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A new stannane, and new radical-based methods for preparation of heterocycles

by

Wen Yang ©

A thesis submitted to the faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

DEPARTMENT OF CHEMISTRY

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FACULTY OF GRADUATE STUDIES AND RESEARCH

The undersigned certify that they have read, and recommend to the Faculty of Graduate Studies and Research for acceptance, a thesis entitled A NEW STANNANE, AND NEW RADICAL-BASED METHODS FOR PREPARATION OF HETEROCYCLES submitted by **Wen Yang** in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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ABSTRACT

This thesis describes two completed studies and two preliminary studies in the area of synthetic radical chemistry:

(1) The development of a polar stannane to facilitate purification of products from radical reactions (Clive, D. L. J.; Yang, W. *J. Org. Chem.* **1995**, *60*, 2607).

(2) The synthesis of a variety of bicyclic heterocyclic compounds, using a tandem process of *diagonal* radical cyclization, intramolecular hydrogen transfer, 5-*endo* ring closure, and intermolecular hydrogen transfer (Clive, D. L. J.; Yang, W. *J. Chem. Soc., Chem. Commun.* **1996**, 1605).

(3) A preliminary study on the cyclization of carbamoyl radicals to form β, γ, and δ lactams. The application of this methodology in the synthesis of A58365A, a blood pressure-lowering agent has been carried to an advanced stage.

(4) A preliminary study on the use of tethered primary alkyl radicals for abstracting hydrogen from the α position of saturated nitrogen-heterocycles.

ACKNOWLEDGMENTS

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

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LIST OF ABBREVIATIONS

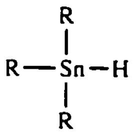
p-AOM	*para*-anisoylmethyl
Bn	benzyl
Boc	*t*-butoxylcarbonyl
CAN	Cerium Ammonium Nitrate
m-CPBA	*m*-chloroperoxybenzoic acid
DIBAL-H	diisobutylaluminum hydride
DMAP	4-(dimethylamino)pyridine
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
de	diastereomeric excess
ee	enantiomeric excess
HMPA	hexamethylphosphoric triamide
$LiAH_4$	lithium aluminum hydride
LDA	lithium diisopropylamide
NMO	4-methylmorpholine N-oxide
PCC	pyridinium chlorochromate
Ph	phenyl
PPTS	pyridinium *p*-toluenesulfonate
TBAF	tetrabutylammonium fluoride
TBDMS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
TES	triethylsilyl
TMS	trimethylsilyl
TPAP	tetrapropylammonium perruthenate
$TsOH{\bullet}H_2O$	*p*-toluenesulfonic acid monohydrate

Chapter One

THE PREPARATION of A NITROGEN-CONTAINING STANNANE for RADICAL CHEMISTRY

I INTRODUCTION

Tributyl- and triphenyltin hydrides[1,2] (figure 1) have been extensively used[3] in synthetic radical chemistry. The major applications are found in reactions such as deoxygenation,[4] dehalogenation,[5] and radical cyclization[6] (Schemes 1-3).



$R_3Sn\text{-}H$

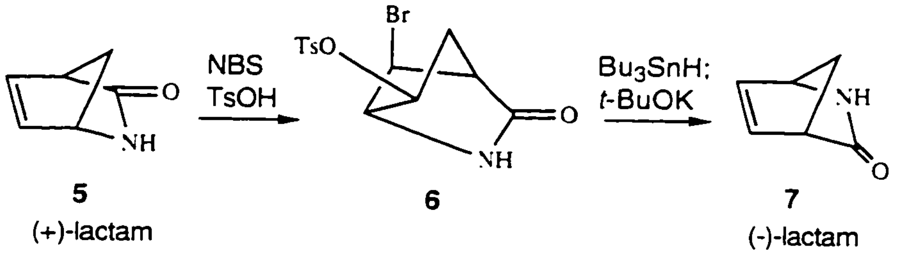
1 R = Ph

2 R = *n*-Bu

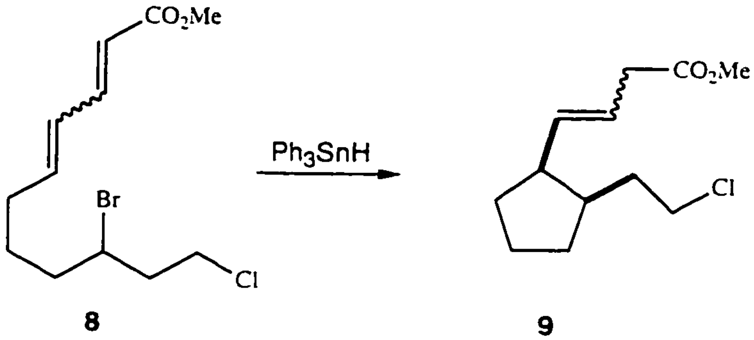
Figure 1

$$\underset{\mathbf{3}}{C_{18}H_{37}O\text{-}C(S)SMe} \xrightarrow{Bu_3SnH,\ xylene} \underset{\mathbf{4}}{C_{18}H_{38}}$$

Scheme 1



Scheme 2

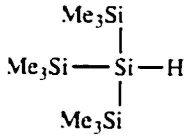


Scheme 3

Unfortunately the by-products produced from these tin-mediated reactions, namely tin halides or sulfides, tend to hydrolyze slowly on silica gel, which makes routine column chromatography separation and purification of the desired product very troublesome.[3] This problem is a serious concern in the pharmaceutical industry where certain impurities resulting from processes such as the Barton deoxygenation[7] have to be reduced below the trace level to ensure the absence of toxic effects.

The simplest way to deal with this problem is to adopt traditional separation methods such as distillation and recrystallization; unfortunately, however, most modern organic reactions frequently involve use of chromatography to effect product isolation.

Many efforts have been made to solve the problem. Although an alternative, non-stannane reagent based on silicon (figure 2) has been developed in the last few years,[8] most of the approaches[9] are still directed towards the modification of tin hydrides; this trend is probably due to the superior reactivity of these established tin compounds. The following is a concise literature review on various ways of solving tin hydride workup problems.



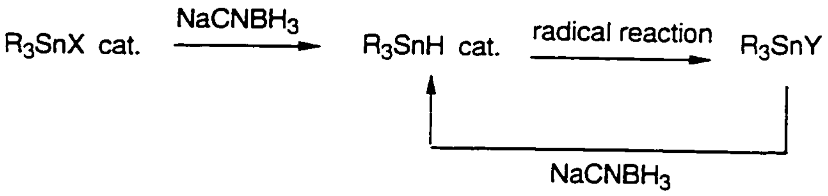
$(Me_3Si)_3Si-H$

10

Figure 2

A. *Catalytic tin hydride.*

This method[10,11,12] uses a combination of a catalytic amount of a tin hydride with a stoichiometric amount of reducing agent such as $LiAlH_4$, $NaCNBH_3$ or $NaBH_4$. During the reaction, a relatively small amount of tin hydride is constantly available for radical chain transfer by repeated regeneration from the corresponding tin halide or sulfide (Scheme 4).



X, Y= halide, sulfide *etc.*

Scheme 4

This invention ensures that only traces of tin hydride are present during the workup stage, a factor which makes easy separation possible. The Stork[12] version ($NaCNBH_3$, Bu_3SnH) has been used frequently in reactions where a low concentration of stannane needs to be maintained, the method provides an elegant alternative to the syringe pump technique. However, this catalytic technique can be used only where the substrate and the product are compatible with the stoichiometric reducing agent present.

B. Fluoride method.[13]

This method is based on the fact that trialkyltin fluorides are pentacoordinated polymeric materials which are not soluble in common organic solvents. Generally, the reaction mixture from a tin mediated reaction is taken up into ether, treated with aqueous KF solution for several hours and filtered through a Celite pad. Presumably, this method is not suitable for compounds containing silicon as a protecting group.

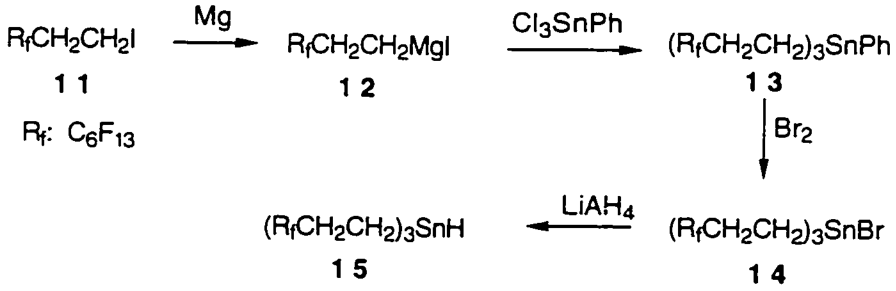
C. *Liquid-liquid extraction methods.*

a. *Acetonitrile-hexane partition.*

Roberts and Berge[14] approached the separation problem by partitioning the reaction mixture between hexane and acetonitrile. This practice is based on the following facts: i) Mutual insolubility of hexane and acetonitrile; ii) the pronounced solubility of tin species in hexane; iii) the preferential partition of other organic molecules into acetonitrile in the binary system.

Unfortunately, the partition of some organic compounds, if not all of them, between these two solvents is not complete. Thus caution should be exercised in working up a small scale reaction using this technique.

b. *Use of fluorous solvents.*

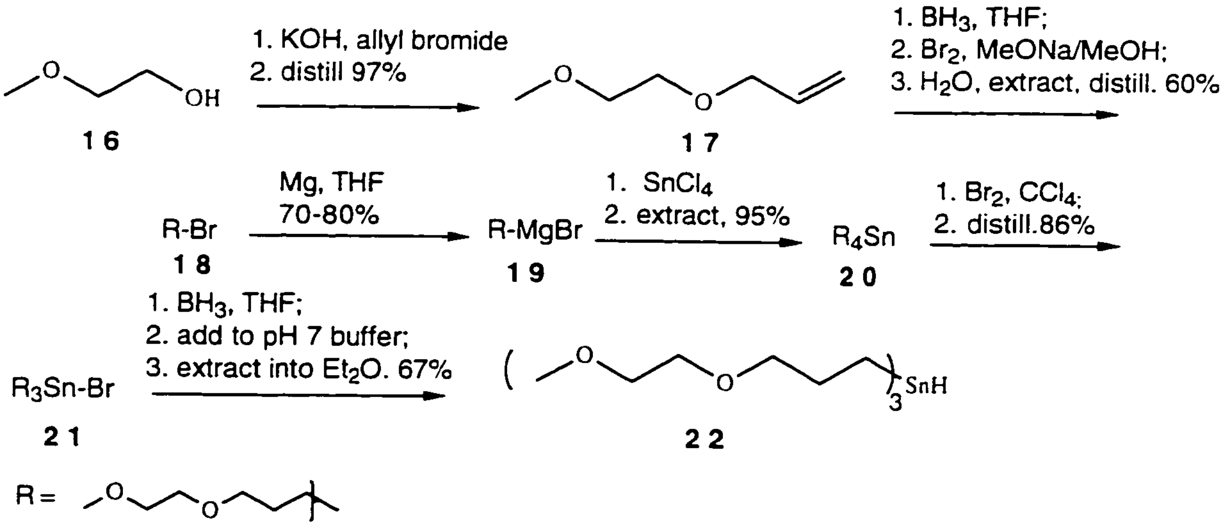


Scheme 5

Very recently Curran *et al.*[15] proposed an interesting partition workup method. The idea is based on the fact that fluorohydrocarbon solvents such as perfluoromethylcyclohexane (PFMC) are not miscible with common organic solvents or aqueous solutions. Most highly fluorinated compounds are only soluble in perfluorohydrocarbon solvents. A special stannane **15** was prepared, starting from 2-perfluorohexyl-1-iodoethane **11**, as shown in Scheme 5. Several typical radical reactions went smoothly when mediated by **15** in a solvent such as benzotrifluoride, which can dissolve both fluoro compounds and the regular hydrocarbons, due to its structural components. The solvent can be removed by evaporation (bp 102 °C). The residue was then partitioned between PFMC and CH_2Cl_2, with the desired product staying in the ordinary organic solvent.

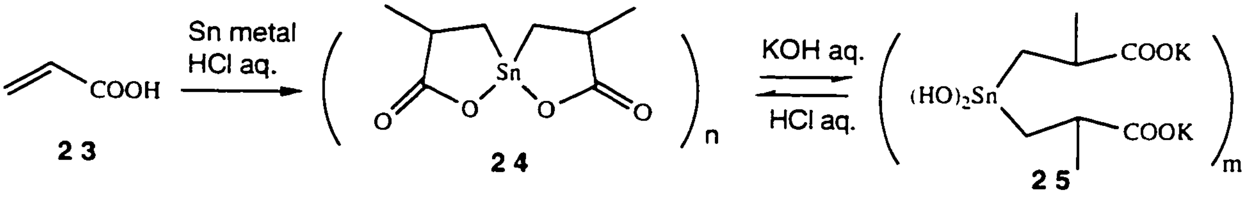
D. Water soluble tin hydrides.

Breslow and Light reported[16] the synthesis of the first water-soluble tin hydride **22** (Scheme 6). Several examples were presented showing the efficient reduction of halides in both aqueous and organic solutions. The authors mentioned the possible recovery of the tin species by acidifying the aqueous solution to $pH < 2$ with HCl, to regenerate the tin chloride, followed by extraction into chloroform. This unique water soluble tin hydride, is very useful when a aqueous solution is required as the reaction medium.



Scheme 6

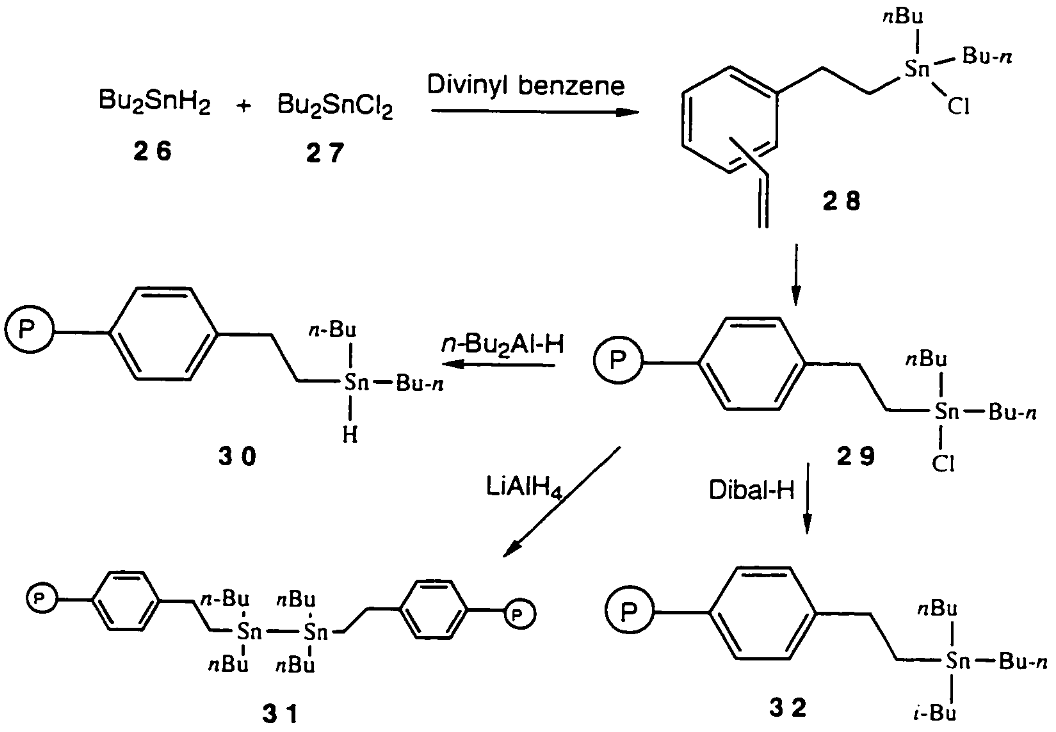
Similarly, Collum *et al.*[17] reported a base-soluble polymeric tin species **24** (Scheme 7). Together with $NaBH_4$ and 4,4'-azobis(4-cyanovaleric acid) (ACVA), this reagent could reduce a number of bromides, and also facilitated certain cyclization process. Two equivalents of sodium borohydride are needed *per* mole of **24**.



Scheme 7

E. Polymer-supported tin hydrides.

Neumann *et al.*[18] developed a stannane (**30**) that is attached to a polymer support. The preparation, which is summarized in Scheme 8, involves the synthesis of a tin-containing monomer, followed by polymerization. In the reduction of the polymer chloride **29**, it was found that the adoption of $LiAlH_4$ led to decomposition of the resulting tin hydride to distannane **31**. The use of $NaBH_4$ in DME caused difficulty in the removal of the solvent. Use of DIBAL-H led to substantial alkylation (compound **32**); finally *n*-Bu_2Al-H was chosen as the best reducing agent.

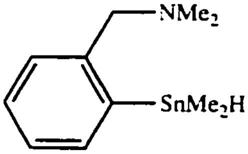


Scheme 8

Several radical dehalogenation reactions were conducted using the polymeric reagent, with acceptable results. However, the recyclability of this tin species was poor (up to seven regenerations are possible); this fact severely limits its application.

F. Nitrogen containing stannane.

During the course of our work, Vedejs *et al.*[19] published the synthesis of a internally activated tin hydride (**33**) (Figure 3). While the authors reported that the reagent could reduce ketones in a protic solvent such as a methanol, and could serve as a radical reagent in an aprotic solvent such as benzene, the instability of this compound to heat (80 °C) does limit its applicability. No radical cyclization example was presented in the paper, and we do not know if the activated tin hydride **33** is such a good hydrogen donor, that a cyclization process would be difficult due to a more favorable direct reduction pathway.



33

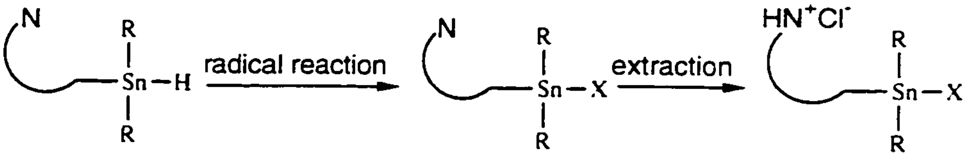
Figure 3

G. Removal through chemical reaction.

Most recently, Crich and Sun[9] suggested that the crude reaction mixtures should be reduced with $NaCNBH_3$ so as to convert the tin species into tin hydrides. These can often be separated chromatographically from the reaction products; unlike tin halides, for example, the stannanes have good chromatographic behavior. Tin halides undergo hydrolysis during chromatography, and separation from other compounds is often difficult.

(II) RESULTS and DISCUSSION

Our aim was to make a nitrogen-containing tin hydride reagent whose reactivity would be close to that of the traditional tin hydrides but which could be removed by simple acid extraction (Scheme 9).



34 **35** **36**

organic phase ⟶ aqueous phase

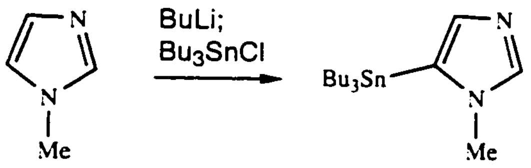
Scheme 9

The synthesis of mixed substituted (sometimes called unsymmetrical) tin compounds is usually carried out via four different routes, in addition to the classical redistribution method[20] (Scheme 10).

$$3\,R_4Sn + SnX_4 \longrightarrow 4\,R_3SnX$$

Scheme 10

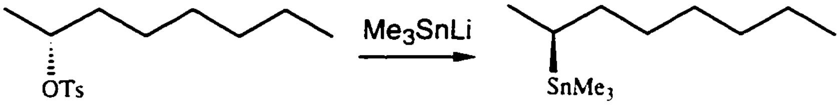
Nucleophilic substitution on tetrahedral tin compounds offers a route to a variety of tin compounds[21] (Scheme 11).



37 **38**

Scheme 11

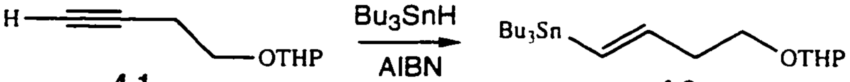
In addition, stannyl anions, which were discovered more than 35 years ago,[22] are quite stable, and their use has opened a new avenue for the preparation of many tin compounds[23] (Scheme 12).



39 **40**

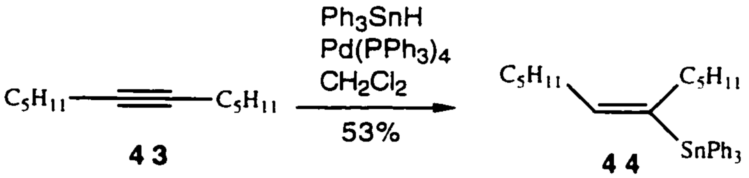
Scheme 12

Another important class of reactions that is characteristic of tin compounds is the addition of the Sn-H bond across a double or triple bond. This hydrostannylation[20,24] reaction (Scheme 13) was used more frequently in the early days of tin chemistry than the other types of reactions.



41 **42**

Scheme 13

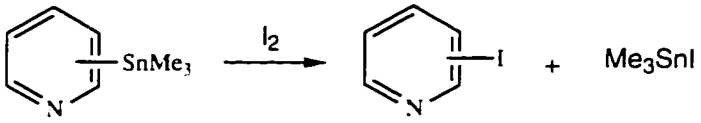


43 **44**

Scheme 14

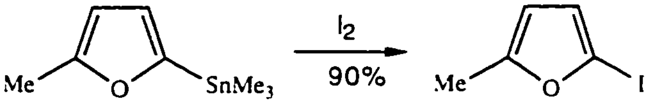
This method is used when the substituents present preclude the adoption of conventional organometallic reagents. The reaction follows a radical pathway and is usually initiated by radical initiators, such as AIBN. A recent development is the transition metal-mediated sequence[25] (Scheme 14), which affords better results in certain cases.

Finally, unsymmetrical tin compounds can be approached through selective cleavage of existing Sn-C bonds.[20] The reagents capable of this reaction include halogens and metallic or non-metallic halides. The selectivity generally depends on the relative ability of the groups attached to tin to accommodate an electrophilic substitution reaction, but may be governed by other factors such as solvent polarity. Two examples are shown in Schemes 15[26] and 16.[27]



45 **46** **47**

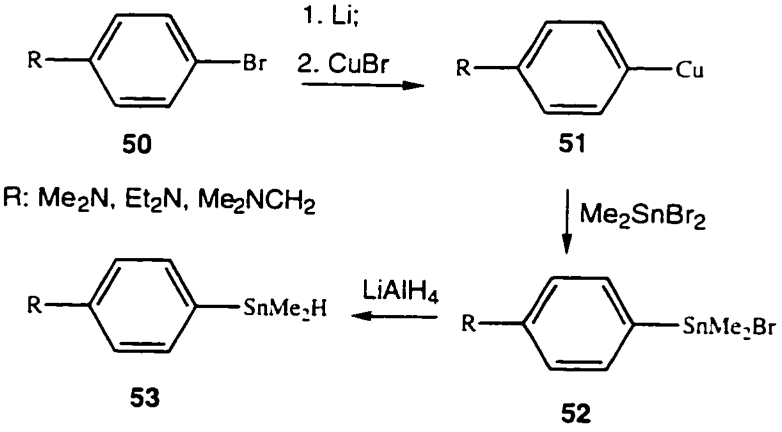
Scheme 15



48 **49**

Scheme 16

We first explored an ionic methodology reported by Van Koten[28] *et al.* hoping we could quickly make our first nitrogen-containing tin hydride (Scheme 17).

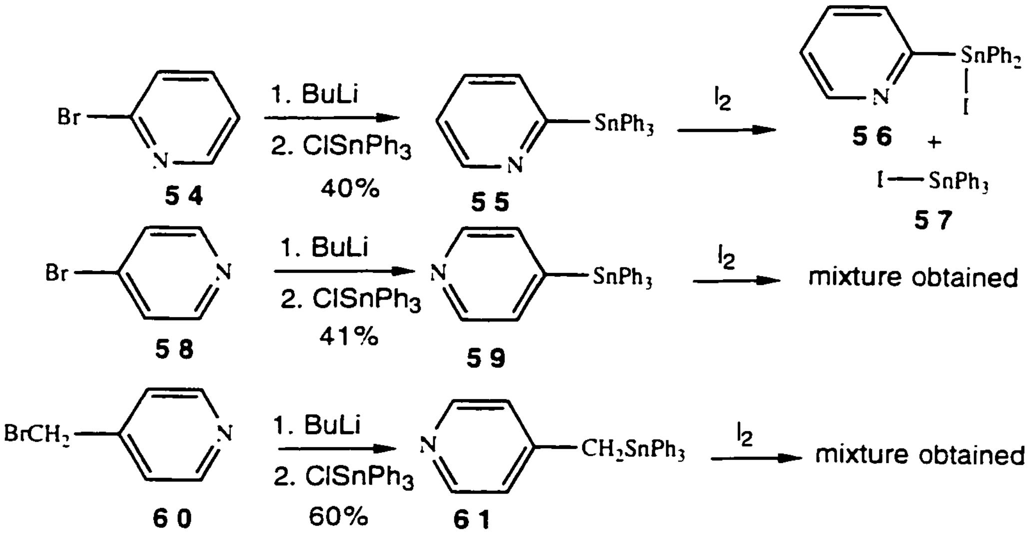


Scheme 17

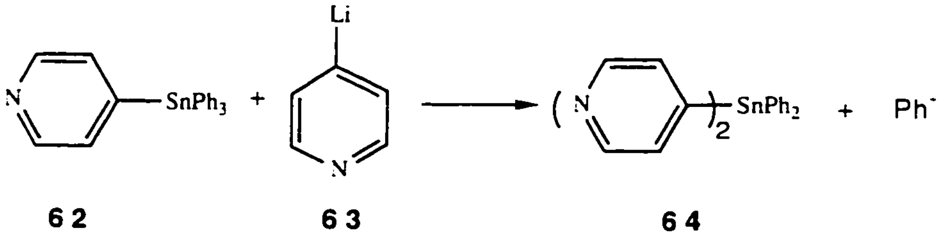
It turned out compounds **51-53** were sensitive to both air and moisture, and usually decomposed rapidly when exposed to air, even in solution. The full characterization of each of these intermediates was very troublesome and, in fact, was never achieved. We abandoned this approach because we realized that such unstable compounds would not be suitable for our purposes.

Our attention was then switched to the task of making a tin hydride with a pyridyl substituent attached (see **55** in Scheme 18). This plan was based on the expectation that a pyridyl group could be attached to tin by reaction of the pyridyl anion with triphenyltin bromide, and subsequent selective cleavage of one of the phenyl groups. The selective removal of a phenyl substituent was predictable, since it is more electron-rich than pyridine, and thus better facilitates an electrophilic halogenation. The 2- and 4-bromo-pyridines and 4-(bromomethyl)pyridine were chosen as our starting materials.

Treatment of pyridyl halides with *n*-butyllithium afforded the nucleophiles. The reaction of these nucleophiles with triphenyltin chloride has been reported[29] but yields were low, and in our hands the required compounds were also obtained in poor yield (Scheme 18). This might be due to transmetallation reactions such as the one shown in Scheme 19.



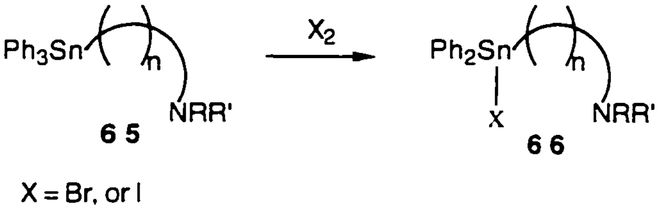
Scheme 18



Scheme 19

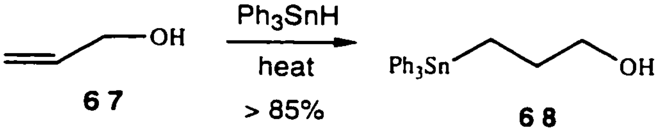
We temporarily accepted these results and used each of the pyridylstannanes for reaction with iodine in a solution of chloroform. The outcome were disappointing. All three compounds gave a mixture of products (Scheme 18). Alternative solvents such as benzene or methanol were tried, but without improvement. Apparently the difference between a benzene ring and a pyridine ring was not great enough to allow high selectivity.

Therefore we started to consider the possibility of using a nitrogen containing moiety attached through a saturated side chain (Scheme 20). This would offer a better chance of selective cleavage in the subsequent halogenation reaction.



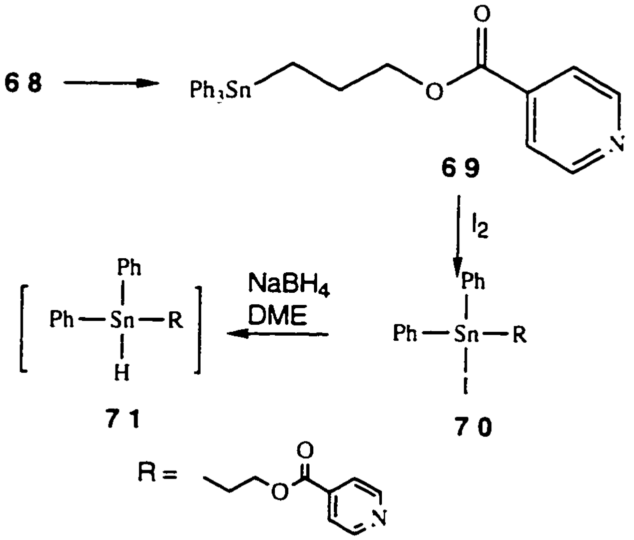
Scheme 20

Hydrostannylation has been practiced ever since van der Kerk[30] and associates demonstrated it in 1956. We decided to use this reliable method in our preparation of a triphenyltin moiety linked to a tether. The reaction of allyl alcohol with Ph_3SnH was conducted according to van der Kerk's original procedure[30] in high yield (Scheme 21). The intention was to make use of the free hydroxyl function in compound **68** for further manipulation.



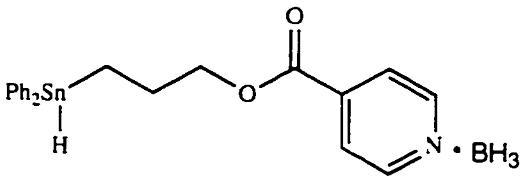
Scheme 21

Compound **68** was esterified with 4-picolyl chloride to give **69**, as shown in Scheme 22.



Scheme 22

Treatment of **69** with iodine in chloroform afforded iodide **70**, as the only product in 80% yield. Reduction with $NaBH_4$ in DME then gave the corresponding tin hydride (initially regarded as **71**) in 95% yield. It turned out later that the structure for compound **71** was not correct, and the actual structure was that of a boron complex (Figure 4). However, we did not attempt to modify the route so as to obtain boron-free products, since we eventually abandoned this approach, as described below.

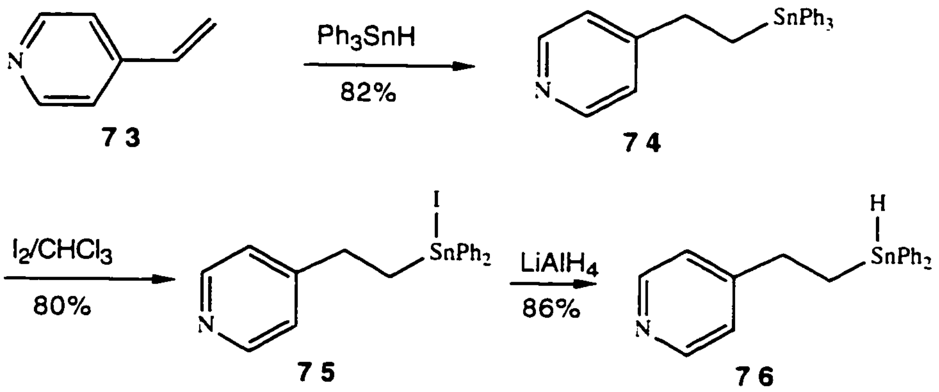


72

Figure 4

We evaluated both **70** and **71** for acid solubility. Unfortunately, neither of them could be extracted efficiently by 3N HCl from an organic solvent such as dichloromethane or ether. At the time, this was attributed to the linking group between the pyridine and the tin center, which might impart strong hydrophobicity. In addition, we felt that too many steps were involved in this sequence, so that the reagent would not be regarded as readily available. At this point, we turned to another approach that, in the event, led to an acceptable reagent.

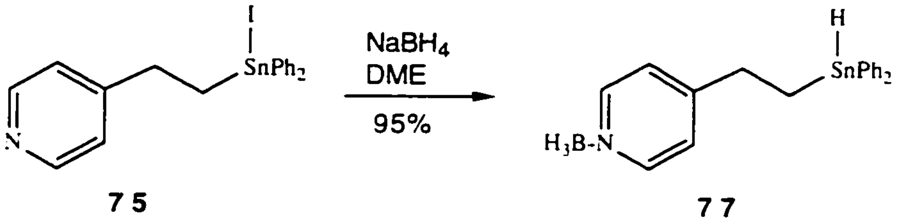
4-Vinylpyridine is a widely used monomer in industry. Like allyl alcohol, its reaction with tin hydride has also been documented[30] for many years. We thought that compound **74** would be an ideal candidate on the grounds both of its availability and stability. Compound **74** was easily prepared by heating a mixture of **73** and triphenyltin hydride in the presence of AIBN. The reaction was usually complete in several hours.



Scheme 23

Next, iodination was carried out in either methanol or chloroform, and in both cases similar results were obtained. We observed exclusive cleavage of one phenyl group to give **75** in high yield.

Iodide **75** was first reduced with $NaBH_4$ in DME. The reaction was complete in five minutes, with the starting material being transformed into a single new species. This turned out to be the boron complex **77** of the desired product. The ^1H NMR spectrum of this compound has a broad signal corresponding to the BH_3 unit, and the elemental composition was confirmed by the mass spectrum.



Scheme 24

Several ways were tried to remove the complexed boron moiety. These included stirring **77** in aqueous NaOH (3N) solution, stirring with Bu_3P, and shaking with a dichloromethane solution of pyridine itself. None of these experiments worked. We therefore tried other reducing agents, as listed in Table 1. As a result of this survey, we quickly established that $LiAlH_4$, reduced **75** to stannane **76** in 86% yield.

Reagents that failed in the reduction of 75

$NaBH_3CN$, DME/THF, 24h

PMHS, neat, 24h

Dibal-H, CH_2Cl_2, DME, r.t.

Dibal-H, hexane

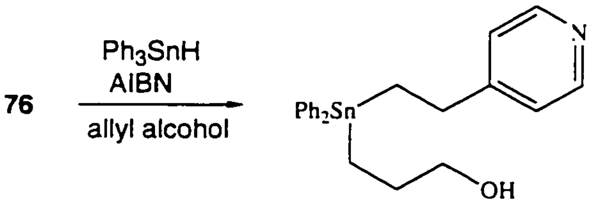
$Bu_4N^+BH_4^-$

Pyridine, $NaBH_4$

Table 1

Compound **76** is a white crystalline material, which shows no significant sign of decomposition when stored for two weeks in refrigerator. It is not volatile, due to the polar pyridyl group, and is odorless.

