *J* = 17.0, 10.2, 6.7 Hz, 1 H), 7.25-7.33 (m, 3 H), 7.40-7.47 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 29.48 (t'), 34.72 (t'), 61.73 (t'), 69.82 (d'), 70.06 (t'), 86.09 (s'), 87.77 (s'), 115.17 (t'), 122.49 (s'), 128.21 (d'), 128.33 (d'), 131.64 (d'), 137.60 (d'); exact mass, *m/z* calcd for $C_{15}H_{17}O_2$ $(M - H)^+$ 229.1228, found 229.1228.

1-Phenyl-3-[2-(phenylseleno)ethoxy]-6-hepten-1-yne (202).

201 **202**

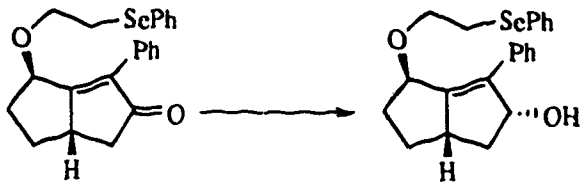
Phenylselenocyanate (0.16 mL, 1.13 mmol) and tributylphosphine (0.28 mL, 1.13 mmol) were added to a stirred and cooled (0°C) solution of alcohol **201** (173 mg, 0.755 mmol) in THF (10 mL). The mixture was stirred at 0°C for 1 h and then water (10 mL) was added. The layers were separated and the aqueous layer was washed with ether (1 x 0 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 5% ethyl acetate--hexane, gave selenide **202** (261 mg, 94%) as a homogeneous [^1H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3090-2800, 1489, 1477, 1437, 1089 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.79-1.96 (m, 2 H), 2.27 (br q, *J* = 7.3 Hz, 2 H), 3.12 (t, *J* = 7.3 Hz, 2 H), 3.71 (dt, *J* = 10.0, 7.4 Hz, 1 H), 4.04 (dt, *J* = 10.2, 7.1 Hz, 1 H), 4.28 (t, *J* = 6.5 Hz, 1 H), 4.99 (br d, *J* = 10.2 Hz, 1 H), 5.07 (dq, *J* = 17.0, 5.1 Hz, 1 H), 5.83 (ddt, *J* = 17.2, 10.2, 6.6 Hz, 1 H), 7.14-7.24 (m, 3 H), 7.24-7.33 (m, 3 H), 7.33-7.42 (m, 2 H), 7.47-7.56 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 26.79 (t'), 29.48 (t'), 34.85 (t'), 68.29 (t'), 69.39 (d'), 86.03 (s'), 87.98 (s'), 115.21 (t'), 122.63 (s'), 126.86 (d'), 128.23 (d'), 128.32 (d'), 129.02 (d'), 129.92 (s'), 131.70 (d'), 132.56 (d'), 137.67 (d'); exact mass, *m/z* calcd for $C_{21}H_{22}OSe$ 370.0836, found 370.0823.

4,5,6,6aα-Tetrahydro-3-phenyl-4α-[2-(phenylseleno)ethoxy]-2(1*H*)-pentalenone (203).

202 **203**

The general procedure for the P-K reaction with NMO was followed, using **202** (141 mg, 0.382 mmol) and octacarbonyldicobalt (1.2 mL, 0.5 M solution in dichloromethane, 0.6 mmol) in dichloromethane (10 mL) for 3 h and 4-methylmorpholine *N*-oxide (270 mg, 2.30 mmol) for 12 h. Flash chromatography of the crude product over silica gel (2 x 18 cm), using 20% ethyl acetate--hexane, gave enone **203** (113.5 mg, 75%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3100-2800, 1704 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.03-1.15 (m, 1 H), 1.98-2.08 (m, 1 H), 2.24 (dd, *J* = 18.1, 2.8 Hz, 1 H), 2.25-2.38 (m, 2 H), 2.86 (dd, *J* = 18.1, 6.4 Hz, 1 H), 3.70 (dt, *J* = 9.8, 6.9 Hz, 1 H), 3.06-3.20 (m, 3 H), 3.83 (dt, *J* = 9.8, 6.8 Hz, 1 H), 4.49-4.54 (m, 1 H), 7.20-7.30 (m, 3 H), 7.30-7.42 (m, 3 H), 7.47-7.55 (m, 2 H), 7.62-7.70 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 27.16 (t'), 29.04 (t'), 33.66 (t'), 41.36 (d'), 43.07 (t'), 66.26 (t'), 75.40 (d'), 127.11 (d'), 128.41 (d'), 128.95 (d'), 129.14 (d'), 129.64 (s'), 131.07 (s'), 132.66 (d'), 137.72 (s'), 176.46 (s'), 208.98 (s'); exact mass, *m/z* calcd for $C_{22}H_{22}O_2Se$ 398.0785, found 398.0787.

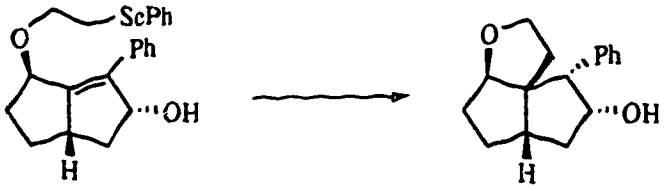
4,5,6,6aα-Tetrahydro-3-phenyl-4α-[2-(phenylseleno)ethoxy]-2(1*H*)-pentalenol (204).



203 **204**

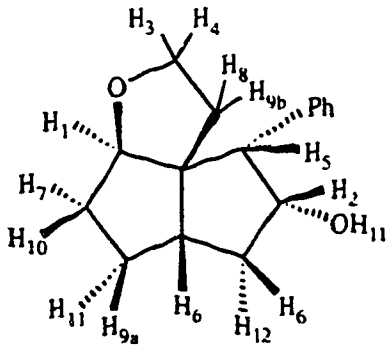
The procedure for the preparation of **190a** was followed, using **203** (47 mg, 0.118 mmol) in methanol (8 mL), cerium(III) chloride heptahydrate (48 mg, 0.130 mmol) and sodium borohydride (5 mg, 0.13 mmol). Flash chromatography of the residue over silica gel (2 x 20 cm), using 20% ethyl acetate--hexane, gave alcohol **204** (32 mg, 68%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3600-3120, 2933, 2857, 1477, 1436 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.19 (dtd, *J* = 12.0, 9.3, 9.2 Hz, 1 H), 1.36 (dt, *J* = 12.8, 8.0 Hz, 1 H), 1.76 (br s, 1 H), 1.88-2.00 (m, 1 H), 2.06-2.16 (m, 1 H), 2.26-2.36 (m, 1 H), 2.78 (dt, *J* = 12.7, 6.9 Hz, 1 H), 2.86-3.02 (m, 1 H), 3.41-3.52 (m, 2 H), 4.62 (br t, *J* = 4.8 Hz, 1 H), 5.39 (br t, *J* = 7.2 Hz, 1 H), 7.17-7.30 (m, 4 H), 7.30-7.44 (m, 1 H), 7.44-7.52 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 27.05 (t'), 30.33 (t'), 34.99 (t'), 42.44 (t'), 45.55 (d'), 67.68 (t'), 74.47 (d'), 82.96 (d), 126.87 (d'), 127.36 (d'), 128.02 (d'), 128.47 (d'), 129.02 (d'), 129.97 (s'), 132.58 (d'), 135.04 (s'), 138.20 (s'), 148.87 (s') ; exact mass, *m/z* calcd for $C_{22}H_{24}O_2Se$ 400.0942, found 400.0922.

***cis-cis*-(5*H*)-1,2,3aα,4,5aβ,6,7,8-Octahydro-8α-phenyl-pentaleno[1,6a-b]furan 7α-ol (205).**



204 **205**

The general procedure for radical cyclization was followed using **204** (56 mg, 0.145 mmol) in benzene (10 mL), tributyltin hydride (0.06 mL, 0.22 mmol) in benzene (5 mL), and AIBN (11 mg, 0.067 mmol) in benzene (5 mL). Flash chromatography of the crude product over silica gel (2 x 20 cm), using 20% ethyl acetate--hexane, gave alcohol **205** (29.8 mg, 87%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3600-3200, 2394, 1033 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.49 (d, *J* = 10.8 Hz, 1 H), 1.62 (m, 2 H), 1.80 (dd, *J* = 13.9, 7.0 Hz, 1 H), 1.89-2.06 (m, 2 H), 2.15 (dt, *J* = 12.3, 7.7 Hz, 1 H), 2.25-2.37 (m, 1 H), 2.37-2.49 (m, 2 H), 3.23 (d, *J* = 4.3 Hz, 1 H), 3.46 (td, *J* = 8.0, 5.2 Hz, 1 H), 3.69 (td, *J* = 8.0, 6.9 Hz, 1 H), 4.43 (t, *J* = 4.6 Hz, 1 H), 4.69 (d, *J* = 5.4 Hz, 1 H), 7.23-7.30 (m, 1 H), 7.30-7.38 (m, 2 H), 7.43-7.50 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 32.21 (t'), 32.62 (t'), 40.44 (t'), 41.52 (t'), 51.10 (d'), 59.31 (d'), 64.80 (s'), 67.64 (t'), 76.56 (d'), 85.80 (d'), 126.87 (d'), 128.58 (d'), 130.39 (d'), 138.60 (s'); exact mass, *m/z* calcd for $C_{16}H_{20}O_2$ 244.1463, found 244.1460.



	Chemical Shift
H_1	= 4.69
H_2	= 4.43
H_3	= 3.69
H_4	= 3.46
H_5	= 3.23
H_6	= 2.37-2.49
H_7	= 2.27-2.37
H_8	= 2.15
$H_9(a)$	= 1.89-1.96
$H_9(b)$	= 1.96-2.06
H_{10}	= 1.80
H_{11}	= 1.62
H_{12}	= 1.49

The stereochemistry of compound **198** was determined by decoupling and NOE enhancement NMR experiments.

Irradiation of H_1:- H_7 ⇒ simplified signal. Due to its chemical shift and the fact that it does not couple to any low field protons, H_1 is assigned as shown. H_1 has a large coupling with H_7, thus H_1 and H_7 are assigned as cis.

Irradiation of H_2:- H_5 ⇒ singlet, H_6 becomes sharper. H_2 is assigned on the basis of its chemical shift and the fact that when it is irradiated H_5 becomes a singlet. H_5 must be the benzylic proton because of its chemical shift and multiplicity.

Irradiation of H_3:- H_4, H_8 and H_{9b} are all simplified.

Irradiation of H_4:- H_3, H_8, and H_{9b} are all simplified. Due to their chemical shifts and the fact that these four protons couple each other but with nothing else, they are assigned as shown. Their stereochemistry was not determined.

Irradiation of H_5:- H_2 ⇒ doublet (J = 4.3 Hz). Thus H_2 is coupled with only one other proton i.e. H_6. The coupling constant J (H_2-H_6) = 4.3 Hz = J (H_2-H_5) suggests that these three protons are all cis.

Irradiation of H_6 (signal is due to two protons):- H_2 ⇒ doublet, 9a ⇒

simplified signal, H_{12} ⇒ singlet. Thus one proton in the H_6 signal is assigned due to its coupling with H_2 and large geminal coupling with H_{12}. The fact that H_{12} collapses to a singlet indicates that H_{12} is not significantly coupled with any other protons, which is only possible if it is on the opposite face to H_2.

Irradiation of H_7:- H_1 ⇒ singlet, H_{9a} ⇒ slight changes, H_{10} and H_{11} ⇒ doublets.

Irradiation of H_8:- H_3, H_4 and H_{9b} are simplified.

Irradiation of H_9(a and b):- (changes due to H_{9b}) H_3, H_4 and H_8 are simplified, (changes due to H_{9a}) H_6 and H_7 are simplified, H_{10} ⇒ large doublet (i.e. large gem coupling with H_7 remains), H_{11} changes.

Irradiation of H_{10}:- H_7 and H_{9a} are simplified.

Irradiation of H_{11}:- H_7 and H_{9a} are simplified, H_6 changes slightly.

Irradiation of H_{12}:- H_6 changes.

Thus, since H_7 is strongly coupled with H_{10} and H_{11}, and they in turn are both coupled with H_{9a}, these four protons are assigned as shown. Coupling between H_{9a} and H_6 indicates that the ring fusion hydrogen is also contained in the H_6 signal. Support for the stereochemistry is gained from NOE measurements: irradiation of H_2 produces enhancements of 9% for H_5, 4% for H_6 and 7% for the hydroxy hydrogen.

2, 2-Dimethyl-4-butanal (206).[186]

206

A solution of allyl alcohol (51 mL, 0.75 mol), isobutyraldehyde (81 g,

1.12 mol) and *p*-toluenesulfonic acid (0.5 g, 2.63 mmol) in *p*-cymene (150 mL) was refluxed through 3Å molecular sieves (30 g) for 48 h, and then distilled at 30 mm Hg. The fraction boiling at 80-90°C was collected and redistilled to give aldehyde **206** (75 g, 89%) as a homogeneous [^{1}H NMR (200 MHz)] colorless oil: bp 130-140°C (760 Hg) [lit.[186] 124-126°C (760 Hg)]: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.07 (s, 6 H), 2.20 (d, *J* = 7.6 Hz, 2 H), 4.99-5.14 (m, 2 H), 5.59-5.83 (m, 1 H), 9.49 (s, 1 H).

4,4-Dimethyl-1-phenyl-6-hexen-1-yn-3-ol (207).

