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RADICAL REACTIONS IN ORGANIC SYNTHESIS

MUTHYALA RAMAIAH
Michigan Applied Science/Technology Laboratories, Pharmaceuticals Research, Dow Chemical Company, Midland, MI 48674, USA

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CONTENTS

1. INTRODUCTION

For many years, free radical species have been known to be intermediates in a large number of chemical reactions and have been credited to produce polymers of industrial importance. Their use for the synthesis of specialty chemicals (homogeneous, low molecular weight molecules) has been limited, mainly due to lack of selectivity.

However, in recent years many well "designed" radical reactions which give high yields of desired products have been discovered. Developments over the last eight years are the primary consideration for this review. It aims to identify methodologies of preparative use and to underscore their interesting applications in organic synthesis. Interest in free radical reactions in organic synthesis has greatly increased and it is now clear that they have become an integral part of synthetic strategies in many laboratories. This review neither makes any pretense of presenting an exhaustive survey of radical reactions nor does it attempt to discuss the mechanistic aspects in any depth. In many instances earlier literature is cited by a review article, when available.[1–5] Due to the rapid arrival of many publications in a relatively short period and also due to the limitation of time and space available for the preparation of this review, it is possible that some important discoveries might have been overlooked unintentionally.

In this review only C-centered radicals are discussed. The majority of free radical reactions which are of interest to the synthetic organic chemist are chain processes and involve three major steps: (1) radical initiation; (2) chain propagation (electron, group or atom transfer; addition, elimination, etc.); and (3) termination.

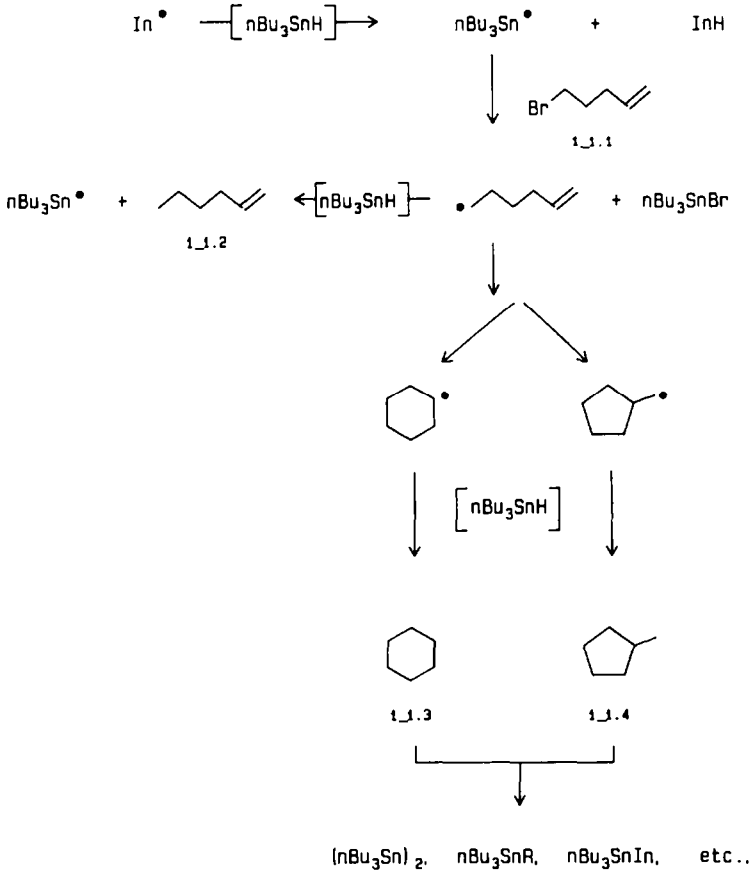
The success of radical reactions for a synthetic application is dependent on the "controlled generation" of the radical itself. This can be accomplished by deriving the radical from a "disciplinary group" (*inter alia*) to deal with otherwise unruly nature of radicals.[72] The disciplinary group

also produces the chain propagating radical. Further, some disciplinary effects can also be produced by the "reagent" which finally transfers an atom (H) or a group in the chain termination step. Undisciplined radicals attack at random and give many products and therefore are not useful for organic synthesis.

A knowledge of the appropriate structure-reactivity relationship is required for the ideal design of preparative procedures. What follows below is a brief overview of useful information; the interested reader may wish to consult the dedicated reviews, monographs and journals for further information.[6-10]

Many radical reactions are initiated directly using thermal or photochemical activation and in some cases an initiator is also employed. Although radical chain processes occur spontaneously at moderate temperatures, it is usually desirable to facilitate the chain propagation either by deliberate addition of an initiator or by other means. Among many, azo bis-isobutyronitrile (AIBN) and related azo compounds are ideal initiators. They are safe, easily handled and have solvent independent decomposition rates. If a reaction must be carried out near or below room temperature, thermal initiators are not practical for the synthetic work and usually, in that case, the method of choice is photo-initiation or redox initiation.

The rate of chain propagation is not very sensitive to the initiator concentration. The product composition depends upon the competition between the various steps as described for a prototype, 5-hexenyl bromide **1–1.1** with tributyltin hydride (TBTH) (Scheme 1–1). If the methylcyclopentane **1–1.4** or cyclohexane **1–1.3** for example, is the desired product, the stannane concentration must be low. This can be accomplished either by working at high dilution or by slow addition of TBTH during the reaction. However, if the desired product is the 1-hexene, **1–1.2**, then the stannane concentration must be very high. Therefore, in complex systems, involving several chain propagation steps, competative reactions such as shown in Scheme 1–1 are common but can often be shifted to a desired direction by proper design of experimental conditions.



SCHEME 1_1

Since the propagation steps of radical reactions are fast processes (with low activation energies), they can usually be run successfully over a wide range of temperatures, provided that the radical initiation is successfully accomplished.

The radical centers are relatively non-polar. Therefore, the rate of reactions is nearly independent of solvent effects. As a result, radical reactions can be conducted in a variety of solvents, although customarily non-hydroxylic solvents are chosen. This may be due mainly to the ready solubility of organic compounds in these solvents.

An understanding of the reactivities of radicals is also important. Radical forming reactions yielding resonance stabilized radicals are faster than those giving radicals lacking such stabilization. Conversely, radicals which are themselves resonance stabilized react more slowly with the same substrates than those which are not. The radicals with electron withdrawing groups react preferentially with electron rich substrates and vice versa. Therefore, radicals can be thought of as electron acceptors or donors, or as having electrophilic or nucleophilic properties.

Radical displacement reactions (transfer of H or halogen) usually show little sensitivity to steric effects. In radical displacement reactions, the intermediate radical is usually in a conformational equilibrium. If it is prochiral, then it may show a preference for the reaction on its less hindered face. Allylic radicals, since the odd electron is delocalized, can react at either end and generally prefer to react at the least-hindered end. On the other hand, for radical additions to multiple bonds, steric effects can be very large and important in determining the success of radical reactions.

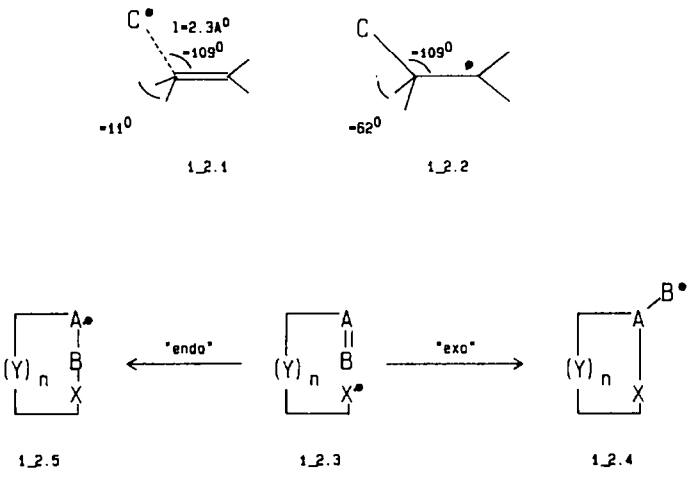
For intermolecular radical reactions, regiospecificity is determined by the reactivity factors (resonance, polarity, or steric). In the case of addition reactions (to double bonds), both energetic and steric factors direct the addition to the least substituted carbon (anti-Markovnikov addition). Steric factors, in particular play an important role with aliphatic olefins. However, aliphatic olefins are generally much less sensitive to stereo-electronic effects compared with their intramolecular counterparts.

For the stereoselectivity of radical addition to an internal double bond, where neither radical nor substrate contains a chiral center, the matter of interest is the relative stereochemistry at the two carbons of the double bond. *cis* and *trans*-Olefins usually give a mixture of *threo*- and *erythro*-products, often in near equal proportion. The regiospecificity in radical reactions can be greatly enhanced by making them intramolecular since these reactions are controlled by molecular geometry.

Intramolecular cyclizations involving the 5-hexenyl radical systems have proved to be quite useful and have been studied in detail. The reaction of 1-bromohex-5-ene, **1–1.1** with TBTH proceeds in a highly regioselective fashion to afford mainly the product **1–1.4**, (of 1,5-ring closure) indicating the formation of the less stable of the two possible products, namely **1–1.4** and **1–1.3**. This is contrary to the prediction based on the thermochemical data and kinetic parameters. This odd behavior of the hex-5-enyl radical and of a variety of related species potentially capable of undergoing ring closures is explained on the basis of the assumption that "the strain engendered in accommodating the mandatory disposition of reactive centers within the transition complexes for 1,6-ring closure outweighs those steric and thermochemical factors expected to favour the formation of more stable possible product".

The transition state for the intra-molecular homolytic addition incorporates the three participating atoms, **1–2.1** (Scheme 1–2) at the vertices of an obtuse triangle, orthogonal to the nodal plane of the π system. Also to be noted is that the structure of the transition state complex is similar to the product **1–2.2**. This is analogous to the Baldwin rules[11] which are derived from the vector approach analysis. Based on this hypothesis, some generalizations have been made regarding the regio- and stereochemistry of radical cyclizations. For intramolecular addition of alkenyl, alkynyl radicals and related species, under kinetic control, ring closure occurs preferencially in an *exo*-mode. *Exo* ring closures of **1–2.3** to **1–2.4** is kinetically favoured over the **1–2.5** *endo* process where Y is a chain of up to 5 atoms, ($n < = 5$), A=B is any double or triple bond and X represents a C, O, N radical center.

The degree of preference for the *exo*-ring closure is dependent upon the length of the carbon chain Y_n. When the chain is short ($n = 1$ or 2), the transition complex for the *endo* process would be highly strained, but when the chain is long and flexible, the difference in strain energy between the transition complexes leading to **1–2.4** and **1–2.5** would be small. It must be noted that for homolytic additions, any structural features which effect the ability of an unsaturated bond and of



SCHEME 1_2

a radical to accommodate the intimate transition complex would also affect the rate and regioselectivity of ring closure. For example, substituents (at the radical site, on the chain and on the multiple bond) affect the homolytic intramolecular addition reactions.

To predict the stereochemical outcome of substituents on the 5-hexenyl systems, some guidelines have been proposed.[12] In *exo* ring closure reactions of hexenyl and related radical systems, a monosubstituent at C-1 to C-4 gives rise to a mixture of *cis* and *trans* disubstituted cyclic products. The general rule is that 1,5-ring closures of 1- or 3-substituted systems afford mainly *cis*-disubstituted products, whereas 2 or 4-substituted systems give mainly *trans* products.[151]

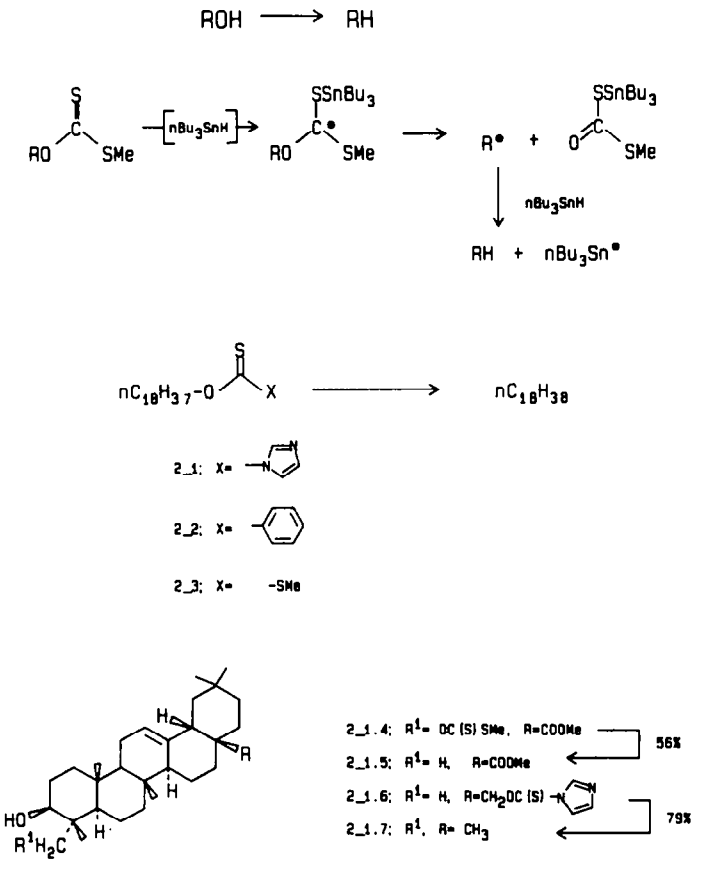
2. FUNCTIONAL GROUP TRANSFORMATION

Radical deoxygenation of alcohols has recently been reviewed.[16] While the deoxygenation of secondary alcohols[318] using the Barton deoxygenation method (Scheme 2–1, the reaction of dithiocarbonate esters with TBTH)[13] occurs at or below the reflux temperature of toluene, the deoxygenation of primary alcohols is usually a problem. However, derivatives of primary alcohols of the type **2–1.1** to **2–1.3** can be deoxygenated at higher temperatures[14] (Scheme 2–1). The preferred experimental conditions for this modified method involves slow addition of the stannane (TBTH) to the thiocarbonyl derivative at reflux temperatures of xylene or *p*-cymene. With thiocarbonyl imidazolides or thionobenzoate esters of hindered and non-hindered primary alcohols, reduction occurs at lower temperatures than with the corresponding xanthate esters of secondary alcohols; e.g. **2–1.4** and **2–1.6** are converted into **2–1.5** and **2–1.7**, respectively, in good yields. Selective deoxygenation of a polyfunctional molecule is therefore possible either by controlling the temperature of the stannane reduction or by preferential formation of the required thiocarbonyl derivative.

An alternate method which complements the Barton deoxygenation method for primary and secondary alcohols is the reduction of toluene sulfonate esters with TBTH in the presence of sodium iodide in refluxing DME (Scheme 2–2).[97] With this method, cholesterol tosylate gives deoxycholesterol in 64% yield. The monotosylate of a 1,2-diol, e.g. **2–2.3** has been converted into a mono alcohol **2–2.4** in 56% yield along with the elimination product **2–2.5** as a by-product.

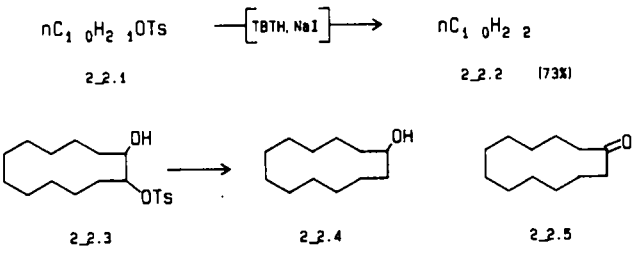
Chloroformates of primary and secondary alcohols produced by the reaction of the alcohol with phosgene are reduced to the corresponding alkanes by the reaction of tri-*n*-propylsilane in the presence of *t*-butylhydroperoxide.[15] However, this method is not practical on any reasonable scale due to the requirement for a large excess of *t*-butylhydroperoxide.

Methods used to effect radical deoxygenation[16] of primary and secondary alcohols are less suitable for tertiary alcohols, because the type of the carbonyl derivative used, e.g. xanthates, are thermally unstable and eliminate to an olefin or rearrange to a thiomethyl carbonyl thioether.

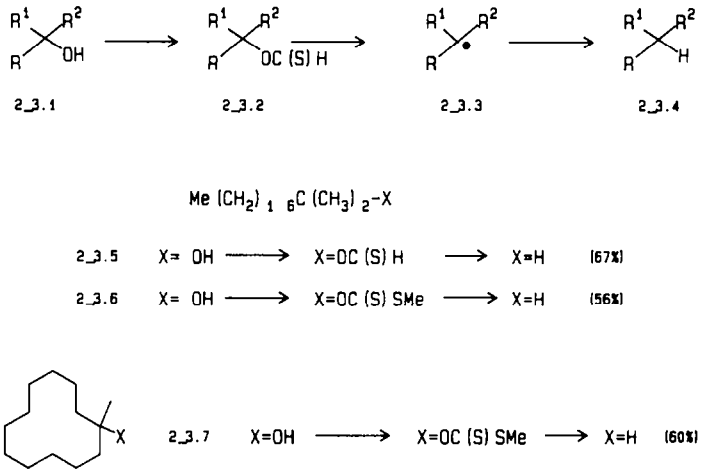


SCHEME 2_1

Deoxygenation of tertiary alcohols is usually accomplished in two operations, namely elimination and hydrogenation. This two-step operation, which invariably involves a neighboring β-carbon, is less desirable if the configuration of the β-C needs to be retained. In some cases, tertiary alcohols have been deoxygenated[17] via their thioformyl derivatives (Scheme 2–3). The preparation of thioformyl derivatives, i.e. **2–3.2** involves two steps. The addition of tertiary alcohols to isocyanides, preferably aryl isocyanides having electron donating groups at *para*-position, is followed by reaction with hydrogen sulfide to give thioformyl esters. Thioformates can be reductively cleaved to hydrocarbons with TBTH under reflux in benzene. Some examples are shown in Scheme 2–3. Derivatives, such as thiomethylcarbonates (ROCOSMe), thiomethylethers ($ROCH_2SMe$) and thiophosphonates ($ROPSPh_2$), have been investigated as alternatives to thioformate esters, but only the thiocarbonates in cases such as **2–3.5** to **2–3.7** give hydrocarbons in about 50% yield along with corresponding olefins.



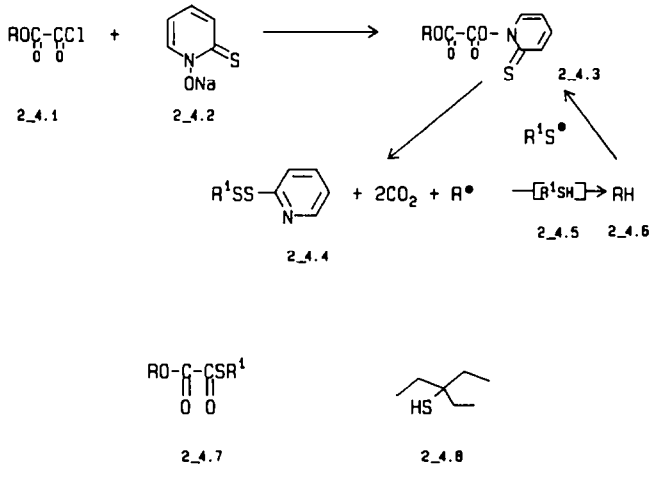
SCHEME 2_2



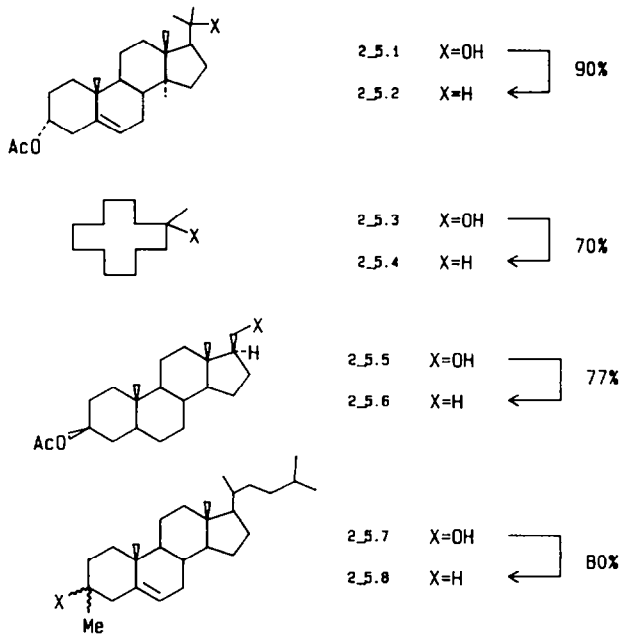
SCHEME 2_3

An improved procedure[18] for the deoxygenation of tertiary alcohols which takes advantage of the radical chemistry of thiohydroxamic-*O*-esters (*inter alia*) is shown in Scheme 2–4. Experimentally, the half oxalic acid chloride of tertiary alcohol, e.g. **2–4.1**, is added in 1 h at 80°C to a benzene solution of the reagent **2–4.2** containing 4-*N*,*N*-dimethylaminopyridine (trace) and an excess of *t*-butylthiol. This one pot procedure gives alkanes in good yields as shown in the Scheme 2–5. The principal byproduct of this method is **2–4.7** (R^1 = *t*-Bu) which is the result of the competitive nucleophilic attack of *t*-butylthiol on the half oxalyl derivative (i.e. starting material). This side reaction can be eliminated by using a bulky thiol such as **2–4.8**. Acid sensitive alcohols are best dehydroxylated by first converting them into trimethylsilyl derivatives.

The tertiary OH groups (protected as benzoyl esters) of acetyl branched-chain sugars can be converted into corresponding deoxy branched sugars[19] (Scheme 2–6). For example, refluxing **2–6.1** and **2–6.3** in toluene with TBTH and a catalytic amount of AIBN at 140°C gives **2–6.2** and **2–6.4**, respectively, in about 80% yield. It should be noted that the reaction takes a stereoselective course with inversion of configuration at the branching point. However, the reduction of the benzoates **2–6.5** and **2–6.6** under identical conditions gives a mixture of the isomeric sugars **2–6.7** and **2–6.8** (4 : 1 ratio) indicating a common radical intermediate. Reductive removal of branched sugar benzoates of this type probably is a special case in deoxygenation methodologies, as simple benzoates do not undergo similar reaction with TBTH.

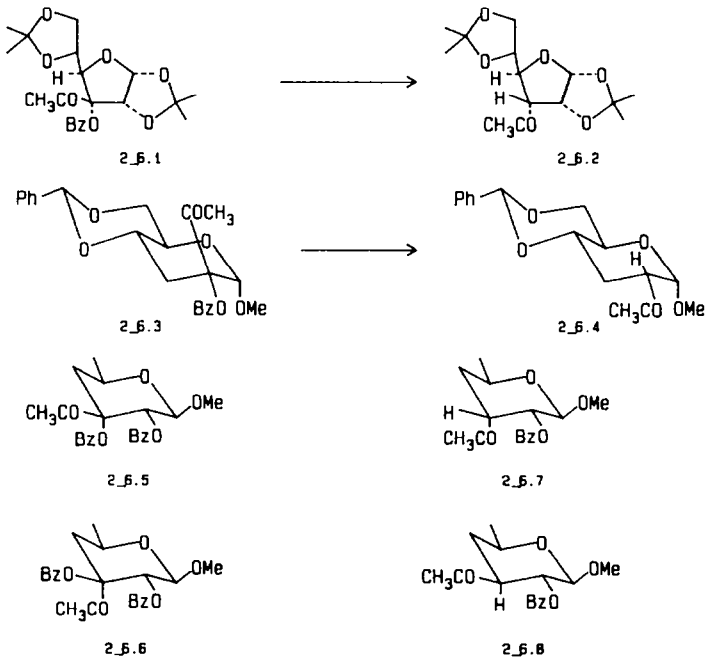


SCHEME 2_4

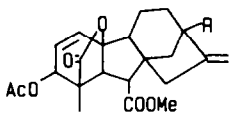


SCHEME 2_5

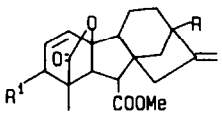
In certain cases, effective preparation of radical precursors is as important as the controlled generation of radicals itself. Usually, starting materials needed for the deoxygenation of tertiary and secondary alcohols, thionocarbonates, for example are prepared under mild but basic conditions. However, it is difficult to prepare such thiocarbonate or thiobenzoate derivatives of certain alcohols, for example of GA_3 methyl ester 3-acetate, **2–7.1**, under usual conditions. Methyl oxalyl esters of secondary and tertiary alcohols can be prepared, however, under mild conditions using oxalyl chloride as coupling reagent in a mixture of dichloromethane and methanol at room temperature.



SCHEME 2_6



2_7.1 R=OH
2_7.2 R=OC (O) C (O) OMe
2_7.3 R=H



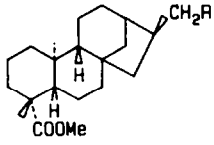
2_7.4 R=OH, R^1=OAc
2_7.5 R=H, R^1=OAc
2_7.6 R=H, R^1=OC (O) C (O) OMe
2_7.7 R=H, R^1=H
2_7.8 R=OAc, R^1=OC (O) C (O) OMe
2_7.9 R=OAc, R^1=H

SCHEME 2_7

These oxalyl esters undergo selective deoxygenation.[20] For example, the methyl oxalyl ester **2–7.2**, prepared from gibberellin A_3 (GA_3) with TBTH and AIBN in refluxing toluene, gives GA_7-methyl ester 3-acetate **2–7.3** in 65% overall yield (4 steps). Gibberellin A_1 methyl ester 3-acetate **2–7.4** has been converted into GA_4 methylester 3-acetate **2–7.5** via an oxalyl ester procedure. Similarly, secondary oxalates **2–7.6** and **2–7.8** give GA_9 methylesters **2–7.7** and **2–7.9**, respectively, along with their starting alcohols when refluxed in toluene in the presence of TBTH and AIBN. However, under similar conditions primary oxalate **2–8.1** does not give the reduction product but gives starting alcohol **2–8.2**. Mechanistic studies indicate[20] that this deoxygenation procedure works best when a stable radical is produced from radical precursors. The yields increase as the stability of the generated radical increases.

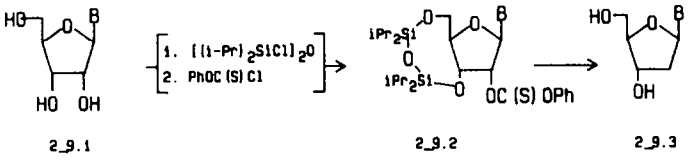
2′ or 3′-Deoxynucleosides are important biologically active compounds. Homolytic deoxygenation methods for the deoxygenation of nucleosides via thionoester derivatives by the tin radical mediated photochemical or thermal process have not been promising. This is due to the lack of selective preparative methods for appropriate precursors, strong absorption of light by substrates in the photochemical process, and competing side reactions. Since phenoxythiocarbonyl derivatives are relatively easy to prepare[21] (using *O*-phenyl chlorothiocarbonate and 4-*N*,*N*-dimethylaminopyridine in acetonitrile), they have been found to be useful precursors for deoxygenation in the nucleoside series. Under thermal reaction conditions using 1.5 equiv of TBTH and 0.2 equiv of AIBN, the deoxygenation of nucleosides gives good yields[22] of products as shown in the Scheme 2–9. The yields for this process are comparable with the deoxygenation procedures using xanthates and thiocarbonyl imidazoles. The use of a phenylthiocarbonyl derivative is a general reaction and applicable to other secondary alcohols. Interestingly, efforts to reductively cleave the phenoxythiocarbonyl group in **2–10.2**, even with excess TBTH in toluene containing AIBN, are only partly successful. However, when N_1-nitrogen is protected with a trimethylsilyl group (using hexamethyldisilazane and ammonium sulfate under reflux for 1 h), reduction occurs smoothly at 75°C in 4 h and gives **2–10.3** in 53% yield after desilylation and purification.[23] Cholesterol **2–10.4** and its 5,6-α epoxide, **2–10.6**, are also converted into the corresponding 3-deoxy products in good yields. Although the phenoxy thiocarbonyl derivatives of alcohols are prepared conveniently from phenyl chlorothiocarbonate under usual esterification conditions (pyridine, dichloromethane), 4-*N*,*N*-dimethylaminopyridine is needed as a catalyst for the esterification of hindered alcohols.

Deoxygenation of secondary alcohols, particularly for sugar alcohols, using Barton's method[16,24] works in most cases; this method, however, needs modification for deoxygenation of certain



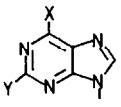
2_8.1 R=OC (O) C (O) OMe
2_8.2 R=OH

SCHEME 2_8

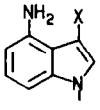


2_9.1 2_9.2 2_9.3

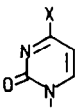
B	Yield (%)
OCH_3	58
A	78
U	68
G	57
T	68
TO	69
TA	65



A; X=NH_2, Y=H
G; X=OH, Y=NH_2

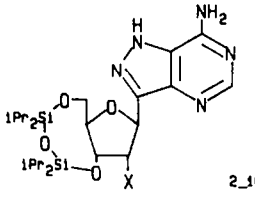


T; X=H
TO; X=CN
TA; X=$CONH_2$

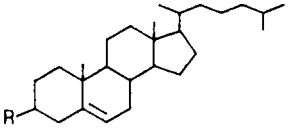


U; X=OH
C; X=NH_2

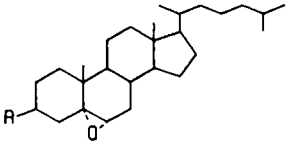
SCHEME 2_9



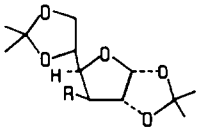
2_10.1 X=OH
2_10.2 X=OC(S)OPh
2_10.3 X=H



2_10.4 R=OH → OC(S)OPh
2_10.5 R=H ← 85%

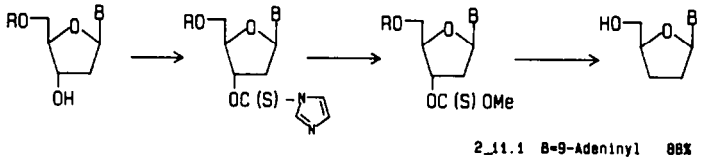


2_10.6 R=OH → OC(S)OPh
2_10.7 R=H ← 78%



2_10.8 R=OH → OC(S)OPh
2_10.9 R=H ← 85%

SCHEME 2_10



2_11.1 B=9-Adeninyl 88%
2_11.2 B=1-Thyminyl 90%
2_11.3 B=9-Guaninyl 85%
2_11.4 B=1-Cytosinyl 39%

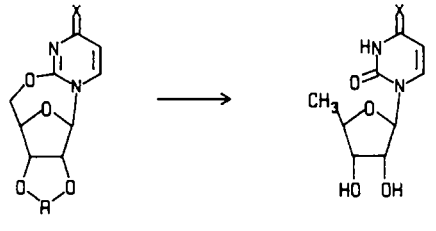
SCHEME 2_11

nucleosides. For example, the use of thiocarbonate rather than dithiocarbonate and *in situ* generation of TBTH from dibutyltinoxide and polymethylhydrosiloxane have been recommended. Using these modifications, preparation of 2′,3′-dideoxynucleosides have been accomplished successfully starting from suitably protected 5′-hydroxy 2′-deoxynucleosides[25] as shown in the Scheme 2–11. The advantage of these modification is that the intermediate thionocarbonates can be purified by crystallization and also this method produces tin radicals very cleanly. Starting thionocarbonates are prepared from the corresponding imidazolides and methanol at 50°C for 2 h. The acetate protecting group on the 5′-hydroxyl group works well with nucleosidic bases such as thymine, adenine and guanine. For the cytosine case, the primary amine of the heterocycle as well as the primary hydroxyl group of the sugar moiety needs to be protected with a pivaloyl group.

The cyclonucleosides such as **2–12.1** and **2–12.2**, in which the 5′-OH group is protected intramolecularly as a phosphate ester with pyrimidine, react with 2 equiv of TBTH in the presence of AIBN in THF under reflux for 6 h to give **2–12.3** and **2–12.4** in 84 and 71% yield, respectively.[26] Under similar reaction conditions isopropylidene derivative **2–12.5** gives **2–12.6** only in 31% yield whereas O^2-methyluridine, 5′-*O*-benzoyl O^2,2′-cyclouridine and O^2,2′-cyclocytidine hydrochloride are not reduced at all. This indicates that the phosphoranediyl group activates the O^2,5′-anhydro bond of **2–12.1** or **2–12.2** as compared with the isopropylidine group. Contrary to the pyrimidine nucleosides, 3′,5′-*O*-(triphenylphosoramidinyl) adenosine or 2′,3′-*O*-(triphenylphosphoramidinyl)-N^3,5′-cycloguanosides do not react with TBTH.

It is interesting to note that deoxygenation of a mixture of the cyclic acetal **2–13.1** with TBTH gives a 2:8 mixture of the *cis* and *trans* products **2–13.2** in 90% yield.[27] The product ratio corresponds to the initial xanthate isomer ratio indicating that the β-oxygen[28] has no effect on H atom abstraction.

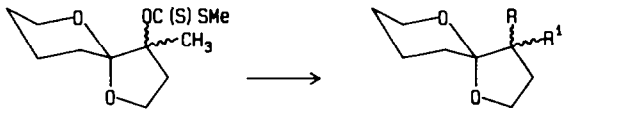
A comment on the scope and limitations of a radical deoxygenation of alcohols should be made.[29–31] Generally the sequence $OH \rightarrow OCS_2Me \rightarrow H$, or a similar sequence involving other radical precursors, proceeds well, except when the OH function is relatively hindered. In that case, some difficulty is encountered for the preparation of the dithiocarbonate and for the subsequent reduction step as well. When no great facial bias is exhibited, reduction products are generally isomeric mixtures.



2_12.1 R=PPh_3, X=O
2_12.2 R=PPh_3, X=NBz
2_12.5 R=$C(Me)_2$, X=O

2_12.3 X=O 84%
2_12.4 X=NBz 71%
2_12.6 X=O 31%

SCHEME 2_12



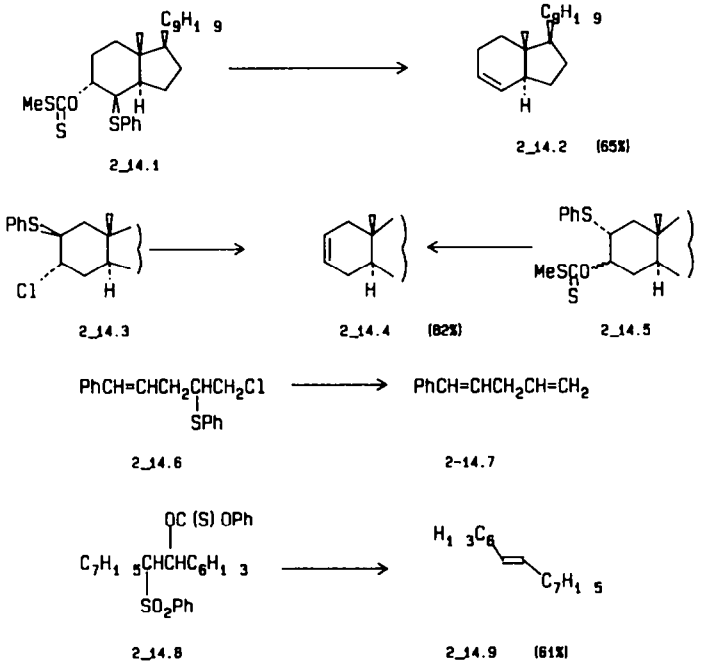
2_13.1 2_13.2 R=H, R^1=CH_3

SCHEME 2_13

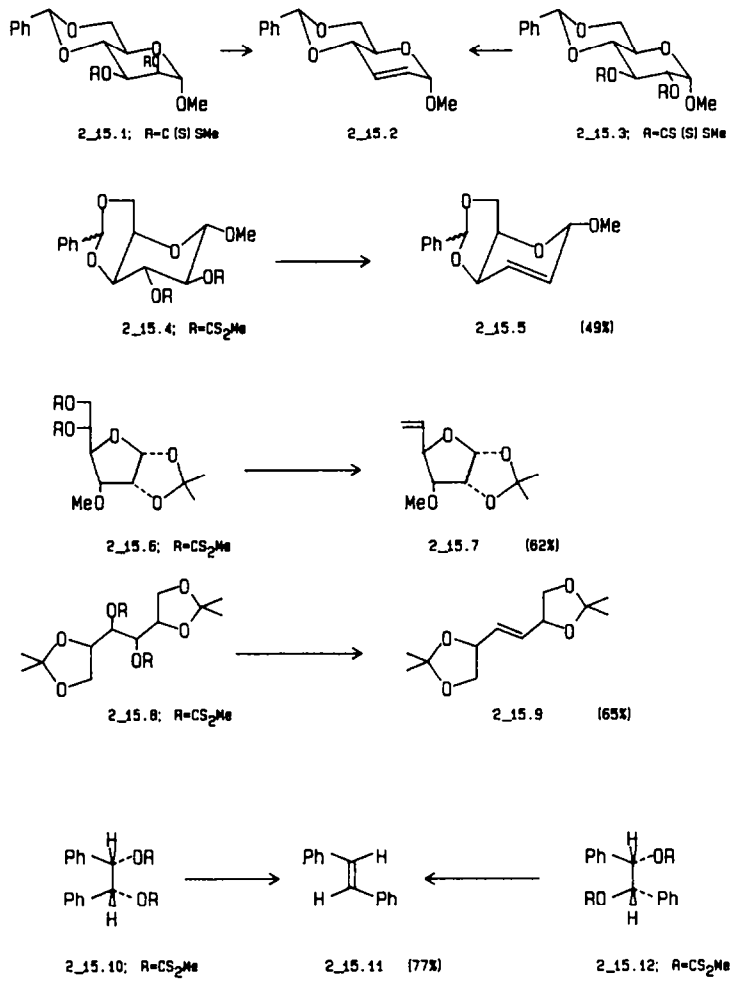
Although the radical deoxygenation of the hydroxy derivatives, e.g. thionocarbonates, with TBTH is a useful synthetic method,[16] the substrates that have a good leaving radical group at the α position undergo 1,2-elimination to provide olefins rather than simple deoxygenation.[32] The reaction of TBTH with the β-thionocarbonate of a phenylsulfide, β-chloro sulfide or sulphone, and bis-thionocarbonate give olefins in good yields (Scheme 2–14). Unlike ionic reactions, this radical reaction is sterically undemanding, a feature which is frequently advantageous with cyclic compounds. For example, the diastereomeric dithiocarbonate derivative **2–14.5** and the diaxial chlorophenylsulfide derivative **2–14.3** give the same product **2–14.4** in 82% yield. This reaction also works well with acyclic compounds such as **2–14.6** to produce a terminal olefin **2–14.7**. Internal olefins such as **2–14.9** are produced exclusively with the *trans* geometry. Since several methods are available to produce α-halo or -hydroxyphenyl sulfides or -sulfones, olefin formation by this method should be useful in preparative chemistry.

Carbohydrates are useful chirons.[33,34] Utilization of vicinal OH groups should therefore allow ready functionalization of carbohydrates and hence enhance their utility in synthesis to a greater extent. Vicinal diols have been converted into alkenes via the radical fragmentation of bis xanthates.[35,36] For example, refluxing xanthates **2–15.1** or **2–15.3**, **2–15.4** and **2–15.6** in toluene with excess TBTH give corresponding olefines **2–15.2**, **2–15.5** and **2–15.7**, respectively, in acceptable yields after chromatography. The mannitol bis xanthate **2–15.8**, and (*meso*) and (±) hydrobenzoin bis-xanthates **2–15.10** and **2–15.12** give only (*E*)-olefins **2–15.9** and **2–15.11**, respectively. This bis xanthate method provides stereospecific alkenes at low temperature under mild and neutral conditions in good yields.

Similar to vicinal dihalides, bis xanthates or halosulfides, vicinally functionalized halo selenides also give olefins;[37] e.g. **2–16.1** when treated with triphenyltin hydride gives **2–16.2**.



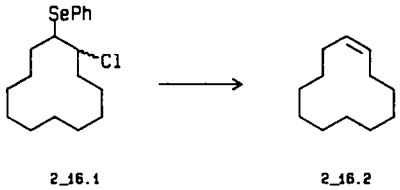
SCHEME 2_14



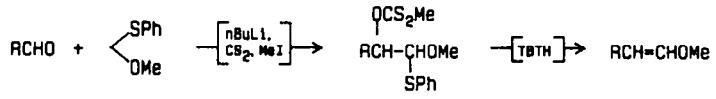
SCHEME 2_15

Vinyl ethers are important synthetic intermediates and/or useful reagents. A method[98] for the preparation of vinyl ethers with one C elongation from aldehyde is shown in Scheme 2–17. The required phenyl dithiocarbonates **2–17.3** are prepared by the addition of methoxymethyl phenylsulfide to the aldehyde, followed by quenching with carbon disulfide and methyl iodide. Reductive elimination is accomplished with TBTH in refluxing benzene. Although the yields of olefins are in the range of 50–82%, the stereochemistry of the reductive elimination products in all cases is a mixture of (*Z*)- and (*E*)-isomers. This is in contrast to the results shown in the Schemes 2–14 and 2–15. The non-stereospecificity of this radical elimination is due to the nature of the leaving radical and the functional groups attached to the vicinal carbons.[38]

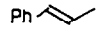
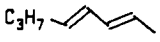
The concept of radical induced preparation of olefins from a vicinal diol has been extended to the preparation of allylic alcohols[39] by generating a radical α to the epoxide function as shown in Scheme 2–18 (**2–18.1** → **2–18.4**). This sequence constitutes a useful alternative to the classical Wharton reaction.[40]



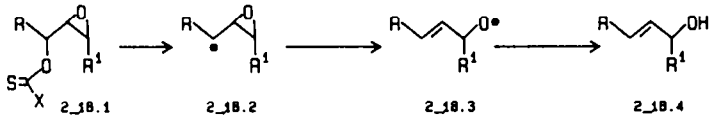
SCHEME 2_16



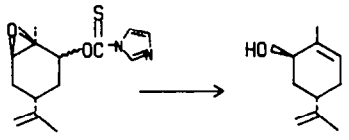
2_17.1 2_17.2 2_17.3 2_17.4

R	2_17.4 (%)	(Z: E)
$PhCH_2$-	73	42: 58
C_8H_{11}-	73	40: 60
$C_{10}H_{21}$-	74	44: 56
Ph-	82	33: 67
	82	25: 75
	50	27: 73

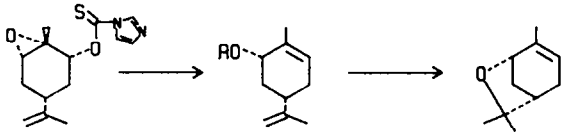
SCHEME 2_17



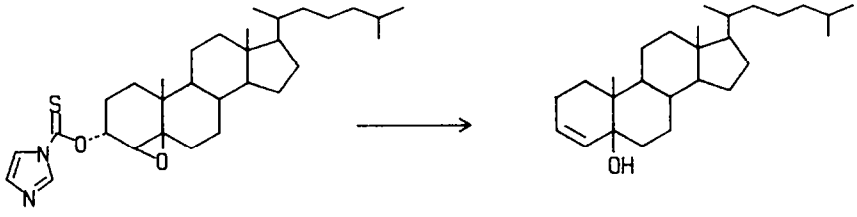
2_18.1 2_18.2 2_18.3 2_18.4



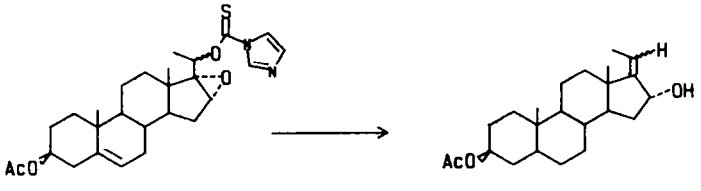
2_18.5 2_18.6



2_18.7 2_18.8, R= ● 2_18.9, R=H 2_18.10



2_18.11 2_18.12



2_18.13 2_18.14

SCHEME 2_18

The stereoisomeric mixture of epoxy-alcohols prepared, for example, from (−)-carvone has been transformed into the thiocarbonyl imidazolide derivative **2–18.5** by standard methods. Addition of TBTH to a refluxing benzene solution of **2–18.5** led to the formation of optically pure (+)-*trans* carveol **2–18.6** in 65% yields. However, under identical conditions (−)-*cis* carveol derivative **2–18.7**, gives carveol **2–18.9** in only 15% yield along with pinol **2–18.10**. The pinol is derived via the addition of alkoxyl radical **2–18.8** to the side chain double bond. The formation of **2–18.10** is minimized and, at the same time, formation of carveol **2–18.9** is maximized to the extent of 47% yield by the addition of thiocarbonylimidazolide **2–18.7** to a ten-fold excess of TBTH (inverse addition).

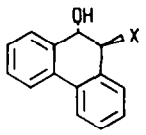
This inverse addition procedure appears to have broad applicability (*inter alia*). Under these conditions, the cholestanol derivative **2–18.11** led to effective quenching of the alkoxyl radical to give **2–18.12** in 55% yield along with a small amount of secondary ring expansion product (*inter alia*). It should be noted that in these rearrangements there is no stereoelectronic requirement for alkoxyl-oxygen cleavage of the epoxide ring. This method is not only an alternative to the Wharton reaction,[40] but has advantages in some cases. For example, reduction of the epimeric alcohol derivatives **2–18.13** under inverse addition conditions gives α-allylic alcohols, **2–18.14** in 60% yield, while the Wharton rearrangement is not successful. It should be noted that extention of the utility of this approach to carbohydrates has not been successful.

The conversion of carboxylic acids to the corresponding nor-hydrocarbons is relatively cumbersome and is usually carried out by pyrolysis of the corresponding peresters in a hydrogen atom donor solvent at elevated temperatures. One of the classical examples of this methodology is the cubane synthesis.[41] Such methodology is not normally useful for functionalized molecules. The decarboxylation of organic acids, with or without concomitant replacement by a functional group, is a useful synthetic transformation.[24,42,43] Esters derived from phenanthrene derivatives **2–19.1**, **2–19.2** or similar compounds which eliminate an aromatic ring or an olefin fragment (i.e. stable fragment) have been used to prepare the corresponding nor-hydrocarbons (see olefin formation via β-elimination) as shown in Scheme 2–19. Reduction of esters **2–19.4** with TBTH/AIBN in refluxing toluene or benzene give hydrocarbon **2–19.6** via carboxyl radical **2–19.5**. Acceptable yields of alkanes are obtained from primary (**2–19.12**), secondary (**2–19.8**, **2–19.10**) and tertiary (**2–19.14**) acids. However, variable yields in the ester forming step are a shortcoming of this method. Also, higher reaction temperatures are required for the decarboxylation of aromatic and α,β-unsaturated acid derivatives, rendering this method less useful for preparatory purposes.

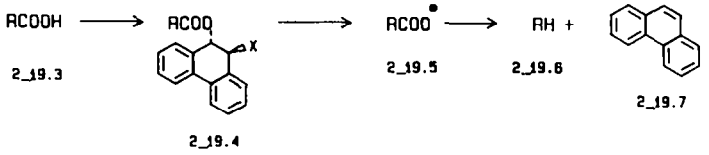
Carboxylic acid esters **2–20.2** derived from thiohydroxamic acids such as *N*-hydroxypyridine-2-thione **2–20.5** have been decarboxylated to hydrocarbons[43] under radical reaction conditions using tin hydride reagents (TBTH, benzene, reflux) (Scheme 2–20). This is a general reaction and gives high overall (2 steps) yields as shown by examples in Scheme 2–21. This methodology works efficiently with primary, secondary and tertiary acids and is compatible with esters, ketones and olefinic functionalities. It is interesting to note that with primary acids, the reactions are faster and give higher yields in benzene at 80°C than in toluene at 110°C. With this commercially available reagent, **2–20.5**, esters are prepared using dicyclohexyl carbodiimide or 4-*N*,*N*-dimethylaminopyridine, or from the corresponding acid chloride and Na salt of **2–20.5**. In an analogous manner, aminyl radicals have been generated.[44]

In the absence of a hydride reagent, i.e. no TBTH, the above reaction takes the course of a decarboxylative rearrangement[43] for the formation of noralkyl pyridyl sulfides via a radical chain reaction (Scheme 2–22). This should be a synthetically useful rearrangement since the products can be used as starting materials for a variety of transformations such as the formation of lithioanions and olefins. Although the decarboxylative rearrangement to pyridyl sulfides proceeds purely thermally in the dark, the reaction is significantly accelerated by light.

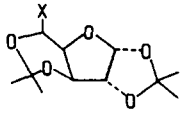
An alternate procedure for a decarboxylative reaction which utilizes non-nucleophilic mercaptanes, such as *t*-butyl mercaptane, as the hydrogen atom donor has been developed (Scheme 2–20). This reaction proceeds as shown in Scheme 2–23.[43] There is no need to isolate ester **2–20.2**; the experiment can be conveniently performed by dropwise addition of the acid chloride to a dry refluxing benzene solution of the *t*-butylthiol containing 4-*N*,*N*-dimethylaminopyridine and the salt of thiohydroxamic acid **2–20.5**. The yields are high. Apart from an unacceptable odor of mercaptans, this procedure effectively replaces tin hydride which is not only expensive, but also produces difficult to remove tin impurities with the product.



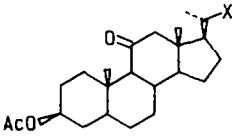
2_19.1. X=Cl
2_19.2. X=SPh



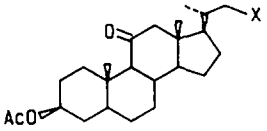
2_19.3 2_19.4 2_19.5 2_19.6 2_19.7



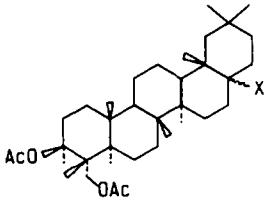
2_19.8 X=COOH
2_19.9 X=H
53%



2_19.10 X=COOH
2_19.11 X=H
88%

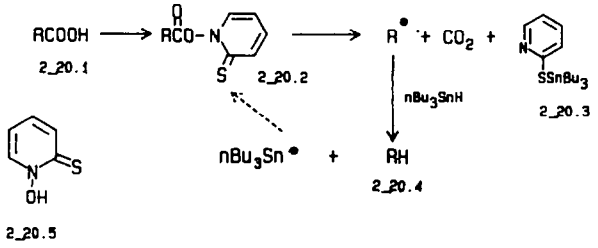


2_19.12 $X=CH_2COOH$
2_19.13 $X=CH_3$
72%



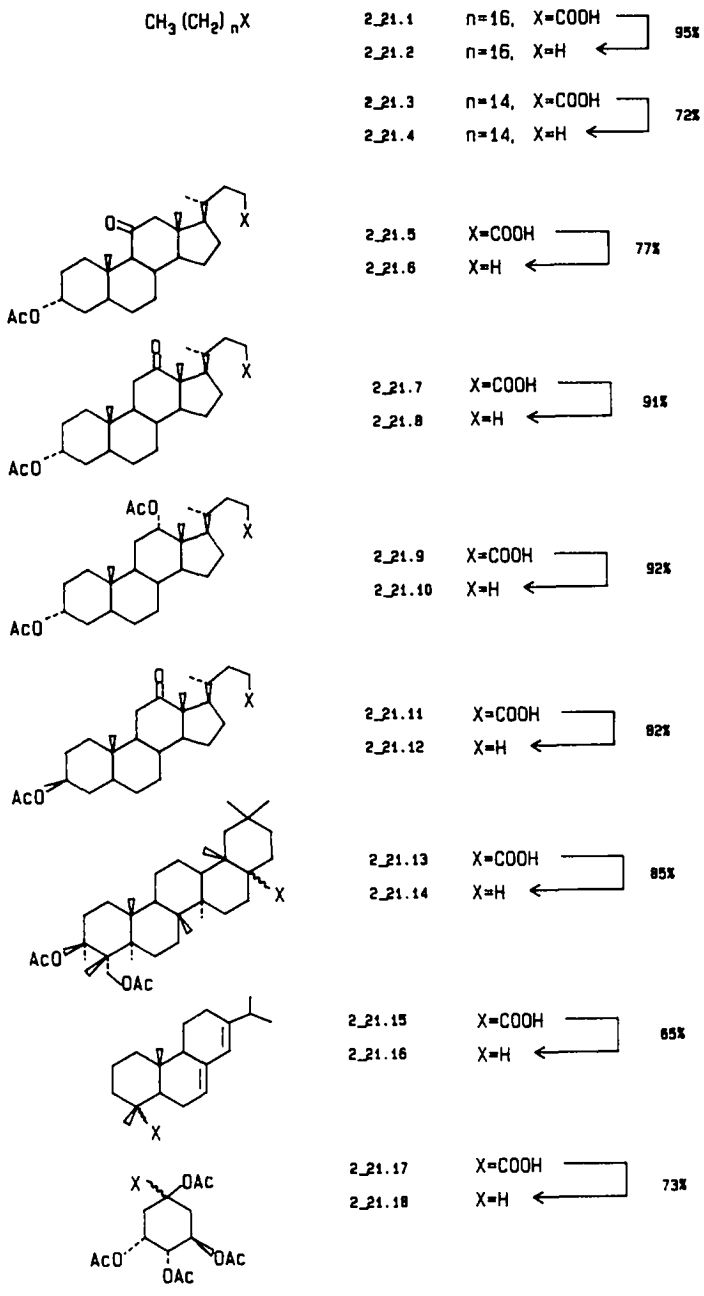
2_19.14 X=COOH
2_19.15 X=H

SCHEME 2_19



2_20.1 2_20.2 2_20.3 2_20.4 2_20.5

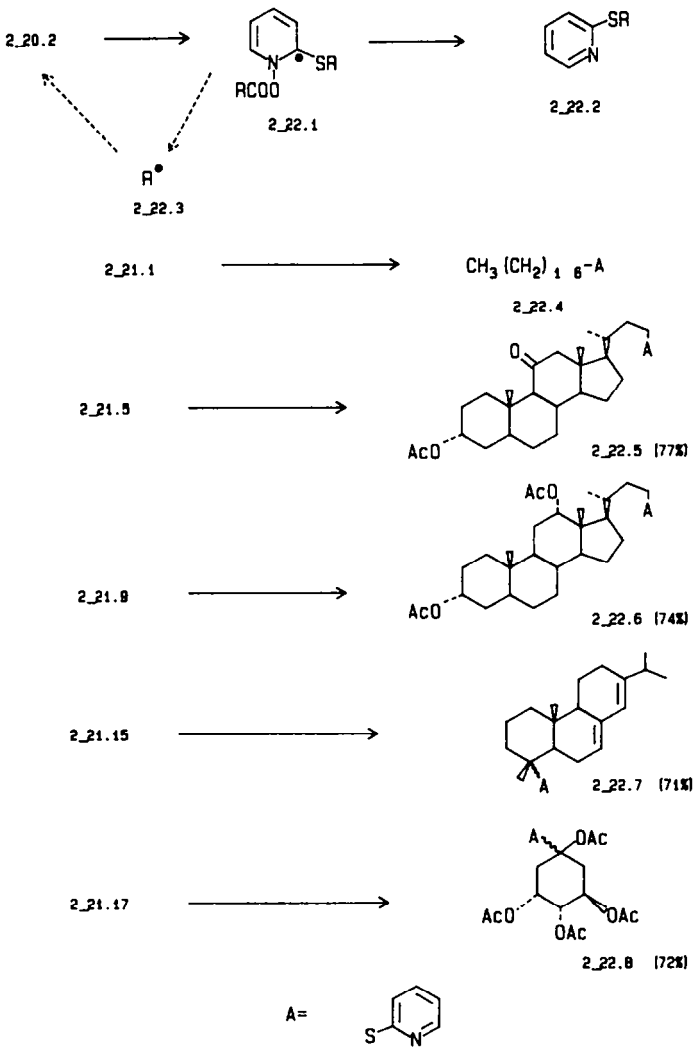
SCHEME 2_20



SCHEME 2_21

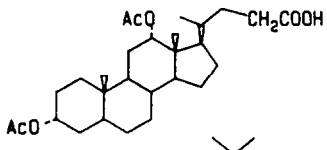
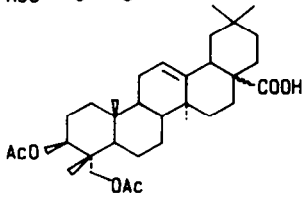
The synthesis of hydroperoxides, especially primary and secondary hydroperoxides, is generally not an easy reaction. The conversion of carboxylic acids into nor-hydroperoxides or nor-alcohols by conventional methods involves several steps. One approach is by capturing the carbon radicals, formed in the reduction of organomercury compounds with SBH, by molecular oxygen.[45] Alternately, carbon radicals generated from the esters of *N*-hydroxypyridine-2-thione **2–20.2** under thermal or photochemical conditions have been captured by oxygen in the presence of *t*-butylthiol to give nor-hydroperoxides in good yields[46] as shown in Scheme 2–24. For the hydroperoxide formation, oxygen saturated toluene is a preferred solvent. Some examples are shown in Table 1.