To fully characterize the material, a hydrostannylation of allyl alcohol was conducted (Scheme 25). The product from this reaction was obtained and fully characterized as **78**.

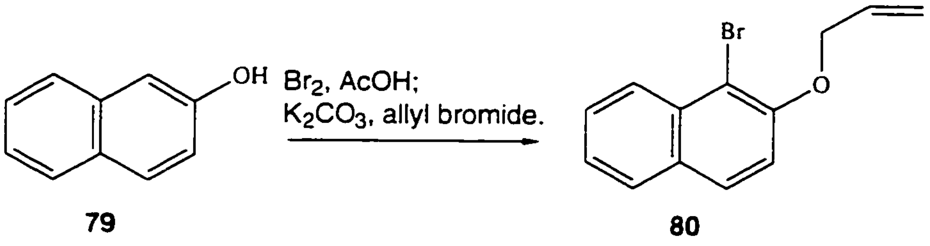


78

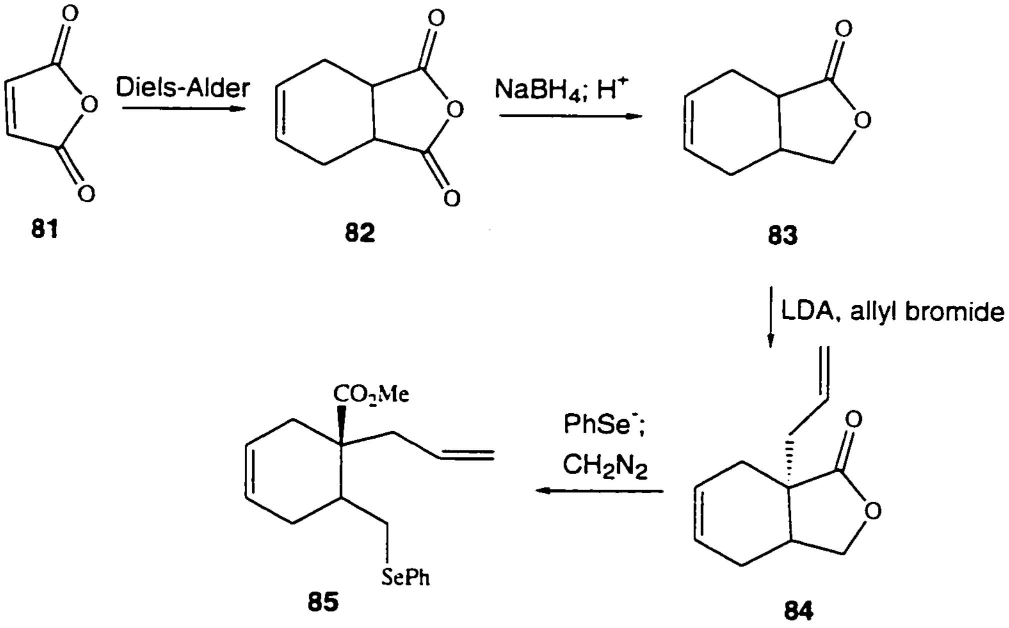
Scheme 25

A series of radical reactions were then conducted, using **76** in place of the regular Ph_3SnH or Bu_3SnH. In each and every case, our compound **76** showed comparable reactivity to that of triphenyltin- or tributyl tin hydride (Table 2). Results for reactions with conventional stannanes are also listed in the Table under the column headed "lit", and it can be seen that yields with our reagent are comparable.

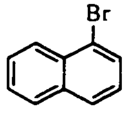
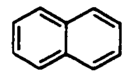
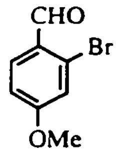
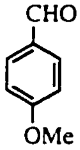
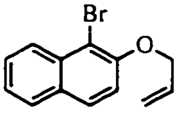
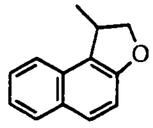
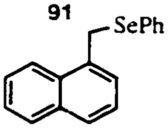
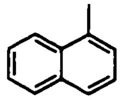
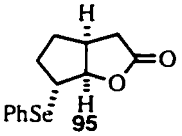
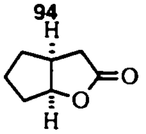
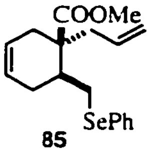
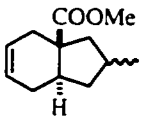
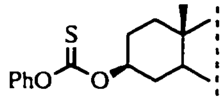
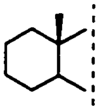
Compounds **80** and **85** were prepared as shown in Schemes 26[31] and 27,[32] according to literature procedures. The other test substrates, were also known compounds, and some had been prepared before in this laboratory. Preparative details are given, where necessary, in the Experimental Section.



Scheme 26



Scheme 27

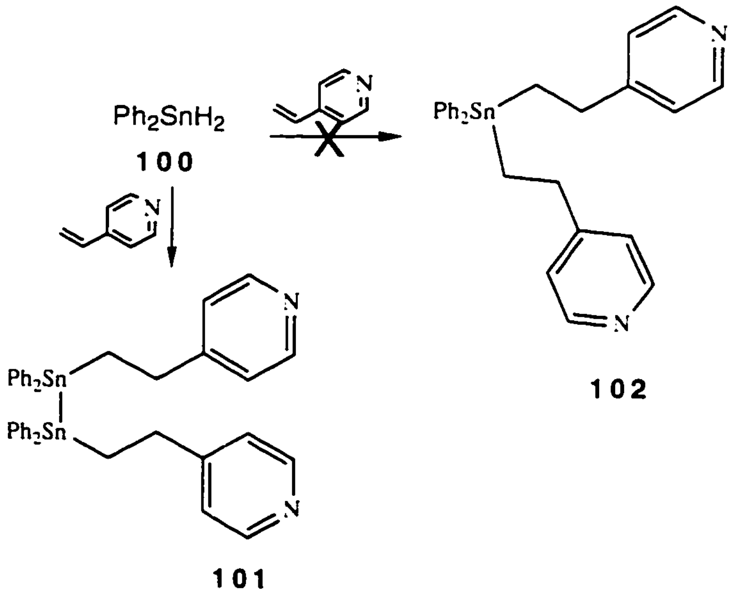
		Bath temp.		Yield with 77	Lit.
1	 **86**	125 °C[a]	 **87**	75%[a]	78-85%[33]
2	 **88**	rt	 **89**	70%[b]	-[c]
3	 **80**	85 °C	 **90**	76%[a]	<71%[31]
4	$C_{12}H_{25}$–SePh **91**	125 °C	$C_{12}H_{26}$ **92**	70%[a]	73%[34]
5	 **93**	125 °C	 **94**	85%[a]	-[c]
6	 **95**	125 °C[a]	 **96**	75%[a]	74%[34]
7	 **85**	85 °C	 **97**	80%[a]	92%[32]
8	 **98**	125 °C	 **99**	90%[a]	-[c]

Note: a. Thermal condition using either boiling benzene or toluene as solvent;
b. Using Et_3B as radical initiator; c. Not previously reported in the literature.

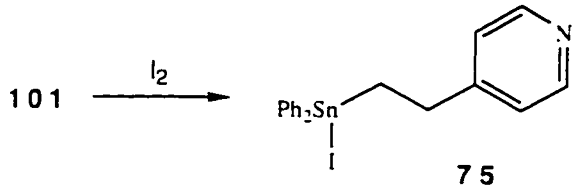
Table 2

The most important aspect for the project – the acid solubility of compounds **75** and **76** – was examined in typical experimental procedures. It turned out that **76** was quite soluble in 3N HCl. However, after three extractions with 3N HCl of an ethyl acetate solution of **76** or of a reaction mixture from a dehalogenation reaction, *ca.* 5% of tin species remained in the organic layer, as judged from the quantity of material recovered by neutralization of the HCl layer. We could not *completely* remove the tin residue from the organic phase. This result is quite surprising. Nonetheless, compound **76** has a significant advantage over traditional reagents (Scheme 1), because its high polarity makes it much easier to separate tin species by chromatography.

Finally, we carried out the reaction shown in Scheme 28, in the hope of obtaining compound **102**, in which the presence of *two* pyridine units should enhance acid solubility. However, the reaction gave compound **101**, the structure of which was easily established by standard distannane cleavage with iodine (Scheme 29).



Scheme 28



75

Scheme 29

Conclusion

We have prepared a pyridine-containing stannane which has reactivity comparable to that of tributyl- and triphenylstannane, and which leads to highly polar tin species that can be removed very easily by chromatography. Extraction of tin species into acid was inefficient, for reasons that are not clear.

III Experimental

General procedures

Argon was purified by passage through a column (3.5 x 42 cm) of BASF R-311 catalyst[35] and then through a similar column of Drierite. Glassware was dried in an oven (120 °C) for at least 3 h before use and either cooled in a desiccator over Drierite, or assembled quickly, sealed with rubber septa, and allowed to cool under a slight static pressure of argon. Reaction mixtures were stirred by Teflon-coated magnetic stirring bars.

Solvents for chromatography or extractions were distilled before use.

Products were isolated from solution by evaporation under water pump vacuum at, or below, 30 °C, using a rotary evaporator.

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

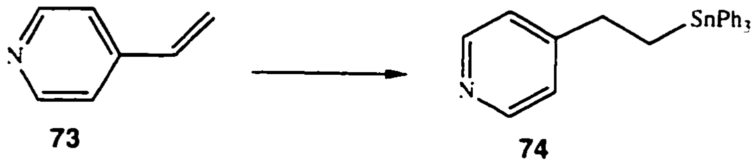
Commercial thin layer chromatography (tlc) plates (silica gel, Merck 60F-254) were used. Spots were detected by examination under UV light or by spraying the plate with a solution of phosphomolybdic acid, followed by charring on a hot plate. Silica gel for flash chromatography was Merck type 60 (230-400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

Dry solvents were prepared under an inert atmosphere and transferred by oven-dried syringes. Dry THF was distilled from Na and benzophenone ketyl. Dry PhH was distilled from Na. Dry CH_2Cl_2, MeOH, pyridine, DMF, and were distilled from

CaH_2, the last two solvents being distilled under water pump vacuum. Commercial (Aldrich) solutions of *n*-BuLi (in hexanes) were assumed to have the stated molarity.

The symbols s', d', t', and q' used for ^{13}C NMR spectra indicate 0, 1, 2, or 3 attached protons.

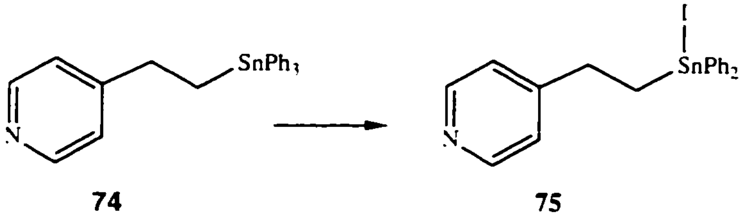
Triphenyl[2-(4-pyridyl)ethyl]tin (74).



4-Vinylpyridine (Aldrich, used as received, 1.55 mL, 14.4 mmol) was added to Ph_3SnH (Aldrich, used as received, 2.52 g, 7.18 mmol), and AIBN (1.0 mg, 0.006 mmol) was added to the mixture. The mixture was lowered into a pre-heated oil bath (80 °C) and stirred for 4 h under a slow stream of dry Ar. At this stage the excess of 4-vinylpyridine was evaporated (rotary evaporator, *ca* 80 °C). Flash chromatography of the residue over silica gel (4 x 40 cm), using 1:1 EtOAc-hexane, gave **74** (2.78 g, 85%) as a pure (^1H NMR, 200 MHz), white solid: mp 112-112.5 °C (lit.[30] 112-113 °C); ^1H NMR (200 MHz, $CDCl_3$) δ 1.68-2.06 (m, $^2J_{SnCH}$ = 53 Hz, 2 H), 2.85-3.22 (m, $^3J_{SnCCH}$ = 47 Hz, 2 H), 7.12 (dd, J = 6.0, 1.5 Hz, 2 H), 7.35-7.76 (m, 15 H), 8.49 (dd, J = 6.0, 1.5 Hz, 2 H); ^{13}C NMR (75.5 MHz, C_6D_6) δ 11.4 (t'), 31.9 (t'), 123.3 (d'), 129.0 (d', $^3J_{SnCCC}$ = 48 Hz), 129.3 (d', $^4J_{SnCCCC}$ = 10.5 Hz), 137.3 (d', $^2J_{SnCC}$ = 35 Hz), 138.5 (s'), 150.3 (d'), 152.8

(s'); broadband proton-decoupled ^{119}Sn NMR (149.213 MHz, $CDCl_3$, Me_4Sn as internal standard) δ -100.53; exact mass *m/z* calcd for $C_{25}H_{23}N^{120}Sn$ 457.08524, found 457.08471. Anal. Calcd for $C_{25}H_{23}NSn$: C 65.83, H 5.08, N 3.07. Found: C 65.51, H 5.05, N 3.03.

Diphenyl[2-(4-pyridyl)ethyl]tin iodide (75).

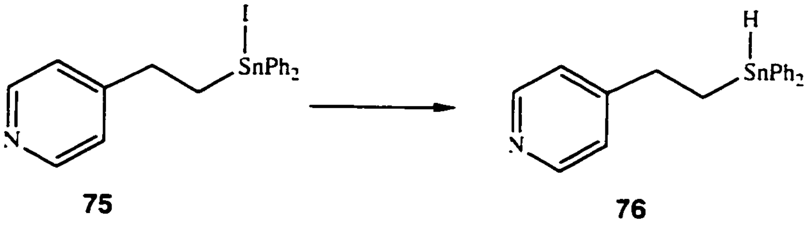


74 **75**

I_2 (1.51 g, 5.94 mmol) was added over *ca* 30 min from a solid addition sidearm tube to a stirred solution of **74** (2.52 g, 5.51 mmol) in bench MeOH (40 mL) (Ar atmosphere). After 4 h (tlc control, silica, 1:3 EtOAc-hexane) the solvent was evaporated, and flash chromatography of the residue over silica gel (4 x 12 cm), using first 1:3 EtOAc-hexane, and then 1:3 MeOH-EtOAc, gave **75** (1.12 g, 40%) as a pure (^1H NMR, 200 MHz), white solid: mp 180-181 °C; ^1H NMR (200 MHz, $CDCl_3$) δ 1.80-2.20 (m, $^2J_{SnCH}$ = 51 Hz, 2 H), 2.82-3.28 (m, $^3J_{SnCCH}$ = 68 Hz, 2 H), 7.12 (dd, J = 6.0, 1.5 Hz, 2 H), 7.35-7.73 (m, 10 H), 8.42 (dd, J = 6.0, 1.5 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) δ 18.0 (t'), 32.3 (t'), 123.8 (d'), 129.3 (d', $^3J_{SnCCC}$ = 60 Hz), 130.4 (d'), 136.4 (d', $^2J_{SnCC}$ = 47 Hz), 137.7 (s'), 150.1 (d'), 152.8 (s'); broadband proton-decoupled ^{119}Sn NMR (149.213 MHz, $CDCl_3$, Me_4Sn as internal standard) δ -61.59;

exact mass m/z calcd for $C_{19}H_{18}IN^{120}Sn$ 506.95078, found 506.96477.

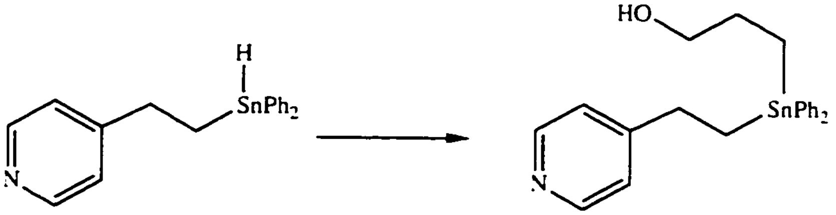
Diphenyl[2-(4-pyridyl)ethyl]tin hydride (76).



A solution of **75** (183.6 mg, 0.36 mmol) in dry THF (10 mL) was added dropwise over *ca* 15 min to a stirred and cooled (0 °C) suspension of $LiAlH_4$ (13.7 mg, 0.36 mmol) in dry Et_2O (10 mL) (Ar atmosphere). Stirring was continued for 15 min at 0 °C. The mixture was then quenched by slow addition of ice-water (*ca* 5 mL), and extracted with Et_2O (3 x 15 mL). The combined organic extracts were dried ($MgSO_4$) and evaporated at room temperature. Flash chromatography of the residue over silica gel (4 x 40 cm), using 1:1 EtOAc-hexane, gave **76** (110 mg, 80%) as a pure (^1H NMR, 200 MHz) liquid which can be stored under Ar in the refrigerator for several weeks: FTIR (cast from CH_2Cl_2) 1836 cm^{-1}; ^1H NMR (400 MHz, C_6D_6) δ 1.12-1.32 (m, $^2J_{SnCH}$ = 53 Hz, 2 H), 2.40-2.61 (m, $^3J_{SnCCH}$ = 54 Hz, 2 H), 6.19 (t, J = 1.8 Hz, $^1J_{(119)SnH}$ = 1851 Hz, $^1J_{(117)SnH}$ = 1776 Hz, 1 H), 6.55 (dd, J = 6.0, 1.5 Hz, 2 H), 7.05-7.20 (m, 6 H), 7.27-7.44 (m, 4 H), 8.45 (dd, J = 6.0, 1.5 Hz, 2 H); ^{13}C NMR (50.3 MHz, C_6D_6) δ 10.6 (t', $^1J_{(119)SnC}$ = 382 Hz, $^1J_{(117)SnC}$ = 366 Hz), 32.3 (t', $^2J_{(119)SnCC}$

= 38 Hz, ${}^{2}J_{(117)SnCC}$ = 17 Hz), 123.3 (d'), 128.9 (d', ${}^{3}J_{SnCCC}$ = 49 Hz), 129.3 (d', ${}^{4}J_{SnCCCC}$ = 16 Hz), 137.4 (d', ${}^{2}J_{SnCC}$ = 37 Hz), 137.6 (s', ${}^{1}J_{SnC}$ = 490 Hz), 150.4 (d'), 152.6 (s'); broadband proton-decoupled ^{119}Sn NMR (149.212 MHz, C_6D_6, Me_4Sn as internal standard) δ -137.006; exact mass *m/z* calcd for $C_{19}H_{19}N^{120}Sn$ 381.05396, found 381.05319. Anal. Calcd for $C_{19}H_{19}NSn$: C 60.05, H 5.04, N 3.69. Found: C 60.27, H 5.02, N 3.70.

3-[Diphenyl[2-(4-pyridyl)ethyl]stannyl]propanol (78).

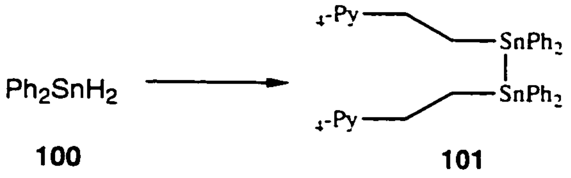


76 **78**

Stannane **76** (140.0 mg, 0.37 mmol), allyl alcohol (0.3 mL, 4.4 mmol), and AIBN (2.5 mg, 0.015 mmol) were dissolved in dry Et_2O (4.0 mL) and the solution was evaporated at room temperature under water-pump vacuum. The residual oil was stirred at 80 °C for 4 h in a preheated oil bath (Ar atmosphere). Flash chromatography of the resulting mixture over silica gel (4 x 30 cm), using 1:1 EtOAc-hexane, gave **78** (104.7 mg, 65%) as a pure (^{1}H NMR, 200 MHz) oil: ^{1}H NMR (200 MHz, $CDCl_3$) δ 1.08-2.10 (m, 6 H), 2.46 (br s, 1 H), 2.72-3.10 (m, ${}^{3}J_{SnCCH}$ = 46 Hz, 2 H), 3.61 (t, *J* = 6.0 Hz, 2 H), 7.08 (dd, *J* = 6.0, 1.5 Hz, 2 H), 7.30-7.63 (m, 10 H), 8.39 (dd, *J*

= 6.0, 1.5 Hz, 2 H); ^{13}C NMR (50.3 MHz, $CDCl_3$) δ 6.4 (s', $^1J_{(119)SnC}$ = 378 Hz, $^1J_{(117)SnC}$ = 361 Hz), 11.0 (t', $^1J_{(119)SnC}$ = 354 Hz, $^1J_{(117)SnC}$ = 339 Hz), 29.4 (t', $^2J_{(119)SnCC}$ = 21 Hz), 32.00 (t'), 65.4 (t', $^3J_{(119)SnCCC}$ = 62 Hz), 123.4 (d'), 128.5 (d', $^3J_{SnCCC}$ = 46 Hz), 128.8 (d', $^4J_{SnCCCC}$ = 16 Hz), 136.7 (d', $^2J_{SnCC}$ = 34 Hz), 139.5 (s'), 149.5 (d'), 154.1 (s'); exact mass *m/z* calcd for $C_{22}H_{25}ON^{120}Sn$ 439.09583, found 439.09639.

1,2-[2-(4-Pyridyl)ethyl)]-1,1,2,2-tetraphenylditin (101).

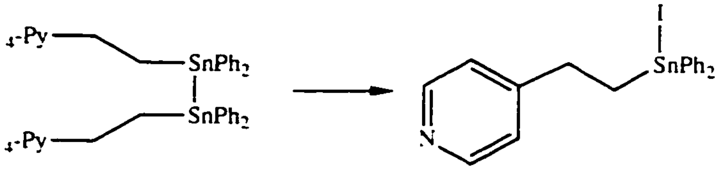


Ph_2SnH_2 was freshly prepared by reducing Ph_2SnCl_2 with $LiAlH_4$, according to a literature procedure.[20]

Ph_2SnH_2 (1.0 g, 3.74 mmol) was mixed with 4-vinylpyridine (1.0 mL, 9.35 mmol) and the mixture was heated at 80 °C with efficient stirring. Evaporation of the volatile material under oil pump vacuum, and flash chromatography of the residue over silica gel (25 x 4 cm), using EtOAc, gave **101** (606.0 mg, 43%) as a white solid containing slight impurities (^1H NMR, 200 MHz): ^1H NMR ($CDCl_3$, 300 MHz) δ 1.70-2.00 (m, 4 H), 2.75-3.05 (m, 4 H), 6.95-7.05 (m, 4 H), 7.20-7.72 (m, 20 H), 8.30-8.50 (m, 4 H); exact mass *m/z* calcd for $C_{38}H_{36}N_2{}^{120}Sn_2$ 760.09222, found 760.08767; calcd for $C_{38}H_{36}N_2{}^{118}Sn^{120}Sn$

758.09167, found 758.08881; calcd for $C_{38}H_{36}N_2{}^{118}Sn_2$ 756.09106, found 756.08953; calcd for $C_{38}H_{36}N_2{}^{116}Sn^{120}Sn$ 756.09180, found 756.08953 and calcd for $C_{38}H_{36}N_2{}^{116}Sn^{118}Sn$ 754.09119, found 754.09185. The identity of **101** was further confirmed by its reaction with I_2 to afford **75**.

Diphenyl[2-(4-pyridyl)ethyl]tin iodide (75).



101 **75**

Iodine (34.0 mg, 0.26 mmol) was added in one portion to a stirred solution of **101** (189.4 mg, 0.25 mmol) in $CHCl_3$ (10.0 mL), and the mixture was stirred for 8 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (20 x 2 cm), using 1:3 MeOH-EtOAc, gave **75** (157.0 mg, 62%), spectroscopically identical with material made from **74**.

General procedure for radical reactions, using 76.

Method a. The substrate was placed in a round-bottomed flask carrying a reflux condenser closed by a septum. The flask was flushed with Ar and the contents were kept under a slight positive pressure of Ar. PhH or PhMe was injected, and the flask was lowered into a preheated oil bath set at 85 °C, or at 125 °C in the case of PhMe. A solution of both **76**

and AIBN in the same solvent was injected in one portion (except for the cyclization reaction, in which case the addition was made over 2-8 h). Refluxing was continued for 2-10 h after the addition. The mixture was cooled and evaporated. Flash chromatography of the residue over silica gel then gave the product.

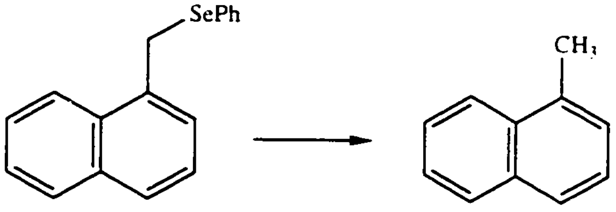
Method b. The stannane **76** in hexane and Et_3B (1 M solution in hexane) were added to a stirred solution of the substrate in hexane contained in a flask fitted with a $CaSO_4$ guard tube. Stirring with exposure to air (through the guard tube) was continued for 11 h, and the solution was then evaporated. Flash chromatography of the residue over silica gel then gave the product.

Decane (92).

$$\underset{\mathbf{91}}{CH_3(CH_2)_{10}CH_2SePh} \longrightarrow \underset{\mathbf{92}}{CH_3(CH_2)_{10}CH_3}$$

General method *a* was followed, using selenide **91** (105.0 mg, 0.323 mmol), **76** (172.3 mg, 0.45 mmol) and AIBN (5.0 mg, 0.03 mmol) in PhH (6.0 mL), and an overnight reflux period. Evaporation of the solvent and flash chromatography of the residue over silica gel (20 x 2 cm), using pentane, gave decane (**92**) (38.4 mg, 0.226 mmol) as a pure (^{1}H NMR, 200 MHz) oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.87 (t, 6 H), 1.09-1.46 (s, 20 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 14.13, 22.77, 29.45, 29.78, 32.03. These data are identical to those of an authentic sample.

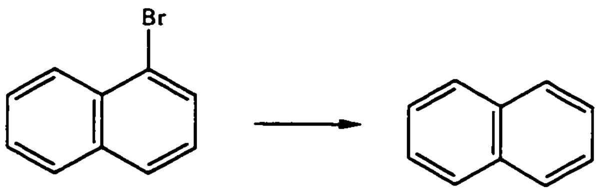
1-Methylnaphthalene (94).



93 94

General method *a* was followed, using selenide **93** (65.8 mg, 0.221 mmol), **76** (183.3 mg, 0.481 mmol) and AIBN (2.0 mg, 0.01 mmol) in PhH (4.0 mL), and an overnight reflux period. Evaporation of the solvent and flash chromatography of the residue over silica gel (20 x 2 cm), using hexane, gave **94** (26.68 mg, 85%) as a pure (^{1}H NMR, 200 MHz) oil: ^{1}H NMR (CDCl$_3$, 200 MHz) δ 2.75 (s, 3 H), 7.27-7.66 (m, 4 H), 7.68-7.86 (m, 1 H), 7.88-8.00 (m, 1 H), 8.01-8.20 (m, 1 H). These data are identical to those of an authentic sample.

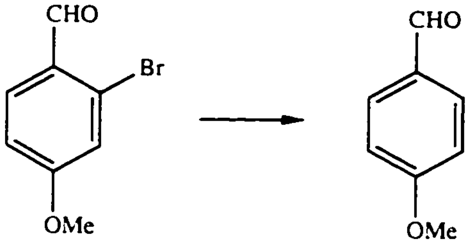
Naphthalene (87).



86 87

General method *a* was followed, using 1-bromonaphthalene (**86**) (141.0 mg, 0.68 mmol), **76** (310.0 mg, 0.81 mmol) and AIBN (10.0 mg, 0.06 mmol) in PhMe (10.0 mL), and an overnight reflux period. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 60 cm), using hexane, gave naphthalene (**87**) (66.0 mg, 75%), identical (tlc, ^{1}H NMR, ^{13}C NMR, mp) with an authentic sample.

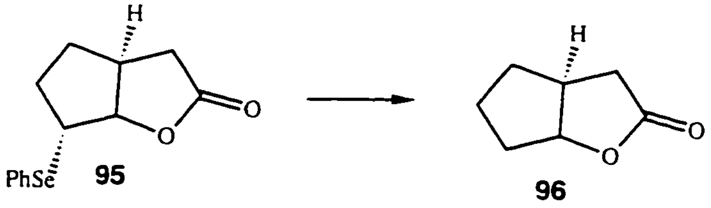
4-Methoxybenzaldehyde (89).



88 **89**

General method *b* was followed, using bromide **88** (51.0 mg, 0.237 mmol), **76** (100.0 mg, 0.262 mmol) and Et_3B (0.02 mL in 1 M hexane solution), and a reaction period of 8 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (20 x 2 cm), using 1:5 EtOAc-hexane, gave **89** (22.5 mg, 70%) as a pure (^{1}H NMR, 200 MHz) oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.95 (s, 3 H), 6.90-7.15 (m, 2 H), 7.75-8.00 (m, 2 H), 9.90 (s, 1 H). These data are identical to those of an authentic sample.

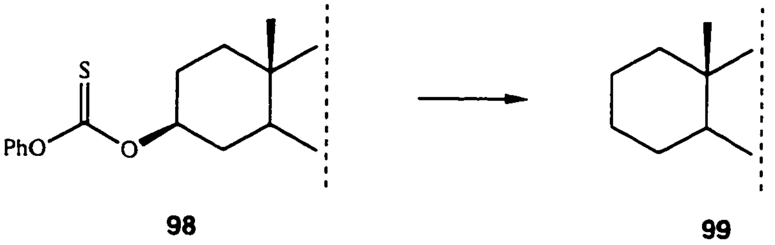
(3aα,6aα)-Hexahydro-2*H*-cyclopenta[b]furan-2-one (96).



Compound **95** was prepared according to a literature procedure.[34]

General method *a* was followed, using **95** (110.6 mg, 0.39 mmol), **76** (223.0 mg, 0.585 mmol) and AIBN (1.0 mg, 0.006 mmol) in PhMe (5.0 mL), and a reflux period of 6 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (20 x 2 cm), using 1:5 EtOAc-hexane, gave **96** (37.0 mg, 77%) as a pure (^{1}H NMR, 200 MHz) oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.35-2.10 (m, 6 H), 2.15-2.40 (m, 1 H), 2.70-3.00 (m, 2 H), 4.86-5.10 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 23.40 (t'), 33.44 (t'), 33.59 (t'), 36.01 (t'), 37.96 (d'), 86.33 (d'), 177.63 (s'). The ^{1}H NMR data are identical to those reported in the literature.[34]

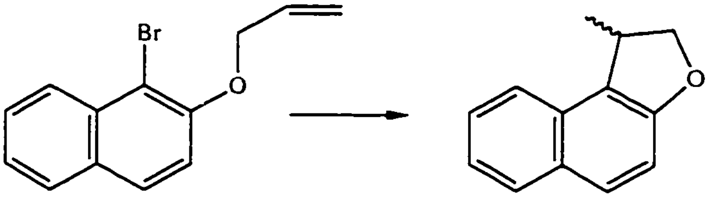
5α-Cholestane (99).



Compound **98** was prepared according a literature procedure.[36]

The deoxygenation was carried out by general method *a*, using **98** (51.6 mg, 0.0983 mmol), **76** (56.2 mg, 0.147 mmol) and AIBN (1.0 mg, 0.006 mmol) in PhMe (5.0 mL), and a reflux period of 8 h. Evaporation of the solvent and flash chromatography of the solvent over silica gel (20 x 2 cm), using hexane, gave **99** (33.0 mg, 90%) as a pure (^{1}H NMR, 200 MHz) oil: ^{1}H NMR (CDCl$_3$, 200 MHz) δ 0.57-2.02 (m, 48 H); ^{13}C NMR (CDCl$_3$, 50.3 MHz) δ 12.09, 12.24, 18.70, 20.65, 22.23, 22.57, 22.80, 23.88, 24.22, 26.89, 28.01, 28.27, 29.13, 32.23, 35.59, 35.84, 36.25, 38.74, 39.55, 40.18, 42.63, 47.11, 54.84, 56.38, 56.70. Exact mass *m/z* calcd for $C_{27}H_{48}$ 372.37561, found 372.37518. The NMR data are identical to those reported in the literature.[37]

1,2-dihydronaphtho[2,1-b]furan (90).



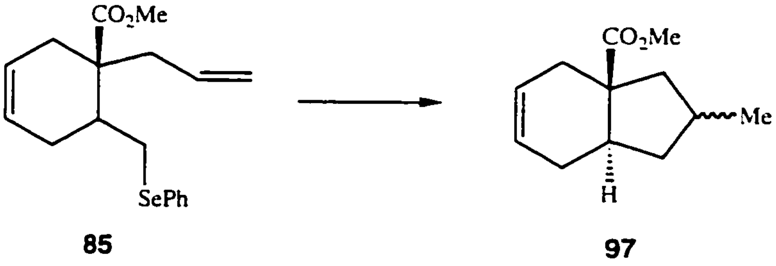
80 **90**

Compound **80** was prepared according to a literature procedure.[31]

The cyclization was carried out by general method *a*, using bromide **80** (397.6 mg, 1.511 mmol) in PhH (5.0 mL), **76**

(863.5 mg, 2.26 mmol) and AIBN (2.0 mg, 0.012 mmol) in PhH (5.0 mL), an addition period of 2 h, and a further reflux period of 4 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (20 x 2 cm), using hexane, afforded **90** (210.0 mg, 76%) as a pure (^{1}H NMR, 200 MHz) oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.45 (d, J = 6.9 Hz, 3 H), 3.84-4.04 (m, 3 H), 4.40 (dd, J = 9.0, 3.5 Hz, 1 H), 4.82 (t, J = 9.1 Hz, 1 H), 7.06-7.55 (m, 3 H), 7.60-7.90 (m, 3 H); ^{13}C NMR ($CDCl_3$, 50.324 MHz) 20.39 (q'), 36.26 (d'), 79.38 (t'), 112.27 (d'), 122.31 (d'), 122.71 (d'), 123.59 (s'), 126.60 (d'), 129.03 (d'), 129.26 (d'), 129.51 (s'), 130.52 (s'), 156.97 (s'). The ^{1}H NMR and ^{13}C NMR data are identical to those reported in the literature.[31]

Methyl (2α,3aα,7aβ)-1,2,3,4,7,7a-Hexahydro-2-methyl-3a*H*-indene-3a-carboxylate (97).



Compound **85** was prepared according to a literature method,[32] as shown in Scheme 27 of the discussion section of this thesis.