206 **207**

n-Butyllithium (15 mL, 1.6 M, in hexanes, 23.94 mmol) was added to a stirred solution of phenylacetylene (2.32 g, 22.8 mmol) in THF (20 mL) at -78°C. After 10 min, aldehyde **206**[189] (5.1 g, 45.6 mmol) in THF (10 mL) was added. After a further 30 min, water (10 mL) was added and the cooling bath was removed. The layers were separated and the organic layer was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (5 x 20 cm), using 5% ethyl acetate--hexane, gave alcohol **207** (3.75 g, 76%) as a homogeneous [^{1}H NMR (200 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3640-3120, 3120-2800, 2200 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.03 (s, 3 H), 1.05 (s, 3 H), 2.16-2.26 (m, 3 H), 4.30 (d, *J* = 6.1 Hz, 1 H), 5.03-5.17 (m, 2 H), 5.88 (ddt, *J* = 16.8, 10.1, 7.4 Hz, 1 H), 7.22-7.34 (m, 3 H), 7.34-7.49 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 22.62 (q'), 22.75 (q'), 38.97 (s'), 42.86 (t'), 70.58 (d'), 86.06 (s'), 88.75 (s'), 117.71 (t'), 122.77 (s'), 128.26 (d'), 128.30 (d'), 131.74 (d'), 134.94

(d'); exact mass, *m/z* calcd for $C_{15}H_{18}O$ 214.1341, found 214.1357.

t-Butyl-2-[3-(4,4 Dimethyl-1-phenyl-6-hepten-1-ynyl)oxy]aceate (208).

207 **208**

Tetrabutylammonium iodide (0.4 g, 1.03 mmol) and *t*-butyl bromoacetate (0.67 mL, 4.1 mmol) were added to a stirred mixture of **207** (0.443 g, 2.07 mmol) in benzene (5 mL) and 50% sodium hydroxide (4.5 mL). After 30 h, ether (10 mL) was added and the mixture was washed with saturated aqueous sodium bicarbonate (5 mL) and water (5 mL). The combined organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography over silica gel (3 x 20 cm), using 10% ethyl acetate--hexane, gave **208** [100 mg, 20% (after correction for 100 mg recovered starting material)] as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.07 (s, 3 H), 1.10 (s, 3 H), 1.49 (s, 9 H), 2.28 (d, *J* = 8.8 Hz, 2 H), 4.17-4.23 (m, 3 H), 5.02-5.10 (m, 2 H), 5.82-5.96 (m, 1 H), 7.27-7.35 (m, 3 H), 7.41-7.48 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 22.67 (q'), 23.25 (q'), 28.16 (q'), 38.69 (s'), 43.14 (t'), 66.46 (t'), 77.92 (d'), 81.39 (s'), 86.13 (s'), 88.83 (s'), 117.50 (t'), 122.73 (s'), 128.28 (d'), 128.37 (d'), 131.74 (d'), 135.00 (d'), 169.61 (d').

Ethyl 4-formyl-7-octenoate (211).

210 **211**

A solution of enamine **210**[188] (2.6 g, 17.2 mmol) and ethyl acrylate (2.8 mL, 25.8 mmol) in dry dioxane (50 mL) was refluxed for 2 h and then cooled to room temperature. Water (10 mL) was added and the mixture was refluxed for 1 h, cooled, and extracted with ether (2 x 50 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 10% ethyl acetate--hexane, gave **211** (2.09 g, 61%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 2979, 2932, 1732, 1641 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.26 (t, *J* = 7.0 Hz, 3 H), 1.50-1.60 (m, 1 H), 1.74-1.86 (m, 2 H), 1.92-2.03 (m, 1 H), 2.06-2.14 (m, 2 H), 2.27-2.41 (m, 3 H), 4.13 (q, *J* = 7.0 Hz, 2 H), 4.97-5.08 (m, 2 H), 5.77 (ddt, *J* = 17.0, 10.0, 6.6 Hz, 1 H), 9.61 (d, *J* = 2.4 Hz, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 14.19 (q'), 23.57 (t'), 27.89 (t'), 30.92 (t'), 31.56 (t'), 50.35 (d'), 60.50 (t'), 115.67 (t'), 137.39 (d'), 172.91 (s'), 204.06 (d'); exact mass, *m/z* calcd for $C_{11}H_{18}O_3$ 198.1256, found 198.1255.

Ethyl 4-(2,2-dibromoethenyl)-7-octenoate (212).

211 **212**

Triphenylphosphine (11.06 g, 42.2 mmol) and carbon tetrabromide (7.0

g, 21.1 mmol) were added to a stirred and cooled (0°C) solution of aldehyde **211** (2.09 g, 10.54 mmol) in dichloromethane (20 mL).[189] The resulting mixture was stirred at room temperature for 1 h, and filtered through a pad of silica gel (2 x 2 cm), which was washed with 5% ethyl acetate--hexane (50 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (3 x 20 cm), using 5% ethyl acetate--hexane, gave ester **212** (3.1 g, 83%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 2978, 2928, 1734 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27 (t, *J* = 7.2 Hz, 3 H), 1.37-1.43 (m, 1 H), 1.49-1.65 (m, 2 H), 1.76-1.86 (m, 1 H), 1.98-2.15 (m, 2 H), 2.28-2.34 (m, 2 H), 2.40-2.51 (m, 1 H), 4.13 (q, *J* = 7.1 Hz, 2 H), 4.97 (dq, *J* = 9.8, 1.5 Hz, 1 H), 5.03 (dq, *J* = 17.0, 1.7 Hz, 1 H), 5.78 (ddt, *J* = 17.0, 10.2, 6.5 Hz, 1 H), 6.11 (d, *J* = 10.0 Hz, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 14.22 (q'), 29.28 (t'), 31.11 (t'), 31.85 (t'), 33.69 (t'), 42.91 (d'), 60.36 (t'), 89.38 (s'), 115.00, (t'), 137.88 (d'), 141.99 (d'), 173.09 (s'); exact mass, *m/z* calcd for $C_{12}H_{18}{}^{79}Br^{81}BrO_2$ 353.9653, found 353.9658.

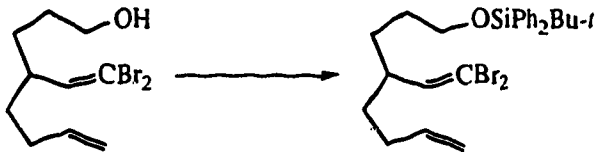
4-(2,2-Dibromoethenyl)-7-octen-1-ol (213).

212 **213**

Lithium aluminum hydride (0.2 g, 5.2 mmol) was added to a stirred and cooled (0°C) solution of ester **212** (2.77 g, 7.83 mmol) in ether (50 mL). The cooling bath was removed and stirring at room temperature was continued for 1 h. Water (10 mL) was added and the layers were separated. The aqueous layer was extracted with ether (2 x 20 mL) and the combined

organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 20% ethyl acetate--hexane, gave alcohol **213** (2.30 g, 94%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3600-3080, 2931, 2853, 1640, 1473 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.27-1.66 (m, 7 H), 1.97-2.16 (m, 2 H), 2.37-2.50 (m, 1 H), 3.65 (t, *J* = 6.3 Hz, 2 H), 4.92-5.09 (m, 2 H), 5.80 (ddt, *J* = 16.8, 10.2, 6.6 Hz, 1 H), 6.14 (d, *J* = 9.6 Hz, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 30.25 (t'), 30.58 (t'), 31.28 (t'), 33.86 (t'), 43.14 (d'), 62.84 (t'), 88.67 (s'), 114.94 (t'), 138.19 (d'), 142.88 (d'); mass (CI), *m/z* calcd for $C_{10}H_{16}{}^{81}Br_2O$ 314, found 332 $(M + 18)^+$.

[[4-(2,2-Dibromoethenyl)-7-octen-1-yl]oxy]*t*-butyldiphenylsilane (214).



213 **214**

t-Butylchlorodiphenylsilane (3.8 mL, 11.1 mmol) and imidazole (2.0 g, 29.4 mmol) were added to a solution of **213** (2.30 g, 7.37 mmol) in dichloromethane (50 mL), and the mixture was stirred at room temperature for 3 h. Water (10 mL) was added and the organic phase was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 2% ethyl acetate--hexane, gave **214** (3.82 g, 94%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 2930, 2856, 1427, 1111 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 (s, 9 H), 1.28-1.45 (m, 2 H), 1.45-1.61 (m, 4 H), 1.97-2.13 (m, 2 H), 2.32-2.43 (m, 1 H), 3.65 (t, *J* = 5.9 Hz, 2 H), 4.97 (br d *J* = 10.3 Hz, 1 H), 5.02 (dq, *J* = 17.0, 1.7 Hz, 1 H), 5.79 (ddt, *J* = 17.0, 10.1, 6.6 Hz, 1 H), 6.10 (d, J= 9.9 Hz, 1 H), 7.34-7.47 (m, 6 H), 7.66-7.72 (4 H); ^{13}C NMR (APT)

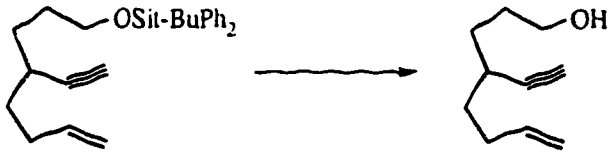
($CDCl_3$, 100.6 MHz) δ 19.27 (s'), 26.94 (q'), 30.00 (t'), 30.55 (t'), 31.31 (t'), 33.84 (t'), 43.09 (d'), 63.69 (t'), 88.53 (s'), 114.85 (t'), 127.66 (d'), 129.60 (d'), 134.05 (s'), 135.63 (d'), 138.32 (d'), 143.13 (d'); mass (CI), *m*/z calcd for $C_{26}H_{34}Br_2OSi$ 550, found 568 $(M + 18)^+$.

t-Butyl[[4-ethynyl-7-octen-1-yl]oxy]diphenylsilane (215).

214 **215**

n-Butyllithium (1.6 M, in hexanes, 9.0 mL, 14.38 mmol) was added to a stirred and cooled (-78°C) solution of dibromide **214** (3.77 g, 6.85 mmol) in THF (40 mL).[189] The solution was stirred at -78°C for 1 h, the cooling bath was removed, and stirring was continued for 1 h. Water (10 mL) was added slowly and the layers were separated. The aqueous layer was extracted with ether (2 x 20 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using hexane, gave enyne **215** (2.61 g, 97%) as a homogeneous [^1H NMR (400 MHz)] colorless oil: FT-IR (film) 3306, 2931, 2857, 1111 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.04 (s, 1 H), 1.41-1.85 (m, 6 H), 2.04 (d, *J* = 2.4 Hz, 1 H), 2.09-2.21 (m, 1 H), 2.22-2.42 (m, 2 H), 3.68 (t, *J* = 6.0 Hz, 2 H), 4.97 (br d, *J* = 10.2 Hz, 1 H), 5.04 (dq, *J* = 17.0, 1.7 Hz, 1 H), 5.80 (ddt, *J* = 17.2, 10.4, 6.5 Hz, 1 H), 7.33-7.46 (m, 6 H), 7.64-7.71 (m, 4 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 18.93 (s'), 26.93 (q'), 30.21 (t'), 30.74 (d'), 31.22 (t'), 31.46 (t'), 34.20 (t'), 63.70 (t'), 69.58 (d'), 87.28 (s'), 114.93 (t'), 127.65 (d'), 129.59 (d'), 134.16 (s'), 135.63 (d'), 138.24 (d'); exact mass, *m*/z calcd for $C_{22}H_{25}OSi$ $(M - C_4H_9)^+$ 333.1675, found 333.1673.

4-Ethynyl-7-octen-1-ol (216).



215 **216**

Tetrabutylammonium fluoride (7.3.mL, 1.0 M in THF, 7.3 mmol) was added to a stirred solution of **215** (2.60 g, 6.66 mmol) in THF (20 mL). After 3 h at room temperature the solvent was evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 20% ethyl acetate--hexane, gave alcohol **216** (0.982 g, 97%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3600-3100, 2939, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.43-1.89 (m, 7 H), 2.08 (d, *J* = 2.1 Hz, 1 H), 2.12-2.22 (m, 1 H), 2.23-2.34 (m, 1 H), 2.35-2.43 (m, 1 H), 3.68 (t, *J* = 6.3 Hz, 2 H), 4.98 (br d, *J* = 10.3 Hz, 3 H), 5.05 (dq, *J* = 17.0, 1.7 Hz, 1 H), 5.812 (ddt, *J* = 17.0, 10.1, 6.5 Hz, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 30.44 (t'), 30.78 (d'), 31.10 (t'), 31.39 (t'), 34.22 (t'), 62.69 (t'), 69.83 (t'), 87.30 (s'), 115.01 (t'), 138.10 (d'); mass (CI), *m/z* calcd for $C_{10}H_{16}O$ 152, found 170 $(M + 18)^+$.

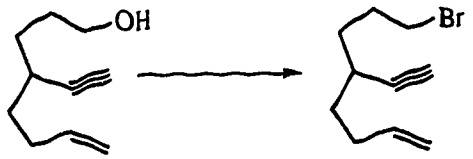
4-Ethynyl-7-octen-1-ol (216).

213 **216**

n-Butyllithium (3.6 mL, 1.6 M, in hexanes, 5.76 mmol) was injected over 5 min into a stirred and cooled (-78°C) solution of alcohol **213** (0.547 g, 1.75 mmol) in THF (20 mL). After 1 h, the cooling bath was removed and

stirring was continued at room temperature for 2 h. The mixture was poured into water (20 mL) and extracted with ether (2 x 30 mL). The combined extracts were dried (MgSO4) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 20% ethyl acetate--hexane, gave alcohol **216** (0.253, 95%), identical with that obtained from compound **215**.

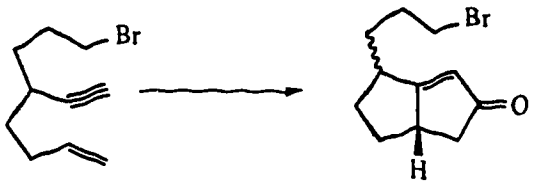
3-(3-Bromopropyl)hept-6-en-1-yne (217).