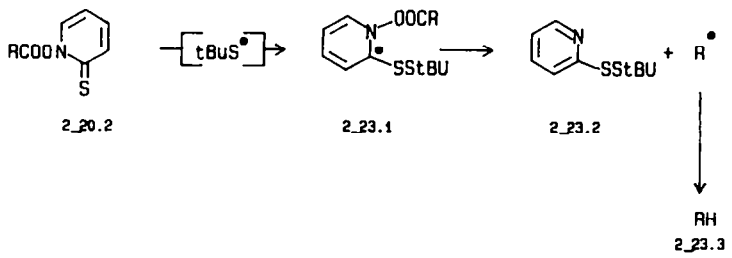
It should be noted that $R^{\bullet}$ has the opportunity for reacting with *t*-butylthiol (Scheme 2–24) before it is reacted with oxygen. Because of the rate difference in their reactivities, the reaction takes



SCHEME 2_22

Table 1. Preparation of nor-hydroperoxides and nor-alcohols from carboxylic acids

Acid	Nor-Hydro-peroxide (%)	Nor-Alcohol (%)
$CH_3(CH_2)_{13}CH_2COOH$	89	75
$(PhCH_2)_2CHCOOH$	85	82
	80	69
	-	97



2_20.2 2_23.1 2_23.2 2_23.3

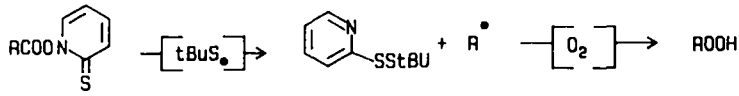
SCHEME 2_23

place in the sequence shown. The hydroperoxides with or without isolation have been reduced with dimethylsulfide or trimethoxyphosphene to give good yields of nor-alcohols (Table 1). Addition of *p*-toluenesulphonyl chloride in pyridine to nor-hydroperoxide at room temperature provides corresponding aldehydes or ketones.

As mentioned above (see Scheme 2–24), nor-alcohols are obtained via the reduction of hydroperoxides which are derived by the interception of carbon radicals. Organoantimony compounds are known to be air sensitive and this property has been utilized for the preparation[47] of nor-alcohols as shown in Scheme 2–25 (**2–25.1** → **2–25.5**). The reaction of esters **2–25.1** derived from a variety of primary, secondary or tertiary carboxylic acids with tris(phenylthio)antimony, **2–25.2**, at room temperature in an open flask affords excellent yields of nor-alcohols. As shown in Scheme 2–25 the radical chain reaction is initiated by the slow decomposition of **2–25.3** in the presence of oxygen. The *in situ* generated thiophenoxide radical serves as a good chain propagator. The antimony compound **2–25.2** can be readily prepared. By-products usually result along with low yield when the reaction is conducted at higher temperature (chlorobenzene, 90°C) in inert atmosphere and with an aqueous work-up. It should be noted that $Sb(SPh)_3$ must be free from thiophenol; otherwise the hydrocarbon (RH) is formed by the expected hydrogen atom transfer. The organometallic species **2–25.3** can be intercepted with other species such as nitrogen tetroxide, although in low yields. Solvents such as chlorobenzene, ether and dichloromethane are suitable.

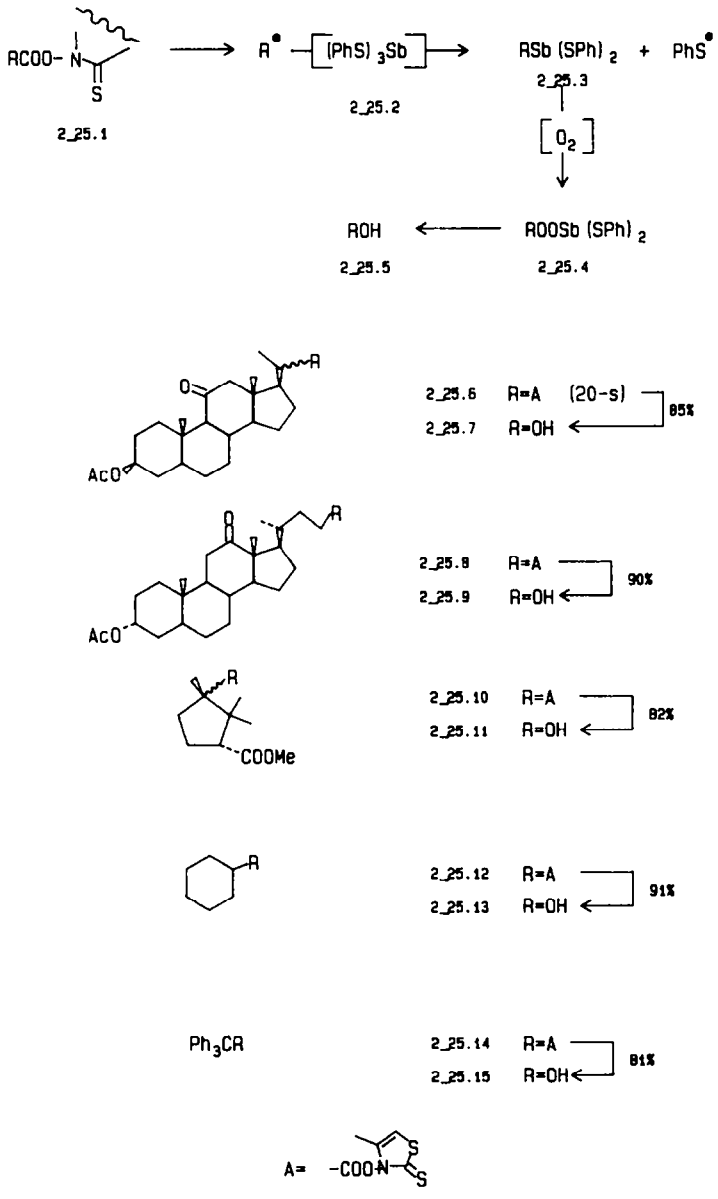
The Hunsdiecker reaction is a useful method for the preparation of nor-alkyl halides from carboxylic acid salts. However, it requires heavy metal (Ag, Tl, Hg, Pd) salts. An alternate process[48] for this reaction involves the decarboxylative halogenation of *N*-hydroxypyridine 3-thione esters **2–20.2** in the presence of trichloromethyl radical, as shown in Scheme 2–26. The experiment can be performed with or without isolation of the intermediate ester **2–20.2**. The addition of the acid chloride to a mixture of CCl_4 or $CBrCl_3$ and a suspension of the sodium salt of *N*-hydroxypyridine-2-thione, **2–20.5** under a nitrogen atmosphere gives alkyl halides. The nor-alkyl halides prepared by this method are shown in the Table 2. For the preparation of iodides, use of iodoform is preferred over elemental iodine. Normally this procedure does not require an initiator; however, using initiators, such as AIBN, this method has been extended to more difficult cases, such as aromatic and α,β-unsaturated acids, including those with electron withdrawing substituents. Usually these substrates undergo ring bromination under Hunsdieker conditions. Successful conversion of a heavily functionalized acid to the nor-bromide (entry 6, Table 2) is noteworthy.[49]

The carbon radicals generated from **2–20.2** are also trapped with diarylsulfides, diselenides, and ditellurides[99] in good yields. For this reaction, either isolated or *in situ* generated anhydride **2–20.2** can be utilized. The preparation of tellurides are accompanied by conducting the reaction under light at 35°C as they are unstable at higher temperatures.



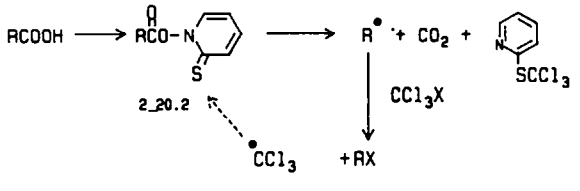
2_20.2 2_23.1

SCHEME 2_24



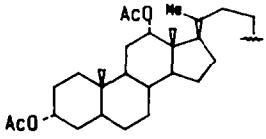
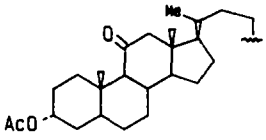
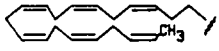
SCHEME 2_25

The reagent **2–20.5** is expensive.[341] As a result, other alternative reagents **2–27.1** to **2–27.3** have been investigated as possible alternatives for the generation of alkyl radicals from carboxylic acids.[50] While **2–27.3** is unsuitable for the preparation of sulfides via rearrangement (Scheme 2–22) or for the preparation of hydrocarbons via reduction (Scheme 2–21) using stannane as the H atom donor, reagents **2–27.1** and **2–27.2** are alternate choices. Reagent **2–27.1** is preferred for hydrogen atom



SCHEME 2_26

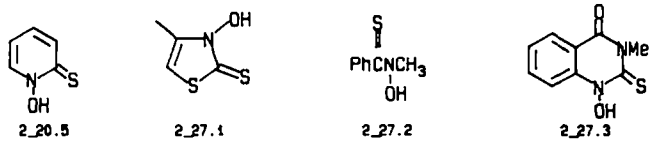
Table 2. Preparation of alkyl halides from carboxylic acids

	ACID (RCOOH) R=	HALIDE (RX)	YIELD (%)
1	$CH_3(CH_2)_4$–	X=Cl	70
		X=Br	95
		X=I	74
2	$PhCH_2\underset{\underset{\sim\sim}{|}}{C}HCH_2Ph$	X=Cl	72
		X=Br	90
3		X=Cl	88
		X=Br	90
4		X=Cl	95
5		X=Br	72
6		X=Br	75

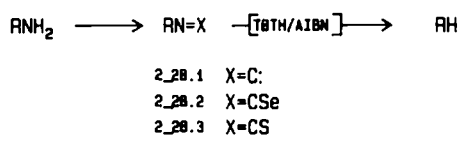
transfer reactions, Hunsdieker and other similar reactions. Reagent **2–27.1** is not commercially available but can be prepared in three steps from chloroacetone.[50]

The selective replacement of an amino function by an H atom is an important reaction for the modification of some natural products, in particular aminoglycoside antibiotics. While replacement of an amino function on aromatic compounds is trivial, such transformation in an aliphatic series is relatively difficult. Although reductions of isocyanides with reagents such as dissolving metals or sodium naphthalinide lead to hydrocarbons,[51] they are not particularly useful due to highly basic conditions normally required. However, these methods have been recommended for the deamination of some primary amines.[51]

Reduction of alkyl isocyanides with trialkylsilane in the presence of di-*t*-butylperoxide provides hydrocarbons.[52] While primary amines such as benzyl isocyanide which gives a quantitative yield of toluene at 120–130°C for 8 h, secondary and tertiary alkyl isocyanides give less than 50% yield of the desired products and are generally accompanied by the corresponding olefins, thus limiting the general utility of this method.



SCHEME 2_27



SCHEME 2_28

For deamination of secondary amines, a method conceptually similar to that used for the deoxygenation of secondary alcohols has been developed.[52-54] Amine derivatives, such as iso-cyanides, -selenocyanates, and -thiocyanates are radical precursors for this deamination procedure as shown in Scheme 2–28.

Isocyanides are best prepared by formylation (formyl acetic anhydride) followed by dehydration (toluene-*p*-sulphonyl chloride/pyridine). Isoselenocyanates are derived from isocyanides by the reaction of elemental selenium. The corresponding isothiocyanate are prepared by reaction of the amine with carbon disulfide and dicyclohexylcarbodiimide.

Individual reaction of iso-cyanides, -selenocyanates and -thiocyanates derived for example from 3_{α}-amino-$5'_{\alpha}$,22_{α}-spirostane, in refluxing benzene with TBTH in the presence of AIBN, has produced the same hydrocarbons in identical yields (Table 3) (entry 2). Primary alkylamines are deaminated at higher temperature (refluxing xylene) (entry 3), while primary amines attached to a tertiary C atom are deaminated at 50°C (entry 4). Either of the anomers of tetra-*O*-acetyl-2-deoxy 2-amino-D-glucose has been deaminated (entry 5) without affecting the anomeric center. The course of the reaction is not effected by the presence of a neighbouring hydroxy or mesyloxy groups as shown in **2–29.1** and **2–29.3**, respectively.

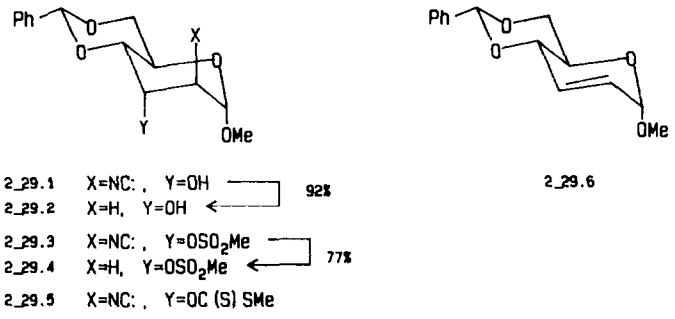
It should be noted that hydroxy, acetoxy, acetal and other functional groups are stable under the reaction conditions. This deamination reaction could not be extended to aromatic isocyanides, or carbodiimide derivatives. Deamination via isothiocyanates and isoselenates proceeds via the corresponding isocyanide. Tri-*n*-butylgermane, but not tri-*n*-hexylsilane can also be utilized in place of TBTH.

Isocyanide **2–29.5** undergoes vicinal radical elimination with TBTH to give olefin **2–29.6** in quantitative yield. This is analogous to the formation of olefins from vicinal bis-dithiocarbonates (*inter alia*) and involves initial formation of the radical at the C atom bearing isocyanide, followed by fragmentation. It is interesting to note that (±) and *meso*-1,2-diisocyano-1,2-diphenylethanes give dibenzyl in 55% yield and toluene (14% yields), but not stilbene.[53]

The usefulness of the radical deamination method, as described above, has been exemplified by the selective deamination of multi-amino compounds.[55] For example, neamine derivatives **2–30.2**, **2–30.4**, **2–30.6** and **2–30.8** have been prepared by taking advantage of the small differences in the

Table 3. Deamination of amines

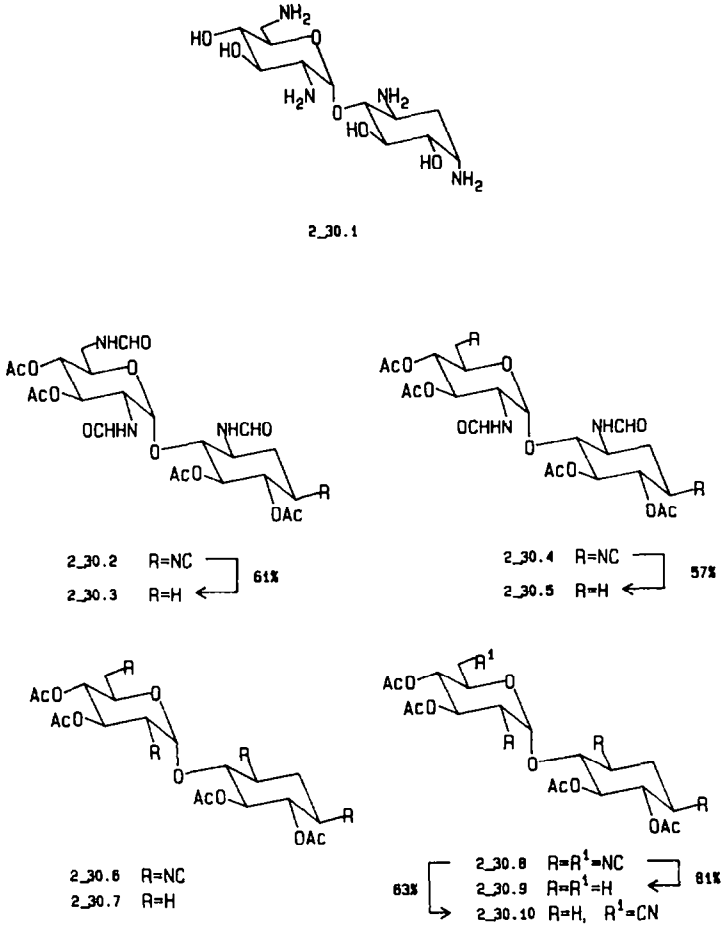
NO	Amine	Amine derivative	Product	Yield (%)
1	3α-Cholestanylamine	X=C:	Cholestane	55
		X=C=S		83
2	3α-Amino-5α, 22α-Spirostane	X=C:	5α, 22α-Spirostane	89
		X=C=S		90
		X=C=Se		88
3	n-Octadecylamine	X=C:	n-Octane	81
		X=C=S		80
4	2-Methyl-2-amino nonadecane	X=C:	2-Methyl nonadecane	91
5	2-Amino-2-deoxy-D-glucose-tetra-acetate	x=c:	2-Deoxy -D-glucose tetraacetate	71



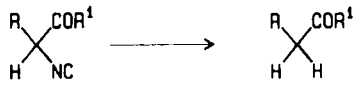
SCHEME 2-29

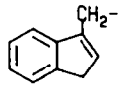
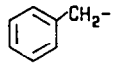
activation energies for isocyanide formation[55] at four sites of neamine **2–30.1**. Isocyano-neamine derivative **2–30.8**, on refluxing in benzene with TBTH, provides complete deamination giving **2–30.9** in 81% yield while at lower temperature gives **2–30.10** in 63% yield. It should be noted that for **2–30.10**, the primary isocyanide at the 6′-position is intact. Similarly **2–30.2**, **2–30.4** and **2–30.6** have been reduced to **2–30.3**, **2–30.5** and **2–30.7** in 61, 57 and 45% yield, respectively. Selective protection of aminoglycosides[56] coupled with this deamination procedure offers a useful methodology for the structural modification of aminoglycoside antibiotics.[57]

The above deamination sequence is applied to amino acids and peptides[58] as shown in Scheme 2–31. Isonitriles of amino acids are generally unstable; therefore the crude isonitriles prepared from



SCHEME 2-30



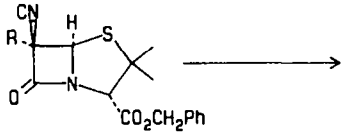
	R	R^1	Yield (%)
2_31.1		OMe	52
2_31.2		OCH_2Ph	
2_31.3	H	OC_2H_5	81
2_31.4	H	$NHCH_2COOEt$	42

SCHEME 2_31

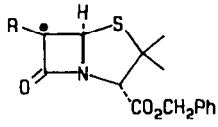
the dehydration of *N*-formylderivatives with $POCl_3$ are directly used for deamination reactions (TBTH/AIBN in refluxing benzene). The deamination of the isocyano pepide, **2–31.4** is particularly noteworthy.

The deamination reaction described above is also applied to β-lactam chemistry, in particular to the preparation of 6-alkylpenicillanates.[59,60,324] The required benzyl 6α-alkyl 6β-isocyanopenicillanates are prepared from readily available 6-aminobenzylpenicillin. The reaction of isocyanopenicillanates **2–32.1** to **2–32.7** with TBTH in refluxing benzene in the presence of a catalytic amount of AIBN provides 6β-alkylpenicillanates **2–32.8** to **2–32.14** in a highly stereoselective fashion. In contrast, the analogous reaction of 6β-isothiocyanatopenicillanates is accompanied by S–C bond cleavage to give rearranged thiazolidines. In the β-lactam series, the rate of reduction of isocyanides, selenides and halogens is in the order of NC > SePh > Br > Cl. The high degree of stereoselectivity in the reduction of 6α-alkyl-6β-isocyanopenicillanate is attributed to the ready accessibility of the tin hydride from the α-face of the radical **2–32.15**.

It is interesting to note that reduction of **2–33.1** with TBTH in benzene at 65°C for 4 h gives 83% yield of 4-unsubstituted monocyclic azitidinones[61] **2–33.2**. However, 3-phthalimido derivative, **2–33.3** (*cis*), does not react in the same manner but other parts of the molecule are reduced before the chloride is reduced. The bulkiness of phthalimido group (steric hindrance) has been attributed to the relatively drastic conditions required for the reduction of **2–33.3**.

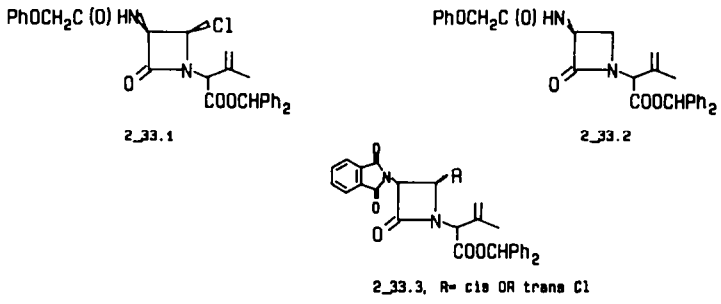


2_32.1	R=$PhCH_2$–	2_32.8	R=$PhCH_2$– 77%
2_32.2	R=$(CH_3)_2C(OH)$–	2_32.9	R=$(CH_3)_2C(OH)$– 63%
2_32.3	R=$MeOOCCH_2$–	2_32.10	R=$MeOOCCH_2$– 61%
2_32.4	R=$MeOOCCH_2CH_2$–	2_32.11	R=$MeOOCCH_2CH_2$– 75%
2_32.5	R=$(Me)_2OOCCH_2$–	2_32.12	R=$(Me)_2OOCCH_2$– 53%
2_32.6	R=MeS–	2_32.13	R=MeS– 33%
2_32.7	R=Me	2_32.14	R=Me 47%



2_32.15

SCHEME 2_32



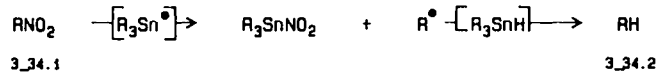
SCHEME 2_33

In recent years aliphatic nitro groups have become valuable synthetic intermediates for the preparation of complex organic molecules.[62] Many simple reactions are now available for the preparation of primary, secondary and tertiary nitro compounds. Nitro groups can be converted into a wide variety of functional groups serving for example, as carbonyl, or aminoalkyl anion equivalents. Nitro groups are stronger electron acceptors than other common groups and find use in single electron transfer (SET) reactions.[100] These SET processes generally occur at low temperature and in high yields and without being effected by steric hindrance.

The synthetic applications of the aliphatic nitro compounds[62,332,333] are enhanced by having a selective and efficient method for the replacement of the nitro group with an H atom. Tin hydrides are good reagents for the H atom transfer.[320] Other methods such as MeSNa in protic solvents, KOH in ethylene glycol and 1-benzyl-1,4-dihydronicotinamide[63] are also effective. For example, treatment of nitro compounds **2–34.1** with TBTH in refluxing benzene in the presence of AIBN (20 mol%) gives reduction products **2–34.2** in good yields. The nitro group, particularly in tertiary and some secondary nitro compounds, also substituted with electron accepting groups, is replaced by H much more readily than are other functional groups. The reduction of nitro group with TBTH is very selective and does not affect other functionalities such as keto-, ester-, cyano-, chloro- and divalent sulphur groups. It is interesting to note that some of these functional groups are reduced with TBTH in the absence of nitro groups. Some selected examples are given in the Table 4.

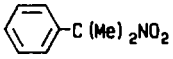
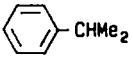
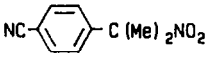
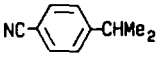
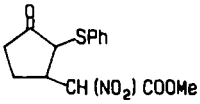
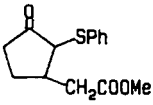
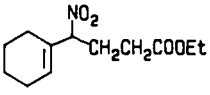
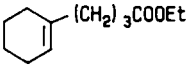
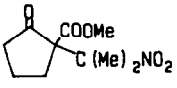
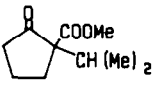
α,β-Unsaturated-nitriles, -esters,-ketones, or -sulfones can be prepared by a two step process[64] as shown in Scheme 2–35. This process consists of the reaction of an α-bromo or chloro-nitroalkane, **2–35.1** with the Na salt of an α-alkyl-ester, -nitrile, -ketone or -sulfone **2–35.3** in HMPA at 120°C. The second step is a result of de-ethoxycarbonylative elimination. The first step is very fast and usually complete in few minutes at room temperature. A similar procedure is used for keto esters. For the preparation of sulfones, the K salt of a sulfone ester is reacted with an α-halo nitro compound under photochemical conditions. Since the C–C bond forming step proceeds via a free radical chain process, the reaction is less sensitive to steric hindrance than usual ionic reactions (e.g. aldol condensation). With this method, highly substituted olefins are formed, albeit as a mixture of *cis* and *trans* isomers.

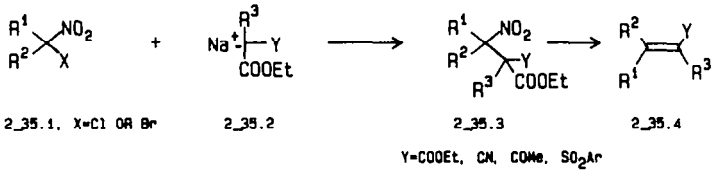
In general, primary and secondary nitro groups having no activating group at an α-position (such as benzylic-, allylic-, ketones and esters) are difficult to replace with an H atom using radical reaction conditions. For example,[65] heating a mixture of 6-nitro-9-nonanolide **2–36.1**, with TBTH (1.3 equiv) and AIBN in benzene for 2 h at 80°C gives only a trace amount of 9-nonanolide **2–36.2**. However, with a large excess of TBTH (5 equiv) and AIBN (0.8 equiv) in toluene at 110°C for 0.5 h, **2–36.1** gives **2–36.2** in 26% yield. Similarly, **2–36.3** is converted to **2–36.4** in 25% yield. The synthetic potential of this methodology is demonstrated by the synthesis of the naturally occurring macrolide, **2–36.7**, using the ring expansion strategy as shown (**2–36.5** → **2–36.7**). This procedure is particularly attractive due to the ready availability of starting materials and also is advantageous in that it does not require tedious high dilution procedures unusually required for macrolide formation.



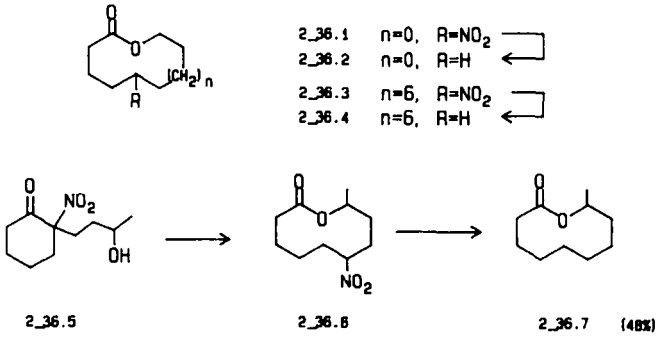
SCHEME 2_34

Table 4. Reduction of nitro group with TBTH

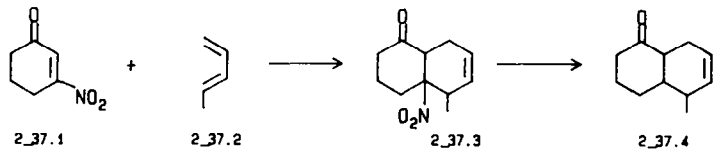
NO	RNO_2	Product	Yield (%)
1			92
2			94
3	$Me_3CCH_2C(Me)_2NO_2$	$Me_3CH_2C(Me)_2H$	75
4	$Me_2CHCH_2C(Me)(NO_2)CH_2CH_2CN$	$Me_2CHCH_2C(Me)HCH_2CH_2CN$	90
5	$PhCH(NO_2)CH_2CH_2COOMe$	$PhCH_2CH_2CH_2COOMe$	64
6			75
7			48
8	$PhSO_2(CH_2)_2C(Me)_2NO_2$	$PhSO_2(CH_2)_2CHMe_2$	91
9			60



SCHEME 2_35



SCHEME 2_36



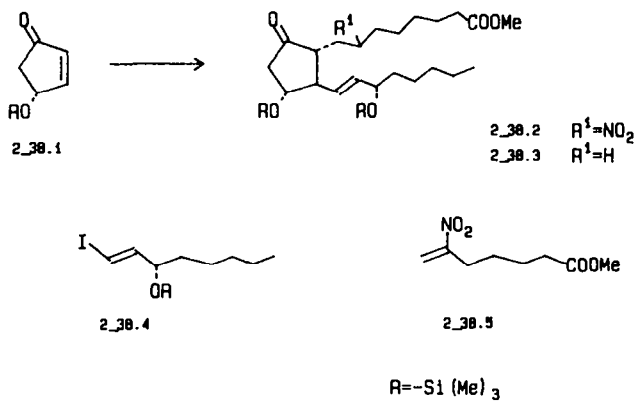
SCHEME 2_37

Nitro olefins are known to be good dienophiles in the Diels–Alder reaction and require milder conditions than those needed for simple olefins. Further, with unsymmetrical dienes the nitro group controls the regiochemistry of cycloaddition. For example, cycloaddition of 3-nitrocyclohex-2-enone, **2–37.1**, with penta-1,3-diene **2–37.2**, followed by denitration with TBTH gives **2–37.4** in 86% yield. The compound **2–37.3** is the reverse positional isomer of the cycloaddition product of cyclohex-2-enone with pent-1,3-diene, **2–37.2**. Diels–Alder adducts with unsymmetrical dienes are usually regioisomerically pure mixture of stereoisomers.[66]

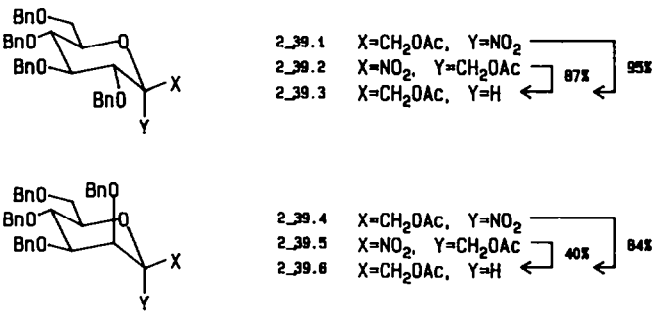
Although direct addition of organometallic reagents to electron deficient olefins is a straightforward reaction, it cannot be applied universally. On the other hand, primary or secondary alkyl anions, stabilized by an α-nitro group, add efficiently to olefins such as α,β-unsaturated-aldehydes, -sulfoxides, -sulfone, -ketones, -esters and -nitriles.[67,68] The nitro group is then effectively removed by reacting with TBTH (1.2 equiv)/AIBN (0.2 equiv) in refluxing benzene for 2 h. A short entry into prostaglandin E_5 ethyl ester, **2–38.3**, has been accomplished from the cyclopentenone derivative, **2–38.1** by a tandem organocopper conjugate addition of appendage **2–38.4**, Michael trapping of the resulting enolate intermediate with nitroolefin **2–38.5** and finally removal of the nitro group by reduction with TBTH in refluxing toluene.[69]

Similar to halo compounds, reductive denitrations of conformationally biased α-nitro ethers are expected to exhibit a high degree of diastereoselectivity.[70] The reductive denitration of tertiary nitroethers of pyranose sugars **2–39.1**, **2–39.2** and **2–39.4**, **2–39.5** using TBTH/AIBN in refluxing benzene leads to C-glycosides **2–39.3** and **2–39.6**, respectively, in good yields with diastereoselective formation of an axial C–H bond. This method produces an alkyl chain with β-orientation and complements other methods for the synthesis of C-glycosides (*inter alia*). However, in the case of furano sugars, for example in the mannose series (Scheme 2–40), an *exo* C–H bond is formed whereas in the ribose series a 1 : 1 ratio of diastereomers (Scheme 2–41) is formed. It can be generalized that steric effects favor *exo* attack (mannose series) and stereoelectronic effects favour *endo* attack (ribose series).

Alkyl mercurials are reductively removed by SBH and are shown to proceed via alkyl radicals (*inter alia*). Reduction of *t*-butylperoxy mercurials **2–42.1** with SBH leads to the formation of epoxides **2–42.4** in addition to the expected reduction products, i.e. dialkyl peroxides **2–42.3** (Scheme 2–42) via the peroxy alkyl radical **2–42.2**. The amount of epoxidation product increases (to the



SCHEME 2–38

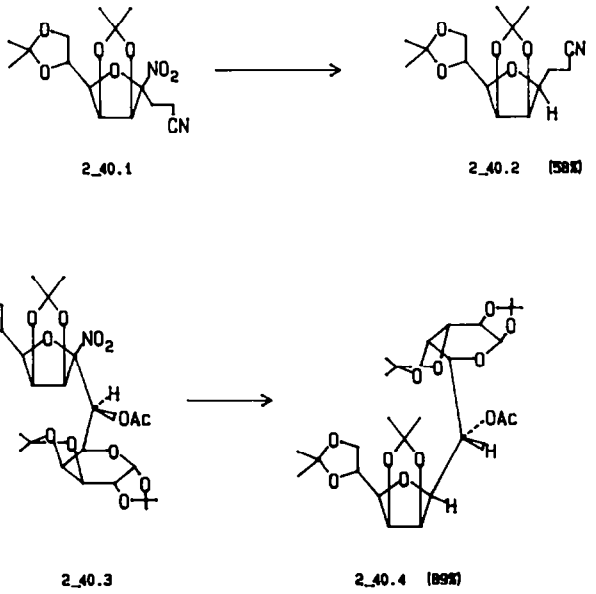


SCHEME 2_39

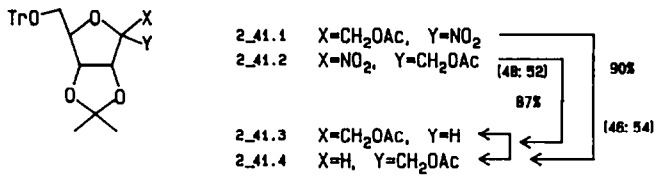
extent of 6 : 1) with the increasing substitution on the terminal alkene and also with an increase in the temperature at which the reduction is carried out.[71] The generality of this process has been exemplified by the transformation of β-peroxycarbon radicals to α,β-epoxy alcohol systems,[101] as shown in Scheme 2–42. For example, peroxy mercuration of 2-cyclohexen-1-ol **2–42.5** with *t*-butyldimethylsilyl hydroperoxide-mercuric trifluoroacetate at $-90°C$ in dichloromethane followed by reduction in THF with aqueous SBH affords 66% of *trans* 2,3-epoxycyclohexanol, **2–42.6**. Similarly, 2-cyclopenten-1-ol, **2–42.7**, is converted to *trans* 2,3-epoxycyclopentanol **2–42.8**. However, acyclic β-peroxy mercurial, **2–42.9**, gives a mixture of *cis* and *trans* epoxide **2–42.10**. This methodology has been related[191] to clavulone biosynthesis by applying it to the reduction of peroxymercurial **2–42.11** at $-78°C$ in THF using trimethoxyborohydride to give epoxy alcohol **2–42.12** in 40% yield.

The solvomercuration [$Hg(OAc)_2$ or $Hg(OTFA)_2$ or $Hg(NO_2)_2$]–demercuration (aqueous NaOH/SBH) of olefins in the presence of water, alcohols and nitriles provide a convenient procedure for ethers[73] and amide formation,[74] respectively, via Markovnikov hydration in a synthetically useful manner. It should be noted that solvomercuration/demercuration reaction of acyclic allylic alcohols shows diastereoselectivity. With alcohols the *erythro* isomer and with esters or hemiacetals the *threo* isomers are formed predominantly. Also, diastereoselectivity can be reversed by changing the substituent in the allylic position.[75]

In the context of utilization of organomercurials in radical reactions, it should be mentioned that mercuric pivalate, in addition to its good solubility in THF, is found higher regio- and



SCHEME 2_40

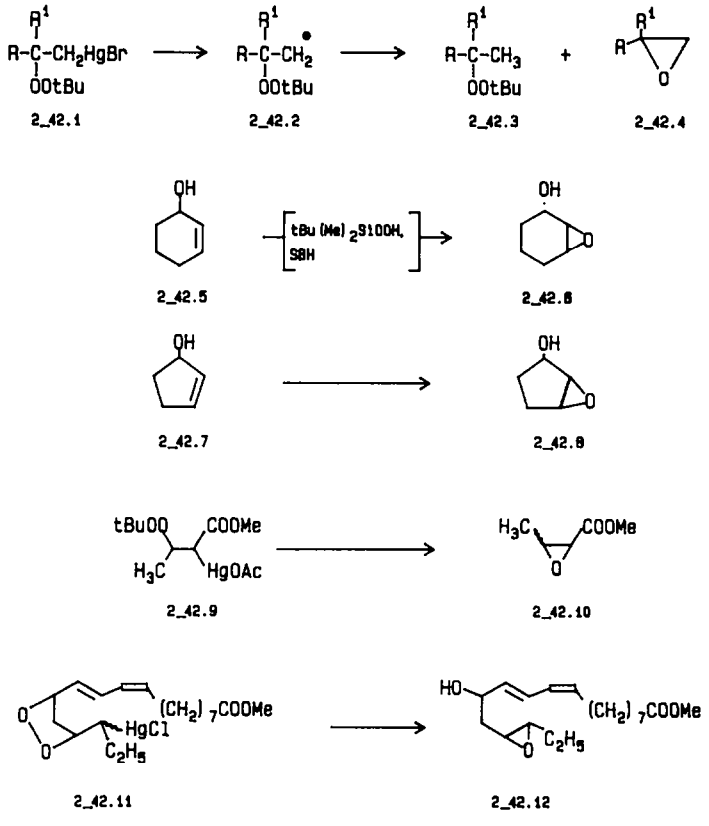


SCHEME 2_41

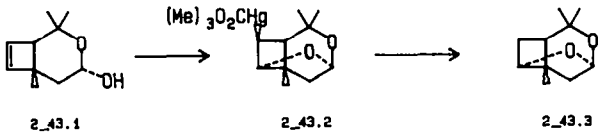
stereoselectivity than conventional Hg(II) reagents in the oxymercuration reaction.[76] For example, intramolecular oxymercuration of **2–43.1** with mercuric pivolate in THF gives **2–43.2** which on reduction with SBH gives isolineatin **2–43.3** in 42% yield.

For the preparation of mixed acetals, conventional methods (vinyl ethers + alcohols + protic acid) are not successful for certain functionalized alcohols. Mercury (Hg^{2+}) catalyzed addition of functionalized alcohols to vinyl ethers, followed by reduction with aqueous SBH in THF, provides a useful method for the preparation of mixed acetals[77] (Scheme 2–44). Yields are good, as shown in the Table 5. When the vinyl ether has an electron withdrawing group (MeCO-, -CN, α,β-unsaturated-esters, -aldehydes), mercuration is very slow, and demercuration with SBH results in reductive elimination. In such cases, particularly in acyclic systems, the use of sodium trithiocarbonate (via a mechanism which does not involve radicals) affords the functionalized mixed acetals. However, oxymercuration of glucal trimethyl ether **2–44.3** with benzyl alcohol, followed by reduction with sodium trithiocarbonate, proceeds to pseudo glucal **2–44.2** whereas SBH gives 2-deoxyglycoside **2–44.4** in 70% yield.

Reactions of alkyl mercurials RHgX with molecules of the general type Q–Q (Q = PhS, PhSe) undergo a free radical chain substitution reaction in the presence of free radical chain initiators (h_ν, 25–45°C, AIBN, 80°C) and give products RQ (via S_H2) in good yields[78] (Scheme 2–45). This reaction

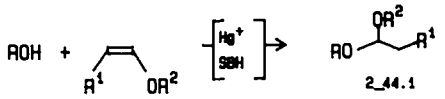


SCHEME 2_42

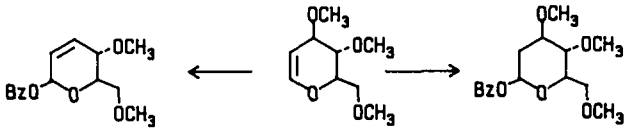


2_43.1 2_43.2 2_43.3

SCHEME 2_43



2_44.1



2_44.2 2_44.3 2_44.4

SCHEME 2_44

Q-Q + RHgX ⟶ R-Q + QHgX

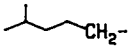
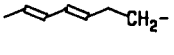
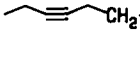
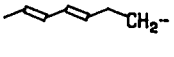
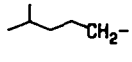
Q-Q	R-Q	Yield (%)
PhSSPh	CH_2=$CHCH_2CH_2SPh$	64
PhSSPh	Cyclo-C_6H_{11}	65
PhSeSePh	Cyclo-C_6H_{11}	72
PhSeSePh	Cyclo-$C_5H_9CH_2$-	73

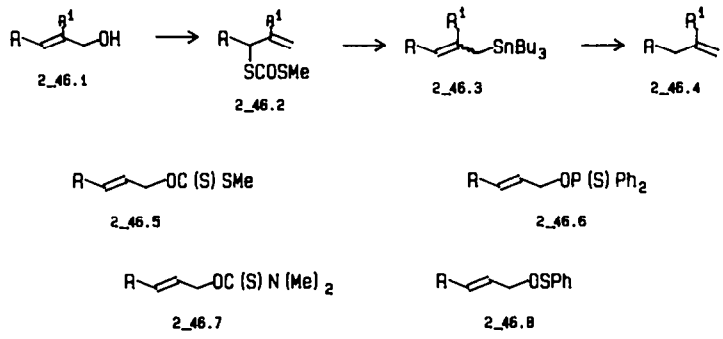
SCHEME 2_45

does not occur for PhHgX or (cyclopropy)HgX. In the above reaction, QQ can be substituted with PhSH to give hydrocarbon RH.

Allylstannanes are recognized to undergo S_H2' substitution with a variety of alkyl halides under free radical conditions (*inter alia*). Similar reactions are known for allyl or propadienyl derivatives of Co, Ir and Rh with carbon centered as well as heteroatom-centered radicals. Also allylstannanes, e.g. allyl and crotyl tributylstannanes undergo photostimulated substitution with heteroatom

Table 5. Preparation of functionalized acetals (2-44.1)

R	R^1	R^2	Yield (%)
	H	C_4H_9	60
	H	C_4H_9	85
	H	C_4H_9	80
	CO_2CH_3	CO_2CH_3	61
	CO_2CH_3	CO_2CH_3	60



2_46.1 2_46.2 2_46.3 2_46.4 2_46.5 2_46.6 2_46.7 2_46.8

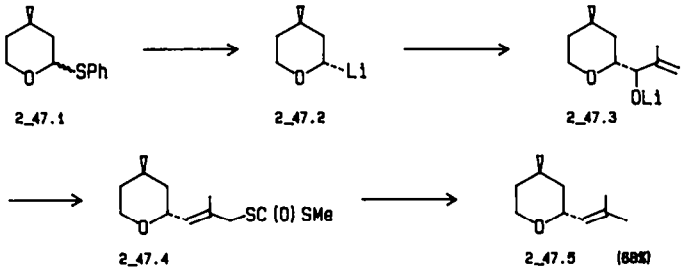
SCHEME 2_46

centered radicals[79] ($RS^{\bullet}$, $RSO_2^{\bullet}$, and $PhSe^{\bullet}$) in good yields. Unsubstituted propargyl triphenylstannanes are not particularly useful reagents for S_H2' process.

Conversion of secondary allylic alcohols to terminal olefins is usually accompanied by the thermodynamically more stable 1,2-disubstituted olefins (internal olefins). A methodology which enables the deoxygenation leading to the energetically less stable terminal olefins involves a three step sequence[80] (**2–46.1** → **2–46.4**) (Scheme 2–46); [3,3]-sigmatropic rearrangement of *O*-allylxanthates followed by the successive stannalysis with TBTH (S_H' process) gives allylic stannanes which on protolysis gives terminal olefins. To avoid the contamination of the regioisomers, this process requires completely directed regiochemistry throughout the entire reaction scheme. Among allylic 1,3-functional group transposing (O → S) reagents **2–46.5** to **2–46.8**, *O*-allylxanthate **2–46.5** is of practical use.[81] Usually, one equiv of TBTH gives good yields of allylstannanes. The stannylation reaction produces gaseous by-products, making this process more convenient. Other electrophiles besides the protons can be used in this destannylation sequence to generate functionalized alkenes. In view of the possible variation of the substituents on allylic alcohols, this method has the advantage over other methods utilizing allylic Grignard reagents.

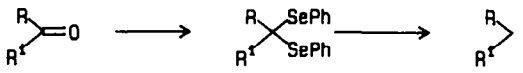
Reductive lithiation of α-phenylthio ethers by lithium 1-(dimethylamino)-naphthalenide (LDMAN) constitutes a general and useful method for the preparation of α-lithioethers.[82] This process has an advantage over the direct deprotonation of ethers. Cyclic α-lithioethers are generally formed with axial orientation via a thermodynamically stable α-radical (followed by second electron transfer) and can be trapped with aldehydes and ketones. This methodology, in combination with selective regiospecific [3,3] sigmatropic rearrangement via S-methylthiocarbonate, for example, **2–47.4**, followed by reduction with excess TBTH (AIBN, toluene, reflux), constitutes the total synthesis[82] of (±) rose oxide in 68% yield as shown in Scheme 2–47.

Organoselenium compounds are useful intermediates for a variety of transformations, e.g. C–C bond formation, cyclizations and functional group manipulations. Monoselenides can be prepared either by reacting an organic bromide with $PhSe^-$, or by cyclofunctionalization of appropriate carboxy-, phenoxy- or hydroxy-olefins or directly from the primary alcohols. Removal of the Se group by a convenient and efficient method enhances the utility of these organometalics. Although the benzene selenyl group can be replaced with hydrogen using Li/ethylamine or Raney Ni, the most



2_47.1 2_47.2 2_47.3 2_47.4 2_47.5 (68%)

SCHEME 2_47



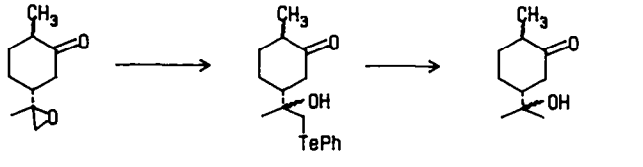
SCHEME 2_48

efficient method appears to be with TBTH[37,83] in refluxing toluene. For these reactions, no free radical initiators are necessary although the presence of AIBN accelerates the rate of reaction. Triphenyltin hydride (TPTH) is more suitable than TBTH and freshly distilled TPTH leads to shorter reaction times. Experimentally, it is preferred to immerse the reaction mixture in a preheated bath at 120°C and add the TPTH in several portions during the course of the reaction. The workup usually involves either chromatography or distillation or successive application of both techniques. It should be noted that the reduction of the PhSe–C bond is possible in the presence of lactone, ether, phenol-ether, urethane and hydroxyl groups, and even in the presence of a bivalent sulphur group. Selenoacetals and ketals, which can readily be prepared from carbonyl compounds, can also be reduced to the corresponding hydrocarbons[37] in good yields (Scheme 2–48).

Organotellurides are usually air and light sensitive and in general are difficult to handle. However they can easily be manipulated in a photographic dark room containing no light source other than a red safety lamp. Tellurides are prepared by displacement of halide or by epoxide opening, using species such as $PhTe^-$ or $MeTe^-$ which are generated from SBH and ditellurides in ethanol. Organotellurides are reduced under much milder conditions (between 25 and 80°C) in benzene solution using triphenyltin hydride as a reducing agent without any added initiator. Organotelluride dichloride is reduced much more readily than the parent telluride. Tellurium based methodologies are also chemoselective as well as mild and give high yields of reduction products (Scheme 2–49).[37]

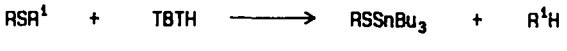
The TBTH is a selective reagent for the cleavage of the C–S bond in unsymmetrical sulfides (RSR′). Reduction occurs only when one of the groups attached to bivalent sulfur is an electron stabilizing group (e.g. benzyl > tertiary > secondary > primary). The reduction of secondary and primary alkyl C–S bonds is so slow as to discount the synthetic utility by this reagent.[84] The reduction of an α-C–S bond in ketones, esters and nitriles is extensive and rapid. AIBN initiated TBTH reductions of dialkyl sulfides (Scheme 2–50) are generally marred by a side reaction (Scheme 2–51) which effectively competes for TBTH. The degree of selectivity in desulfurization is determined by the rate of these two processes.[84]

Reduction of ketones and aldehydes to the corresponding hydrocarbons via their dithioketals and acetals is a well-accepted method in synthetic chemistry. As alternatives to the usual procedures (Wolff-Kishner, Raney Ni etc.), the reduction of dithioacetals or ketals with TBTH in the presence of AIBN is of synthetic use (Scheme 2–52). The interesting point of this reaction is that the TBTH is not only an effective but also a selective agent for the complete or partial desulfurization of 1,3-dithiolanes. It can cleave and discriminate between primary, secondary and benzylic C–S bonds when the stoichiometry of stannane is controlled. Two equivalents of TBTH are sufficient for complete

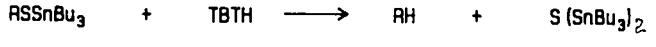


2_49.1 2_49.2 2_49.3 (70%)

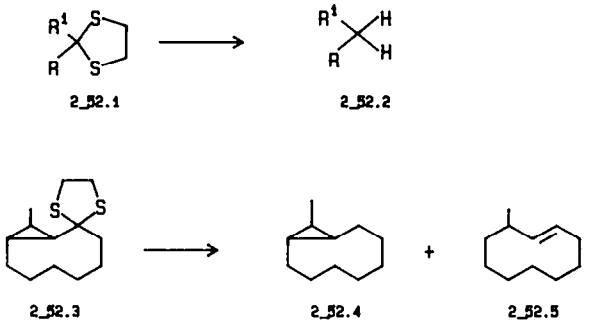
SCHEME 2_49



SCHEME 2-50



SCHEME 2_51



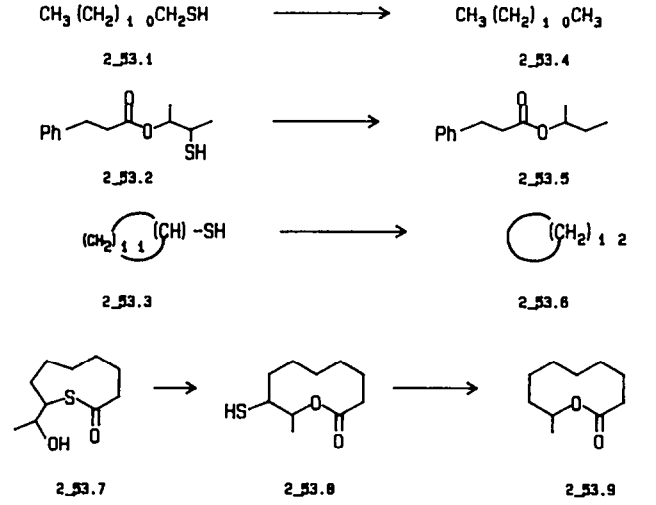
SCHEME 2_52

conversion of the dithioacetal to an alkane. It is noteworthy that reduction of allylic dithiolane **2–52.3** gives the expected **2–52.4** along with its isomer **2–52.5** in a 4.2 : 1 mixture (74% yield).[85]

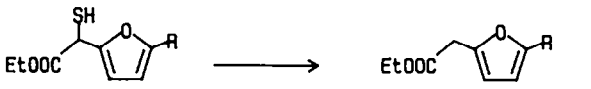
Mercaptans are usually desulfurized with Raney Ni. However this methodology is limited to substrates without other reducible groups such as aliphatic ketones, olefins and benzyl ethers. A method for selective desulfurization of mercaptans (RSH) to the corresponding hydrocarbons (RH) has been the reduction of *in situ* formed alkyltin sulfides with TBTH. For example, the primary and secondary mercaptanes **2–53.1** to **2–53.3** on heating with TBTH (2.1 equiv) in the presence of AIBN in refluxing benzene give corresponding hydrocarbons **2–53.4** to **2–53.6** in good yield.[86] This methodology is applied to the synthesis of naturally occurring lactone **2–53.9** in 80% yield from **2–53.8**, by a strategy[86] involving intramolecular (S → O) acyltransfer of hydroxyalkyl thiol lactone **2–53.7**.

Usually attachment of a two carbon unit on a furan ring involves a multistep sequence. However, treatment of the α-mercapto alkylated furans **2–54.1** (prepared from photochemical addition of phenacyl sulfides and furans) with TBTH and AIBN in benzene at 80°C gives the desulfurized products in good yields[87] (80–95%) (Scheme 2–54).