The cyclization was carried out by general method *a*, using compound **85** (50.0 mg, 0.14 mmol), **76** (108.8 mg, 0.28

mmol) and AIBN (5.0 mg, 0.03 mmol), and an addition time of 8 h. Refluxing was continued for a further 3 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (20 x 2 cm), using 1:3 EtOAc-hexane, gave **97** (22.0 mg, 80%) as a pure (^{1}H NMR, 200 MHz) oil: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.94-1.11 (m, 4 H), 1.35 (m, 1 H), 1.70-2.35 (m, 7 H), 2.79 (m, 1 H), 3.57-3.63 (two close s, 3 H), 5.62 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.324 MHz) (signals assigned to major isomer) δ 22.91, 28.71,30.39, 36.80, 37.04, 43.74, 46.80, 51.25, 52.99, 125.88, 128.06, 136.35. The NMR data are identical to those reported in the literature.[32]

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Chapter Two

STEREOCONTROLLED SYNTHESIS of TETRAHYDROFURAN, PYRROLIDINE, CHROMANOL, AND γ-LACTONE SYSTEMS, and A GENERAL PREPARATION of LACTAMS BY CARBAMOYL RADICAL CYCLIZATION

Introduction

Due to their existence in various natural and significant non-natural products, heterocycles such as tetrahydrofurans,[1] pyrrolidines[2] and lactones[3] have been the focus of many synthetic efforts. Current approaches extend from traditional ionic chemistry to recently developed methodology based on the use of transition metals. Not surprisingly, because radical chemistry has been widely applied in the construction of carbocycles during the last dozen years or so, many reports on heterocycle synthesis using this general strategy have also appeared. These new approaches have, in large part, complemented and at times improved on the more classic methods. The popularity of radical methodology is due to the compatibility of radicals with a large number of functional groups and the increasing experience among synthetic organic chemists in this general area.

The following is a concise review of preparations of heterocycles (tetrahydrofurans, pyrrolidines, γ-lactones and lactams) by radical methods.

I. Radical syntheses of tetrahydrofurans

Substituted tetrahydrofuran units are common heterocyclic substructures in biologically active compounds, such as the polyether and ionophore natural products and the furanose form of carbohydrates[4]. There are many methods[1] available for the construction of tetrahydrofurans, among them are a number of radical methods that have been developed recently. This radical approach can be analyzed in four categories, depending on the relative position of the radical and the radical acceptor.

a. *Radicals β to oxygen (Figure 1).*

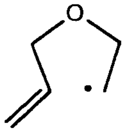
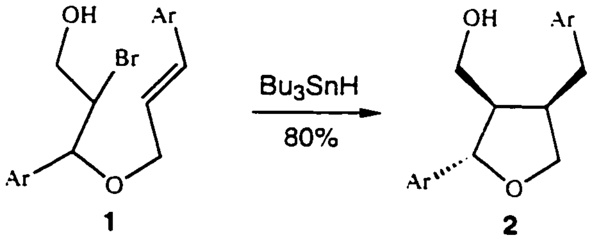


Figure 1

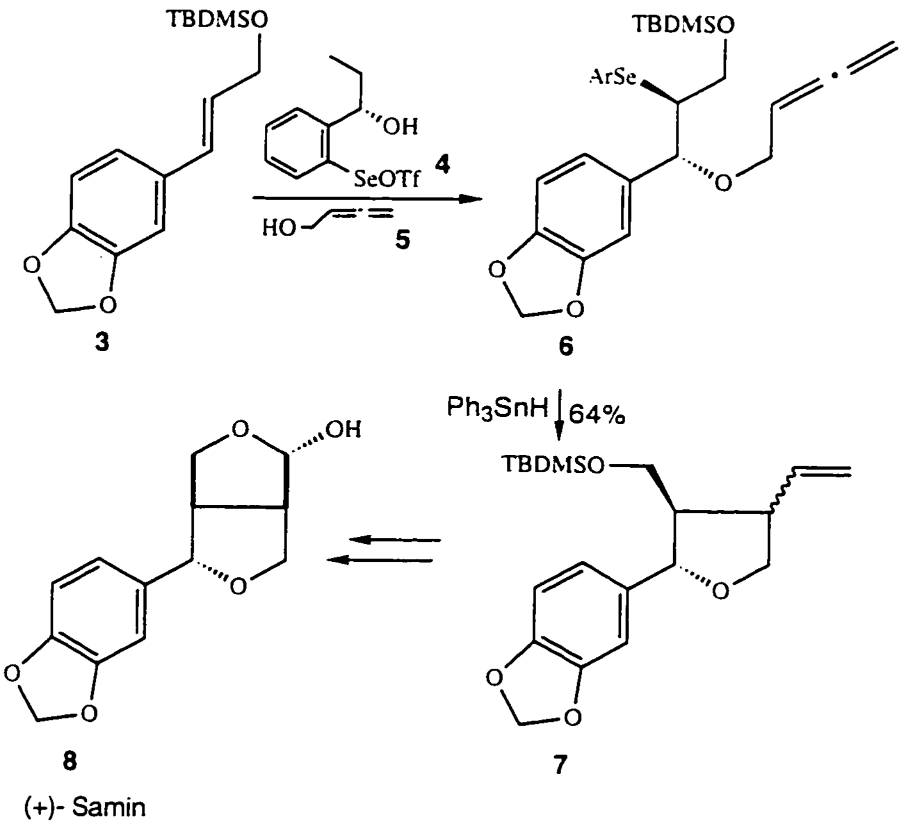
This category is by far the most frequently reported method, and has become popular due to the easy preparation of the radical precursors and the similarity of the ring closure process to the corresponding all-carbon series. A typical example is the synthesis[5] of a 3-substituted tetrahydrofuran **2** in 80% yield. It is noteworthy that the free hydroxy group in the starting bromide **1** does not require protection – a general characteristic of radical reactions.



Ar = 3,4 - methylenedioxyphenyl

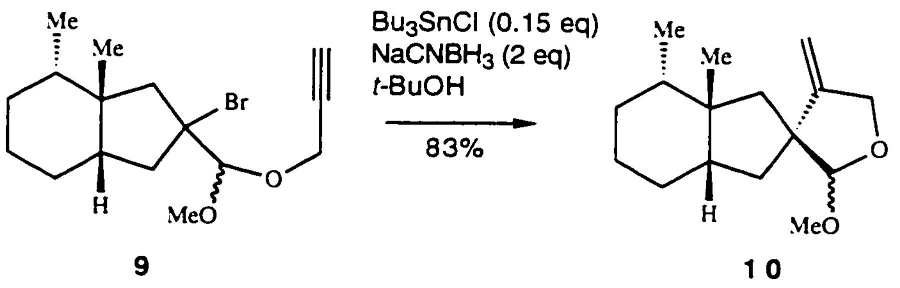
Scheme 1

Starting from selenide **6**, the substituted tetrahydrofuran skeleton of (+)-samin has been prepared and converted into the natural product **8**[6]. The radical step proceeded by 5-*exo* trigonal cyclization onto the allene unit. This work also illustrates the use of a chiral selenium reagent (**4**), which allowed the formation of a chiral radical precursor (**6**) with high de (16:1).



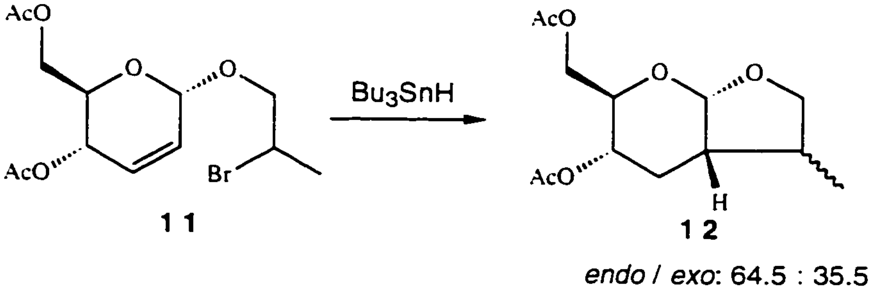
Scheme 2

A method that is catalytic in stannane[7] may also be adopted to achieve satisfactory cyclization yields. This procedure maintains a low tin hydride concentration in the medium, and was used, for example, in the efficient conversion of **9** into **10** (Scheme 3).[8]



Scheme 3

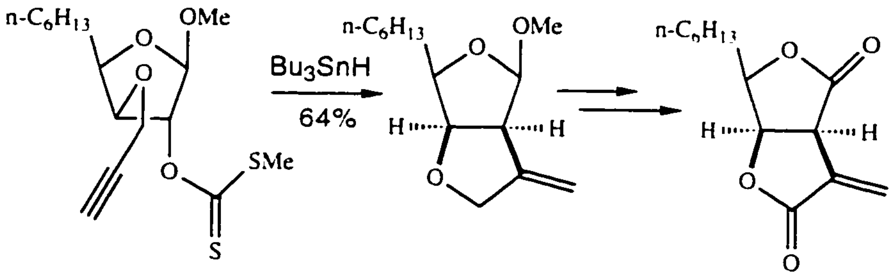
The approach summarized in Figure 1 has been applied many times in carbohydrate systems, and Scheme 4 shows an example from De Mesmaeker's group. In this case[9] the radical generated in the side chain cyclizes onto the monosaccharide ring. While the cis ring fusion is easy to understand, the *endo* orientation of the methyl group in the major product is consistent with the model proposed by Beckwith[10] for the cyclization of 1-substituted hexenyl radicals.



Scheme 4

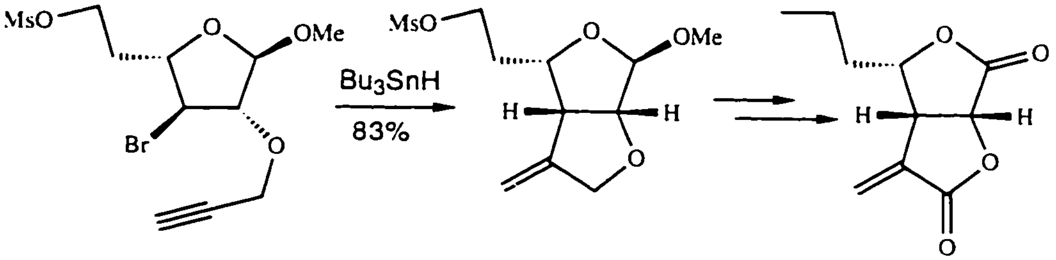
It is also possible to generate the radical on a ring carbon so that the radical adds to an unsaturated side chain, as in the total synthesis of sporothriolide (**15**) (Scheme 5)[11] and of (±)-ethisolide (**18**) (Scheme 6).[12]

In general, the availability of several hydroxy groups in a carbohydrate allows radicals to be generated by Barton deoxygenation, and the radicals can then cyclize onto a suitably located double or triple bond.



1 3 **1 4** **1 5**

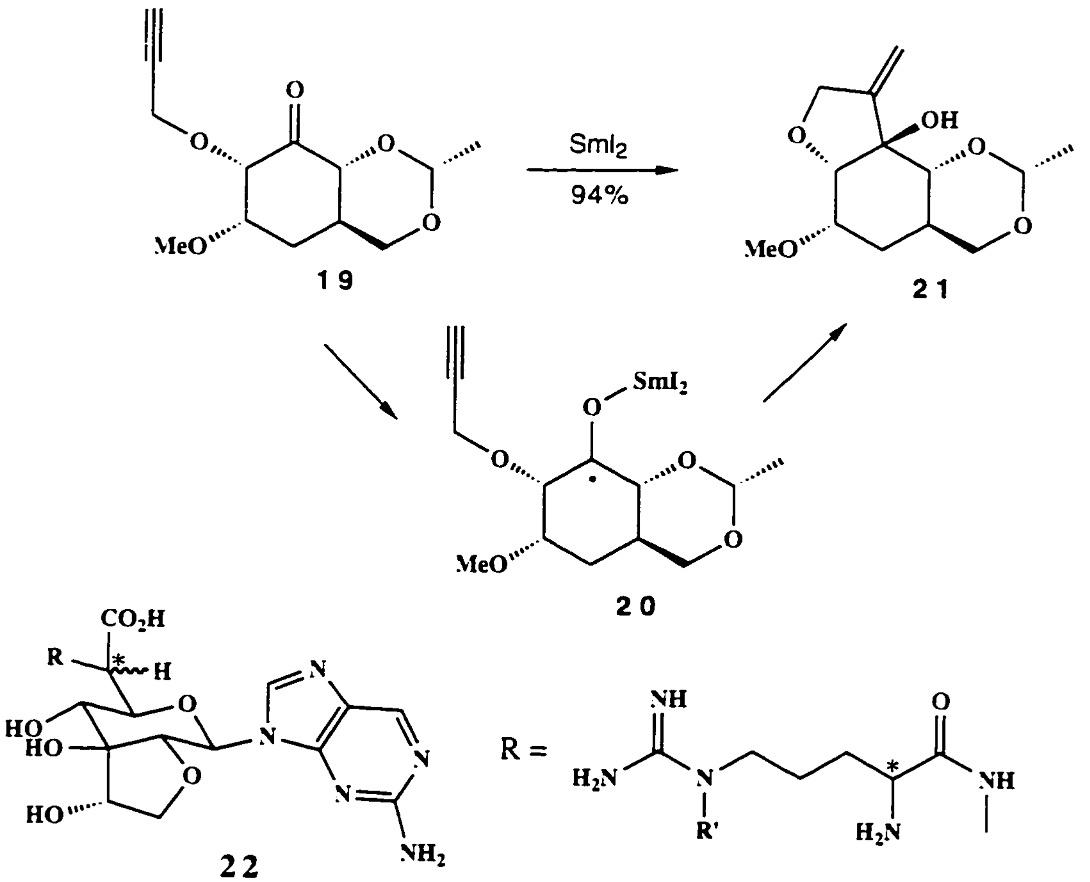
Scheme 5



1 6 **1 7** **1 8**

Scheme 6

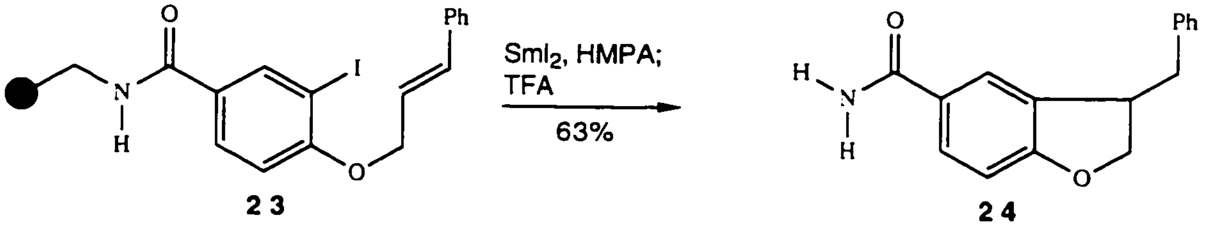
Generation of the β-oxy radicals shown in Figure 1 is not restricted to the use of tin hydrides, and other reagents, such as samarium diiodide, can be used.[13] Such an application is provided by the report[14] of Fairbanks and Sinaÿ in their synthesis of the carbohydrate section of the nucleoside antibiotics minaramycins A and B (Scheme 7). Reaction of samarium diiodide with the carbonyl function generates radical **20**, which cyclizes to give, after workup, the alcohol **21** in 94% yield. This compound represents the carbohydrate sector of the antibiotics.



Miharamycin A (R' = OH), B (R = H).   * stereochemistry not defined yet.

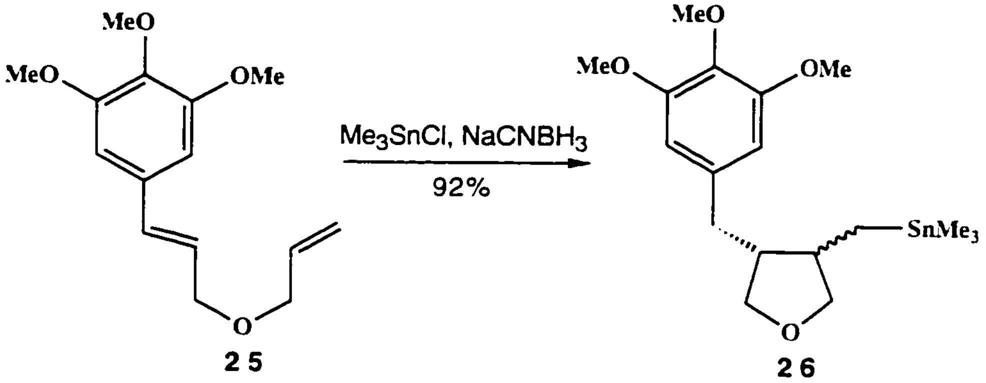
Scheme 7

Another example of the use of samarium diiodide is to be found in a recent application to combinatorial chemistry (Scheme 8).[15] Here the radical reaction was conducted on a resin-bound substrate, and afforded the cyclized product in reasonable yield, after cleavage from the resin.

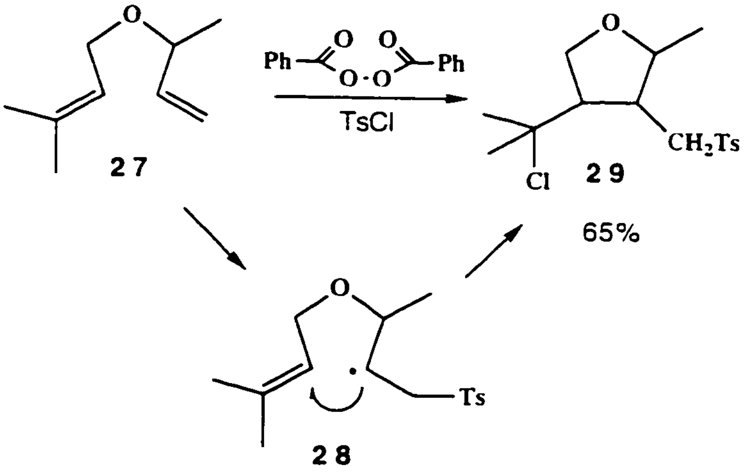


Scheme 8

In addition to the above mentioned methods, β-oxy radicals can be generated by Kolbe electrolysis[16] or *in situ*, through the addition of a radical onto the double bond of an allyl ether unit, as shown in Schemes 9 and 10. Compound **26** was formed by addition of trimethylstannyl radicals to the allyl ether **25**, followed by cyclization.[17] In the case of Scheme 10, the toluenesulfonyl radical performs the same role, and is itself generated from tosyl chloride. This group transfer reaction was terminated through the abstraction of chloride from tosyl chloride by the tertiary radical formed after cyclization.[18]



Scheme 9



Scheme 10

b. Radicals γ to oxygen (Figure 2).

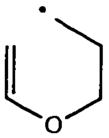
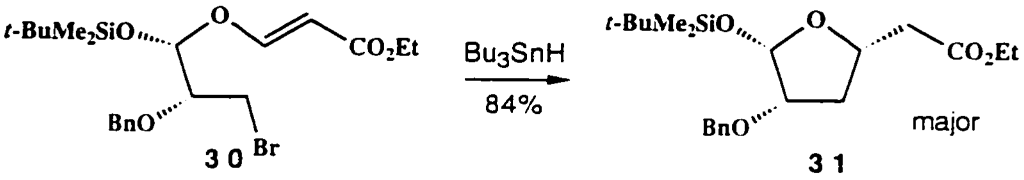


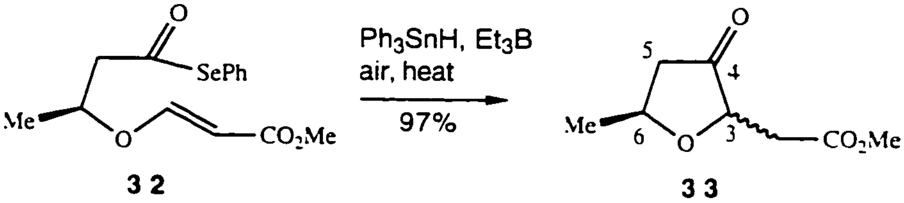
Figure 2

Radical closures onto the double bond of a vinyl ether are not common due to the difficulty in preparing suitable substrates. A radical sequence (Scheme 11) has been reported[19] in which a radical from an sp^3 carbon adds efficiently to a β-alkoxyacrylate moiety. In this process, cyclization is clearly facilitated by the electron-withdrawing ester group. The trisubstituted tetrahydrofuran was obtained in 84% yield.



Scheme 11

Acyl radicals also undergo this type of cyclization,[20] and very high yields can be obtained under optimized conditions. In the process summarized by Scheme 12, the 3,6-*cis* isomer was isolated as the major product (*cis/trans* 94/6). In the example of Scheme 12, it is not clear what effect, if any, complexation of triethylborane has on the double bond reactivity.



cis/trans 94/6

Scheme 12

c. *Oxygen-centered radicals (Figure 3).*

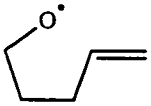
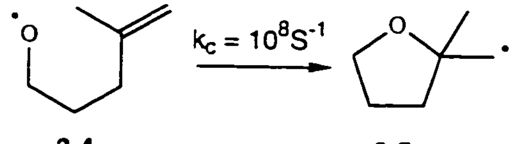


Figure 3

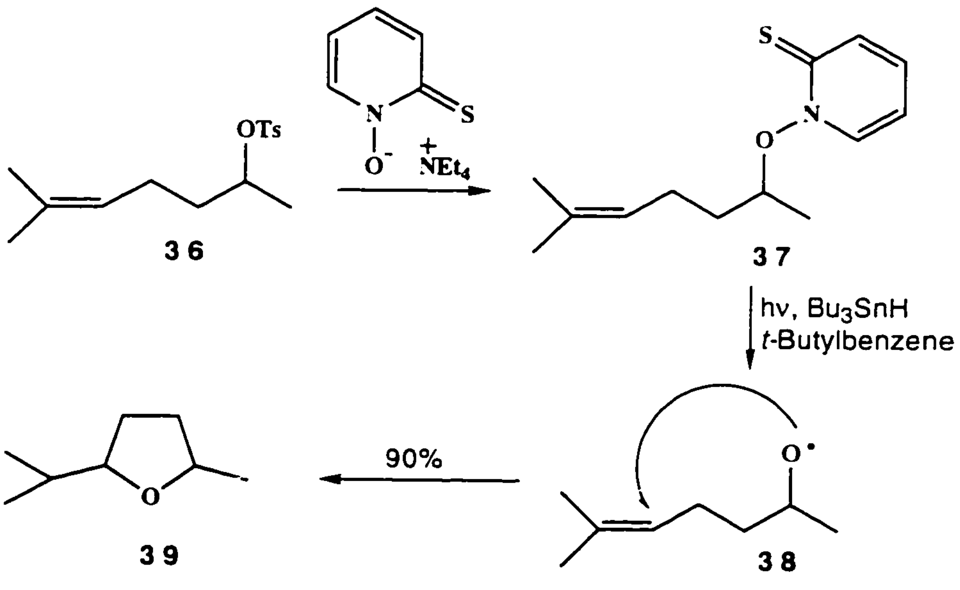
The addition of an alkoxy radical to a double bond is a very fast process.[21] Strictly *exo* selectivity is followed even when steric hindrance exists, and the reaction generally is *irreversible* (Scheme 13).[21]



34 **35**

Scheme 13

However, the adoption of oxygen centered radicals in synthesis is not widespread, owing to the occurrence of serious competing reactions such as 1,5 hydrogen transfer, β-fragmentation,[22] and the limited methods available for generating these radicals. However, simple tetrahydrofurans have been made by cyclization of oxygen-centered radicals, and a recent example is shown in Scheme 14.[23]



Scheme 14

d. Radicals α to oxygen (Figure 4).

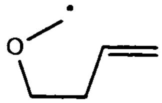
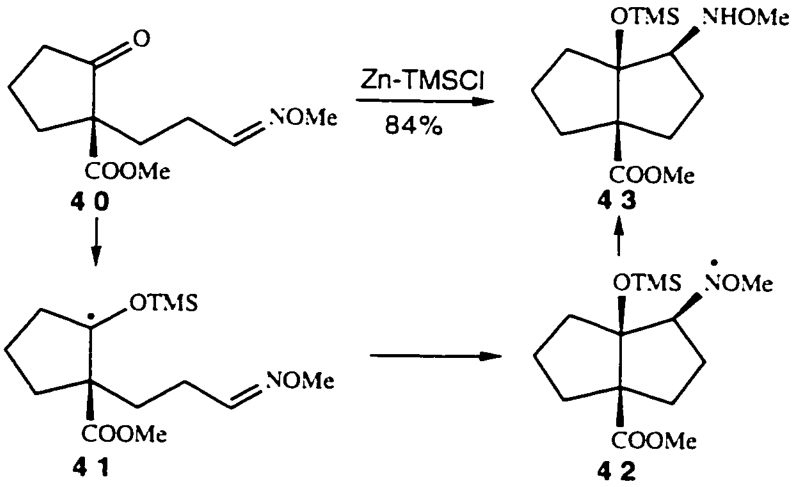


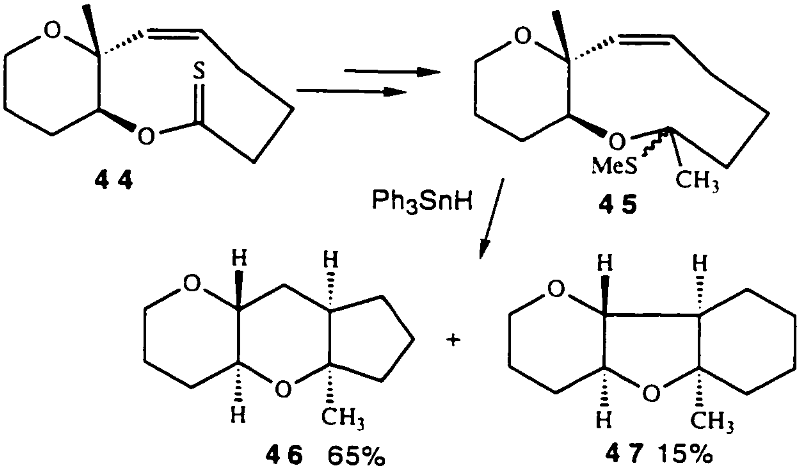
Figure 4

Surprisingly, the application of alkoxymethyl radicals in the syntheses of tetrahydrofurans is not common, even though such an approach looks appealing, since, in principle, the precursor can be made by simply attaching a one-carbon synthon onto a homoallylic or related alcohol. It should be pointed out that even though many syntheses involving an alkoxymethyl radical have been reported,[24] the oxygen atom in most of these cases was not part of the final ring system and the radical α to the oxygen was mostly generated by reduction of a carbonyl, as illustrated by the transformations summarized in Scheme 15.[24a] Here a radical α to oxygen was formed by reductive addition of zinc metal, and the initial carbonyl represented a masked tertiary alcohol function in the final product (**43**).



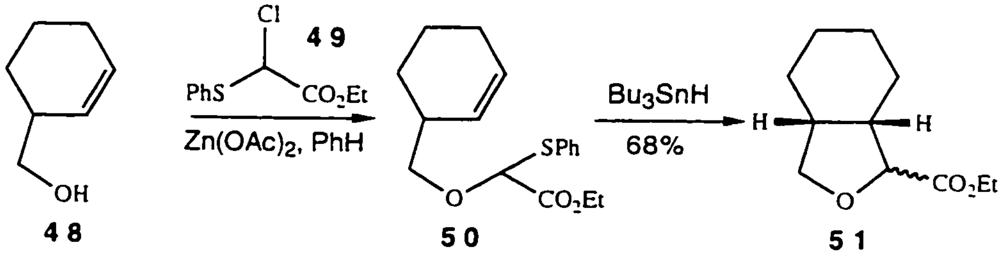
Scheme 15

Usually a substituent group is connected to the alkoxymethyl radical moiety in order both to stabilize the radical, and to facilitate synthesis of the precursor. For example, in the synthesis of ring fused ethers, a methylthio group was formed α to an ether oxygen by nucleophilic addition to a thiolactone, followed by *S*-alkylation (**44-45**, Scheme 16).[25] Radical cyclization then provided a mixture of compounds with the tetrahydrofuran **47** as the minor product.



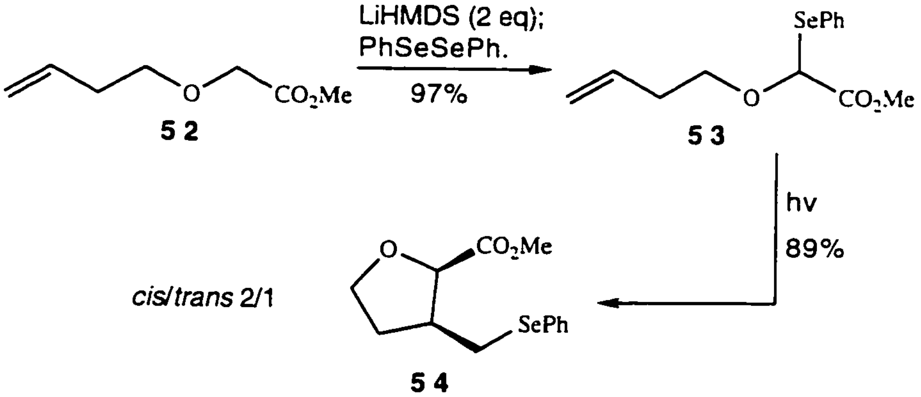
Scheme 16

In a different, but more general approach (Scheme 17), the Speckamp group has reported[26] the synthesis of radical precursors stabilized by an ester, as shown in Scheme 17. Cyclization of **50** afforded the *cis* ring fused compound **51** in 68% yield, as a 1:1 mixture of epimers.



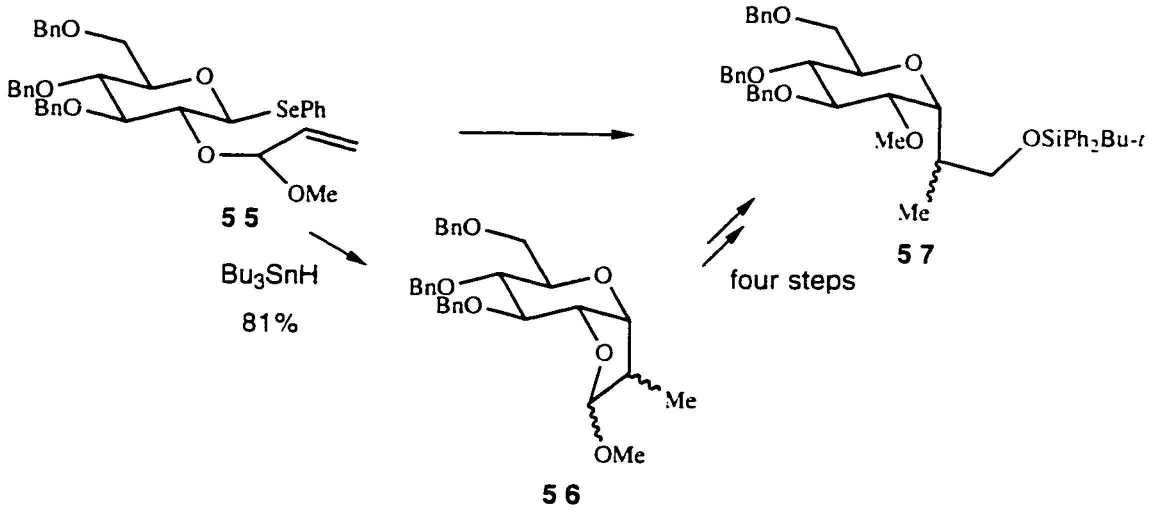
Scheme 17

Recently, Renaud *et al.* reported[27] a more efficient way to introduce a phenylseleno group in similar substrates. As shown in Scheme 18, the existence of the ester function makes it possible to generate a carbanion, which was quenched with PhSeSePh to afford the α-alkoxyalkyl radical precursor **53**. Selenide **53** underwent very efficient cyclization to **54**.



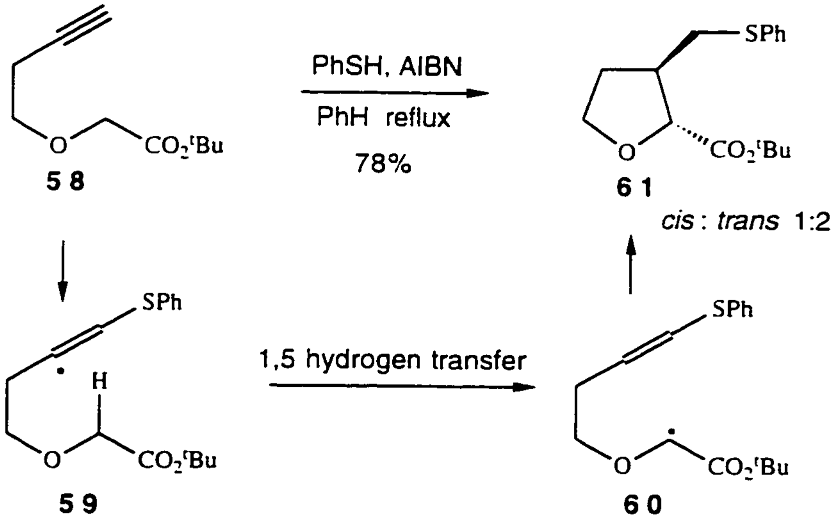
Scheme 18

Radicals at the anomeric center of a carbohydrate can be generated with exceptional ease, and many applications are found in *C*-glycosylation. An example related to tetrahydrofuran preparation is presented in Scheme 19.[28]



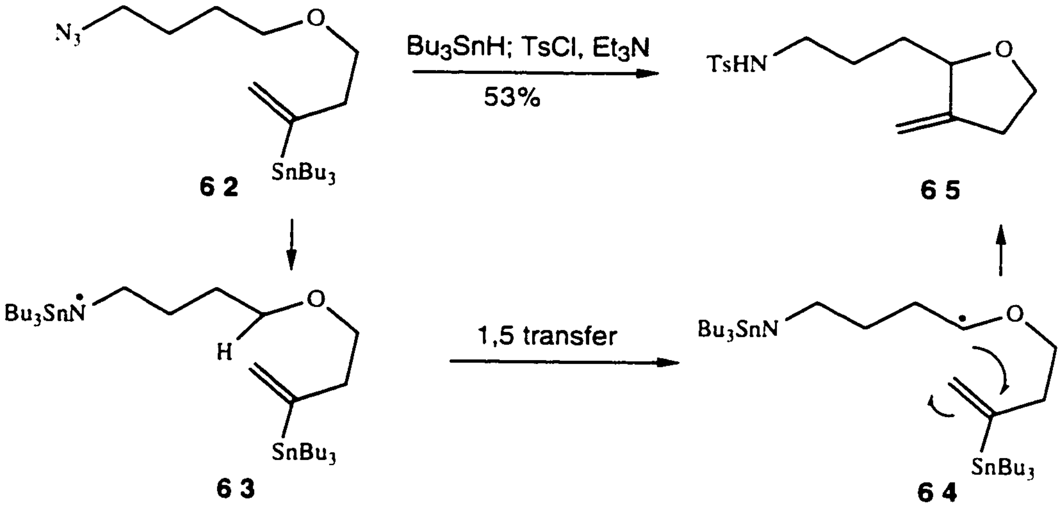
Scheme 19

Generating an alkoxyalkyl radical by means of intramolecular hydrogen transfer is also possible, as Burke *et al.* have shown[29] (Scheme 20). In this case, the addition of a PhS radical to the double bond formed a reactive olefinic radical **59**, which is capable of abstracting hydrogen intramolecularly to form a more stable radical species **60**. Cyclization of **60** then afforded the final tetrahydrofuran **61** in 78% overall yield, as a 2:1 isomer mixture in favor of the trans product. This isomer distribution is the opposite of that found by the related sequence of Scheme 18; the reasons for the difference are not clear.