216 **217**

Carbon tetrabromide (400 mg, 1.21 mmol) and triphenylphosphine (316 mg, 1.21 mmol) were added to a stirred solution of alcohol **216** (153 mg, 1.01 mmol) in dichloromethane (10 mL) at 0°C. After 8 h, the mixture was filtered through silica gel (2 x 2 cm) with 20% ethyl acetate--hexane (50 mL). Evaporation of the filtrate and flash chromatography of the residue over silica gel (2 x 2 cm), using 5% ethyl acetate--hexane, gave enyne **217** (179 mg, 82%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (film) 3299, 2936, 1640 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.47-1.71 (m, 4 H), 1.90-2.04 (m, 1 H), 2.04-2.33 [m (including d, J = 2.4 Hz, (1 H), at δ 2.08), 4 H], 2.33-2.45 (m, 1 H), 3.44 (t, J = 6.7 Hz, 2 H), 4.98 (br d, J = 10.0 Hz, 1 H), 5.05 (dq, J = 17.1, 1.8 Hz, 1 H), 5.80 (ddt, J = 17.1, 10.2, 6.8 Hz, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 30.22 (d'), 30.40 (t'), 31.31 (t'), 33.23 (t'), 33.56 (t'), 34.12 (t'), 70.16 (d'), 86.68 (s'), 115.12 (t'), 137.88 (d'); exact mass, *m/z* calcd for $C_{10}H_{14}{}^{79}Br$ $(M - H)^+$ 213.0278, found 213.0276.

4,5,6,6a-Tetrahydro-4-[3-bromopropyl]-2(1*H*)-pentalenone (218).



217 **218**

(a) Silica gel method:- The general procedure for the P-K reaction with silica gel was followed, using **217** (213 mg, 0.99 mmol) and octacarbonyldicobalt (5.0 mL, 0.3 M solution in dichloromethane, 1.5 mmol) in dichloromethane (10 mL) for 2 h, silica gel (10 g, 20% $^{w}/_{w}$ water). The mixture was heated for 10 h at 45°C. Flash chromatography of the crude product over silica gel (2 x 20 cm), using 20% ethyl acetate--hexane, gave enone **218** (75.6 mg, 31%) as a colorless oil. The material was a mixture of diastereomers [^{1}H NMR (400 MHz)]: FT-IR (film) 2958, 1706, 1623 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.09-1.30 (m, 1 H), 1.45-3.32 (m, 8 H), 2.62 (dd, *J* = 17.9, 6.2 Hz, 1 H), 2.70-2.89 (m, 1 H), 2.91-3.03 (m, 1 H), 3.37-3.50 (m, 2 H), 5.84-5.91 (m, 1 H); exact mass, *m/z* calcd for $C_{11}H_{15}{}^{81}BrO$ 244.0286, found 244.0281.

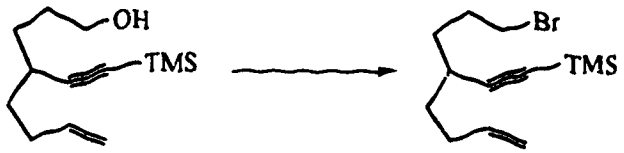
(b) 4-Methylmorpholine *N*-Oxide Method:- The general procedure for the P-K reaction with NMO was followed, using **217** (200 mg, 0.929 mmol), octacarbonyldicobalt (0.3 M solution in dichloromethane, 3.1 mL, 0.93 mmol) in dichloromethane (20 mL) for 2 h, and 4-methylmorpholine *N*-oxide (0.652 g, 5.57 mmol) for 48 h. Flash chromatography of the crude product over silica gel (2 x 20 cm), using 20% ethyl acetate--hexane, gave enone **218** (90.5 mg, 40%) as a colorless oil. The material was a mixture of two diastereomers [^{1}H NMR (400 MHz)] and was identical with that obtained by the silica gel method.

4-[2-(Trimethylsilyl)ethynyl]-7-octen-1-ol (222).

213 222

Following a literature procedure,[189] *n*-butyllithium (4.2 mL, 1.6 M, in hexanes, 6.76 mmol) was added over 10 min to a stirred solution of dibromide **213** (0.64 g, 2.05 mmol) in ether (20 mL) at -78°C. After 30 min the cooling bath was removed and stirring was continued for 1 h. The cooling bath was then replaced and chlorotrimethylsilane (0.57 mL, 4.51 mmol) was added over 10 min. After 1 h the cooling bath was removed and stirring was continued for a further 4 h. Acetic acid (1 M solution in water, 10 mL) was added and stirring was continued for 8 h. The mixture was poured into saturated aqueous sodium bicarbonate (20 mL). The layers were separated and the organic layer was washed with water (1 x 10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 20% ethyl acetate--hexane, gave **222** (0.43 g, 93%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3600-3140, 3000-2320, 2185, 1249 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.23 (s, **9** H), 1.48-1.82 (m, 7 H), 2.06-2.30 (m, 2 H), 2.37 (br quintet, *J* = 7.0 Hz, 1 H), 3.64 (t, *J* = 6.5 Hz, 2 H), 4.94 (br d, *J* = 10.0 Hz, 1 H), 5.01 (dq, *J* = 17.1, 1.7 Hz, 1 H), 5.79 (ddt, *J* = 17.1, 10.1, 6.7 Hz, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 0.22 (q'), 30.47 (t'), 31.10 (t'), 31.46 (t'), 31.87 (d'), 34.24 (t'), 62.60 (t'), 85.99 (s'), 110.14 (s'), 114.85 (t'). 138.24 (d'); mass (CI) calcd. for $C_{13}H_{24}OSi$ 224, found 242 $(M + 18)^+$.

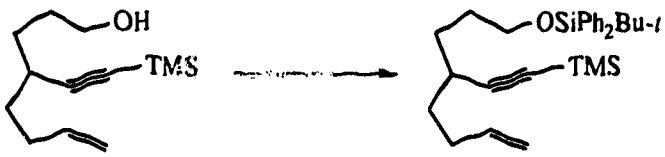
[3-(3-Bromopropyl)-6-hepten-1-yn-1-yl]trimethylsilane (223).



222 223

Carbon tetrabromide (2.14 mmol, 0.71 g) and triphenylphosphine (2.14 mmol, 0.56 g) were added to a solution of alcohol **222** (1.78 mmol, 0.40 g) in dichloromethane at 0°C. The cooling bath was removed and stirring was continued for 2 h. The solution was filtered through a pad of silica gel (2 x 3 cm) with 10% ethyl acetate--hexane (50 mL). The filtrate was evaporated and flash chromatography of the residue over silica gel (2 x 20 cm), using 5% ethyl acetate--hexane, gave **223** (0.47 g, 91%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3100-2800, 2080, 1249 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.16 (s, 9 H), 1.47-1.70 (m, 4 H), 1.90-2.33 (m, 4 H), 2.36-2.47 (m, 1 H), 3.46 (t, J = 6.6 Hz, 2 H), 4.99 (br d, J = 10.4 Hz, 1 H), 5.06 (dq, J = 17.1, 1.7 Hz, 1 H), 5.80 (ddt, J = 17.0, 10.2, 5.2 Hz, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 30.57 (t'), 31.40 (d'), 31.46 (t'), 33.26 (t'), 33.69 (t'), 34.24 (t'), 87.44 (s'), 109.48 (s'), 115.01 (t'), 138.13 (d'); exact mass, *m/z* calcd for $C_{13}H_{23}{}^{79}BrSi$ 286, found 304 $(M + 18)^+$.

3-[3-(*t*-Butyldiphenylsilyloxy)propyl]-6-hepten-1-yn-1-yl]trimethylsilane (225).

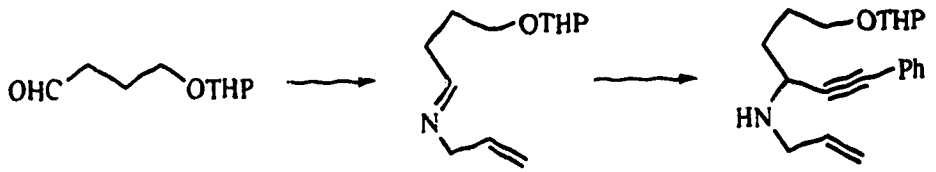


222 225

Imidazole (37 mg, 0.54 mmol) and *t*-butylchlorodiphenylsilane (0.07

mL, 0.27 mmol) were added to a stirred solution of alcohol **222** (44 mg, 0.18 mmol) in dichloromethane (10 mL). After 5 h the solvent was evaporated and flash chromatography of the residue over silica gel (1 x 20 cm), using 5% ethyl acetate--hexane, gave **225** (90 mg, 99%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3000-2800, 2160 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.16 (s, 9 H), 1.06 (s, 9 H), 1.42-1.74 (m, 5 H), 1.74-1.87 (m, 1 H), 2.10-2.34 (m, 2 H), 2.34-2.48 (m, 1 H), 3.71 (t, *J* = 6.4 Hz, 2 H), 4.99 (br d, *J* = 10.2 Hz, 1 H), 5.06 (br d, *J* = 17.1 Hz, 1 H), 5.84 (ddt, *J* = 17.1, 10.2, 6.8 Hz, 1 H), 7.33-7.49 (m, 6 H), 7.63-7.77 (m, 4 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 0.32 (q'), 19.29 (s'), 26.93 (q'), 30.33 (t'), 31.30 (t'), 31.58 (t'), 31.88 (d'), 34.24 (t'), 63.78 (t'), 85.73 (s'), 110.41 (s'), 114.81 (t'), 127.64 (d'), 129.57 (d'), 134.13 (s'), 135.62 (d'), 138.44 (d'); exact mass, *m/z* calcd for $C_{28}H_{39}OSi_2$ $(M - CH_3)^+$ 447.2539, found 447.2540.

N-2-Propenyl-[1-phenyl-6-[(tetrahydro-2*H*-pyran-2-yl)oxy]-1-hexyn]-3-amine (227).



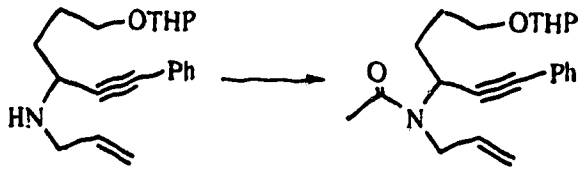
181 **226** **227**

Allylamine (2.3 mL, 30.2 mmol) was added to a stirred solution of aldehyde **181**[232] (2.6 g, 15.1 mmol) in benzene (50 mL) at 0°C. After 1 h, the cooling bath was removed and the solution was refluxed through 3 Å molecular sieves (20 g) for 2 h. The solution was cooled and evaporated to give the crude imine **226** (3.2 g), which had FT-IR (CH_2Cl_2 cast) 3010-2760, 1658 cm^{-1}.

n-Butyllithium (14.8 mL, 1.6 M, in hexanes, 23.6 mmol) was added to a

stirred solution of phenylacetylene (2.5 mL, 23.6 mmol) in THF (50 mL) at -78°C. After 30 min boron trifluoride etherate (2.9 mL, 23.6 mmol) was added, followed after a further 10 min, by a solution of imine **226** (2.5 g, 11.8 mmol) in THF (10 mL). The resulting solution was stirred at -78°C for 1 h, the cooling bath was removed and stirring was continued for 2 h. Water (10 mL) was added and the layers were separated. The aqueous layer was washed with ether (20 mL). The combined organic layers were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 20 cm), using 2% methanol--dichloromethane, gave amine **227** (1.57 g, 42%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 2941, 2869, 1489 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.32-1.96 (m, 11 H), 3.36 (ddt, *J* = 13.8, 6.2, 1.4 Hz, 1 H), 3.43-3.54 (m, 2 H), 3.57 (ddt, *J* = 14.0, 5.8, 1.4 Hz, 1 H), 3.64 (dd, *J* = 7.8, 5.3 Hz, 1 H), 3.78-3.92 (m, 2 H), 4.61 (t, *J* = 3.1 Hz, 1 H), 5.13 (dq, *J* = 10.0, 1.5 Hz, 1 H), 5.26 (dq, *J* = 17.0, 1.7 Hz, 1 H), 5.96 (ddt, *J* = 17.0, 10.2, 6.0 Hz, 1 H), 7.23-7.36 (m, 3 H), 7.39-7.51 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 19.49 (t'), 25.42 (t'), 26.41 (t'), 30.65 (t'), 32.89 (t'), 32.92 (t'), 49.90 (d'), 50.08 (t'), 62.13 (t'), 62.16 (t'), 67.09 (t'), 83.97 (s'), 90.56 (s'), 98.65 (d'), 116.22 (t'), 123.25 (s'), 127.86 (d'), 128.15 (d'), 131.59 (d'), 136.41 (d'); exact mass, *m/z* calcd for $C_{20}H_{26}NO_2$ $(M - H)^+$ 312.1964, found 312.1962.

_N_-2-Propenyl-_N_-[1-phenyl-6-[(tetrahydro-2_H_-pyran-2-yl)oxy]-1-hexyn-3-yl] acetamide (228).

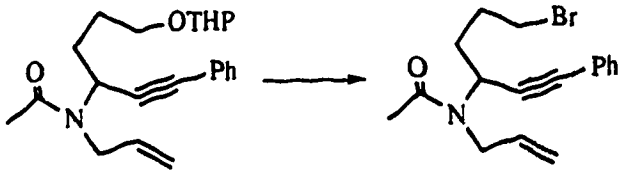


227 **228**

Sodium hydride (0.26 g, 60% dispersion in oil, 6.49 mmol) was added to

a solution of amine **227** (1.35 g, 4.33 mmol) and acetyl chloride (0.46 mL, 6.5 mmol) in THF (50 mL) at 0°C. The cooling bath was removed and the mixture was stirred at room temperature for 2 h, and then poured into ice water (20 mL). The layers were separated and the organic layer washed with water (10 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 2% methanol--dichloromethane, gave amide **228** (1.17 g, 76%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 2940, 2868, 1653, 1405 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.45-1.93 (m, 10 H), 2.12 (s, 3 H), 3.37-3.54 (m, 2 H), 3.70-3.90 (m, 2 H), 3.99-4.23 (m, 2 H), 4.59 (t, *J* = 3.5 Hz, 1 H), 5.19-5.28 (m, 2 H), 5.72 (br t, *J* = 6.5 Hz, 1 H), 5.93 (ddt, *J* = 17.5, 10.4, 6.1 Hz, 1 H), 7.27-7.37 (m, 3 H), 7.37-7.46 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 19.52 (t'), 21.94 (q'), 25.34 (t'), 26.43 (t'), 30.62 (t'), 31.27 (t'), 46.53 (d'), 46.56 (d'), 47.66 (t'), 62.20 (t'), 66.75 (t'), 84.59 (s'), 87.40 (s'), 98.74 (d'), 116.63 (t'), 122.67 (s'), 128.18 (d'), 128.26 (d'), 131.53 (d'), 134.84 (d'), 170.64 (s'); exact mass, *m/z* calcd for $C_{22}H_{29}NO_3$ 355.2147, found 355.2141.