Saturated 5-membered heterocycles have been prepared by reductive removal of a thione (C=S) moiety using excess TBTH (3–5 equiv) in toluene in the presence of AIBN (Scheme 2–55). Usually



SCHEME 2_53

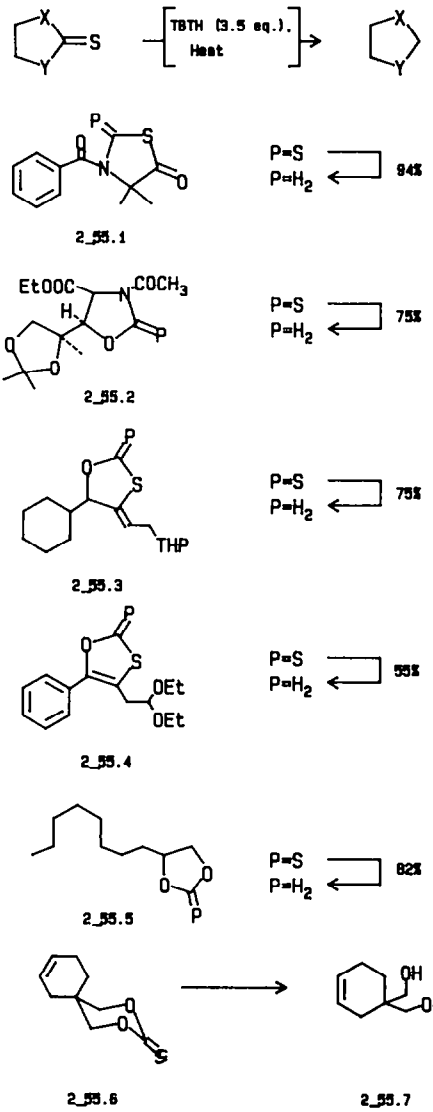


2_54.1 2_54.2, R=H
2_54.3, R=Et

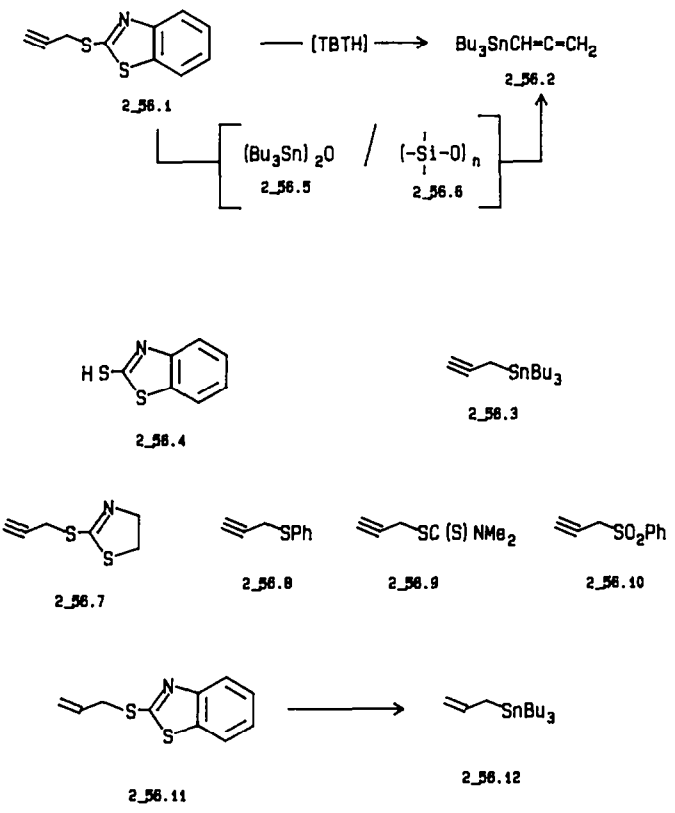
SCHEME 2_54

reactions are very fast (2 h). Workup involves chromatography and the yields are good.[88] Monosubstituted thionamides (H—N—C=S) **2–55.2** require acylation of nitrogen prior to the reduction. 1,3-Dioxalan-2-thione **2–55.5** is converted into the corresponding 1,3-dioxalane. However, reduction of 1,3-dioxane-2-thione derivative **2–55.6** results in ring opening to hydroxy formate **2–55.7**. It should be noted that under the above conditions, the reaction takes a different course from that of Barton's deoxygenation method.

Allylic sulfides, analagous to xanthates (*inter alia*), react with TBTH in two types of $S_{H'}$ (expelling allylic or alkyl) and one type of S_H2' process. The $S_{H'}$ mode is predominant or exclusive depending



SCHEME 2_55

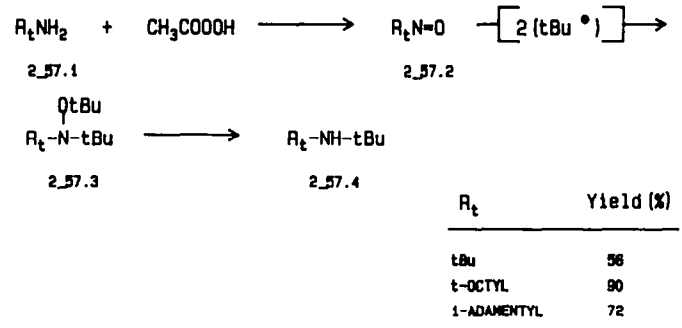


SCHEME 2_56

on the stability of the expelled S radical. For example, allylic phenyl sulfides are reduced much faster than allyl methyl sulfides.[84] Allylstannanes containing functional groups, such as cyano, ester, or sulfonyl groups are prepared by the hydrostannolysis of the corresponding allylic sulfones with TBTH under neutral conditions.[89]

The reaction of organotin hydride with a double or a triple bond normally yields a hydrostannylated species. The tri-*n*-butyltin radical generated either from TBTH (2 equiv) and AIBN or from a photochemical reaction, when reacted with 2-(propargylthio)benzothiozole, **2–56.1**, gives tributylstannylallane **2–56.2** in 90–93% yield[90] without contamination with propargyltri-*n*-butylstannane, **2–56.3**. When an equimolar amount of TBTH is employed, 2-mercaptobenzothiazole, **2–56.4**, is isolated in 36% yield in addition to the desired stannylallene **2–56.2** in 65% yield. This stannylation reaction can also be carried out by the *in situ* generated[91] stannane from bis(tri-*n*-butyltin)oxide **2–56.5** and polymethyl hydrogen siloxane **2–56.6**. Among other propargylic S compounds, **2–56.7** to **2–56.10**, **2–56.7** and **2–56.8** give desired allenes in good yields. The elimination of the stable S centered radical is the key to the success of this reaction. Unlike the attack of the tin radical on chloride, in the case of propargyl chloride, attack on the S atom does not occur.[334] Also allylic stannylation proceeds under similar conditions at 90°C for 5 h to give tri-*n*-butyltin, **2–56.12**, in 88% yield from **2–56.11**.

Lithium dialkylamine reagents, particularly hindered amines, are important organic bases in organic synthesis. In some cases, the regiochemical enolate alkylation depends on the nature of the base, particularly in the situation where steric bias is operative. Availability of highly hindered amines such as di-*t*-alkylamines is not frequent and also the synthesis is not convenient by the known methods. A general synthetic procedure for the preparation of di-*t*-alkylamines involves a three-step sequence[92] as shown in the Scheme 2–57. The conversion of the *t*-alkylamine **2–57.1** to nitroso compound **2–57.2** is best carried out with peracetic acid in ethyl acetate at 0°C. The nitroso

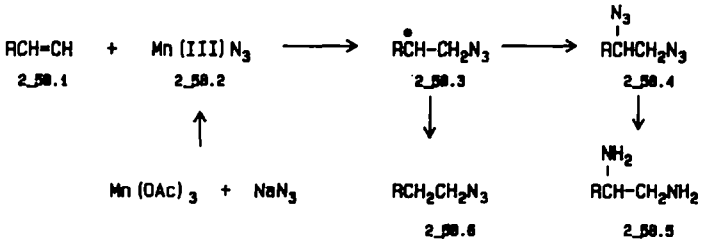


SCHEME 2-57

compound is then converted to a tri-*t*-alkylhydroxylamine **2–57.3** via a sequential trapping of two *t*-butyl radicals generated from *t*-butyl hydrazine and PbO_2. The reduction of **2–57.3** with either sodium in ammonia–THF, or best with sodium naphthalide in an inert atmosphere, gives good yields of di-*t*-alkylamines. The purification of nitroso **2–57.2** and tri-*t*-alkylhydroxylamines **2–57.3** is not needed for the subsequent reaction. The reactions are easily monitored and need no special precautions except in the final reduction step which requires exclusion of moisture and air.

Vicinal diamines are usually prepared by a series of standard S_N2 displacement reactions utilizing a highly nucleophilic azide anion, followed by reduction. A method[93] for the direct conversion of alkenes into 1,2-diazides (and in turn to amines) is shown in Scheme 2–58. $Mn(III)N_3$ generated from $Mn(OAc)_3$ and NaN_3 is believed to be the reacting species via two consecutive ligand transfer oxidations. Experimentally, 1,2-diazides are prepared by heating a brown solution of manganese(III) acetate, sodium azide (16 equiv) and the alkene in glacial acetic acid at 70–116°C until the solution turns colorless. The yields of 1,2-diazides are highly dependent on the reaction concentration (Table 6). The major side product is the 1-azidoalkane **2–58.6** derived from the initially formed radical **2–58.3**. Reduction of 1,2-diazides to 1,2-diamines can be accomplished by hydrogenation over Lindlar's catalyst. Adam's catalyst can also be used. *Caution*: metal azide complexes are known to be explosives. Analagously, Mn(III) chloride species have been prepared and used as effective chlorinating agents of alkenes.[94]

Homolytic decomposition of azo compounds is known to expel nitrogen.[95] Hindered hydrazones enhance such homolytic decomposition.[96] Hindered hydrazones prepared from ketones or aldehydes with trityl or diphenyl-4-pyridylmethyl hydrazines have been alkylated at −30 to −40°C with alkyl halides via Li salts **2–59.3** to give azines **2–59.4**. The reaction of these azines with H atom transfer reagents such as ethanethiol at or below ambient temperature produces alkanes **2–59.6** (Table 7) in 42–67% yield via radical **2–59.5**. Alternately, Li salts **2–59.3** are reacted with a ketone or an aldehyde to give *β*-hydroxyl azines **2–59.7** which are then converted either into alcohols **2–59.8** by the addition of thiol, or into tri- or tetra-substituted olefins **2–59.9** by reacting with PCl_3 and triethylamine (Table 8). For the preparation of alcohols, diphenyl-4-pyridylmethylhydrazones are preferred, as they enable facile removal of the basic residue by a dilute acid wash of the reaction mixture. It should be noted that this method provides the coupling of two same or different ketones to give tetra-substituted double bonds without crossover.



SCHEME 2_58

Table 6. Preparation of 1,2-diazides (2–58.4)

Alkene (2_58.1)	1,2-diazide (%)
1-Octene	68
(E)-4 Octene	76
5-Butyl-4-nonene	72
Cyclohexene	59 (4:1, cis:trans)
Cyclooctene	51 (6:1, cis:trans)

Table 7. Preparation of alkanes from azocompounds

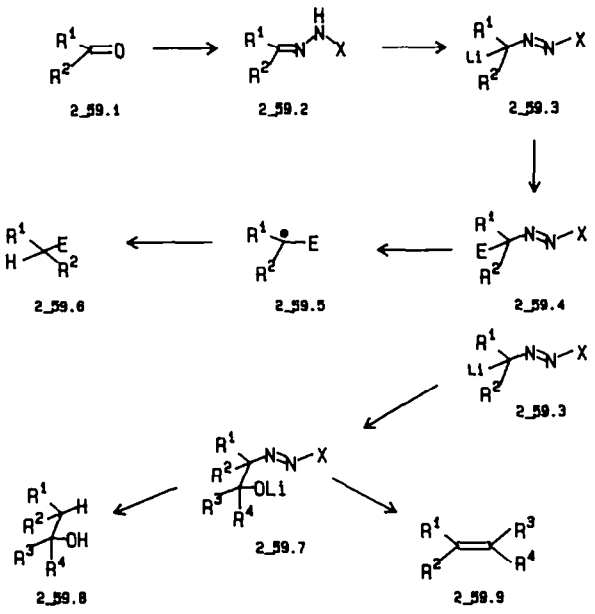
R^1	R^2	E	Yield (%) 2_59.6
$-(CH_2)_5-$		nC_7H_{15}	67
"		nC_4H_9	43
"		$PhCH_2-$	69
Me	Me	"	42
"	"	$nC_{10}H_{21}$	60

Table 8. Preparation of alcohols (2–59.8) and olefins (2–59.9) from azocompounds

R^1	R^2	R^3	R^4	Yield (%) 2_59.8	Yield (%) 2_59.9
$-(CH_2)_5-$		$-(CH_2)_5-$		35	24
Me	H	Ph	H	74	-
Me	Me	Ph	H	85	45
$-(CH_2)_5-$		Me_2CH-	H	70	-
"		Ph	H	80	47
nC_6H_{13}	Me	H	nC_7H_{15}	-	55 (E:Z, 3:2)
nC_6H_{13}	Me	Ph	H	-	60 (E:Z, 65:35)

3. INTERMOLECULAR C–C BOND FORMATION

Organomercurials are useful synthetic intermediates.[102-104] Alkyl radicals are produced when alkyl mercurials are reacted with hydride reagents[105] and reactions (Giese reaction) of organomercurials have been explored for the C–C bond formation in a regio- and stereoselective fashion.[106,107] For example, the reaction of organomercurials **3–1.1** with SBH in the presence of electron deficient olefins leads to the synthesis of mono- and di-functional alkanes (Scheme 3–1). Yields are in the range of 45–65%. The concept displayed in this scheme is a powerful synthetic strategy for C–C bond formation (*inter alia*). Obtaining the maximum yields depends upon a number of factors, e.g. mole ratios of the reactants, reaction temperature, mode of addition, solvent and the reducing agent. Normally, at least a ten-fold excess of electron withdrawing olefin is needed for obtaining good yields. The reactions are generally conducted at 0°C to ambient temperature.[108-111]

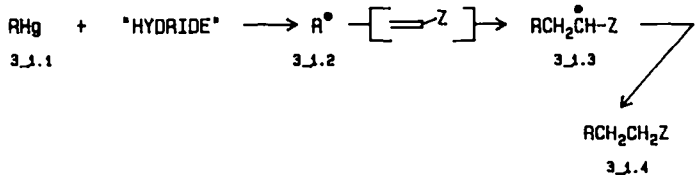


SCHEME 2_59

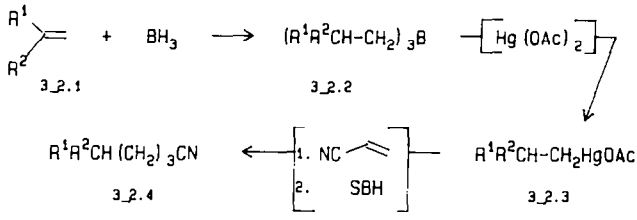
In order for this reaction to be of preparative significance, particularly in predicting the yields and product ratios of possible isomers, the available information such as the effects of substituents on the reactivity, the selectivity of the radical additions, etc., should be utilized.[112-114]

The interesting point of the general reaction[107] mentioned in Scheme 3–1 is the different selectivity of the alkyl radicals **3–1.2** and the adduct radical **3–1.3** in the competition for the H atom (the H atom is believed[105] to be derived from RHgH). Dimerization, disproportionation, polymerization, trapping of oxygen and β-bond cleavage do not generally compete with H atom transfer.[115]

Electron-rich alkenes have been coupled with electron deficient alkenes in a one pot process[119] by using a three-step sequence as shown in Scheme 3–2. Regiospecific hydroboration of electron-rich olefins with a hindered borane (to avoid regio-isomers), such as dicyclohexylborane, is a well-known synthetic operation.[116] Organoboranes are easily converted into organomercurials by known procedures[102] which, by reduction with SBH in the presence of an electron deficient alkene such as acrylonitrile, provide C–C bond formation. The overall yield of this three-step one-pot synthesis varies between 50–70% (Table 9). This method also works well with other electron deficient olefins containing acids, ketones, anhydrides and imide moieties.[119] However, with phenyl and chlorine olefins, yields are considerably lower. In the presence of acidic groups, greater amounts of borohydride are required. The regioisomeric hydroboration products of terminal olefins do not lead to impurities due to the fact that only the bond between the primary alkyl group and boron is cleaved by the mercuric salt.[117,329] It should be noted that this method is advantageous over the method utilizing direct addition of organoboranes to electron withdrawing olefins since the latter method works only with α,β-unsaturated ketones.[118] The overall yield of this three-step one-pot synthesis



SCHEME 3_1



SCHEME 3_2

varies between 50 and 70% (Table 9). This method also works well with other electron deficient olefins containing acids, ketones, anhydrides, and imides.[6] However, with phenyl and chlorine containing olefins, yields are considerably lower. In the presence of acidic groups, greater amounts of borohydride are required.

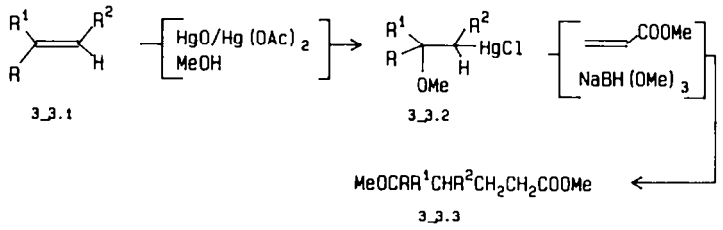
2-Alkoxyalkylmercury halides **3–3.2** prepared from solvomercuration of olefins **3–3.1** in methanol react with electron deficient alkenes in the presence of SBH to provide[109,110] alkoxy alkanes **3–3.3** as shown in Scheme 3–3. These two steps can be combined to perform the reaction in one pot. 2-Alkoxy mercurials derived from substituted mono- and 1,2-dialkyl alkenes react, for example with methylacrylate to give alkanes in the range of 48–65% yield (Table 10), whereas mercurials derived from tetra-alkyl alkenes give alkane esters in low yields. For a one-pot reaction, the presence of HgO is necessary to neutralize the generated acetic acid when mercury acetate is used in the mercuration step; otherwise, the addition reaction reverses during reduction stage.

3-Methoxylalkyl mercurials derived from cyclopropanes are also good substrates for C–C bond formation (Scheme 3–4). For example,[120,121] reduction of organomercurials **3–4.2** derived from the corresponding cyclopropane **3–4.1** with SBH or sodium trimethoxyborohydride in the presence of electron deficient alkenes **3–4.3** produces methoxy compound **3–4.4**. It should be noted that experimentally, organomercuric chlorides and bromides are more convenient to manipulate than the corresponding acetates. As a result, prior to reduction, organomercury acetates are usually converted into the corresponding chlorides by exchanging the counter ion using chloride ion in aqueous solution. The conversion of organomercury(II) acetates into the chlorides can be best achieved by reacting with trimethylsilyl chloride under homogeneous and nonaqueous conditions; this method is rapid and gives high yield.[71]

From the Table 11 it should be noted that for C–C bond formation, the olefins containing electron withdrawing groups such as nitriles appear to be better than those with ester groups. Unlike the reaction shown in Scheme 3–2 mono- to tetra-substituted alkenes are used in this reaction successfully. In contrast to 2-alkoxy alkyl radicals as shown in Scheme 3–3, in which the use of sodium trimethoxyborohydride is preferred, 3-alkoxy alkyl radicals can effectively form C–C bonds in the presence of the inexpensive SBH (Method A.)

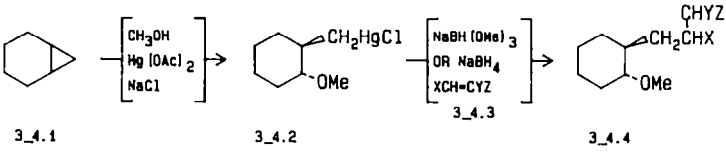
Table 9. Reductive coupling of alkene (**3–2.1**) with acrylonitrile

Olefin		Yield (%)	Olefin		Yield (%)
R^1	R^2		R^1	R^2	
H	$-C(CH_3)_3$	47	H	$-(CH_2)_8CO_2Et$	57
H	$-C_6H_4-4-CH_3$	50	H	-OEt	55
H	$-CH_2-C_6H_4-2OAc$	65	H	$-CH_2OC_6H_5$	55
H	$-CH_2-C_6H_4-2-OH$	48	CH_3	$-C_2H_5$	65
H	$-CH_2CH_2Br$	53	CH_3	$-C_3H_7$	57
H	$-CH_2OAc$	51	CH_3	$-CH_2Cl$	50
H	$-CH_2CH_2OTs$	71			

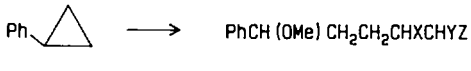


3_3.1 3_3.2 3_3.3

SCHEME 3_3



3_4.1 3_4.2 3_4.3 3_4.4



3_4.5 3_4.6

SCHEME 3_4

Substituted cyclopropanes **3–5.1** have been coupled[122,180] with olefins such as **3–5.2** via methoxymercuration to produce **3–5.3**. In this case also, experimental procedures have been developed to accomplish C–C bond formation without isolating mercury salts. Usually, this one-pot procedure gives better yields than the procedures using isolated intermediates. Also, it should be noted that reduction of 2,2,3,3-tetramethyl-3-methoxypropyl mercurial produces radical **3–5.5** which rearranges to radical **3–5.6** via intramolecular H abstraction. In the presence of α,β-unsaturated carbonyl compounds, both of these radicals (**3–5.5** and **3–5.6**) are trapped to yield product **3–5.7** and **3–5.8**, respectively. With substituted fumaric esters, the main products are the rearranged adduct **3–5.7**. This chemoselectivity has been attributed to the enhanced nucleophilicity of the alkoxy alkyl radicals over the unsubstituted alkyl radicals. It has been estimated that nucleophilicity of an alkoxy radical is three times that of a methyl radical.[122]

Cyclopropylmercury bromide **3–6.1** couples with alkenes **3–6.2** via cyclopropyl radical[123] to yield products **3–6.3**. Products of this type should be useful in organic synthesis.[124]

It has been noted (*inter alia*) that the reductive alkylation of organomercurials with SBH gives high yields of alkylated products. However, 2-alkoxy substituted organomercurials give low yields of alkylated products but predominantly give reduction products. As a consequence,[109] sodium

Table 10. Alkoxy esters (**3–3.3**) from olefin (**3–3.1**)

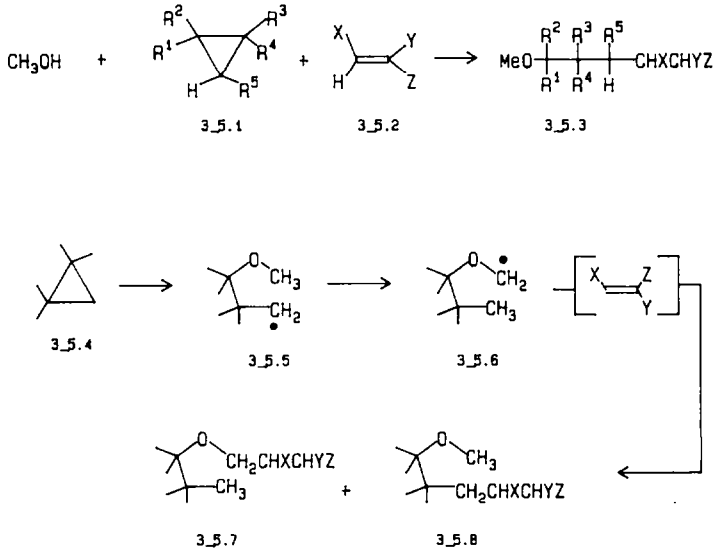
Alkene (3_3.1)			Yield (%)	Alkene (3_3.1)			Yield (%)
R	R^1	R^2	(3_3.3)	R	R^1	R^2	(3_3.3)
H	H	H	50	CH_3	C_3H_7	H	30
H	C_4H_9	H	48	CH_3	C_3H_7	CH_3	53
H	C_6H_5	H	50	CH_3	CH_3	CH_3	32
H	$-(CH_2)_3-$		65				
H	$-(CH_2)_4-$		58				

Table 11. Preparation of alkoxyalkanes (3–4.4)

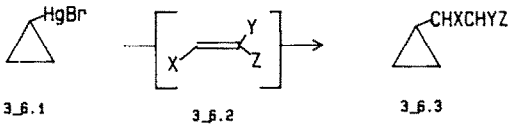
Alkane (3_4.4) X	Y	Z	Method A (%)	Method B (%)
H	H	CN	80	90
H	H	CO_2Me	76	77
H	H	C_6H_5	34	38
H	CH_3	CN	80	70
H	CH_3	CO_2Me	68	67
H	Cl	CN	76	87
H	Cl	CL	44	51
CN	H	CN	84	90
CO_2Et	H	CO_2Et	80	95
CO_2Et	H	CO_2Et	35	42
CH_3	H	CN	22	21
CH_3	H	CO_2Me	13	12
CO_2Et	CH_3	CO_2Et	60	67

trimethoxyborohydride has been substituted for SBH. The insolubility of hydrophobic electron deficient alkenes in the alkaline aqueous medium has been suggested to be a possible reason for low yields of products when SBH is used as a reducing agent. In some cases, yields have been improved[125] by using DMF as a solvent, which provides a homogeneous reaction mixture.[109]

A surfactant catalysed reductive alkylation of 2-alkoxy mercurials is used as an alternative[125] to the use of an expensive trimethoxyborohydride reagent. C–C coupling occurs in good yields when a mixture of the oxymercurial dissolved in 10% aqueous NaOH and a solution of the electron deficient olefin in dichloromethane containing catalytic amount of Triton X-100 (non-ionic surfactant) is treated with a solution of SBH in aqueous NaOH. This procedure can be adapted easily to a "one-pot" method by *in situ* preparation of the oxymercurial from the olefin and the Hg(II) salt in water or alcohol. It should be noted that in the surfactant catalysed reactions, neither the stereochemistry nor the regiochemistry is different from the reaction of sodium trimethoxy borohydride. Usual phase transfer catalysts (PTC) such as quaternary ammonium compounds do not work.



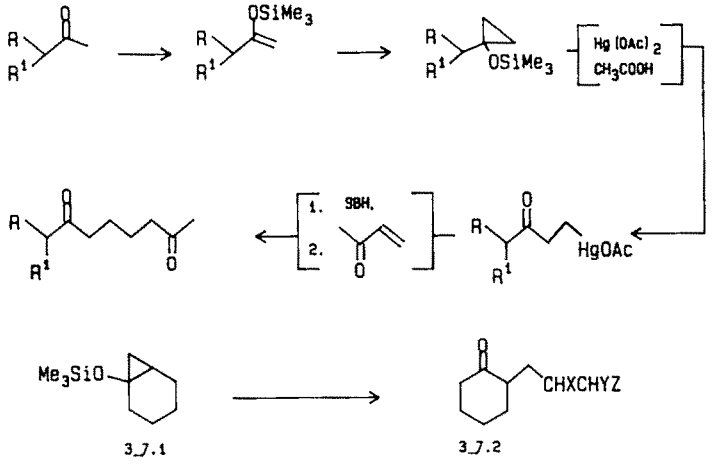
SCHEME 3_5



3_6.1 3_6.2 3_6.3

X	Y	Z	Yield (%)
H	H	CO_2Me	53
H	H	CN	61
H	Cl	CN	61
CO_2Et	H	CO_2Et	61

SCHEME 3_6



3_7.1 3_7.2

SCHEME 3_7

A process consisting of four steps for the synthesis of 1,6-diketo or -keto esters has been developed[126] starting from a ketone or an aldehyde as shown in the Scheme 3–7. Carbonyl compounds are first converted to trimethyl silyl cyclopropane derivatives via a Simon–Smith reaction on the corresponding silylenol ethers. Mercuration of these cyclopropyl ethers in acetic acid, followed by reduction with SBH (without isolating intermediate organomercurials) in the presence of an alkene provides C–C bond products. For example, acetone has been converted into 2,7-diketo octane as shown in Scheme 3–7 (R, R^1 = H). The scope of this reaction has been demonstrated by preparing several nitriles and esters **3–7.2** from **3–7.1** in about 50–70% yield (Table 12).

Table 12. Preparation of (3–7.2)

X	Y	Z	Yield (%)
H	H	CN	68
H	H	$COCH_3$	64
H	H	CO_cH_3	62
H	CH_3	CO_2CH_3	60
CO_2CH_3	H	CO_2CH_3	58
H	Cl	CN	50
H	CH_3	CO_2CH_3	50

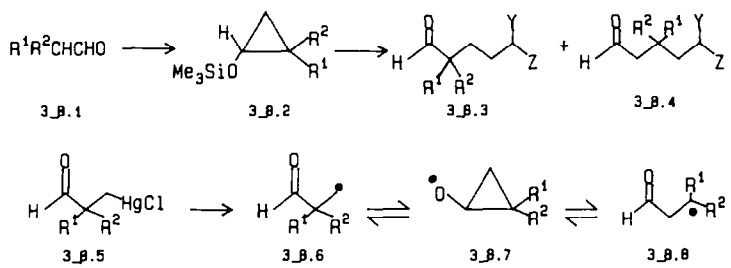
Table 13. Preparation of aldehydes (**3–8.3**)

R^1	R^2	X	Y	Z	Yield (%)
C_4H_9	H	H	H	CN	60
C_4H_9	H	H	H	CO_2Me	52
C_4H_9	H	H	H	COMe	61
C_4H_9	H	H	Cl	CN	65
C_4H_9	H	H	CH_3	CN	40
C_4H_9	H	CO_2Et	H	CO_2Et	60
CH_3	CH_3	H	H	CN	51
CH_3	CH_3	H	H	CO_2Me	49
CH_3	CH_3	H	Cl	CN	51
CH_3	CH_3	H	CH_3	CN	30
CH_3	CH_3	CO_2Et	H	CO_2Et	45

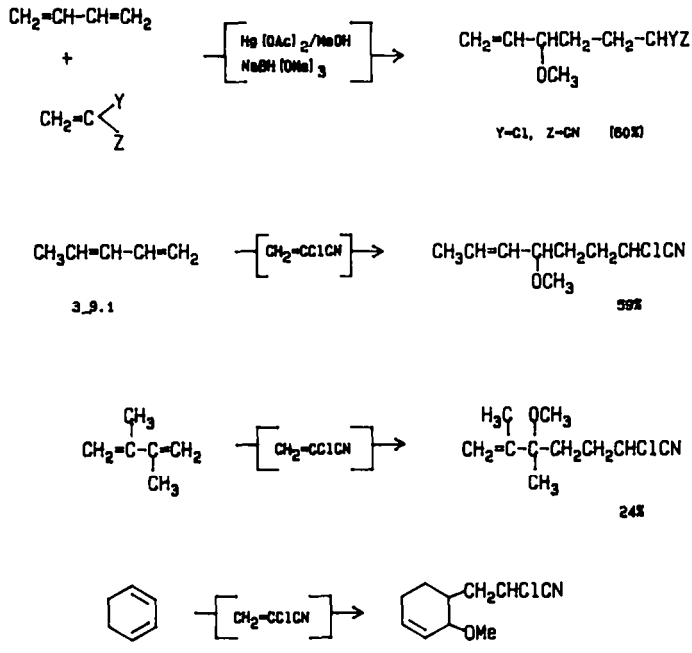
In a similar reaction sequence (acetic acid as solvent during mercuration), cyclopropylsilyl enol ethers **3–8.2** derived from aldehydes **3–8.1** yield products **3–8.3** in 30–65% yield[127] (Table 13) after desilylation with KF in acetone. However, when solvomercuration of **3–8.2** is carried out in water expected organomercuric salt **3–8.5** is formed but reduction with SBH in the presence of alkene gives a mixture of products, **3–8.3** and **3–8.4** in 30–55% yield. Instead of excess alkene, use of 0.33 mole of alkene increased the relative yield of **3–8.4**. Preparatively, a meaningful yield of **3–8.4** can be accomplished from acrylic and fumaric esters. The radicals **3–8.7** and **3–8.8** have been suggested as possible intermediates for the formation of **3–8.4**. Radicals of the type **3–8.7** (1,2 rearrangement)[128] have been invoked in model biological systems such as methylmalonylCoA rearrangements.[129]

In the examples shown above, the alkyl mercurials do not contain any other functional groups which can be used for further synthetic transformations. As shown in Scheme 3–9,[130] 1,3-dienes can be coupled with electron withdrawing olefins via a solvomercuration, reduction sequence. In this method, usually $HgO/Hg(OAc)_2$ (1 : 1 ratio) is reacted with a three-fold excess of 1,3-butadiene in methanol between -10 and 20°C to give the methoxy mercurial which, without isolation, is reacted with a three-fold excess of an alkene in the presence of a two-fold excess of $NaHB(OMe)_3$, to give a 20–60% yield of functionalized olefins. Although the solvomercuration of a mono- and di-substituted diene is a quantitative reaction, the intermediate olefinic alkyl radical, e.g. **3–10.1**, generated during reduction undergoes intramolecular radical addition[130] to give exo **3–10.2** and endo **3–10.3** products along with reduction product **3–10.4** (Scheme 3–10).

A method[131] that utilizes free radical substrates containing unprotected β-OH group complements the method that utilizes the radical C–C coupling of alkyl radicals containing a protected β-OH group.[125] This method is particularly useful for the formation of substituted lactones. A number of olefins have been converted into stable, crystalline chloromercury derivatives via the corresponding hydroxy mercurials, by ligand exchange with chloride ion (Scheme 3–11). Reductive



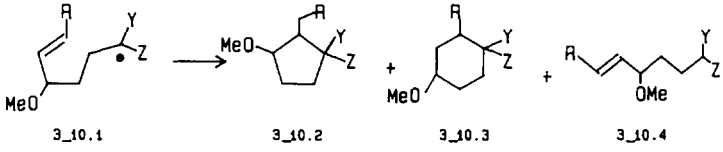
SCHEME 3_β



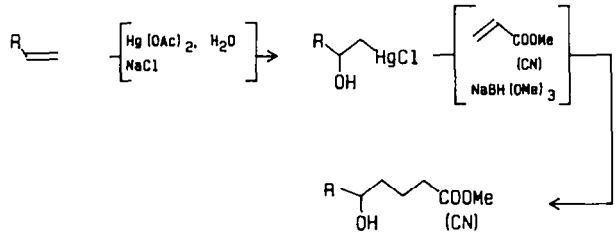
SCHEME 3_9

coupling of these mercurals with acrylonitrile and methylacrylate has been carried out in methylene chloride by using 3 equiv of sodium trimethoxyborohydride. Both of these acceptors give fair to good yields of coupled products. It should be noted that in the majority of cases, acrylonitrile proved to be more effective than methylacrylate. The product esters and nitriles have been converted into lactones in fair to excellent yields by usual procedures. The scope of this method, i.e. hydroxymercuration–reductive coupling, has been exemplified by applying it to the total synthesis of an antibiotic, malingolide **3–12.1**, as shown in the Scheme 3–12.

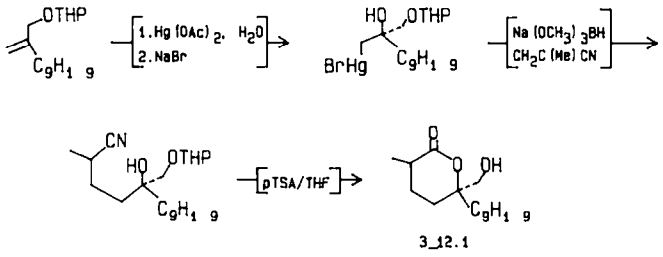
Unlike β-alkoxy mercurials, β-hydroxy mercurials when reduced with SBH in the presence of electron deficient olefins, do not generally result in C–C bond formation in good yields. However, Barluenga's procedure,[125] i.e. surfactant catalyzed reduction of hydroxymercurials with SBH with



SCHEME 3_10



SCHEME 3_11



3_12.1

SCHEME 3_12

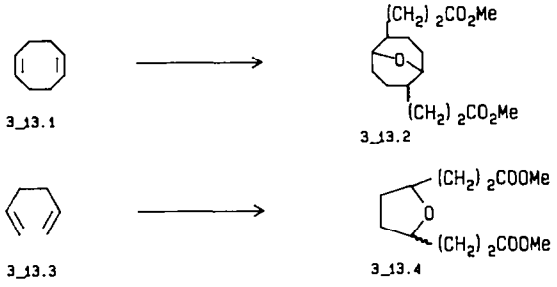
methyl acrylate, provides hydroxy esters. The yields in many cases are better than those obtained from sodium triethoxyborohydride. Under these conditions, *cis–cis* 1,5-cyclooctadiene, **3–13.1**, with methylacrylate gives 1,5-epoxide **3–13.2** in 40% yield as a 70:30 *trans*:*cis* mixture, while an equimolar mixture of *cis*- and *trans*-**3–13.4** is obtained from 1,5-hexadiene **3–13.3**.

The scope of the radical C–C bond formation via β-alkoxy mercurials has been extended to β-azamercurials (β-nitro-, azido-, and sulphonamido-mercurials).[132,133] These have been prepared from a variety of olefins. C–C bond formations have been accomplished by reducing them with sodium trimethoxyborohydride in the presence of acrylonitrile and methylacrylate (Table 14). Nitro- and azido-mercurials have failed to give coupling products with either acrylonitrile or methylacrylate. However, amino- and acetamido-mercurials undergo coupling with acrylonitrile in modest to good yields, while with methylacrylate simple reduction without trapping has been generally predominant. Aminomercurials, which have been coupled with dichloroethylene or chloroacrylonitrile (entries 9, 10; Table 14), have been suggested[134] to be useful starting materials for pyrrolizidine alkaloids.

Contrary to the result[134] observed for entry 1, Table 14, exclusive *trans* product is obtained by simply changing the experimental conditions. The cause for this unexpected stereoselectivity has been attributed to rapid stirring and addition of SBH. To a mixture of organomercurial and 1-chloroacrylonitrile in methanol at −15°C, one equiv of SBH is added very rapidly. The fast reaction of intermediate radical **3–14.2** derived from mercurial **3–14.1** does not allow it to equilibrate from a *trans* to a *cis* radical before addition to the activated olefin. Similar stereoselectivity is observed with cyclopentyl derivative **3–14.7**.

In addition, the highly preferential formation of one isomer at the chloronitrile carbon in **3–14.4** (labeled*) is noteworthy. This unusual result has been explained by the assumption that the radical **3–14.3** is stable enough to react with the bulky RHgH reagent so slowly that the hydrogen atom is delivered from the less-hindered face of the molecule. The preferential attack therefore, is dependent on the existence of constraints due to the stereofacial differentiation.

More conveniently, amides (such as formamide, acetamide), urethanes (such as methyl-carbamate) and ureas can be directly used in aminomercuration of olefins,[135,325,326] if anhydrous mercury nitrate in methylenechloride is used. By using the procedure, several organomercurials are prepared from olefins such as ethylene, propylene, 1-hexene and cyclohexenes. In the same pot, coupling is accomplished with electrophilic olefins such as acrylonitrile, butenone and methyl

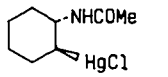
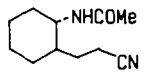
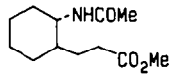
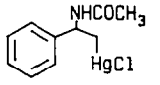
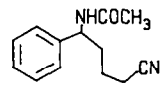
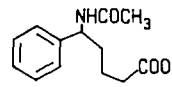
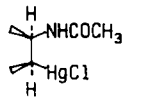
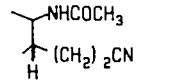
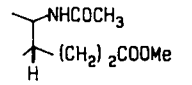
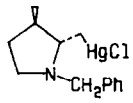
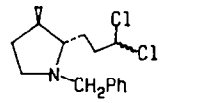
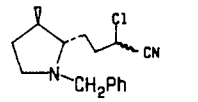
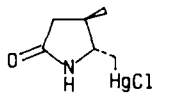
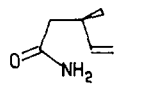


3_13.1 3_13.2

3_13.3 3_13.4

SCHEME 3_13

Table 14. Aza-carbofunctionalization of olefins

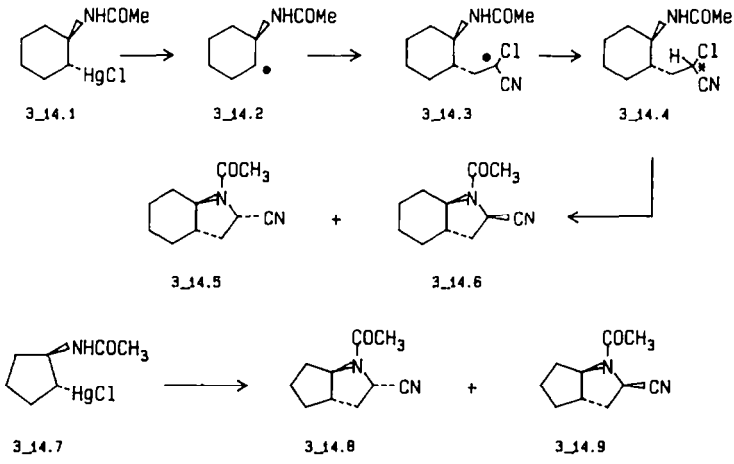
NO	Mercurial	Olefin	Product	Yield (%)
1		A		78 (3:2 cis:trans)
2	"	B		78
3	$CH_3(CH_2)_5CHCH_2HgCl$ NHCOMe	A	$CH_3(CH_2)_5CH(CH_2)_3CN$ NHCOMe	67
4		B	$CH_3(CH_2)_5CH(CH_2)_3COOMe$ NHCOMe	40
5		A		67
6		B		
7		A		74 (68:32)
8		B		26
9		C		43
10		D		26
11		D		-

A= CH_2=CHCN, B= CH_2=CHCOOMe, C= CH_2=CCl_2, D= CH_2=C(Cl)CN

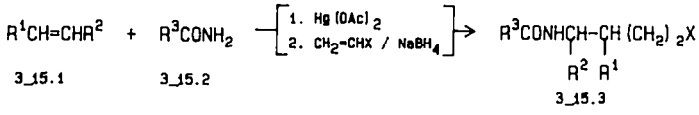
acrylate using aqueous SBH as reducing agent (Scheme 3–15). In nearly all cases (Table 15) the intermediate acylamino alkyl mercury compounds are soluble in the reaction medium. It should be noted that the products with cyclohexene consist of more than 90% *trans* isomer.

The Giese reaction has also been applied[136] to the construction of substituted heterocyclic compounds leading to natural products. In these examples (Scheme 3–16), it should be noted that, during the radical reaction, nitrogen is protected with a carbobenzyloxy (CBZ) group (Scheme 3–16).

The organomercurials derived from *N*-methoxy carbonyl-6-amino-hept-1-ene, **3–17.1**, with mercuric acetate in THF are reduced with SBH in methanol in the presence of ethyl acrylate. This has led to a mixture of *cis* and *trans* piperidines **3–17.4** (1 : 2 ratio) in 62% overall yield.[137] The ratio corresponds to the initial ratio of the amino mercurial. The formation of a stereoisomeric mixture in this cyclization contrasts with the results obtained with *N*-acyl derivatives of 5-aminohex-1-ene



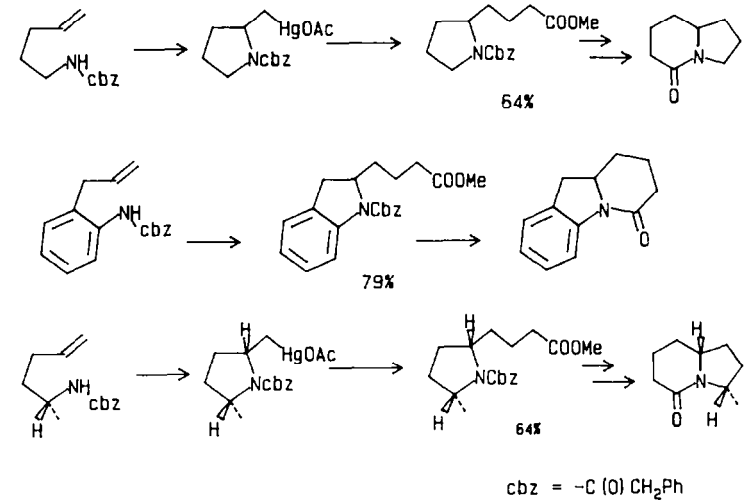
SCHEME 3_14



SCHEME 3_15

which gives entirely *trans* 2,5-dimethylpyrrolidine.[138] This sequence has been utilized to prepare a *trans*-2,6-dialkylpiperidine, solenopsin A **3–17.6 (3–17.2 → 3–17.6)**.

C-Glycosides serve as potential chiral synthetic building blocks for a variety of natural product syntheses. As a consequence, synthetic methods for the stereospecific preparation of C-glycosides and deoxy alkyl sugars have been explored for some time. The existing methods, involving ionic mechanisms, are either poorly diastereoselective or require improvements in the experimental procedures used, in order for them to be of preparative value. Carbohydrate radicals have been generated from a variety of precursors such as bromides, iodides, mercurials, S-methyl thiocarbonates and thiocarbonyl imidazolides, etc. (see functional group transformation).



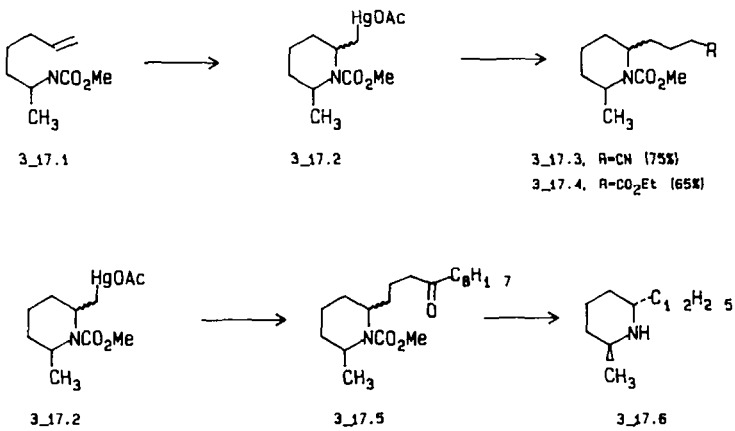
SCHEME 3_16

Table 15. Preparation of *N*-substituted amides (3–15.3)

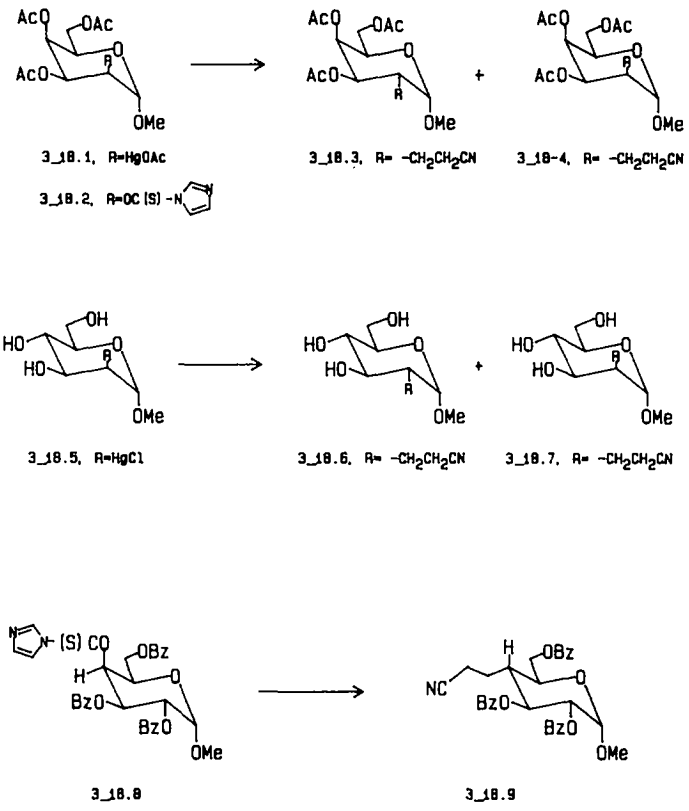
R^1	R^2	R^3	X	Yield (%)
H	H	MeCO	CN	32
CH_3	H	CH_3	CN	30
CH_3	H	MeO	CN	68
nC_4H_9	H	CH_3	CN	77
nC_4H_9	H	CH_3	COOMe	50
nC_4H_9	H	MeO	CN	71
nC_4H_9	H	MeO	COMe	40
nC_4H_9	H	MeO	COOMe	61
$-(CH_2)_4-$		H	CN	40
$-(CH_2)_4-$		CH_3	CN	44
$-(CH_2)_4-$		CH_3O	CN	63
$-(CH_2)_4-$		NH_2	CN	57

Stereo- and regio-chemically generated sugar organomercurials,[139] e.g. **3–18.1** or thiocarbonyl derivatives **3–18.2**, on reduction with tetrabutylammonium borohydride or with TBTH, in the presence of ten-fold excess of α,β-unsaturated nitriles give a mixture of branched deoxy sugars **3–18.3**, and **3–18.4** in 50–67% yield. Similarly, glucal mercurial **3–18.5** (containing free OH groups) with TBTH gives a mixture of **3–18.6**, and **3–18.7** in good overall yields. It should be noted that the major 2-deoxy alkyl sugars have alkyl groups in an equatorial position. However, deoxy alkylation of thiourethane **3–18.8** with TBTH in the presence of acrylonitrile gives exclusively **3–18.9** in 30% yield,[140] along with an equivalent amount of the non-alkylated reduction product. This is in contrast to the observed preferential deuterium incorporation in an axial position.[141] Also, it should be noted that stereoselectivity depends on the nature of alkene substituents. For example, with acrylonitrile **3–18.5** gives a 2 : 1 ratio of equatorial (**3–18.6**) to axial (**3–18.7**) bond formation and with fumarodinitrile almost exclusive equatorial C–C linkage is observed. This stereoselectivity is attributed to the steric differentiation of the α- and the β-face of the sugar ring. Unlike 1-glucosyl radicals[142] (*inter alia*), it appears at least in above cases, that the electronic effects do not influence stereochemistry, appreciably.

Unlike pyranose sugars, furanose sugars appear to be more sensitive to steric hindrance. Reduction of 3-*O*-thiocarbonyl-*S*-methyl glucofuranose **3–19.1**, with catalytically generated[143]

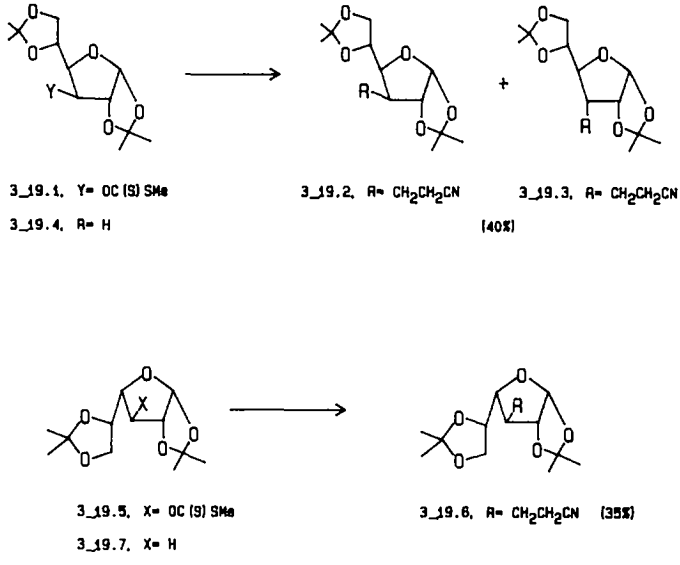


SCHEME 3_17

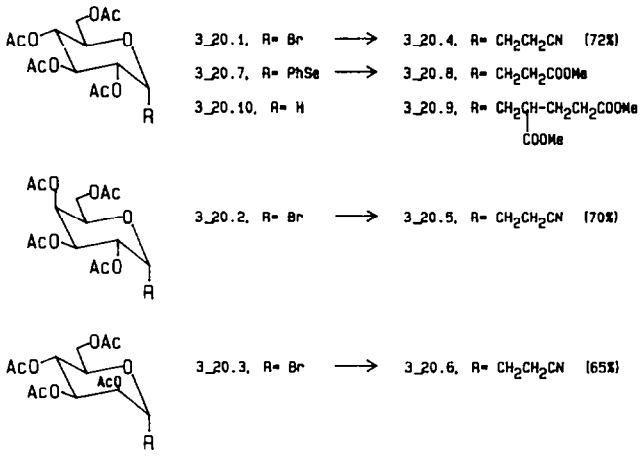


SCHEME 3_18

TBTH in the presence of excess acrylonitrile gives a mixture of **3–19.2** and **3–19.3** (3 : 1 ratio) in 40% yield, whereas galactofuranose **3–19.5** has produced **3–19.6** exclusively, in 35% yield. In both of these cases reduced sugars **3–19.4**, and **3–19.7** are present as by-products.[140] It should be cautioned[143] that the SBH-tin chloride dehalogenations are expected to have different stereoselectivity compared with that using a stoichiometric amount of the tin hydride reagent.[144]



SCHEME 3_19

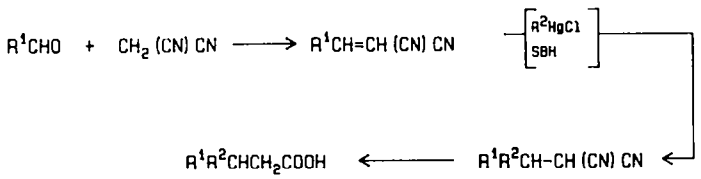


SCHEME 3_20

Photolysis of α-D-glucopyranosyl bromides **3–20.1** to **3–20.3** with TBTH and excess acrylonitrile in boiling ether for 6–12 h gives α-D-pyranoside **3–20.4** to **3–20.6** in good yields.[145] Interestingly, phenyl selenide **3–20.7** with methylacrylate, in refluxing toluene gives C-glycoside **3–20.8** in 40% yield along with a double adduct **3–20.9**.[146] Attempts to reduce the level of **3–20.9** by lowering the acrylate concentration were unsuccessful. This high stereospecific α-anomeric C–C bond formation is in line with deuteration[181] at C-1 of glyco-pyrans or -furans and appears to be due to the anomeric effect[182] and conformational stability of σ radicals.[142]

It is interesting to note that although deoxy sugars (C–H bond formation) are obtained in better than 90% yield via radical intermediates,[141] the C–C bond formation of sugar radicals does not occur to the same extent. Contrary to the sugar derivatives, the diastereoselective C–C bond formation of β-alkoxycycloalkyl radicals derived from cyclopentene, cyclohexene, dihydropyran and dihydrofuran is different and is often poor. In the latter cases, the formation of the *trans* isomer predominates.[147] Studies with several alkenes have shown that the stereoselectivity increases with decreasing reactivity of alkene and is greater with 5- than 6-membered rings. While dihydrofuran reacts with methylacrylate to give *trans* and *cis* isomers in 93 : 7 ratio, the cyclopentene gives an 88 : 12 ratio; cyclohexene in a 65 : 35 ratio.[131,147]

Intermolecular trapping of alkyl radicals with electron deficient alkenes containing an α-alkyl substituent (e.g. Me group) is not a particularly useful synthetic reaction[106,115] (*inter alia*). In the case of a Me group, the rate retarding effect (or reversibility of a radical addition to an olefin) can be counterbalanced by placing two cyano groups at the β-position of the alkene.[148] This concept has been utilized for the preparation of alkanoic acids **3–21.1** (Scheme 3–21) by coupling alkylidinemalononitriles with alkyl radicals generated from the alkyl mercuric chlorides and SBH; followed by hydrolysis and decarboxylation (Table 16). The yields of alkanoic acids are low but because of their ease of preparation, this method should have some applications in synthesis. The required cyano olefins have been prepared by the Knoevengel reaction of aldehydes with malononitrile.