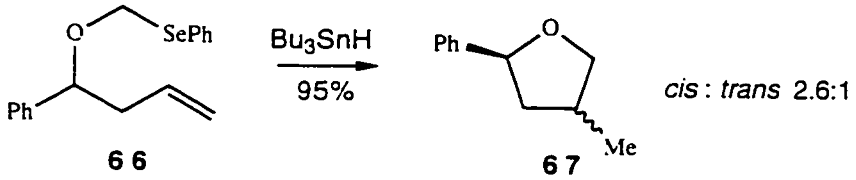
Scheme 20

Another example was reported recently[30] (Scheme 21). In this case, 1,5 hydrogen transfer was induced by an aminyl radical derived from stannane reaction of an azide moiety. This sequence was followed by consecutive 5-*exo* cyclization and β-elimination of tributylstannyl radical. A 53% yield was obtained after tosylation of the amine.

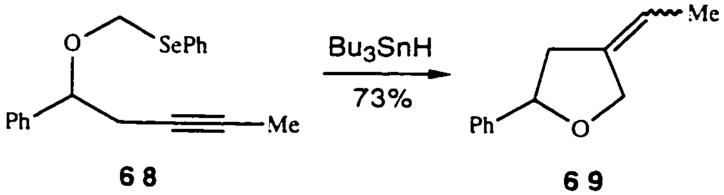


Scheme 21

Systematic studies of tetrahydrofuran synthesis using alkoxymethyl radicals were conducted in Rawal's group.[31] Synthetic routes for the preparation of appropriate radical precursors were also examined and these results will be discussed later in this chapter. Two examples from Rawal's group of alkoxymethyl radical cyclization onto double and triple bonds are shown in Schemes 22 and 23. In both cases 5-*exo* cyclization occurred efficiently, and the method is clearly a good one for the preparation of tetrahydrofurans, although there is little control over the relative stereochemistry of substituents.



Scheme 22



Scheme 23

II. Radical approach to pyrrolidines

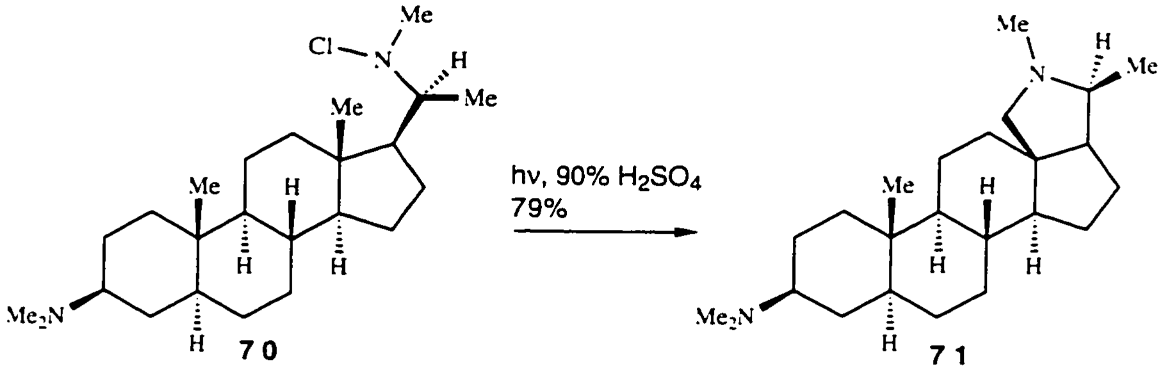
The synthesis of pyrrolidines has received extensive attention due to the fact that many members of this compound class have significant biological properties.[2]

General approaches include the intramolecular ene strategy developed by Oppolzer,[32] electrophilic cyclization of unsaturated amine derivatives,[33] tandem cationic aza-Cope-Mannich sequences developed by Overman,[34] and the 1,3 dipolar cycloaddition of azomethine ylides with olefins, studied by Padwa,[35] As has occurred in other areas of synthesis, radical-based approaches have also been applied to the synthesis of pyrrolidines, and a concise review is presented in the following section.

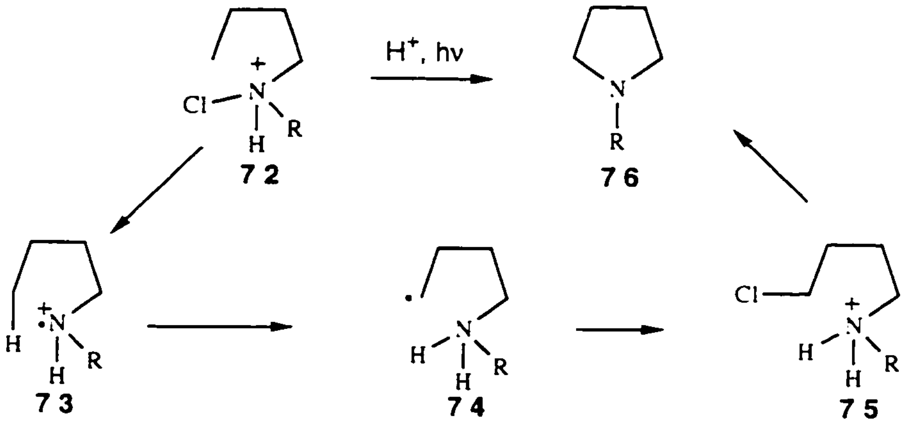
A. *Nitrogen centered radicals.*

Nitrogen centered radicals have long been studied and occasionally applied in the synthesis of nitrogen containing heterocycles,[36, 37] but the subject has not been a main area of synthetic radical chemistry, due partly to the unusual reactivity of nitrogen centered radicals[36] and, until recently, the lack of good methods for their generation. However, recently, one can observe a clear development of the subject from both a theoretical and synthetic perspective.

The Hofmann-Löffler-Freytag[37] reaction was probably the first example of radical chemistry leading to pyrrolidines from acyclic amines, and the reaction has been used in the synthesis of complex molecules, as in Corey's route to dihydroconessine[38] (Scheme 24). The mechanism[37] involves homolytic cleavage of the Cl-N bond by irradiation to form the cationic radical **73** in the strongly acidic reaction medium. This nitrogen radical abstracts hydrogen by 1,5 hydrogen transfer to generate a new radical **74**, which then affords chloro amine **75**, and upon neutralization the pyrrolidine **76** is formed.



Scheme 24



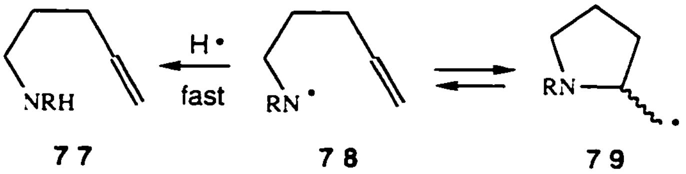
Scheme 25

The applicability of the Hofmann-Löffler-Freytag process is limited because of the requirement for a strongly acidic reaction medium, which few functional groups can tolerate without protection.

Recently, cyclizations of nitrogen centered radical have been reported which adopt milder conditions and offer better compatibility with common functional groups. These new developments include the use of aminyl, iminyl, and amidyl radicals. The behavior of each of these will now be discussed.

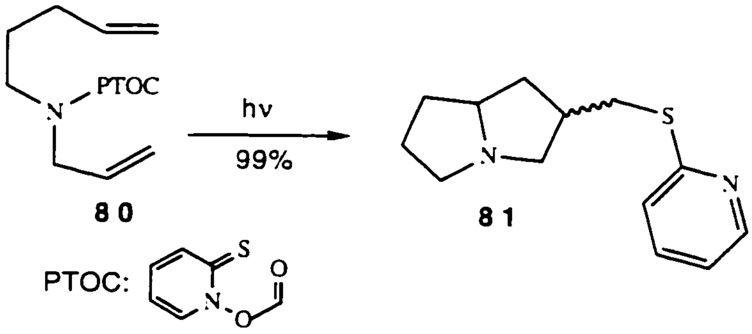
a. *Aminyl radicals.*

Neutral aminyl radicals are nucleophilic and they usually abstract hydrogens swiftly via inter- or intramolecular pathways.[36] The rate of direct hydrogen abstraction from a hydrogen donor is generally faster than the competing cyclization.[22] Moreover, unlike alkoxy radicals, the aminyl radical cyclization is *reversible*.[22] The cyclization rate of *ca* 3×10^3 s^{-1} is even smaller than the reverse ring opening process, whose rate is *ca* 7×10^3 s^{-1} (Scheme 26).[22]



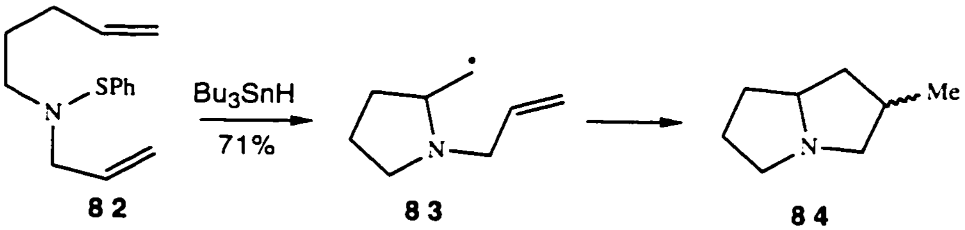
Scheme 26

In order to overcome the inherent disadvantages of aminyl radicals for use in cyclization reactions, new strategies and modifications of traditional practice have been investigated. Newcomb *et al.* adopted an atom transfer approach by using the Barton ester **80** (Scheme 27).[39] Upon irradiation, an aminyl radical was generated and cyclized in a tandem sequence to afford the product **81** in 99% yield. The excellent yield of this reaction may be attributed to the efficient addition of the aminyl radical onto the double bond followed by two subsequent irreversible reactions, namely further 5 *exo* cyclization and trapping by the sulfur group.

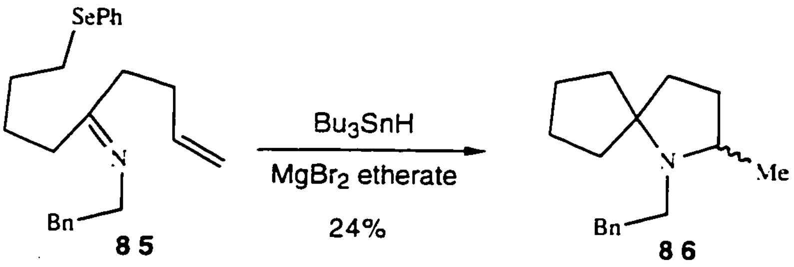


Scheme 27

Bowman *et al.* reported[40] an extensive study on the generation of aminyl radicals through the cleavage of weak N-S bonds in aryl sulfenamides. When tin hydrides are used, the cyclization usually proceeds in poor yield, unless side reactions are avoided by special means, as in the previous case, and in the reaction shown in Scheme 28, where a tandem sequence was again used for this purpose. The second cyclization is irreversible.



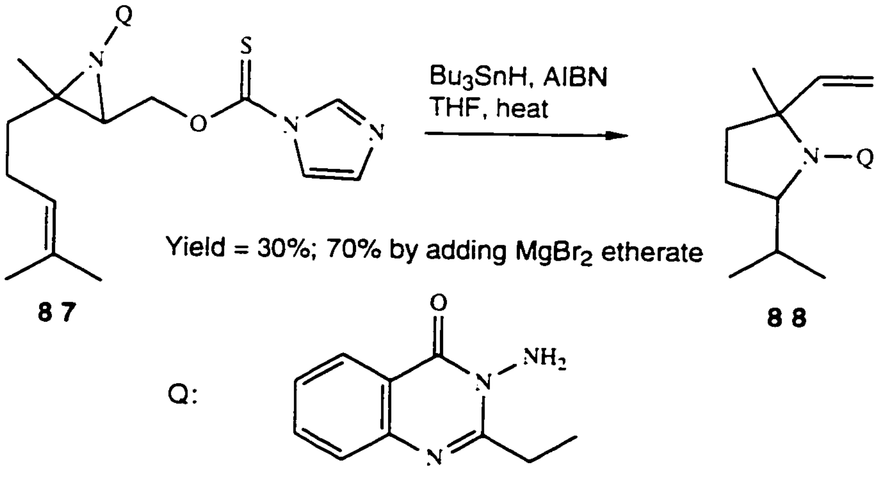
Scheme 28



Scheme 29

In the reaction summarized in Scheme 29[41] a Lewis acid was added to make the intermediate aminyl radical less likely to abstract hydrogen and also to impede direct reduction. It is now established that in the presence of either mineral acid or Lewis acid, a thus-formed cationic nitrogen radical becomes more stable and electrophilic, and these changes make a high yielding cyclization onto double or triple bonds possible.

The special effect of Lewis acid additives on aminyl radical reactivity is displayed again in Scheme 30.[42] In this case, the aminyl radical was formed by opening of the aziridine ring. By adding magnesium bromide, the cyclization yield was doubled.



Scheme 30

b. Iminyl radicals.

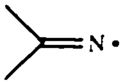
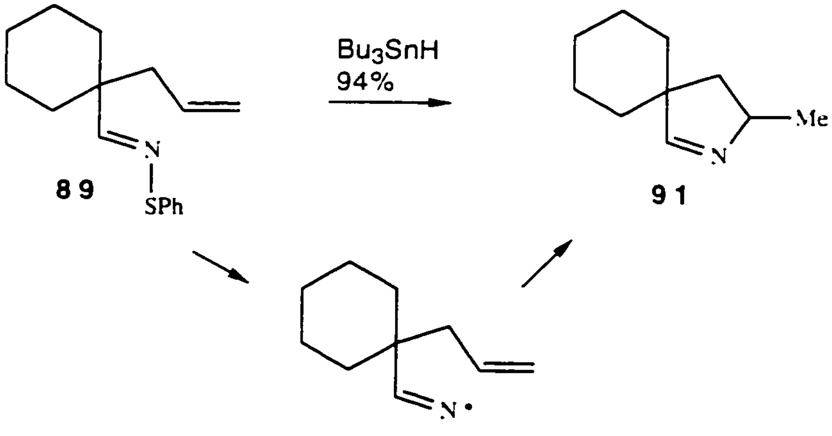


Figure 5

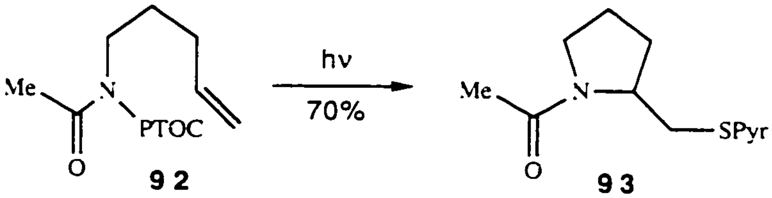
Iminyl radicals (Figure 5 and Scheme 31) are electrophilic and readily cyclize onto weakly nucleophilic alkenes.[43] They can be generated from many substrates such as oxime benzoates,[44] xanthyl hydrazones,[45] S-aryls,[46] etc. Many examples have been published of cyclizations leading to pyrrolidine derivatives,[43-46] and a typical process is shown in Scheme 31.[46]



Scheme 31

c. Amidyl radicals.

Amidyl radicals are generated by cleavage of *N*-substituted amides, and suitable nitrogen substituents include halogen,[47] nitroso,[48] and PTOC.[49] An example with the later is shown in Scheme 32.



Scheme 32

These special aminyl radicals with an electron-withdrawing group attached on the nitrogen, have significantly different behavior, and competing hydrogen transfer does not pose as a problem.[22]

B. α-Amino radicals (Figure 6).

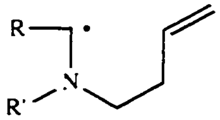
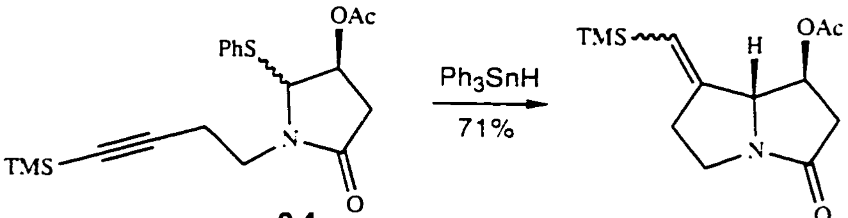


Figure 6

Carbon centered radicals α to nitrogen have been studied extensively by both physical organic chemists and synthetic chemists. It is believed[50] that a radical next to a heteroatom such as oxygen and nitrogen is greatly stabilized. A three electron two orbital theory has been proposed[50] to account for this stability.

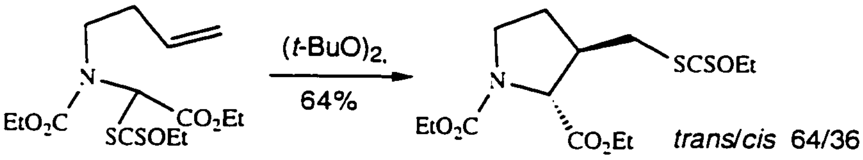
The use of α-amino radicals to gain access to pyrrolidines was pioneered by Hart *et al.* in the early stages of modern radical chemistry. An illustrative example from Hart's extensive work is shown in Scheme 33.[51] The substrate **94** was prepared in several steps by reduction of a lactam carbonyl group, followed by substitution of the resulting hydroxyl by a phenylthio group. Treatment of **94** under standard radical conditions afforded the cyclized compound **95**. The stereochemistry was controlled by the acetyl group, and **95**, with the ring fusion hydrogen *syn* to the acetate was the major product (71% yield).



94 **95**

Scheme 33

Speckamp *et al.* have shown the possibility of making various pyrrolidines by using carbon centered glycine radicals, as summarized in Scheme 34.[52] The reaction was conducted under group transfer conditions, where the newly formed radical after cyclization was trapped by the sulfur species from **96** in the solution to generate another nitrogen centered radical.



96 **97**

Scheme 34

There are not many applications of α-amino radicals in pyrrolidine synthesis, despite the cyclization efficiency. This situation is mainly due to the difficulty of making the radical precursors. It is obvious from the last two examples, that in these particular cases, preparation of the starting materials was greatly facilitated by the presence of appropriate functional groups in the molecule, and a close examination of this aspect of α-amino radical chemistry will be presented later in this chapter.

C. *β-Amino radicals (Figure 7).*

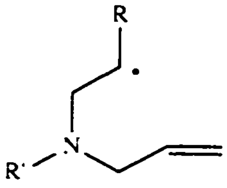
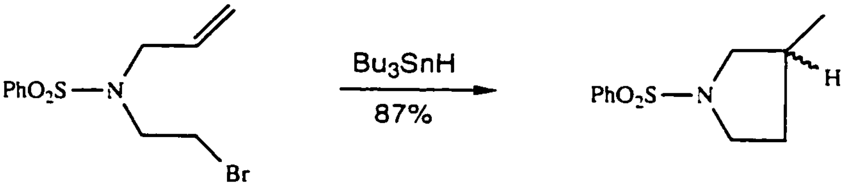


Figure 7

Unlike their α-amino counterparts, the β-amino radical precursors are much easier to make, as the attachment of an allylic unit on the nitrogen atom is a simple transformation.

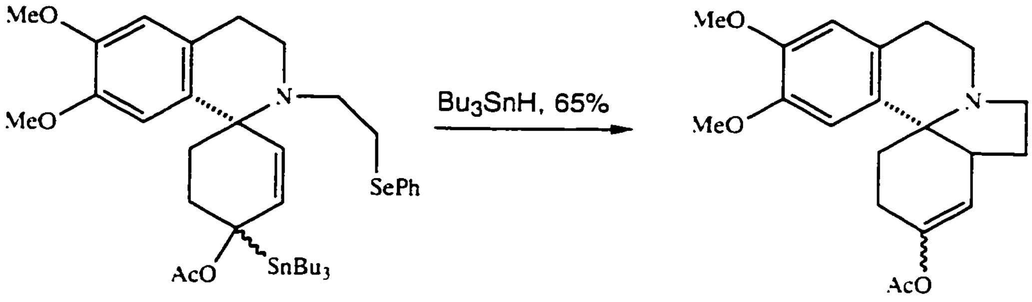
Padwa *et al.* reported[53] the synthesis of several simple pyrrolidines through this approach (Scheme 35). The high yield in the cyclization proved that the reactivity of β-amino radicals is very close to that of the all carbon analogs.



98 **99**

Scheme 35

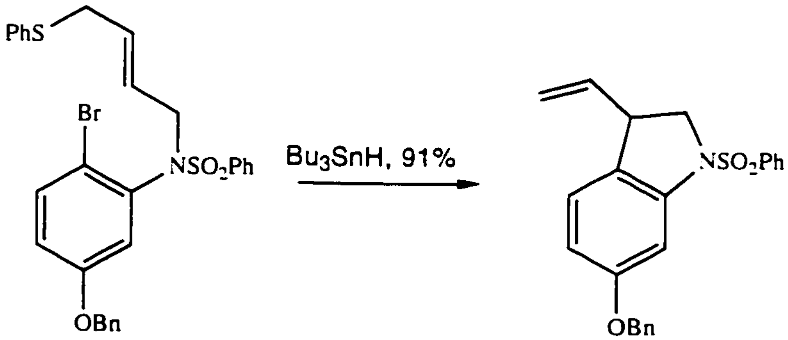
A variation of this method has been applied[54] in the key step during a synthesis of 3-demethoxyerythratidinone. The installment of a Bu_3Sn unit in the molecule makes this particular reaction an intramolecular Keck allylation.[55]



100 **101**

Scheme 36

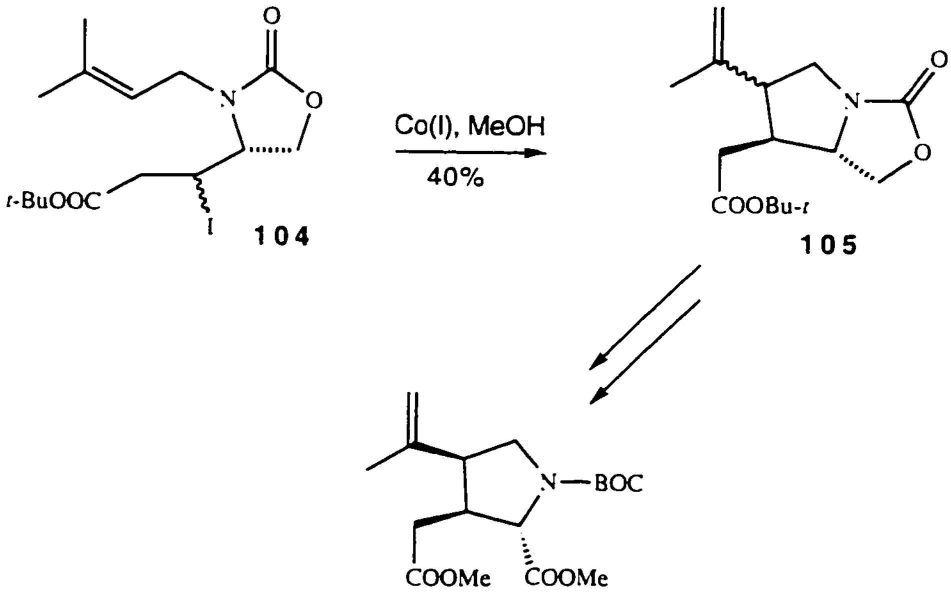
The bonds connecting the halogen-bearing carbon and the nitrogen can be part of an aromatic ring, and an example of this type is provided by synthetic work towards (+)-CC-1065 (Scheme 37).[56] Here the allylic group that is expelled is a PhS radical, and the reaction proceeded in very high yield.



102 **103**

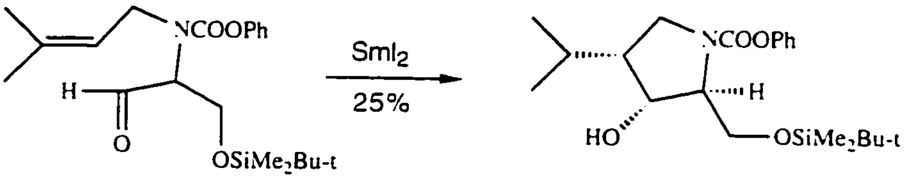
Scheme 37

β-Amino radicals can be generated by using reagents other than tin hydrides, as reported[57] for a synthesis of (-)-α-kainic acid (Scheme 38). A cobalt(II) complex was formed, and under visible light irradiation C-Co bond was cleaved homolytically. The resulting β-amino radical cyclized, and the newly formed radical was trapped by the cobalt species. Dehydrocobaltation then provides pyrrolidine **105** as a mixture of isomers in moderate overall yield (less than 40%).



Scheme 38

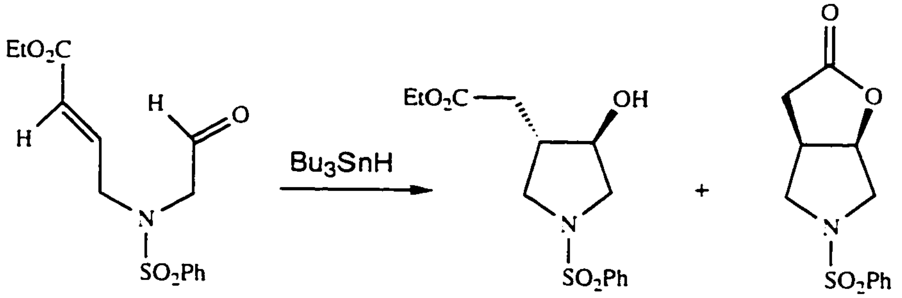
In another paper from the same group at Oxford,[58] the use of samarium diiodide as a radical mediator was described. Thus the reductive addition of samarium diiodide onto the aldehydic carbon-oxygen double bond in **107** afforded a transient β-amino radical, which cyclized to afford the pyrrolidine **108**. The yields of these reactions range from 0 to 76%, depending on the nature of the nitrogen and oxygen protecting groups and the type of radical acceptor (alkene or alkyne).



107 **108**

Scheme 39

The same type of reaction can be accomplished[59] by the standard tin hydride method (Scheme 40). In the example shown, the cyclization afforded an equal amount of *trans* and *cis* isomers. The latter spontaneously formed the fused lactone **111**.

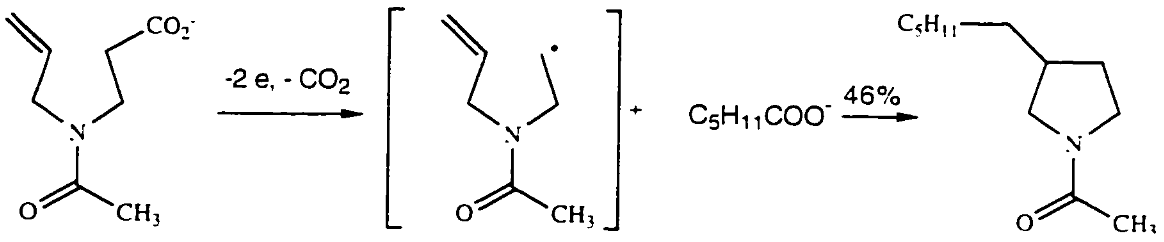


109 **110** **111**

33% 32%

Scheme 40

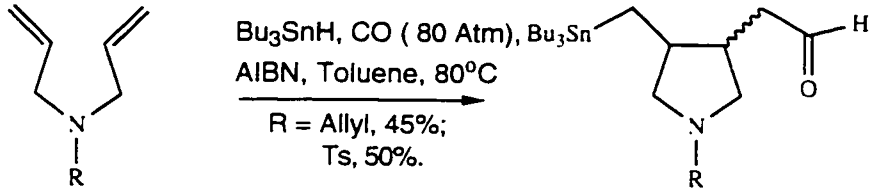
It is not surprising that β-amino radicals generated by the electrochemical Kolbe method also cyclize to pyrrolidine compounds. For example, carboxylate **112** gave[60] a moderate yield (50%) of pyrrolidone **114** (Scheme 41). However, the disadvantage of this non-chain radical reaction is the requirement of a large excess of trapping agent (in this case, $C_5H_{11}CO_2H$) present in the medium.



112 **113** **114**

Scheme 41

More recently, a carbonylation process has been reported[61] (Scheme 42) in which a β-amino radical generated by addition of a Bu_3Sn radical to a double bond cyclizes to form the pyrrolidine skeleton. The new radical was then trapped by carbon monoxide in the system to afford the pyrrolidine aldehydes **116**.



115 **116**

Scheme 42

D. γ-Amino radicals (Figure 8).

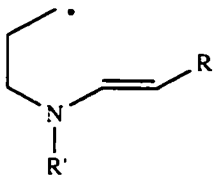
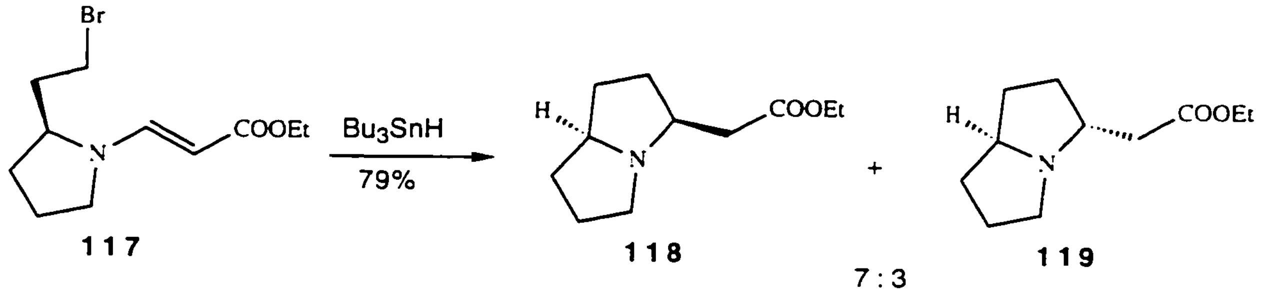


Figure 8

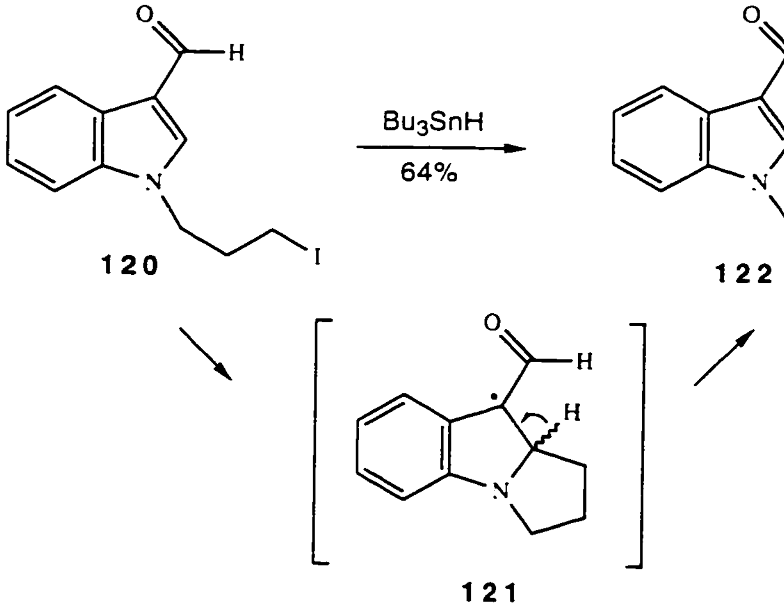
In order to generate a pyrrolidine ring using a γ-amino radical the double bond has to be part of an enamine system. From a synthetic point of view it is usually difficult to construct such a structure and, as a result, few examples of this category are to be found in the literature.

Lee *et al.*[62] were able to prepare a series of pyrrolidines via γ-aminoacrylates similar to **117** (Scheme 43). In the particular case shown, the cyclization afforded a 7:3 mixture of isomers **118** and **119**.



Scheme 43

In a similar approach, a γ-amino radical was found to cyclize onto the enamine moiety of an indole structure (Scheme 44).[63] Quite interestingly, the indole aromatic system was restored by an unexpected oxidative elimination process following the cyclization (Scheme 44).



Scheme 44

E. Reverse addition, i.e., addition of a carbon radical onto a C-N multiple bond (Figure 9).

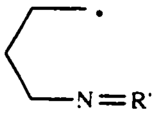
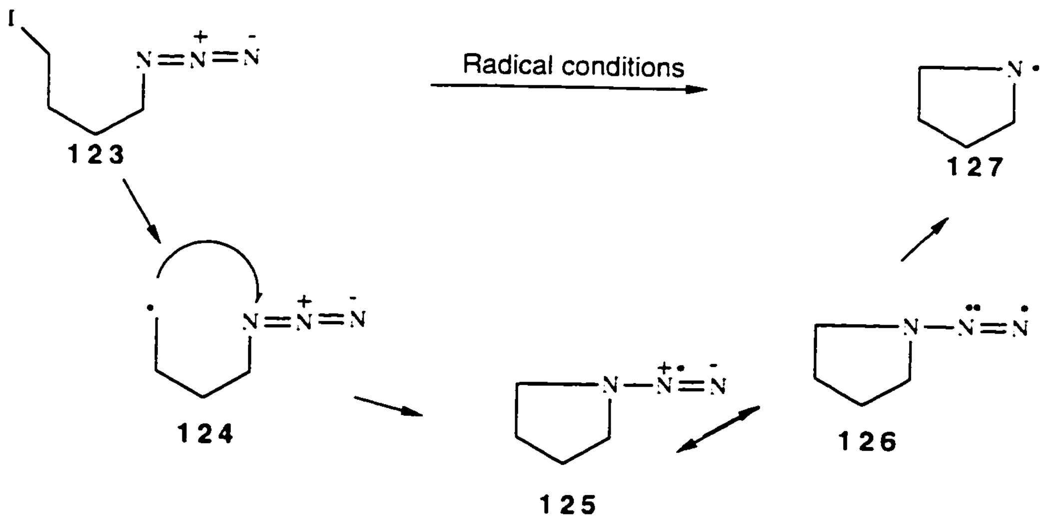


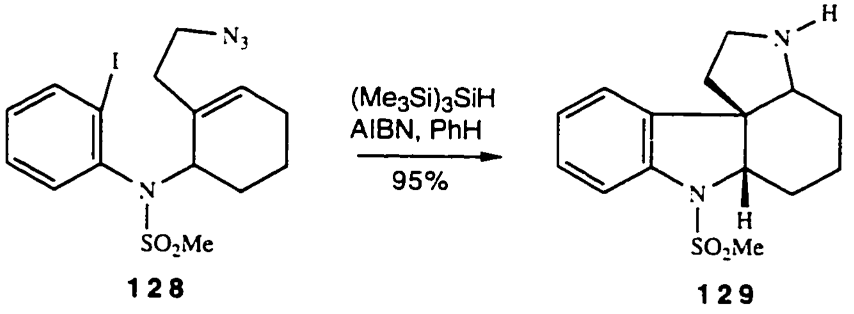
Figure 9

Recently Kim[64] has developed a novel sequence that is outlined in Scheme 45. A carbon radical was generated by the normal tin hydride method at the δ position from the nitrogen terminus. This radical cyclized onto the azide nitrogen double bond, and resulting in displacement of one equivalent of nitrogen. The final aminyl radical was then quenched by abstracting hydrogen from the stannane.