N-2-Propenyl-N-(6-bromo-1-phenyl-1-hexyn-3-yl) acetamide (229).

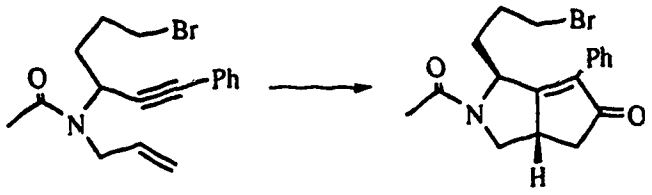


228 **229**

Carbon tetrabromide (1.5 g, 4.52 mmol) was added to a stirred solution of amide **228** (1.01 g, 3.01 mmol) in dichloromethane (10 mL) at 0°C. After 10 min, triphenylphosphine (2.4 g, 9.0 mmol) was added and the cooling bath was removed.[195] After 24 h the solution was filtered through silica gel (2 x 3 cm) with ether (50 mL). The filtrate was evaporated and flash

chromatography of the residue over silica gel (2 x 20 cm), using 30% ethyl acetate--hexane, gave bromide **229** (0.61 g, 60%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3130-2800, 1651, 1407 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.80-2.15 [m (including s, (3 H), at 2.11), 7 H], 3.46 (td, *J* = 6.1, 2.1 Hz, 2 H), 3.97-4.23 (m, 2 H), 5.21-5.28 (m, 2 H), 5.70 (t, *J* = 7.5 Hz, 1 H), 5.92 (ddt, *J* = 15.4, 10.5, 5.1 Hz, 1 H), 7.27-7.36 (m, 3 H), 7.36-7.44 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 21.98 (q'), 29.39 (t'), 33.04 (t'), 33.12 (t'), 46.61 (d'), 47.73 (t'), 85.08 (s'), 86.86 (s'), 116.92 (t'), 122.47 (s'), 128.30 (d'), 128.44 (d'), 131.62 (d'), 134.69 (d'), 170.77 (s'); exact mass, *m/z* calcd for $C_{17}H_{20}{}^{81}BrNO$ 335.0708, found 335.0704.

2-Acetyl-2,3,3aα,4-tetrahydro-1α-(3-bromopropyl)6-phenylcyclopenta[c]pyrrol-5(1*H*)-one (230).

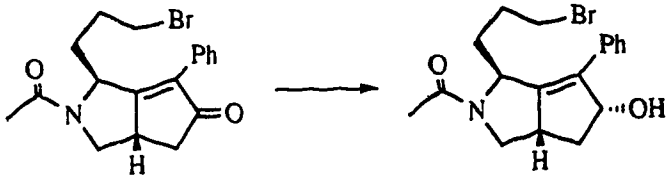


229 **230**

The general procedure for the P-K reaction with NMO was followed, using **229** (104 mg, 0.311 mmol) and octacarbonyldicobalt (1.1 mL, 0.3 M, in dichloromethane, 0.33 mmol) in dichloromethane (10 mL) for 2 h, and 4-methylmorpholine *N*-oxide (218 mg, 1.87 mmol) for 6 h. Flash chromatography of the crude product over silica gel (2 x 20 cm), using 80% ethyl acetate--hexane, gave enone **230** (72 mg, 64%, and approximately 10% of a minor isomer) [^{1}H NMR (400 MHz)]. Enone **230** had: FT-IR ($CHCl_3$) 1711, 1648, 1412 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.86 (quintet, *J* = 7.2 Hz, 2 H), 2.00-2.19 [m (including s, (3 H), at 2.08), 5 H], 2.39 (dd, *J* = 18.0, 3.7 Hz, 1 H), 2.91

(dd, J = 18.0, 6.7 Hz, 1 H), 3.14 (t, 9.7 Hz, 1 H), 3.33-3.46 (m, 2 H), 3.50-3.60 (m, 1 H), 4.07 (t, J = 9.2 Hz, 1 H), 5.15 (t, J = 6.1 Hz, 1 H), 7.33-7.50 (m, 5 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 22.48 (q'), 29.16 (t'), 32.94 (t'), 33.28 (t'), 40.06 (d'), 40.91 (t'), 52.43 (t'), 56.19 (d'), 128.28 (d'), 128.65 (d'), 128.76 (d'), 130.24 (s'), 136.03 (s'), 170.41 (s'), 174.08 (s'), 205.99 (s'); exact mass, *m/z* calcd for $C_{18}H_{20}{}^{81}BrNO_2$ 363.0657, found 363.0668.

2-Acetyl-1,2,3,3aβ,4,5-hexahydro-1β-(3-bromopropyl)-6-phenylcyclopenta[c]pyrrol-5α-ol (231).



230 **231**

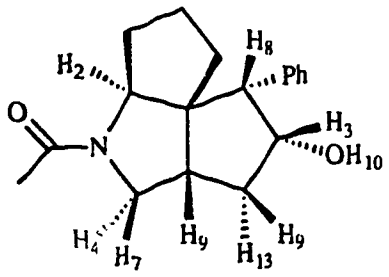
The procedure for the preparation of **190a** was followed, using **230** (83 mg, 0.23 mmol) in methanol (10 mL), cerium(III) chloride heptahydrate (128 mg, 0.34 mmol) and sodium borohydride (13 mg, 0.34 mmol). Flash chromatography of the crude product over silica gel (2 x 20 cm), using 4% methanol--ethyl acetate, gave alcohol **231** (80.5 mg, 96%) as a homogeneous [^1H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3540-3120, 1621, 1444, 1425 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.48-1.80 (m, 5 H), 1.93-2.12 [m (including s, (3 H), at δ 2.08), 4 H], 2.84 (dt, J = 12.4, 6.9 Hz, 1 H), 3.09-3.24 (m, 3 H), 3.38-3.46 (m, 1 H), 3.89 (t, J = 8.4 Hz, 1 H), 5.03-5.11 (m, 1 H), 5.46-5.54 (m, 1 H), 7.21-7.44 (m, 5 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 22.59 (q'), 29.05 (t'), 32.05 (t'), 33.46 (t'), 40.34 (t'), 44.45 (d'), 53.49 (t'), 55.21 (d'), 81.95 (d'), 127.57 (d'), 127.67 (d'), 128.71 (d'), 134.09 (s'), 136.26 (s'), 143.57 (s'), 170.07 (s'); exact mass, *m/z* calcd for $C_{18}H_{22}{}^{81}BrNO_2$ 365.0813, found 365.0827.

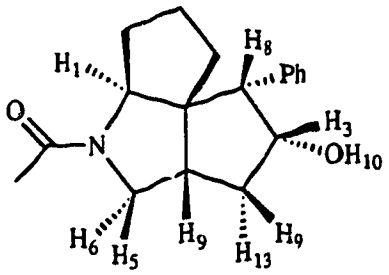
***cis-cis*-2-Acetyl-1,2,3,3aα,5aβ,6,7,8-octahydro-8α-phenyl-dicyclopenta[b,c]pyrrol-7α-ol (232).**

231 **232**

The general procedure for radical cyclization was followed using bromide **231** (76.0 mg, 0.208 mmol) in benzene (10 mL), tributyltin hydride (0.083 mL, 0.312 mmol) in benzene (5 mL), and AIBN (17 mg, 0.10 mmol) in benzene (5 mL). Flash chromatography of the residue over silica gel (2 x 20 cm), using 2.5% methanol--ethyl acetate, gave alcohol **232** (containing a small amount of tributyltin residue). The impure alcohol was purified by flash chromatography over neutral alumina (1 x 15 cm), using 2.5% methanol--ethyl acetate to give **232** (43 mg, 72%) as a mixture (67:33) of two isomers [^{1}H NMR (400 MHz)]: mp 149-153°C; FT-IR (CH_2Cl_2 cast) 3560-3120, 2934, 2868, 1620, 1454 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.31-1.54 (m, 4 H), 1.60 (br d, *J* = 11.4 Hz, 0.67 H), 1.67 (br d, *J* = 10.8 Hz, 0.33 H), 1.69-1.87 (m, 2 H), 2.06 (s, 3 x 0.33 H), 2.08 (s, 3 x 0.67 H), 2.22 (br s, 1 H), 2.38-2.53 (m, 2 H), 2.97 (d, *J* = 4.1 Hz, 0.67 H), 3.01 (d, *J* = 4.3 Hz, 0.33 H), 3.45 (dd, *J* = 12.3, 7.0 Hz, 0.67 H), 3.56 (br d, *J* = 10.8 Hz, 0.33 H), 3.70 (dd, *J* = 10.8, 7.1 Hz, 0.33 H), 4.01 (d, *J* = 12.0 Hz, 0.67 H), 4.38-4.43 (m, 0.33 H), 4.43-4.47 (m, 0.67 H), 4.50-4.54 (m, 0.67 H), 4.84 (br d, *J* = 6.4 Hz, 0.33 H), 7.25-7.37 (m, 3 H), 7.42-7.46 (m, 2 x 0.33 H), 7.49-7.54 (m, 2 x 0.67 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 22.06 (q'), 23.00 (q'), 24.66 (t'), 24.99 (t'), 34.56 (t'), 35.86 (t'), 39.06 (t'), 39.23 (t'), 42.17 (t'), 43.20 (t'), 48.51 (d'), 49.83 (d'), 53.04 (t'), 55.56 (t'), 58.98 (d'), 59.45 (d'), 63.21 (d'), 63.52 (s'), 64.50 (d'), 65.42 (s'), 75.80 (d'), 75.98 (d'), 126.97 (d'), 127.03 (d'), 128.32 (d'), 128.48 (d'), 130.45 (d'), 130.53

(d'), 138.14 (s'), 138.92 (s'), 168.75 (s'), 169.41 (s'); exact mass, *m/z* calcd for $C_{18}H_{23}NO_2$ 285.1729, found 285.1728. Saturation of the signals at δ 2.97 and 3.01 in the ^1H NMR spectrum produced enhancements of 5% in the signals at δ 4.43-4.47 and 4.50-4.54.





Chemical Shift

H_1 = 4.84
H_2 = 4.50-4.54
H_3 = 4.38-4.43
H_4 = 3.45
H_5 = 3.56
H_6 = 3.70
H_7 = 4.01
H_8 = 2.97, 3.01
H_9 = 2.38-2.53
H_{10} = 2.22
H_{13} = 1.60

Amide **232** is a mixture of two rotamers (2 : 1) as shown by its efficient conversion ($LiAlH_4$) to a single amine. The stereochemistry of compound **232** was determined by decoupling and NOE enhancement NMR experiments.

Irradiation of H_1 and H_2 caused only slight changes in the high field region (approx. δ 1.5) and thus, based on their chemical shifts, H_1 and H_2 were assigned as shown.

Irradiation of H_3 (both signals):- H_8 ⇒ pair of singlets (each doublet collapses to a singlet), H_9 is simplified. On the basis of their coupling and chemical shifts H_3 and H_8 were assigned as shown.

Irradiation of H_4:- H_7 ⇒ doublet, H_9 is slightly changed.

Irradiation of H_5:- H_6 ⇒ singlet, H_9 is slightly changed.

Irradiation of H_6:- H_5 ⇒ doublet, H_9 is slightly changed.

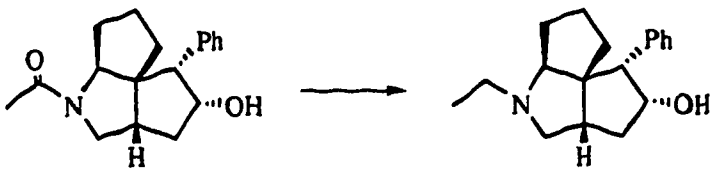
Irradiation of H_7:- H_4 ⇒ singlet, H_9 is slightly changed.

Thus H_4, H_5, H_6 and H_7 are assigned as shown on the basis of chemical shifts, and the fact that H_5 and H_7 are quartets which become doublets when H_9 is irradiated. H_4 and H_6 are doublets which become singlets when H_9 is irradiated, indicating negligible trans coupling.

Irradiation of H_8:- $H_3 \Rightarrow$ pair of doublets (one for each rotamer). Since H_{10} is a broad singlet and does not couple with H_3, the remaining coupling must be J (H_3-H_9) and is approximately equal to J (H_3-H_8) i.e. 4.0 - 4.4 Hz. This suggests that H_8, H_3 and H_9 are on the same face of the cyclopentane ring.

Irradiation of H_9:- H_5 and $H_7 \Rightarrow$ doublets, $H_{13} \Rightarrow$ pair of singlets (one for each rotamer), $H_3 \Rightarrow$ pair of doublets. The H_3 doublets have J = 4.2 Hz, i.e. the same as H_8; therefore they are not coupled by H_{13}. Thus H_{13} only has geminal coupling, i.e. no trans coupling. Irradiation of H_8 (both signals causes NOE enhancements of 5.4% for H_3 (both signals combined), and 14% for the aromatic signal.

cis-cis-2-Ethyl-1,2,3,3aα,5aβ,6,7,8-octahydro-8α-phenyl-dicyclopenta[b,c]pyrrol-7α-ol (233).