SCHEME 3_21

Table 16. Preparation of alkanoic acids (3–21.1)

R^1	R^2	Yield (%)
CH_3	C_6H_{11}	50
n-C_3H_7	C_6H_{11}	45
i-C_4H_9	C_6H_{11}	45
i-C_4H_9	t-Bu	20
CH_3	t-Bu	50

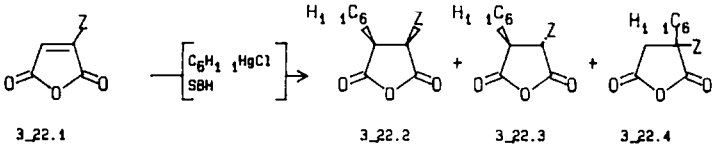
Table 17. Preparation of dialkyl cyclic anhydrides (3–22.2 and 3–22.3)

Z	Yield (%) (ratio)
OAc	75 (94: 6)
CH_3	84 (89: 11)
C_6H_{11}	82 (80: 20)
t-C_4H_9	83 (95: 5)
Ph	60 (73: 27)

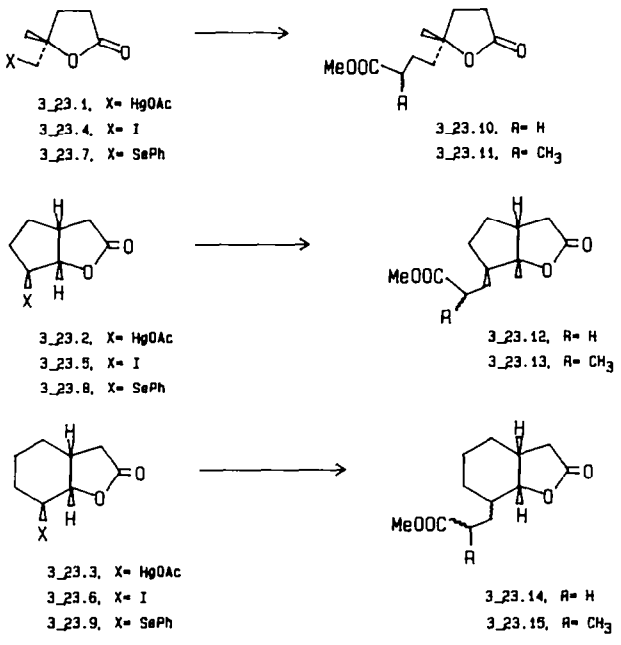
In a radical chain process, the reaction of cyclohexylmercuric chloride with SBH and monoalkylunsaturated cyclic anhydrides, substitution occurs on the least substituted carbon atom, giving mainly *cis* adducts in good yield (Scheme 3–22) (Table 17). The regioselectivity is attributed to the steric effects. One exception to this is fluoro maleic anhydride. In this case the attack occurs predominantly at the substituted C atom because of its electron releasing effect.[149]

A comparative study, for the C–C coupling reaction of the radicals derived from the acetoxymercurio (**3–23.1** to **3–23.3**), iodo (**3–23.4** to **3–23.6**) and phenylseleno (**3–23.7** to **3–23.9**) lactones has been reported.[150] The acetoxymercurio lactones **3–23.1** to **3–23.3** are uniformly unsatisfactory, when treated with sodium trimethoxyborohydride in methylene chloride containing the large excess of ethyl acrylate as a trapping agent. The observed major reaction pathway involves hydrogen atom transfer to give reduction products **3–23.1** to **3–23.3** (X = H). Reproducible moderate yields (45–65%) of coupled products **3–23.10**, **3–23.12**, **3–23.14** are obtained with iodolactones under the above reaction conditions, while phenylseleno lactones have provided the same products in 68–80% yield. In this technology, loss of stereochemical integrity at the developing radical center occurs, resulting in the diastereomeric mixture, particularly when a reducible group is on the 6-membered ring. This is because *exo–endo* differentiation in 6-membered rings is less pronounced. The *cis* fused bicyclo[3,3,0] systems, e.g. **3–23.8** lead to the formation of only one of the two diastereomers. The phenylseleno lactones are generally stable readily characterizable compounds and are available in high yields compared with iodides and mercurials.

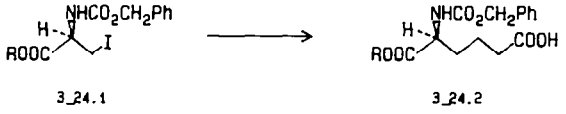
Nucleophilic displacement on β-haloamino acid derivatives with C-nucleophiles usually leads to dehydro derivatives and this strategy also requires extensive protection and deprotection. However,



SCHEME 3_22



SCHEME 3_23



SCHEME 3_24

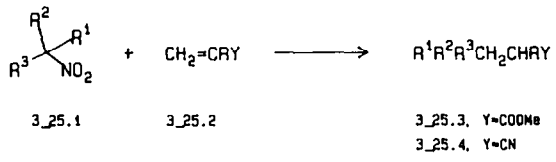
radical mediated coupling reactions of β-iodoaminoacids have been successfully accomplished[146] as shown in Scheme 3–24. For example, the protected iodoamino acid **3–24.1** reacts with acrylic acid (2 equiv added in two portions) and AIBN (1 mg/h), by slow addition of TBTH (2 equiv) in refluxing benzene, to give **3–24.2** in 30% yield.

The reduction of alkyl iodides, in the presence of electron withdrawing olefins with TBTH (generated[143] from a catalytic amount of tributyltin chloride and excess SBH) in toluene at 110°C gives[140] excellent yields of the corresponding alkanes (Table 18). Under similar conditions *S*-methylthiocarbonates provide slightly lower yields.

It has been shown that the aliphatic nitro compounds are good alkyl radical precursors (*inter alia*) and they have been used for C–C bond formation reactions. Heating a mixture of a nitroalkane, e.g. **3–25.1**, with an olefin **3–25.2**, TBTH (2.5 equiv) and AIBN in benzene for 5–10 min gives good

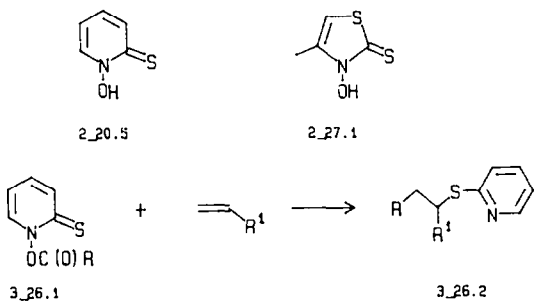
Table 18. Alkanes from reductive alkylation of alkyl-iodides and -thiocarbonyls

RX	Alkene	Yield (%)	RX	Alkene	Yield (%)
$nC_6H_{13}I$	CH_2=CHCN	80	cyc-$C_6H_{11}I$	CH_2=CCl_2	91
t-C_4H_9I	CH_2=CHCN	87	cyc-$C_6H_{11}I$	CH_2=C (Me) CN	86
cyc-$C_6H_{11}I$	CH_2=CHCN	95	c-$C_6H_{11}OC$ (S) SMe	MeCH=CHCN	63
cyc-$C_6H_{11}I$	CH_2=CHCOMe	85	c-$C_6H_{11}OC$ (S) SMe	CH_2=$CHCO_2$Me	50
cyc-$C_6H_{11}I$	CH_2=$CHCO_2$Me	85	c-$C_6H_{11}OC$ (S) SMe	CH_2=C (Me) CN	45
cyc-$C_6H_{11}I$	CH_2=CHC_6H_5	83	c-$C_6H_{11}OC$ (S) SMe	MeCH=CHCN	40



3_25.1 3_25.2 3_25.3, Y=COOMe
3_25.4, Y=CN

SCHEME 3_25



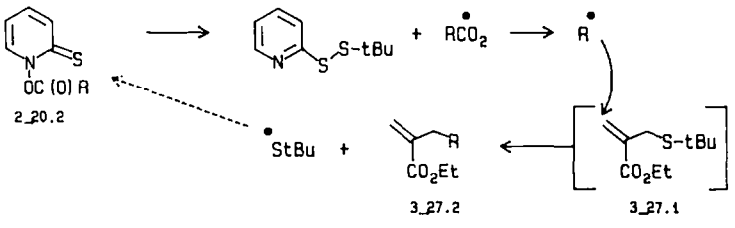
2_20.5 2_27.1 3_26.1 3_26.2

SCHEME 3_26

yields of products **3–25.3** and **3–25.4**. The advantage of this procedure over Geise's method is that there is no need to use excess olefin, the reaction times are shorter and less side products are formed. Using this procedure tertiary nitro compounds are converted into quaternary C compounds.[227]

The radicals generated from the decarboxylative rearrangement of esters derived from thiohydroxamic acids show controlled behavior giving selective chemical reactions[152] (*inter alia*). Radicals, generated from the carboxylic acid esters of thiohydroxamic acids **2–20.5** or **2–27.1** (Scheme 3–26), add to electron deficient olefins to give C–C coupled products with variable efficiency[153,337] (Table 19). Addition to singly activated olefins affords adducts with a sulfur function (entries 1–6, Table 19), while addition to olefins with α,β-double activation gives products which are the result of addition and elimination (entries 7, 8, 11). In the case of certain olefins (entries 8, 10), the stereochemistry of the addition is well defined. Addition to acetylenes gives olefins as a mixture of geometric isomers (entries 12, 13).

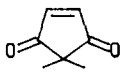
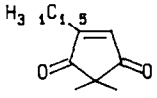
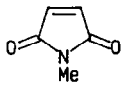
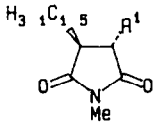
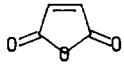
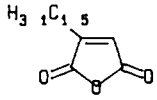
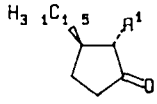
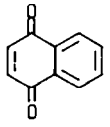
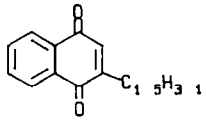
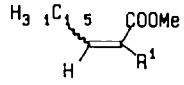
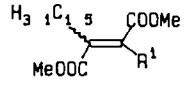
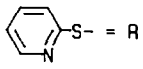
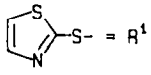
Allylation of C-radicals is a useful synthetic operation (*inter alia*). Addition of alkyl radicals generated from carboxylic acid anhydrides of thiohydroxamic acids (*inter alia*) to an olefin, such as the reagent **3–27.1**, gives the corresponding 2-carbethoxy allyl derivatives with a shift of double bond and concommitant elimination of thiyl radical, which further carries the radical chain (Scheme 3–27).[154,337] The reaction is performed by dropwise addition of the carboxylic acid chloride to a mixture of **2–20.5** and **3–27.1** in chlorobenzene at reflux under nitrogen (Table 20). It should be noted that the yields in general are better than those obtained with simple activated olefins (compare yields in Table 19), and the reactions are cleaner, with little or no polymerization. Also, tertiary radicals are coupled in good yields (entries 2, 7).



2_20.2 3_27.2 3_27.1

SCHEME 3_27

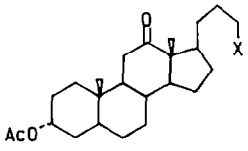
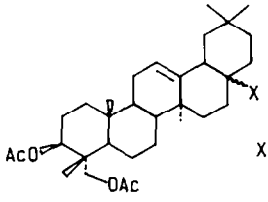
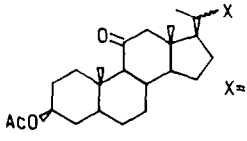
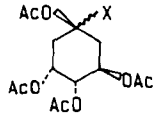
Table 19. Reductive alkylation of thiohydroxamic acid anhydrides

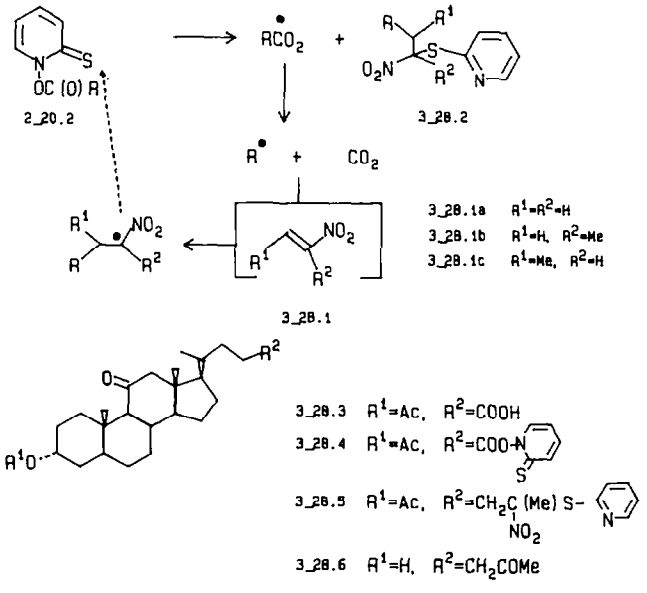
NO	Radical[a]	Olefin	Product[b],[c],[d]	Yield (%)
1	$C_{1\ 5}H_{3\ 1}$	CH_2=CHCN	$C_{1\ 5}H_{3\ 1}CH_2CH$ (R) CN	59
2	$C_{1\ 5}H_{3\ 1}$	CH_2=CHCOOMe	$C_{1\ 5}H_{3\ 1}CH_2CH$ (R) COOMe	83
3	$C_6H_{1\ 1}$	CH_2=$CHNO_2$	$C_6H_{1\ 1}CH_2CH$ (R) NO_2	45
4	$C_{1\ 5}H_{3\ 1}$	CH_2=C (Cl) CN	$C_{1\ 5}H_{3\ 1}CH_2C$ (R) ClCN	40
5	$C_{1\ 5}H_{3\ 1}$	NCCH=CHCN (t)	$C_{1\ 5}H_{3\ 1}CH$ (CN) CH (R) CN	60
6	$C_{1\ 5}H_{3\ 1}$	CH_2=CHCOMe	$C_{1\ 5}H_{3\ 1}CH_2CH$ (R) COMe	43
7	$C_{1\ 5}H_{3\ 1}$			70
8	$C_{1\ 5}H_{3\ 1}$			93
9	$C_{1\ 5}H_{3\ 1}$			69
10	$C_{1\ 5}H_{3\ 1}$			30
11	$C_{1\ 5}H_{3\ 1}$			26
12		H—≡—COOMe		38
13		MeOOC—≡—COOMe		50
				

[a] Entries 1–5 with **2–20.5**: entry 6–13 with **2–27.1**.
[b] Entries 1–4: light (300 W tungston lamp) in benzene, N_2.
[c] Entries 7–9: light (100 W medium pressure mercury lamp) in benzene, N_2.
[d] Entries 5, 6, 10–13: reflux in toluene, N_2.

Using tin hydride reactions of nitro compound which involve nitro radical anion with tributyl tin cation as counterion, C-glycosides with tertiary anomeric C atoms have been prepared in good yields.[155] Nitro olefins polymerize under ionic conditions, particularly with bases. Interestingly, they are inert to radical conditions. Analogous to alkyl radical addition to olefins containing electron withdrawing groups, nitro-olefins are good radiocophiles.[153,156] Acid esters **2–20.2**, prepared from the carboxylic acid chloride and thiohydroxamic acid **2–20.5** (*inter alia*), and nitro olefin **3–28.1** are irradiated in the presence of camphorsulphonic acid (2 equiv) for approximately 30 min at −20 to 0°C to give good yields of **3–28.2** (Scheme 3–28). It is essential that the reaction medium should be acidic; otherwise, the presence of trace amounts of basic impurities results in reduced yields. Nitropropenes such as **3–28.1a** to **3–28.1c** can be used equally well (Table 21). Adducts of 2° and especially 3° carboxylic acids with 2-nitropropene **3–28.1b** are labile and difficult to purify. It is

Table 20. Reductive alkylation of carboxylic acids (via addition–elimination) with **3–27.1**

1		X= COOH	⟶ $-CH_2C(=CH_2)COOEt$	(76%)
2		X= COOH	⟶ $-CH_2C(=CH_2)COOEt$	(74%)
3		X= COOH	⟶ $-CH_2C(=CH_2)COOEt$	(74%)
4		X= COOH	⟶ $-CH_2C(=CH_2)COOEt$	(56%)
5	$CH_3(CH_2)_{14}-X$	X= COOH	⟶ $-CH_2C(=CH_2)COOEt$	(69%)
6	$(PhCH_2)_2CH-X$	X= COOH	⟶ $-CH_2C(=CH_2)COOEt$	(60%)
7	ADAMENTAN-X	X= COOH	⟶ $-CH_2C(=CH_2)COOEt$	(71%)
8	CYCLOHEXYL-X	X= COOH	⟶ $-CH_2C(=CH_2)COOEt$	(74%)



SCHEME 3_28

Table 21. Preparation of **3–28.2** and **3–29.1** from **2–20.2**

NO	R	R^1	R^2	Yield (%) 3_28.2	Yield (%) 3_29.1
1	$Me(CH_2)_{1-4}$-	H	H	81	100
2	Cyclohexyl-	H	H	70	89
3	1- Adamantyl-	H	CH_3	97	95
4	$Me(CH_2)_{1-4}$-	H	CH_3	65	
5	$PhCH_2CH_2$-	H	CH_3	71	

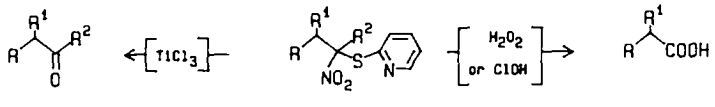
interesting to note that quantitative formation of α-nitrosulfide **3–28.5** is obtained from steroid acid **3–28.3**. β-Alkyl substituents of the olefinic component are known to exert considerable inhibitory action on radical additions rendering β-substituted olefins almost useless for synthetic process[148] (*inter alia*). However, despite the presence of terminal Me groups as in **3–28.1c**, reaction occurs smoothly with an adamantyl radical (Table 21, entry 7).

The nitrosulfides are versatile synthetic intermediates. For example, adducts derived from nitroethylene **3–28.1a** are readily converted into the corresponding carboxylic acids **3–29.1** by exposure to alkaline hydrogen peroxide[156] (Scheme 3–29). Chlorination with sodium hypochlorite followed by alkaline hydrolysis also achieves the same transformation, but less efficiently. The overall sequence in Scheme 3–28 and Scheme 3–29 represents a mild conversion of a carboxylic acid into the next higher homologene, complementing the classical Arndt–Eistert reaction (which involves the use of diazomethane rendering it relatively non-useful for large scale work). The reductive cleavage of adducts **3–28.2** with $TiCl_3$ gives the corresponding aldehyde or ketones **3–29.3**. By this method, the steroidal α-nitrosulfide **3–28.5** gives 25-keto steroid **3–28.6** with simultaneous cleavage of the 3α-acetoxy group in 90% yield.

Radicals derived from **2–20.2** add to nitro olefins such as **3–30.1** generating a new nitro olefin **3–30.2** by the addition of alkyl radicals, followed by elimination of a phenylthio radical. Addition of a second radical derived either from **2–20.2** or from a different ester **3–30.3** produces symmetrical **3–30.5** or unsymmetrical **3–30.4** nitrosulfides. The reductive cleavage of nitrosulfides with $TiCl_3$ produces symmetrical or unsymmetrical ketones, respectively. This double addition generally gives lower yields.[156]

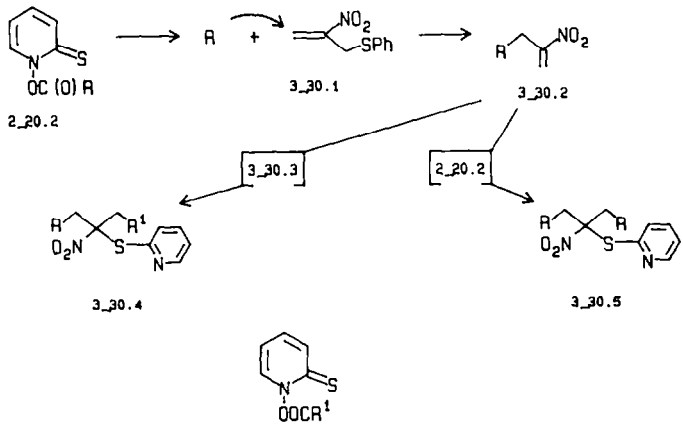
In general, quaternary C centers are formed from tertiary alcohols either from cationic reactions or $S_{RN}1$ reactions. Although (*inter alia*) the Giese procedure and other similar reactions[140,157] are not useful, for the preparation of quaternary C centers, radicals produced from half oxalate esters of a tertiary alcohol **2–6.3** are[156] (Scheme 3–31). The radicals produced in this reaction give C–C bond formation[158] with a variety of activated olefins. The reactions are usually conducted in refluxing benzene containing the ester and the olefin for 1 h.

A cleaner and efficient process[158] for the preparation of quaternary Cs is carboethoxyallylation of radicals generated from the esters of the type **2–6.3** (Scheme 3–32). For example, in refluxing chlorobenzene, 1-adamantanol ester **2–6.3** (R = adamantyl) furnishes the 1-adamantyl radical which adds efficiently to an olefin, such as **3–32.1**, with concomitant expulsion of the *t*-butylthiol radical (S_H2'). Similar reaction with olefin **3–32.2**, results in the formation of allylation products. The allyl-*t*-butylsulfide **3–32.2** is readily available and its ease of removal from the reaction by distillation is advantageous as compared to allyltributylstannane (*inter alia*).

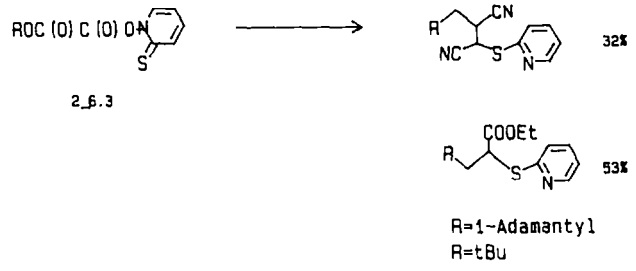


3_29.3 3_28.2 3_29.1

SCHEME 3_29



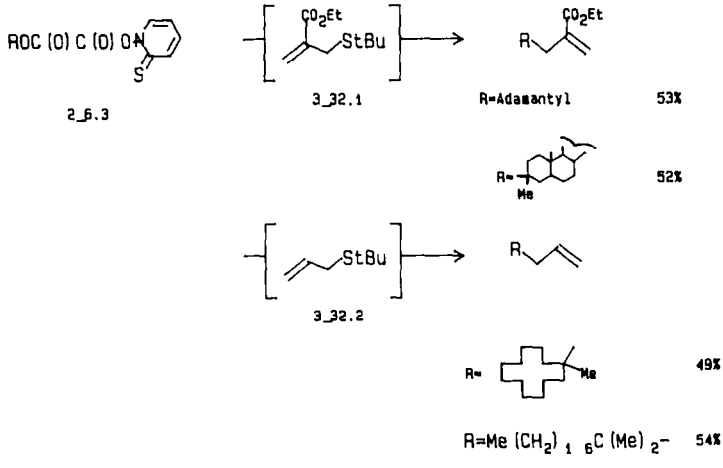
SCHEME 3_30



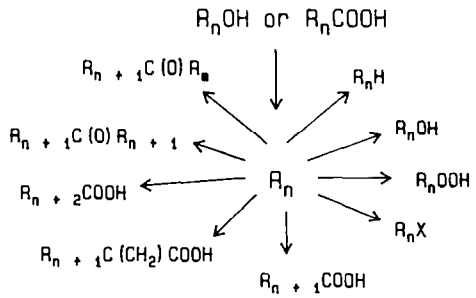
SCHEME 3_31

The utility of thiohydroxamic esters of carboxylic acids (mixed anhydrides), and alcohols (glyoxalates) is summerized in Scheme 3–33.

In contrast to the normal behavior of propionate radicals, β-substituted propionate radicals such as **3–34.2**, derived from the conjugate addition of alkyl radicals to β-stannyl acrylates **3–34.1**, eliminate the stannyl group generating β-substituted acrylate systems[159] **3–34.3** (Scheme 3–34). Similar addition elimination reactions have been described with sulfur substituted acrylate systems (*inter alia*). This reaction is general and produces adducts from a variety of radicals derived from primary, secondary and tertiary bromides[160] (Table 22). The reaction is usually conducted by heating bromides in benzene (1 ml/mmol) with β-stannyl compounds **3–34.4** or **3–34.5** (2 equiv) in the presence of AIBN for 24–36 h. The major side product in this reaction is the adduct derived from the isobutyronitrile radical (from AIBN). Triphenylstannyl acrylate **3–34.9** gives comparable



SCHEME 3_32

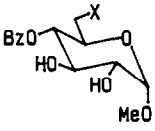
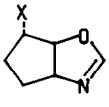
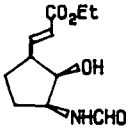
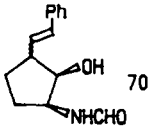


SCHEME 3_33

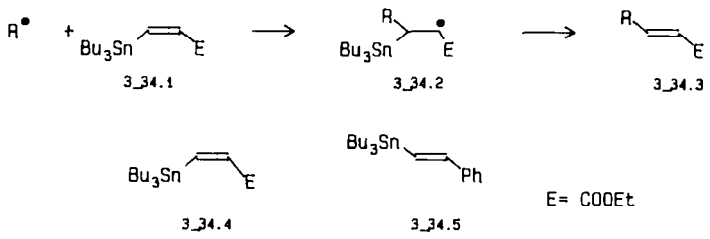
results to that of **3–34.4**, which in turn is more reactive than the β-stannyl styrene **3–34.5**. Vinyl stannanes, **3–34.6** to **3–34.8**, however, are not reactive under these conditions. The scope of this reaction has been extended by applying it to the synthesis of a key intermediate in the total synthesis of an antibiotic, "compound 270", **3–34.10**, starting from **3–34.11** (entry 8, Table 22). It should be noted that the free radical chain reaction between an organomercurial (e.g. PhHgBr) and (*E*)- or (*Z*)-**3–34.1** forms **3–34.5** in a stereospecific manner, although the selectivity in the formation of (*Z*)-1,2 disubstituted alkenes from a (*Z*)-precursor sometimes is low.[171,321]

The allyl transfer reaction from allyl tri-*n*-butylstannane is a valuable synthetic method (*inter alia*). Very few compatible methods are available for the replacement of halogen with a carbon appendage, particularly when a leaving group is present at β-position. The reaction of allyl tri-*n*-

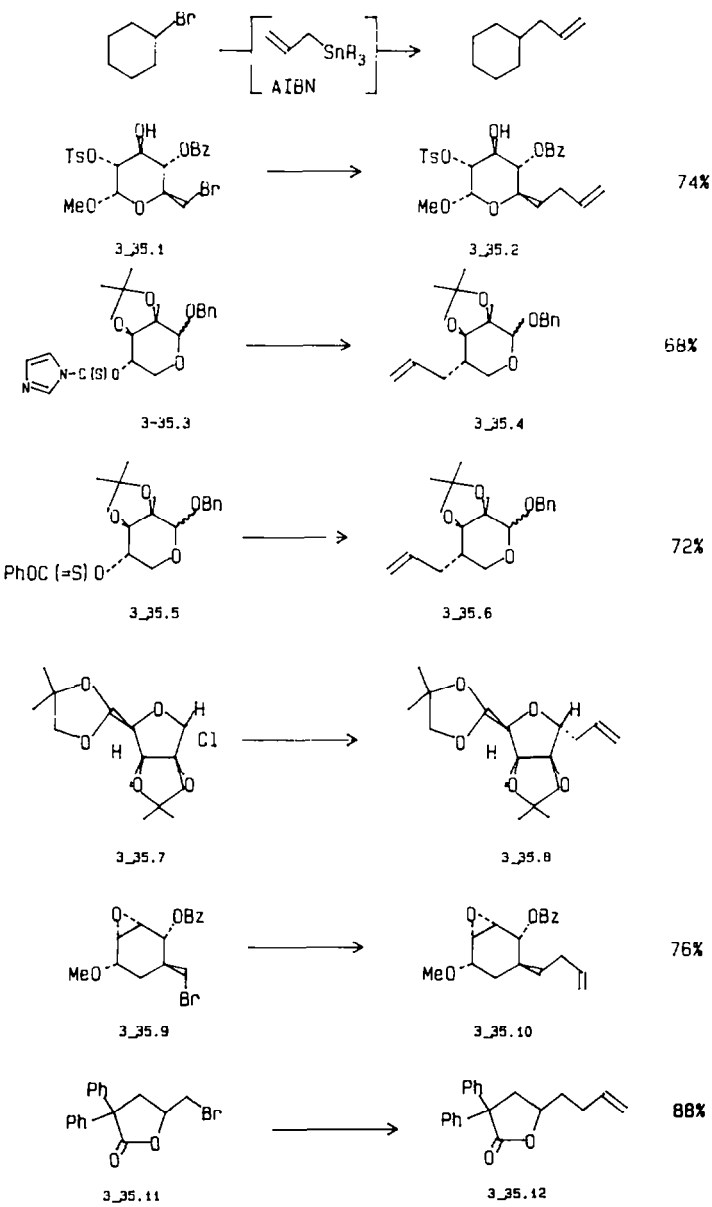
Table 22. Reactions of alkyl halides with β-stannylcompounds

NO	Radical precursor A, X=Br	Product, Yield (%) B, X= -CH=CHCO$_2$Et	C, X= -CH=CHPh
1		52	52
2		63	22
3		74	82
4		-	32
5		43	41
6		57	51
7		49	42
8		 79	 70

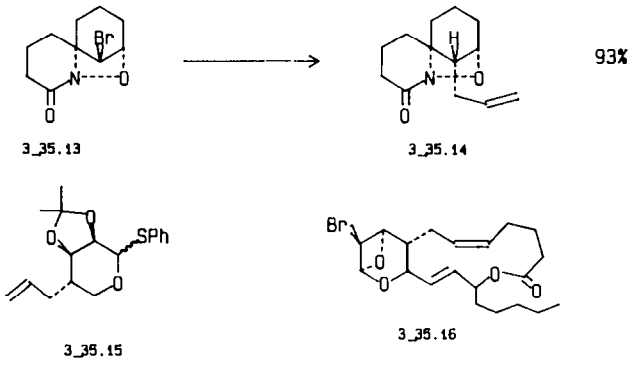
3_28.11



SCHEME 3_34



SCHEME 3_35



SCHEME 3_35

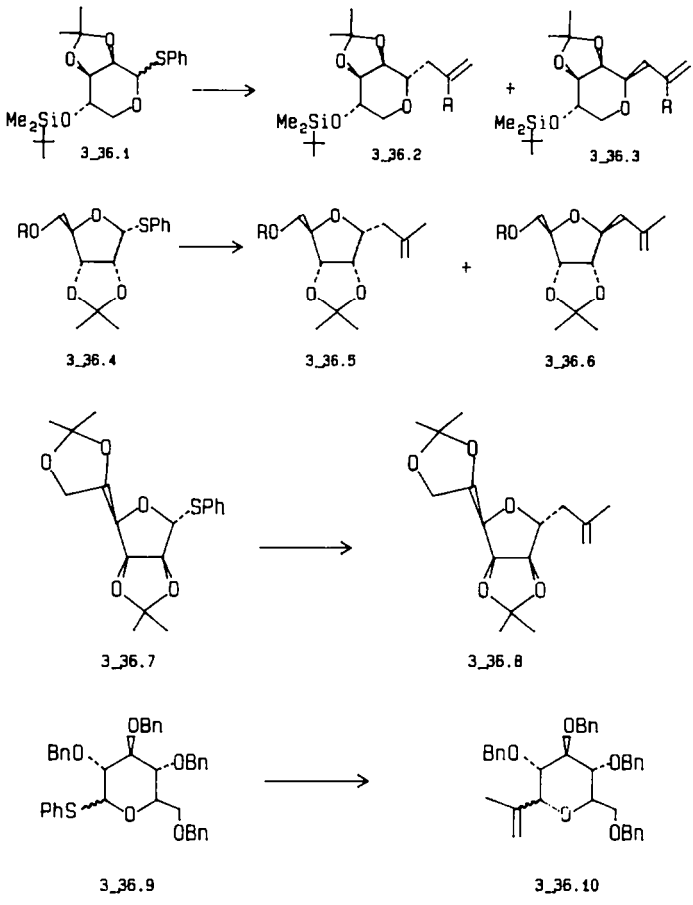
butylstannane with halides provides a general method for C–C bond formation as shown in the Scheme 3–35. The C centered free radical chain initiation is accomplished either thermally or photochemically, by reacting two equiv of allyl-*n*-butylstannane with one equiv of substrate in degassed toluene solution (1 ml/mmol of substrate). C–C bond formation occurs in good yields.[157] Other functional groups besides bromides, which are capable of producing C-radicals can be used for this coupling process. Also, this process tolerates the presence of functional groups such as acetals, ketals, ethers including THP ethers and benzyl ethers, epoxides, lactones, free OH groups, esters and sulfonate esters. Although chemical or photochemical initiation can be utilized with halides or selenides, with thioacylimidazoles, **3–35.3**, chemical initiators such as AIBN are found to be less suitable.

Free radical processes are expected to be devoid of retention of stereochemistry at the radical site. However, it should be noted that substrate **3–35.5** gives complete equatorial incorporation of the allyl unit. Mannose derivative **3–35.7** is found to yield a product with α-allyl appendage due to the attack of the reagent from the least hindered face of the radical intermediate. The compound **3–35.14** is an intermediate in the total synthesis of (±)-perhydrohisterionicotoxin.[183]

Although this radical approach has been successful for the synthesis of C-glycosides, reaction of the thiophenylglycoside **3–35.15** with methallylstannane is unsuccessful, due to the intramolecular cyclization of the initially formed radical at the anomeric center with the existing olefin side chain.[184] Such unwanted reactions can be avoided by appropriate precautionary measures. For example, during the total synthesis of thromboxane A_2, the side chain *trans* double bond in **3–35.16** is kept away from reaching the radical center by the formation of a macrolactone prior to the generation of the radical intermediate.[161,162]

Simple thioethers have been generally unsuitable as substrates for the free radical allylation processes, while the corresponding phenylselenides or bromides have given allylated products in good yields (*inter alia*). However, when an activating group, e.g. an α-alkoxy substituent, is present, the phenylthio group can be used successfully as a radical precursor. Also the phenythio group is superior in this regard to halides or thionocarbonates,[163] in some cases. The reaction of thiophenyl glycoside of l-lyxose derivative **3–36.1** with methalyl tri-*n*-butylstannane (2 equiv) using photochemical initiation gives a mixture of anomers α-**3–36.2** and β-**3–36.3** (R = Me) in 87% yield (92 : 8 ratio). Similarly, **3–36.1** gives allyl tri-*n*-butylstannane in 82% yield as a 90 : 10 mixture of α and β isomers, **3–36.2** and **3–36.3** (R = H). Application of this reaction to the ribofuranose series, e.g. to benzyloxymethyl protected substrate **3–36.4** (R = $PhCH_2OCH_2$—), is unsuccessful while the silyl protected derivative (R = dimethyl *t*-butylsilyl or diphenyl *t*-butylsilyl) yields a mixture of products **3–36.5** and **3–36.6** in 79–80% yield.[327,339] The isomeric ratio is rationalized by the effective steric approach from the β-face of the molecule. This allylation procedure has also been investigated with mannose and glucose derivatives **3–36.7** and **3–36.9**. The compound **3–36.7** gives a 91% yield of the α-methallylated product **3–36.8** (99 : 1 α : β selectively), while **3–36.9** (α or β anomer) gives a 1 : 1 mixture of α and β methallylated products **3–36.10**.

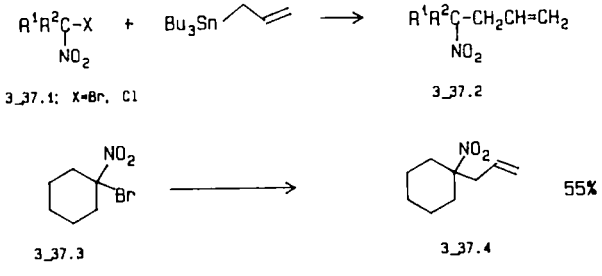
In general, it is difficult to introduce an alkyl groups, such as a methyl, ethyl or allyl group, at the α-position of a nitro group either by nucleophilic (via α-anion) or electrophilic (via Grignard reagents) reactions. α-Nitroalkyl radicals which can be generated from gem halo nitro compounds undergo C–C bond formation with allyltributylstannane via a radical chain process (S_H2') (Scheme



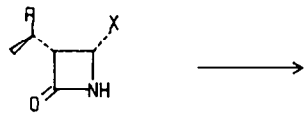
SCHEME 3_36

3–37).[164] The reaction is usually carried out either with a radical initiator (AIBN) at 100°C or with light at 25°C (conventional medium-pressure mercury lamp equipped with a pyrex filter). Bromo and chloro nitro compounds undergo allylation, but iodo compounds do not. Although simple alkyl halides react with allylstannane to give allylated products in good yield (*inter alia*), nitrohalides **3–37.1** are more reactive in the S_H2' reaction.

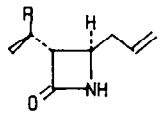
Since the discovery of thienamycin, the therapeutic potential of carbapenems has been widely recognized. The allyl group at the 4-position of azitidine is of particular importance since it can readily be converted into a two-carbon fragment, providing ready access to the precursors of carbapenem. The known ionic methods involve strong acidic or basic conditions or require low temperature to introduce a carbon substituent into azitidine. Allyl group transfer, for example from tri-*n*-butyl allylstannane **3–38.14** to azididine **3–38.2** or **3–38.3**, occurs in good yields[165] in the presence of a catalytic amount of AIBN in toluene at 90°C. Interestingly, a photoinitiated radical reaction does not work in this case. Under these conditions, conversion of fluoroethyl substrate **3–**



SCHEME 3_37

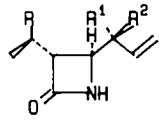


3_38.1 X=H, R=OH
3_38.2 X=SC(S)OEt, R=OSi(Ph)$_2$tBu
3_38.3 X=SC(S)SEt, R=H
3_38.4 X=SC(S)OEt, R=F

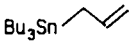


3_38.5 R=OSi(Ph)$_2$tBu 72%
3_38.6 R=H 79%
3_38.7 R=F 67%

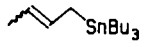
3_38.8 X=SEt
3_38.9 X=S(O)Et
3_38.10 X=SC(S)Et, R=OSi(Ph)$_2$tBu



3_38.11 R=OSi(Ph)$_2$tBu, R^1=Me, R^2=H
3_38.12 R=OSi(Ph)$_2$tBu, R^1=H, R^2=Me



3_38.14



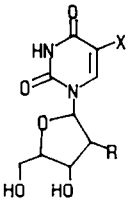
3_38.13

SCHEME 3_38

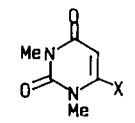
38.4 to the corresponding product **3–38.7** requires 20 h. In all cases, the allyl group is introduced from the sterically less hindered face of the β-lactam thus giving the products with *R*-configuration at the newly created chiral center. This stereochemistry is essential for the antibacterial activity of bicyclic β-lactam antibiotics. With crotylstannanes **3–38.13**, azitidine **3–38.2** gives products **3–38.11** and **3–38.12** as a diasteriomeric mixtures in variable ratios. It is noteworthy that in the thermal reaction in the presence or absence of AIBN, threo isomers are predominant by-products.

In general, alkyl stannanes having substituents at the 1- or 2-position do not react with alkyl radicals generated from alkyl halides under photochemical or thermal conditions.[166] The photocoupling of allylsilanes with alkyl halides is also not a particularly good reaction for C–C bond formation. However, allylation of heterocyclic iodides **3–39.1** to **3–39.4** (vinyl iodides) is accomplished in good yields by irradiation of allyl trialkylsilanes or stannanes with a 100 W high pressure Hg lamp through a pyrex filter in acetonitrile–water (5 : 1) in 50% yield[167] (Scheme 3–39). In contrast to the usual methods, i.e. transition metal catalyzed coupling reactions, these reactions can be conducted without the protection of free OH groups and they also allow the use of aqueous solvents.

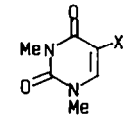
Analogous to allylstannanes, prop-2-ynylstannanes can act as allene transfer reagents under radical conditions (Scheme 2–56). Alkyl radicals produced from alkyl bromides and iodides react



3_39.1 X=I, R=OH
3_39.5 X=-$CH_2CH{=}CH_2$, R=OH 50%
3_39.2 X=I, R=H
3_39.6 X=-$CH_2CH{=}CH_2$, R=H 47%

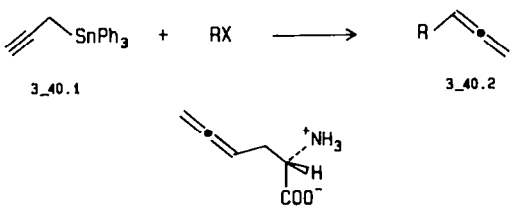


3_39.3 X=I
3_39.7 X=-$CH_2CH{=}CH_2$ 80%



3_39.4 X=I
3_39.8 X=-C(Me)$_2$CH=CH_2 27%

SCHEME 3_39



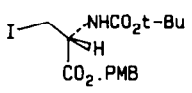
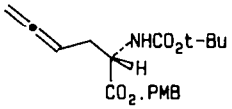
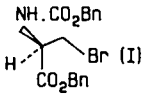
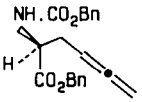
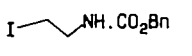
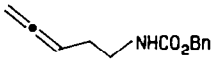
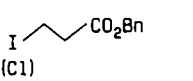
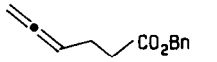
SCHEME 3_40

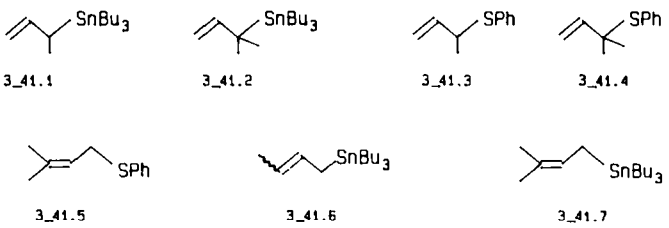
smoothly with triphenylprop-2-ynylstannane **3–40.1** in the presence of AIBN in degassed benzene at reflux to provide terminal allenes **3–40.2**, as shown in Scheme 3–40.[168] In this method, an excess of triphenylprop-2-ynylstannane is required as this reagent isomerizes[169] to the more stable triphenylprop-1,2-dienylstannane under the reaction conditions. This reaction has been applied to a stereospecific synthesis of the naturally occurring allenic aminoacid, 1-2-aminohexa-4,5-dienoic acid **3–40.3**. It is particularly noteworthy that it is applicable to highly functionalized amino acids as shown by the examples in the Table 23. The procedure is compatible with most standard protecting groups used for amino acids, and good to reasonable yields are obtained.

A general note may be added regarding allylation of radicals via allyltin compounds. The efficiency of the free radical chain reaction between allyltin compounds and the organic halides, depends on the nature of the halide and ease of halogen abstraction by a stannyl radical. Electrophilic radicals produced from negatively substituted halomethanes (with Cl, CN) attack the π bond of allyltin compounds with ease. Aralkyl and alkyl radicals are less reactive and need higher concentrations of allyltin.[170]

In spite of the radical mediated non-reducing reaction conditions, allylation with allyltin is limited with regard to substitution on the allylstannes. For example, allylstannanes having Me substitution at C-3, as in **3–41.1** and **3–41.2**, cannot generally be employed, since these materials undergo facile allylic rearrangement to their thermodynamically more stable isomers **3–41.6** and **3–41.7** under the reaction conditions. Phenylthio compounds **3–41.3** and **3–41.4** on the other hand appear to be alternatives to **3–41.1** and **3–41.2** (Scheme 3–42). Irradiation of radical precursors, e.g. alkyl halides, selenides and mixed thionocarbonates **3–42.1**, in the presence of phenylthio compounds **3–41.3** or **3–41.4** and hexabutylditin leads to the products **3–42.2** in good yield as shown in Table 24.[330] The preferred substrates are bromides and iodides. As expected, a *cis–trans* mixture of olefinic products results with **3–41.3**. The success of this reaction depends on the critical balance between relative rates of the chain carrying steps in the order shown in Scheme 3–43. When halogen abstraction by tin radical is slow, as with arylbromides or iodides, the reaction of **3–41.3** or **3–41.4** with the stannyl radical is the preferred pathway. Attempts to extend this process to sulfides **3–41.5** bearing

Table 23. Preparation of allenic amino acids

NO	Substrate	Product	Yield (%)
1			55%
2			60% (55%)
3			46%
4	 (Cl)		55% (<5%)
5	1-Bromoadamantane	Adamantane-1-CH=C=CH_2	45%



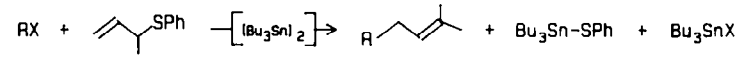
SCHEME 3_41

alkylsubstitution at the allylic terminus have been unsuccessful. Despite the numerous possibility for side reactions, the success of this chain process is noteworthy.

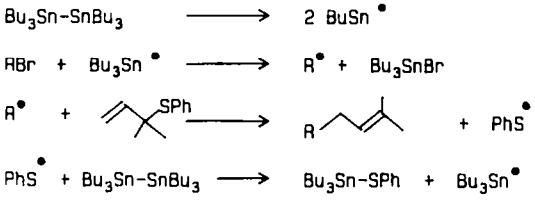
β-Styrenyl or β,β-diphenylvinyl derivatives **3–44.1** and **3–44.2** undergo a free radical chain reaction with alkylmercury halides (RMgX, R = primary, secondary, tertiary alkyl) to yield alkenes **3–44.3** and **3–44.4** by an addition–elimination sequence,[321] without contamination of the dimer R–R. Predominantly, the (*E*)-isomer is formed with **3–44.1**. The reaction is initiated either by light or AIBN or benzoyl peroxide. It should be noted that the 1-alkenylmercurials are more reactive than the 1-alkenyltins.[171]

When α-iodo stannyl esters **3–45.1** are refluxed with a catalytic amount of AIBN and excess electron rich olefins, lactones **3–45.4** are obtained[172] via radical **3–45.3**. The yields range from 58 to 78%. Lactone yields are higher with iodostannyl esters compared to their bromo counterparts. This reaction also works well with electron rich alkenes but not with electron deficient alkenes. γ-Ethoxybutyrolactones are not stable to these reaction conditions. The reaction offers an alternative to existing lactone synthesis methods (*inter alia*).

Recently, peroxide initiated radical additions of carboxylic acids and their derivatives to heteroaromatic[173] and unsaturated compounds (α-olefins) have been reviewed.[174] Acetate radicals generated from Mn(III) in acetic acid add to olefins resulting in a γ-lactone annulation of predictable regio- and stereochemistry[175] (Scheme 3–46). The reaction conditions have been optimized to maximize the lactone yield [olefin, 0.1 M; Mn(III)acetate, 0.083 M 2.5 equiv of Mn(III); KOAc, 0.5 M] (Table 25). The isolated yields are in the range of 60–80%, which compare favorably with other multi-step routes to lactone annulation. The regiochemistry of Mn(III) mediated lactone annulations can be predicted and is generally high. Due to the preferential formation of tertiary > secondary > primary radicals, alkenes show regioselectivity. A benzylic radical intermediate is favored over a radical α to an ester group (entry 13). The stereochemistry is not so pronounced in some cases and is dependent on the nature of the alkene utilized. Substituted acyclic alkenes give *trans*-disubstituted lactones with stereoselectivity ranging from 3.3 : 1 (entry 2) to 67 : 1 (entry 11), while an essentially identical mixture of *trans/cis* products is obtained from both *trans*- and *cis*-4-octene (entries 2 and 3). As expected annulation onto a cyclopentene moiety produces only the *cis* fused lactone, while cyclohexene, cycloheptene and cyclooctene show a regular progression toward

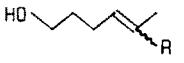
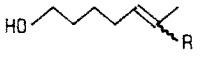
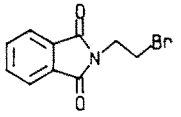
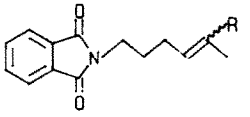
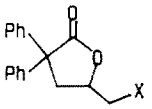
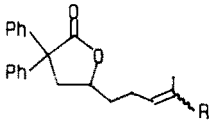
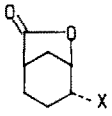
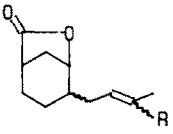


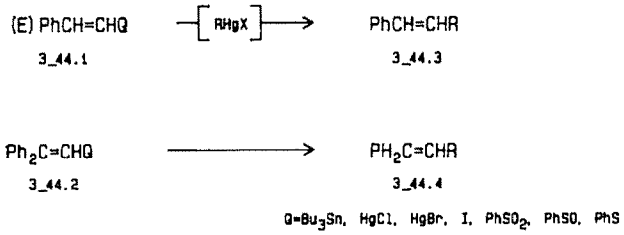
SCHEME 3_42



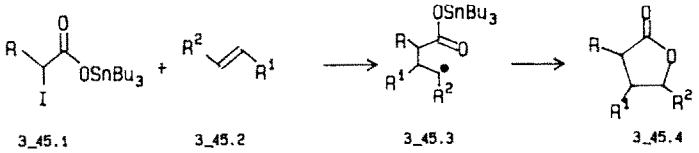
SCHEME 3_43

Table 24. Allylation of sulfides **3–41.3** and **3–41.4** with (Bu_3Sn–$SnBu_3$)

Substrate	Product	Yield (%)
1-Bromoethanol		R=Me 69% R=H 60%
3_Bromopropanol		R=Me 69% R=H 68%
		R=Me 33% R=H 57%
		X R=Me R=H (%) I 58 68 Br 68 67 PhSe 28 36
		X R=Me R=H (%) I 57 67 PhSe 42 64

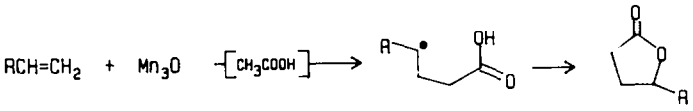


SCHEME 3_44



R	R^1	R^2	3_45.4 Yield (%)
H	H	Bu	76
H	$-CH_2CH_2-$		78
H	H	C_8H_{17}	76
H	H	CH_2SiMe_2	56
H	H	OEt	36
H	H	CH_2OH	73
H	H	COOEt	-
Me	H	Bu	75
Me	$-OCH_2CH_2-$		72

SCHEME 3_45

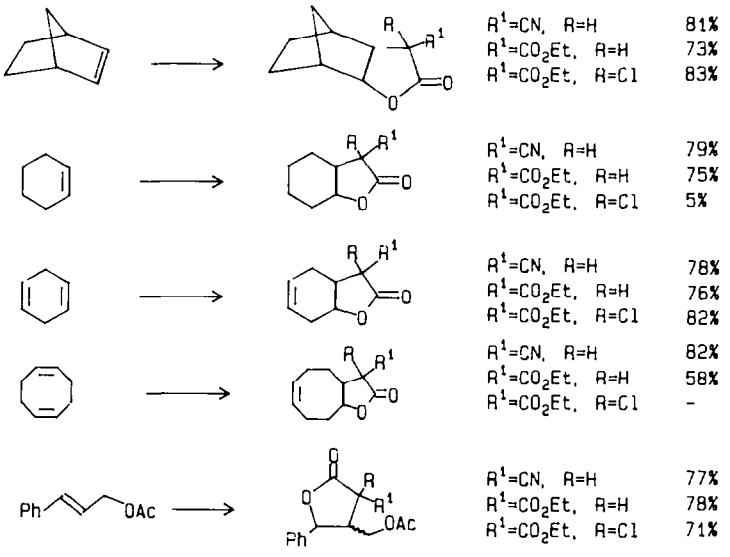


SCHEME 3_46

Table 25. Preparation of lactones from olefins and MnO_3

NO	Alkene	Lactone	Yield (%)
1	$C_8H_7CH=CH_2$		79
2	$C_3H_7-C_3H_7$ (Z)		60 (3.3: 1) c:t
3	$C_3H_7-C_3H_7$ (E)		69 (3.4: 1) c:t
4			29 (1: 5.4)
5			75
6			68
7			63
8			80
9			43
10			40
11			68 (67:1)
12			57 (3.8:1)
13			82 (26:1)

a) In addition to lactones, other products such as allylic acetates -acetoxy acids are also produced.



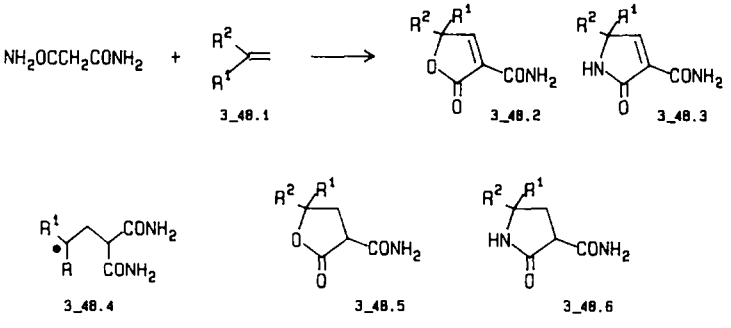
SCHEME 3_47

more *trans* fused lactones. It should be noted that, in general, the thermodynamic stability of ring annulated lactones differs substantially from their all carbocyclic counterparts.

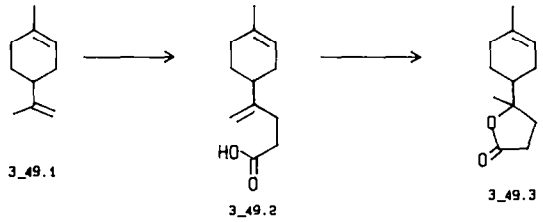
Electron withdrawing groups α to the carboxylic acid function accelerate the Mn(III) mediated carbolactonization of an olefin. The use of more reactive carboxylic acid substrates, such as cyanoacetic acid, ethyl hydrogen malonate and ethyl hydrogen chloromalonate, serves as reactive equivalents of acetic acid. These substrates enhance the utility of the Mn(III) promoted intermolecular carbo-lactonization[176,177] (Scheme 3–47). The best yields are obtained by using excess olefin at 23°C for 15 min. Longer reaction times invariably lead to by-products derived from initially formed adducts with a second mole of the olefin. However, this side reaction is not a severe problem with ethyl malonate, and as a result there is no need to use excess olefin in this case. Reactive olefins give good yields of lactones with chloromalonate, otherwise excess Mn(III) (2–3 equiv) is needed. It should be noted that dichloroacetic acid, benzensulfonylacetic acid and acetoacetic acids are less satisfactory for the lactone formation.

The reaction of olefins **3–48.1** with malonamide in the presence of Mn(III) acetate give 2-buten-4-olide **3–48.2** and 1H-pyrrol-2-(5H)-ones **3–48.3** in one step in moderate yields.[178] The formation of α,β-unsaturated lactones **3–48.2** and -amides **3–48.3** occurs, due to the second oxidation of the initially formed lactones **3–48.5** and amides **3–48.6**. The lactam **3–48.6** predominates, when R and R^1 stabilizes the initially formed radical **3–48.4**. It should be noted that this method does not work for lactam formation with simple olefins, such as cyclohexene, and therefore is limited to 1,2-disubstituted aromatic olefins.