Scheme 45

The merit of this methodology was clearly displayed[65] in a synthetic approach to aspidospermidine (Scheme 46). In a single step, three fused rings were established with high stereochemical control and in 95% yield. The weak hydrogen donor tris(trimethylsilyl)silane [$(Me_3Si)_3SiH$] was adopted in this case instead of tin hydride in order to facilitate the tandem process by suppressing premature hydrogen abstraction from stannane.



Scheme 46

F. Synthesis of pyrrolidines from γ-lactams.

Pyrrolidines can also be approached indirectly via synthesis and carbonyl reduction of γ-lactams.

The radical preparation of lactams can be classified in the same way as was done for the preparation of simple pyrrolidines.

a. β-Amido radical.

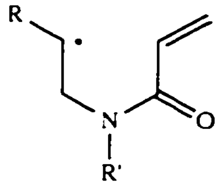
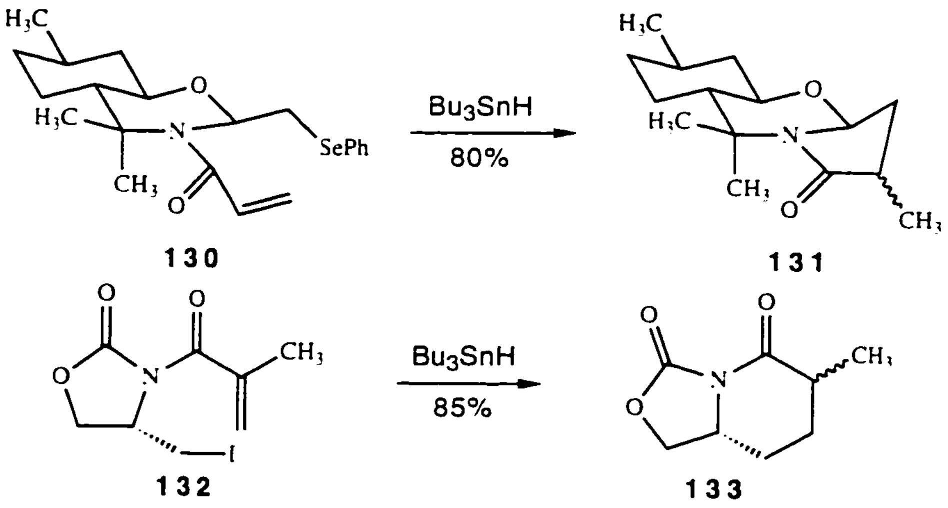


Figure 10

β-Amido radicals generated in acrylamide derivatives (see Figure 10) may cyclize in two different ways – the 5-*exo* mode leading to the γ-lactams,[66] or the 6-*endo* one producing the six-membered analogs. This latter pathway is frequently favored when the α position of the carbonyl is substituted, and this preference is shown in the second of the examples in Scheme 47.[67]



Scheme 47

b. α-Acyl radicals (Figure 11).

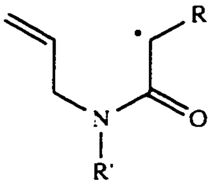
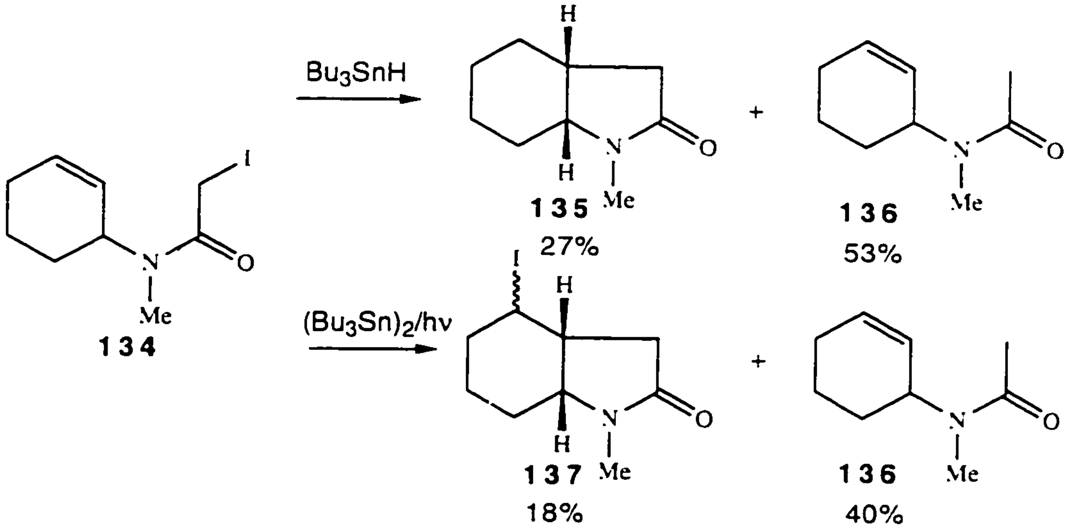


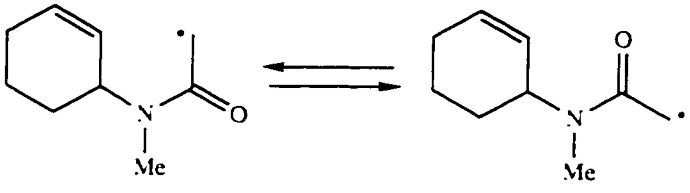
Figure 11

The adoption of a radical center α to the carbonyl position would appear attractive due to the easy assembly of the required substrates. However, the preferred conformation of the resulting amides may not be appropriate for cyclization.



Scheme 48

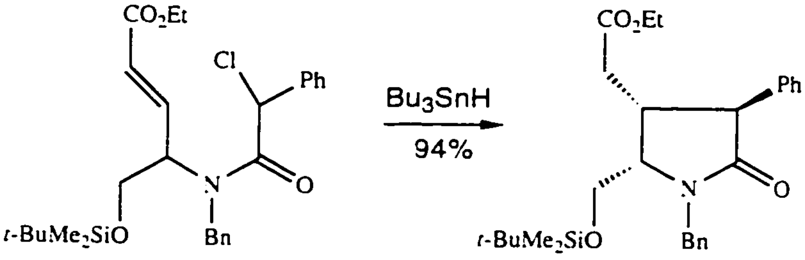
As shown in Scheme 48,[68] when the cyclization of **134** was conducted under high dilution conditions using tributylstannane, the desired lactam **135** was obtained in a yield of only 27%, while the yield of direct reduction product was 53%. Even under standard atom transfer conditions, which should avoid the reduction problem significantly, **136** was still isolated as the major product. It is assumed that an equilibrium mixture of conformers exists, as shown in Scheme 49, due to the barrier of restricted rotation about amide bonds. Only conformer **138** is capable of cyclization. Since the lifetime of the wrong rotamer is generally shorter than that of amide bond rotation, a large percentage of direct hydrogen abstraction is observed, resulting in the main product **136**.



138 **139**

Scheme 49

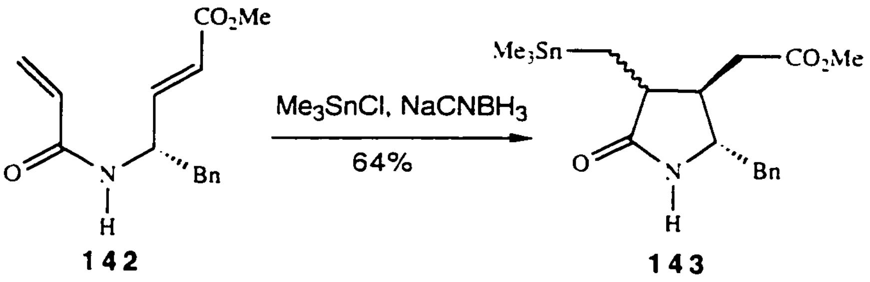
Despite the problems arising from unfavorable conformations, it is still possible in some cases to conduct such cyclizations. Parsons *et al.* reported[69] a few γ-lactam syntheses (Scheme 50). The yield in such closures was found to be determined by the substituents on the radical-bearing carbon, and the case where this carbon carried a phenyl group was particularly favorable.



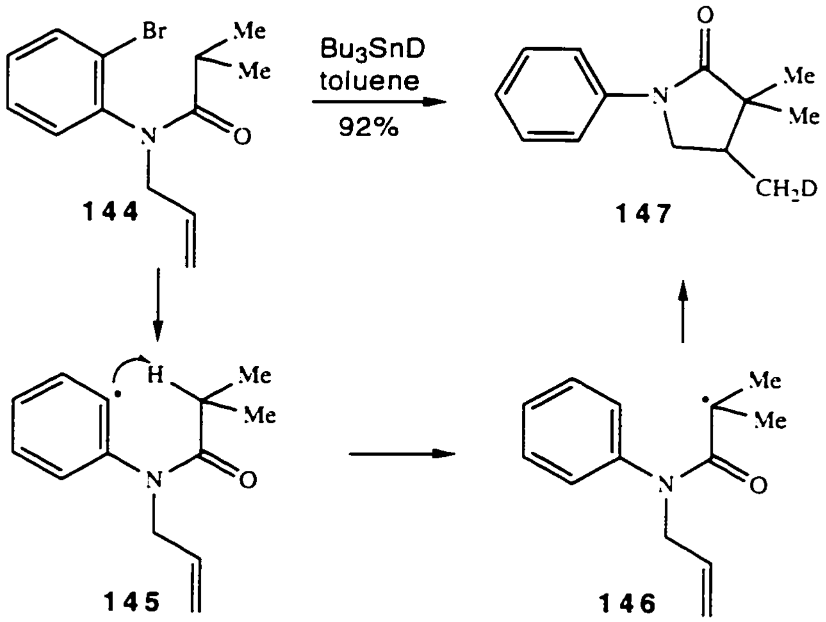
140 **141**

Scheme 50

Radicals α to an amide carbonyl can also be generated by a pre-cyclization/addition of a radical to a double bond (Scheme 51),[70] or through intramolecular radical translocation, as illustrated in Scheme 52.[71]



Scheme 51



Scheme 52

c. *5-Endo cyclizations (Figure 12).*

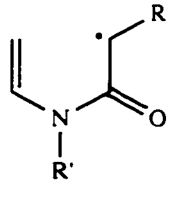
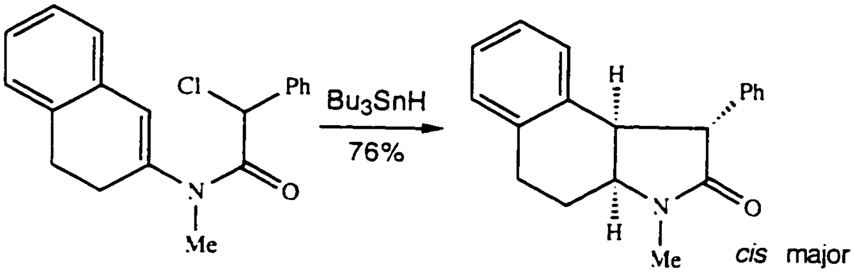


Figure 12

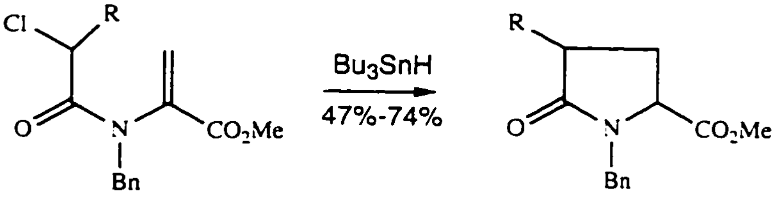
A special feature of the synthesis of lactams by radical closure is the application of the unusual[72,73] 5-*endo* cyclization. For example, the amide **148** gave the product of 5-*endo* closure **149** in good yield (Scheme 53).[74] The major product had the phenyl group *syn* to the adjacent ring fusion hydrogen.



148 **149**

Scheme 53

The Parsons group reported[75] the preparation of a number of pyroglutamates using the same methodology (Scheme 54), and in their case the radical resulting from closure was additionally stabilized by an ester group.

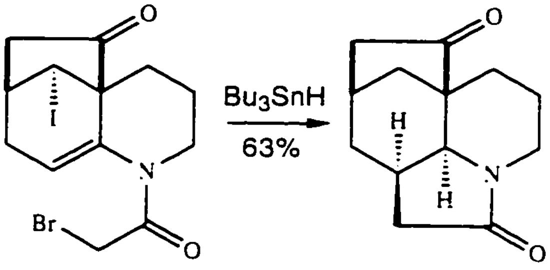


150
R = H, Me, Ph

151

Scheme 54

Such cyclizations can be done with a high degree of stereochemical control; in the example of Scheme 55[76] the tetracyclic product was produced with the indicated stereochemistry. Evidently, the observed ring fusions represent the most stable isomer.



152 **153**

Scheme 55

d. Cyclization of carbamoyl radicals (Figure 13).

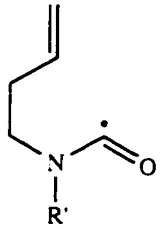
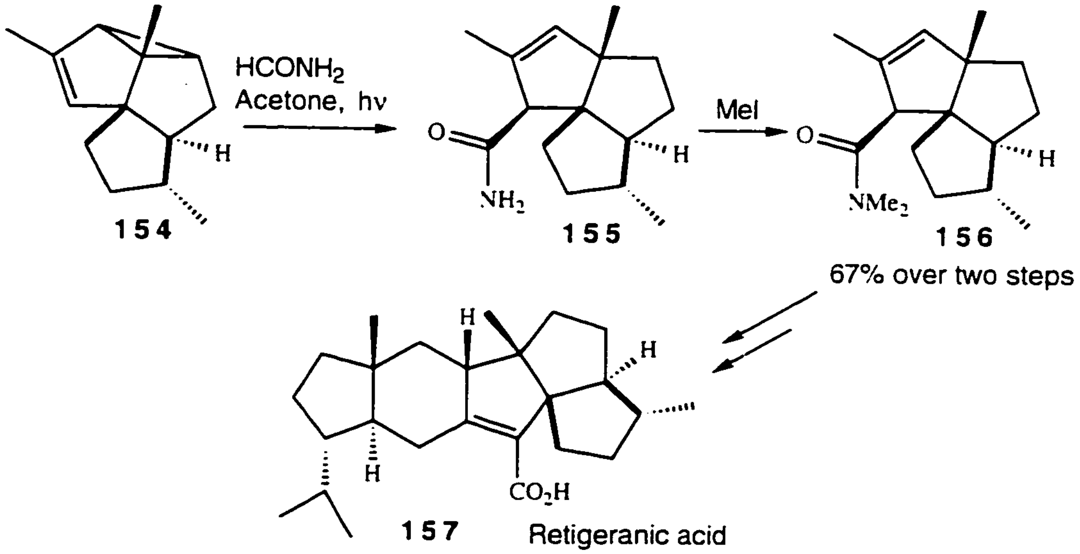


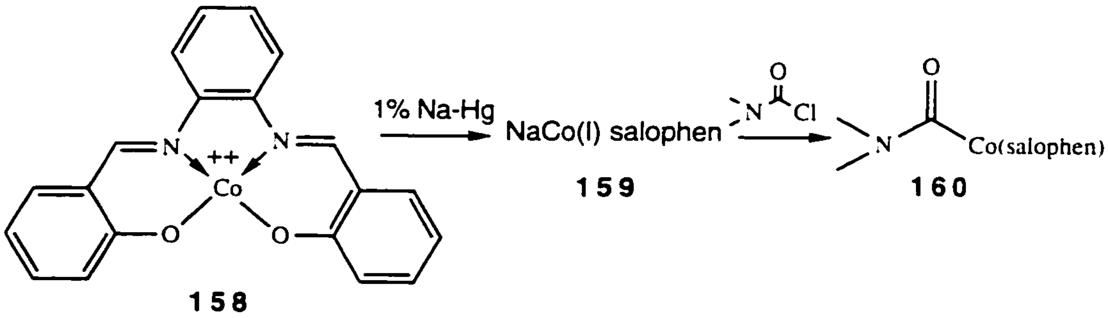
Figure 13

Carbamoyl radicals have been known since the early sixties; however, the applications in general synthesis have been quite limited. Elad and Rokach[77] first demonstrated a synthetic use, in which photolytically generated formamide radicals added to both unsubstituted and substituted alkenes. Wender *et al.* adopted this idea for the synthesis of the sesterterpene (-)-retigeranic acid, as shown in Scheme 56.[78] Here a photolytically generated formamide radical added to the double bond with concurrent opening of the cyclopropane ring. The stereochemistry of attack on **154** is probably determined by the biased molecular environment.



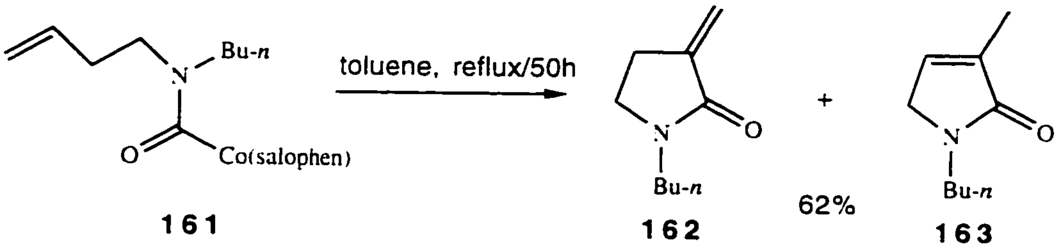
Scheme 56

So far, to the best of my knowledge, the only publication on carbamoyl radical cyclization, leading to lactams, is the work of the Pattenden group, using cobalt salophen methodology.[79]

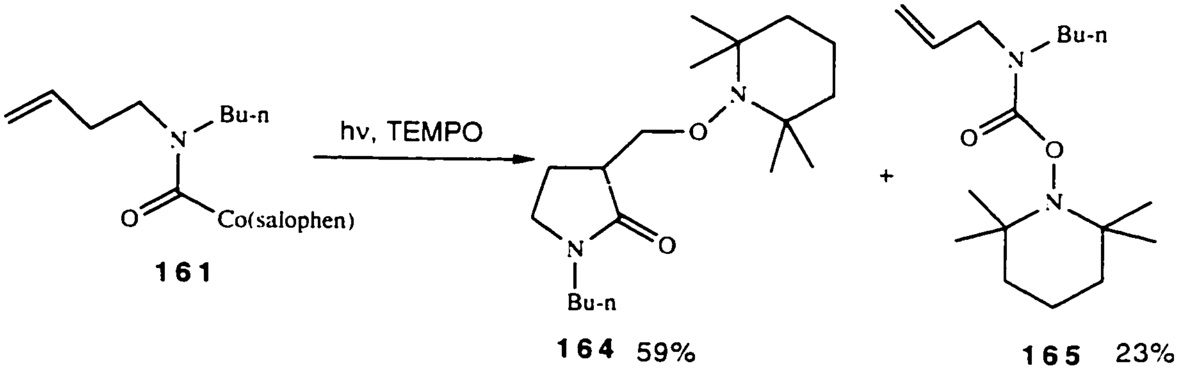


Scheme 57

The cobalt(II) salophen **158**, as shown in Scheme 57, was reduced to the sodium salt of cobalt(I) salophen when treated with sodium amalgam. This species reacts with the carbamoyl chloride by oxidative addition to the C-Cl bond to yield the cobalt(III) salophen complex **160**.



Scheme 58



Scheme 59

Upon irradiation of complex **161**, for example, a carbamoyl radical was generated, cyclization occurred, followed by trapping of the newly formed radical with the cobalt(II) species. Dehydrocobaltation then afforded **162** and **163**.[79] Sometimes the complex can be isolated before the β-elimination.[79] The complex can be cleaved by heating with TEMPO (Scheme 59).[79] This methodology can also be used to prepare β- and δ-lactams.[79] A typical example of γ-lactam synthesis is displayed in Scheme 58.

III. Radical cyclization to γ-Lactones.

γ-Lactones, especially α-methylene γ-lactones, have been found to have important biological properties, especially antitumor activity.[80] The synthesis of γ-lactones via radical chemistry has been studied extensively, and the methods used can be classified as follows.

a. *Radical α to the carbonyl (Figure 14).*

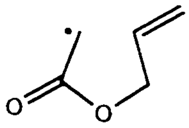
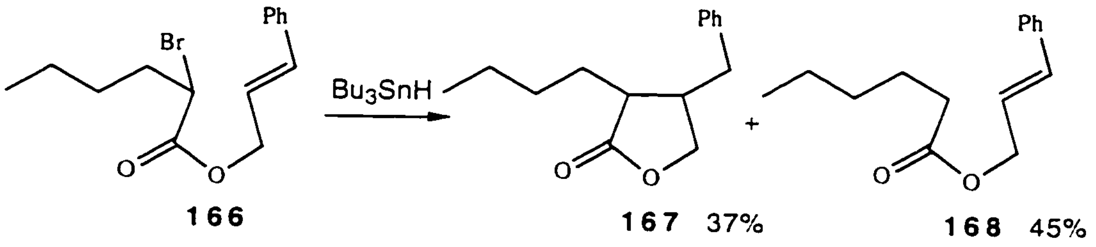


Figure 14

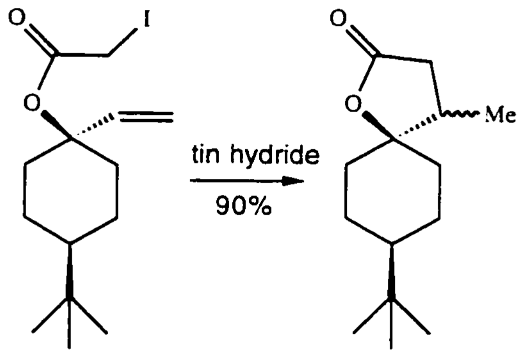
An α-halo substituted allyl ester is the most obvious starting material for use in the synthesis of γ-lactone structures by radical closure. However, this method is complicated by a conformational problem of the same type as in the amide case, as the favored conformation of an ester has the ether oxygen lone pair and the carbonyl oxygen *anti* to one another.[81] The barrier to rotation is smaller than in the case of amides, however. This conformational problem lies at the basis of the result summarized in Scheme 60, where a reduction process overwhelms the cyclization.[82]



166 **167** **168**

Scheme 60

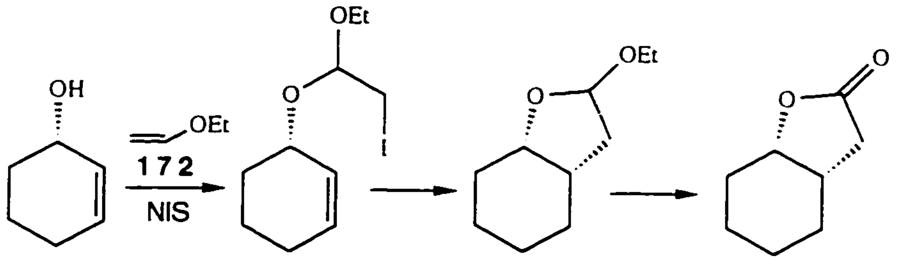
However, in some situations, successful cyclizations of this type do proceed, and γ-lactones can be obtained in high yield. An example is provided by the transformation of **169** into **170** (Scheme 61).[83]



169 **170**

Scheme 61

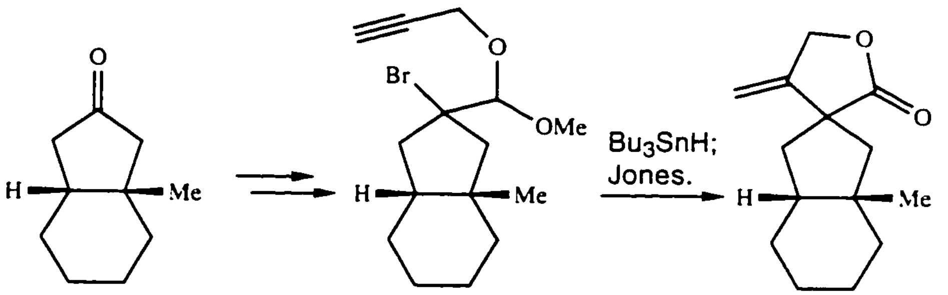
The conformational problem is avoided in the elegant acetal cyclization method introduced by Stork (Scheme 62).[84] The starting iodoacetals are easily formed from allylic alcohols, and cyclization gives lactol derivatives that are convertible into lactones by oxidation.



171 **173** **174** **175**

Scheme 62

Many syntheses since adopted this or similar approaches to prepare the lactone moiety. In the total synthesis of (±)-norbakkenolide A, for example, this strategy was used[85] to construct the spiro-γ-lactone **178** in high yield (Scheme 63).

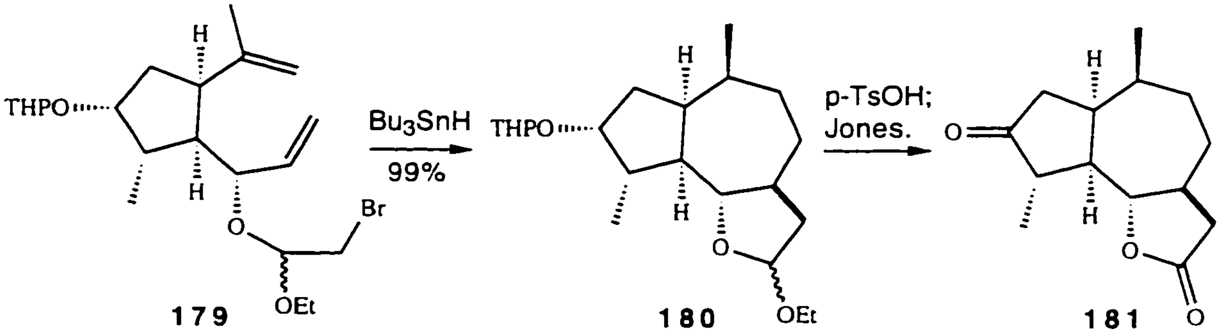


176 **177** **178**

90% for cyclization

Scheme 63

Another example is found in the total synthesis of (+)-cladantholide reported recently[86] (Scheme 64). Bromoacetal **179**, upon reaction with tin hydride, cyclizes in a tandem way, first by the common 5-*exo* mode, and then in a very unusual 7-*endo* fashion, to give compounds **180** in almost quantitative yield. The initial 5-*exo* cyclization setting up the *trans* ring fusion is expected on the basis of the chair transition state proposed by Beckwith.[10] The second step, with exclusive 7-*endo* cyclization predominating over the alternative 6-*exo* closure, is at first sight, surprising, but can be explained by suppression of the *exo* mode because of the double substitution of the alkene.



Scheme 64

b. Radical β to alkyl oxygen. (Figure 15).

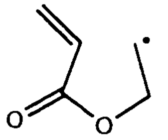
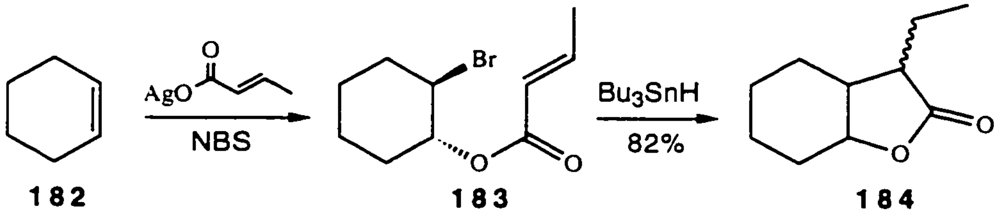
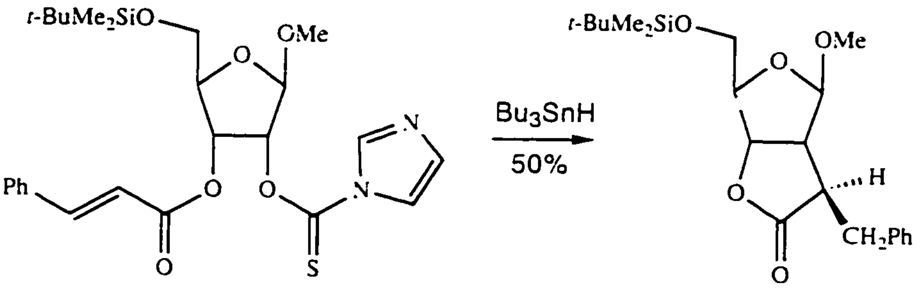


Figure 15

The approach based on the generation of radicals β to the alkyl oxygen represents one of the early pioneering studies (Scheme 65) in the field of synthetic radical cyclization methodology.[87]



Scheme 65



185 **186**

Scheme 66

A more recent example is found in the stereoselective synthesis[88] of several fused γ-butyrolactones on sugar templates (Scheme 66). In this reaction, a new stereocenter is formed with excellent diastereoselectivity at the off-template position.

c. *Radical α to alkyl oxygen (Figure 16).*

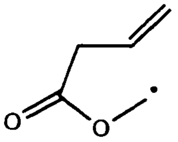
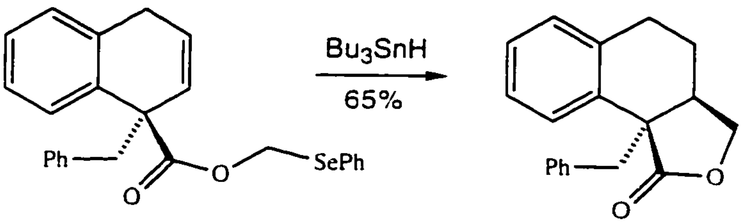


Figure 16

Only a limited number of examples of this kind of cyclization have been reported. Scheme 67 illustrates one case studied[89] by Beckwith's group in a comparative examination of the rates of cyclization of different types of radical.



187 188

Scheme 67

d. Alkoxycarbonyl radicals (Figure 17).

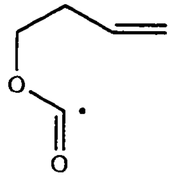
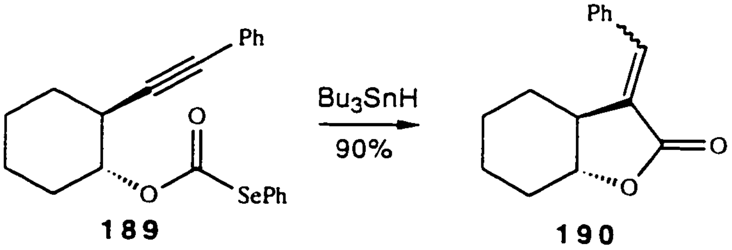


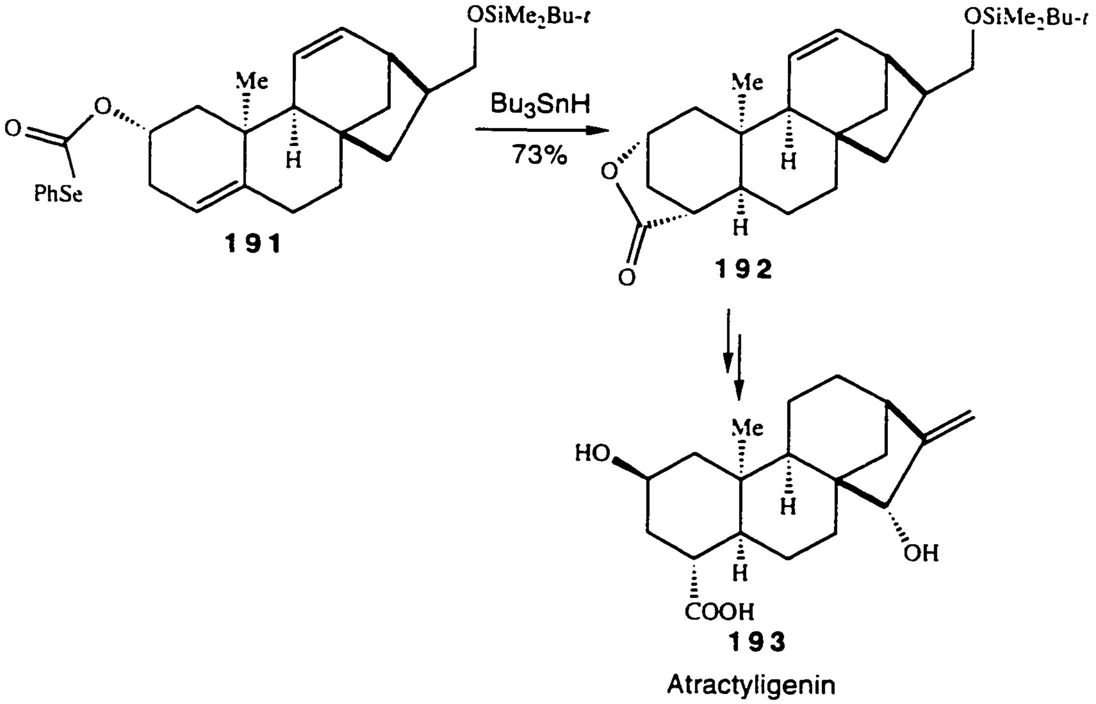
Figure 17

Pioneered by Bachi,[90] the radical sequence shown in Scheme 68 constitutes a straightforward synthesis of lactones. It provides a unique way to construct a C-C bond by attaching a C=O unit from a simple starting material (from phosgene). This process is based on the fact that the alkoxycarbonyl radical generated by cleavage of the C-Se bond is capable of cyclizing onto a double or triple bond, rather than degrading to an alkyl radical by expulsion of carbon dioxide. A typical example from Bachi's laboratory is displayed in Scheme 68.[90]



Scheme 68

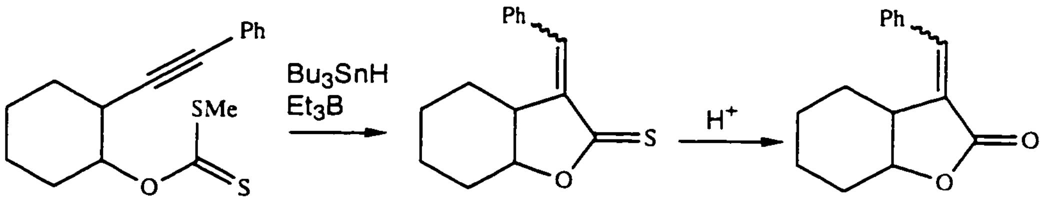
An application of this methodology in complex natural product synthesis is found in the total synthesis of the diterpenoid (±)-atractyligenin **193**.[91] The carboxylic acid moiety in the natural product was introduced via radical lactone formation and subsequent hydrolysis. Thus a transfer of stereochemical information was achieved through the radical process.