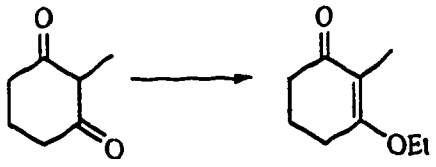


232 **233**

Lithium aluminum hydride (1.6 mg, 0.041 mmol) was added to a solution of amide **232** (5.9 mg, 0.021 mmol) in ether 10 mL, and the mixture was refluxed for 15 h, and then cooled to room temperature. Water (5 mL) was added and the layers were separated. The aqueous layer was extracted with ether (5 mL) and the combined ether layers were dried ($MgSO_4$), and

evaporated. Flash chromatography of the residue over silica gel (0.5 x 10 cm), using 5% methanol--dichloromethane, gave the amine (5.6 mg, 99%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3300-2600 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.11 (t, *J* = 7.6 Hz, 3 H), 1.32-1.44 (m, 2 H), 1.54-1.76 (m, 3 H), 1.80 (dt, *J* = 11.2, 8.0 Hz, 1 H), 2.19-2.33 (m, 2 H), 2.50-2.70 (m, 3 H), 2.80 (br d, *J* = 8.8 Hz, 1 H), 2.89 (d, *J* = 3.2 Hz, 1 H), 3.47 (dd, *J* = 8.7, 4.8 Hz, 1 H), 4.19-4.29 (m, 1 H), 7.20-7.47 (m, 3 H), 7.63-7.70 (m, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 13.35, 23.16, 25.68, 38.16, 43.89, 44.41, 48.56, 59.18, 64.05, 64.96, 76.96, 126.19, 127.81, 130.60; exact mass, *m/z* calcd for $C_{18}H_{25}NO$ 271.1936, found 271.1934.

3-Ethoxy-2-methyl-2-cyclohexenone (245).[202]

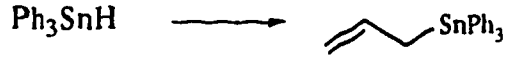


244 **245**

p-Toluenesulfonic acid (0.42 g, 2.2 mmol) was added to a solution of 2-methyl-1,3-cyclohexanedione (10 g, 79.2 mmol) in ethanol (46 mL) and benzene (160 mL). The solution was then heated and the water--benzene azeotrope distilled off at such a rate that after 6-8 h the volume had been reduced by half. The solution was cooled, washed with 10% sodium hydroxide which had been saturated with sodium chloride (2 x 20 mL), dried ($MgSO_4$), and evaporated. Hexane (50 mL) was added. The product crystallized and was filtered off and dried. Ethoxy enone **245** (5.1 g, 41%) was obtained as the first crop, and no attempt was made to recover more. The enone had: mp 59-61°C; FT-IR ($CHCl_3$ cast) 1694, 1607, 1334 cm^{-1}; ^{1}H NMR

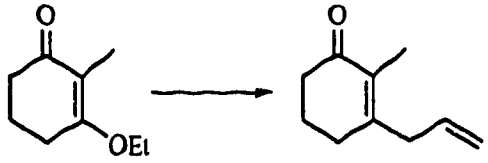
($CDCl_3$, 200 MHz) δ 1.36 (t, *J* = 7.6 Hz, 3 H), 1.70 (t, *J* = 1.5 Hz, 3 H), 1.98 (br quintet, *J* = 6.6 Hz, 2 H), 2.34 (dd, *J* = 7.2 Hz, 2 H), 2.55 (td, *J* = 6.2 Hz, 2 H), 4.07 (q, *J* = 7.1 Hz, 2 H); exact mass, *m/z* calcd for $C_9H_{14}O_2$ 154.0994, found 154.0997.

Triphenyl(2-propenyl)stannane.[203]



Magnesium (2.43 g, 0.1 mol) in THF (30 mL) was activated by addition of 3-bromopropene (2 drops), and then a solution of 3-bromopropene (4.7 g, 38.8 mmol) and triphenyltin chloride (9.6 g, 24.9 mmol) in THF (25 mL) was added over 2 h. The mixture was refluxed for a further 6 h, cooled to room temperature and poured into saturated aqueous sodium bicarbonate (20 mL). The layers were separated and the organic layer was evaporated. The residue was diluted with ether (50 mL), washed with potassium fluoride in 50% water--methanol (20 mL), dried ($MgSO_4$), and evaporated to give a white solid: FT-IR (CH_2Cl_2 cast) 1620, 1428, 726 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 2.45 (d, *J* = 8.3 Hz, 2 H), 4.80 (dd, *J* = 10.1, 1.1 Hz, 2 H), 4.98 (dd, *J* = 16.8, 1.6 Hz, 2 H), 6.07 (ddt, *J* = 16.8, 10.1, 8.5 Hz, 1 H), 7.30-7.45 (m, 9 H), 7.45-7.62 (m, 6 H); exact mass, *m/z* calcd for $C_{18}H_{15}{}^{120}Sn$ $(M - C_3H_5)^+$ 351.0196, found 351.0196.

2-Methyl-3-(2-propenyl)-2-cyclohexenone (246).[204]

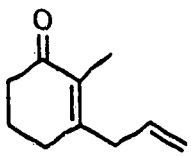


245 **246**

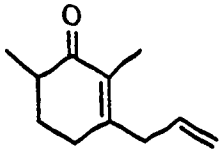
Following a literature procedure,[203] phenyllithium (7.7 mL, 2.0 M

solution in cyclohexane/ether, 70/30, 15.4 mmol) was added to a solution of triphenyl(2-propenyl) stannane (5.0 g, 12.8 mmol) in ether (20 mL) at room temperature. Stirring was continued for 30 min, then ethoxyenone **245** (1.48 g, 9.6 mmol) in ether (5 mL) was added and stirring continued for 2 h. Following concentration, flash chromatography of the residue over silica gel (5 x 20 cm), using 10% ethyl acetate--hexane, gave **246** (1.39 g, 96%) as a homogeneous [^{1}H NMR (200 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3120-2800, 1665 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.79 (t, J = 1.5 Hz, 3 H), 1.92 (br quintet, J = 6.6 Hz, 2 H), 2.27-2.47 (m, 4 H), 3.00 (d, J = 8.3 Hz, 2 H), 4.99-5.20 (m, 2 H), 5.65-5.90 (m, 1 H); exact mass, m/z calcd for $C_{10}H_{14}O$ 150.1045, found 150.1044.

2,6-Dimethyl-3-(2-propenyl)-2-cyclohexenone (247).



246

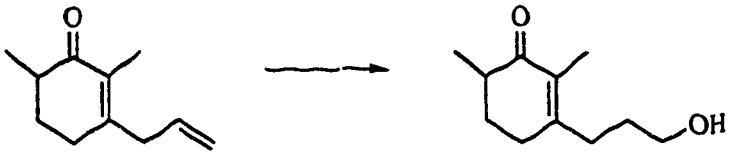


247

Enone **246**[204] (0.75 g, 4.95 mmol) in THF (10 mL) was added over 10 min to a stirred and cooled (-78°C) solution of LDA [prepared by addition of *n*-butyllithium (3.7 mL, 1.6 M, in hexanes, 5.9 mmol) to a solution of diisopropylamine (0.9 mL, 6.4 mmol) in THF (30 mL) at 0°C]. After 30 min *n*-butyllithium (3.7 mL, 1.6 M, in hexanes, 5.9 mmol) was added, followed after another 30 min by methyl iodide (1.23 mL, 19.8 mmol). The cooling bath was removed and, after 1 h, the solvent was evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 10% ethyl acetate--hexane, gave **247** (496 mg, 61%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: ^{1}H

NMR ($CDCl_3$, 400 MHz) δ 1.14 (d, J = 7.2 Hz, 3 H), 1.58-1.74 (m, 1 H), 1.78 (s, 3 H), 1.97-2.08 (m, 1 H), 2.28-2.43 (m, 3 H), 2.88-3.08 (m, 2 H), 5.03-5.13 (m, 2 H), 5.70-5.85 (m, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 10.85 (q'), 15.65 (q'), 29.86 (t'), 30.42 (t'), 39.40 (t'), 40.79 (d'), 116.67 (t'), 131.05 (s'), 133.26 (d'), 154.57 (s'), 202.05 (s').

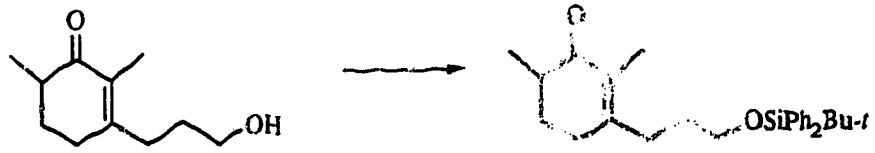
3-(3-Hydroxypropyl)-2,6-dimethyl-2-cyclohexenone (249).



247 249

Enone **247** (50 mg, 0.305 mmol) in THF (5 mL) was added to a solution of 9-BBN dimer (82 mg, 0.671 mmol) in THF (5 mL). The mixture was refluxed for 1 h, and then cooled to room temperature. Ethanol (1 mL), 6 N sodium hydroxide (0.3 mL) and 30% hydrogen peroxide (0.6 mL) were added in succession, and the mixture was stirred at 50°C for 1 h, and then cooled to room temperature. Potassium carbonate (5 g) was added and the mixture was filtered. The filtrate was evaporated and flash chromatography of the residue over silica gel (2 x 20 cm), using 50% ethyl acetate--hexane, gave alcohol **249** (38.9 mg, 70%) as a homogeneous [^1H NMR (200 MHz)] colorless oil: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.13 (d, J = 7.2 Hz, 3 H), 1.50-1.81 (m, 8 H), 1.93-2.10 (m, 1 H), 2.20-2.45 (m, 4 H), 3.68 (t, J = 6.4 Hz, 2 H).

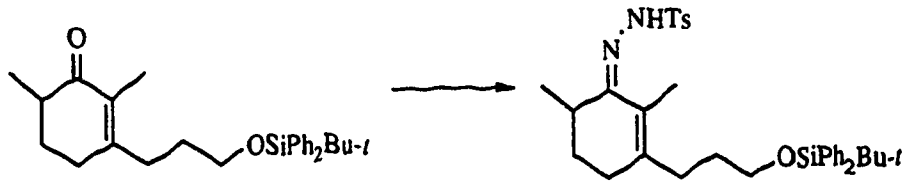
3-(3-*t*-Butyldiphenylsiloxypropyl)-2,6-dimethyl-2-cyclohexenone (250).



249 **250**

t-Butylchlorodiphenylsilane (230 mg, 0.83 mmol) and imidazole (52 mg, 0.76 mmol) were added at room temperature to a stirred solution of alcohol **249** (127 mg, 0.696 mmol) in dichloromethane (10 mL). After 9 h the mixture was evaporated and flash chromatography of the residue over silica gel (2 x 20 cm), using 10% ethyl acetate--hexane, gave enone **250** (167 mg, 57%) as a homogeneous [^{1}H NMR (80 MHz)] colorless oil: ^{1}H NMR ($CDCl_3$, 80 MHz) δ 0.82-2.62 [m (including s, (9 H), at δ 1.20), 26 H], 3.40 (t, J = 6.4 Hz, 2 H), 7.14-7.85 (m, 10 H).

3-(3-*t*-Butyldiphenylsiloxypropyl)-2,6-dimethyl-2-cyclohexenone *p*-toluene-sulfonyl hydrazone (251).



250 **251**

p-Toluenesulfonylhydrazide (89 mg, 0.48 mmol) was added to a solution of enone **250** (167 mg, 0.397 mmol) in ethanol (2 mL) and the mixture was refluxed for 16 h, cooled and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 10% ethyl acetate--hexane, gave **251** (29.5 mg, 14%) as a homogeneous [^{1}H NMR (200 MHz)] colorless oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.93 (d, J = 6.8 Hz, 3 H), 1.06 (s, 9 H), 1.50-1.70 (m, 3

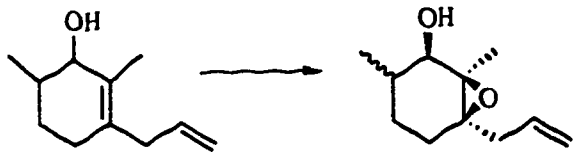
H), 1.76 (s, 3 H), 2.14-2.35 (m, 4 H), 2.41 (s, 3 H), 2.78 (br s, 1 H), 3.63 (t, J = 6.0 Hz, 2 H), 7.24-7.48 (m, 8 H), 7.57-7.72 (m, 4 H), 7.82-7.92 (m, 2 H).

2,6-Dimethyl-3-(2-propenyl)-2-cyclohexenol (252).

247 **252**

The procedure used for the preparation of **190a** was followed, using enone **247** (310 mg, 1.89 mmol) in methanol (10 mL), cerium(III) chloride heptahydrate (773 mg, 2.1 mmol) and sodium borohydride (79 mg, 2.08 mmol). Flash chromatography of the residue over silica gel (3 x 20 cm), using 10% ethyl acetate--hexane, gave alcohol **252** (140 mg, 45%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3600-3100, 3100-2800, 1636 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.01 (d, J = 6.7 Hz, 3 H), 1.34-1.48 (m, 2 H), 1.48-1.67 (m, 2 H), 1.80 (s, 3 H), 1.99 (br t, J = 5.0 Hz, 2 H), 2.72 (dd, J = 14.1, 6.9 Hz, 1 H), 2.77 (dd, J = 14.1, 6.4 Hz, 1 H), 3.68 (d, J = 3.2 Hz, 1 H), 4.92-5.06 (m, 2 H), 5.73 (ddt, J = 16.8, 10.0, 6.5 Hz, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 16.94 (q'), 17.25 (q'), 24.76 (t'), 30.22 (t'), 34.31 (d'), 37.70 (t'), 73.01 (d'), 114.93 (t'), 129.58 (s'), 132.30 (s'), 135.55 (d'); exact mass, m/z calcd for $C_{11}H_{18}O$ 166.1358, found 166.1359.

(1α,2β,6α) 1,3-Dimethyl-6-(2-propenyl)-7-oxabicyclo[4.1.0]heptan-2-ol (253).