An improved synthesis of norbisabolide **3–49.3**, a C-12 terpene lactone has been described



SCHEME 3_48



SCHEME 3_49

using Mn(III) acetate. Limonene **3–49.1** is reacted with manganese triacetate in a solvent mixture containing acetic acid, sodium acetate and acetic anhydride at 100–120°C to give olefinic acid **3–49.2**. This intermediate on heating with formic acid at 80°C, gives **3–49.3** in 95% overall yield.[179]

4. INTRAMOLECULAR C–C BOND FORMATION

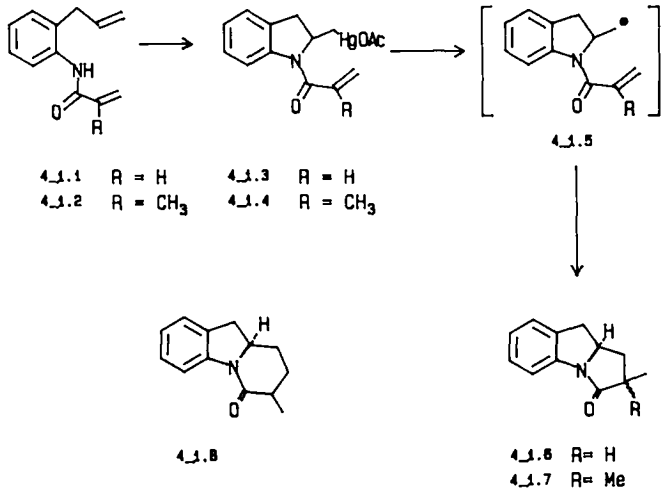
4.1. *Via alkyl radicals*

While intramolecular cyclizations through carbonium ion intermediates have been extensively studied for a long time, radical initiated cyclizations have been explored only in recent years.[185–189] The two processes can differ fundamentally in their synthetic direction allowing alternative preferential ring formations. For example, in cationic cyclizations, 6-membered rings are generally obtained except where increased electronic stabilization of the carbonium ion overrides the competing 6-membered ring formation.[190,191] In contrast, radical initiated cyclizations generally lead to 5-membered rings under kinetic control (*inter alia*). However, electronic stabilization of an initial reacting radical center may cause reversal of a kinetically favored 5-membered ring closure. Thus, 6-membered rings can sometimes be obtained.[190] Electronic stabilization of a cyclized intermediate radical does not seem to be more important than the steric effects in the cyclization process itself. Further, control of cyclizations can arise from the required orbital overlap of the π system with the electron deficient reacting radical center (*exo* addition). This results in the requirement of having at least three atoms between the double bond and the reacting center (see Introduction).

It should be mentioned that contrary to the intramolecular C radical addition to olefins, hetero atom radicals, such as silyl and germyl radicals, cyclize in an *endo* fashion.[192] This may be at least in part due to the increased chain length of the Si– or the Ge–C bond and the pyramidal configuration of hetero atom radicals as opposed to the planar carbon radical.

Reductive alkylation via organomercurials (Giese reaction) has been applied to the intramolecular C–C bond formation reactions as well. The success of this reaction depends on the exclusive reduction of the organomercurial which occurs prior to the reduction of other functional groups present in the molecule. For example,[193] reduction of organomercurial **4–1.3**, obtained from **4–1.1** via intramolecular addition of the amide to an olefin in the presence of mercuric acetate with SBH gives a mixture of cyclized products **4–1.6** (α- and β-isomers) in 34 and 11% yield, respectively, while a single product, **4–1.7**, is obtained from a similar reaction with **4–1.4** (Scheme 4–1). In the later case, surprisingly, a 28% yield of β-elimination product, i.e. starting material **4–1.2**, is isolated. Usually such eliminations are not common in radical reactions. In no case formation of the compound **4–1.8** is observed.

Many synthetic approaches to the fused bicyclic β-lactam antibiotics are based on the annelation of non-fused β-lactams bearing the appropriate appendages. This transformation is usually performed either by an ionic or a carbenoid reaction. Free radical species, such as **4–2.1** or **4–2.2**, generated from the corresponding halolactams undergo *exo*- and *endo*-cyclizations along with a substantial amount of reduction products.[194] The course of these reactions is highly influenced by the nature of the substituents on the unsaturated side chain. When the multiple bond has no substituent at the terminal position (R = H), the cyclization proceeds exclusively through the *endo* addition mode giving 7-membered rings. This is in sharp contrast with a few reported cyclizations of simple hept-6-enyl radicals[195] which afford 6-membered ring products, deriving from *exo*-addition mode. Chlorolactams are relatively unstable and difficult to manage, while seleno- and sulfidolactams are more suitable for this reaction. Under the standard reaction conditions (1.1 equiv of

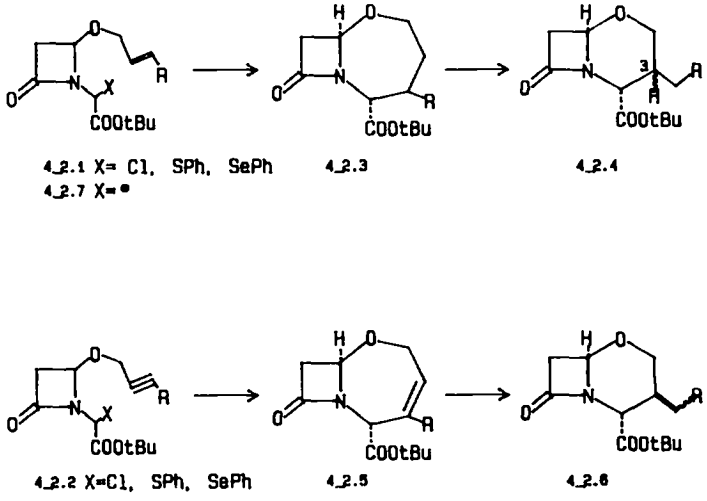


SCHEME 4_1

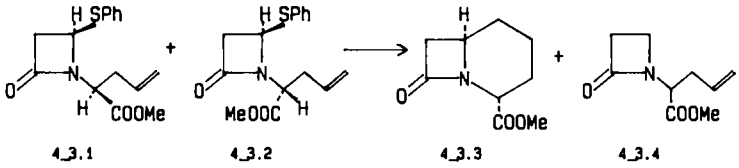
TBTH and 2–4 mol% AIBN, refluxing toluene), the reaction of phenylseleno- and the phenylsulfido-lactams takes a similar course to that of the chloro derivative, giving about the same ratio of annelated to unannelated products. In general, yields of cyclized products from **4–2.1** or **4–2.2** (R = H) are not synthetically attractive for cephalosporin type ring structures (6-membered rings), and attempted generation of the free radical from the benzyloxy derivative **4–2.1** or **4–2.2** (X = $PhCH_2O$—) has not been unsuccessful.

Annelations leading to fused β-lactam rings have been diverted to the *exo*-addition mode by substituting the H atom of the terminal multiple bond with a carbomethoxy group (R = COOMe) or a phenyl group (R = Ph). The bicyclic compound **4–2.4** (R = COOMe, or R = Ph) is obtained in 68% yield as a mixture of two epimers at carbon 3. As a result of radical addition to triple bonds, the vinylic compound **4–2.6** results as a mixture of the (*E*)- and (*Z*)-isomers, in a yield of 64%. In all these reactions reduction products without cyclization are major common by-products.

Radical cyclization of a mixture of diastereomeric phenylthio lactams **4–3.1** and **4–3.2** with TBTH and AIBN in refluxing benzene affords only carbocepham **4–3.3** in 43% yield together with the desulfurized compound **4–3.4**. The other possible carbopenam (by an *exo* mode) is not produced.[196] Interestingly, in this reaction the recovered starting material is exclusively **4–3.2**.



SCHEME 4_2

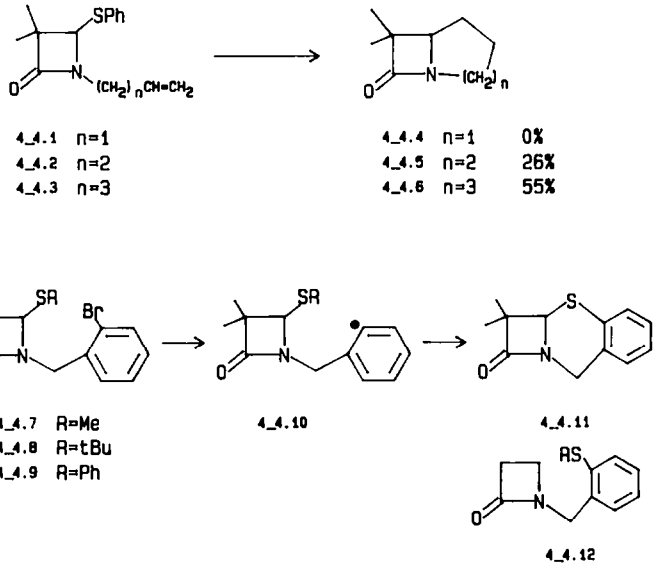


SCHEME 4_3

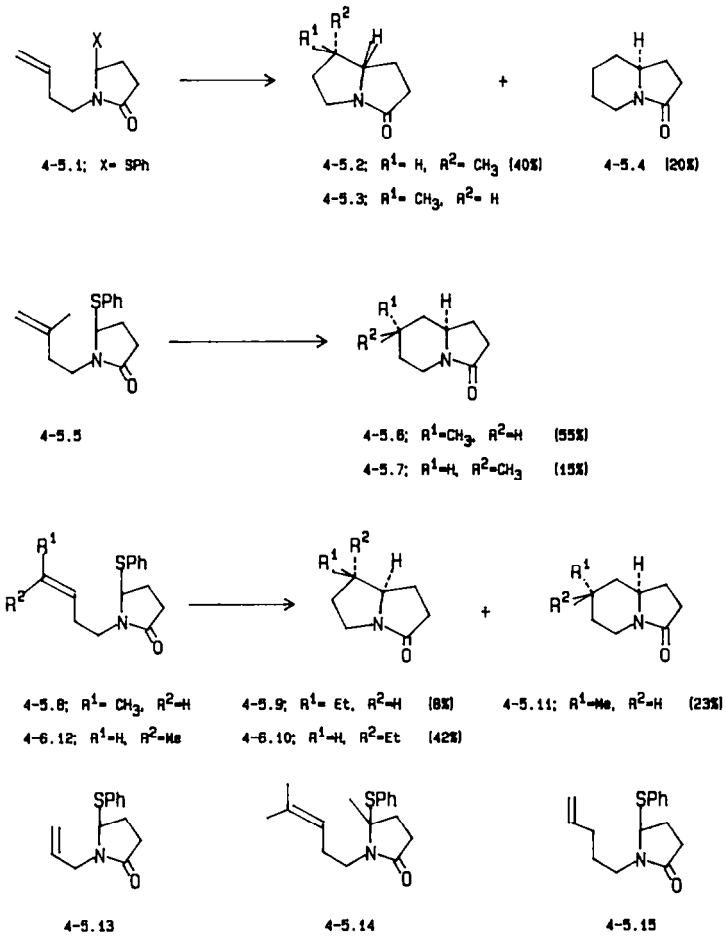
It is noteworthy that other radical ring closures leading to the fused β-lactam systems behave similarly, i.e. preferential *endo* attack. For example, heating thioether **4–4.2** with TBTH (0.05 M) and a trace of AIBN as an initiator in benzene at 80°C gives poor yields (20%) of only one bicyclic compound **4–4.5** (*endo* mode). Its higher homologue **4–4.3**, similarly gives only one cyclized product **4–4.6** but in higher yields (55%), whereas the lower homologue **4–4.1** does not cyclize at all.[258,259] The preference for the *endo* ring closure is attributed to the strain in the *exo* transition structures engendered by the azitidinyl ring. Tricyclic β-lactam **4–4.11** is obtained in 42% yield from **4–4.8**. The methyl thioether **4–4.7** gives **4–4.11** upon similar treatment but in low yield (21%), while no cyclized product is obtained with **4–4.9**. A noteworthy feature of these reactions is the failure to afford aryl thioether **4–4.12** via intramolecular homolytic displacement (S_H2) of the azitidinyl substituent by the radical **4–4.10**.

Indolizidines and pyrrolizidines are important substructures found in many alkaloids and have been synthetic targets for many researchers. α-Acylamino radical cyclizations[197,198] appear to be ideal candidates for the synthesis of these natural products. Treatment of **4–5.1**, with TBTH and AIBN in benzene at reflux gives a mixture of *exo*-cyclic-**4–5.2**, **4–5.3** and *endo*-cyclic-**4–5.4** lactams, along with uncyclized product **4–5.1** (X = H, 12% yield).[197] It should be noted that the ratio of *exo* and *endo* cyclization products is 2 : 1. Usually, such a large *exo* : *endo* ratio is not observed in simple hexenyl radical systems. The stereoselectivity is parallel to the results obtained in related carbocyclic systems.[199] This unusual result has been attributed to the bond angle widening due to the insertion of s_p2 hybridized nitrogen in the chain containing the olefin and also radical centers.[197] Close examination of other examples indicates that this is a general phenomenon when the amide carbonyl is not part of the newly formed ring. When the amide carbonyl is part of the newly formed ring, exclusive formation of the *exo* product is observed.

Substitution on the double bond in **4–5.1** plays an important role on the regiochemical course of the radical cyclization.[198] It is possible to guide the α-acyclamino radical cyclization toward the



SCHEME 4_4



SCHEME 4-5

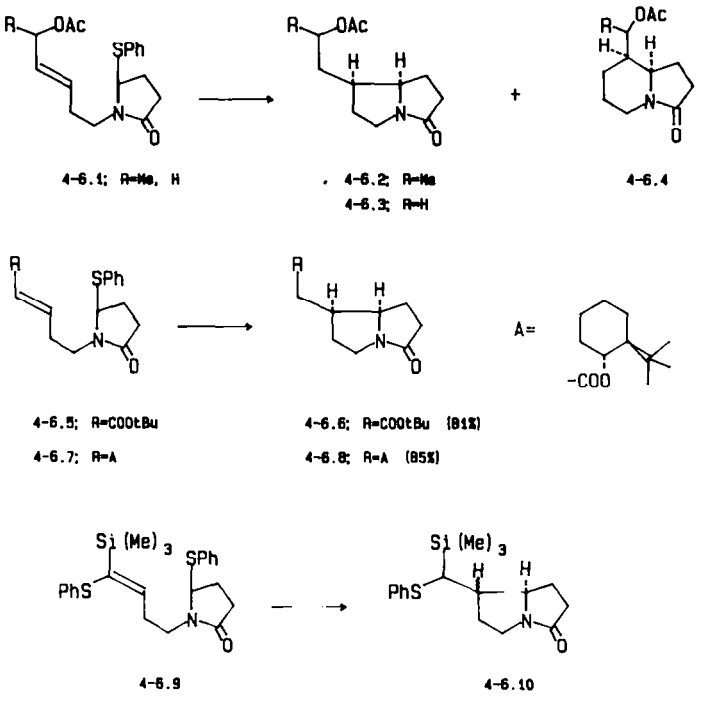
formation of indolizidinone or pyrrolizidinone formation by the proper choice of the substitution on the olefin moiety. For example, the reduction of thiophenoxy lactam **4–5.5** containing an internal olefin substitution, with TBTH and AIBN in refluxing benzene leads exclusively to *endo* cyclization products **4–5.6** and **4–5.7** with modest stereoselectivity.

Terminal (*E*)-alkyl substitution, e.g. **4–5.8**, gives a mixture of **4–5.9** to **4–5.11** in the same *endo* : *exo* cyclization ratio as observed for the parent radical **4–5.1**, (X = •), while the terminal (*Z*)-alkyl substituted compound **4–5.12** leads to almost exclusive formation of *exo*-cyclization products **4–5.9** and **4–5.10** in 52% yield. Interestingly, under similar reaction conditions, thiolactams **4–5.13** and **4–5.14** are merely reduced without cyclizations where as **4–5.15** gives 6- and 7-membered cyclization products in 3 : 1 ratio (75% yield), along with small amounts of the reduction product.

Although compound **4–5.1**, on treatment with TBTH and AIBN, gives a 2 : 1 mixture of *exo* and *endo* cyclization products, under similar conditions, **4–6.1** gives *exo* adducts **4–6.2** in 86% yield along with a small amount of *endo* adduct **4–6.4**. The *exo* and *endo* ratio[200] is 21 : 1. This high selectivity is due either to the electronic or steric effects of the acetoxy group in the transition state. Similarly, treatment of **4–6.5** with neat or dilute TBTH/AIBN gives only *exo* adduct **4–6.6** with a 9 : 1 diastereomeric ratio.

One of the problems associated with many free radical cyclizations is the reduction of the radical (i.e. H atom abstraction) prior to cyclization. This problem can be dealt with by using a high dilution technique, although such conditions are operationally cumbersome. When a good donor–acceptor relationship is present, the cyclization of free radicals is quite fast, and in such cases high dilution techniques are unnecessary.

It should be noted that treatment of the ester **4–6.7** with TBTH gives **4–6.8** in 85% yield, without

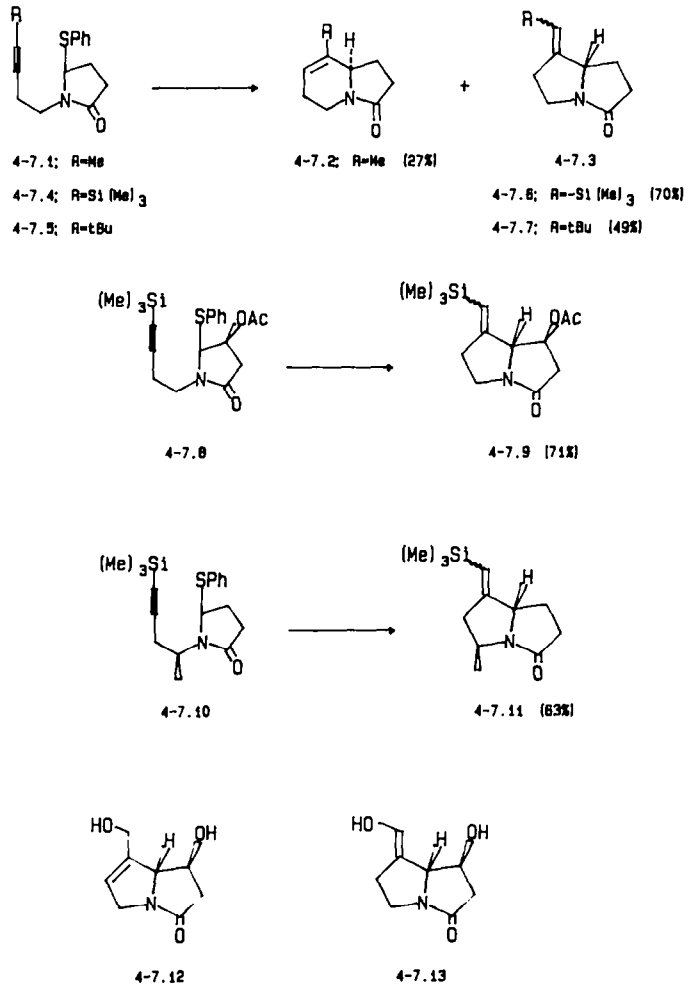


SCHEME 4-6

significant asymmetric induction.[200] However, the optically active addition products have been observed in low optical yields by the radical reaction of cyclohexanone with 2-octene in l-menthol using benzoyl peroxide as a radical initiator.[201] Asymmetric induction via thiol radical addition to an olefin in the presence of catalytic amounts of chiral substances, such as l-menthol, has been observed.[202,203] Also observed are very low enantiomeric excess in the free radical addition reactions of l-menthyl mercaptoacetate to prochiral olefins, such as crotonates (enantioface differentiation), or achiral thiols to l-menthyl crotonate (diastereoface differentiation).[204]

Radical precursor **4–6.9**, upon treatment with TBTH and AIBN, gives a diastereomeric mixture of products **4–6.10** (4.5 : 1 ratio), which can be converted into hydroxymethylene derivatives in two steps in low yields via the sila Pummerer rearrangement followed by reduction. Interestingly, the vinyl sulfoxide of **4–6.9** is not suitable for a radical cyclization reaction.[200]

α-Acylamino radicals generated from thiophenoxylactams also undergo intramolecular addition to proximal triple bonds.[205,206] This addition occurs with high stereoselectivity. For example, **4–7.1** gives exclusively the *endo* product **4–7.2** in low yield (27%) along with a substantial amount of the reduction product **4–7.2** (SPh = H) (61%), but no *exo* cyclization product **4–7.3** is observed. However, **4–7.4** and **4–7.5**, under similar conditions, undergo cyclization[205] to *exo* products **4–7.6** (70% yield) and **4–7.7** (49% yield). It is noteworthy that no products derived from *endo* cyclization have been found in the latter two cases. Although the nature of steric and electronic effects have not been determined from a synthetic point of view, cyclization of radicals derived from **4–7.4** could have potential use in pyrrolizidine alkaloid syntheses. Also, it should be noted from these examples, that by simply changing to a bulky substituent at the terminal acetylenic group, the regiochemical course can not only be changed from an *endo*- to *exo*-process, but the ratio of the cyclization product to reduction product can also become preparatively meaningful. Phenylthiolactam **4–7.8**, under high dilution conditions (10–12 ml/mmol), gives cyclized products **4–7.9** (71% yield; 2 : 1 mixture of geometric isomers), upon treatment with TBTH and AIBN.[206] The diastereoselectivity observed here is notable. Using similar conditions, **4–7.10** produces diastereomerically homogeneous geometric isomers **4–7.11** (63% yield). The compound **4–7.9** has been utilized for the preparation of naturally occurring pyrrolizidine alkaloids, such as (+)-heliotridine **4–7.12** and (+)-hastanecine **4–7.13**, by a series of standard transformations.



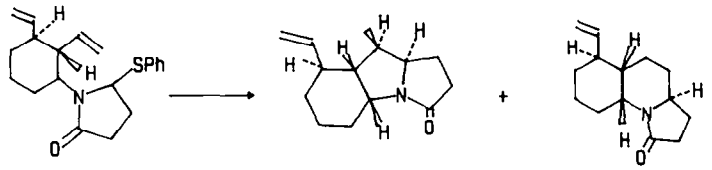
SCHEME 4-7

It should be noted that, for the generation of α-acylamino radicals, α-thioacetates, thiols and 2,4-dinitrophenylthio derivatives as radical precursors are either unreactive or unsuitable.[198] Although methylthio lactams are suitable for this purpose, qualitatively the reactions with them are slower compared to phenylthiolactams.[200]

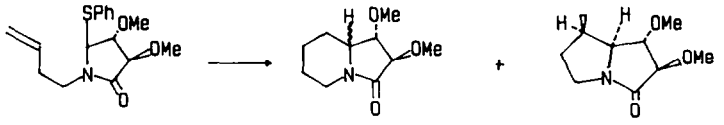
The thiophenoxy lactam **4–8.1** gives *exo*-**4–8.2** and *endo*-**4–8.3** cyclization products with TBTH.[198] It is noteworthy that no reduction product is observed and both modes of cyclizations proceed with high stereoselectivity at the radical center. This stereoselectivity is attributed to the pronounced conformational preferences expected for the intermediate radical. Cyclization of lactam **4–8.4** derived from tartaric acid has given a separable mixture of lactams **4–8.5** and **4–8.6** albeit in moderate yields, inferring the possibility of enantioselective entry to the alkaloid synthesis.[198]

Treatment of allenes **4–9.1** or **4–9.3** with TBTH and AIBN have failed to generate the desired radicals that could undergo cyclization. However, the corresponding selenides **4–9.2** and **4–9.4**, produce indolizidines **4–9.5**, **4–9.6** and pyrrolizidinones **4–9.7**, **4–9.8**, respectively. The compounds **4–9.7** and **4–9.8** have been converted[198] into the pyrrolizidine alkaloid supinidine **4–9.9**.

A method for the preparation of perhydroindanes has been described[260] as shown in Scheme 4–10, by an intramolecular homolytic addition of a suitably functionalized primary hexenyl radical **4–10.1** or **4–10.2**. For example, heating **4–10.3**, (R = H, Me, OMe) with a slight molar excess of TBTH in benzene at 65°C for 16 h affords solely the bicyclic compound **4–10.4**. As expected on stereochemical grounds, the ring junction is *cis*. Neither uncyclized reduction products nor compounds arising from ring closure onto the more substituted double bond are found. However, similar treatment of bromides **4–10.5**, (R = OMe, Me) give products **4–10.6**, (R = OMe, Me) and **4–10.7**,

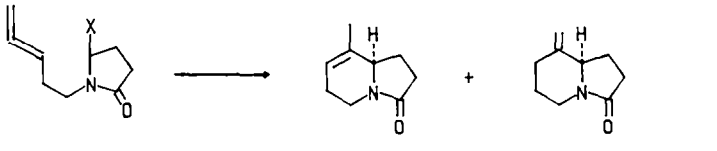


4-8.1 4-8.2 (51%) 4-8.3 (31%)

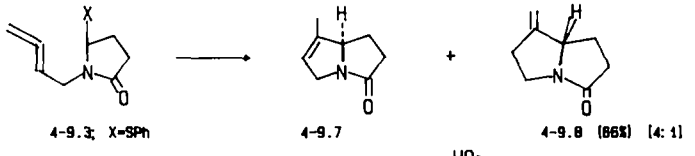


4-8.4 4-8.5 (28%) 4-8.6 (31%)

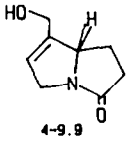
SCHEME 4-8



4-9.1; X=SPh
4-9.2; X=SePh
4-9.5 4-9.6 (60%) [7: 1]

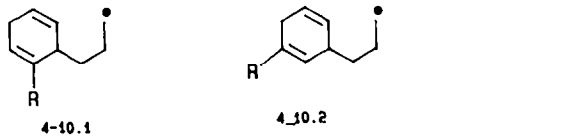


4-9.3; X=SPh
4-9.4; X=SePh
4-9.7 4-9.8 (86%) [4: 1]

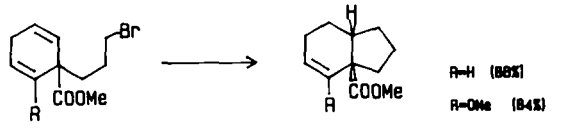


4-9.9

SCHEME 4-9

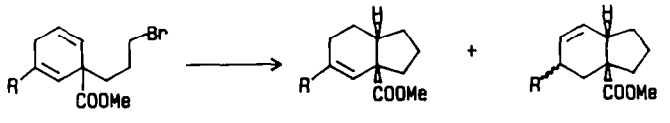


4-10.1 4_10.2



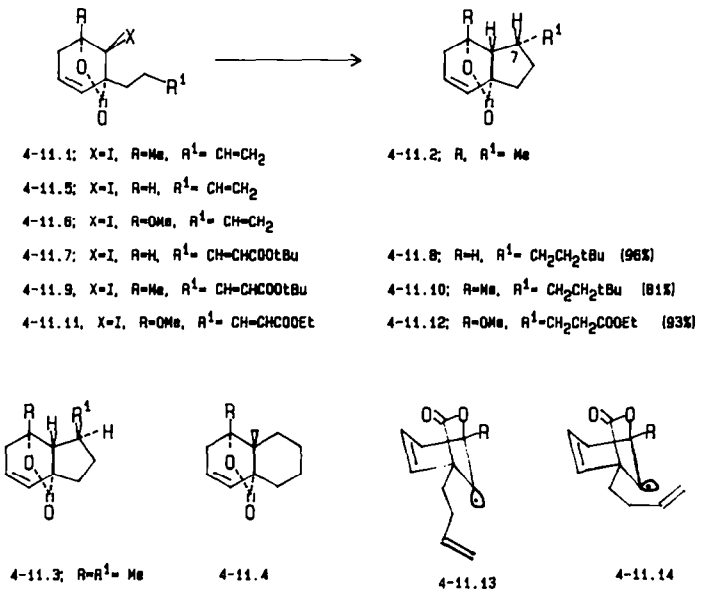
4-10.3 4-10.4

R=H (88%)
R=OMe (84%)
R=Me (79%)



4-10.5; R=Me, OMe 4-10.6 4-10.7

SCHEME 4-10



SCHEME 4-11

(R = OMe, Me) arising from the ring closure onto the unsubstituted and substituted double bonds, respectively.

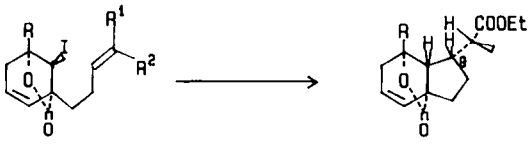
Synthesis of highly functionalized perhydroindanes have been described[199] (Scheme 4–11) involving secondary hexenyl radicals. The iodo olefin **4–11.1** with TBTH and AIBN in benzene under reflux gives a separable mixture of isomeric lactones **4–11.2** to **4–11.4** and **4–11.1** (X = H) via radical **4–11.1**, (X = •) in 87% yield. One of the notable aspects of this example is the 2 : 1 ratio of the *exo* : *endo* cyclization products **4–11.2** and **4–11.4**. This appears to be a general phenomenon, as similar product mixtures (*exo* : *endo*) are produced with **4–11.5** and **4–11.6**. This observation is contrary to the much larger *exo* : *endo* ratios observed for simple 5-hexenyl radicals,[114] but the observed stereoselectivity at C-7 of **4–11.2** is consistant with the results obtained in simple carbocyclic systems.

By choosing olefinic substrates containing terminal electron withdrawing groups, annelations have been guided to the exclusive formation of perhydroindanes (*exo* mode) **4–11.8**, **4–11.10** and **4–11.12**. It should be noted that, in these cases, in addition to high *exo* : *endo* product ratio, both *exo* and *endo* cyclizations proceed with high stereoselectivity at the ring junction.

It has been generally accepted that tin mediated radical dehalogenation occurs with stereochemical randomization.[207] However, in bicyclic systems, e.g. **4–11.1**, the initially formed axial radical **4–11.13** isomerizes to the equatorial position **4–11.14**, i.e. towards the oxygen bridge before C–C bond formation occurs. Such isomerizations have been observed in other bicyclic oxo- and amide compounds.[157,208] The thermodynamic stability of the radical **4–11.14** or the conformational rigidity of the product **4–11.2** accounts for the formation of the new 5-membered ring with the *trans* ring junction of the perhydroindane system, and/or for the *cis* ring junction of the substructure, oxabicyclo[3,3,0]octane system.

Another possible reason for the stability of the equatorial radical **4–11.14** could be the interaction of its singly occupied molecular orbital with the non-bonding orbital of the ring oxygen. Recently, such non-bonding interaction of radicals with a β-oxygen loan pair has been proposed.[210] It should be noted that such interactions have not been observed with simple β-alkoxycyclohexane radicals.

While control of stereochemistry of substituents on cyclic compounds is relatively easy, control of side chain stereochemistry is difficult. Methodologies which control the side chain stereochemistry are therefore extremely useful and important in organic synthesis. Free radical cyclization of *trans* iodoolefinic ester **4–12.1** (TBTH, AIBN, benzene, 60°C) gives perhydroindane **4–12.3** in a highly stereoselective manner in 81% yield, along with a small amount of other diastereomers.[211] Similarly, *cis* olefinic ester **4–12.2** under the above reaction conditions undergoes cyclization to give **4–12.3** in



4-12.1; R=H, R^1=COOEt, R^2=Me 4-12.3

4-12.2; R=H, R^1=Me, R^2=COOEt

SCHEME 4-12

37% yield. It should be noted that the olefin geometry influences the stereochemical outcome at C-10, but does not play a significant role in controlling the stereochemistry at C-9.

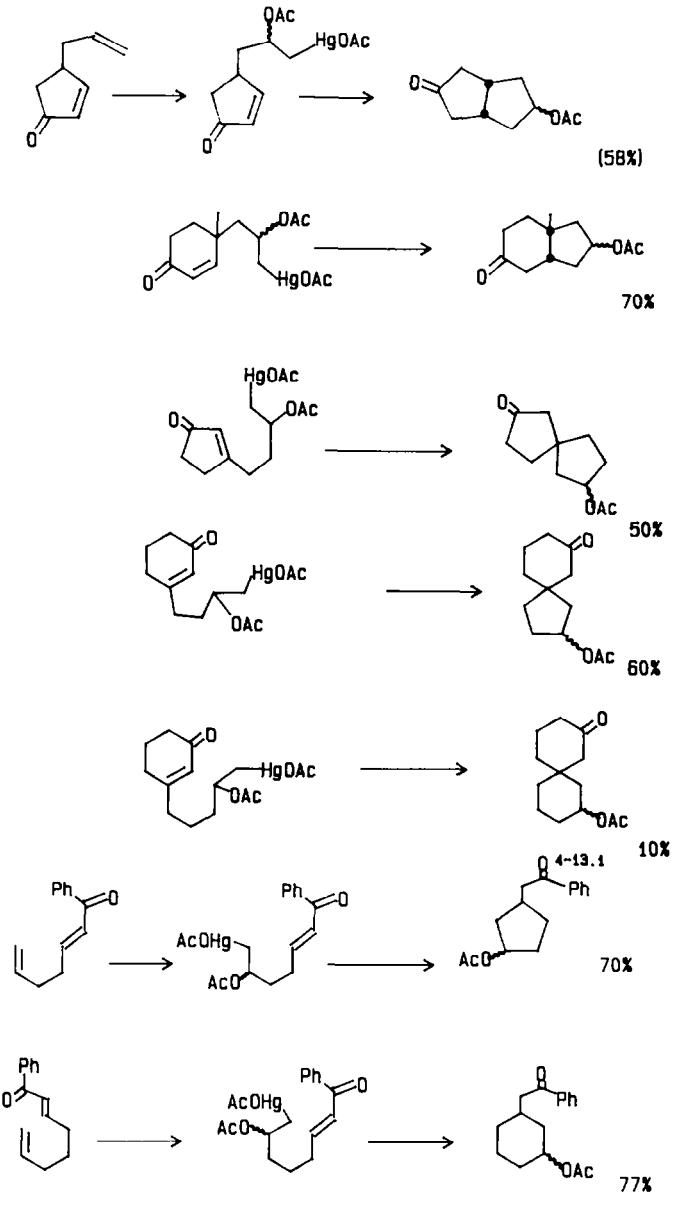
An intramolecular reductive demercuration method has also been applied[212] to the preparation of fused and spiro carbocycles as shown in Scheme 4–13. Here, sodium trimethoxyborohydride in methylene chloride has been found to be a preferred reducing agent. It should be noted that solvomercuration is selectively carried out on the isolated double bond. Solvents such as acetic acid, methanol and water can be used in the mercuration reaction. Methanol is the preferred solvent if one chooses to combine the mercuration and reductive cyclization sequence in one pot, to obtain keto-ethers. Acetic acid is used as the solvent for the purpose of eventual preparation of cyclic diketones, since acetates are easily transformed into other functional groups. This reductive cyclization step does not appear to be a synthetically useful reaction, when the quaternary C being formed is a part of a 6-membered ring, e.g. **4–13.1**. Further, the reduction without cyclization and reductive reversion to the starting olefin are serious side reactions.

An alternate synthetic methodology (*inter alia*) for the preparation of pyrrolidines has been reported,[213] as shown in Scheme 4–14. Cyclization of 2-bromoethylsulfonamide **4–14.1** with TBTH and a catalytic amount of AIBN in refluxing benzene gives **4–14.2** in 87% yield. This method appears to be general, as **4–14.4** and **4–14.6** are prepared from **4–14.3** and **4–14.4**, respectively, in better than 90% yield. As expected with 5-hexenyl systems, internal olefin substitution generally leads to enhanced endocyclization in these heterocycles. These cyclizations are governed by stereoelectronic factors. Reductive cyclization of sulfonamide **4–14.7** gives **4–14.8** only in 36% yield, whereas the corresponding *N*-benzyl derivative **4–14.9** gives exclusive reduction (no cyclization).

Radical induced addition of thiolacetic acid to *N,N'*-diallylsulfonamide **4–15.1** gives the diastereomeric pyrrolidines **4–15.3**, in which the *cis* isomer predominates to the extent of 2 : 1. The closely related *N,N'*bis(2-methyl-2-propenyl)benzenesulfonamide system **4–15.4** with thioacetic acid, gives the 1,5-cyclization product **4–15.5**. Interestingly, in none of these cases, the 6-*endo* mode ring closure is observed. This has been attributed to the fact that the shorter C–N bond distance enhances the 5-*exo* ring cyclization pathway.[214]

Lactones are important subunits in many natural products and also serve as building blocks for complex molecules. Existing non-radical methodologies for their preparation involve C–O bond formation under basic or acidic conditions. However, under radical conditions, for example treatment of the mixed bromoacetal **4–16.1** with TBTH (cat. AIBN, 4 h, reflux in benzene)[215] **4–16.2** is produced. It should be noted that as predicted from the guidelines[114] (see Introduction), lactol substituents are *trans* disposed in these cases. Extension of this methodology to the mixed bromoacetals derived from cyclic allylic alcohols give *cis* ring junction compounds **4–16.3** → **4–16.7** indicating regio and stereocontrolled C–C bond formation.[215] Also, to be noted in this radical cyclization process is the formation of quaternary centers with ease, e.g. **4–16.8**. 1,4-H atom transfer to the initially formed radical, (for example, to **4–16.11**) is not a competing process, but 1,5-H transfer leading to the allylic tertiary radical **4–16.12** of greater stability occurs to some extent. In such cases a simple modification of a homoallylic alcohol, i.e. having a carbomethoxy group as shown in **4–16.5**, gives 90% yields of bicyclic acetals (**4–16.9** and **4–16.10**; 85 : 15 ratio), indicating the favorable effect of an α,β-unsaturated ester group.

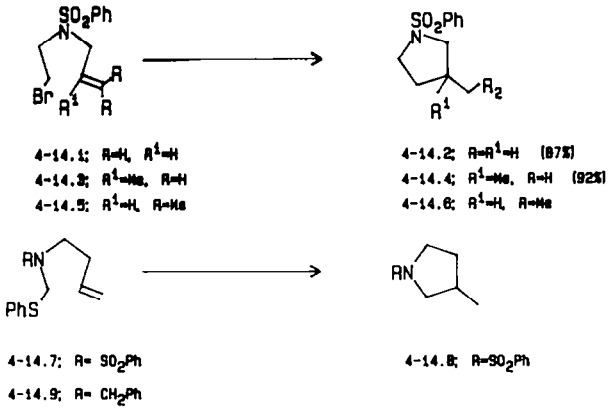
Although radical formation from halides and other derivatives with TBTH is convenient, the work-up of these reactions usually demands special operations such as chromatography or extractions with a KF solution to remove tin compounds. For this reason, polymer bound tin hydride reagent appears to be ideal.[216] For example, bromoacetals of the type **4–17.1** have been cyclized to



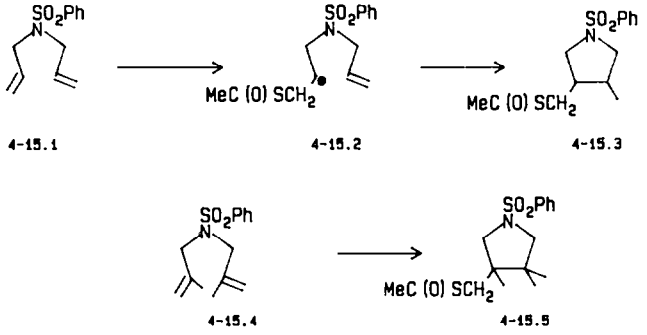
SCHEME 4-13

5-membered cyclic acetals either (A) by TBTH and AIBN in benzene (0.2 M sol) at room temperature or 50°C or (B) by a catalytic amount of TBTH generated from di-*n*-butyltin halide bound to a cross-linked polymer in the presence of SBH under UV irradiation conditions at room temperature (Scheme 4–17).[216] The latter method is superior in obtaining higher yields as well as in its ease of work-up. The recovered polymer bound tin halide can be reused several times without loss of activity. 2-Alkoxy tetrahydrofurans can best be converted into butylrolactones by a Jones oxidation in acetone. The method is particularly useful for C–C bond formation at the sterically bulky carbon atom, e.g. **4–17.6**, and also for the preparation of mixed cyclic acetals **4–17.10**. This method, when applied in conjunction with the intra-molecular $S_{H'}$ process, gives[216] the cyclic acetal **4–17.8** (see Ref. 215). Such $S_{H'}$ processes work well under high dilution conditions.[336]

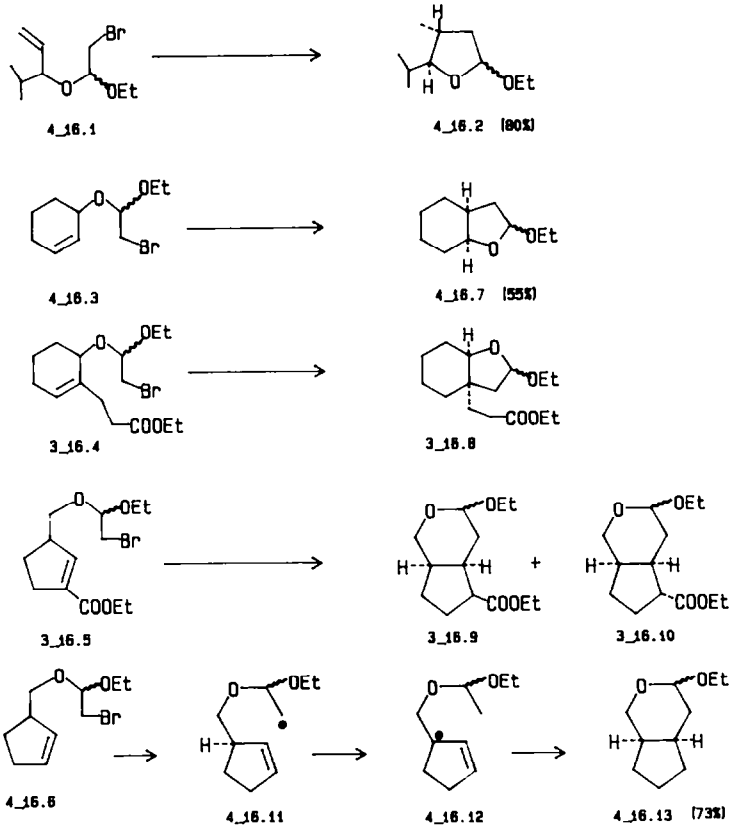
The C–C bond formation at the α-position of the sulphones is generally carried out by alkylation of the α-sulphonyl C anion. As an alternative to this approach, C–C bond formation can be accomplished via α-sulphonyl radicals.[217] 1-Bromoalkoxysulfones, **4–18.1** are cyclized to give exclusively 5-membered heterocycles upon treatment with TBTH, (AIBN, benzene, 70°C 7–13 h) (Scheme



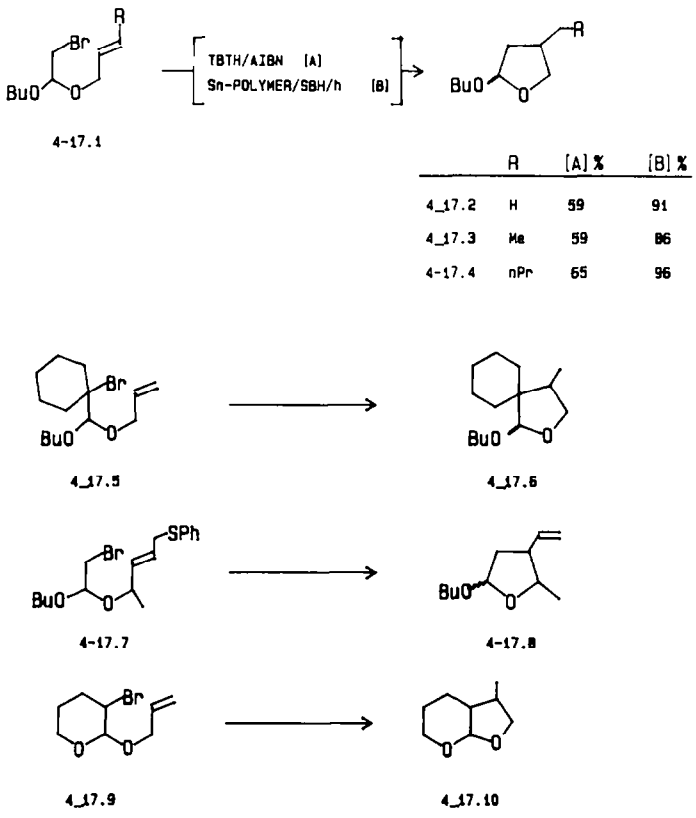
SCHEME 4-14



SCHEME 4-15



SCHEME 4_16

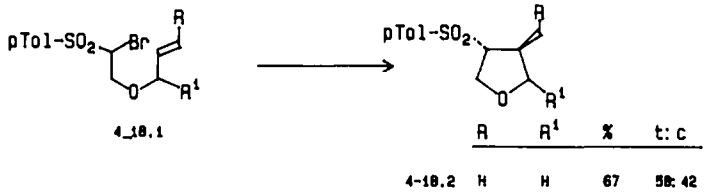


	R	[A] %	[B] %
4_17.2	H	59	91
4_17.3	Me	59	86
4-17.4	nPr	65	96

SCHEME 4_17

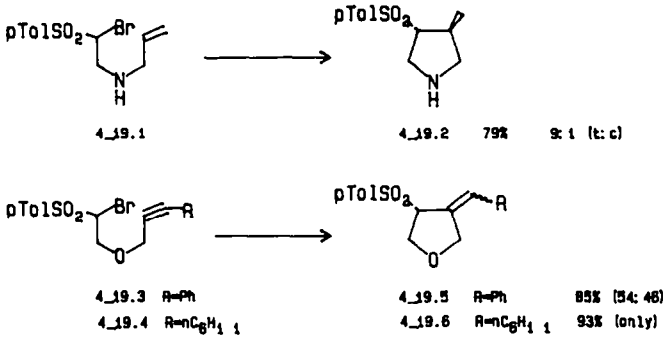
4–18) in moderate yields. The major product in this reaction is the *trans* isomer, in contrast to the preferential formation of the *cis* isomer. The substituents on the olefinic C have a marked effect on the stereochemical course of the cyclization. The substrates having more bulky substituents produce predominantly *trans*-rich products in the order H < Me < *n*-Pr. In spite of the bulkiness of the sulfonyl function at the α-position, these radicals cyclize exclusively to give 5-membered heterocycles (*exo* adducts), but not 6-membered ones (*endo* adducts). This methodology has been extended to N heterocycles (Scheme 4–19). It should be noted that the stereoselectivity is noticeably higher in the pyrrolidine case **4–19.2**. Under these conditions, acetylenic α-bromo sulphones **4–19.3**, **4–19.4** also cyclize to give 5-membered rings as a mixture of two geometric isomers **4–19.5** and **4–19.6**, respectively. Both bulkiness of the substituents and the heteroatoms in the ring appear to govern the stereochemistry of the α-sulphonyl radical cyclizations.

The TBTH is a very commonly used reagent for the C radical generation from a variety of substrates. However, C radicals can also be generated by the use of a Co complex.[218,340] Using this method, a two-step procedure for the synthesis of α-methylene-γ-butyrolactones has been



	R	R^1	%	t: c
4-18.2	H	H	67	58: 42
4_18.3	Me	H	56	76: 24
4_18.4	nPr	H	63	99: 1
4_18.5	H	Me	79	-

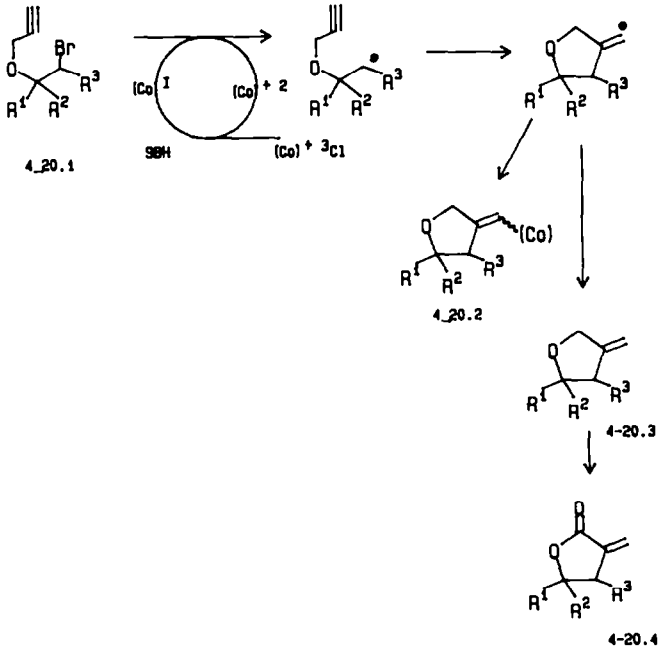
SCHEME 4_18



SCHEME 4-19

developed.[219] This involves the reductive cyclization, for example, of 2-(2-propynyl)oxy-ethyl bromides **4–20.1** in the presence of a catalytic amount of cobaloxime(I) (Co^{1-}) [(bis dimethylglyoximato)(pyridine)cobalt(I)] followed by the oxidation of the resultant 3-methylene-oxolones **4–20.3** with chromic acid–pyridine complex in dichloromethane. The catalyst, cobaloxime(I) is generated *in situ* via the reduction of chlorocobaloxime(III) by SBH at 50–60°C. Yields are generally good (Table 26). *cis* Fused oxolanes are obtained with cyclic bromo compounds. A catalytic amount of cobaloxime(I) is preferred to avoid the formation of the Co–C bond as in **4–20.2**. It should be noted that cobaloxime(I) reacts preferentially with functional groups which are strong electrophiles, such as tosylates, halides, unsaturated carbonyl and nitriles. Oxidation of **4–20.3** to α-methylene lactones **4–20.4**, with a variety of oxidizing agents has been examined and the yields of lactone **4–20.4** are substrate dependent. It should be noted that this method introduces the C=O group at the last stage of the lactone synthesis.

A β-methylene-γ-butyrolactone structural unit is present in some natural furanoid terpenes, e.g. bakkenolide **4–21.4**. Interestingly, not very many methods are available for their preparation. A method[220] which involves the reductive cyclization of 2-bromoalkanal acetals **4–21.2**, catalyzed by cobaloxime(I), is shown in the Scheme 4–21. The reduction is effected by 10–15 mol% of cobaloxime(I) and SBH in ethanol. The yields are good. This synthetic method is generally applied to α,α-disubstituted β-methylene-γ-lactones.



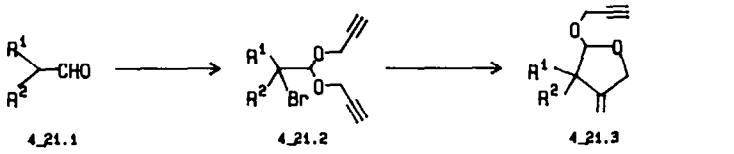
SCHEME 4-20

Table 26. Preparation of methyleneoxolanes (**4–20.3**)

R^1	R^2	R^3	Yield (%)
Ph	Ph	H	85
Ph	Me	H	73
Ph	H	H	78
H	$-(CH_2)_8-$		64
H	$-(CH_2)_8-$		48

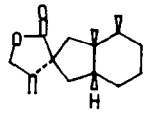
Regioisomeric γ-substituted β-methylenelactones **4–21.3** are prepared from a slightly different starting acetal,[222] compared to the acetals mentioned in the above method. Thus, propargylic alcohols have been reacted with ethyl vinylether in the presence of *N*-bromosuccinimide to give bromoacetals **4–22.1** in moderate yields, which are cyclized with TBTH to give 4-methylene-tetrahydrofurans **4–22.2**. Oxidation with Jones reagent then gives β-methylene lactones **4–22.3**.

Electrochemically regenerated cobaloxime(I) from cobaloxime(III) has also been used for the reductive C–C bond formation from brominated acetylenic olefins as shown in Scheme 4–23 in good yields[221] (also *cf.* Refs. 219, 220). The experiment is generally carried out in methanol, containing Et_4NOTs as a supporting electrolyte in a divided cell under argon, using 50 mol% of chloro-pyridinecobaloxime(III) and a small amount of 40% NaOH at 59°C. The process usually takes 2–3 faraday/mol of electricity. Under these conditions, cyclization, for example **4–23.7**, produces a mixture of geometric stereoisomers **4–23.9** in 81% yield, whereas TBTH–AIBN in benzene at



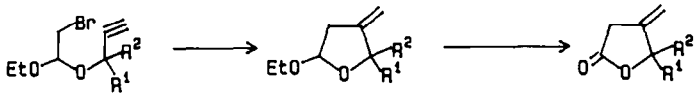
4_21.1 4_21.2 4_21.3

R^1	R^2	Yield (%)
Me	Pr	73
Et	Et	78
Et	Bu	75
$-(CH_2)_5-$		64



4_21.4

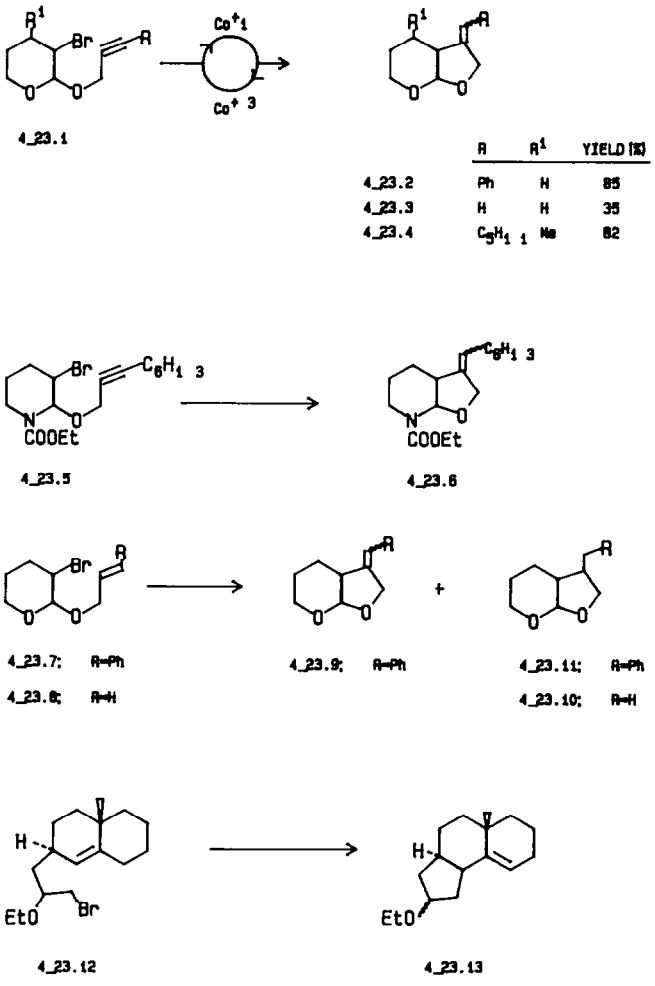
SCHEME 4_21



4_22.1 4_22.2 4_22.3

R^1	R^2	4_22.3 (%)
Me	H	60
	$-(CH_2)_5-$	63

SCHEME 4_22

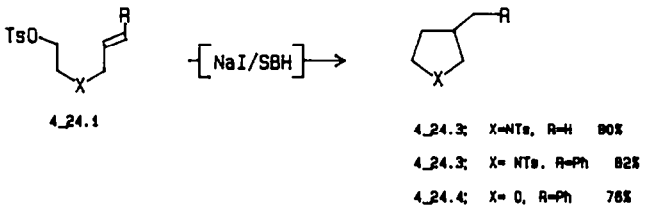


SCHEME 4_23

80°C affords normal radical cyclizations **4–23.11**. A strikingly different result is obtained with **4–23.8** → **4–23.10**. Similar radical cyclization of **4–23.12** has produced a C–C double bond product with concomitant double bond migration (**4–23.13**) complementing the tin hydride mediated cyclization (*inter alia*). The formation of **4–23.9** and **4–23.13** are explained by postulating a Co complex such as shown in Scheme 4–20 (**4–20.2**). The interesting feature of this procedure is that the reaction can be carried out in protic solvents such as methanol, contrary to the trialkyltin hydride promoted radical reactions. Further, these reactions proceed to only 5-membered rings,[221] even if there is a possibility for the formation of other rings.