Scheme 69

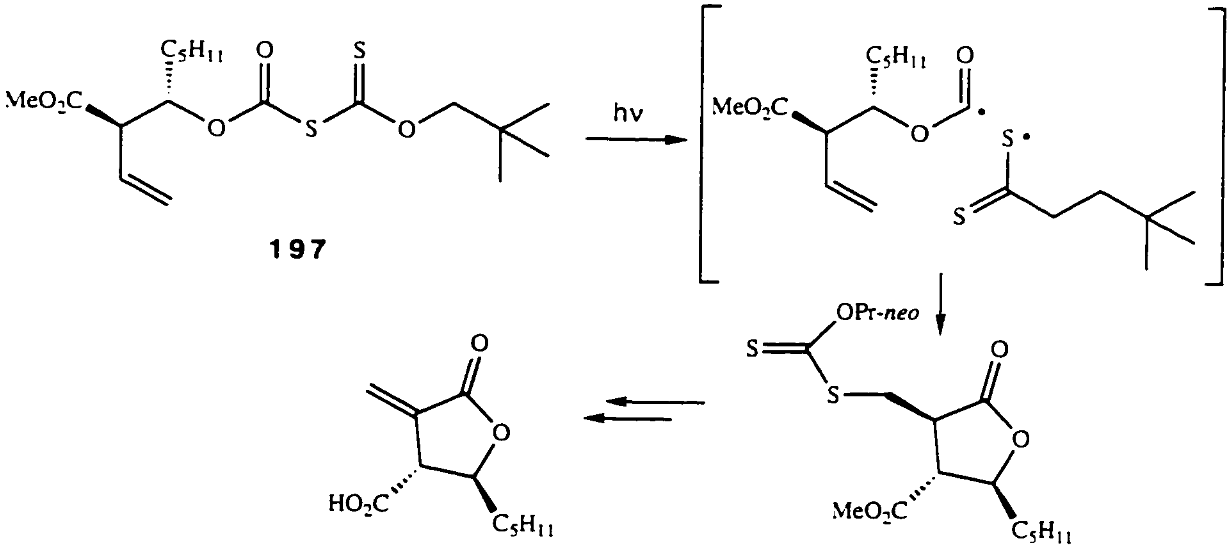
Similar developments have been reported by the groups of Oshima[92] and Zard.[93] Scheme 70 shows the reaction of thiocarbonate **194** leading to γ-lactones **196** after treatment with acid. The use of sulfur instead of selenium gives cleaner reaction mixtures in this case.

A group transfer reaction (Scheme 71) initiated photochemically has also been used to make lactones. The new radical formed after cyclization was trapped by the sulfur group, and the product **198** was elaborated into (±)-methylenolactocin **199**.



194 **195** **196** 95%

Scheme 70



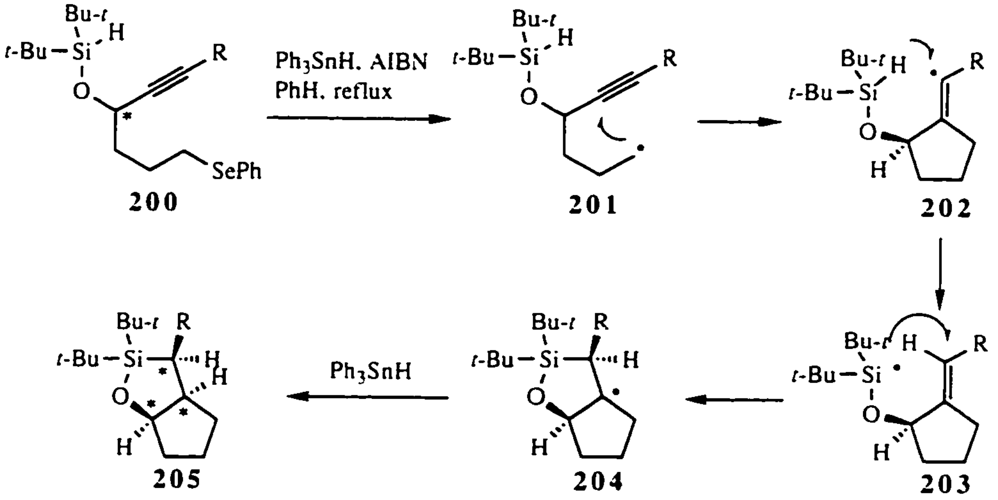
197

199 **198**

Scheme 71

(II) Results and Discussion

Recently the unusual radical sequence shown in Scheme 72 has been developed in this group.[94]



Scheme 72

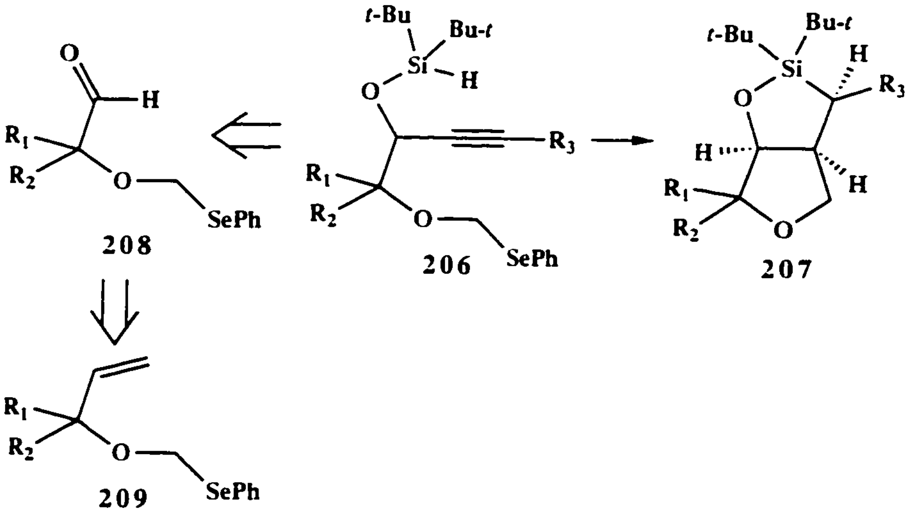
As indicated, the radical precursor **200** generates an alkyl radical **201**, which cyclizes via the 5-*exo* mode to afford the reactive vinylic radical **202**. The Si-H bond is then cleaved by a 1,5 hydrogen transfer sequence, followed by 5-*endo* cyclization of the resulting silicon-centered radical, to form the oxasilole ring. The final radical **204** is then quenched by abstracting hydrogen intermolecularly and from the less hindered side of the fused ring system.

The most notable feature of this tandem process is the fact that all three stereocenters in the product are strictly controlled by the stereochemistry of the carbon bearing the siloxy group in compound **200**. Consequently, in applying this reaction sequence there exists the possibility of using an optically pure alcohol, so as to obtain an optically pure reaction product. There also exists a large number of readily available chiral building blocks such as hydroxy acids and α-amino acids that might be used to make the starting materials for the reactions shown in Scheme 72. In either event, the sequence of Scheme 72 should allow the construction of optically pure bicyclic compounds, bearing a range of functionality.

We first decided to extend the reactions of Scheme 72 by making tetrahydrofuran, γ-lactone, chromanol and pyrrolidine systems. Eventually, a lactam synthesis was also developed.

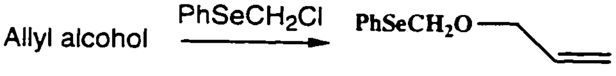
Synthesis of tetrahydrofurans by alkoxymethyl radical cyclization.

In order to make tetrahydrofurans by the above route (**206**-**207**) we needed to prepare an aldehyde of type **208**, bearing a (phenylseleno)methoxy group, and a retrosynthetic analysis for such a compound is shown in Scheme 73.



Scheme 73

A. Attempts at displacement by hydroxyl.



Scheme 74

The synthesis was first approached following Beckwith's method for (phenylseleno)methylation of alcohols.[89] Starting from allyl alcohol, we planned to attach a CH_2SePh moiety on the oxygen through nucleophilic substitution of $PhSeCH_2Cl$. However, it turned out this is not an easy task. As shown in Table **1**, several different conditions were tried, but without success. In most cases the starting material was recovered and, occasionally, a side product was isolated.

$$\text{Allyl alcohol} \xrightarrow{\text{PhSeCH}_2\text{Cl, NaH, THF overnight}} \text{starting material}$$

$$\text{Allyl alcohol} \xrightarrow{i\text{Pr}_2\text{NEt, CH}_2\text{Cl}_2\text{, reflux}} \text{starting material}$$

$$\text{Allyl alcohol} \xrightarrow{\text{NaH; PhSeCH}_2\text{Cl/NaI, DME}} \text{starting material}$$

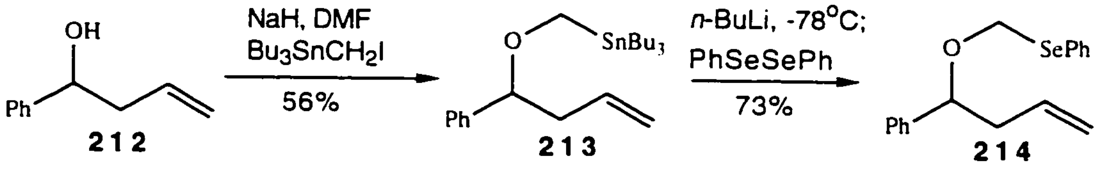
$$\text{Allyl alcohol} \xrightarrow{\text{NaH, PhSeCH}_2\text{I, THF}} \text{starting material}$$

$$\text{Allyl alcohol} \xrightarrow{\text{AgOTf, PhSeCH}_2\text{Cl, ether}} (\text{PhSe})_2\text{CH}_2\ \mathbf{211}$$

Table 1

Our observations confirmed earlier reports on the low reactivity of the selenium reagent.[31,89,95]

A three-step sequence (Scheme 75) has been developed[31] to gain access to monoselenoacetals. The method involves first making of stannane-substituted methyl ether (see **213**) and then generating the derived alkoxymethyl anion, which is trapped with diphenyl diselenide (Scheme 75). This method was later used[95] in the construction of tetrahydropyran systems by alkoxymethyl radical cyclization.

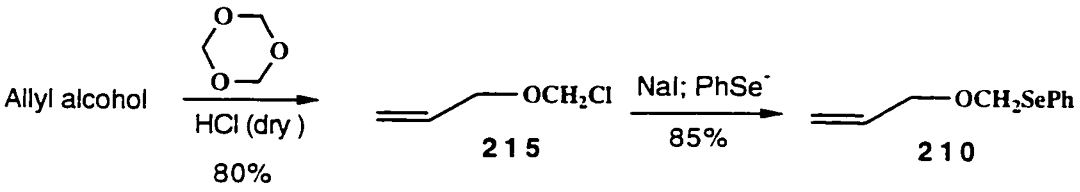


Scheme 75

We were reluctant to follow the above procedure, as the yields for hindered alcohols may not be satisfactory.

B. *Displacement by selenium.*

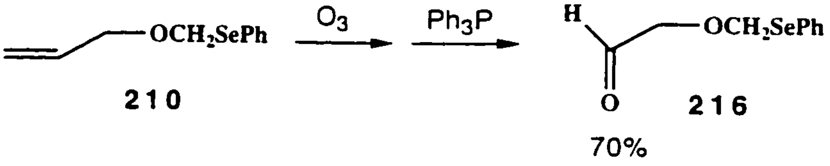
We eventually reversed the alkylation problem by changing the status of the selenium moiety from an electrophile to a nucleophile, as outlined in Scheme 76. The chloromethyl ether was prepared according to a similar transformation previously described by Corey *et al.*[96]



Scheme 76

The reaction of allyl alcohol with HCl in the presence of *s*-trioxane was fast, even though occasionally side products was formed, and the yield of the required chloromethyl ether **215** usually reached at least 80%, after distillation (Scheme 76). The phenylselenide anion for the displacement was generated conveniently by sodium borohydride reduction of diphenyl diselenide in ethanol. The reaction was conducted by first stirring a mixture of **215** and sodium iodide in dimethoxyethane for one hour, followed by addition of the freshly prepared phenylselenide anion. The desired product (**210**) was then easily obtained by column chromatography.

In the next step we needed to cleave the double bond to generate the aldehyde group. Selenium compounds, of course, are well-known to be vulnerable towards most oxidation reagents, but we were able to effect the ozonolysis without incident by adopting a procedure described by Clive and Postema.[97] In this method, double bond cleavage by ozone is done at a low temperature, and the ozonide reduction is carried out without allowing the temperature to rise to a level at which selenoxide elimination occurs. In the event, we obtained the required aldehyde in 70% yield (Scheme 77).

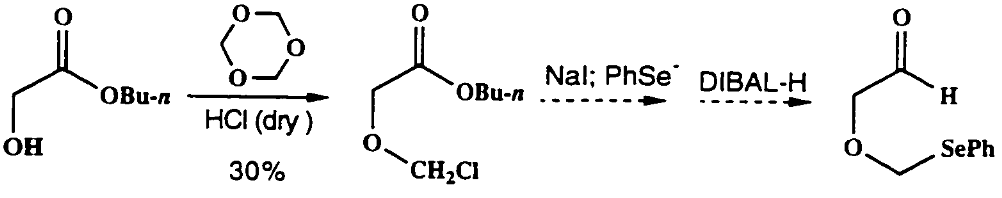


210 **216**

Scheme 77

Although the reaction worked, we found it inconvenient on a large scale because of the separation problems in dealing with large amounts of triphenylphosphine oxide.

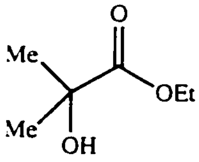
The ozonolysis can be avoided, however, if we started our synthesis from an α hydroxy acetic ester, such as compound **217** (Scheme 78). A reduction step might be used, instead of the oxidation by ozone, to obtain aldehyde **216**.



217 **218** **216**

Scheme 78

It turned out, however, that reaction of **217** with HCl was low yielding, and the result was even poorer with the more hindered alcohol **219**.



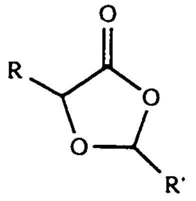
219

Figure 18

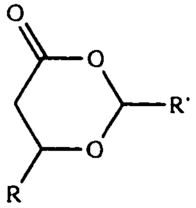
We were prompted, therefore, to develop a better method to make these bifunctional molecules containing both an alkoxymethyl radical precursor and an additional group for further manipulation.

C. *Regioselective opening of 1,3-dioxolan-4-ones.*

Recently both 1,3-dioxan-4-ones and 1,3-dioxolan-4-ones (Figure 19),



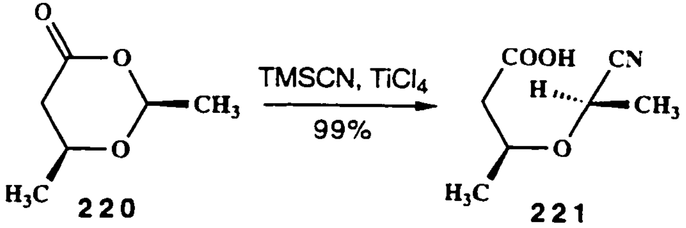
1,3-dioxolan-4-one



1,3-dioxan-4-one

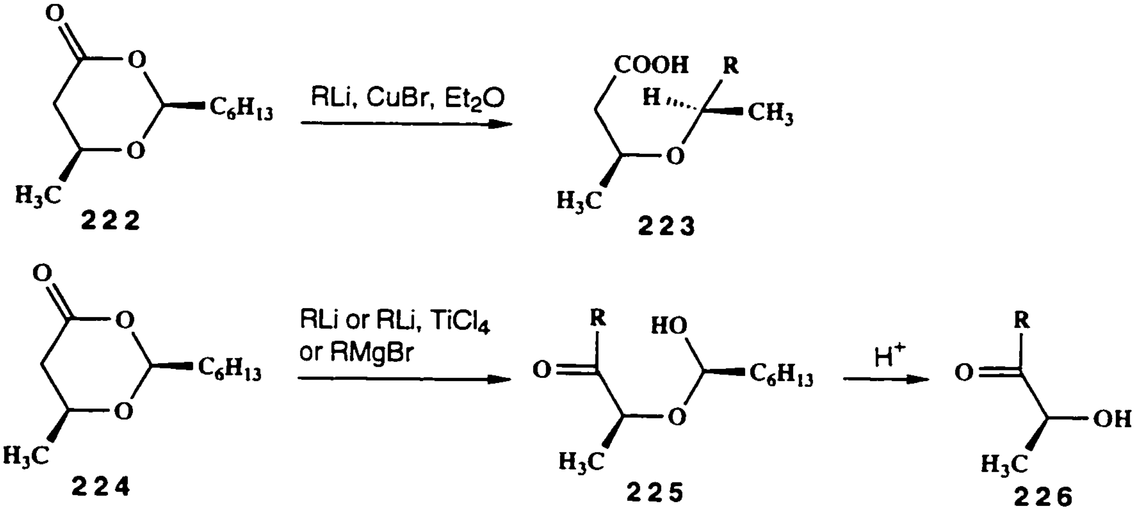
Figure 19

derived from optically pure hydroxyacids, have attracted attention as synthetic intermediates. Treatment of **220** with trimethylsilyl cyanide in the presence of titanium tetrachloride, gives **221** in 99% yield (Scheme 79) by nucleophilic opening at the acetal carbon.[98]



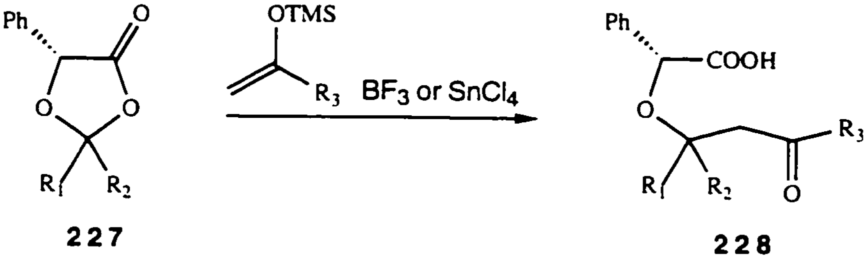
Scheme 79

Attack at the carbonyl carbon has also been observed, and this is illustrated in the second equation of Scheme 80.[99]



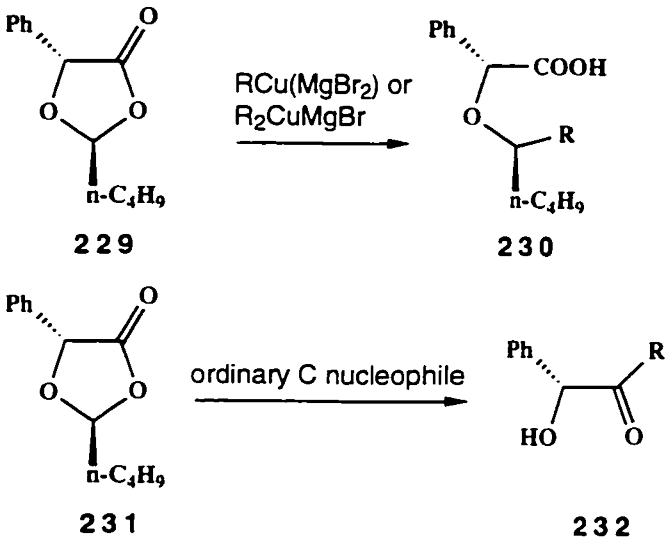
Scheme 80

In the 1,3-dioxolan-4-one series, silyl enol ethers



Scheme 81

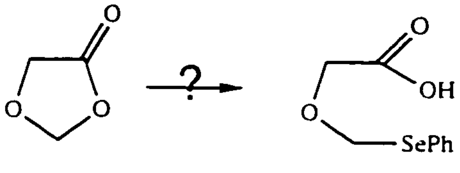
react, in the presence of boron trifluoride or tin tetrachloride, exclusively at the acetal position, leading, for example, to compound **228**.[100] The reaction with organometallics is more complicated: opening occurs at the carbonyl position when ordinary nucleophiles such as RLi or RMgBr are used, and, surprisingly, the same mode of opening is observed with higher order *lithium* cuprates. On the other hand, cuprates derived from Grignard reagents attack and break the acetal linkage (**229-230**).[101]



229 **230** **231** **232**

Scheme 82

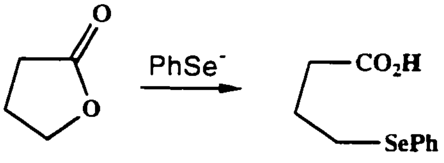
We decided to study the possibility of opening **233** at the acetal position with phenylselenide anion in order to gain access to synthon **234** (Scheme 83). Partial reduction of the carboxyl in **234** would then give us the required aldehyde **216**.



233 **234**

Scheme 83

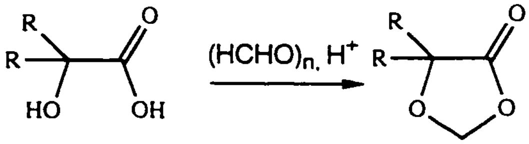
The plan shown in Scheme 83 is based on the fact that a carboxylate is a better leaving group than an alkoxy group, and the proposed reaction has analogy in the well-established[102] conversion of a γ-lactone into a phenylseleno carboxylic acid (Scheme 84).



235 **236**

Scheme 84

We adopted a classical method[103] for preparing the 1,3-dioxolane-4-ones (Scheme 85). The simplest in



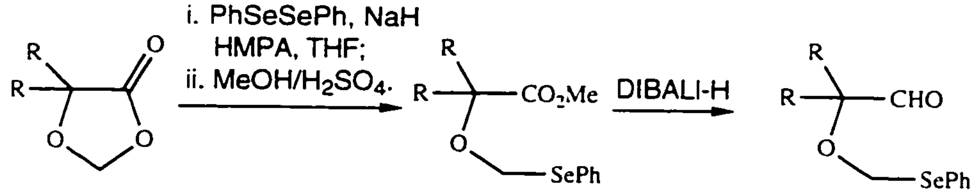
R=H **237** **233**

R=Me **238** **239**

Scheme 85

this series is **233**, which was prepared by condensing glycolic acid with paraformaldehyde. In agreement with the literature report, a low yield (10-20%) was obtained. We accepted the low yield for that simple case, since it is known that introduction of substituents at the α position would afford better yields.[103] In the case of **237**, it should also be mentioned that the two starting materials (glycolic acid and paraformaldehyde) are very cheap.

There are several ways for generating phenylselenide anions,[102a] and their reactivity depends on the procedure used. In analogy to reported methods for lactone opening,[102] the reagent was generated by NaH reduction of PhSeSePh, and we were pleased to find that the reaction went according to plan, as shown in Scheme 86. In each case the initial ring-opened product was esterified, and the ester was subjected to DIBAL-H reduction, to generate the desired aldehydes.



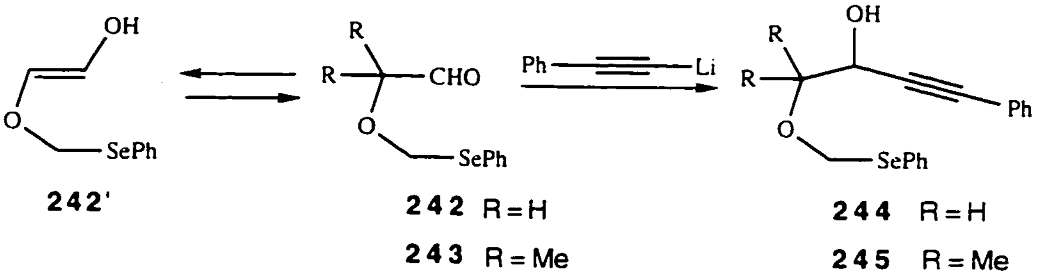
R = H **233**
R = Me **239**

240
241

242
243

Scheme 86

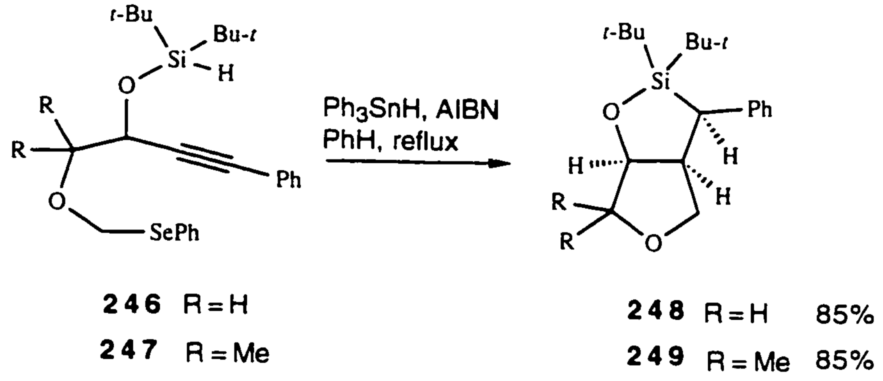
The addition of a phenyl acetylide to the aldehyde group, however, was initially troublesome. The reaction conditions (-78 °C, THF) applied successfully with the carbon analogues[94] (i.e., the starting materials for the reactions of Scheme 72) did not afford any desired alcohol **244**, even when 10 equivalents of acetylide were used. As starting material was recovered in these experiments, we assumed that enolization was occurring, but even the use of cerium



Scheme 87

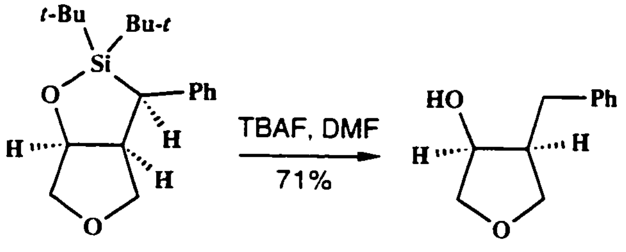
acetylides was unsuccessful. However, we were relieved to find that when the temperature of the solution was raised from -78 °C to -35 °C, the desired addition occurred smoothly (87%). The more hindered aldehyde **243**, which cannot enolize, reacted with lithium phenylacetylide at -78 °C (90%).

Finally, each of the alcohols **244**, **245** were silylated, using di-*tert*-butylchlorosilane [*t*-Bu_2SiHCl] in the presence of triethylamine. Slow addition of triphenyltin hydride to a solution of **246** in refluxing benzene afforded the desired compound **248** in 85% yield. The stereochemistry of this



Scheme 88

bicyclic compound, as suggested by the established mechanism, was further confirmed by converting **248** into **250** (Scheme 89). The *cis* disubstituted tetrahydrofuran **250** had identical spectra data to those previously reported.[104]

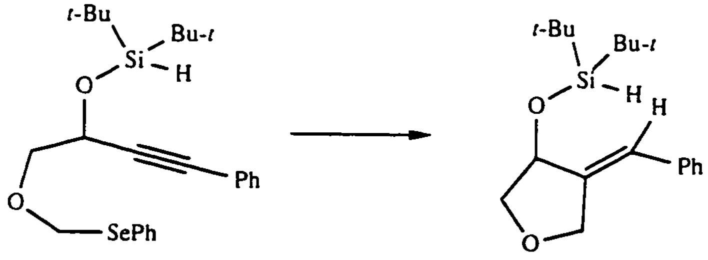


248 **250**

Scheme 89

Compound **247** also cyclized in the expected manner to **249**.

In these cyclizations, dilute conditions must be used, but on one occasion, the stannane was added quickly, and the ^{1}H NMR spectrum of the crude product showed an olefinic signal with an integration corresponding to one proton. We suspect that the reaction had taken the course shown in Scheme 90.



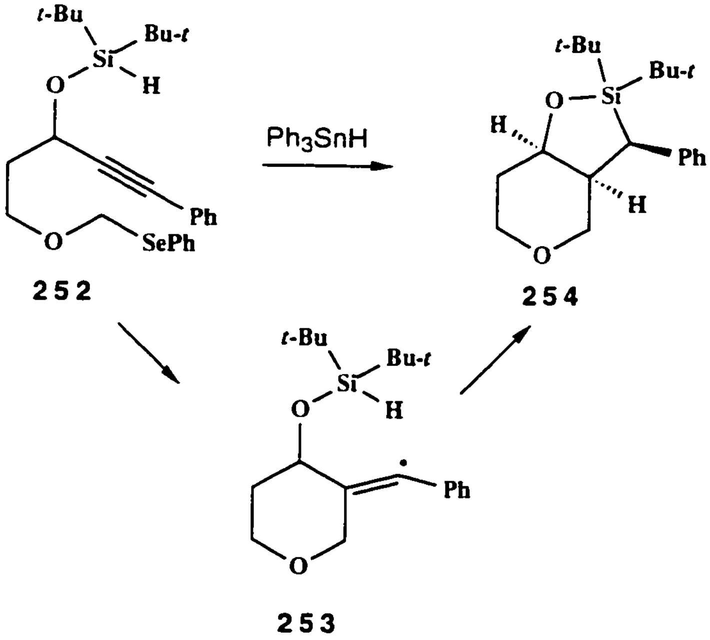
246 **251**

Scheme 90

We had thus succeeded in developing a route to the tetrahydrofuran system, via a tandem sequence of radical reactions.

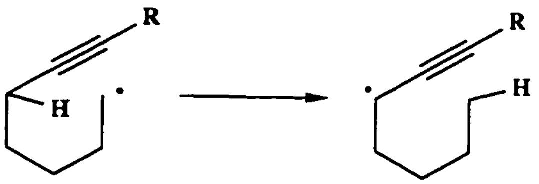
Synthesis of the chromanol system by alkoxymethyl radical cyclization.

We next investigated the possibility of 6-*exo* closure, so as to afford a tetrahydropyran (Scheme 91).



Scheme 91

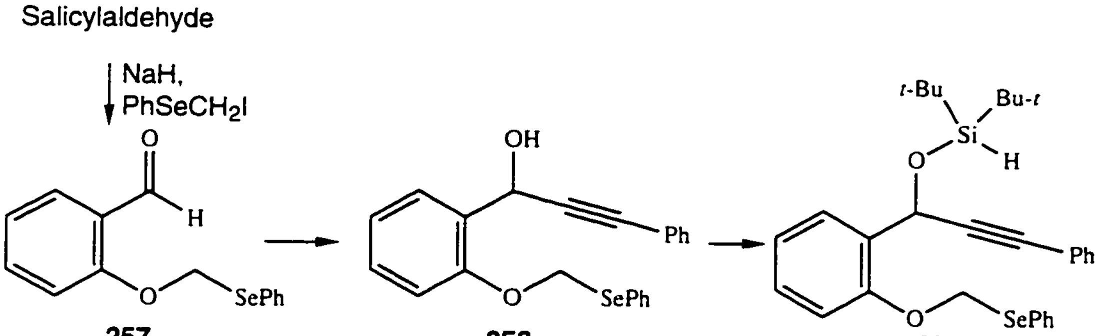
Radical cyclizations of the 6-*exo* type are frequently plagued by competing reduction[105] via intramolecular 1,5 hydrogen transfer (Scheme 92), and so we were very interested in the outcome of a similar reaction involving the alkoxymethyl radical, as depicted in Scheme 91. There was some evidence that alkoxymethyl radicals would not abstract allylic or propargylic hydrogen, as efficient 6-*exo*-trigonal closures had been observed[106] (our case would be a 6-*exo-digonal* closure).



255 **256**

Scheme 92

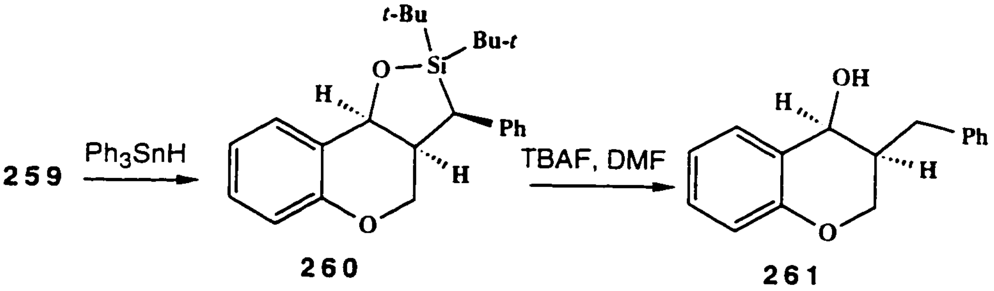
We decided to examine substrate **259**, which was synthesized by the sequence in Scheme 93.



257 **258** **259**

Scheme 93

The cyclization was conducted under the standard conditions established for the tetrahydrofuran system described above, and we were pleased to observe that the cyclized compound **260** was obtained as the only product (^1H NMR of crude product mixture) in 85% yield (Scheme 94).

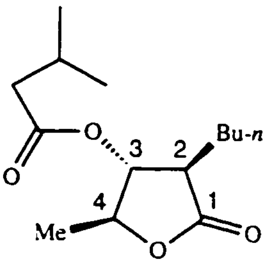


Scheme 94

It is noteworthy that intramolecular hydrogen abstraction does not occur to any appreciable extent, if at all, even though the hydrogen that would be removed is benzylic as well as propargylic. However, the factors that are responsible for the small, or non-existent, extent of hydrogen abstraction have not been identified. The facility of such hydrogen transfer would depend not only on the accessible geometries[84] of the system, and the strength of the C-H_a bond, but also on certain characteristics of the radical (here $ArOCH_2\bullet$), such as resonance stabilization.[107] The relative importance of these factors is unknown, but we note that efficient 6-*exo-trigonal* closures of alkoxymethyl radicals have also been observed in systems that lack the additional activating features of the propargylic hydrogen in **259**,[106] and the absence of intramolecular transfer during these reactions or in the 6-*exo-digonal* closure described here,[94,108] may be a general and synthetically useful characteristic of alkoxymethyl radicals. Hydrogen transfer is also insignificant or absent in the cyclization of acyl[109] or 1,1-difluoroalkyl[110] radicals.

Stereocontrolled synthesis of an optically active γ-lactone by acyl radical cyclization.

β-Oxygenated γ-butyrolactones have been isolated from several different natural sources and also obtained as degradation products of certain metabolites.[3] A representative of this important compound class is (+)-blastmycinone (**254**).[3] The general structural features that are often met is the functionalization of the lactone skeleton at all three possible locations, the C-3 position having an oxygen substituent.



262
(+)-Blastmycinone

Figure 20

Many syntheses of β-oxygenated γ-butyrolactones have been reported[3] and new approaches keep emerging, evidently due to their pharmaceutical importance. We were interested in establishing whether γ-lactones could be made by the tandem sequence described above (Scheme 72) and, in the event, our results suggest that our approach may be applicable to compounds such as blastmycinone, but we have not worked on that target.

In order to prepare γ-lactones by our method we needed to generate radicals of the type shown in Figure 21. Acyl radicals were known to cyclize onto multiple bonds, and so we were confident that such radicals could be used in the tandem sequence we had in mind.