252 253

t-Butyl hydroperoxide (0.153 mL, 4.15 M in benzene, 0.636 mmol) was added to a stirred and cooled (6°C) mixture of **252** (96 mg, 0.578 mmol), sodium bicarbonate (65 mg, 0.77 mmol) and vanadyl acetylacetonate (15 mg, 0.058 mmol) in benzene 10 mL. After 30 min water (10 mL) was added, and the layers were separated. The aqueous layer was extracted with ether (1 x 10 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 10% ethyl acetate--hexane, gave epoxide **253** (87 mg, 83%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94 (d, *J* = 6.5 Hz, 3 H), 1.06-1.15 (m, 1 H), 1.22 (ddd, *J* = 24.9, 12.1, 4.8 Hz, 1 H), 1.28-1.39 (m, 1 H), 1.76 (ddd, *J* = 14.9, 11.9, 5.8 Hz, 1 H), 1.94 (ddd, *J* = 15.1, 4.8, 2.1 Hz, 1 H), 2.02 (br s, 1 H), 2.32 (dd, *J* = 14.3, 6.8 Hz, 1 H), 2.44 (dd, *J* = 14.1, 7.5 Hz, 1 H), 3.59 (d, *J* = 3.6 Hz, 1 H), 5.08-5.16 (m, 2 H), 5.72-5.85 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 16.56, 19.20, 21.41, 29.10, 34.91, 38.56, 65.46, 67.58, 72.18, 117.92, 133.24.

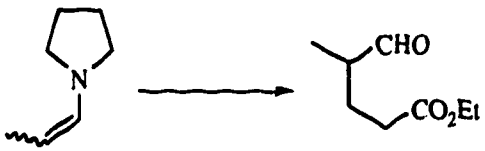
(1α,6α) 1,3-Dimethyl-6-(2-propenyl)-7-oxabicyclo[4.1.0]heptan-2-one (248).

253 248

The procedure used for the preparation of **166** was followed, using

DMSO (0.07 mL, 0.96 mmol) and oxalyl chloride (0.05 mL, 0.53 mmol) in dichloromethane (10 mL), alcohol **253** (87 mg, 0.48 mmol) in dichloromethane (5 mL) and triethylamine (0.25 mL, 1.7 mmol). Flash chromatography of the crude product over silica gel (2 x 20 cm), using 10% ethyl acetate--hexane, gave epoxy ketone **248** (57 mg, 66%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.13 (d, *J* = 7.2 Hz, 3 H), 1.48 (s, 3 H), 1.59-1.68 (m, 2 H), 1.93-2.03 (m, 2 H), 2.12 (dt, *J* = 14.6, 3.5 Hz, 1 H), 2.39 (ddt, *J* = 14.4, 7.0, 1.3 Hz, 1 H), 2.53, (ddt, *J* = 14.6, 7.0, 2.3 Hz, 1 H), 5.13-5.21 (m, 2 H), 5.74-5.84 (m, 1 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 12.09, 16.25, 24.35, 27.35, 38.41, 42.04, 63.57, 66.23, 118.62, 132.55, 207.93.

Ethyl 4-methyl-5-oxopentanoate (254).

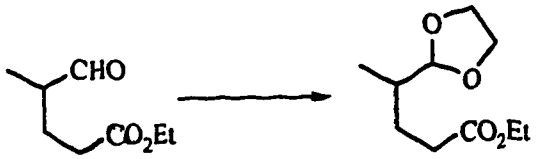


255 **254**

A solution of enamine **255** (13.2 g, 119 mmol) and ethyl acrylate (19.3 mL, 178 mmol) in dioxane (100 mL) was refluxed for 3 h, cooled to room temperature, and diluted with water (10 mL). The mixture was refluxed for 1 h, cooled to room temperature, diluted with ether (50 mL), washed with 5% hydrochloric acid (1 x 10 mL), saturated aqueous sodium bicarbonate (1 x 10 mL), and water (1 x 10 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (6 x 20 cm), using 10% ethyl acetate--hexane, gave **254** (15.1 g, 80%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (neat) 2960, 1733, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.14 (d, *J* = 7.0 Hz, 3 H), 1.26 (t, *J* = 7.2 Hz, 3 H), 1.70 (sextet, *J* = 7.2 Hz, 1

H), 2.06 (sextet, J = 7.2 Hz, 1 H), 2.37 (t, J = 7.5 Hz, 2 H), 2.43 (sextet d, J = 7.0, 1.5 Hz, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 13.12 (q'), 14.06 (q'), 25.30 (t'), 31.38 (t'), 45.40 (d'), 60.33 (t'), 172.81 (s'), 203.87 (s'); exact mass, *m/z* calcd for $C_8H_{14}O_3$ 158.0943, found 158.0922. Anal. Calcd for $C_8H_{14}O_3$: C, 60.74; H, 8.92. Found: C, 60.45; H, 8.77.

Ethyl 4-(1,3-Dioxolan-2-yl)pentanoate (256).



254 **256**

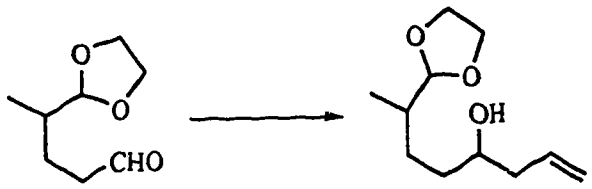
A solution of aldehyde **254** (8.0 g, 50.5 mmol), ethylene glycol (6.28 g, 101 mmol) and *p*-toluenesulfonic acid monohydrate (50 mg, 0.26 mmol) in benzene (100 mL) was refluxed for 3 h, using a side-arm dropping funnel packed with 4Å molecular sieves (20 g) between the reaction flask and the reflux condenser. The solution was cooled and evaporated. Flash chromatography of the residue over silica gel (20 x 5 cm), using 10% ethyl acetate--hexane, gave ester **256** (8.8 g, 86%) as a homogeneous [^1H NMR (400 MHz)] colorless oil: FT-IR (neat) 2978, 2883, 1735 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.95 (d, J = 6.9 Hz, 3 H), 1.25 (t, J = 7.0 Hz, 3 H), 1.48-1.59 (m, 1 H), 1.70-1.80 (m, 1 H), 1.84-1.94 (m, 1 H), 2.29-2.45 (m, 2 H), 3.81-3.98 (m, 4 H), 4.12 (q, J = 7.0 Hz, 2 H), 4.69 (d, J = 4.4 Hz, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 13.80 (q'), 14.19 (q'), 26.67 (t'), 32.06 (t'), 36.36 (d'), 60.15 (t'), 64.93 (t'), 64.98 (t'), 107.26 (d'), 173.64 (s'); exact mass, *m/z* calcd for $C_{10}H_{18}O_3$ 202.1205, found 202.1187. Anal. Calcd for $C_{10}H_{18}O_3$: C, 59.39; H, 8.97. Found: C, 59.54; H, 8.92.

4-(1,3-Dioxolan-2-yl)pentanal (257).

256 **257**

Diisobutylaluminum hydride (13.5 mL, 1.0 M solution in hexanes, 13.5 mmol) was added dropwise over 20 min to a stirred and cooled (-78°C) solution of ester **256** (2.57 g, 12.7 mmol) in pentane (20 mL). Stirring was continued for 1 h, and then saturated aqueous ammonium chloride (10 mL) was added and the cooling bath was removed. When the mixture had attained room temperature it was extracted with ether (2 x 25 mL) and the combined extracts were washed with water (2 x 5 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 30% ethyl acetate--hexane, gave aldehyde **257** (1.2 g, 60%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR ($CHCl_3$ cast) 2976, 1736, 1713 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.96 (d, *J* = 7.0 Hz, 3 H), 1.48-1.60 (m, 1 H), 1.71-1.82 (m, 1 H), 1.84-1.95 (m, 1 H), 2.44-2.62 (m, 2 H), 3.30-4.02 (m, 4 H), 4.69 (d, *J* = 4.2 Hz, 1 H), 9.77 (t, *J* = 1.6 Hz, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 14.13 (q'), 23.66 (t'), 36.31 (d'), 41.64 (t'), 46.94 (t'), 65.02 (t'), 107.25 (d'), 202.64 (s'); exact mass, *m/z* calcd for $C_8H_{15}O_3$ $(M + H)^+$ 159.1020, found 159.1018.

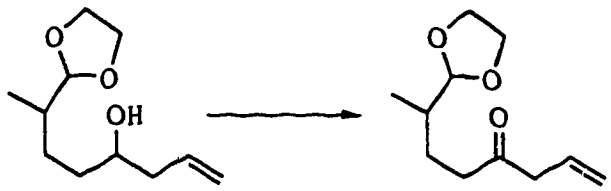
7-(1,3-Dioxolan-2-yl)-1-octen-4-ol (258).



257 258

Phenyllithium (2.0 M solution in hexanes, 5.2 mL, 10.4 mmol) was added over 10 min to a stirred and cooled (cold-water bath) solution of triphenyl(2-propenyl)stannane (4.06 g, 10.4 mmol) in ether (40 mL). The cooling bath was removed and after 30 min a solution of aldehyde **257** (1.04 g, 6.58 mmol) in ether (10 mL) was added over 10 min. Stirring was continued for a further 2 h and then saturated aqueous ammonium chloride (10 mL) was added. The mixture was filtered through a pad (2 x 3 cm) of Celite and the filtrate was extracted with ether (1 x 50 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 50% ethyl acetate--hexane, gave alcohol **258** (1.1 g, 83%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (neat) 3600-3200, 2974, 2735, 2881 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.95 (d, J = 6.8 Hz, 3 H), 1.15-1.79 (m, 5 H), 2.00 (br s, 1 H), 2.16 (br sextet, J = 7.3 Hz, 1 H), 2.26-2.36 (m, 1 H), 3.60-3.68 (m, 1 H), 3.80-4.01 (m, 4 H), 4.69 (dd, J = 4.6, 1.8 Hz, 1 H), 5.08-5.17 (m, 2 H), 5.78-5.90 (m, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 13.91 (q'), 13.99 (q'), 27.35 (t'), 27.51 (t'), 34.13 (t'), 34.20 (t'), 36.73 (d'), 36.91 (d'), 41.71 (t'), 41.93 (t'), 64.94 (t'), 64.96 (t'), 70.67 (d'), 70.99 (d'), 107.50 (d'), 107.56 (d'), 117.85 (t'), 117.94 (t'), 134.86 (d'), 134.92 (d'); mass (CI), *m/z* calcd for $C_{11}H_{20}O_3$ 200, found 218 (M + 18)$^+$. Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 66.05; H, 9.72.

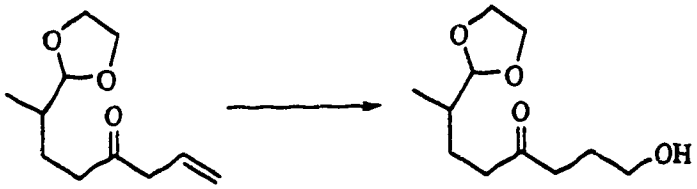
7-(1,3-Dioxolan-2-yl)-1-octen-4-one (259).



258 **259**

Chromium(VI) oxide (3.03 g, 30.3 mmol) was added to a stirred solution of pyridine (4.9 mL, 60.6 mmol) in dichloromethane (50 mL). Stirring at room temperature was continued for 15 min and then a solution of alcohol **258** (1.01 g, 5.05 mmol) in dichloromethane (10 mL) was added over 10 min. Stirring was continued for a further 1 h, and saturated aqueous ammonium chloride (10 mL) was then added. The mixture was stirred for 10 min and extracted with dichloromethane (1 x 50 mL). The organic extract was washed with water (2 x 5 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 20% ethyl acetate--hexane, gave ketone **259** (707 mg, 71%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 2971, 2940, 1730, 1172 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94 (d, *J* = 6.8 Hz, 3 H), 1.43-1.54 (m, 1 H),1.64-1.76 (m, 1 H), 1.76-1.87 (m, 1 H), 2.44-2.60 (m, 1 H), 3.18 (dt, *J* = 7.0, 1.4 Hz, 2 H), 3.80-3.98 (m, 4 H), 4.66 (d, *J* = 4.4 Hz, 1 H), 5.10-5.20 (m, 2 H), 5.93 (ddt, *J* = 17.0, 10.0, 4.5 Hz, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 14.08 (q'), 25.34 (t'), 36.28 (d'), 39.95 (t'), 47.59 (t'), 64.85 (t'), 64.93 (t'), 107.35 (d'), 118.55 (t'), 130.73 (d'), 208.45 (s'); exact mass, *m/z* calcd for $C_{11}H_{18}O_3$, 198.1256, found 198.1243.

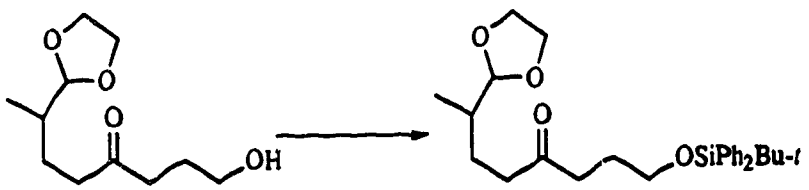
1-Hydroxy-7-(1,3-dioxolan-2-yl)octan-4-one (260).



259 **260**

Following a literature procedure,[208] a solution of 9-BBN (146 mg, 1.19 mmol) in THF (5 mL) was added over 5 min at room temperature to a stirred solution of enone **259** (226 mg, 1.14 mmol) in THF (5 mL). The resulting solution was then refluxed for 1 h with continued stirring, cooled, and diluted successively with ethanol (95%, 3 mL), aqueous sodium hydroxide (6 N, 1 mL), and hydrogen peroxide (30%$^{v}/_{v}$, 2 mL). The resulting mixture was refluxed for 1 h and cooled, diluted with ether (20 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 70% ethyl acetate--hexane, gave alcohol **260** (183 mg, 74%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 3600-3200, 2958, 2881, 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94 (d, J = 6.9 Hz, 3 H), 1.41-2.07 (m, 7 H), 2.41-2.60 (m, 3 H), 3.65 (t, J = 6.1 Hz, 1 H), 3.79-3.99 (m, 5 H), 4.66 (d, J = 4.6 Hz, 1 H); exact mass, m/z calcd for $C_{11}H_{20}O_4$, 216.1362, found 216.1357.

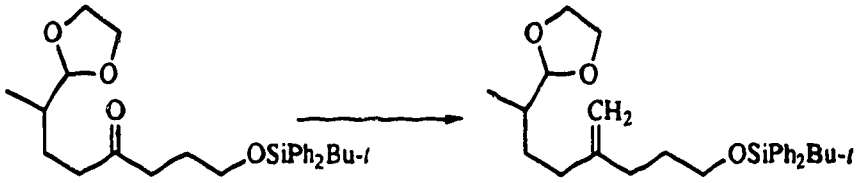
1-(*t*-Butyldiphenylsilyloxy)-7-(1,3-dioxolan-2-yl)]-4-octanone (261).