The radical deoxygenation of primary alcohols via their tosylates in the presence of sodium iodide has been discussed (*inter alia*). The radicals generated in this methodology have also been used[97] for the synthesis of heterocyclic compounds as shown in Scheme 4–24. The reaction is presumed to take place via the *in situ* formation of alkyl iodide. It is interesting to note that reduction of appropriately substituted olefinic alkyl tosylates with Zn/sodium iodide give cyclized products in poor yields[223,322] (see below).

The facile conversion of primary and secondary sulphonates to the corresponding hydrocarbon by refluxing in DME with sodium iodide and Zn, proceeds through radical intermediates. However, these intermediate radicals, for example, **4–25.2** generated from tosylate **4–25.1**, attack a triple bond located at the γ-position to give a reductively cyclized product **4–25.4** in 22% yield,[223] along with a reduced product **4–25.3**. The corresponding α-ol mesylate does not give cyclized product. The ethylenic compound **4–25.5** undergoes stereoselective cyclization to the all *cis* isomer **4–25.6** in 30% yield. The stereochemistry of this cyclization is analogous[209] to the cyclization of cyclohexyl radical

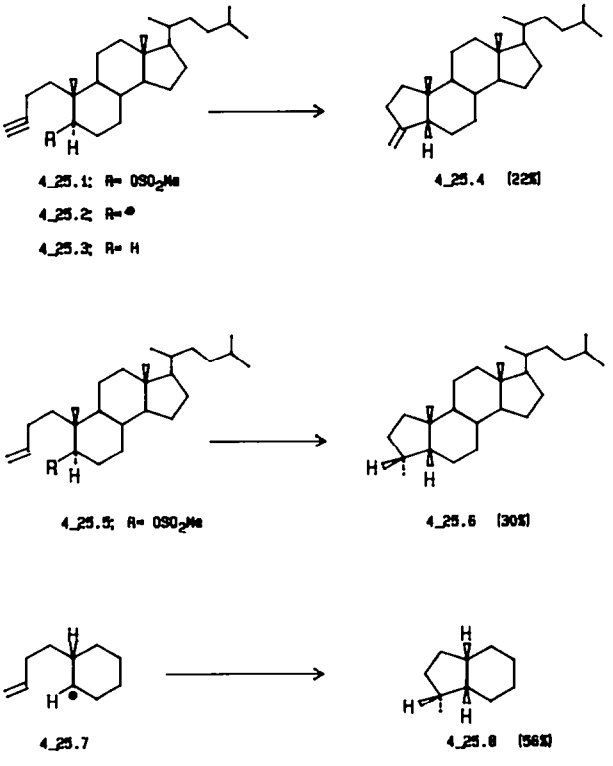


SCHEME 4_24

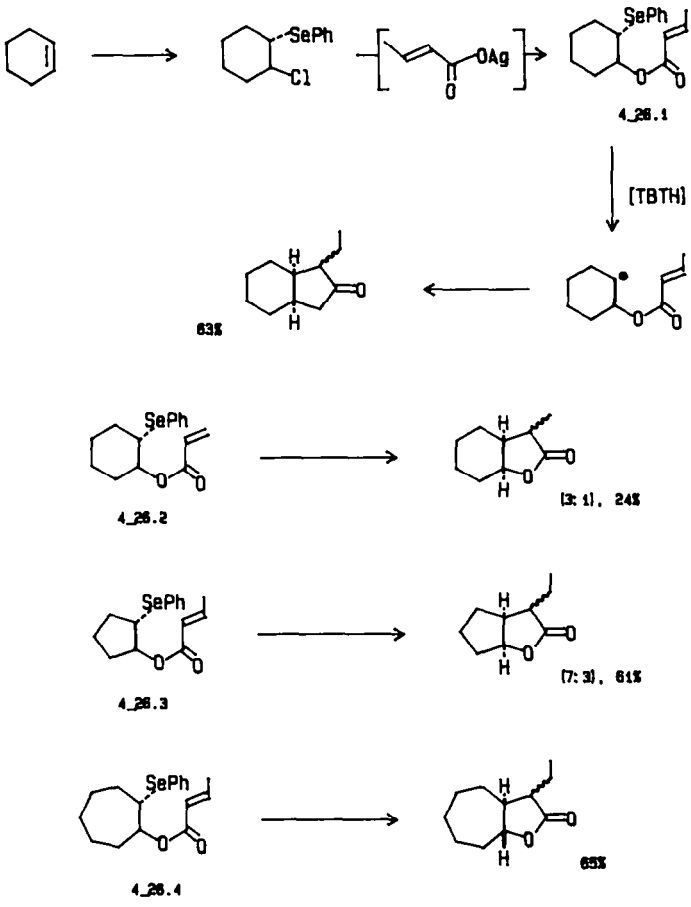
4–25.7, generated from the corresponding chloro derivative using TBTH as a radical source to give the all *cis* compound **4–25.8**.

Upon reduction with TBTH in benzene containing AIBN at reflux temperatures, phenylselenocrotonate **4–26.1** produces lactones in acceptable yields[224] (Scheme 4–26). Lactones derived from 5- and 6-membered ring olefinic esters (**4–26.3** and **4–26.2**) are *cis* fused and diastereomeric mixtures at the α-position of lactones, while the 7-membered ring olefinic ester **4–26.4** gives *cis* and *trans* ring junction products. The relative stereochemistry at the three asymmetric centers of the major isomer corresponds to that observed with acyclic 5-hexenyl systems, i.e. β-alkyl group. The seleno adducts derived from (*Z*)- and (*E*)-but-2-ene afford almost identical product mixtures in 66% yield. Similar results are obtained with iodocrotonates. Seleno acrylate esters give lower yields compared with seleno crotonates. Also to be noted is that inter-molecular free radical addition to α,β-unsaturated esters, lactones and ketones occurs at the β-position. However in the intramolecular cyclization reactions, a reversal of the regioselectivity is generally observed, due to stereoelectronic factors (5-*exo* mode cyclization).

In line with the well-known intermolecular radical addition reactions of trichloroacetate to olefins, allyltrichloroacetates **4–27.1** undergo copper catalyzed regioselective intramolecular C–C bond formation to give γ-butyrolactones **4–27.2**[225] (Scheme 4–27) in good yields (Table 27). Various transition metals and their complexes have shown efficient catalytic activity in the intermolecular

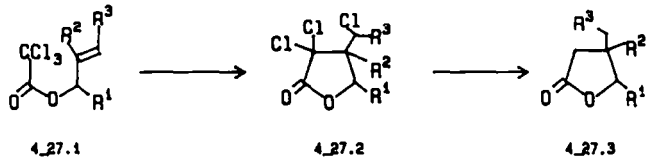


SCHEME 4_25



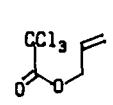
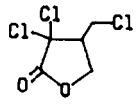
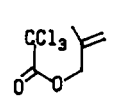
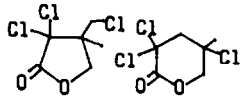
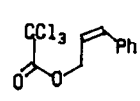
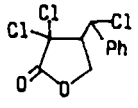
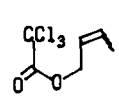
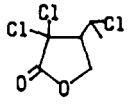
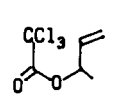
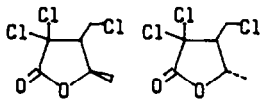
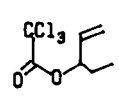
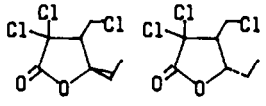
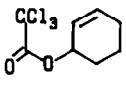
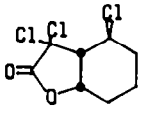
SCHEME 4_26

reaction, but for the intramolecular reaction, efficiency has been limited to Cu salts (CuCl). The preferred solvent has been acetonitrile. In this cyclization, only 5-membered ring lactones (*exo* mode) are formed, except when there is a bulky substituent at the site of attack by the initially formed radical (entry 2, Table 27). Further, the ratio of diastereomeric dichlorolactones is independent of the starting olefin geometry. Only one diastereomer is obtained from either *cis* or *trans* cinnamyl trichloroacetate (entry 3). This is another example of radical cyclization where the stereocenter in the side chain has diasteriomeric selectivity (also see Scheme 4–12). Further, in the case of trichloroacetates of secondary allylic alcohols, the stereochemistry between the alkyl substituent and the introduced chloromethyl group in the lactones is primarily *cis* and the ratio of *cis* to *trans* is 9 : 1 (entries 5, 6, Table 27). The high regio- and stereoselectivity of this cyclization is expected to induce asymmetric induction at the new chiral center if optically active secondary allylic alcohols were chosen as starting materials. The γ-butyrolactones can be prepared by the removal of Cl atoms with TBTH and AIBN reduction. This reaction has been applied to the synthesis of naturally occurring pyrethroid intermediates.[226]



SCHEME 4_27

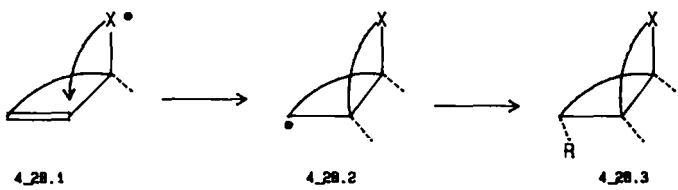
Table 27. Preparation of lactones from allyltrichloroacetates

NO	Allyltrichloro-Acetate	Lactone	Yield (%)	Diastereomer Ratio
1			72	
2			38, 29	
3			61	
4			78	7: 3
5			62	9: 1
6			68	9: 1
7			38	

The nitro compounds with suitably located double or triple bonds, react with TBTH (1.3 equiv) and AIBN (0.3 equiv) at 80°C for 2 h, to give exclusively *exo*-mode cyclized products in good yields (Table 28).[227] The formation of the *cis*-fused bicyclic compounds are preferred over that of *trans* compounds. It should be noted that this process is applicable only for the formation of quaternary C centers.[227]

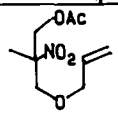
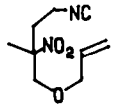
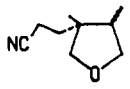
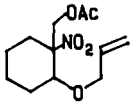
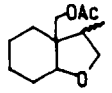
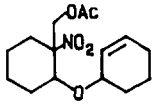
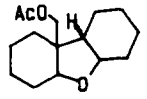
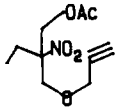
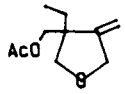
The control of the stereochemistry of various substituents on ring compounds is an important aspect of synthetic organic chemistry. One such concept is represented in the general Scheme 4–28. It should be noted that in the bicyclic systems **4–28.2**, the radical is always captured from the opposite side of the incoming radical center X. This can be demonstrated by the preparation of cyclic acetal **4–29.3** in which the newly formed decalin ring fusion is *trans* (Scheme 4–29).[229] This methodology has been applied to the synthesis of an intermediate **4–30.2**, leading towards the total synthesis of reserpine (Scheme 4–30).[69]

A removable chain connection to an allyl alcohol via a silyl ether is conceptually similar to the mixed acetal synthetic strategy, as shown in Scheme 4–31. However, this removable strategy differs



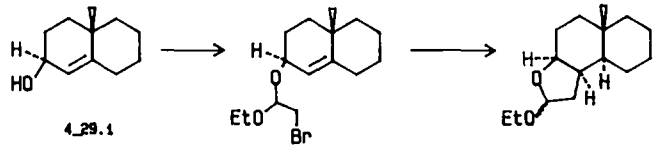
SCHEME 4_28

Table 28. Synthesis of quaternary carbon compounds

NO	Tertiary Nitro Compound	Products	Yield (%) [a]
1			90 (1: 1.8)
2			85% (1: 2.3)
3			74% (1: 4.4)
4			67 (1.1.8)
5			78

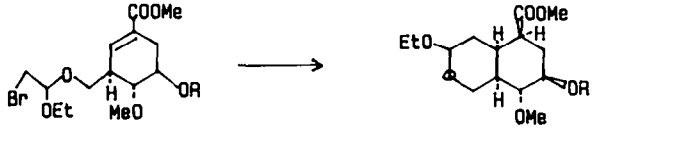
[a] Isomer ratio.

from the acetal strategy, in the introduction of a one rather than a two C chain at the α-C of the allylic alcohol. The 1,3-diol system, a subunit present in many natural products, has been assembled[228] by intramolecular silylmethyl radical addition to an internal olefin followed by oxidative cleavage of Si–C bond as shown in Scheme 4–31. The (bromomethyl)dimethylsilyl ether **4–31.1** is subjected to reaction with TBTH and AIBN in benzene under reflux (0.025–0.05 M solution) to give the cyclized product which on fluoride assisted oxidation with hydrogen peroxide gives the 1,3-diol **4–31.2**. The starting silyl ethers can readily be prepared from commercially available (bromomethyl)dimethylchlorosilane and an allylic alcohol in dichloromethane in the presence of trimethylamine at room temperature. It should be noted that 5-*exo* mode cyclizations (leading to 1,3-diols) predominate but 6-*endo* mode cyclizations (leading to 1,4-diols) also occur with substrates with-



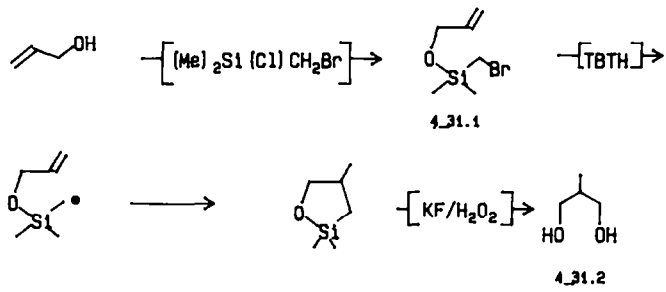
4_29.1 4_29.2 4_29.3

SCHEME 4_29



4_30.1 4_30.2 R= $OSiMe_3$

SCHEME 4_30

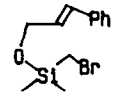
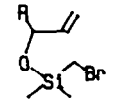
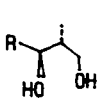
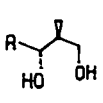
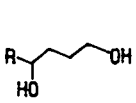
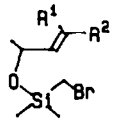
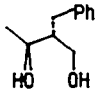
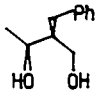
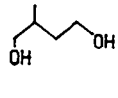
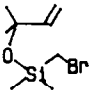
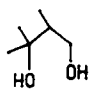
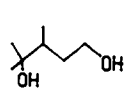


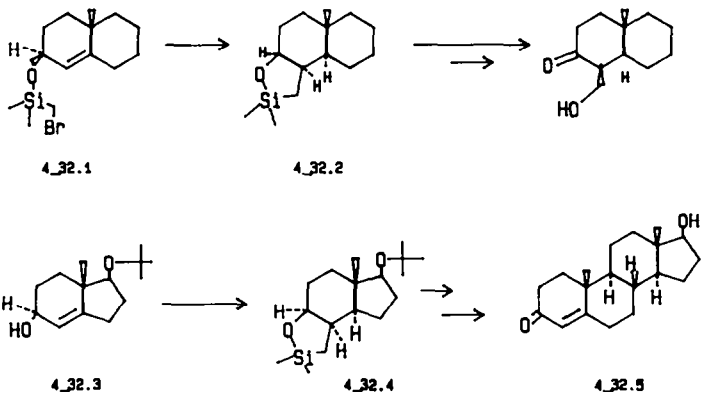
SCHEME 4_31

out a terminal functionality on the double bond (entries 2–6, 9 and 10, Table 29). Stereoselective preparation of *threo*-1,3-diols from silylethers of secondary alcohols are noteworthy (entries 2–8). Also, a terminal 2-phenyl function leads to exclusive formation of the *threo* diol (entry 8). The practical usefulness of this cyclization lies not only in the one-pot procedure, but also in the possible differentiation of the diol functions by monoacetylation prior to oxidation of the silane functionality.

Under the above reaction conditions bicyclic ring formation occurs with preferential *cis* ring junction.[228,229] For example, the reaction of the bromomethylsilylether of bicyclic allylic alcohol

Table 29. Preparation of diols from allylic bromomethylsilylethers

NO	Substrate	Diols (Ratio)			Yield (%)
1					85
					
2	R= Me	(69)	(5)	(16)	95
3	R= iPr	(82)		(18)	90
4	R= tBu	(71)		(29)	91
5	R= $-CH=CH_2$	(61)	(11)	(28)	85
6	R= Ph	(54)	(5)	(41)	88
					
7	R^1=H, R^2=Ph	(84)	(16)		85
8	R^1=Ph, R^2=H	(100)			94
9					
		(35)	(65)		52
10					
		(91)	(9)		83



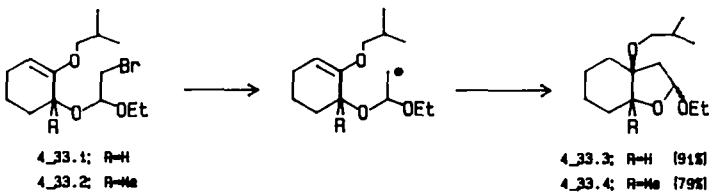
SCHEME 4_32

4–32.1 in benzene with TBTH produces cyclic siloxane **4–32.2** in 65% yield.[229] Under the same reaction conditions, allylic alcohol **4–32.3** is converted into *trans* hydrindane **4–32.4** and finally into 19-nortestosterone **4–32.5**. A noteworthy point of these reactions is that the process is equivalent to the net *trans* addition of a functionalized alkane (one C unit) to the double bond of allylic alcohols so that when a ring junction is generated, the junction H is introduced *trans* to the original OH function of the allylic system[229] (stereochemical control of C–C bond formation).

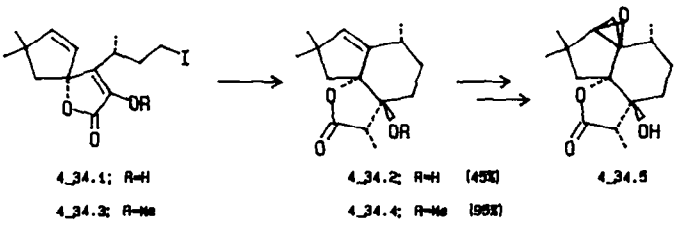
Carbon radicals generally do not add to a C atom of a C=O group. However enolizable ketones undergo intramolecular radical additions. A structural unit, β-oxy γ-butyrolactone with the β-oxy residue located at the ring junction is found in some unusual and biologically interesting natural products. Such compounds have been assembled by the intramolecular addition of a C radical to the α-center of a functionalized vinyl ether (Scheme 4–33).[230] The radical generated, for example from the bromoacetal **4–33.1** and TBTH produces cyclic acetal ether **4–33.3** in 91% yield. This procedure also works with other enol ethers, e.g. **4–33.2** and is applied to the stereoselective intramolecular radical cyclization leading to a key transformation in the total synthesis of alliociolide **4–34.5** (Scheme 4–34).[231] Treatment of **4–34.1** with TBTH (0.02 M in benzene, AIBN, 85°C, 20 h) gives deoxyalliaciolide **4–34.2** in 45% yield. Similarly **4–34.3** is converted into **4–34.4** in 95% yield.

The radical generated, for example from **4–35.1** and bis (dimethylglyoxamato) pyridine cobalt(I) chloride using Tada's method[219] (*inter alia*), produces cyclic olefinic acetals **4–35.2** to **4–35.4** in 70–95% yield (Scheme 4–35).[230] The formation of the olefins is the result of 1,2-elimination of Co–H from the intermediate cobaloximato species **4–35.5** which is formed in the initial radical cyclizations on to the vinylethers.

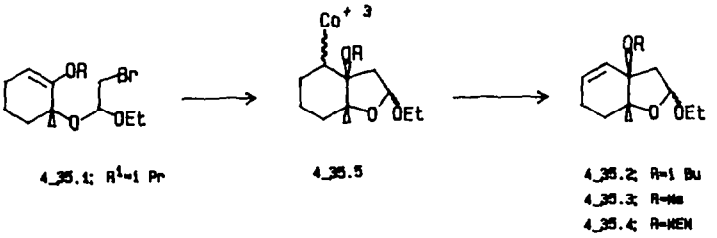
Functionalized bicyclic systems such as gibberlic acid, steviol, etc., having a bridgehead OH group stimulated new synthetic methodologies[232,233] (also see Schemes 4–33 and 4–34) for their preparation. The reaction of a carbonyl C with organometallic reagents is an effective method for C–C bond formation. But syntheses of cyclic tertiary alcohols by the intramolecular reaction of organometallic reagents are generally unsuccessful. Although electrochemical reduction has been recognized as a promising method for the formation of C–C bonds,[234,235] widespread use of this method is not common. However, a regio- and stereoselective method for the synthesis of 5- and 6-membered cyclic tertiary alcohols through the intramolecular cyclization of nonconjugated olefinic ketones, initiated by electron transfer from an electrode to the C=O group appears to be a



SCHEME 4_33



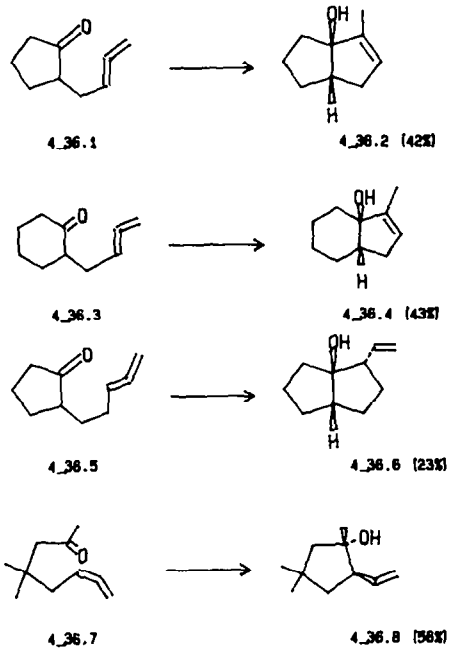
SCHEME 4_34



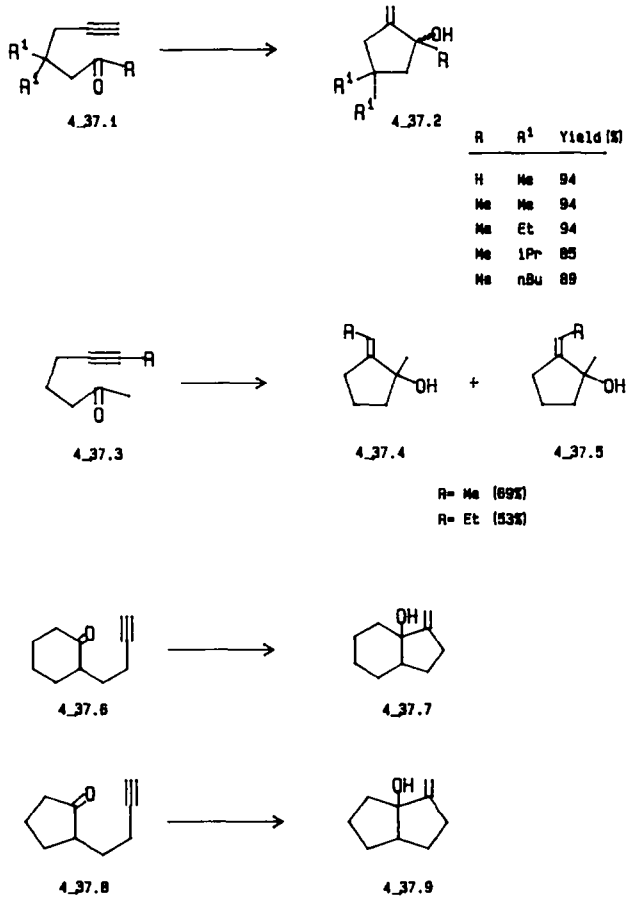
SCHEME 4_35

useful reaction.[236] Electrolysis[237] of a keto allene, for example **4–36.1**, results in the cyclization to cyclopentenol **4–36.2** in 42% yield. Similarly, other terminal allenic ketones **4–36.3**, **4–36.5**, and **4–36.7** are reductively cyclized to **4–36.4**, **4–36.6**, and **4–36.8**, respectively (*exo*-mode) incorporating a bridgehead OH group and a double bond at the predisposed position. It should be noted that the stereochemistry at the ring junction is *cis* with a *trans* relationship between the vinyl group and the bridgehead OH group.

Under above electrolytic conditions, keto alkynes **4–37.1** give high yields of 2-methylen-1-alkylcyclopentanols **4–37.2**. However, introduction of alkyl groups on the terminal C atom of the acetylenic carbon, e.g. **4–37.3**, results in the formation of by-products with a decrease in the yield



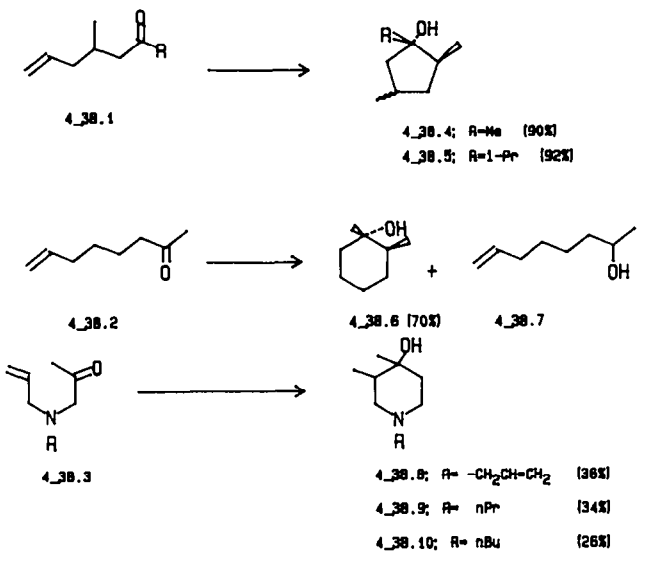
SCHEME 4_36



SCHEME 4_37

of the cyclized product.[238] In this case, the cyclized product is predominantly the (*Z*)-isomer **4–37.5**. In contrast with the observed reverse stereoselectivity in the reductive cyclization of steroidal acetylenic ketones with a naphthalene radical anion (*inter alia*), the preferential formation of the (*Z*)-isomer in the electroreduction of **4–37.3** is noteworthy. Also, the non-conjugated acyclic olefinic ketones **4–38.1** in methanol/dioxane (preferred solvent system) or in DMF containing tetraethylammonium *p*-toluenesulfonate as the supporting electrolyte give *cis* 1,2-dialkylcyclopentanols in good yields. The stereoselective formation of *cis* cyclic tertiary alcohols **4–38.4** and **4–38.5** is to be noted, since the reaction of 2-alkylcyclopentanones with Grignard reagents do not show predominance for the formation of the *cis* isomer. The alkyl substituent on the inner C atom of the double bond inhibits the cyclization, while the substituent located on the C atom between the double bond and the C=O group does not obstruct the cyclization. The electro reduction of **4–38.2** in methanol/dioxane solvent gives *cis*-1,2-dimethylcyclohexanol **4–38.6** in a 70% yield along with secondary alcohol **4–38.7**, while in DMF exclusive formation of **4–38.7** (75% yield) is observed. 6-Membered N heterocycles have also been prepared as single isomers **4–38.8** to **4–38.10** from tertiary amines **4–38.3**. The method is applicable for the synthesis of cyclic tertiary alcohols of 5- and 6-membered rings only, and also it does not work for aromatic ketones.

A ring formation method, which involves a free radical generation from ketones by the reaction of the reagent mixture, Zn–trimethylchlorosilane, followed by internal addition to a π bond, is shown[239] in Scheme 4–39. These cyclization reactions generally proceed in good yields in the presence of 2,6-lutidine in THF at reflux (Table 30). The function of 2,6-lutidine is to prevent proton or zinc chloride catalyzed elimination of the tertiary trimethylsiloxy group. The yields range from 56 to 84%. With cyclohexanone and cyclopentanone derivatives, the major product has *cis* ring fusion. In this methodology, π bond functionalities can be acetylenes, olefins, α,β-unsaturated esters, nitriles and methoxyoximes. As shown in Table 30, this method exhibits considerable generality for ring

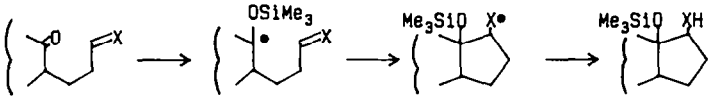


SCHEME 4_38

formation. However, the cyclization reactions with the possibility of forming 6-membered rings are not facile and also, are stereochemically nonselective.

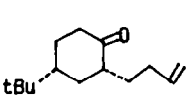
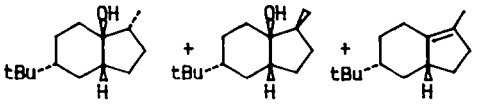
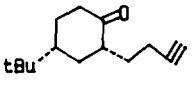
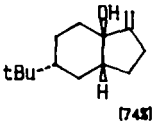
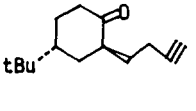
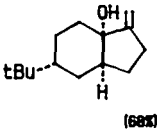
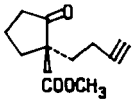
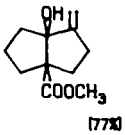
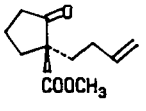
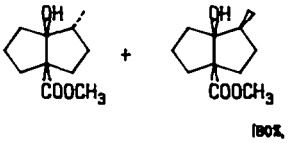
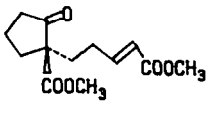
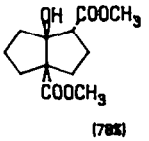
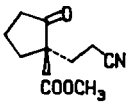
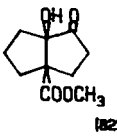
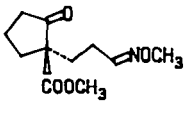
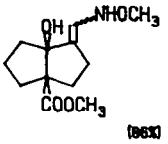
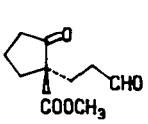
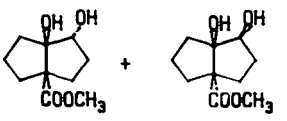
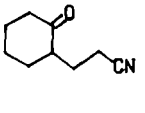
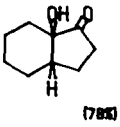
Analogous to the above reaction, reductive radical induced cyclization of substituted 5-hexanals has also been utilized for the intramolecular 5-membered ring formation.[338] For example, secologanin tetraacetate **4–40.1**, on treatment with Mg (20 equiv) and trimethylsilyl chloride (6 equiv) in THF at room temperature for 80 h gives a mixture of four stereoisomers of loganin tetraacetate in a combined yield of 55%. The major isomers, loganine and epi-loganin are formed in 25 and 17% yield, respectively. Other variations, such as Na, Zn or Al in THF with trimethylsilyl chloride and Zn with or without 2,6-lutidine do not work. The scope of the radical induced cyclization of 5-hexanal system with Mg/trimethylsilyl chloride is extended to other examples such as **4–40.4** to **4–40.6**.

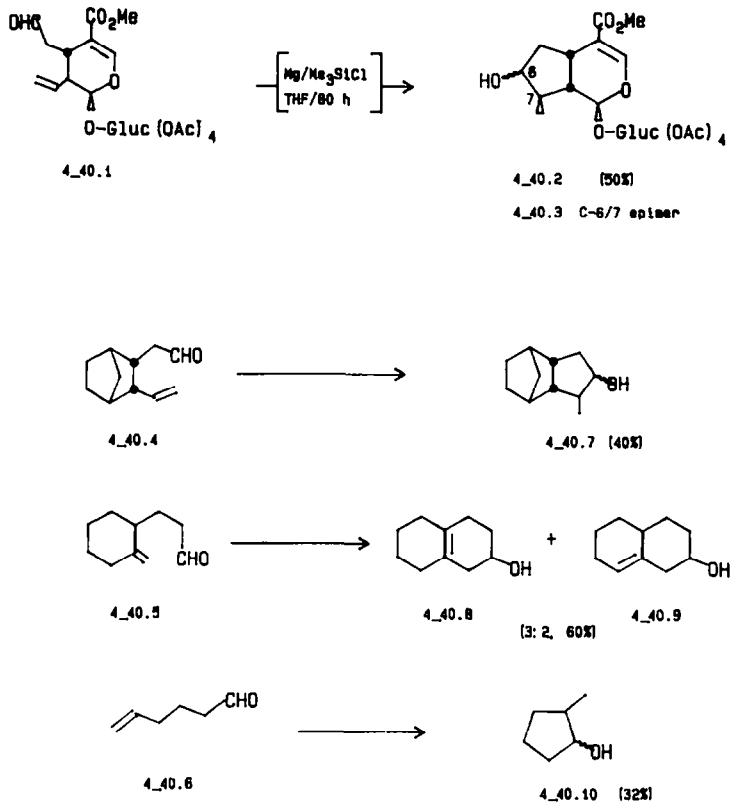
Usually, chain termination of intramolecular radical cyclizations occurs with H atom abstraction. Therefore, regiospecific intermolecular trapping of a radical arising from an initial radical cyclization reaction with a functionalized one C species is a useful reaction[240] (Scheme 4–41). Also, such methodologies are synthetically valuable in the sense that all other successful intermolecular trapping of C radical reactions involve C fragments containing more than 2 C atoms (*inter alia*). The reagent which transfers one C unit is *t*-butyl isocyanide. The radical **4–42.2** derived, for example from cyclization of bromo acetal **4–42.1** with hexaphenylditin (1 equiv) under photolytic conditions, has been trapped with *t*-butylisocyanide. No trapping occurs if TBTH is used and in this case the usually expected cyclic acetal is the exclusive product. The trapping of cyanide is successful with a variety of substrates, e.g. **4–42.4** to **4–42.6** (primary, secondary and vinylic compounds, respectively) and the stereochemistry of the cyano center is determined by the relative ease of access to the cyclized radical. The H atom transfer in the case of **4–43.3** is only 95% of selective, whereas cyanide transfer in the case of **4–43.1** is 100%. Trapping the cyclized radical with simple vinyl ketones or ethylenic ketones does not work. However, successful trapping can be accomplished with α-trialkyl silyl α,β-unsaturated ketones, e.g. **4–43.5** → **4–43.6**.



SCHEME 4_39

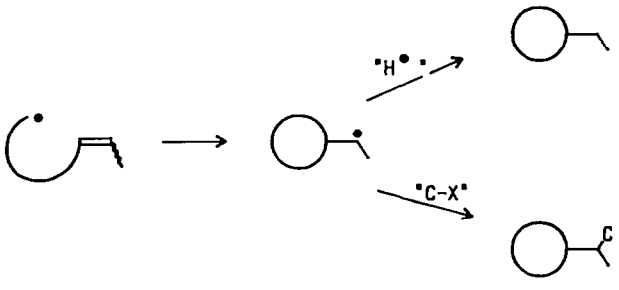
Table 30. Preparation of cyclopentanols from ketones and zinc trimethylchlorosilane

NO	Ketone	Cyclopentanol (%)
1		 (66%) (7%) (4%)
2		 (74%)
3		 (68%)
4		 (77%)
5		 (80%, 5: 1)
6		 (78%)
7		 (82%)
8		 (86%)
9		 (75%, 20: 56)
10		 (78%)

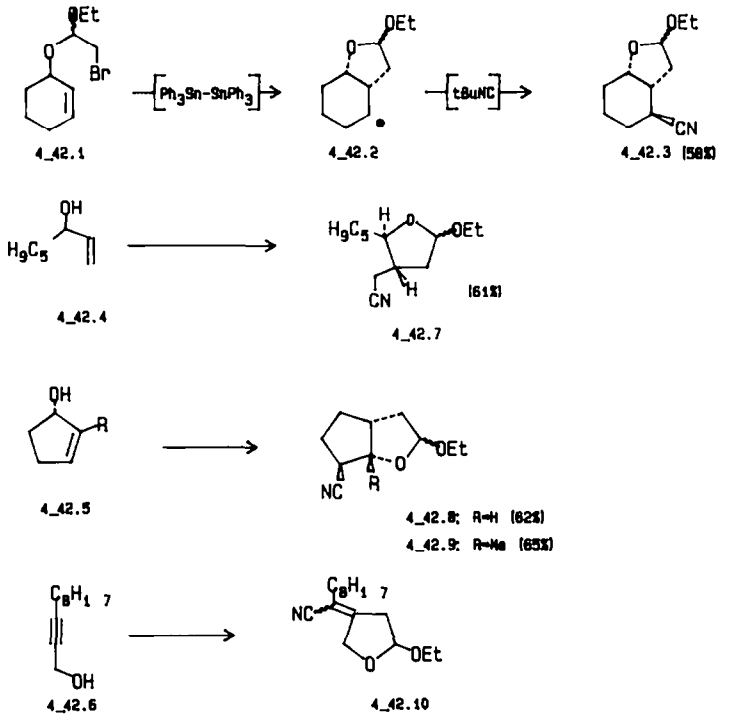


SCHEME 4_40

It is well known that Kolbe electrolysis of carboxylic acid salts produces alkyl radicals. When suitably substituted olefinic acids are subjected to electrolysis, ring formation takes place in low yield. Kolbe electrolysis of a mixture of saturated carboxylic acids and unsaturated carboxylic acid salts, in which unsaturation is separated by 4 or 5 atoms, appears to be a useful synthetic method for C–C bond formation.[241] In this reaction, first an intramolecular radical cyclization of unsaturated acid salt **4–44.1** occurs, which is then followed by an intermolecular coupling of the cyclized radical with a radical $^{\bullet}R^4$ derived from the co-acid **4–44.2**, to give alkylated cyclized products as shown in Scheme 4–44. 3–4 Molar excess of co-acid (R^4COOH) is used to obtain maximum yield. A variety of alkyl groups can be used. When R^1 and R^3 are alkyl groups, preferential ring formation occurs over the formation of the uncyclized products **4–44.5**, which are common by-products in many cases. Ring junctions with cyclic allyl ethers, e.g. **4–44.6** are *cis* and the predominant diastereomer adopts the carboxy alkyl side chain in *exo*-position. Spiro tetrahydrofurans **4–44.9** are also prepared



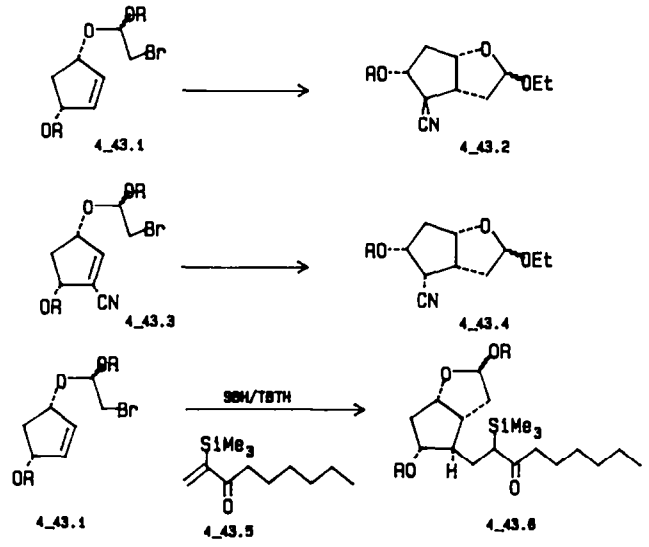
SCHEME 4_41



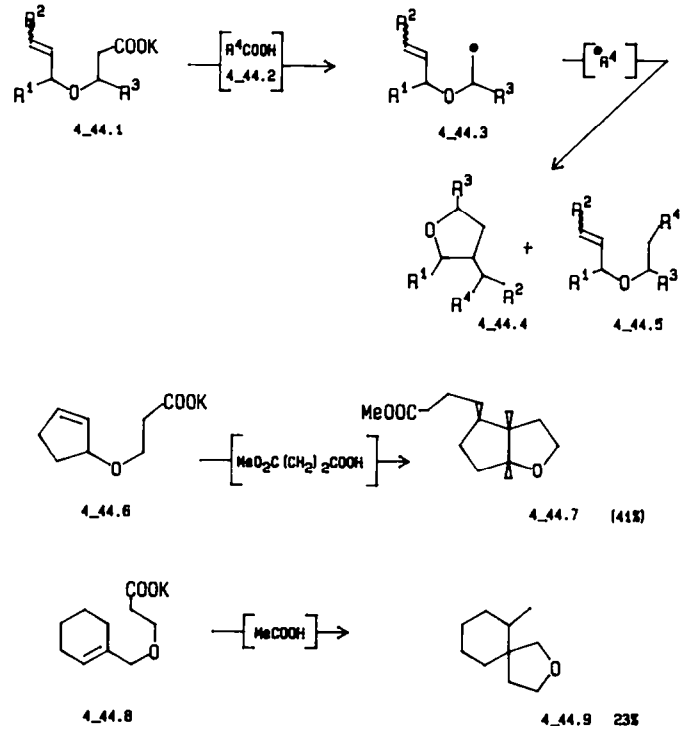
SCHEME 4_42

in this manner. In the case of intramolecular radical cyclization, chain termination is usually by H atom (*inter alia*), except in one case[240] (Scheme 4–42), where a one C fragment, the isonitrile group is used as a chain terminator. However, in this case (Scheme 4–44) one has the option of choosing any length of C chain by selecting an appropriate co-carboxylic acid.

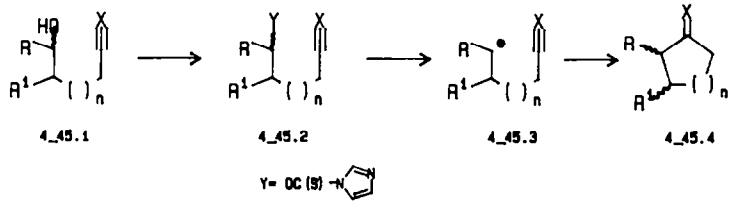
Intramolecular C–C bond formation is not limited to radicals derived from halo compounds and TBTH. For example, the radical of the type **4–45.3** generated from deoxygenation of alcohols **4–45.1** via their thiocarbonylimidazole derivatives **4–45.2**, undergoes intramolecular ring closure to suitably located triple bonds (C≡C, N≡C) leading to cyclic products (Table 31).[242] Cyclization is carried out by slow addition of triphenyltin hydride and AIBN solution in benzene at reflux to the



SCHEME 4_43



SCHEME 4_44

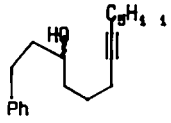
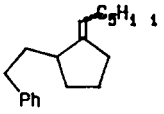
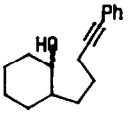
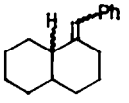
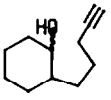
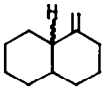
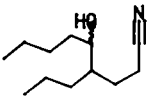
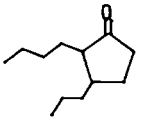
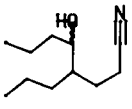
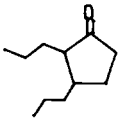
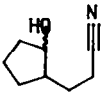
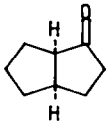
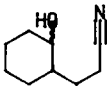
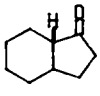
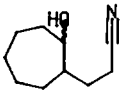
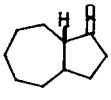


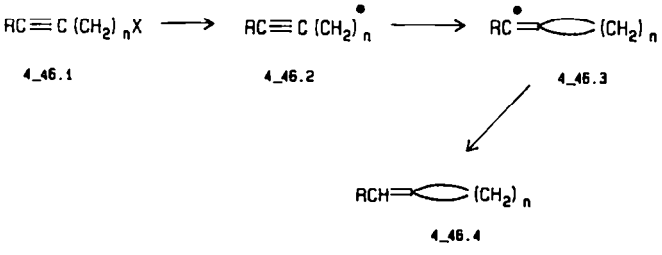
SCHEME 4_45

thiocarbonylimidazolides. In the case of nitrile cyclizations, for the convenience of work-up the initially formed imines have been hydrolyzed to carbonyl compounds. It should be cautioned that cyano radical cyclizations to 6-membered ring formation is not a particularly synthetically useful reaction when an H atom is present on the α-C of the cyano function.[243]

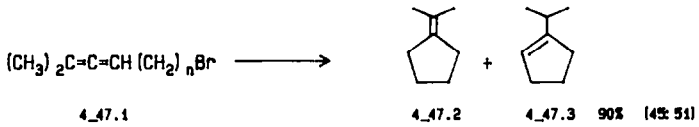
It is appropriate to comment on the utilization of olefinic, acetylenic and allenic radicals in organic synthesis. In general, intramolecular radical addition to acetylenic bonds occurs stereospecifically to give *trans* addition products,[335] and also to give cyclopentylidines preferentially.[244] However, the behavior of the ω-acetylenic alkyl radical as a function of the number of atoms separating two reacting centers parallels the olefinic radical series. Also, the use of Cr(II) for the radical generation from ω-alkynyl halides gives results comparable to those obtained with tin hydride.[245] Highly regioselective cyclization occurs (*exo*-mode) when the halide is separated by 4 and 5 carbon atoms (Scheme 4–46). When $n = 4$, radicals, for example from **4–46.1** ($n = 4$) cyclize more efficiently than when $n = 5$. Also, a phenyl group at the terminus of acetylene **4–46.1** (R = Ph) promotes cyclization more readily than does an alkyl group. The beneficial influence of the phenyl substituent has been attributed to the stabilization of the developing radical in the transition state. The *endo*-mode has been observed in complicated systems where substituents modify the relative stabilities of the radical intermediates. Consequently, some control over the regiochemistry of these radical cyclizations can be exercised by an appropriate choice of substituents (*inter alia*).

Table 31. Synthesis of ketones from cyano and acetylenic radicals

NO	Alcohol	Cyclized Product	Yield (%)
1			81
2			79
3			24
4			72
5			73
6			15
7			47
8			65



SCHEME 4_46

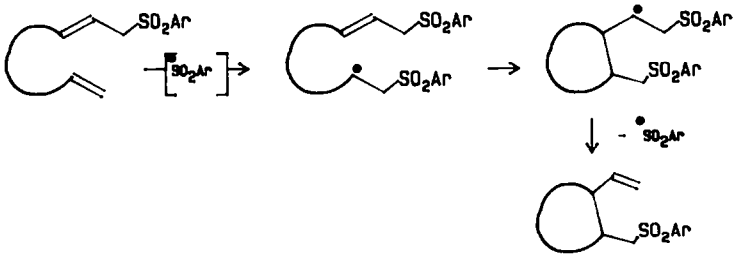


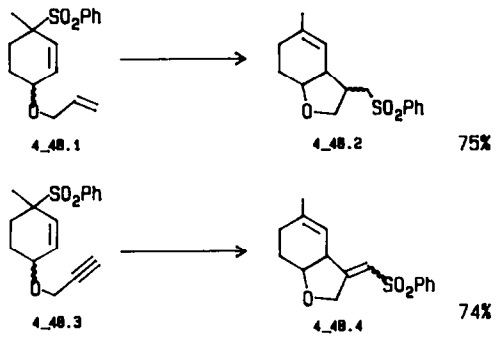
SCHEME 4_47

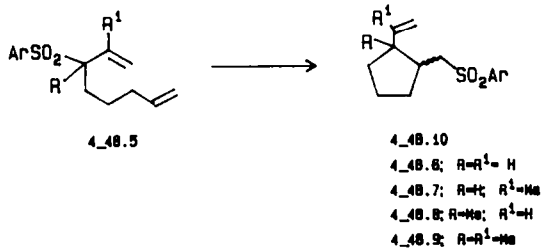
Analogous to the intramolecular reactions of olefinic and acetylenic free radicals, allenic free radicals have synthetic potential (*inter alia*) for the formation of functionalized carbocycles.[261] The TBTH reduction of allenic halides **4–47.1** ($n > 4$) gives a mixture of products. For example, radical cyclization is efficient when $n = 3$, and occurs exclusively at the central allenic sp C, whereas when $n = 4$ or 5 addition occurs at the SP C as well as at the near sp^2 C but not at the far sp^2 C.

Appropriately substituted olefinic allyl sulfones undergo cyclization via 1,3-rearrangement of the allyl sulfone group by a radical chain process as outlined in Scheme 4–48 (S_H2' process).[246] For example, **4–48.1** is converted into bicyclic sulfone **4–48.2** in 75% yield on treatment with dibenzoylperoxide (5 mol%) in carbontetrachloride under reflux (3 h). Similarly, propynyl derivative **4–48.3** has been converted into **4–48.4** [(*Z*):(*E*) ratio 10:1]. Analogous results are obtained with the open chain olefinic sulfone **4–48.5**. The successful cyclization to **4–48.8** and **4–48.9** indicates that quaternary C centres can be formed by this reaction.

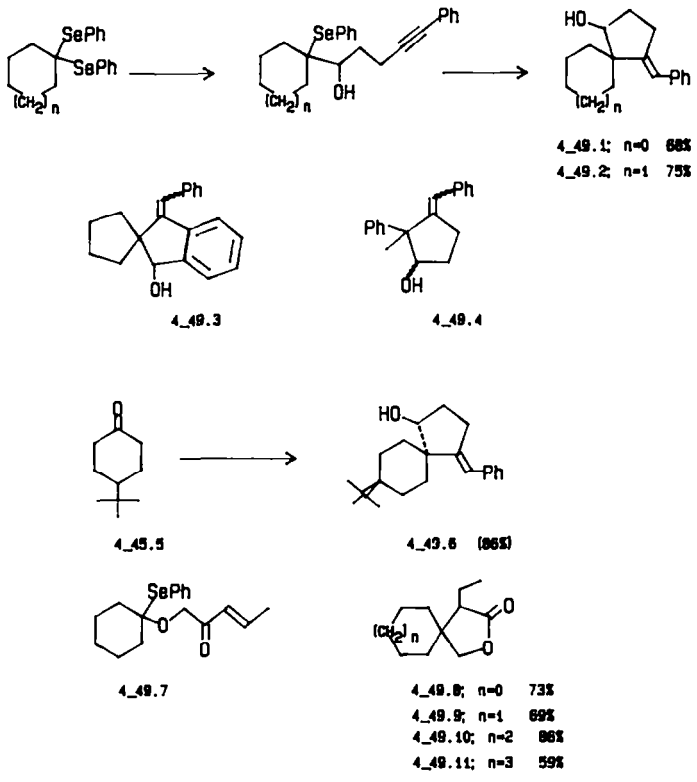
Stereospecific generation of spirostructures and quaternary C centers are often difficult (*inter alia*). Sequential transformation of ketone diselenoacetals provides a method for the construction of such







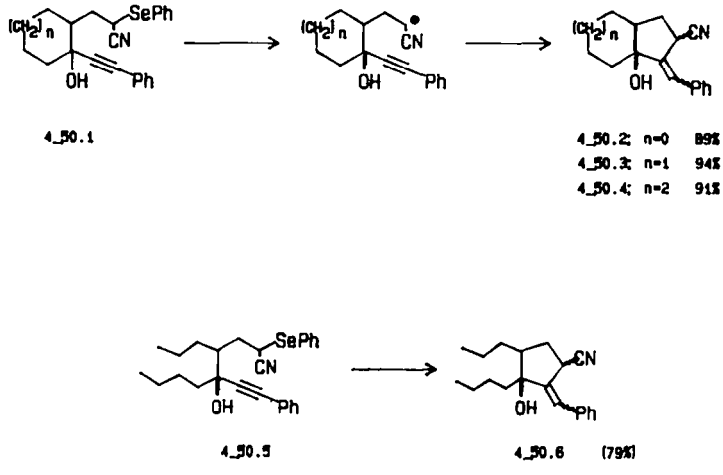
SCHEME 4_48



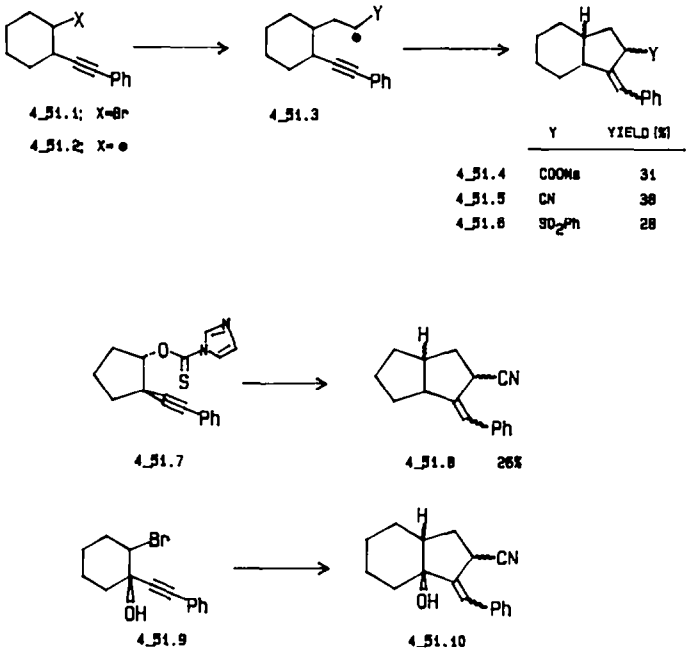
SCHEME 4_49

structures. Initial carbanion-based alkylation of diselenoacetals, followed by homolytic cyclization with triphenyltinhydride provides tertiary and spiro cyclic compounds in good yields,[247] as shown in Scheme 4–49. Among other structures which have been produced by this method, are **4–49.3** and **4–49.4** in 91 and 64% yield, respectively. In the case of 4-*t*-butylcyclohexanone **4–49.5** *cis* and *trans* (1 : 1 ratio) spiro compound **4–49.6** is produced in 86% yield. This methodology has been applied to the synthesis of α-alkyl spiro lactones **4–49.8** to **4–49.11** in good yields.