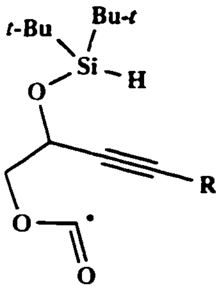
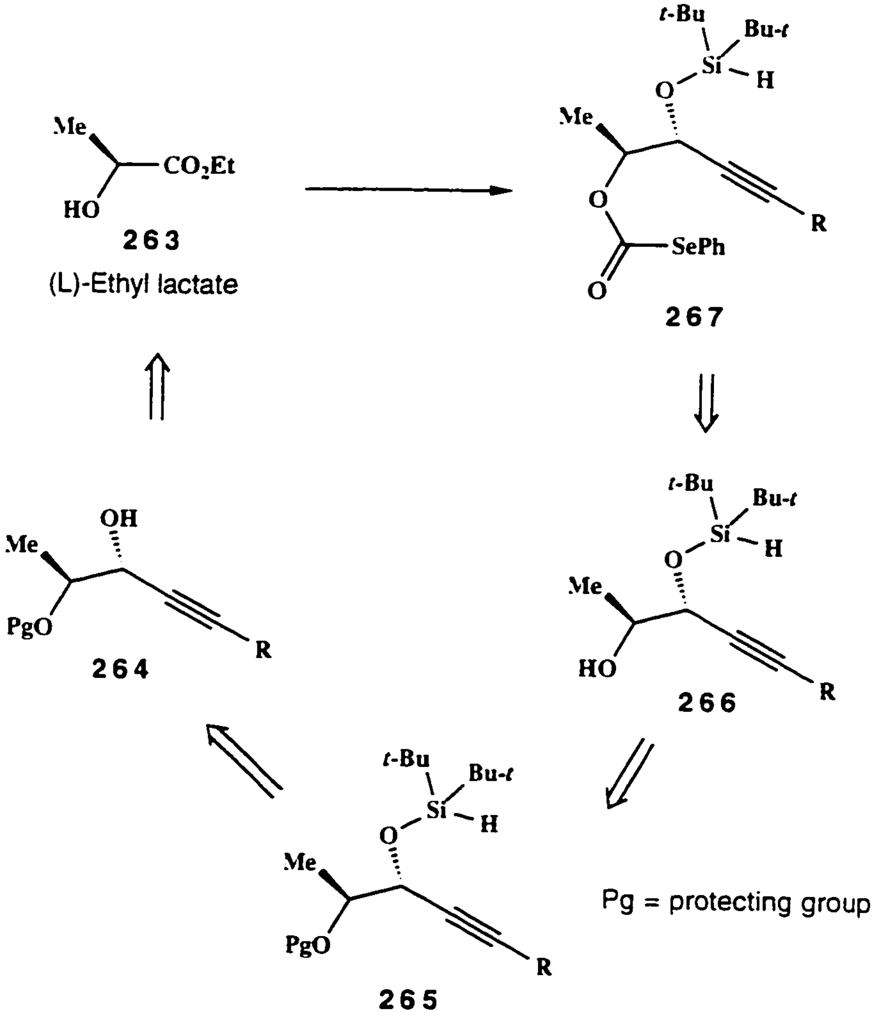


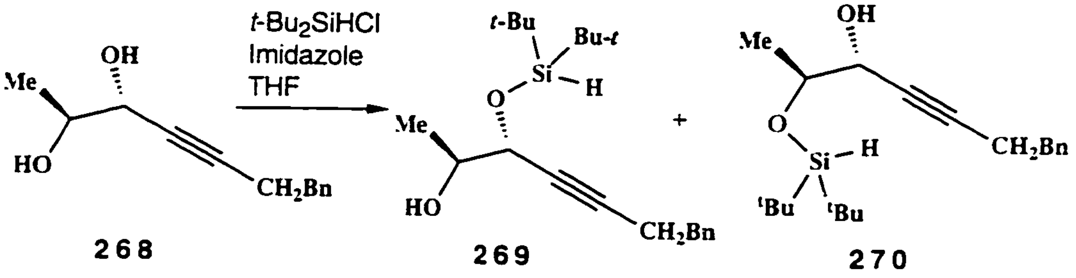
Figure 21

Ethyl (*L*)-lactate (**263**) was used as the starting material to make the required radical precursor **267** (Scheme 95), and the retrosynthetic analysis is shown in the Scheme.



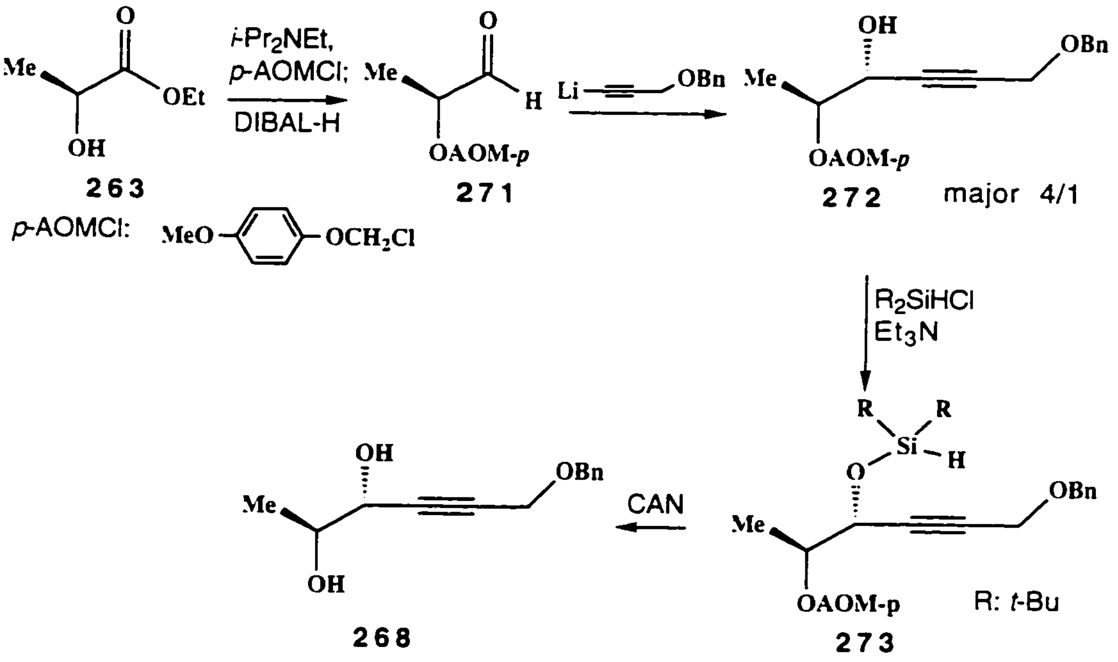
Scheme 95

We appreciated that a shorter route to **267** might be possible, if the reactivity of the two hydroxy groups (see **264**, Pg = H), are substantially different. This situation would make protection of the lactate hydroxyl unnecessary. In the event, treatment of **268** (see below for preparation) with di-*tert*-butylchlorosilane gave a mixture. The ^1H NMR spectrum of the crude material showed two Si-H signals. We believe that both of the isomers **269** and **270** had formed, and so we did not pursue the possibility of the shorter route.



Scheme 96

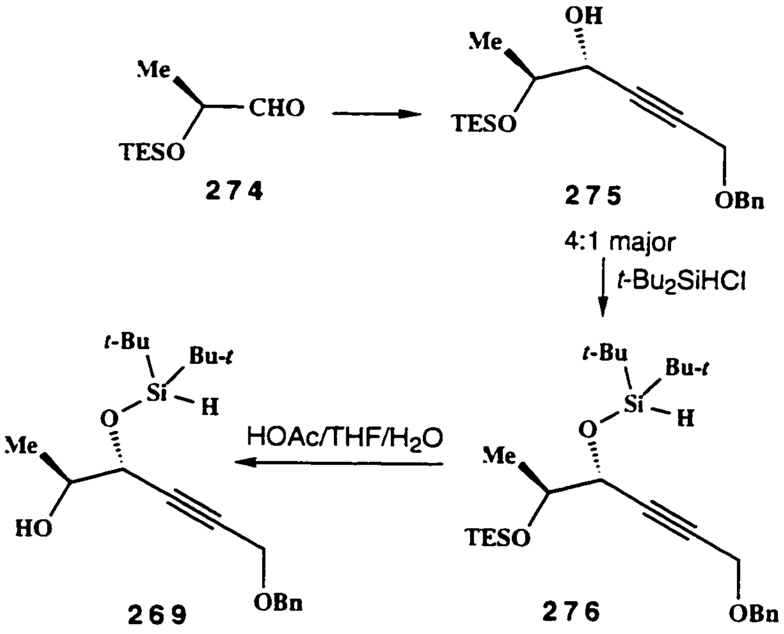
It was, therefore, necessary to chose a suitable protecting group for **264**. This protecting group should be easily cleaved in the presence of the t-Bu$_2$SiH unit, whose reactivity was not known, beyond the general expectation that it would be removable by the action of fluoride ion, and probably by acid. After careful consideration, we adopted the *para*-anisoylmethyl (*p*-AOM) group, which had performed very well in a number of delicate situations in our laboratory.[111] The group can be removed under neutral conditions by oxidation with cerium ammonium nitrate (CAN).



Scheme 97

As shown in Scheme 97, ethyl (*L*)-lactate was protected and reduced to aldehyde **271**. Acetylide addition then afforded a 4:1 mixture of alcohols and, in accordance with the Cram's rule, we tentatively assign the stereochemistry shown to the major isomer. Silylation gave **272**, but, unfortunately, the key deprotection step with CAN[111] also removed the silyl group.

We turned next to the use of a fairly labile silyl unit. We expected that the *t*-Bu_2SiH group should have a degree of stability to hydrolytic conditions analogous to that of *t*-$BuMe_2Si$. The latter has been proved to be stable under mildly acidic conditions[112] that are adequate to cleave a Et_3Si group, and so we were prompted to try the route summarized in Scheme 98.

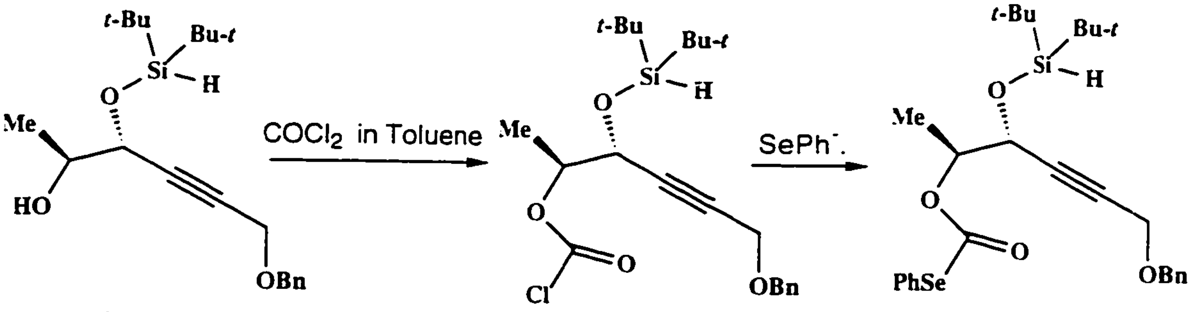


Scheme 98

Protection of ethyl (*L*)-lactate with triethylsilyl chloride, and partial reduction (DIBAL-H) went smoothly to give compound **274**. Acetylide addition then afforded similar results as in the *p*-AOM series, and once again, a mixture of diastereomers was produced in a ratio of *ca* 4:1. On the basis of Cram's rule, we assigned the *anti* stereochemistry to the major product, and this assignment was later confirmed (see below). No effort was made to enhance the stereoselectivity.

Silylation to produce **276** was followed by mild acidic deprotection, which afforded **269** in good yield, and this result confirmed our earlier estimate of the relative sensitivity of the two silicon groups.

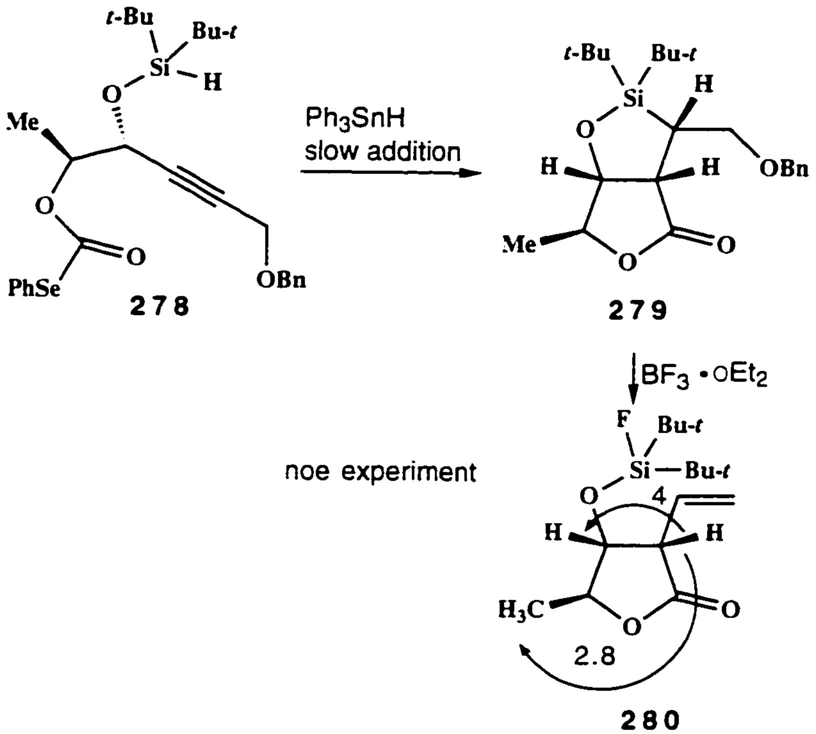
We next modified a literature procedure for preparing selenocarbonates.[90] Alcohol **269** was treated (Scheme 99) with a 1:1 v/v solution of phosgene in toluene, *without* any added base. After removal of the unreacted phosgene under water pump vacuum by concentration to half the initial volume, the residue was passed through a short silica gel column to obtain the chloroformate in quantitative yield. Unlike ethyl chloroformate itself, compound **277** is quite stable towards hydrolysis. Our modification of the literature synthesis of seleocarbonates lay in the choice of selenium unit: instead of benzeneselenol, a compound easily oxidized upon exposure to atmosphere and characterized by a strong and disagreeable smell, we used PhSeNa generated from diphenyl diselenide and sodium borohydride in ethanol. Reaction was completed in 6-8 h with formation of the desired selenocarbonate **278** in good yield (80%).



269 **277** **278**

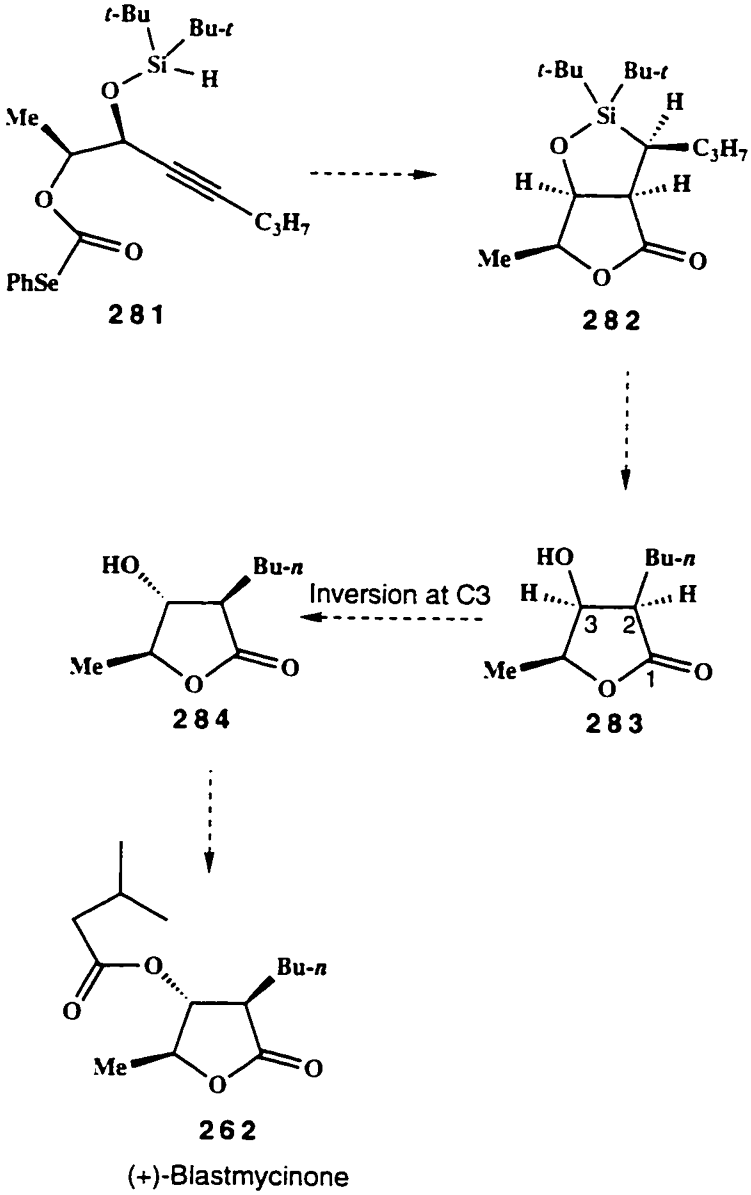
Scheme 99

Cyclization of **278** was uneventful, when the experiment was done by slow addition of stannane and AIBN, and the cyclized product **279** was isolated in very good yield (85%). The stereochemistry was assigned by analogy to prior work in this laboratory, and the stereochemical assignments to the carbons of the furan substructure were confirmed by decoupling and NOE experiments on the derived olefin **280**. NOE measurements with **279** itself were not decisive.



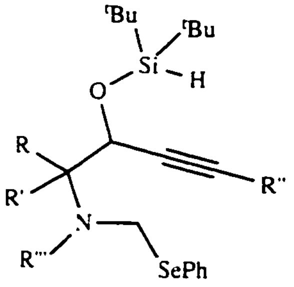
Scheme 100

The above lactone synthesis may be applicable to blastmycinone **262**, along the lines shown in Scheme 101, and future work in this direction is planned in this laboratory.



Scheme 101

Synthesis of the pyrrolidine ring system by aminoalkyl radical cyclization.

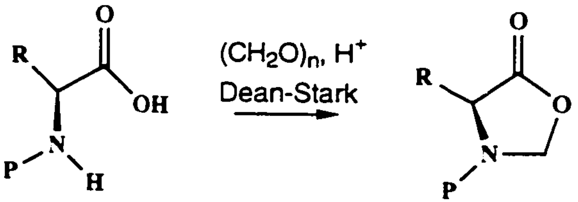


R, R', R'': alkyl or aryl group.
R'''': common N protecting group.

Figure 22

As in the case of tetrahydrofuran synthesis, we were interested in the properties of radicals α to nitrogen in order to apply our cascade sequence to pyrrolidines. For this purpose, we needed to obtain a substrate of the general structure shown in Figure 22.

Amino acids seemed to be suitable starting materials, and the fact that the derived oxazolidin-5-ones are easily made[113] (Scheme 102), suggested that we could introduce selenium in a manner analogous to that which had served us well in the preparation of the tetrahydrofuran system.



285

286

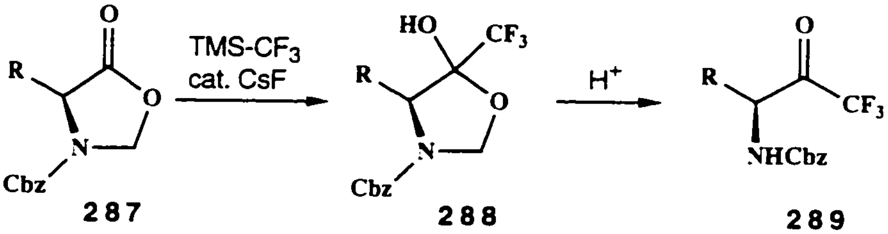
80-90%

R = amino acid side chain.

P = Boc or Cbz.

Scheme 102

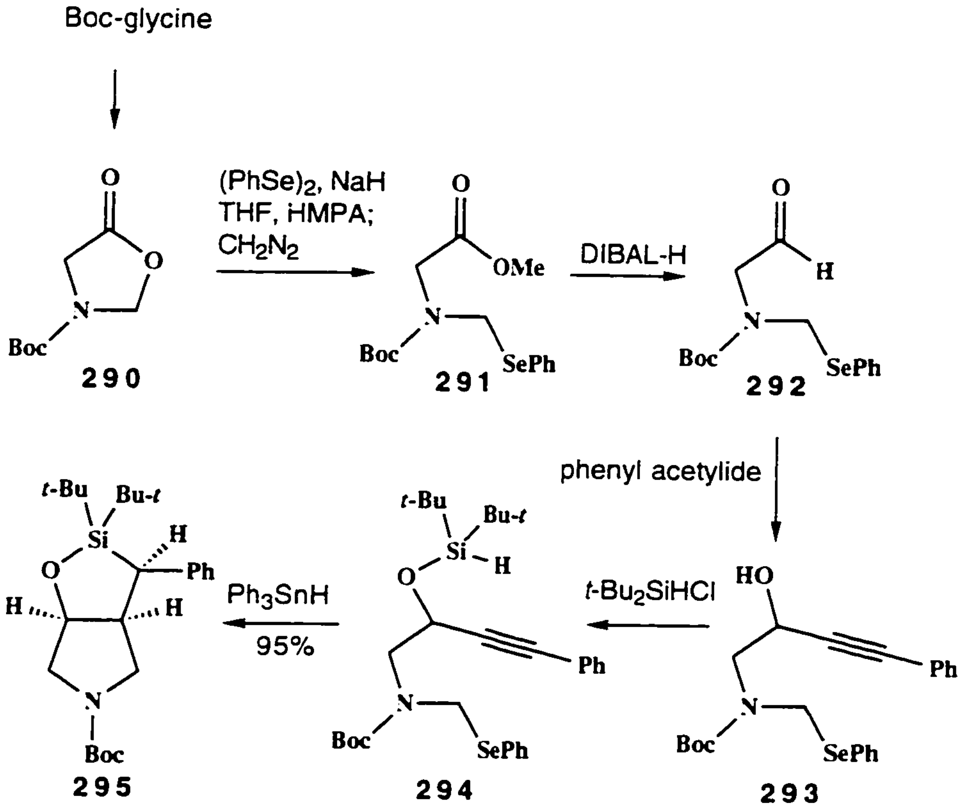
The reaction of oxazolidinones with nucleophiles has not been well-studied. Baldwin *et al.*[113c] in their synthesis of protected α-amino trifluoromethyl ketones (Scheme 103), found that Ruppert's reagent (Me_3SiCF_3), in the presence of a catalytic amount of cesium fluoride, added to the carbonyl carbon. Acid treatment then gave ketones of type **289**.



Scheme 103

In our case, the nucleophile would be $PhSe^-$, and we did not expect to observe reaction at the carbonyl, since acyl selenides would be expected to be good acylating agents.

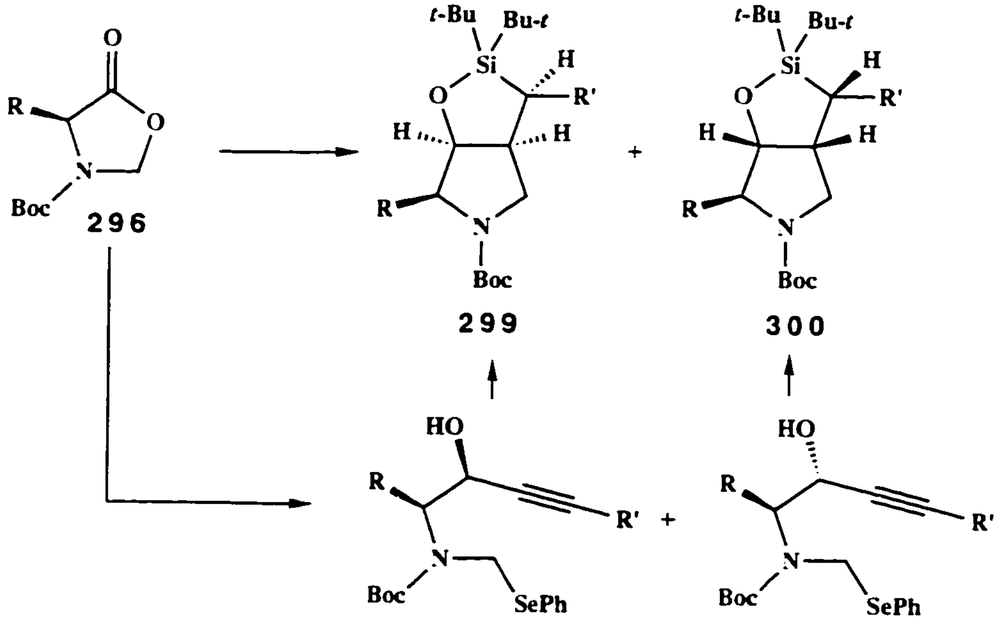
Boc-glycine was adopted as the starting material. Reaction with paraformaldehyde (Scheme 104) afforded **284** in 80% yield. Treatment with $PhSe^-$ generated by reaction of sodium borohydride with diphenyl diselenide gave us a complex mixture of products. Liotta has listed[102a] a reactivity gradient for many phenyl selenide anions: NaSePh/18-Crown-6/THF > NaSePh/HMPA/THF > LiSePh/HMPA/THF > LiSePh/THF > PhSeSePh/$NaBH_4$/THF/EtOH and, to our delight, the application of the NaH/PhSeSePh/THF/HMPA combination[102a] afforded, after esterification with diazomethane, the desired product **285** in 80% yield. Subsequent transformations (see Scheme 104) were similar to those used in the tetrahydrofuran series.



Scheme 104

The radical sequence again worked well, and produced the bicyclic pyrrolidine **295** in excellent yield.

A noteworthy feature of the above efficient conversion of BOC-glycine into **295** is that the method may offer a general route (Scheme 105) for amino acid-derived polysubstituted pyrrolidines, although implementation of this approach will require that the step in which the PhSe$^-$ group is introduced be carefully examined to see if epimerization occurs. Studies along these lines are currently under way in this laboratory.



Scheme 105

Synthesis of Lactams by carbamoyl radical cyclization, and a synthetic approach to (±)-A58365B.

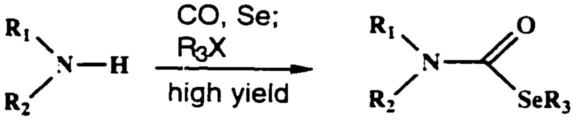
Carbamoyl radicals offer a direct route to lactams and thus pyrrolidines. As indicated in the review section, the Pattenden group has studied the cyclization of carbamoyl radicals derived from cobalt salophen derivatives.[79]

This method is a non-chain process, and the intermediate radical must be generated in stoichiometric amounts. An advantage of this feature is that direct trapping of the cyclized product as a cobalt complex occurs, and in favorable cases the complex may be isolated and manipulated further. On the other hand, the trapping process may make a tandem reaction difficult to effect. Another problem associated with this methodology is the unexpected isomerization that sometimes occurs (see Scheme 58), where the double bond in the product moves from an *exo* to an *endo* position.

We were interested in developing for the carbamoyl series a sequence similar to the selenocarbonate strategy described above for lactone synthesis.

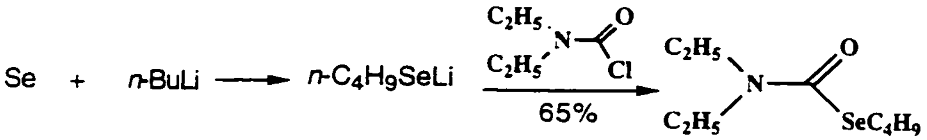
We thought it advisable to evaluate selenocarbamates as the radical precursors, instead of carbamoyl chlorides, because the greater bond strength of the C-Cl bond would require a higher temperature for radical cleavage, and might therefore bring about decarbonylation.

An obvious way to prepare the required phenylselenocarbamates would be from the corresponding carbamoyl chlorides, but there are other general synthetic routes available. Treatment of amines with carbon monoxide and selenium, in the presence of an alkyl halide gives carbamoyl selenides (Scheme 106),[114] Alternatively, a selenolate anion,[114] which can be generated *in situ*, can be allowed to react with a carbamoyl chloride (Scheme 107).



301 **302**

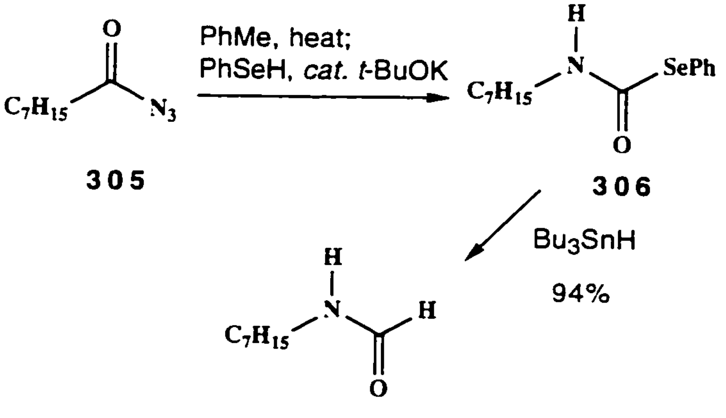
Scheme 106



303 **304**

Scheme 107

In a study on the conversion of carboxylic acids into isonitriles, Barrett and associates[115] reacted an isocyanate (generated in situ from an acyl azide **305**) with benzeneselenol in the presence of a catalytic amount of t-BuOK to obtain compound **306**. A radical sequence was then used to reduce **306** to formamide **307** in quantitative yield (Scheme 108).



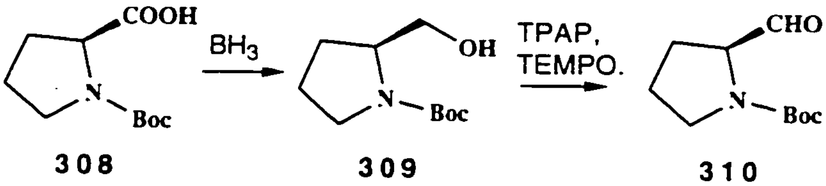
305 **306** **307**

Scheme 108

The effectiveness of the last reaction indicated that carbamoyl radicals are quite stable, presumably due to resonance involving the peptide bond, and so we were encouraged to proceed with our investigation on the possible use of carbamoyl radical cyclization from a carbamoyl selenide precursor.

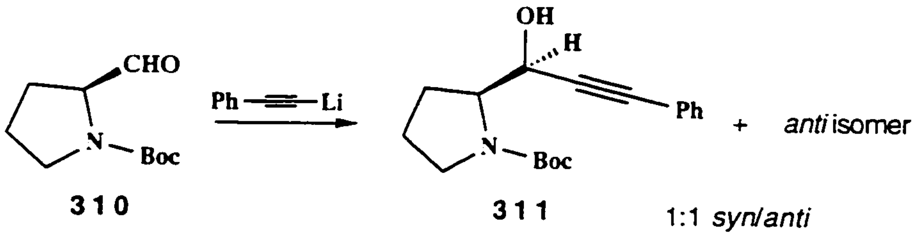
As in the case for selenocarbonate synthesis, we tried to avoid the use of benzeneselenol, and to use instead the anion PhSe$^-$, generated *in situ*.

(*S*)-Proline was chosen as the starting material for our investigation, and the derived



Scheme 109

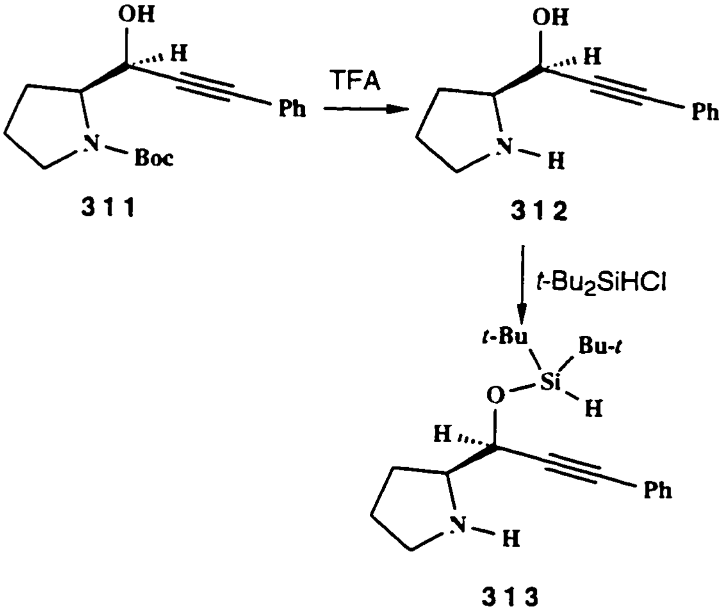
prolinal **310** was made either by partial reduction of the corresponding ester or, as shown in Scheme 109, by a reduction-oxidation sequence. The oxidation can be carried out by Swern and other oxidation protocols, but we favor the TPAP-TEMPO combination,[116] which offers the advantage of an easy workup procedure.



Scheme 110

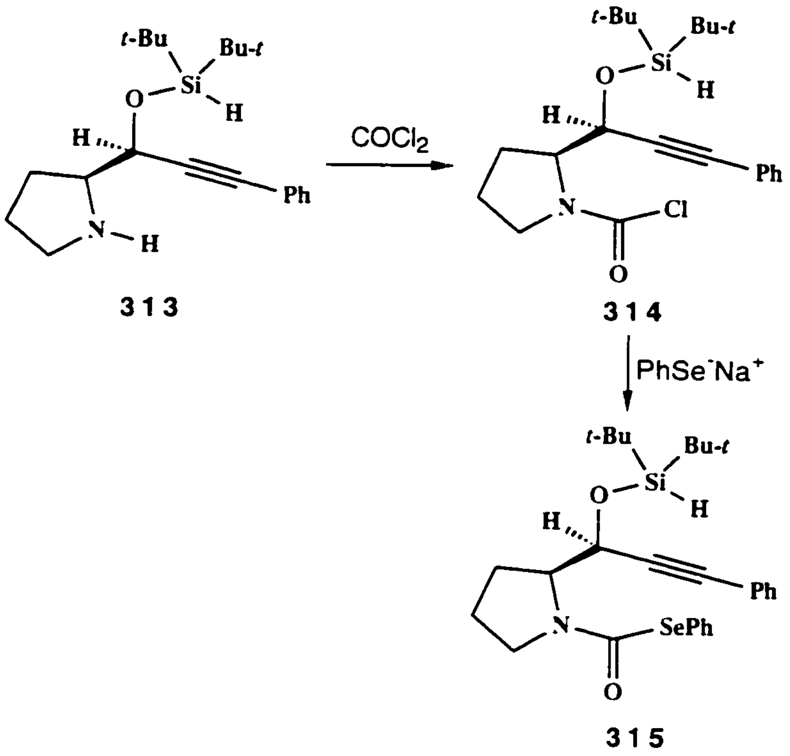
Addition of lithium phenylacetylide to aldehyde **310** produced an almost 1:1 mixture of two diastereoisomers (^{1}H NMR) (Scheme 110). These were separated by column chromatography and the more polar isomer **311** (whose stereochemistry was established later) was used for further work. No effort was made at this point to determine the stereochemistry.