260 **261**

t-Butylchlorodiphenylsilane (0.48 mL, 1.83 mmol) and imidazole (367 mg, 250 mmol) were added to a stirred solution of **260** (198 mg, 0.92 mmol) in dichloromethane (20 mL). After 10 h at room temperature, the mixture was washed with saturated aqueous sodium bicarbonate (1 x 10 mL), and water (1 x 10 mL), dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 18 cm), using 10% ethyl acetate--hexane, gave ketone **261** (346 mg, 83%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 2957, 2951, 1714, 1111 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.93 (d, *J* = 6.8 Hz, 3 H), 1.04 (s, 9 H), 1.41-1.53 (m, 1 H), 1.63-1.75 (m, 1 H), 1.76-1.89 (m, 3 H), 2.39-2.55 [m (including t, *J* = 7.5 Hz, (2 H), at δ 2.52), 4 H], 3.67 (t, *J* = 6.0 Hz, 2 H), 3.76-3.94 (m, 4 H), 4.65 (d, *J* = 4.5 Hz, 1 H), 7.30-7.44 (m, 6 H), 7.60-7.70 (m, 4 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 14.10 (q'), 19.15 (s'), 25.53 (t'), 26.64 (t'), 26.84 (q'), 36.35 (d'), 38.92 (t'), 40.44 (t'), 63.04 (t'), 64.82 (t'), 64.91 (t'), 107.37 (d'), 127.59 (d'), 133.80 (s'), 135.46 (d'), 210.50 (s'); exact mass, *m/z* calcd for $C_{27}H_{38}O_4Si$, 454.2539, found 454.2549. Anal. Calcd for $C_{27}H_{38}O_4Si$: C, 71.32; H, 8.42. Found: C, 71.31; H, 8.24.

1-*t*-Butyl[[7-(1,3-dioxolan-2-yl)-4-methylene-octan-1-yl]oxy]diphenylsilane (262).

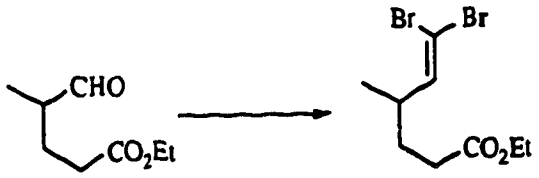


261 **262**

A mixture of potassium *t*-butoxide (210 mg, 1.88 mmol) and methyltriphenylphosphonium bromide (430 mg, 1.88 mmol) in benzene (5 mL) was refluxed for 30 min.[201] The condenser was then replaced by a

distillation apparatus, which was flushed with argon. The solution was then heated such that half the volume was removed by distillation over ca. 1 h. The residue was then cooled to room temperature and ketone **261** (426 mg, 0.94 mmol) in benzene (5 mL) was injected over 2 min with stirring. The mixture was refluxed for 2 h, cooled to room temperature, and diluted with water (10 mL). The layers were separated and the aqueous layer was washed with ether (1 x 20 mL). The organic layers were combined, dried ($MgSO_4$), and filtered through a silica gel pad (2 x 2 cm) with ether (50 mL). The combined filtrate was evaporated and flash chromatography of the residue over silica gel (2 x 20 cm), using 10% ethyl acetate--hexane, gave enyne **262** (360 mg, 85%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 2930, 2857, 1427, 1111 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.94 (d, J = 6.9 Hz, 3 H), 1.06 (s, 9 H), 1.22-1.35 (m, 1 H), 1.63-1.77 (m, 4 H), 1.93-2.04 (m, 1 H), 2.04-2.17 (m, 3 H), 3.67 (t, J = 6.4 Hz, 2 H), 3.78-3.97 (m, 4 H), 4.68 (d, J = 4.0 Hz, 1 H), 4.71 (br d, J = 7.4 Hz, 2 H), 7.33-7.45 (m, 6 H), 7.63-7.74 (m, 4 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 13.79 (q'), 19.25 (s'), 26.93 (q'), 29.61 (t'), 30.88 (t'), 32.23 (t'), 33.54 (t'), 36.60 (d'), 63.68 (t'), 65.00 (t'), 107.66 (d'), 109.03 (t'), 127.62 (d'), 129.53 (d'), 134.15 (s'), 135.60 (d'), 149.42 (s'); exact mass, m/z calcd for $C_{28}H_{40}O_3Si$ 452.2747, found 452.2704.

Ethyl 6,6-dibromo-4-methyl-5-hexenoate (263).

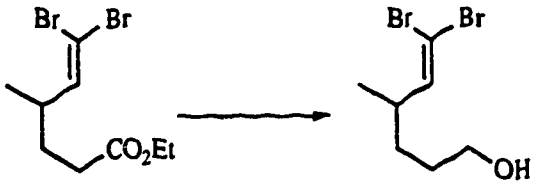


254 **263**

Following a literature procedure,[189] a mixture of triphenylphosphine

(9.9 g, 37.8 mmol), zinc dust (2.5 g, 38.2 mmol) and carbon tetrabromide (12.4 g, 37.4 mmol) in dichloromethane (100 mL) was stirred at room temperature for 2 days. A solution of aldehyde **254** (2.86 g, 18.7 mmol) in dichloromethane (10 mL) was added. The mixture was stirred for a further 10 h and filtered through a pad of silica gel (2 x 2 cm) with 10% ethyl acetate--hexane (100 mL). The combined filtrates were evaporated, and flash chromatography of the residue over silica gel (4 x 20 cm), using first hexane and then 5% ethyl acetate--hexane, gave **264** (5.12 g, 90%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (film) 2966, 1735, 1177 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.04 (d, J = 6.8 Hz, 3 H), 1.27 (t, J = 7.0 Hz, 3 H), 1 58-1.79 (m, 2 H), 2.31 (t, J = 7.6 Hz, 2 H), 2.43-2.58 (m, 1 H), 4.14 (q, J = 7.1 Hz, 2 H), 6.16 (d, J = 9.6 Hz, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 14.25 (q'), 19.23 (q'), 30.96 (t'), 32.05 (t'), 37.99 (d'), 60.42 (t'), 88.42 (s'), 143.69 (d'), 173.21 (s'); exact mass, m/z calcd for $C_9H_{14}O_2{}^{79}Br^{81}Br$ 313.9340, found 313.9307.

6,6-Dibromo-4-methyl-5-hexenol (264).

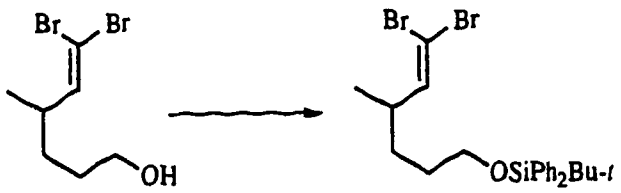


263 **264**

Lithium aluminum hydride (0.4 g, 10.5 mmol) was added to a stirred and cooled (0°C) solution of ester **263** (5.0 g, 15.9 mmol) in ether (40 mL). The cooling bath was removed and stirring at room temperature was continued for 1 h. Then water (10 mL) and 5% aqueous sodium hydroxide (5 mL) were added in succession. The layers were separated and the aqueous layer was washed with ether (1 x 20 mL). The combined ether layers were dried

($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 20% ethyl acetate--hexane, gave alcohol **264** (3.65 g, 84%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (film) 3519, 2932, 1458, 1057, 783 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.03 (d, J = 6.2 Hz, 3 H), 1.33-1.51 (m, 2 H), 1.51-1.62 (m, 2 H), 1.79 (br s, 1 H), 2.42-2.56 (m, 1 H), 3.63 (t, J = 6.3 Hz, 2 H), 6.18 (d, J = 9.7 Hz, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 19.31 (q'), 30.34 (t'), 32.25 (t'), 38.17 (d'), 62.71 (t'), 87.67 (s'), 144.00 (d'); exact mass, m/z calcd for $C_7H_{11}O^{81}Br$ (M - HBr)$^+$ 191.9973, found 191.9947.

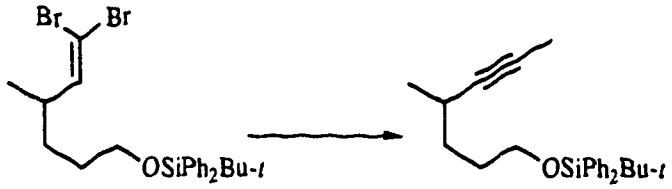
[[6,6-Dibromo-4-methyl-5-hexen-1-yl]oxy]*t*-butyldiphenylsilane (265).



264 **265**

t-Butylchlorodiphenylsilane (6.7 mL, 26.7 mmol) and imidazole (3.5 g, 51.3 mmol) were added to a stirred solution of **264** (3.60 g, 13.23 mmol) in dichloromethane (100 mL). After 8 h the solvent was evaporated and flash chromatography of the residue over silica gel (4 x 20 cm), using 2% ethyl acetate--hexane, gave silyl ether **265** (6.5 g, 96%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 2958, 2930, 2856, 1427, 1111 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.08 (d, J = 6.7 Hz, 3 H), 1.17 (s, 9 H), 1.42-1.70 (m, 4 H), 2.47-2.60 (m, 1 H), 3.76 (t, J = 6.2 Hz, 2 H), 6.24 (d, J = 9.4 Hz, 1 H), 7.41-7.53 (m, 6 H), 7.72-7.81 (m, 4 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 19.25 (s'), 19.34 (q'), 26.95 (q'), 30.15 (t'), 32.28 (t'), 38.07 (d'), 63.67 (t'), 87.5 (s'), 127.66 (d'), 129.60 (d'), 134.00 (s'), 135.60 (d'), 144.19 (d'); exact mass, m/z calcd for $C_{19}H_{21}{}^{79}Br^{81}BrOSi$ (M - C_4H_9)$^+$ 452.9708, found 452.9748.

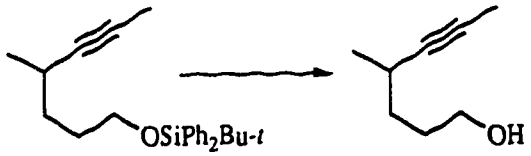
***t*-Butyl[[4-methyl-2-heptyn-1-yl]oxy]diphenylsilane (266).**



265 **266**

n-Butyllithium (15.8 mL, 1.6 M, in hexanes, 25.3 mmol) was added to a stirred and cooled (-78°C) solution of dibromide **265** (6.15 g, 12.1 mmol) in THF (40 mL). After 1 h the cooling bath was removed, and after a further 1 h, methyl iodide (1.2 mL, 19.3 mmol) was injected in one portion. The resulting mixture was stirred for 8 h, water (10 mL) was then added and the mixture was extracted with ether (2 x 50 mL). The organic extract was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (4 x 20 cm), using 5% ethyl acetate--hexane, gave alkyne **266** (4.39 g, 100%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (film) 2958, 2930, 2857, 1427, 1111 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 9 H), 1.12 (d, J = 7.2 Hz, 3 H), 1.37-1.55 (m, 2 H), 1.58-1.81 [m (including d, J = 2.1 Hz, (3 H), at δ 1.77), 5 H], 2.30-2.41 (m, 1 H), 3.68 (t, J = 6.5 Hz, 2 H), 7.30-7.44 (m, 6 H), 7.63-7.71 (m, 4 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 3.53 (q'), 19.27 (s'), 21.52 (d'), 25.75 (q'), 26.92 (q'), 30.48 (t'), 33.56 (t'), 63.88 (t'), 75.65 (s'), 83.83 (s'), 127.63 (d'), 129.55 (d'), 134.16 (s'), 135.63 (d'); exact mass, m/z calcd for $C_{20}H_{23}OSi$ $(M - C_4H_9)^+$ 307.1517, found 307.1519.

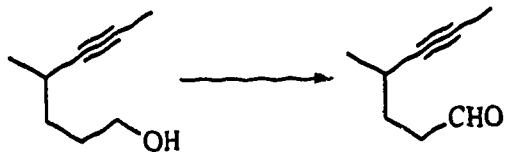
4-Methyl-5-heptyn-1-ol (267).



266 **267**

Tetrabutylammonium fluoride (13.6 mL, 1.0 M, in THF, 13.6 mmol) was added at room temperature to a stirred solution of **266** (4.5 g, 12.3 mmol) in THF (50 mL). After 8 h the solvent was evaporated and flash chromatography of the residue over silica gel (3 x 18 cm), using 20% ethyl acetate--hexane, gave alcohol **267** (1.50 g, 96%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (film) 3600-3100, 2931, 21871, 1452, 1112 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.15 (d, J = 7.0 Hz, 3 H), 1.38-1.56 (m, 3 H), 1.60-1.84 [m (including d, J = 2.4 Hz, (3 H), at δ 1.79), 5 H], 2.35-2.47 (m, 1 H), 3.59-3.71 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 3.46 (q'), 21.52 (d'), 25.83 (q'), 30.69 (t'), 33.46 (t'), 62.88 (t'), 75.94 (s'), 83.60 (s'); mass (CI), *m/z* calcd for $C_8H_{14}O$ 126, found 144 $(M + 18)^+$.

4-Methyl-5-heptynal (268).

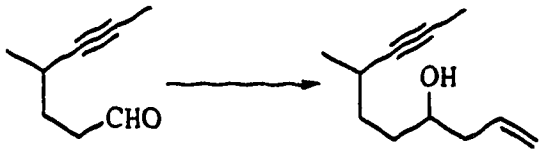


267 **268**

The procedure for the preparation of **166** was followed, using alcohol **267** (1.5 g, 11.9 mmol) in dichloromethane (20 mL), oxalyl chloride (1.5 mL, 17.2 mmol), and dimethyl sulfoxide (2.0 mL, 28.2 mmol) in dichloromethane (50 mL), and triethylamine (7.5 mL, 54 mmol). Evaporation of the solvent

and flash chromatography of the residue over silica gel (3 x 20 cm), using 5% ethyl acetate--hexane, gave aldehyde **268** (1.25 g, 85%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (film) 2988, 2924, 1709 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.16 (d, *J* = 7.0 Hz, 3 H), 1.58-1.70 (m, 1 H), 1.72-1.84 [m (including d, *J* = 2.4 Hz, (3 H), at δ 1.78), 4 H], 2.36-2.50 (m, 1 H), 2.50-2.69 (m, 2 H), 9.81 (t, *J* = 1.6 Hz, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 3.32 (q'), 21.31 (d'), 25.54 (q'), 29.40 (t'), 41.92 (t'), 76.85 (s'), 82.48 (s'), 202.20 (d'); exact mass, *m/z* calcd for $C_8H_{11}O$ $(M - H)^+$ 123.0809, found 123.0808.