The δ-acetylenic radicals stabilized by a nitrile group generated from α-phenylselenonitriles **4–50.1**, by slow addition of triphenyltinhydride and AIBN in refluxing benzene undergo 5-exo ring closure to give 5-membered ring products (Scheme 4–50). Although the products are isomeric



SCHEME 4_50



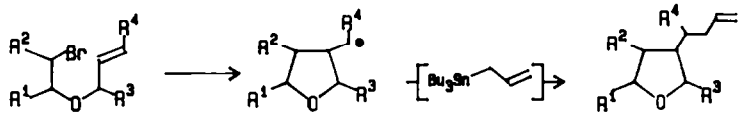
SCHEME 4_51

mixtures, the yields are good.[248] The starting alcohols are constructed from ketones in two steps: 1,4-addition of cyclic or acyclic enamines to 2-phenylseleno acrylonitrile; hydrolysis of the enamine to a ketone, followed by addition of phenylacetylene.

An extension of the above, the δ-acetylenic radical cyclization method is shown in Scheme 4–51. This involves the initial addition of β-acetylenic radicals **4–51.2** to Michael acceptors in an intermolecular fashion, generating a new radical **4–51.3** which then adds intramolecularly to the acetylenic bond to give cyclopentanes as stereoisomeric mixtures in relatively low yields (Scheme 4–51).[249] The precursors for **4–51.2** are prepared in three steps from an epoxide or in two steps from α-halo ketones. Michael acceptors are acrylonitrile, methylacrylate or phenylvinylsulfone. Usually, cyclohexyl radicals **4–51.2** generated from the corresponding bromides are reasonably reactive in this procedure, whereas those derived from the thiocarbonylimidazoles are not reactive. However, the cyclopentyl radical gives a 26% yield of the product **4–51.8** only with thiocarbonylimidazolide derivative, **4–51.7**. Tertiary OH groups are stable to these reaction conditions. For example, bromo acetylenic radicals of the type **4–51.9** are used for the preparation of the functionalized 5-membered carbocycles **4–51.10**. It should be noted that these reactions are analogous to the tandem radical cyclizations (*inter alia*) involving at least two different radicals, namely one alkyl and one alkenyl radicals in that sequence.

Allyl tri-*n*-butylstannane is known to be a useful allylating reagent under ionic as well as radical conditions (*inter alia*). Under radical conditions it undergoes S_H2' substitution with alkyl halides. Radical chain reaction of the β-bromoethers **4–52.1** with allyl tri-*n*-butylstannane (3 mol equiv) in the presence of a catalytic amount of AIBN in benzene (1 ml/mol of substrate) at 80°C for 20–24 h, proceeds first to a cyclized radical **4–52.2**, which then undergoes intermolecular C–C bond formation to yield **4–52.3** (Scheme 4–52).[250] This reaction complements other methods in which the radicals are terminated by electrophilic carbon radicals, rather than by an H atom.[240,242] The method has also been applied to the synthesis of a variety of tetrahydrofuranyl derivatives. Also, in this method there is no need to protect free OH group and the experiment can be conducted in one pot. In addition it should be noted that the 2,3-disubstituted furans are produced as a 1 : 1 mixture of *cis* and *trans* isomers.

Application of this reaction in an intramolecular sense has led to the preparation of pyrrolidine alkaloid, (±)-isoretonecanol **4–53.3** as shown in the Scheme 4–53. Irradiation of **4–53.1** (450 W Hanovia lamp, with Pyrex filter) leads to **4–52.2** with good stereoselectivity (11.3 : 1) in modest yield.



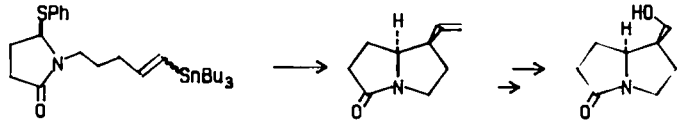
R^1	R^2	R^3	R^4	YIELD (%)
$-(CH_2)_4-$		H	H	48
$-(CH_2)_4-$		Me	H	43
$-(CH_2)_4-$		H	Me	49
Ph	H	H	H	35
Ph	H	Me	H	25
Me_2	CH_2OH	H	H	35

SCHEME 4_52

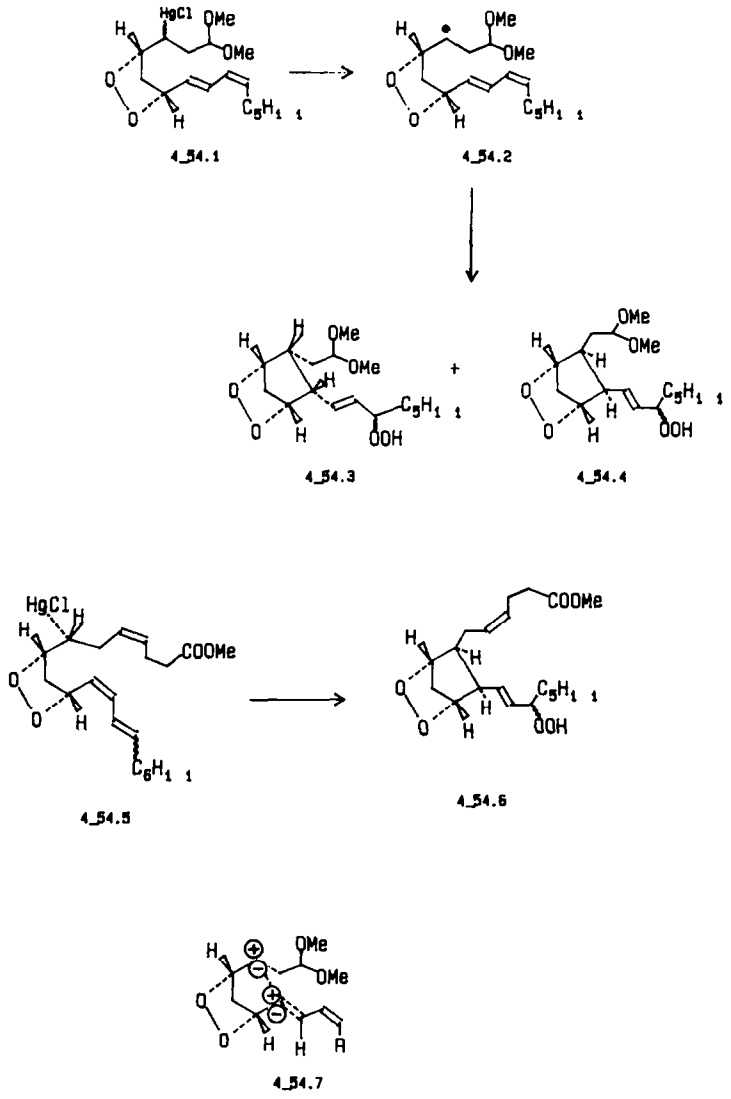
Homolytic demercuration of diastereomeric 1,2-dioxolanes **4–54.1** allows conversion to β-peroxy radicals **4–54.2** upon treatment with TBTH at −40°C. These radicals gradually decompose in the presence of air at −10 to 0°C to form endoperoxides **4–54.3** and **4–54.4** (1 : 1 ratio) in 70–90% yield.[210] Similar demercuration of the 1,2-dioxolane **4–54.5** results in cyclization to endoperoxide **4–54.6**, which can finally be converted into 8-epi $PGF_{2\alpha}$. The formation of the identical mixture (1 : 1 ratio) of endoperoxides **4–54.3** and **4–54.4** from the two diastereomeric mercurials **4–54.1** has been interpreted in terms of a common radical conformer **4–54.7**, wherein the geometry shown occurs by the delocalization of the radical into the *p*-orbital of the β-peroxy oxygen lone electron pair and as well as into the diene unit.

Similar to intermolecular C–C bond formation (*inter alia*), suitably substituted cyanoacetates or acetoacetates and other active methylene compounds undergo intramolecular carbolactonization[251,252] with Mn(III). The intramolecular version of this carbolactonization, described earlier, has been applied to the preparation of polycyclic polylactones (Scheme 4–55). Olefinic keto acids **4–55.1** to **4–55.5** are stirred with Mn(III) acetate in acetic acid at 23–40°C for 20 min to 24 h to give good yields of lactones **4–55.6** to **4–55.10**. It has been expressed that this carbolactonization is not a result of conventional free radical but rather a Mn-stabilized "radicaloid" species.[252] This reaction also works with malonates, cyanoacetates and chloroacetates.

Intramolecular oxidative cyclization of unsaturated acids with Mn(III) acetate is not possible, since the solvent acetic acid is oxidized preferentially. However, unsaturated β-keto esters or acids are oxidized much more readily than is acetic acid (*inter alia*). Free radical cyclization reactions in which the chain process is terminated by oxidation of the radical center **4–56.3** to give carbocation **4–56.4** which loses a proton to give a new alkene, complements the vinyl radical cyclizations (Scheme 4–56). Several substituted β-keto-acids, -esters and -diketones have been subjected to Mn(III) oxidation to give good yields of 5- and 6-membered rings having a vinyl side chain[253] (Table 32). The carbocations **4–56.4** derived from esters either lose a proton to form an alkene or react with solvent. These oxidative cyclizations are best accomplished in a solvent mixture containing acetic acid, potassium acetate and acetic anhydride, with two equiv of manganese acetate and one equiv of $Cu(OAc)_2$ at 60°C for 1 h. *In situ* generated Mn(III) from $KMnO_4$ and $Mn(OAc)_2$ is the preferred reagent. It should be noted that the terminal double bonds in the products are more susceptible for further attack by electrophiles or electrophilic radicals. In this series the β-keto ester moiety of the cyclopentanones is oxidized more readily than in the case of the cyclohexanones, and the rate is



SCHEME 4_53

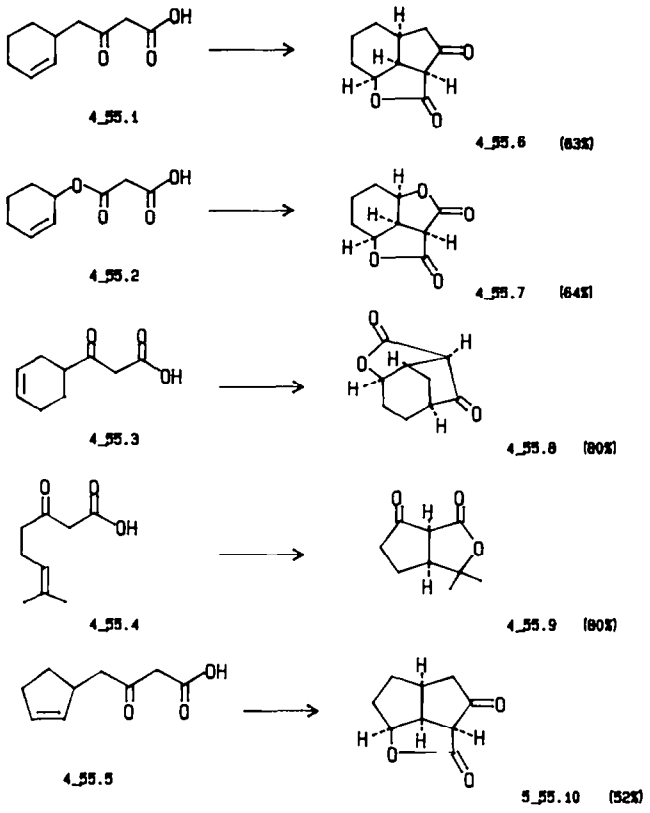


SCHEME 4_54

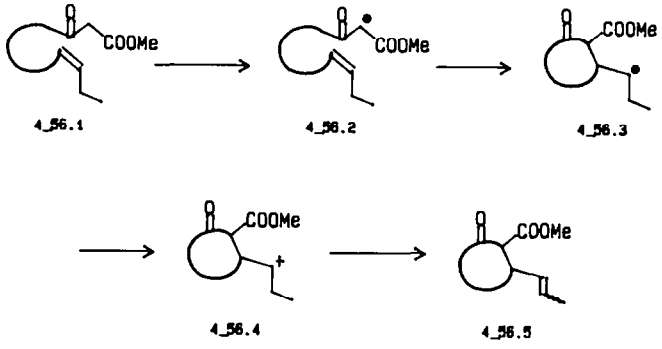
competitive to that of oxidation of the starting acyclic β-keto esters. Oxidative free radical cyclizations of β-substituted keto esters (e.g. products in this case), proceeds in much higher yields than these of unsaturated β-diketones. Also to be noted is that (*Z*)-alkenes give (*E*)-alkenes stereospecifically (entries 1 and 2).

Application of radical-olefin cyclizations have been extended to chiral polyoxygenated substrates. Individual reactions of geometric isomers **4–57.1** and **4–57.2**, on heating with TBTH/AIBN in benzene, give an identical mixture of two isomeric products **4–57.3** and **4–57.4** in 80–90% yield.[254] The ratio of **4–57.3** and **4–57.4** depends on the olefin geometry. The (*Z*)-olefin, **4–57.1**, exhibits consistently greater stereocontrol than does the corresponding (*E*)-isomer **4–57.2**. The major product, **4–57.3**, has the side chain in an *exo* orientation, indicating the importance of the interaction of the ester functionality with either the ethereal oxygen of acetal or the H atom on the C-4. Also, some degree of control is exerted by the oxygen substituent at C-6. For example, while *cis* alcohol, **4–57.1** (R = H), affords a 6 : 1 ratio of products, the corresponding benzoates and pivolates give 10 : 1 and 11 : 1 ratio, respectively, in favor of the *exo*-isomer, indicating the significance of steric rather than electronic effects.

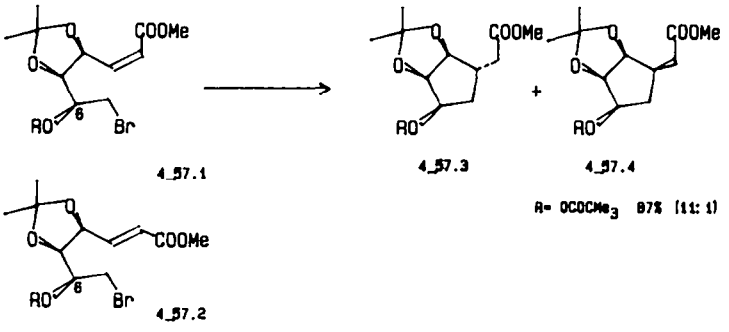
The synthetic potential of the intramolecular C–C bond formation, in natural product synthesis via radical intermediates was forseen almost a decade ago. For example, reaction of bicyclic bromide



SCHEME 4_55

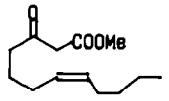
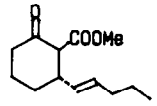
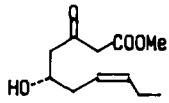
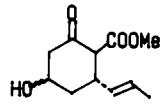
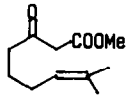
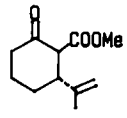
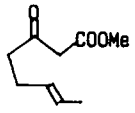
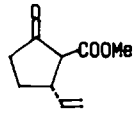
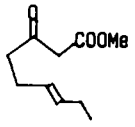
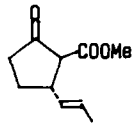
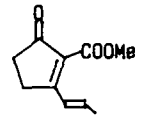
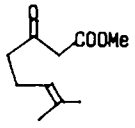
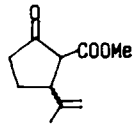
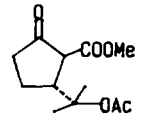
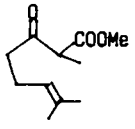
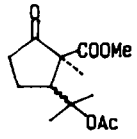
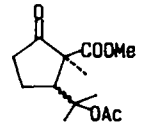


SCHEME 4_56

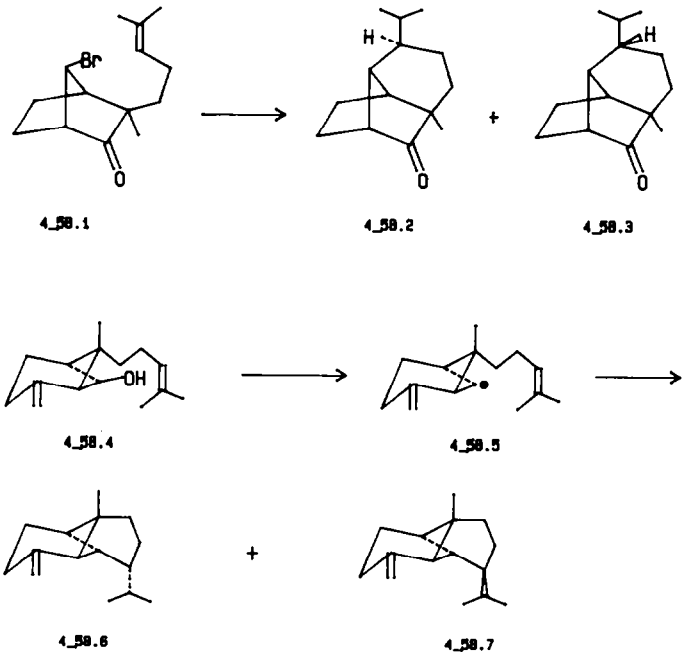


SCHEME 4_57

Table 32. Oxidative free radical cyclization of unsaturated β-ketoesters

NO	Ester	Product	Yield (%)
1			75
2			49
3			21
4			21
5		 	36, 10
6		 	8, 10
7		 	27, 20

4–58.1 with TBTH in benzene at 36°C results in 3:2 ratio of norsativone **4–58.2** and copacamphenilone **4–58.3** in 62% yield.[255] More recently,[256] under similar reaction conditions β-copaene **4–58.6** and β-ylangene **4–58.7** have been prepared from alcohol **4–58.4** via thiocarbonylimidazolide (15%). The low yield is probably a result of the instability of the strained cyclobutyl radical **4–58.5**. Dihydroagarofuran **4–59.2** and β-agarofuran **4–59.1** have been synthesized from (−)-carvone.[257] Chloroether **4–59.4** on treatment with TBTH/AIBN in cyclohexane gives a diastereomeric mixture (3 : 7 ratio) of **4–59.2** and **4–59.3** in 67% yield. Although unsubstituted acetylenic halide **4–59.5** gives mostly polymeric material, the acetylenic silane **4–59.6** gives a 4 : 1 geometric mixture of vinylsilanes **4–59.7** in 72% yield. Removal of the silane group is best accomplished with *p*-toluenesulfinic acid in refluxing acetonitrile. This gives β-agarofuran **4–59.1** in 92% yield, which on reduction with diimide (hydrogen peroxide and hydrazine) gives **4–59.2**.

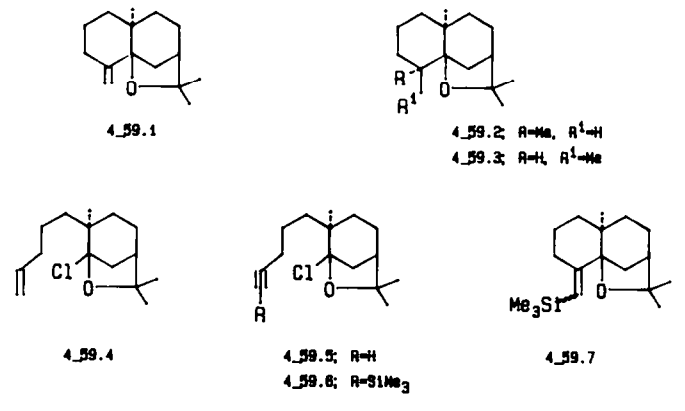


SCHEME 4_58

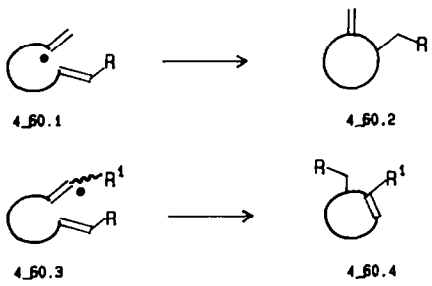
4.2. *Via vinyl radicals*

C–C bond formation via vinyl radicals is an important synthetic operation. It has an advantage over alkyl radicals (Scheme 1–1) in the sense that the product retains a vinyl functionality which is then available for further synthetic transformation. Also, the intramolecular addition of a vinyl radical to a multiple bond results in a product with the double bond at a predictable position (Scheme 4–60). Further, carrying a functional group within the appendage of the radical precursor provides a functionality which could be useful for further transformation.[262,263] The success of vinyl radical cyclizations depends critically on the relative rates of the cyclization process and also on the H abstraction prior to the cyclization. In general, cyclization predominates at low hydride concentration.

Generally, vinyl radicals are generated from a vinyl halide–tin hydride procedure (*inter alia*), although other precursors are also readily available.[264] It is suggested that vinyl radicals are possible intermediates in the Wharton reaction[40] which is normally utilized to convert certain unsaturated acyl oxiranes to allyl alcohols. For example, treatment of oxiranes **4–61.1**, with excess hydrazine in



SCHEME 4_59

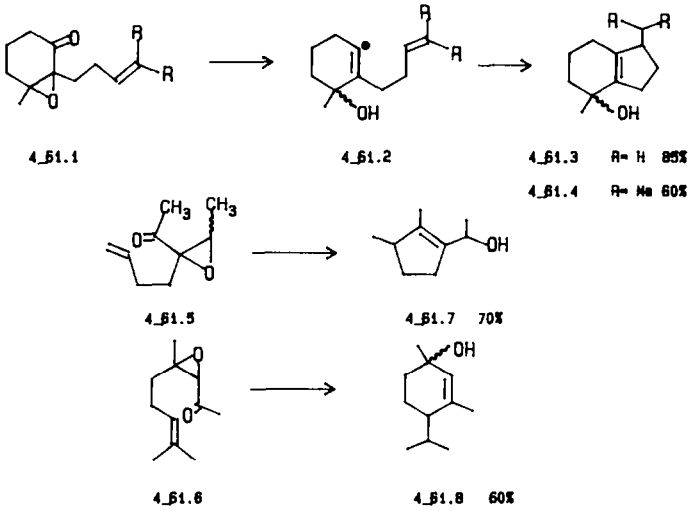


SCHEME 4_60

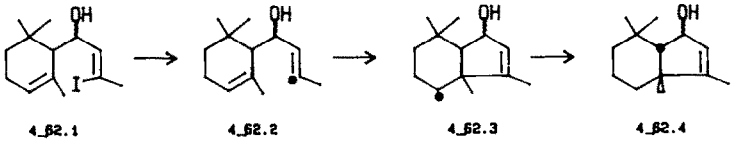
methanol, results in the cyclization to **4–61.3** via vinyl radical **4–61.2** (Scheme 4–61).[275] Although geometric factors effect cyclizations, this is a useful reaction for the preparation of simple 5- and 6-membered rings, e.g. **4–61.7** and **4–61.8**. However, production of a vinyl radical using this procedure has limited scope.

Vinyl halides are ideal starting materials for the generation of vinyl radicals. The initiation of the radical chain reaction can be accomplished with TBTH under thermal or photochemical conditions. For example, UV irradiation of vinyl iodide **4–62.1** with a slight excess of TBTH and a catalytic amount of AIBN gives **4–62.4** in good yields.[265] This reaction proceeds via vinyl radical **4–62.2**, which adds to the proximal double bond in an *exo* fashion to produce radical **4–62.3**. It should be noted that during these cyclizations, quaternary C centers such as in **4–62.6** and **4–62.8** are formed. This indicates, unlike intramolecular alkyl radical cyclizations, that steric hindrance is not strongly felt in the transition state. In bicyclic systems, ring junctions are *cis*. Functional groups such as free OH groups, cyano and ester functionalities tolerate the reaction conditions. It should be noted that **4–62.6** could be visualized as a model for the C/D ring system of the cardiac aglycones.

One of the useful features of vinyl as well as alkyl radicals is that they do not lead to β-elimination of hydroxy or alkoxy function as shown with **4–63.1**. The regiochemical preference in the cyclization reactions of the vinyl radicals, is qualitatively similar to that of alkyl radical analogues. Preference for the formation of the smallest possible ring is higher (Scheme 4–64). However, cyclizations can be directed exclusively to 6-membered rings instead of 5-membered rings by substitution on the acceptor double bond as in **4–65.3**. It is interesting to note that either isomer, **4–66.1** and **4–66.2**, as a radical precursor is satisfactory for the cyclization to produce the same compound **4–66.3**, indicating a rapid inversion of intermediate vinyl radicals. This reaction has been applied to the construction of polycyclic molecules **4–67.3** and **4–67.5**.[262,263,266]

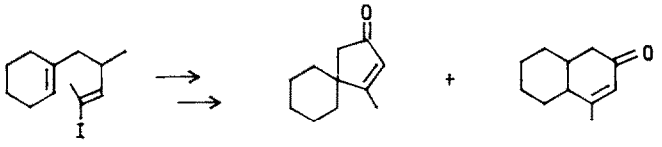


SCHEME 4_61



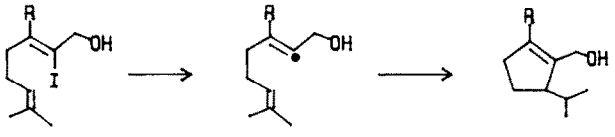
4_62.1 4_62.2 4_62.3 4_62.4

4_62.5 4_62.6



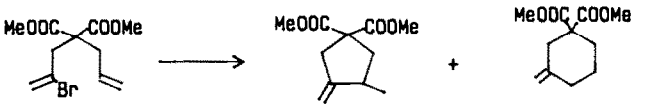
4_62.7 4_62.8 4_62.9

SCHEME 4_62

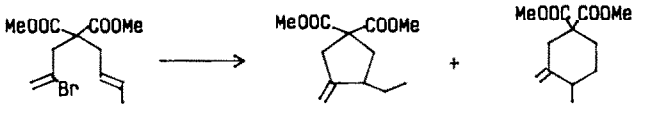


4_63.1 4_63.2 4_63.3

SCHEME 4_63



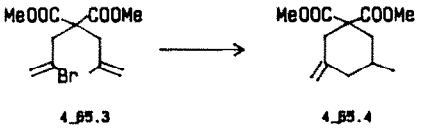
4_64.1 4_64.2 4_64.3 (3:1)



4_64.4 4_64.5 4_64.6 (2:1

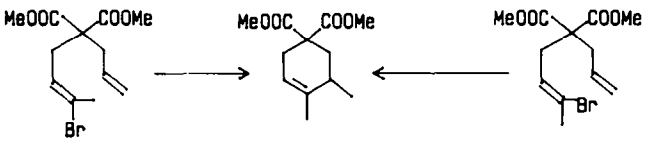
SCHEME 4_64

4_65.1 4_65.2



4_65.3 4_65.4

SCHEME 4_65

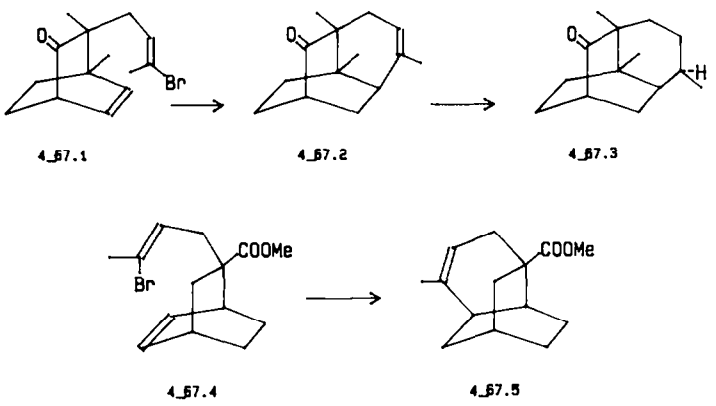


SCHEME 4_66

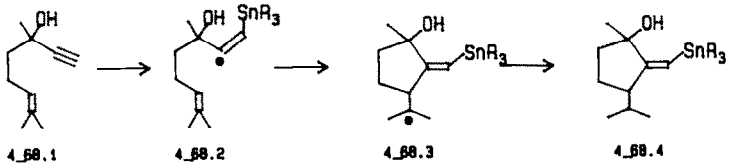
Addition of TBTH to terminal acetylenes is a well-established synthetic method for the preparation of vinyl stannanes. However, in systems of the type **4–68.1**, in which a double and a triple bond are present in the same molecule, the initially generated vinyl radical **4–68.2** undergoes intramolecular cyclization to produce another radical **4–68.3** and finally to give vinyl stannanes in a stereospecific manner.[262] Other useful transformations are shown with **4–68.5** to **4–68.7**.

The trialkyltin hydride mediated homolysis of vinyl halide **4–69.1** adds intramolecularly to a stereoproximal acceptor alkene moiety (α,β-unsaturated ketones) as shown in Scheme 4–69.[267] This is analogous to the intramolecular addition of an alkyl radical to α,β-unsaturated ketones (Scheme 4–1). It should be noted that trialkyltin hydride is a very selective reagent, in the sense that it generates vinyl radicals from vinyl halides without effecting a ketone functionality. In general, cyclizations take place in good yields. This methodology has been applied to the regioselective exocyclization to produce bridged compounds, e.g. **4–69.2** to **4–69.4**, **4–69.6** and fused ring systems **4–69.8**, **4–69.9**. However, **4–69.10** does not cyclize under these conditions, indicating the necessity for a carbonyl group. It should be mentioned that such a requirement of having a C=O group is found to be unnecessary with intramolecular alkyl and alkenyl radical cyclizations (*inter alia*). It has been noted that while vinyl iodides and bromides are useful for the generation vinyl radicals, the vinyl chlorides are not useful as radical precursors. Benzene appears to be the preferred solvent in these reactions. Interestingly, the aryl iodide **4–70.1** and vinyl bromide **4–70.3** each have been cyclized to **4–70.2** (85% yield) and **4–70.4** (50% yield), respectively.[260]

Traditional synthetic methods for the preparation of α-methylene γ-lactones[337] involve the introduction of the α-methylene group in the last step of the synthesis. However, using radical reactions it is possible to introduce an *exo*-methylene group followed by incorporation of a C=O group at the end of the synthesis. This is accomplished[222] by the intramolecular addition of a vinyl radical, generated from a halomethyl acetal **4–71.1**, to a suitably positioned internal double bond as shown in the Scheme 4–71. The C=O group is introduced by the acidic oxidation. The vinylic bromoacetals **4–71.1** are prepared from butoxyallene and excess allylic alcohol in the presence of NBS at −20 to 0°C. Monocyclic systems give *trans*-rich products, whereas bicyclic systems give *cis*-fused products. It should be noted that even though the starting bromoacetals have a very reactive

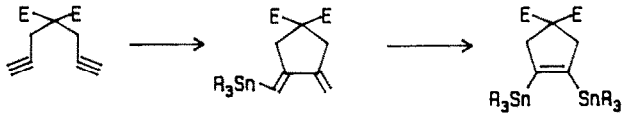


SCHEME 4_67

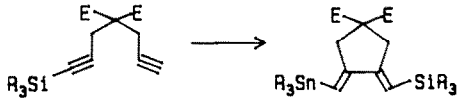


4_68.1 4_68.2 4_68.3 4_68.4

4_68.5 4_68.8



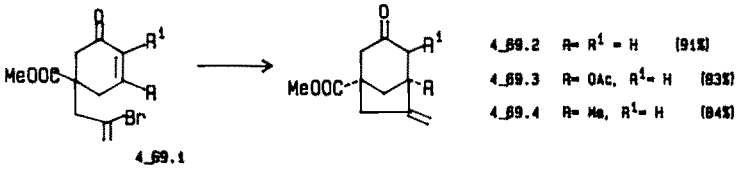
4_68.6 4_68.9 4_68.10



4_68.7 4_68.11

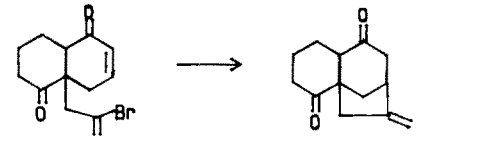
E=COOEt

SCHEME 4_68

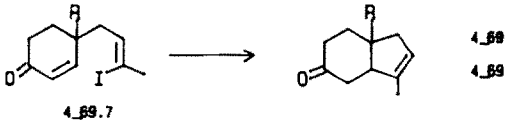


4_69.1

4_69.2 R= R1 = H (91%)
4_69.3 R= OAc, R1= H (83%)
4_69.4 R= Me, R1= H (84%)

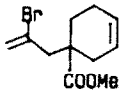


4_69.5 4_69.6 (85%)



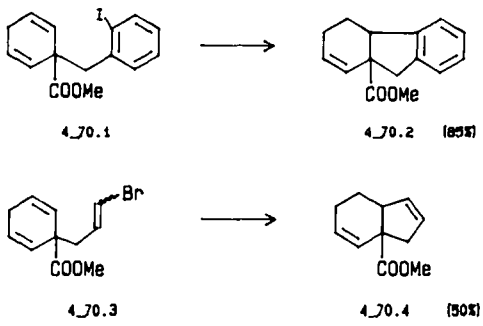
4_69.7

4_69.8 R= H (85%)
4_69.9 R= Me (83%)

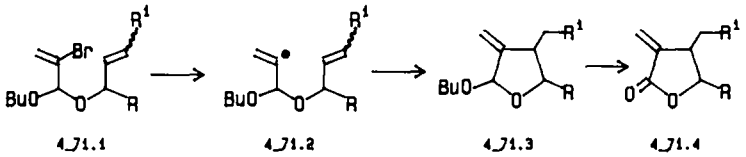


4_69.10

SCHEME 4_69



SCHEME 4_70

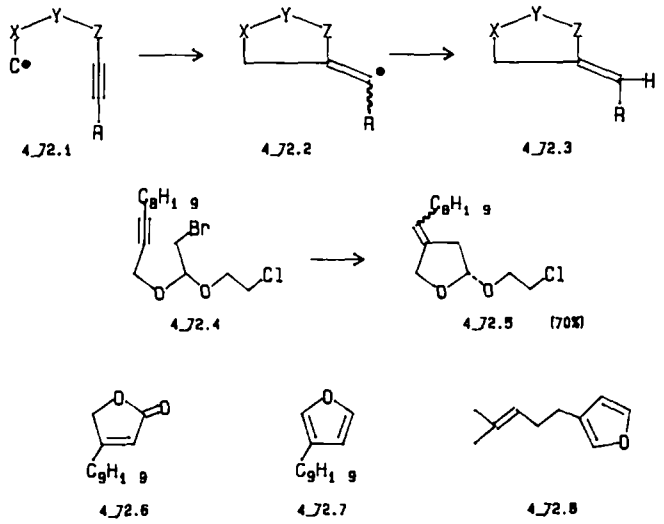


R	R^1	Yield (%)
H	H	62
Me	H	65
$-(CH_2)_3-$		68

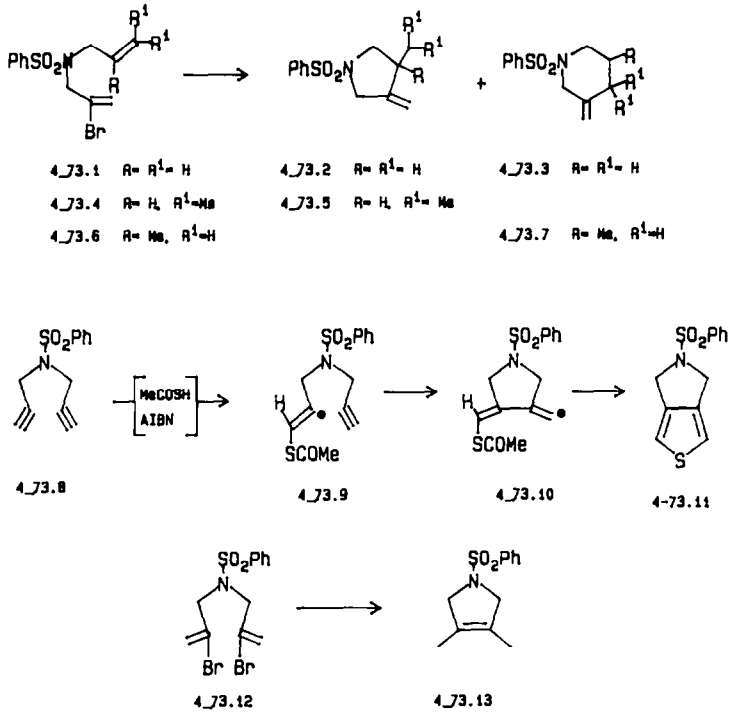
SCHEME 4_71

H atom at C-3 (allylic and acetal H atom), any undesirable products derived from the abstraction of this H atom are not observed.

An alternate method for the generation of vinyl radicals has been developed[268] to supplement the classical method, i.e. from the reaction of a vinyl halide with a stannane or from epoxy ketones with hydrazine. The intermolecular addition of a free radical (preferably a carbon radical) to an alkyne to generate a vinyl radical, capable of under going intramolecular olefin addition is difficult due to the lack of initial chemo- and regioselectivity. However, geometric constraints associated with the radical center connected to an acetylenic bond by a chain of 3 or 4 atoms as in **4–72.1**,



SCHEME 4_72



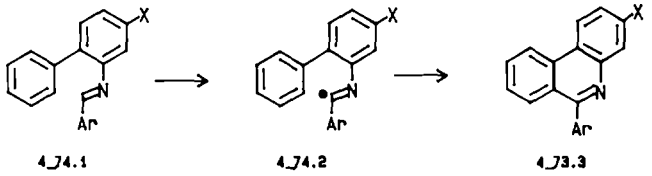
SCHEME 4_73

enables the regiochemical generation of the requisite vinyl radical, **4–72.2**, which can give the cyclization product with the double bond in a specific position, as shown with **4–72.3**. For example, bromoacetal **4–72.4** with TBTH (1.1 equiv and cat AIBN) in refluxing benzene gives cyclic acetal **4–72.5** which is converted into butenolides **4–72.6** (Na/THF/ammonia, −78°; pyridinum-chlorochromate, DBU) or furans **4–72.7** (*p*-toluenesulfonic acid, 4 Å molecular sieves, refluxing benzene). This reaction has been utilized for the synthesis of the naturally occurring *β*-substituted furan, perillene **4–72.8**.

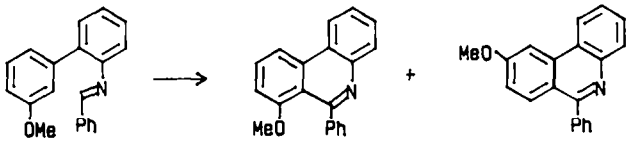
Vinyl radical cyclizations have also been utilized for the preparation of nitrogen heterocycles. Reductive cyclization of aza-vinyl bromide **4–73.1** with TBTH gives *exo*- and *endo*-cyclization products **4–73.2** and **4–73.3** in 73% yield (1 : 2 ratio). This is in contrast to the considerably large *exo* : *endo* ratio observed in the closely related carbocyclic system (Scheme 4–62). It appears that, due to substitution patterns on the olefins, stereoelectronic factors dictate the ratio of *exo*- or *endo*-cyclization products.[213] For example, **4–73.4** gives exclusively the *exo* product **4–73.5**, whereas **4–73.6** gives **4–73.7**. Radical induced addition of thiolacetic acid with *N*,*N*-bis(2-propynyl)benzene-sulphonamide **4–73.8** gives **4–73.11** as a major product in 55% yield via the intramolecular addition of vinyl radical **4–73.9**. Bis vinyl bromide **4–73.12** with TBTH gives only **4–73.13**. In these types of reactions, formation of 1,5-cyclization is generally the preferred path.

Although many routes to phenanthridenes are available, alternative methods are still of interest. Among these methods, formation of the heterocyclic ring starting from a biphenyl derivative is widely used. Building the heteroaromatic ring via imidoyl radicals **4–74.2** derived from the readily available Schiff's bases **4–74.1** by H abstraction, appears to be an alternative[269] (Scheme 4–74) to the traditional methods. H abstraction is accomplished with diisopropyl peroxycarbonate (2 equiv) in benzene at 60°C. Yields are much higher than those from known methods. It should be noted that difficulty accessible arylmethoxyphenanthridenes **4–74.5** and **4–74.6** are available by this method.

An useful aromatic annelation reaction[319] leading to substituted quinolines **4–75.4**, has been accomplished by the reaction of arylimidoyl radicals with alkynes (Scheme 4–75).[270] In a typical experiment, the *N*-benzylidineamine **4–75.1** (5 mmol) and di-isopropyl peroxydicarbonate (DPDC) 10 mmol) are kept at 60°C in benzene with an appropriate alkyne, until decomposition of DPDC is complete.



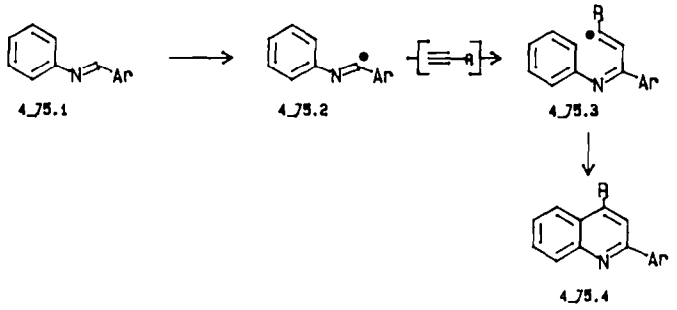
4_74.1 4_74.2 4_73.3



4_74.4 4_74.5 4_74.6

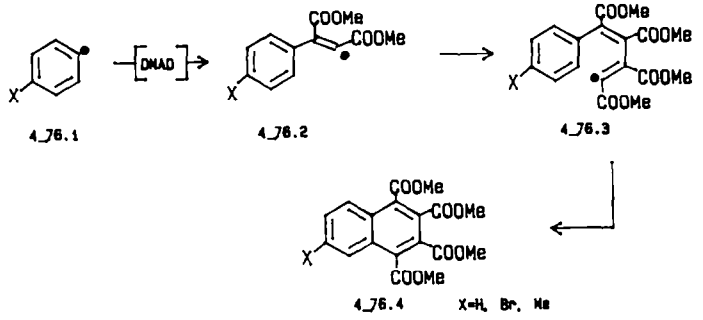
Ar	X	4_74.3 (%)	Ar	X	4_74.3 (%)
C_6H_5	H	85	$4Cl\text{-}C_6H_4$	H	82
C_6H_5	Cl	90	$4Cl\text{-}C_6H_4$	Cl	60
C_6H_5	OMe	66	$4Cl\text{-}C_6H_4$	OMe	85
$4\text{-}NO_2\text{-}C_6H_4$	H	86	$4\text{-}OMe\text{-}C_6H_4$	H	86
$4\text{-}NO_2\text{-}C_6H_4$	Cl	67	$4\text{-}OMe\text{-}C_6H_4$	Cl	75
$4\text{-}NO_2\text{-}C_6H_4$	MeO	87	$4\text{-}OMe\text{-}C_6H_4$	MeO	77

SCHEME 4_74



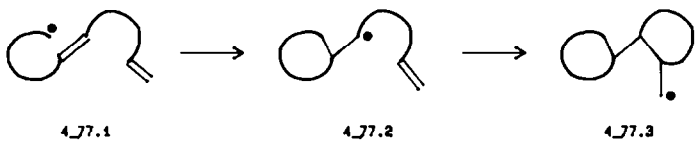
4_75.1 4_75.2 4_75.3 4_75.4

SCHEME 4_75



4_76.1 4_76.2 4_76.3 4_76.4 X=H, Br, Me

SCHEME 4_76



4_77.1 4_77.2 4_77.3

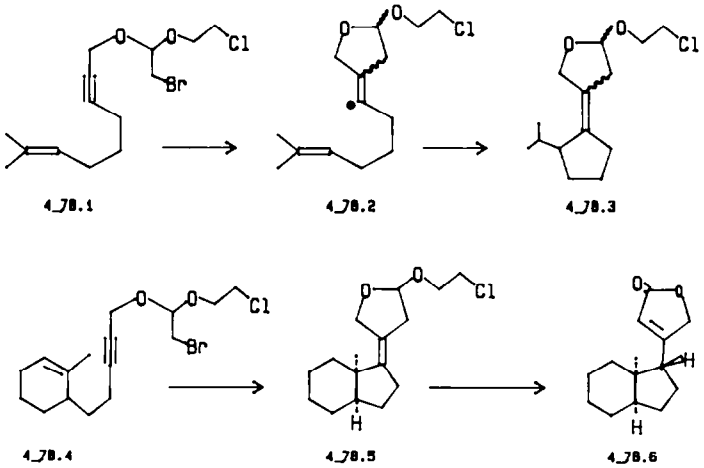
SCHEME 4_77

Aryl radicals derived from aryl diazonium salts react with two moles of acetylenic compounds such as dimethyl acetylenedicarboxylate to give 1,2,3,4-tetramethoxycarbonylnaphthalenes (Scheme 4–76).[271]

4.3. *Tandem cyclizations*

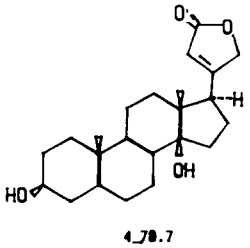
Tandem radical cyclizations, i.e. formation of two or more consecutive ring closures from alkyl radicals are important advancements in radical cyclization. This type of reaction is presented in a general Scheme 4–77. These reactions are accomplished by generating an internal radical within the bonding distance of a multiple bond to generate a new radical **4–77.2** which again should be reachable to the next olefin. This approach is analogous to well-known cation-initiated polyene condensation reactions in a highly stereospecific fashion.

An alternate method (Scheme 4–72) for the formation of a vinyl radical is the intramolecular addition of an alkyl radical to alkyne. Also, it has been shown that vinyl radicals are capable of adding to a multiple bond. These two steps have been combined to give double ring compounds by choosing appropriate substrates as shown in Scheme 4–78.[268] The apparent relationship of **4–78.6** with cardiac aglycone **4–78.7** should be noted.[268] Other examples, shown in Scheme 4–79, illustrate the power of the tandem radical cyclization process in the regio- and stereocontrolled



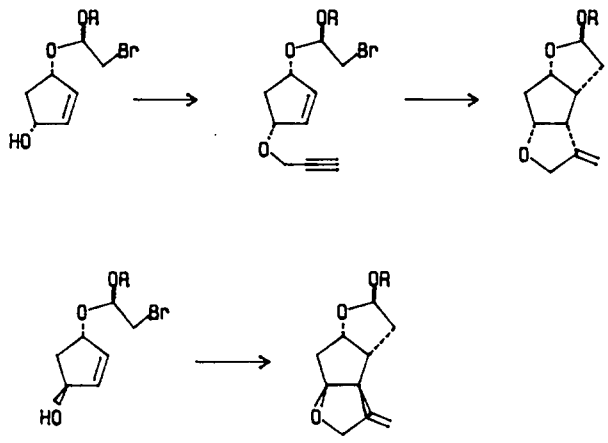
4_78.1 4_78.2 4_78.3

4_78.4 4_78.5 4_78.6



4_78.7

SCHEME 4_78

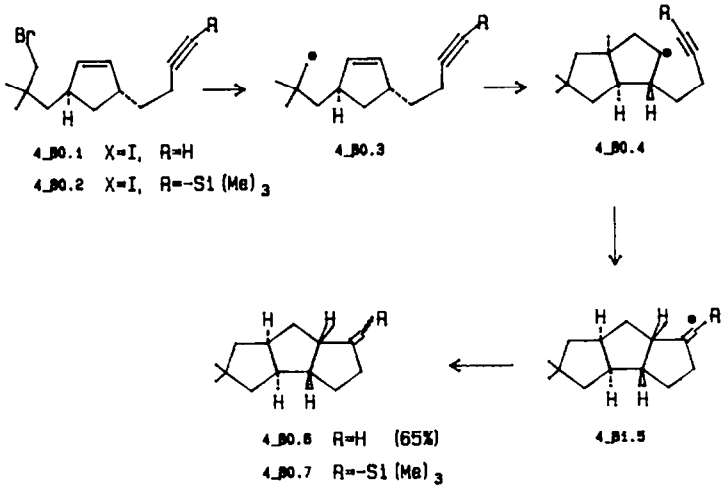


SCHEME 4_79

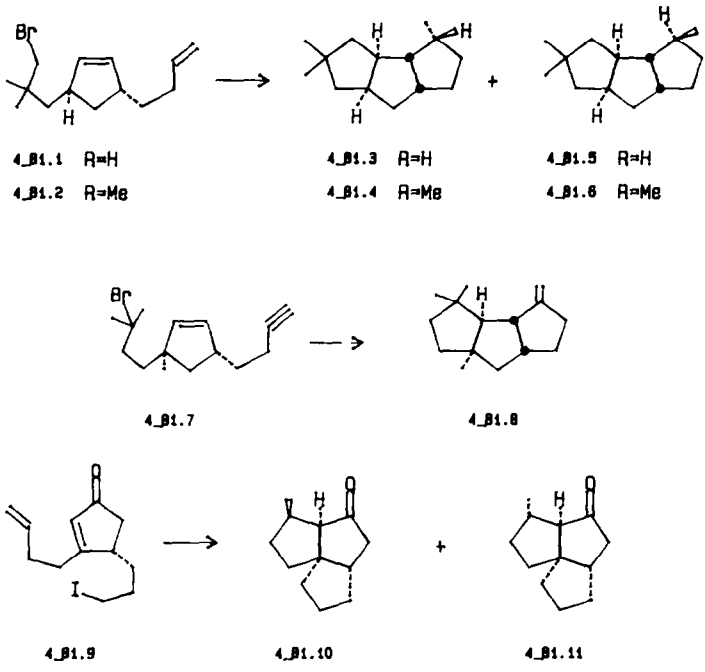
formation of functionalized cyclopentane systems, useful in the total synthesis of natural products such as prostaglandins.[262]

The radical initiated tandem cyclizations provide a method[169,323] for the construction of linearly condensed cyclopentanoids as shown in the Scheme 4–80. Hirustene **4–80.6** has been produced in a single step from a relatively simple *trans*-3,5-disubstituted cyclopentene **4–80.1** by reduction with TBTH and a catalytic amount of AIBN in benzene for 1 h. Under similar conditions, **4–81.1** and **4–81.2** produce an 8 : 1 ratio of two diastereomers **4–81.3**, **4–81.5** and **4–81.4**, **4–81.6**, respectively, in about 90% yields. Cyclization of **4–80.2** produces two geometrical isomers **4–80.7** (3 : 1 ratio) in 72% isolated yield. Desilation of **4–80.7** does not proceed with either hydriodic acid or refluxing acetic acid. However, Büchi's method[272] (*p*-toluenesulfinic acid, acetonitrile at room temperature) produces hirustene **4–80.6** without the major impurities which have been detected in the direct cyclization of **4–80.1**. Similar tandem cyclization of **4–81.7** produced delta[9,12] capnellene **4–81.8** in 60% yield.[273] Also this method has been extended to angular polycyclopentanoids (triquinacene type) **4–81.10**, **4–81.11**. It has been noted that the C=O group in **4–81.9** is critical for the success of this latter cyclization.[273]

Tandem cyclizations consisting of three consecutive ring closures from an alkatrienyl radical is a very interesting concept for the synthesis of polyquinane type molecules.[274] Synthesis of such systems normally requires several synthetic operations under ionic reaction conditions. However, synthetic strategies involving radical conditions require fewer steps and produce desired products



SCHEME 4_80



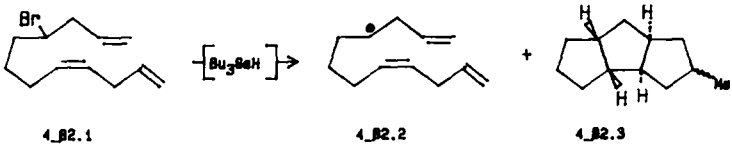
SCHEME 4_β1

in a highly stereo and regiochemical fashion. For example, heating the bromide **4–82.1** in benzene at 80°C with tributylgermane (0.02 M) and a trace of AIBN for 20 h gives a separable mixture of products, from which compound **4–82.3** is isolated as a isomeric mixture in 27% yield. In this reaction, ring junction stereochemistry depends critically on the configuration of the internal double bond. The tributylgermane has been chosen because of its relatively low rate of hydrogen atom transfer to alkyl radicals compared with TBTH. When TBTH is used, the reaction affords a number of unsaturated compounds and smaller yields of tricyclic products.

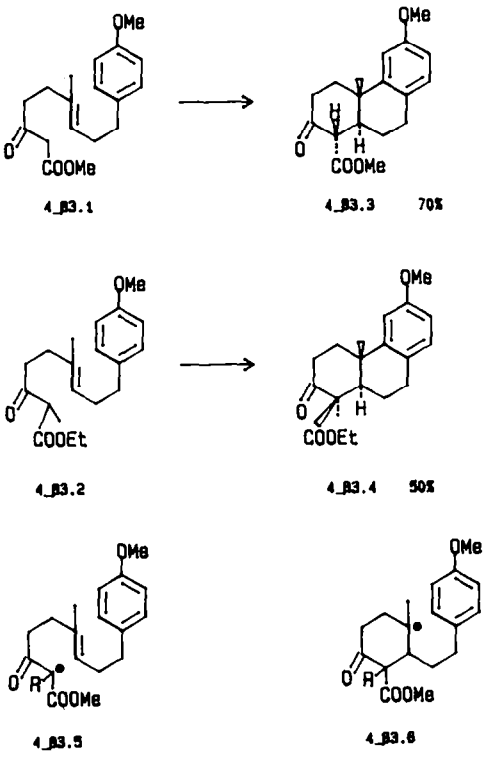
The inter- and intramolecular cyclizations of olefinic β-keto esters have been described using Mn(III) as the radical initiator. With suitable substrates more than one ring is formed in this type of reaction. For example, treatment of β-keto esters **4–83.1** and **4–83.2** with Mn(III) acetate (2 equiv) in acetic acid at room temperature gives **4–83.3** and **4–83.4** in 70 and 50% yield, respectively. The reaction proceeds via enolate radical **4–83.5** (R = H or Me), which adds to the double bond to give tertiary radical **4–83.6** (R = H or Me). This radical then adds to the aromatic ring followed by another electron transfer and finally proton elimination. The addition to the double bond is stereospecific and gives a *trans* ring junction. It should be noted that the carboethoxy group in **4–83.4** occupies the β-face. Other oxidative cyclization reagents, for example, benzoyl peroxide at 80–10°C, give only trace amounts of **4–83.4**.[253]

4.4. *Transannular reactions*

Transannular reactions are very common when suitably substituted medium size rings are exposed to ionic reaction conditions. Such reactions are also observed under homolytic conditions. Reduction of dithiocarbonate **4–84.1** with TBTH (or of phosphate ester **4–84.2** with Li/ethylamine) undergoes facile transannular cyclization to polyquinane structure **4–84.4** in 67–76% yield via radical **4–84.3**[276]



SCHEME 4_β2

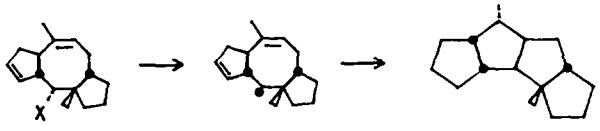


SCHEME 4_β3

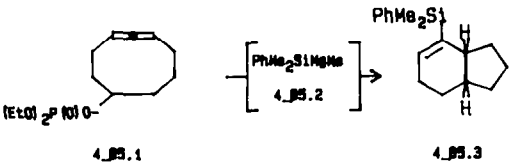
(Scheme 4–84). It should be noted that under these conditions the double bond in the 5-membered ring of **4–84.1** also gets reduced.