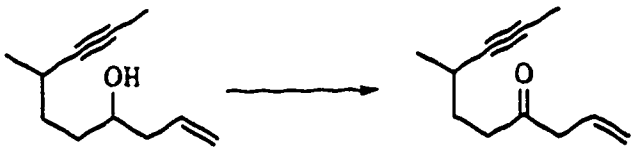
7-Methyl-1-decen-8-yn-4-ol (269).



268 **269**

Phenyllithium (12.0 mL, 1.8 M in 70:30 cyclohexane--ether, 22.6 mmol) was injected over 5 min to a stirred and cooled (0°C) solution of triphenyl(2-propenyl)stannane (8.5 g, 21.7 mmol) in ether (30 mL). The cooling bath was removed and the mixture was stirred at room temperature for 30 min. Aldehyde **268** (1.17 g, 9.42 mmol) in ether (10 mL) was then added over 10 min. The mixture was stirred for 8 h, and then filtered through a pad (2 x 2 cm) of Celite. Evaporation of the filtrate and flash chromatography of the residue over silica gel (3 x 20 cm), using 10% ethyl acetate--hexane, gave alcohol **269** (1.42 g) which was oxidized immediately.

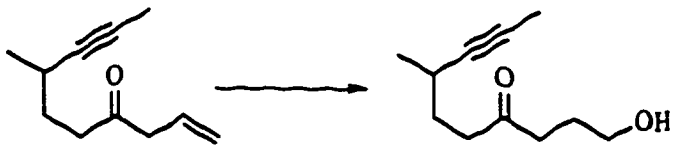
7-Methyl-1-decen-8-yn-4-one (270).



269 **270**

Chromium trioxide (5.0 g, 50.0 mmol) was added to a stirred solution of pyridine (8.1 mL, 100 mmol) in dichloromethane (50 mL). After 10 min a solution of alcohol **269** (1.35 g, 8.1 mmol) in dichloromethane (5 mL) was added and the mixture was stirred for 2 h. Water (20 mL) was added and the layers were separated. The aqueous phase was washed with ether (2 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 5% ethyl acetate--hexane, gave enone **270** [1.1 g, 82% (72% over two steps from 4-methyl-5-heptynal **268**)] as a homogeneous [^1H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 2967, 2930, 2920, 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.14 (d, *J* = 7.0 Hz, 3 H), 1.51-1.63 (m, 1 H), 1.68-1.82 [m (including d, *J* = 2.4 Hz, (3 H), at δ 1.78), 4 H], 2.34-2.45 (m, 1 H), 2.52-2.70 (m, 2 H), 3.20 (dt, *J* = 7.0, 1.4 Hz, 2 H), 5.11-5.21 (m, 2 H), 5.94 (ddt, *J* = 17.0, 10.0, 7.0 Hz, 1 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 3.46 (q'), 21.44 (d'), 25.48 (q'), 30.79 (t'), 40.21 (t'), 47.85 (t'), 76.47 (s'), 82.80 (s'), 118.69 (t'), 130.71 (d'), 208.57 (s'); exact mass, *m/z* calcd for $C_{11}H_{16}O$, 164.1201, found 164.1190.

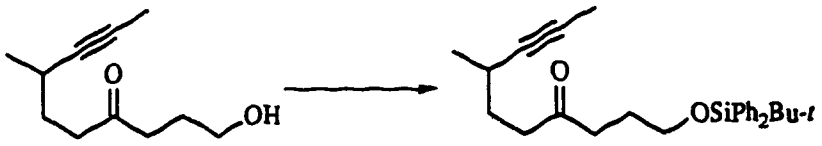
1-Hydroxy-7-methyl-8-decyn-4-one (271).



270 **271**

Following a literature procedure,[208] 9-BBN dimer (0.94 g, 3.85 mmol) was added to a stirred solution of enone **270** (1.056 g, 6.39 mmol) in THF (20 mL). The mixture was refluxed for 1 h, and then cooled to room temperature. Ethanol (95%, 12 mL), aqueous sodium hydroxide (6 N, 4 mL) and hydrogen peroxide (30%$^{v}/_{v}$, 8 mL) were added and the mixture was refluxed for 1 h and then cooled to room temperature. The layers were separated and the aqueous layer was washed with ether (1 x 20 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 50% ethyl acetate--hexane, gave alcohol **271** (0.995 g, 85%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (CH_2Cl_2 cast) 2964, 2931, 1713, 1083 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.13 (d, J = 7.0 Hz, 3 H), 1.49-1.63 (m, 1 H), 1.66-1.98 [m (including d, J = 2.3 Hz, (3 H), at δ 1.77), 7 H], 2.33-2.45 (m, 1 H), 2.53-2.67 (m, 4 H), 3.65 (t, J = 6.0 Hz, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 3.46 (q'), 21.65 (d'), 25.52 (q'), 226.53 (t'), 30.91 (t'), 39.68 (t'), 40.74 (t'), 62.30 (t'), 76.50 (s'), 82.81 (s'), 211.63 (s'); exact mass, m/z calcd for $C_{11}H_{18}O_2$ 182.1307, found 182.1292.

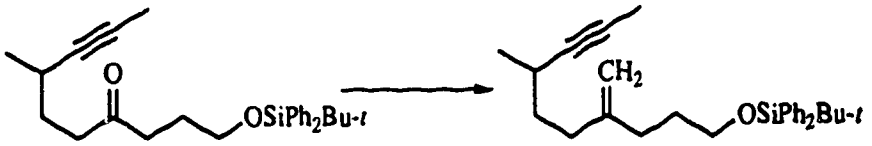
1-(*t*-Butyldiphenylsilyloxy)-7-methyl-8-decyn-4-one (272).



271 **272**

t-Butylchlorodiphenylsilane (2.0 mL, 7.7 mmol) and imidazole (1.05 g, 15.4 mmol) were added to a stirred solution of alcohol **271** (0.935 g, 5.13 mmol) in dichloromethane (50 mL). After 8 h, the solvent was evaporated and flash chromatography of the residue over silica gel (4 x 20 cm), using 5% ethyl acetate--hexane, gave ketone **272** (1.70 g, 78%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (film) 2960, 2930, 2857, 1715, 1111 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 9 H), 1.13 (d, *J* = 7.0 Hz, 3 H), 1.50-1.61 (m, 1 H), 1.64-1.78 [m (including d, *J* = 2.3 Hz, (3 H), at δ 1.77), 4 H], 1.83 (br quintet, *J* = 6.7 Hz, 2 H), 2.33-2.42 (m, 1 H), 2.46-2.63 (m, 4 H), 3.67 (t, *J* = 6.0 Hz, 2 H), 7.31-7.44 (m, 6 H), 7.61-7.70 (m, 4 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 3.47 (q'), 19.25 (s'), 21.48 (d'), 25.58 (q'), 26.73 (t'), 26.92 (q'), 31.01 (t'), 39.27 (t'), 40.71 (t'), 63.13 (t'), 76.38 (s'), 82.91 (s'), 127.68 (d'), 129.64 (d'), 133.90 (s'), 135.57 (d'), 210.59 (s'); exact mass, *m/z* calcd for $C_{23}H_{27}O_2Si$ $(M - C_4H_9)^+$ 363.1780, found 363.1771. Anal. Calcd for $C_{27}H_{36}O_2Si$: C, 77.09; H, 8.63. Found: C, 76.68; H, 8.63.

***t*-Butyl[[7-methyl-4-methylene-8-decyn-1-yl]oxy]diphenylsilane (273).**

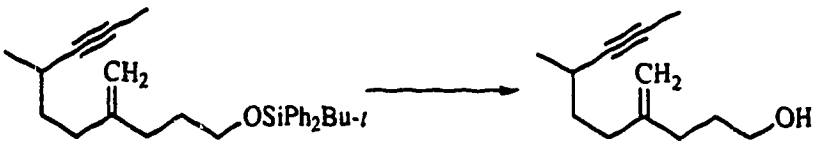


272 **273**

The procedure for the preparation of **262** was followed,[201] using

potassium *t*-butoxide (1.23 g, 10.9 mmol) and methyltriphenyl phosphonium bromide (3.19 g, 10.9 mmol) in benzene (50 mL), and ketone **272** (0.92 g, 2.19 mmol) in benzene (5 mL). Flash chromatography of the crude product over silica gel (4 x 20 cm), using 2% ethyl acetate--hexane, gave enyne **273** (0.90 g, 98%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (film) 2959, 2930, 2357, 1111 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 9 H), 1.13 (d, *J* = 7.0 Hz, 3 H), 1.50 (br q, *J* = 7.4 Hz, 2 H), 1.70 (br quintet, *J* = 7.0 Hz, 2 H), 1.78 (d, *J* = 2.4 Hz, 3 H), 2.00-2.22 (m, 4 H), 2.30-2.42 (m, 1 H), 3.68 (t, *J* = 6.3 Hz, 2 H), 4.71 (d, *J* = 5.0 Hz, 2 H), 7.28-7.46 (m, 6 H), 7.63-7.71 (m, 4 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 3.55 (q'), 19.29 (s'), 21.44 (d'), 25.75 (q'), 26.94 (q'), 30.87 (t'), 32.39 (t'), 33.92 (t'), 35.47 (t'), 63.68 (t'), 75.81 (s'), 83.71 (s'), 109,.01 (t'), 127.66 (d'), 129.58 (d'), 134.15 (s'), 135.63 (d'), 149.25 (s'); exact mass, *m/z* calcd for $C_{28}H_{38}OSi$ 418.2687, found 418.2692. Anal. Calcd for $C_{28}H_{38}OSi$: C, 80.32; H, 9.15. Found: C, 80.43; H, 8.91.

7-Methyl-4-methylene-8-decyn-1-ol (274).

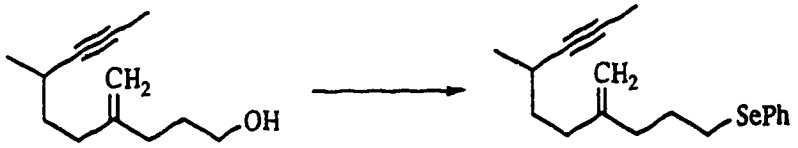


237 **274**

Tetrabutylammonium fluoride (1.0 M in THF, 2.2 mL, 2.2 mmol) was added to a stirred solution of compound **273** (852 mg, 2.03 mmol) in THF (50 mL). After 2 h the mixture was evaporated. Flash chromatography of the residue over silica gel (3 x 20 cm), using 20% ethyl acetate--hexane, gave alcohol **274** (310 mg, 85%) as a homogeneous [^{1}H NMR (400 MHz)] colorless oil: FT-IR (film) 3600-3120, 2931, 2870, 1644, 1450 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400

MHz) δ 1.14 (d, *J* = 7.0 Hz, 3 H), 1.52 (br q, *J* = 7.6 Hz, 2 H), 1.70 (br quintet, *J* = 7.2 Hz, 2 H), 1.79 (d, *J* = 2.3 Hz, 3 H), 1.88 (br s, 1 H), 2.03-2.14 (m, 3 H), 2.20 (quintet, *J* = 7.5 Hz, 1 H), 2.32-2.43 (m, 1 H), 3.64 (t, *J* = 6.5 Hz, 2 H), 4.76 (s, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 3.43 (q'), 21.33 (d'), 25.66 (q'), 30.65 (t'), 32.38 (t'), 33.71 (t'), 35.35 (t'), 62.63 (t'), 75.83 (s'), 83.57 (s'), 109.18 (t'), 149.02 (s'); mass (CI), *m/z* calcd for $C_{12}H_{20}O$ 180, found 198 $(M + 18)^+$.

4-Methyl-7-methylene-10-(phenylseleno)-2-decyne (275).



274 **275**

Tributylphosphine (0.28 mL, 1.12 mmol) and phenylselenocyanate (0.16 mL, 1.12 mmol) were added to a stirred and cooled (0°C) solution of alcohol **274** (1.35 mg, 0.749 mmol) in THF (10 mL). After 1 h the mixture was diluted with ether (20 mL) and water (10 mL). The layers were separated and the aqueous layer was extracted with ether (2 x 10 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 2% ethyl acetate--hexane, gave selenide **275** (220 mg, 93%) as a homogeneous [^1H NMR (400 MHz)] colorless oil: FT-IR (film) 2965, 2930, 2878, 1477, 1437 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.13 (d, *J* = 6.6 Hz, 3 H), 1.49 (q, *J* = 7.6 Hz, 2 H), 1.79 (d, *J* = 2.3 Hz, 3 H), 1.84 (quintet, *J* = 7.5 Hz, 2 H), 1.99-2.20 [m (including t, *J* = 7.4 Hz, (3 H), at δ 2.13), 5 H], 2.29-2.41 (m, 1 H), 2.90 (t, *J* = 7.4 Hz, 2 H), 4.73 (d, *J* = 13.4 Hz, 2 H), 7.17-7.31 (m, 3 H), 7.43-7.54 (m, 2 H); ^{13}C NMR (APT) ($CDCl_3$, 100.6 MHz) δ 3.54 (q'), 21.40 (d'), 25.71 (q'), 27.50 (t'), 28.17 (t'), 33.69 (t'), 35.38 (t'), 36.13 (t'), 74.88 (s'),

83.60 (s'), 109.71 (t'), 126.73 (d'), 129.63 (d'), 130.50 (s'), 132.57 (d'), 148.32 (s'); exact mass, *m*/z calcd for $C_{18}H_{24}Se$ 320.1043, found 320.1037.

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