Silylmagnesium compounds ($PhMe_2SiMgMe$) **4–85.2**, prepared from $PhMe_2SiLi$ and MeMgI, are useful reagents. With suitably substituted acetylenic- or allenic-halides, -tosylates, and -phosphonates, reagent **4–85.2**, in the presence of transition metals such as Cu (CuI), initiates a radical mediated intramolecular C–C bond formation in good yield.[277] This technique has also been used with allenic substrates. For example, unstable allenic phosphonate **4–85.1** undergoes silylation with **4–85.2** to give *cis* bicyclo[4.3.0]nonane in 50% yield.[277]

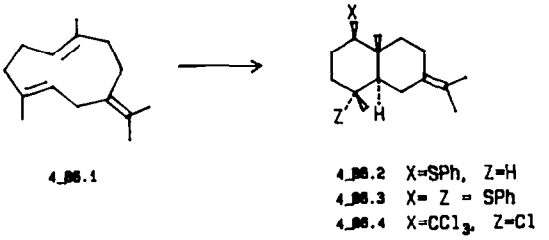
The radical induced transannular cyclizations of cycloalkyl 1,5-dienes show similar stereoselectivity as that of the cation-induced cyclizations.[278] For example, irradiation of germacrane **4–86.1**, with benzenethiol in cyclohexane gives **4–86.2** in 34% yield. Similarly, with diphenyldisulfide or with carbontetrachloride, **4–86.1** gives adducts **4–86.3** and **4–86.4** in 51% and 32% yield, respectively. No other stereoisomers are produced in this reaction. It should be noted that the direction and stereoselection of this radical cyclization are similar to those effected by electrophiles. It has been postulated that both types, i.e. C–C and C–X bonding, are synchronous, generating a transition state resembling a *trans* decalin.



SCHEME 4_β4



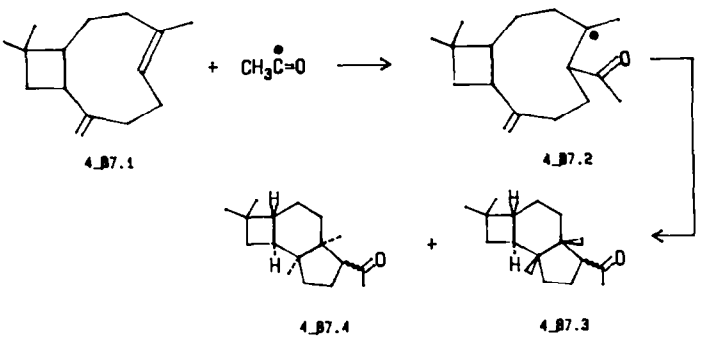
SCHEME 4_85



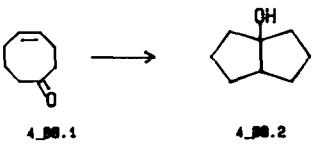
SCHEME 4_86

The radical initiated addition of acetaldehyde to alkenes usually proceeds via Markownikoff directed attack of the acetyl radical at the double bond. The radical addition of acetaldehyde (di-*t*-butyl peroxide at 125°C) to caryophyllene **4–87.1** gives isomeric methyl ketones **4–86.3** and **4–87.4** via radical **4–87.2** in 54% yield.[279]

Cathodic intramolecular cyclization is a useful tool in the synthesis of bicyclic 3° alcohols possessing the OH groups on the ring junction C (*inter alia*). Electroreduction of cycloocta-4-enone, **4–88.1** in methanol/dioxane solvent system containing tetraethyl ammonium-*p*-toluenesulphonate as a supporting electrolyte, produces bicyclo[3.3.0]octanol **4–88.2** in 69% yield.[236]



SCHEME 4_87



SCHEME 4_88

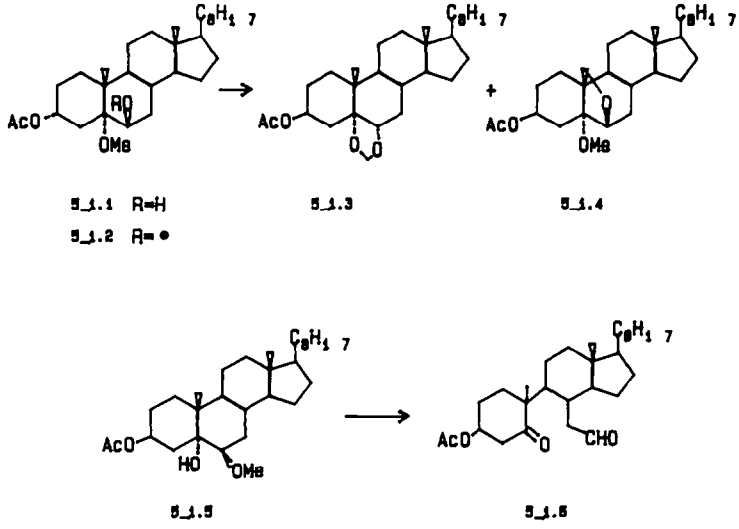
5. SYNTHESIS VIA β-SCISSION

The selective cleavage of a C–C bond in cyclic compounds constitutes an important methodology in synthetic organic chemistry. Approaches to the cleavage of the ring fusion bond in bicyclic compounds under heterolytic fragmentation, requires a bifunctional intermediate with strict stereo-electronic constraints.[280,281] Such stereochemical requirements can be circumvented through the use of an alkoxyl radical, situated at a strategic position. Alkoxyl radicals undergo a variety of reactions such as oxidation, H abstraction, intramolecular additions and β-fragmentation, or a combination of all of these.[282] *A priori* analysis of factors such as relative stability of resultant free radicals, ring strain, and/or stereo-electronic factors does not determine the direction of β-fragmentation in unsymmetrical substrates and the direction is the result of an interplay of several factors. A variety of methods are available for the preparation of alkoxyl radicals[282,283] and their synthetic applications have recently been discussed.[282,286,294]

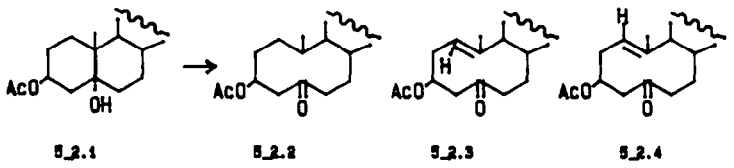
The Barton reaction[285] involving oxy radicals is especially useful for the functionalization of non-activated C atoms through a 6-membered transition state. When such a transition state is forbidden, the intermediate alkoxyl radicals are consumed via intermolecular H abstraction, disproportionation or decomposition by radical elimination. In the absence of inter- and intramolecular abstraction of H atoms (usually δ), oxy radicals are known to undergo β-fragmentation followed by recombination leading to epimerization.[287] 3β-Acetoxy-5$_\alpha$-methoxy cholestane-6$_\beta$-ol, **5–1.1** reacts with excess $Pb(OAc)_4/I_2$ under light to produce **5–1.3** and **5–1.4** in 36 and 27% yield, respectively, via radical **5–1.2**, while **5–1.5** under similar conditions produces the keto aldehyde **5–1.6**. It should be noted that in the latter case (**5–1.6**), cleavage of C5–C6 bond has occurred preferentially.[288]

The decomposition of alkoxyl radical is a useful synthetic method for the preparation of medium-size rings.[289] For example, 3-acetoxy 5α-cholestanol **5–2.1** (partial structures are shown), on irradiation in the presence of mercuric oxide–iodine reagent gives the 10-membered ring ketones **5–2.2** to **5–2.4**. The relative yield depends on the amount of mercuric oxide–iodine used. With a large excess of this reagent, compound **5–2.3** is the major product (64% yield).[290] Interestingly, **5–2.3** is a starting material for synthesis of 1α-hydroxy-vitamin D_3.

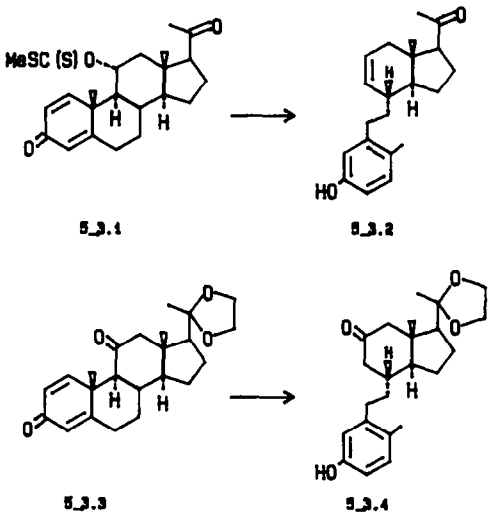
The conversion of an intact steroidal C skeleton into a 9,10-secosteroid is an important strategy for the synthesis of vitamin D structures. A radical or radical anion fragmention of the 9,10-C–C bond in an appropriately derivatized steroid molecule is ideal for such strategy. For example, treatment of 11-α-xanthate **5–3.1** with TBTH and AIBN in refluxing toluene for 40 h gives the 9,10-secosteroid **5–3.2** in 25% yield, whereas treatment with SmI_2 in THF at 20°C for 5 min gives **5–3.2** in 88% yield.[291,292] It should be noted that no cleavage of the 9,10-bond of either 1,2-dihydro or the 6,7-dihydro derivative of **5–3.1** has been observed. Exposure of pregna-1,4-diene-3,11,20 trione-20-ethylene acetal, **5–3.3** in Li–ammonia (with no proton source) gives 9,10-secosteroid **5–3.4** in 70% yield, while **5–3.1** gives a complex mixture containing no desired product.



SCHEME 5–1

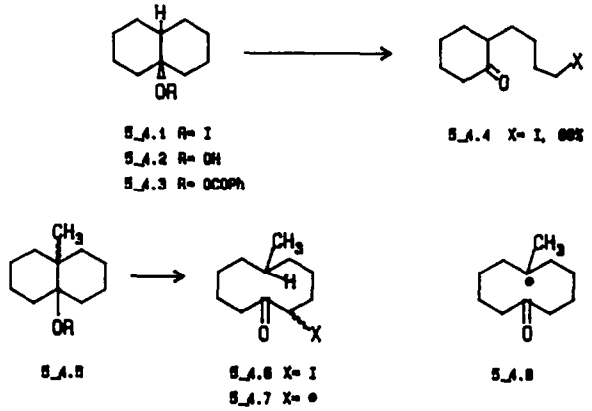


SCHEME 5_2

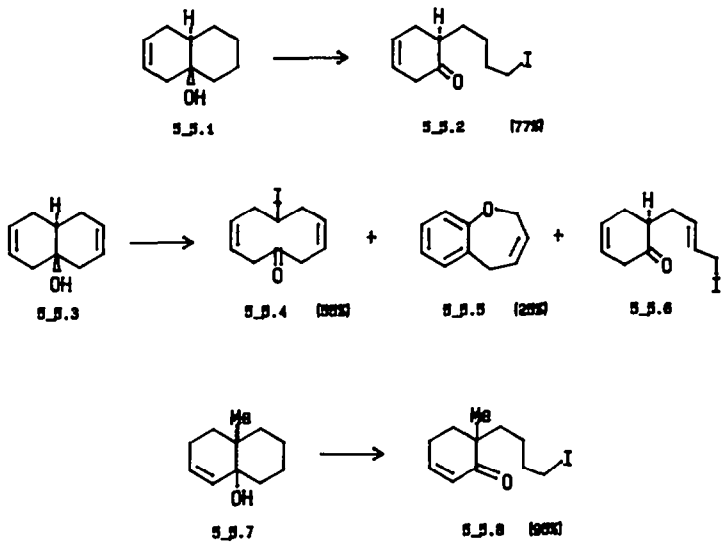


SCHEME 5_3

Thermally induced β-scission of the alkoxyl radical derived either from hypoiodide **5–4.1** or hydroperoxide **5–4.2** produces exclusively **5–4.4** (X = I or X = OH), whereas exclusive cleavage of the ring junction bond occurs[293] with the corresponding perbenzoate **5–4.3**. However, with hypoiodide reagents, the alkyl substitution at the ring junction directs the β-scission in decalinol systems. For example, at 70°C either of two methyl decalinol epimers **5–4.5** gives predominant cleavage of the ring fusion bond via radical **5–4.7** which then undergoes a secondary reaction affording the 2-iodo-6-methylcyclodecanone epimers **5–4.6**. It should be noted that the C radical **5–4.7** abstracts an H atom from the C atom adjacent to the C=O function in a transannular fashion (via a 6-membered transition state) followed by quenching with iodide.



SCHEME 5_4



SCHEME 5_5

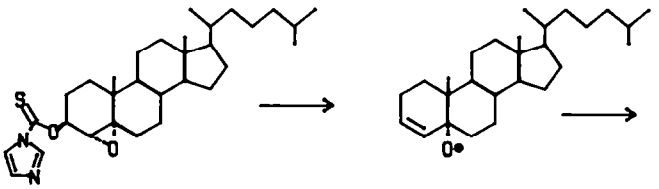
The introduction of unsaturation into the bicyclo[4.4.0]decanol framework has a substantial influence on the course of ring cleavage.[293] For example β-scission of the alkoxyl radical from **5–5.1** gives solely cyclohexenone **5–5.2** in 77% yield while *trans* dienol **5–5.3** gives a mixture (2 : 1 ratio) of cyclodecadienone **5–5.4** and dehydrobenzoxepin **5–5.5** (25% yield). The latter, **5–5.5**, is the result of the initially formed allylic iodide **5–5.6**. Both diastereomers (α- and β-OH) **5–5.7** undergo ring cleavage exclusively away from the double bond, generating **5–5.8** in 95% isolated yield.

Mechanistic studies,[328] for example on the *cis* or *trans* isomer of the 9-decalinoxyl radicals generated from a variety of reagents (hydrobromite/AgOAc; —OBr/AgOAc/HgBr; HgO; $ONO_2/h\nu$), indicate that there is a delicate balance of kinetic and thermodynamic factors in determining the direction of ring opening. The study also reveals, that for example, each isomer of **5–4.2**-*cis* and **5–4.2**-*trans* 9-decalinoxy radicals undergo fast, but reversible 9,10-bond fission (ring junction), and that 1,9-bond fission is slower than 9,10-bond fission, but is essentially irreversible. The reaction temperature is a dominant factor and determines the direction of β-scission.

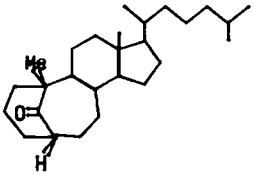
Attempted deoxygenation of epoxy alcohol derivative **5–6.1** using TBTH under normal conditions (*inter alia*), i.e. addition of TBTH to a refluxing solution of **5–6.1** in benzene, gives **5–6.3** via radical **5–6.2** in good yield.[39] It should be noted that among three possible β-bonds in **5–6.2**, C5–C6 bond scission occurs exclusively (see Ref. 293 and Scheme 5–5). Similarly, isomers **5–6.4** and **5–6.5** prepared from hecogenin have given the same product **5–6.6** under normal reaction conditions, while under inverse conditions (i.e. addition of xanthate to excess TBTH) these produce the saturated analog of **5–6.6** but not the anticipated tertiary alcohol. This indicates that the secondary rearrangement of the allylic alkoxyl radical occurs in preference to the abstraction of a hydrogen atom from the sterically more demanding α-face.[39]

A highly useful reaction has been described for the synthesis of 6-chlorohexan-2-one **5–7.3** by decomposing 1-methylcyclopentyl hypochlorite **5–7.2** at 40°C in quantitative yield.[294] The rearrangement of this type from tertiary cycloaliphatic hypohalites provides a useful synthetic approach to ω-halo ketones, which are often difficult to prepare otherwise.

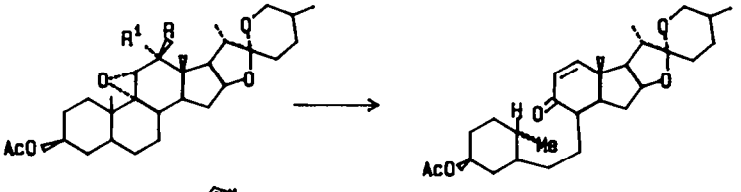
Although a great deal is known about the mechanism of the α-alkoxy hydroperoxide reaction with metal ions, very few synthetic applications are reported.[295,296] Recently these have received some attention in synthesis due to the ready availability of the 1-hydroxycycloalkyl hydroperoxides via silyvinyl ethers.[297] The metal ion (Fe^{2+}) promotes ring opening of cyclic silyloxy hydroperoxides to either α,ω-dicarboxylic acids **5–8.4** having double the number of original C atoms (Scheme 5–8, A) or to monocarboxylic acids **5–8.5** possessing terminal methylene groups (Scheme 5–8, B). Experimental conditions appear to be simple: $FeSO_4$ (1.2 equiv) in methanol at 0°C is added to the



5_5.1 5_5.2



5_5.3

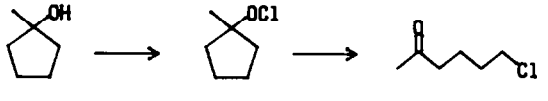


5_5.4 R= -OCS-N , R^1= H

5_5.5 R= H, R^1= -OCS-N

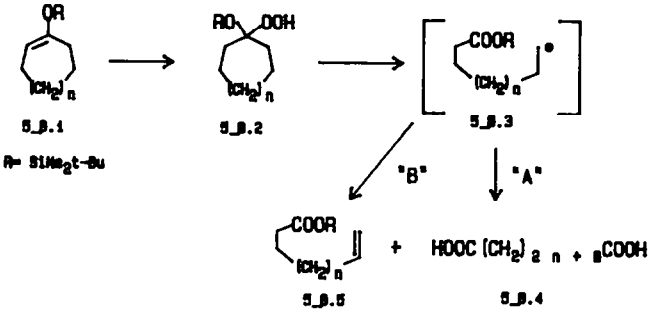
5_5.6

SCHEME 5_6



5_7.1 5_7.2 5_7.3

SCHEME 5_7



5_8.1 5_8.2 5_8.3

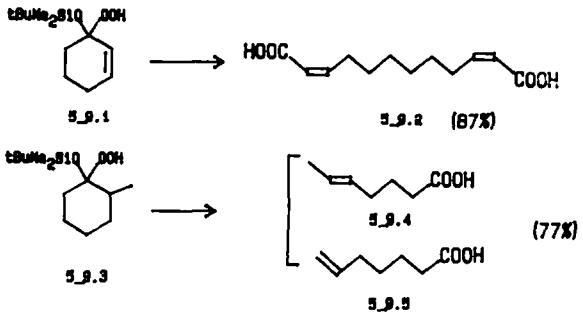
R= $SiMe_2t$-Bu

"B" "A"

5_8.5 5_8.4

n	5_8.5 (%)	5_8.4 (%)
0	54	-
1	53	53
2	68	44
3	72	73

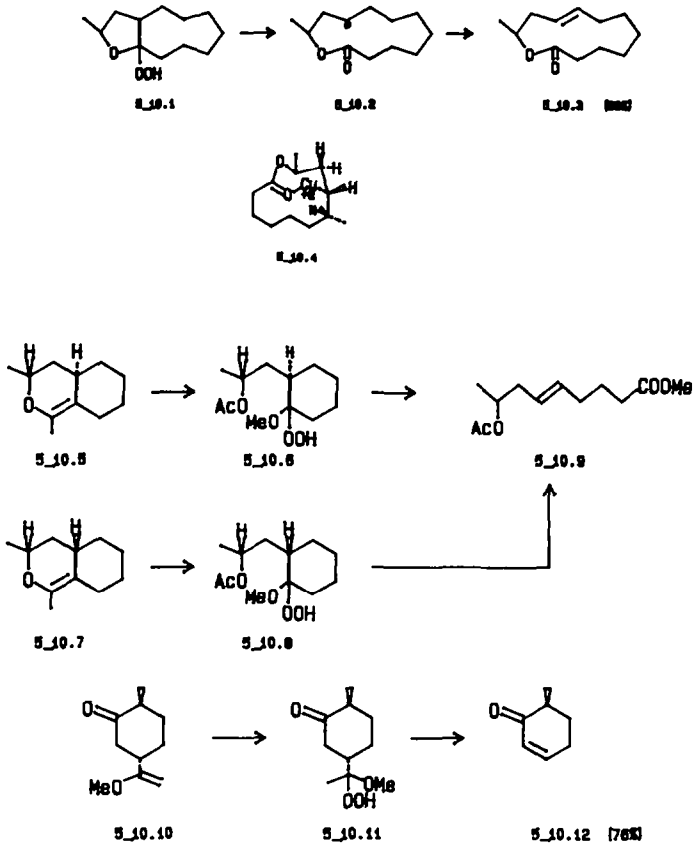
SCHEME 5_8



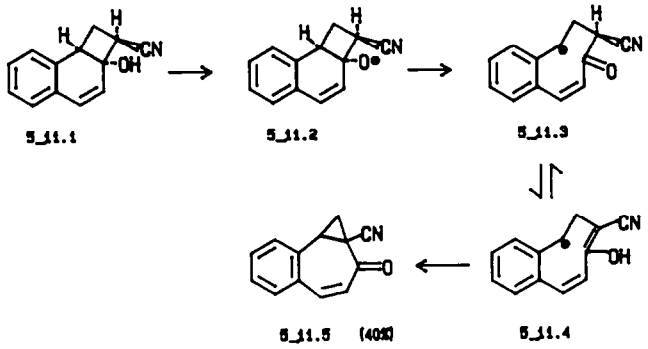
SCHEME 5_9

hydroperoxide and followed by acid hydrolysis gives dicarboxylic acids **5–8.4**. A mixture of silyloxy peroxide **5–8.2** and $Cu(OAc)_2$ (3.1 equiv) in methanol is treated with $FeSO_4 \cdot 7H_2O$ (1.2 equiv) to give olefinic acid **5–8.5**. In the latter process (route B), the intermediate C radical **5–8.3** produced by metal ion induced decomposition of the hydroperoxide is oxidatively intercepted by the cupric salt, resulting in the formation of the elimination product. It should be noted that with ferrous sulphate, the α-silyloxy hydroperoxide **5–9.1** produces **5–9.2** regiospecifically in 87% yield, whereas $Cu(OAc)_2$–$FeSO_4$ prompts the hydroperoxide **5–9.3** to give a 1 : 1 mixture of **5–9.4** and **5–9.5** in 77% yield.[297]

Bicyclic α-alkoxyhydroperoxides have also been utilized for the synthesis of olefinic lactones.[298] For example, addition of ferrous sulphate to a solution of **5–10.1** in methanol saturated with copper acetate results in fragmentation to give macrolide (±)-recifeiolide **5–10.3** in 96% yield. It should



SCHEME 5_10



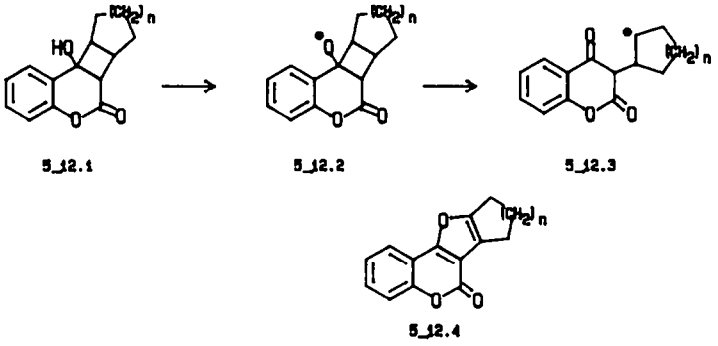
SCHEME 5_11

be noted that the intermediate radical **5–10.2** is oxidatively intercepted by cupric salt. The presumed Cu complex **5–10.4**, which can eliminate only one of the two available *syn*-hydrogens, dictates the stereo- and regiochemistry of the olefin. Formation of the secondary (ring junction bond cleavage) over the primary radical has been interpreted as being due to the weakening of the central C–C bond by antiperiplanar overlap with the lone electron pair of the tetrahydrofuryl oxygen. Under similar reaction conditions diastereomers **5–10.6**, and **5–10.8** have been converted into the *trans* homoallylic alcohol **5–10.9** in 70% yield.

A facile synthesis of (+)-6-methylcyclohex-2-ene **5–10.12** has been developed by treating the hydroperoxide **5–10.11** with copper acetate/ferrous sulphate. In this case, the ketone functionality directs the elimination of the presumed Cu intermediate.

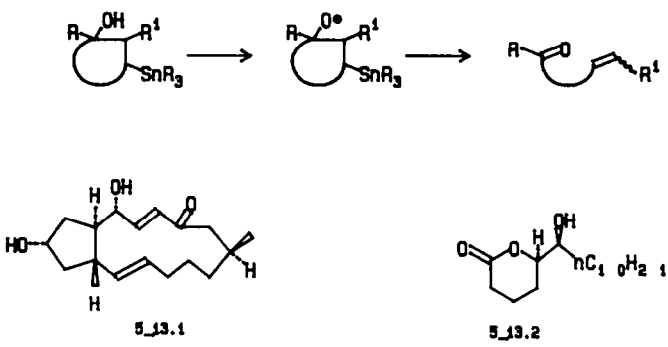
A two-step procedure involving photochemical addition of acrylonitrile to β-naphthol followed by irradiation in the presence of $HgO–I_2$ in benzene,[299] has been developed for the preparation of homotropane **5–11.5**, as shown in Scheme 5–11. It should be noted that the C radical in **5–11.4** adds to the α-C of the nitrile in a transannular fashion. However, O atom insertion into C radicals **5–12.3** → **5–12.4** occurs under similar conditions[300] (Scheme 5–12). Such methodology should complement the existing methods for the formation of heterocycles from cyclobutanones.

Lead tetraacetate is a well-known reagent for the generation of alkoxyl radicals and has been extensively used for the functionalization of non-activated C atoms.[301] Oxidative fragmentation of γ-hydroxyalkyl stannanes with lead tetraacetate in refluxing benzene affords keto olefines in a regio- and stereospecific manner (Scheme 5–13).[302] The starting materials, i.e. γ-hydroxyalkyl stannanes, are prepared by alkylation of the corresponding γ-keto stannanes followed by reduction. It should



n	Yield (%)
1	39
2	10
3	29

SCHEME 5_12

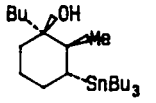
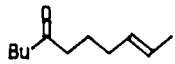
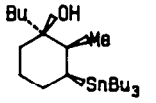
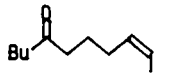
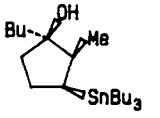
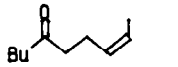
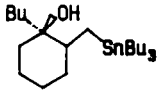
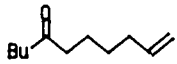
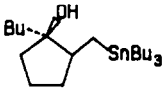
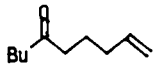
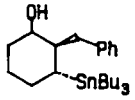
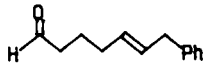
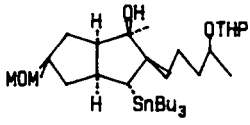
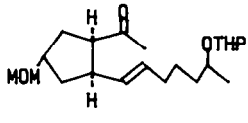


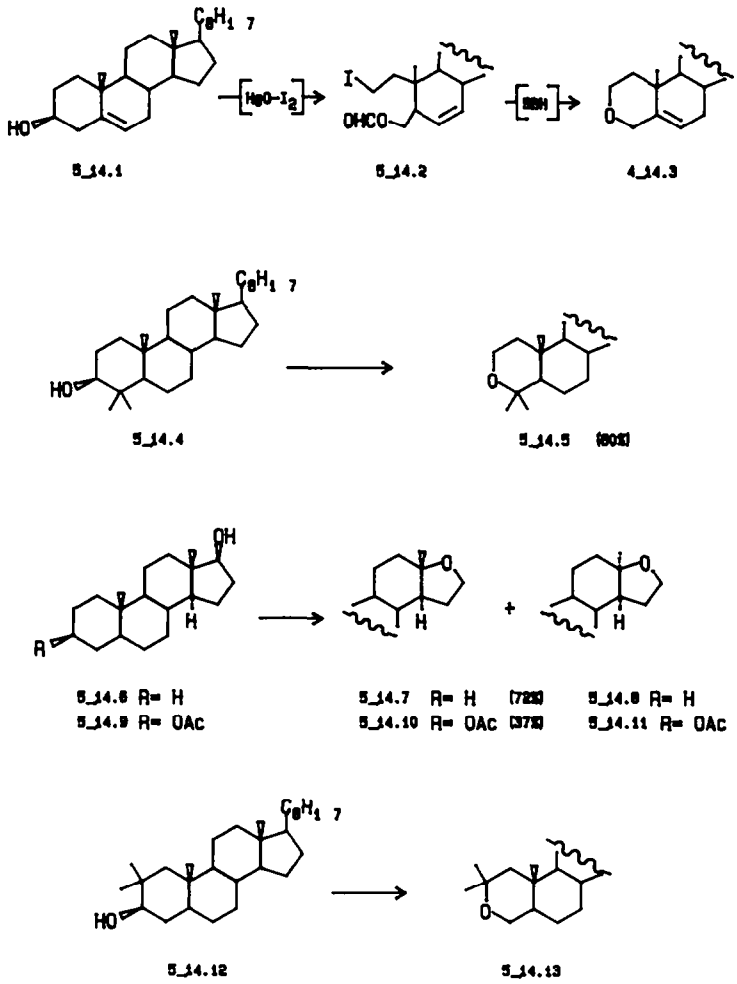
SCHEME 5_13

be noted from Table 33, that *trans*- and *cis*-isomers (entries 1, 2) undergo stereospecific fragmentation to *trans* and *cis* olefins, respectively. Terminal olefins (entries 4, 5) and olefinic aldehydes (entry 6) are also obtained in good yields. This methodology has been applied to a key step in the total synthesis of (±)-Berfeldin A **5–13.1** and to a mosquito pheromone **5–13.2**.[303] It should be noted that under similar reaction conditions, γ-hydroxy silanes do not react.

Preparation of oxa-, aza- and thia-steroids are not convenient by known methods since they usually require a multitude of steps. However, using radical reactions oxa steroids have been prepared by a two-step transformation from hydroxy steroids, as shown in Scheme 5–14. It should be noted that the ring size of the oxa steroid is the same as that of the starting steroid which carries the

Table 33. Fragmentation of β-hydroxyalkyl stannanes with lead tetraacetate

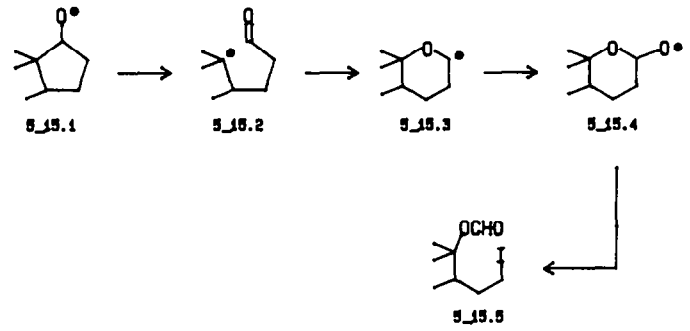
NO	Alkyl Stannane	Product	Yield (%)
1			95
2			91
3			84
4			91
5			81
6			77
7			76



SCHEME 5_14

hydroxyl group. The irradiation of cholestenol, **5–14.1** in benzene (3 h, room temp) with excess $HgO–I_2$ reagent gives formate ester **5–14.2**, which on reduction with SBH in THF (reflux 3–5 h), gives **5–14.3** in nearly quantitative yield.[304] Similarly, cholestanol derivative **5–14.4**, in which the OH group is situated in the A ring gives synthetically useful yields of oxa-steroid **5–14.5**. However, 1- and 6α- or β-hydroxycholestanol derivatives give a mixture of products, making this method preparatively not useful.[288,305,306] Application of this method to the conversion of 5α-androstan-17β-ol **5–14.6** and its 3β-acetate **5–14.9** gives a mixture of products, in which the predominant isomer is 17β-oxo derivatives **5–14.7** and **5–14.10**, respectively. It should be noted that in these cases the chirality of the C adjacent to alkoxy radical is disturbed. This method is successful only when the alkoxyl radical is susceptible to β-scission. The procedure is carried out under essentially neutral conditions. The noteworthy aspects of this reaction are the intramolecular combination of carbonyl oxygen (**5–15.2** → **5–15.3**) with a C-centered radical and a regiospecific β-scission of **5–15.4** to **5–15.5** as shown in Scheme 5–15.

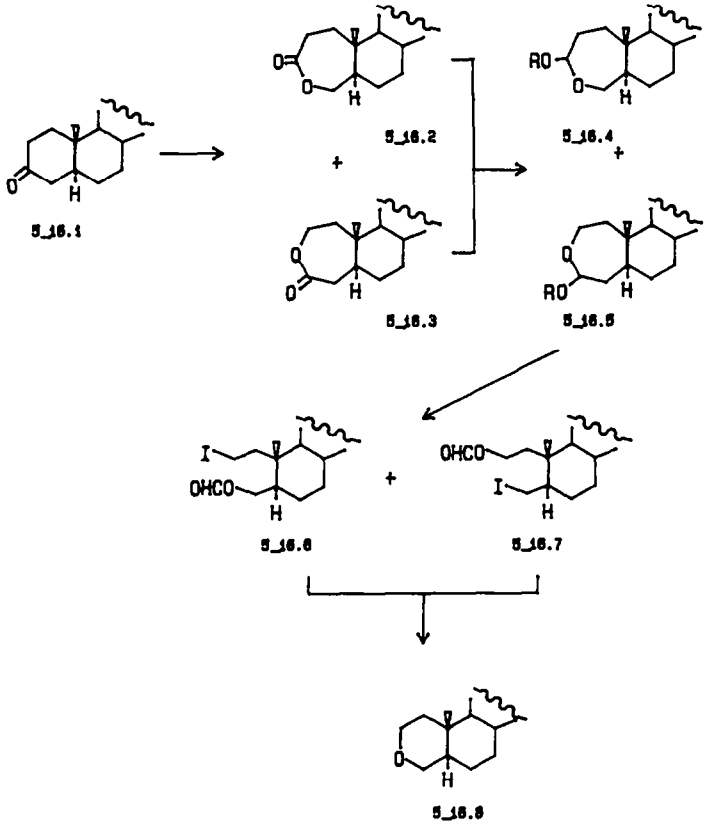
A four-step method for the synthesis of cyclic ethers (oxa-steroids) is shown in Scheme 5–16 using 3-oxocholestane as an example.[307] This method, which starts from cyclic ketones instead of a cyclic alcohol, complements the above two-step method.[305] Following the reaction as shown in the Scheme 5–16, several ketones have been converted into cyclic ethers in good yields (Table 34). Although Baeyer–Villigar oxidation of ketones gives a mixture of isomeric lactones, single oxa steroids are obtained directly from the mixture. The interesting point of this transformation is that, unlike the method described[305] in Scheme 5–14, the chirality of C atom adjacent to the carbonyl group of the starting ketone is maintained (entries 2–5, Table 34).



SCHEME 5_15

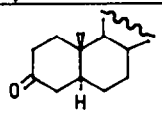
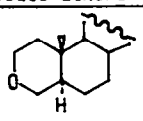
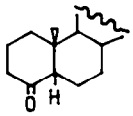
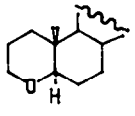
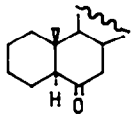
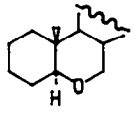
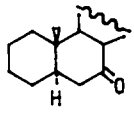
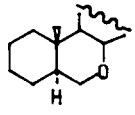
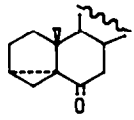
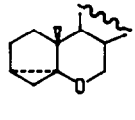
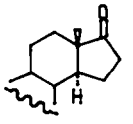
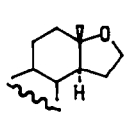
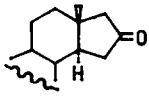
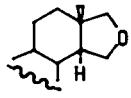
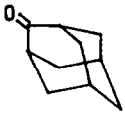
Following the above schemes, a general method[308] for the synthesis of thia- and aza-steroids from steroidal ketones is shown in Scheme 5–17. The reactions of the iodoformates **5–16.6** or **5–16.7** with trimethylsilyl iodide, followed by reaction either with sodium sulfide or with benzylamine or propylamine, give cyclic sulfides **5–17.1** and *N*-benzyl-**5–17.3** or *N*-propyl-3-aza-5α-chloestane **5–17.4**, respectively. Similarly, diiodide **5–17.6** derived from 5α-androstane 16-one **5–17.5** gives 16-thia-5α-androstane **5–17.7** and *N*-benzyl-16-aza-5α-androstane **5–17.8** in 85 and 69% yield, respectively. However, the attempted transformation of 5α-cholestan-6-one **5–17.9** into 6-thia-5α-cholestane **5–17.12** via diodide **5–17.10** is not successful but mesylate **5–17.11** gives **5–17.12** in 40% yield. These transformations are stereospecific.

Along the lines described in the Scheme 5–14 to 5–17, several medium-sized lactones have been synthesized.[309] The key step involves a regioselective β-scission of alkoxy radicals generated from bridge-head lactols. *In situ* generated hypoiodides **5–18.2**, prepared from lactols **5–18.1**, which are



SCHEME 5_16

Table 34. Preparation of cyclic ethers from cyclic ketones

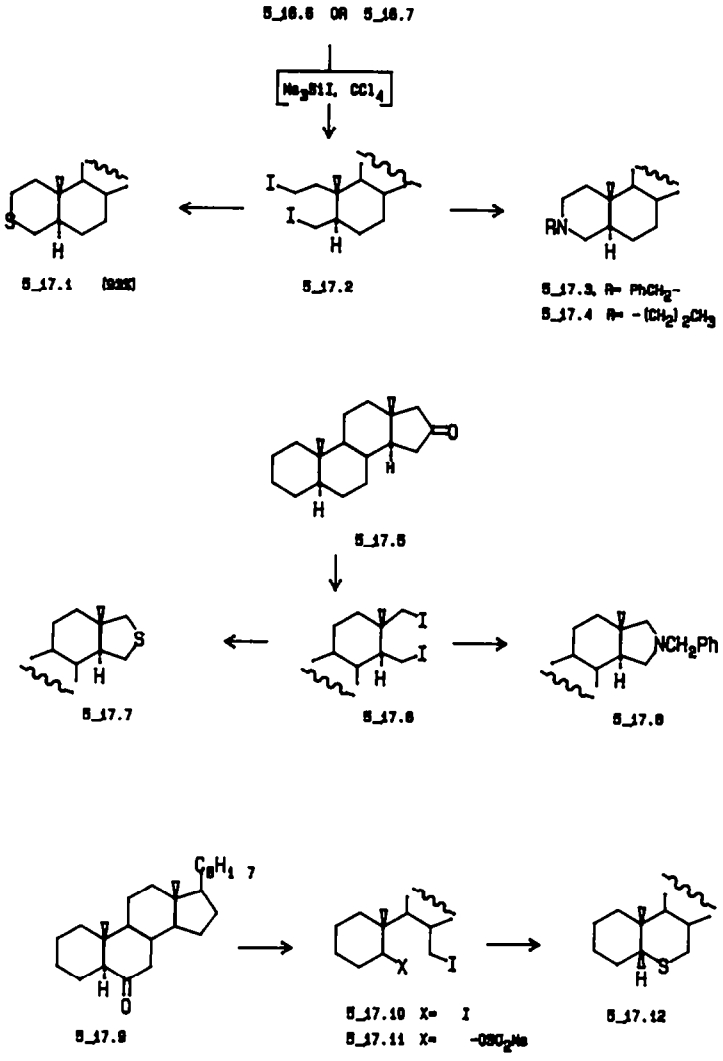
NO	Cyclic Ketones[b,c]	Cyclic Ethers	Yield (%)[a]
1			30
2			23
3			37
4			58
5			9
6			39
7			35
8			23
9			37

[a] Overall yield (4 steps).
[b] Entries 1–5, partial structures of cholestane derivatives.
[c] Entries 6 and 7, partial structures of androstane derivatives.

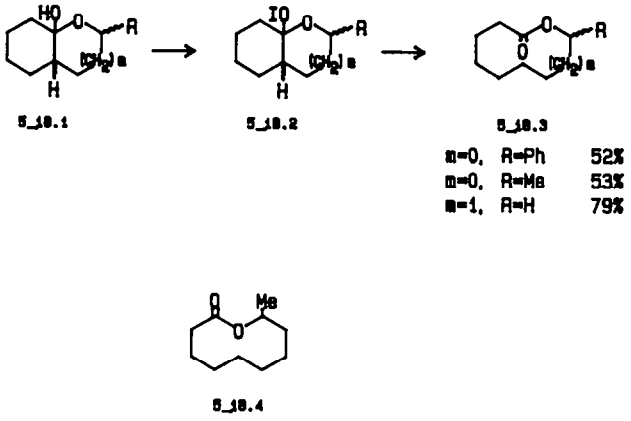
in turn prepared from cyclic ketones via alkylation with ω-hydroxy halides, are irradiated in benzene containing a small amount of pyridine to give iodo lactones **5–18.3** in good yields. The usefulness of this methodology has been shown by the synthesis of the naturally occurring lactone, phoracantholide **5–18.4**.

6. MISCELLANEOUS REACTIONS

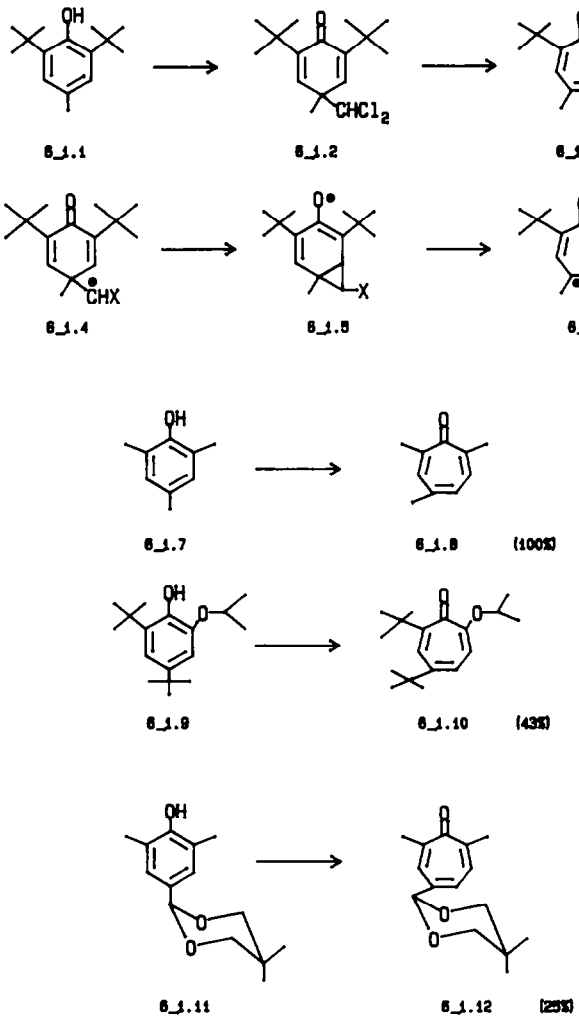
A simple method[310] for the conversion of substituted phenols into tropones and tropolones is shown in the Scheme 6–1. 2,4,6-Trisubstituted phenol **6–1.1** reacts with dichloro- or dibromo-



SCHEME 5_17



SCHEME 5_18

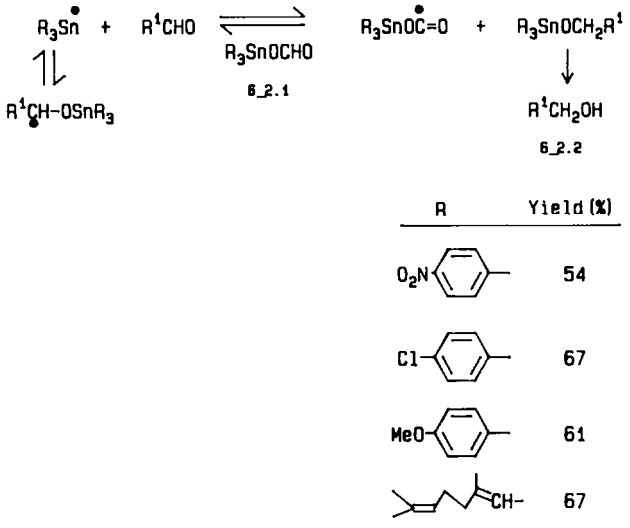


SCHEME 6_1

carbene to give the corresponding cyclohexadienones. Among the methods studied for the carbene addition, a PTC (cetyltrimethylammonium bromide, haloform, sodium hydroxide 50%) catalysed method has been found to be the best. The reduction of cyclohexadienone **6–1.2** with TBTH (2.5 equiv) in benzene under reflux for 4 h in the presence of AIBN, gives a good yield of tropone **6–1.3** via a series of rearrangements and ring expansion (**6–1.4** → **6–1.5** → **6–1.6**). Although the carbene addition generally gives a mixture of *ortho*- and *para*-isomers, the mixture of these isomers can be used directly (without separation) to give a single product. Hindered phenols give low yields of tropones.

Selective reduction of aldehydes to alcohols is possible by a variety of reagents. Triphenyltin formate **6–2.1** for example, may be considered as a useful chemoselective reagent for the reduction of certain aldehydes. Triphenyltin formate in diglyme at 160°C (24–36 h) reduces aldehydes to alcohols **6–2.2** in good yields (Scheme 6–2).[311] Ketones are reduced either slowly or not at all. Mesitylene, decane and other non-hydroxylic solvents of low polarity can be used.

Substrates capable of providing radical stabilization due to the captodative substituents are expected to be oxidized by Fremy's salt **6–3.1**. Oxidation of aromatic aldehydes with Fremy's salt, **6–3.1** in 1 : 1 pyridine/conc. ammonium hydroxide solution, has led to a one-pot synthesis[331] of substituted aryl *S*-triazines **6–3.2** and primary amides **6–3.3**. *S*-triazines **6–3.2** are easily separable from amides **6–3.3** due to their ready solubility in methylenechloride. Oxidation of isolated imines (possible intermediates) from aldehydes give similar results under the above reaction conditions.

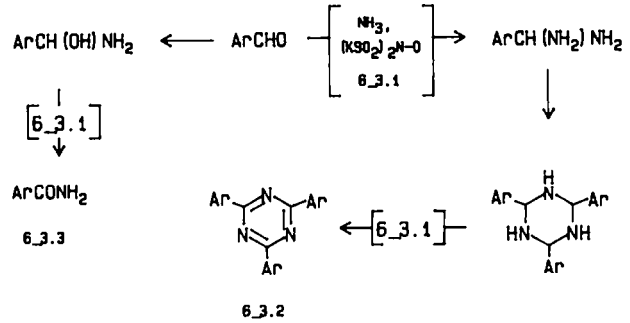


SCHEME 6_2

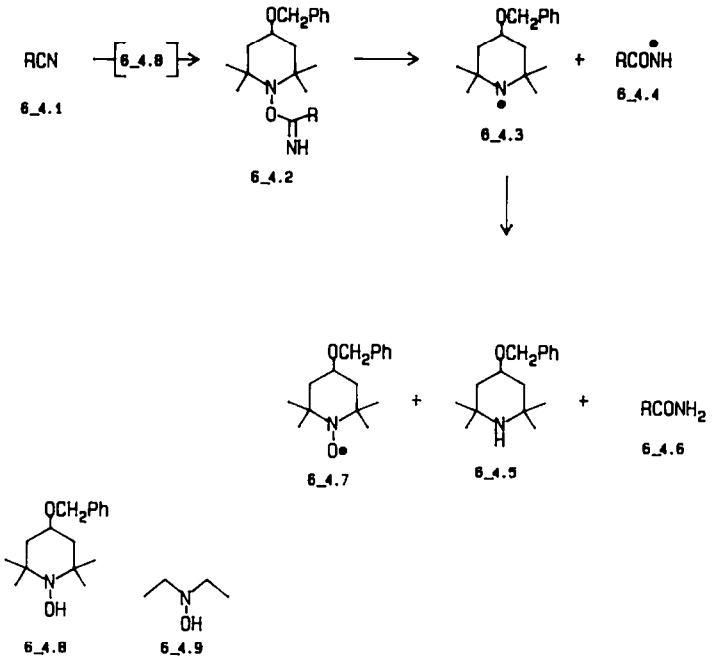
This reaction, however, cannot be extended to aliphatic aldehydes. Due to long reaction times and the required excess of Fremy's salt, this reaction has limited use.

Preparation of amides from nitriles is a common reaction in organic synthesis, and many methods are available for such transformations. Nitriles are hydrated to amides in high yields by the action of excess dialkyl hydroxylamine such as, **6–4.8** (3 equiv) in dichloromethane at 50°C in the absence of oxygen (Scheme 6–4).[312] Aromatic nitriles are more reactive than aliphatic nitriles and give better yields. From 1,4-dicyanobenzene, monoamide is formed exclusively. The α-chloroacrylonitrile affords the corresponding amide 69% yield, whereas the acrylonitrile gives only 22% yield of amide. Due to the stability the nitroxyl radical **6–4.7** towards adducts and products, no by-products are formed. Since the amides are almost insoluble in dichloromethane they are easily separated from the reaction mixture. With diethylhydroxylamine **6–4.9** the yields are lower and in addition, dichloromethane is not a suitable solvent with this reagent.

In general, the addition of radicals to electron withdrawing olefins proceeds more efficiently than does their addition to simple olefins (*inter alia*). Also, the temperature of the reaction has marked effect on such selectivity. A high degree of selectivity at low temperature is normally expected. For thermally unstable or volatile reactants or intermediates, the use of low temperature radical initiators has the advantage over the usual thermal initiators. *t*-Butyl *p*-benzoylperbenzoate **6–5.1**, a photoinitiator, has been shown to be a convenient, variable thermal (−24 to 78°C) radical initiator.[313] The nature of the radical centers produced by photochemical dissociation (360 nm) of **6–5.1** are essentially identical with those produced from either benzoyl peroxide or *t*-butyl perbenzoate. As shown in the Scheme 6–5, the acetyl radical is added selectively to the acrylate moiety in



SCHEME 6_3



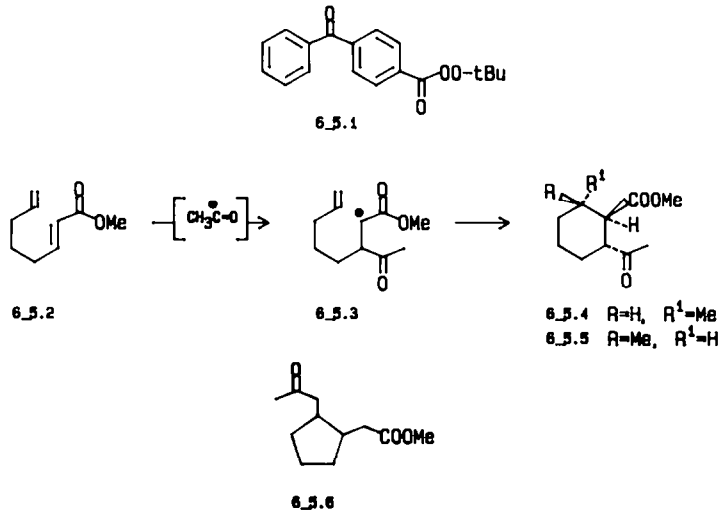
SCHEME 6_4

6–5.2 to give **6–5.4** and **6–5.5**. No products corresponding to **6–5.6** are observed, and the ratio of **6–5.4** and **6–5.5** increases as the temperature is lowered.

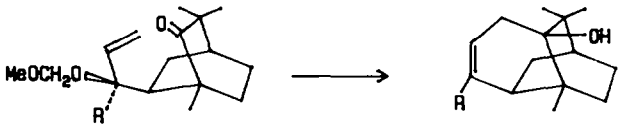
Ketyl radical anions attack stereospecifically on proximal olefinic and acetylenic bonds[322] and also on allylic systems bearing a good leaving group. The stereochemical course of the allylic system has been demonstrated for the intramolecular C–C bond formation through the synthesis of (−)-norpatchoulenol, the enantiomeric form of the natural isomer and also for the synthesis of (+)-patchoulenol and (±)-pachoulol[314] (Scheme 6–6).

In addition to the construction of complex molecules, it is possible to utilize free radical reactions to establish the configuration of stereocenters. For example, reduction of xanthate **6–7.1** with TBTH gives 74% yield of 2 : 1 mixture of **6–7.2** indicating the allyl group in **6–7.1** is in the axial position.[315]

The oxymercuration–demercuration reaction, for example, of linalool **6–8.1** results in the C–C

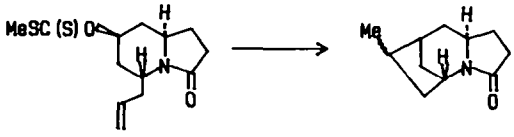


SCHEME 6_5



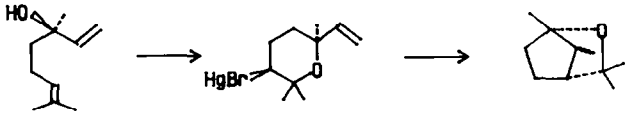
6_8.1 R=H
6_8.2 R=Me
6_8.3 R=H
6_8.4 R=Me

SCHEME 6_6

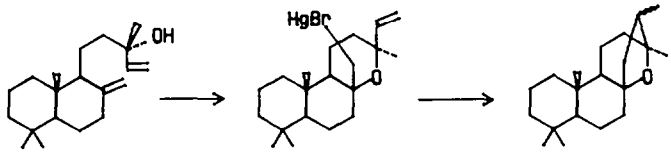


6_7.1 6_7.2

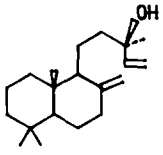
SCHEME 6_7



6_8.1 6_8.2 6_8.3



6_8.4 6_8.5 6_8.6



6_8.7

SCHEME 6_8

bond formation at the terminal double bond via the radical derived from organomercurial intermediate **6–8.2** in which mercury is *cis* to the vinyl group.[316] Such additions of radical forming centers to a proximal vinyl group in cyclic ethers, for example, **6–8.5**, have been utilized for the synthesis of 13-epimanool **6–8.6** in 72% yield, but not with manool **6–8.7**.

7. CONCLUSIONS

Free radical reactions, to be truly useful in organic synthesis, must be chemo-, regio-, diastereo-, and/or enantio selective. Radicals react at very different rates with various functional groups. By a

judicious choice of reagents, solvents, etc., it is possible to devise a synthetic procedure that is capable of effecting a highly selective transformation. Also, when a chain propagating reaction is conceived, it is possible, under controlled conditions, to avoid radical–radical interaction and obtain clean, high yielding reactions. In this review an attempt has been made to show that the radical reactions are as efficient, or even better in some cases, as their counterparts, i.e. ionic reactions. Because of space and time limitations some other aspects of radical reactions, such as remote functionalizations, heteroatom radical reactions etc., have not been included. The scope of radical reactions speaks for itself from the examples cited here and several publications after the cut-off point for the preparation of this manuscript. It is clear that the trend in organic synthesis is towards the utilization of free radical reactions.[317]

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