In order to install the required silyl group on the hydroxyl, care must be taken in choosing a proper reaction order, since we also need to remove the Boc group under relatively strongly acidic conditions (trifluoroacetic acid/dichloromethane), to which the *t*-Bu_2SiHO-unit might not be stable. This potential problem was avoided by taking advantage of the relatively weak bond between nitrogen and silicon, compared with a Si-O bond. Removal of the Boc group first, gave material that could be silylated selectively on oxygen, and in this way the masked amine **313** was obtained.



Scheme 111

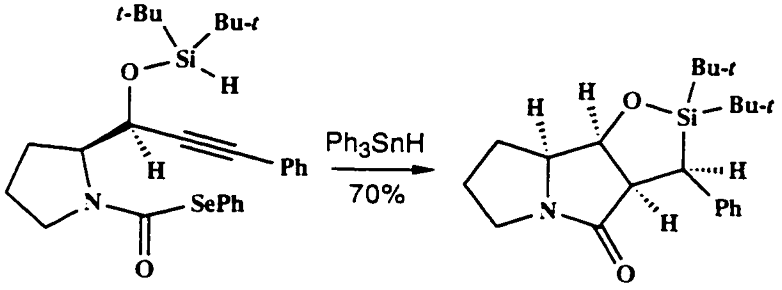
For preparation of the carbamoyl chloride (Scheme 112), the conditions reported by Pattenden *et al.*[79] (use of triphosgene) led to a reaction that was too slow, and so once again we used a solution of phosgene in toluene, but this time in the presence of a base. The reaction was conducted by addition of the phosgene solution by pipette to a stirred solution of **313** and pyridine in THF. The reaction was usually finished in less than an hour. The carbamoyl chloride **314** was stable to chromatography over silica gel.



Scheme 112

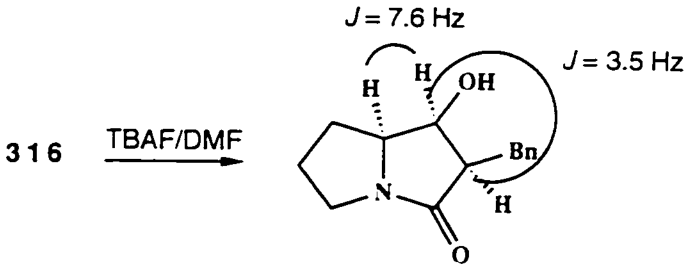
The freshly prepared carbamoyl chloride was then dissolved in THF and added to a freshly prepared ethanol solution of $PhSe^-$, again made from sodium borohydride and diphenyl diselenide. This experiment afforded the carbamoyl phenyl selenide **315**. The compound is very stable; it is not sensitive to water and can be stored at room temperature at least for several months without significant decomposition.

Radical cyclization was carried out using our standard method of slow addition of both triphenylstannane and AIBN to a refluxing solution of **315** in benzene. To our delight, we obtained compound **316** in 70% yield (Scheme 113). It was the only product formed in significant amount, as the ^{1}H NMR spectrum of the crude reaction mixture was very similar to that of the pure isolated product. Evidently, decarbonylation or direct reduction of the carbamoyl radical did not occur, and in this case, intramolecular hydrogen abstraction is unlikely, as there is no six-membered transition state available. The stereochemistry of the tricyclic product was established by comparing coupling constants of the derived **317** (obtained by treatment with TBAF, Scheme 114) with those of a closely related compound (**318**) reported[117] in the literature. The values were, of course, distinctly different from those of compound **319**.[117]



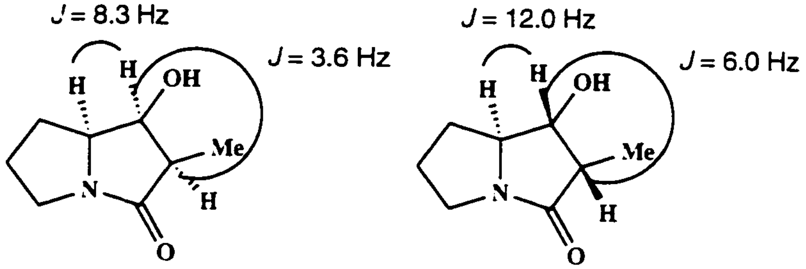
3 1 5 **3 1 6**

Scheme 113



317

Scheme 114



318 **319**

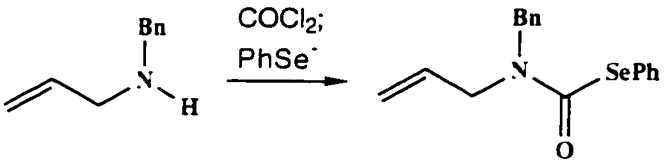
Figure 23

Cyclization of simple carbamoyl radicals (without intramolecular hydrogen transfer from silicon).

(a) Formation of the β-lactam system

Because of the satisfactory behavior of carbamoyl radicals in the formation of **316**, we decided to investigate the possibility that carbamoyl radicals might undergo 4-*exo* cyclization, leading to β–lactams.

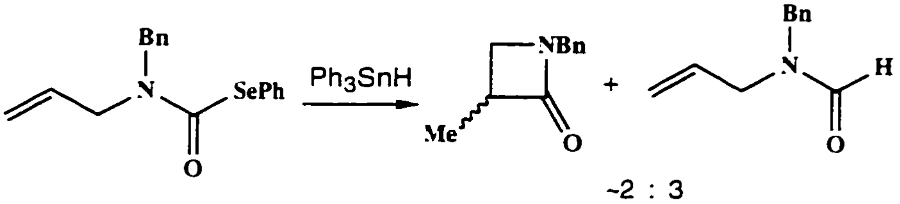
Accordingly, a simple model substrate was made from allyl benzylamine **320**. Reaction with phosgene followed by phenyl selenide addition afforded **321**.



320 **321**

Scheme 115

The cyclization was conducted in refluxing benzene, by slow addition of both triphenylstannane and AIBN.



321 **322** **323**

32%

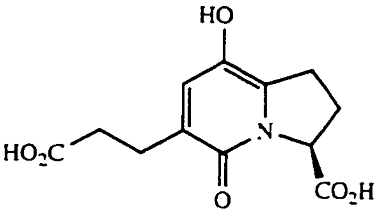
Scheme 116

As shown in Scheme 116, the ^{1}H NMR spectrum of the crude reaction mixture, after removal of solvent, revealed the complete consumption of starting material (**321**). A substantial amount of the formamide **323** was obtained, apparently from the direct hydrogen abstraction by the intermediate carbamoyl radical. The β-lactam **322** was isolated in a yield of *ca*. 32% (slight impurity present). The ^{1}H NMR data agree with the values reported[118] in the literature.

This result (*ca*. 32% yield) is similar to that obtained by the cobalt salophen methodology,[79] and the present method may prove to be a useful alternative, especially if it can be applied to allylic amines derived from amino acids without loss of optical purity.

(b) Formation of the δ-lactam system

Our attention was next focused on the construction of six-membered lactams, which are present directly or in a masked form in many natural product structures.[119] Such a lactam, for example, is seen in the blood pressure-lowering agent A58365A[120] (Figure 24).



324

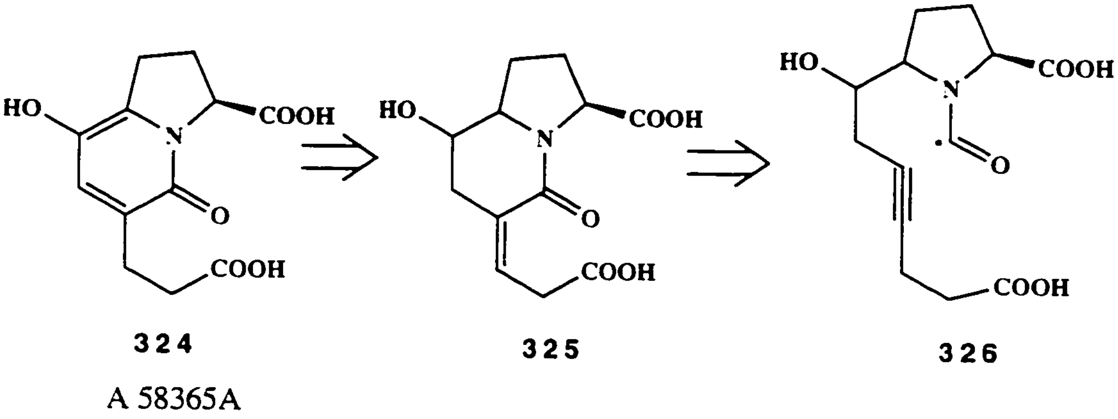
A58365A

Figure 24

Enantiomerically homogeneous A58365A in the natural *S*-configuration was synthesized by Danishefsky and Fang in 1989.[120c] The synthesis was done in 11 steps, but the authors pointed out that there were clearly some significant yield problems in "this first generation synthesis".

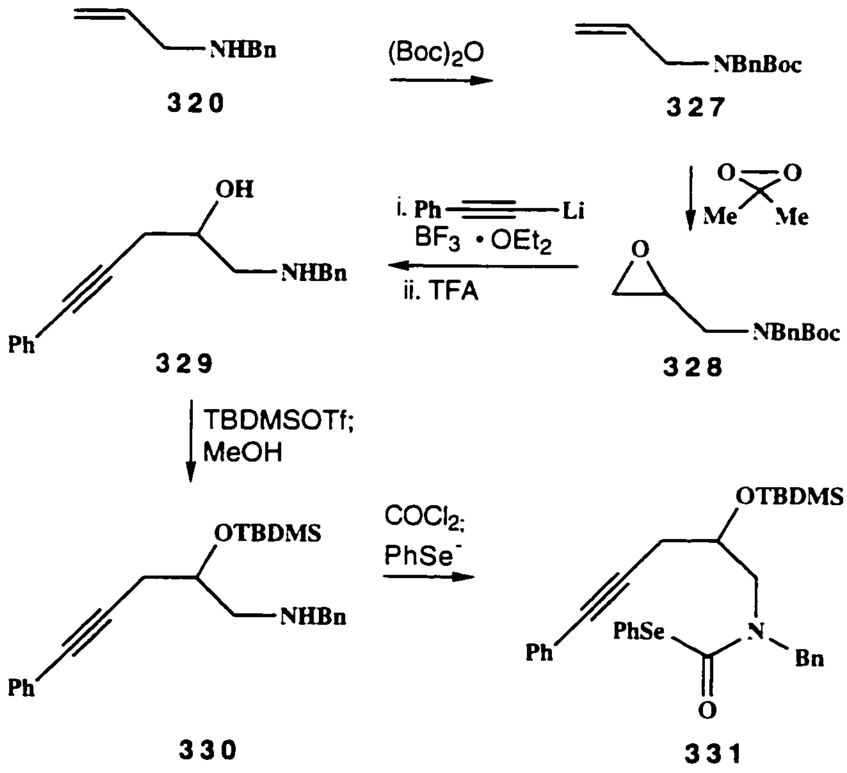
The racemic compound has been synthesized by an approach based on anodic oxidation.[120b]

It occurred to us that the cyclization of carbamoyl radicals might provide a convenient route to optically pure A58365B. Our retrosynthetic analysis of the natural product is shown in Scheme 117. In principle, the pyridone ring can be formed by oxidation of alcohol **325** with concurrent double bond isomerization from the *exo* to the *endo* position. This transformation should be easy because of the driving force of conjugation. The preliminary target then becomes the six-membered lactam **325**, and it should be possible to construct this by the carbamoyl radical cyclization methodology we had previously applied to the γ-lactam system. We appreciated that the required 6-*exo* cyclization may not be as favorable as the 5-*exo* closure of our earlier study, and there also existed in the present case the possibility of intramolecular transfer of a propargylic hydrogen.



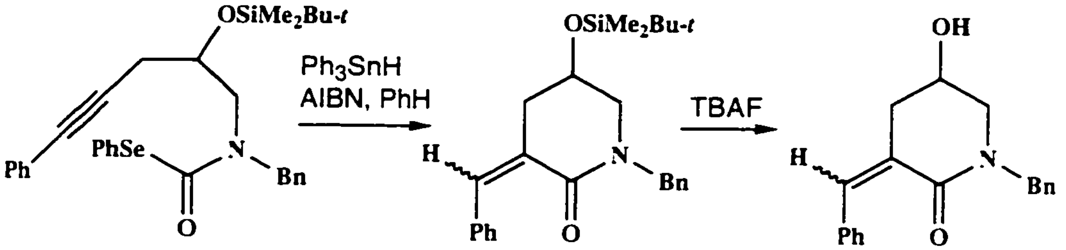
Scheme 117

A model study was first conducted, as shown in Scheme 118. The allyl benzylamine **320** was masked using $(Boc)_2O$. Epoxidation with dimethyldioxirane in acetone then gave **328**. Opening of the oxirane ring with phenyl acetylide was greatly facilitated by addition of boron trifluoride etherate,[121] and deprotection with trifluoroacetic acid then afforded **329**. The hydroxyl was next protected by silylation, using *tert*-butyldimethylsilyl triflate [t-BuMe$_2$SiOTf] in the presence of 2,6-lutidine. Workup involved addition of several drops of methanol, followed by the usual partitioning between water and an organic solvent. It is possible that during workup any *N*-silylated material is hydrolyzed. In any event, compound **330** was obtained in satisfactory yield (61% over three steps). Next, the carbamoyl chloride was prepared, adopting the previous procedure, and treatment with PhSe$^-$ gave the cyclization precursor **331**.



Scheme 118

The cyclization (scheme 119) was done by our standard method of slow addition of stannane and initiator. Again the ^1H NMR spectrum of the crude product mixture showed total consumption of the starting material. However, as in the β-lactam case, the separation of pure products was made difficult by the close R_f values of the cyclized product and the reduction product. The silicon protecting group was therefore removed to ease the separation problem, and compound **333** was obtained in 64% yield over two steps. As an approximation, the yield of the cyclization was assumed to be 70-80%, based on our experience with many TBAF deprotection reactions, which give yields of *ca*. 90%.



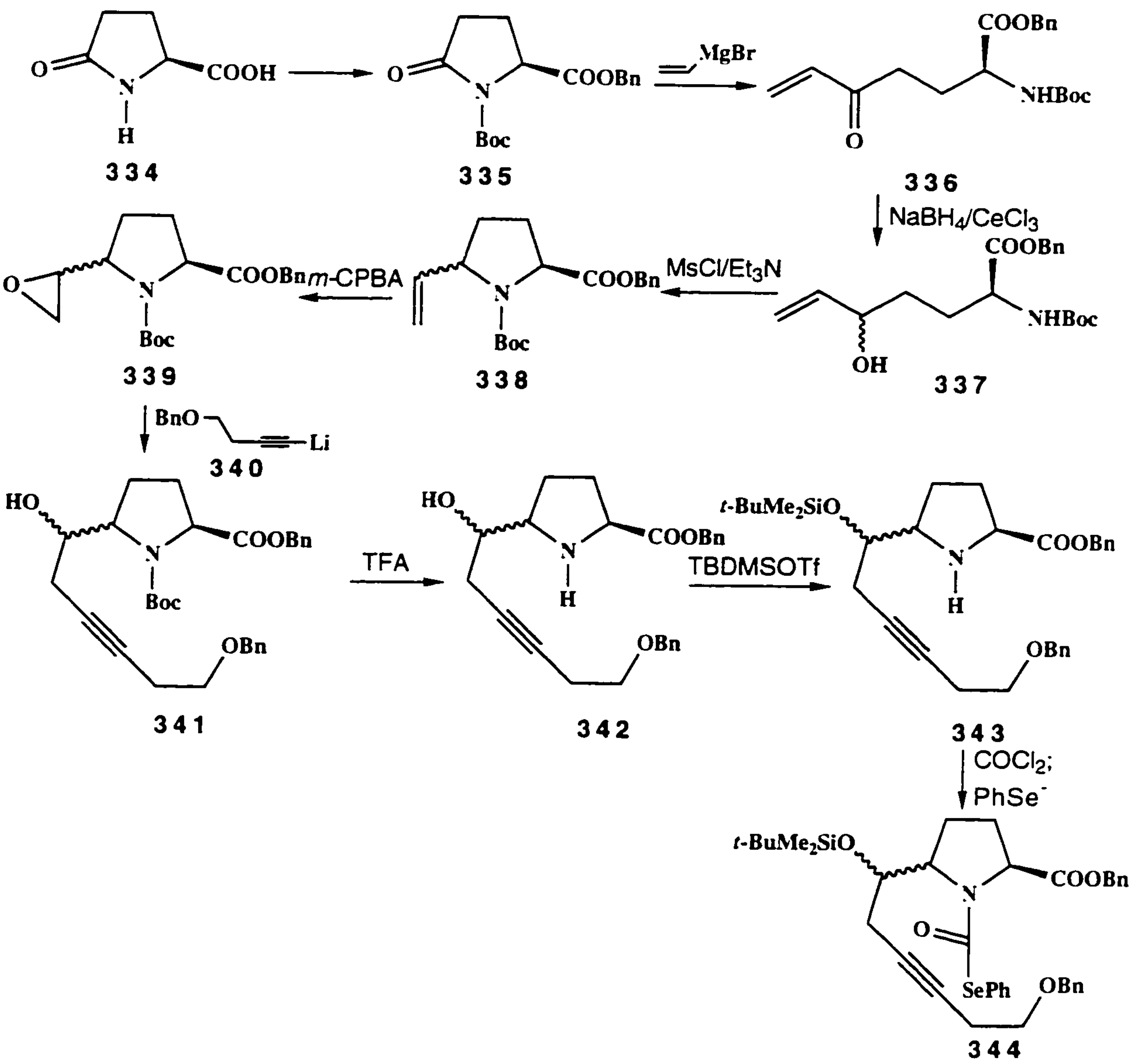
331 **332** **333**

ca. 64% over two steps

Scheme 119

This model study reveals the efficiency of the 6-*exo* carbamoyl radical cyclization, and hence prompted us to begin the synthesis of A58365A, using the same approach.

We started with natural (*L*)-pyroglutamic acid to take advantage of the existing stereocenter (Scheme 120). Intermediate **334** has been reported in the literature.[122] We used a slightly modified route to make this compound (as a mixture of two diastereomers). Each of the steps proceeds in good (>80%) yield. No effort was made to separate the two isomers, since the chiral center connected to the double bond would eventually be converted to sp^2 hybridization. The disadvantage of carrying on the sequence with a mixture of diastereoisomers is mainly in the difficulty of spectral interpretation. However, we felt that since the subsequent steps involved are all straightforward, this difficulty could be accepted.



Scheme 120

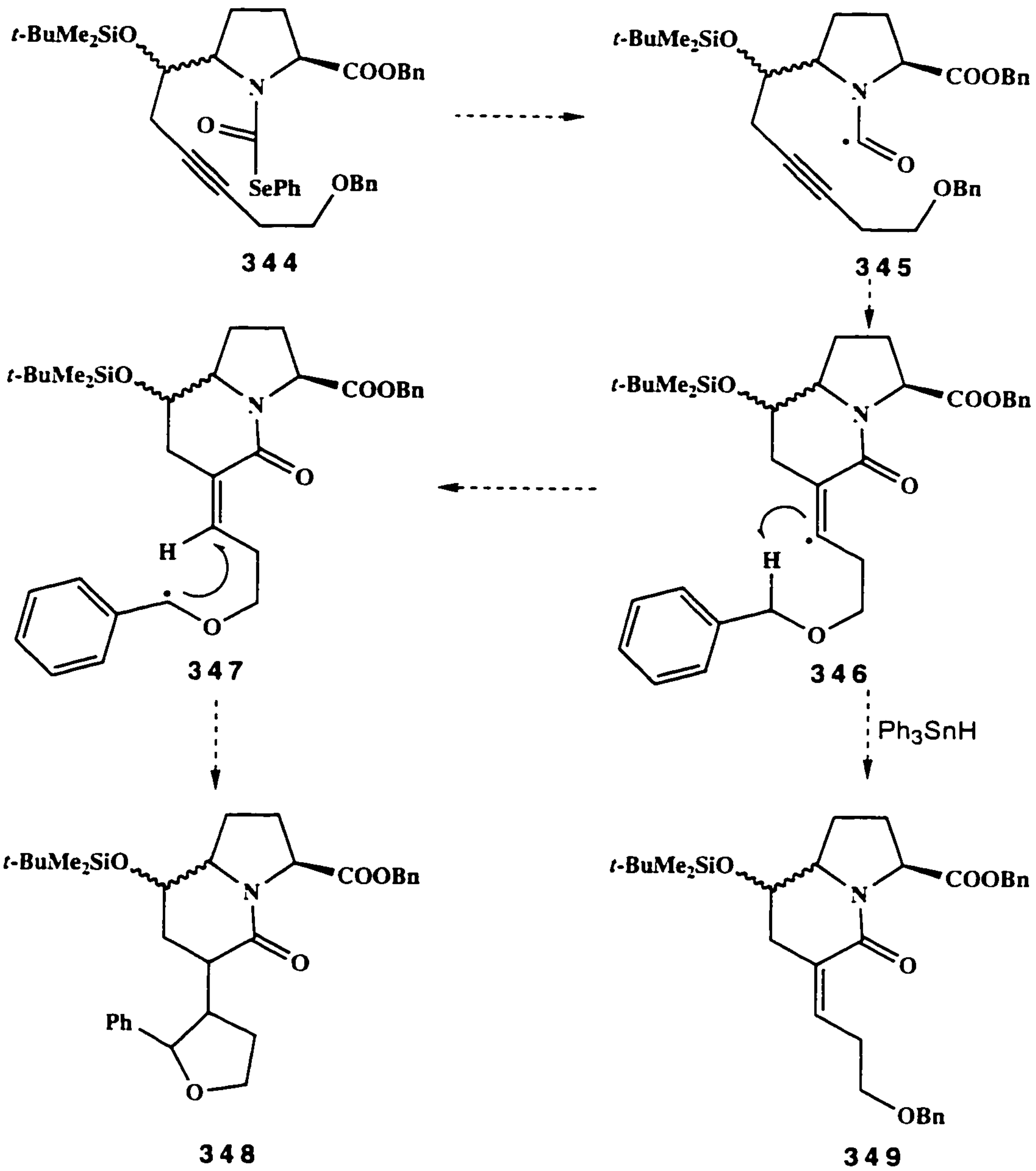
Epoxidation of **338** was very slow with dimethyldioxirane. After conducting a series of experiments, we found that the use of *m*-chloroperbenzoic acid in hot (*ca*. 50 °C) ethyl acetate is the best method. Frequently several equivalents of *m*-chloroperbenzoic acid had to be added, but we could achieve a yield of 80 % for this step.

Reaction with acetylide **340** in the presence of boron trifluoride etherate smoothly afforded **341**, which was treated with neat trifluoroacetic acid directly after aqueous workup. The deprotection went smoothly to give the amino alcohols **342**.

The sequence used in the model study was followed to selectively protect the hydroxy group in the presence of the nitrogen, so as to obtain amine **343**. Reaction of **343** with phosgene in the presence of pyridine gave the crude carbamoyl chloride for next step. This was treated with $PhSe^-$, generated, as before, from diphenyl diselenide and sodium borohydride in ethanol. The reaction was much slower than with the model compound, even with several equivalents of $PhSe^-$ present. The reaction was worked up after *ca*. 15 h, and the product was isolated in 40% yield, together with most of the unreacted starting material recovered.

The selenocarbamate **344** was subjected to the radical cyclization conditions. To our disappointment, even though the ^1H NMR spectrum of the crude product mixture showed the absence of any starting material, we could not isolate or detect any of our desired compound **349**, and the NMR spectrum showed no vinylic proton signals.

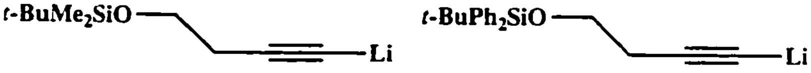
Closer examination of the radical precursor **344**, offered one plausible explanation for the absence of vinylic signals in the ^1H NMR spectrum of the crude product. This explanation is summarized in Scheme 121.



Scheme 121

We propose that the carbamoyl radical **338** was generated, and then cyclized by the 6-*exo* mode to form intermediate **339**. If the new radical abstracts hydrogen from triphenylstannane, then the expected product would be formed. However, the new vinylic radical could abstract a benzylic hydrogen intramolecularly, via a 1,5 transfer. This type of abstraction has precedent,[123] and would give **347**. The new stabilized benzylic radical would then cyclize onto the double bond in a 5-*exo* fashion to give **348** which, of course, lacks vinylic hydrogen.

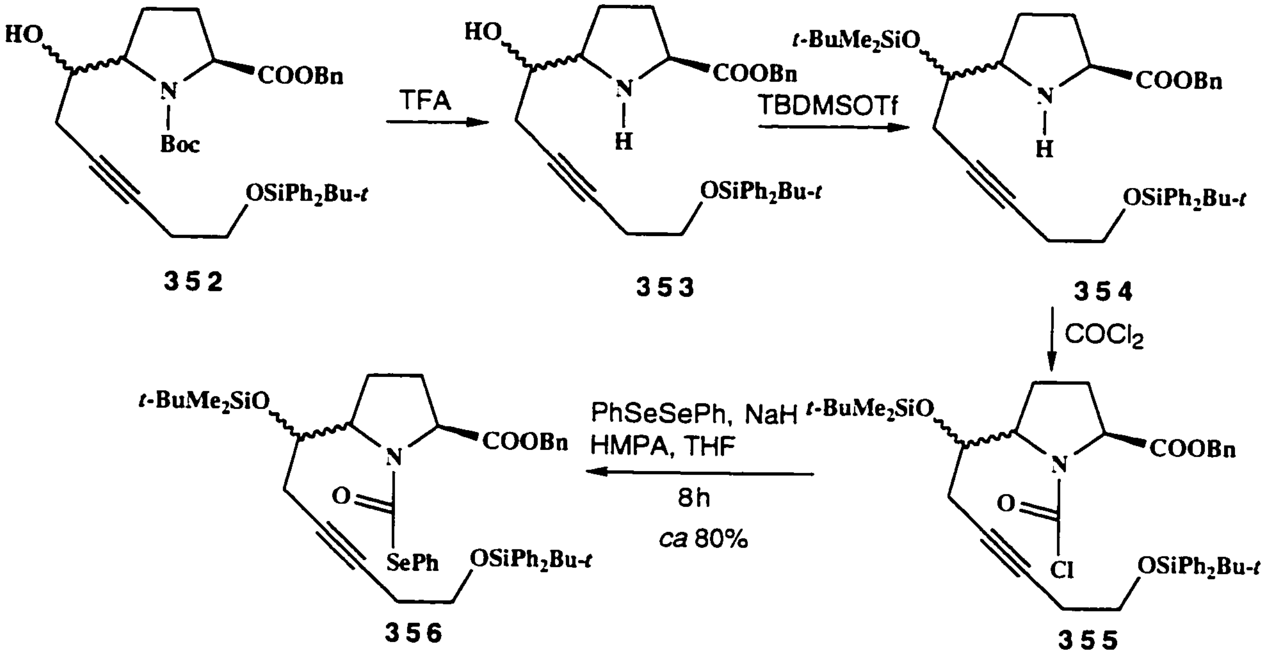
Based on this tentative interpretation, we set out to repeat the synthesis, but using a different protecting group in place of the original benzyl unit on the acetylene. A *tert*-butyldimethylsilyl-masked acetylide **350** was used first and it reacted with epoxide **339**. Unfortunately, the *t*-BuMe$_2$Si group was partially cleaved during the boron trifluoride-promoted ring opening of the epoxide. This problem was subsequently avoided by using a less acid labile *t*-BuPh$_2$Si- protecting group. As shown in Scheme 122, acetylide **351** reacted with epoxides **339** to afford compounds **352**.



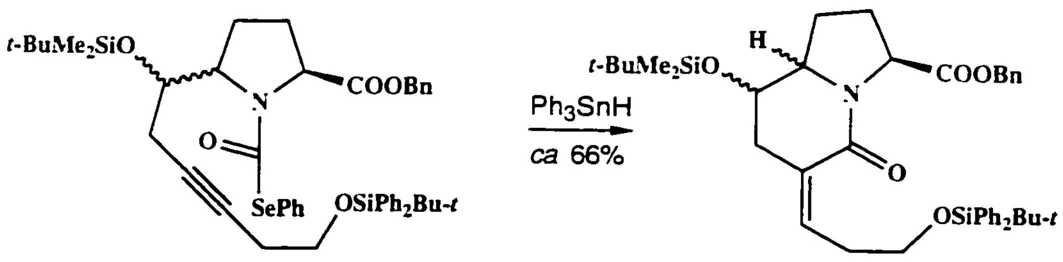
350 **351**

Figure 25

These were next deprotected at room temperature using 50% (v/v) trifluoroacetic acid in dichloromethane. However, some of the *t*-BuPh$_2$Si group was lost during the process. We eventually found it necessary to maintain the reaction temperature around -10 °C in order to avoid substantial loss of the silicon moiety. The previous method to form the phenylselenocarbamate was followed; it worked well and gave **356** in *ca*. 80% yield. We noticed that the intermediate carbamoyl chloride could be chromatographed over silica gel, and reaction with $PhSe^-$ was even slower than in the preparation of **344**. A large excess of reagent and a reaction time of several days were required. When we used $PhSe^-$ (prepared from sodium hydride reduction of diphenyl diselenide in THF) in the presence of HMPA, the reaction was much faster (6-8 h, *ca*. 1.5 equivalents of $PhSe^-$) (Scheme 122).



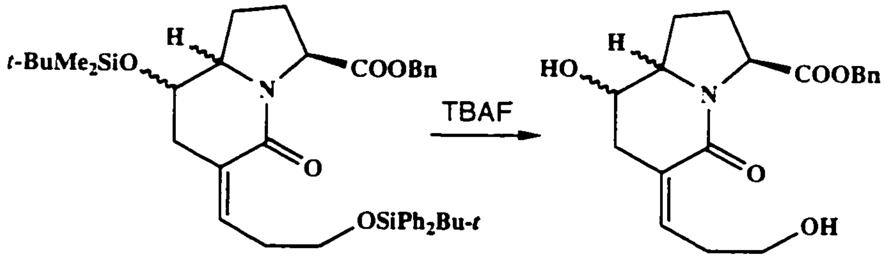
Scheme 122



356 357

Scheme 123

Cyclization was conducted under our standard conditions, and it led to the desired compound **357** in a yield of *ca*. 66%. The ^{1}H NMR spectrum showed a one hydrogen signal at 6.9 ppm as a multiplet, and we take this signal to be characteristic of the conjugated vinylic proton in the desired product. Upon removal of both silicon protecting groups, this multiplet turned into two separate triplets, presumably indicating the presence of *Z*/*E* isomers. Further work is underway to fully characterize **357**, and take it on to the natural product.



357 358

Scheme 124

Conclusion

The sequence summarized by Scheme 72 can be extended to the preparation of hetereocyclic systems of the tetrahydrofuran, γ-lactone, chromanol, pyrrolidine, and γ-lactam classes.

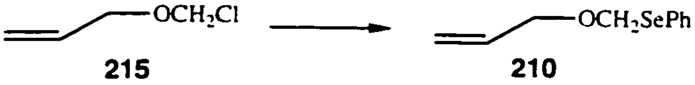
Carbamoyl radicals can be generated thermally by using a stannane, and they cyclize to form four-, five-, and six-membered rings. The latter process is being studied as a route to the blood pressure-lowering agent A58365B, and work on that project is at an advanced stage.

III Experimental

General procedures

The same general procedures specified in Chapter 1 apply to the following experiments.

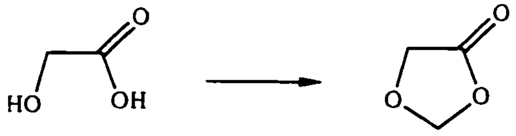
Allyl (phenylseleno)methyl ether (210).



NaI (672 mg, 4.50 mmol) was added in one portion to a stirred solution of **215** (457.2 mg, 4.47 mmol) in DME (15.0 mL). The mixture was stirred at room temperature overnight. A solution of freshly prepared PhSeNa solution [from PhSeSePh (780.0 mg, 2.5 mmol) and $NaBH_4$ (*ca* 250 mg, 6.5 mmol)] in EtOH (10.0 mL) was added. The mixture was further stirred for 10 h. Et_2O (50 mL) was added and the organic solution was washed with water (20 mL x 2), brine (20 mL x 2) and dried (Na_2SO_4). Evaporation of the solvent and flash chromatograph of the residue over silica gel (2 x 20 cm), using 1:5 EtOAc-hexane, gave **210** (795.0 mg, 80%) as a pure (^1H NMR, 300 MHz), yellowish oil: FTIR ($CHCl_3$, cast) 3055, 2951 cm^{-1},; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.18 (t, J = 1.4 Hz, 1 H), 4.19 (t, J = 1.5 Hz, 1 H), 5.19-5.40 (m, 4 H), 5.95 (m, 1 H), 7.38-7.50 (m, 3 H), 7.60-7.73 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 65.0, 71.4 (J_{C-Se} = 119 Hz), 118.0, 127.2, 129.2, 132.7, 133.08, 133.7;

exact mass m/z calcd for $C_{10}H_{12}O^{80}Se$ 228.00534, found 228.00498.

1,3-Dioxolan-4-one (233).

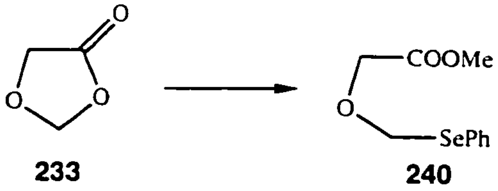


237 **233**

The literature general method[103] was used with some modifications.

Glycolic acid (2.28 g, 30 mmol) and paraformaldehyde (1.29 g, 36 mmol) were dissolved in PhH (80.0 mL). *p*-TsOH.H_2O (242.0 mg, 1.40 mmol) was added and the mixture was refluxed for 12 h, using a Dean-Stark apparatus. The reaction mixture was cooled, washed with 5% aqueous $NaHCO_3$ (40 mL), water (40 mL) and brine (40 mL), and dried (Na_2SO_4). Evaporation of the solvent and flash chromatograph of the residue over silica gel (2 x 20 cm), using 1:3 EtOAc-hexane, gave dioxolanone **233** (450.0 mg, 14%) as a pure (^1H NMR, 300 MHz), colorless oil: ^1H NMR ($CDCl_3$, 300 MHz) δ 4.2 (s, 2 H), 5.5 (s, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 62.28 (t'), 96.02 (t'), 171.49 (s'). The ^1H NMR and ^{13}C NMR data are identical to those reported in the literature.

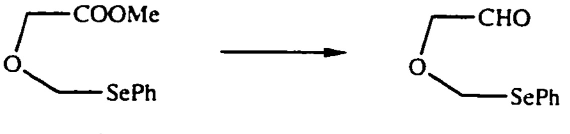
Methyl [(Phenylseleno)methoxy]acetate (240).



NaH (80% dispersion in mineral oil, 142.0 mg, 3.56 mmol) was added in one portion to a stirred solution of PhSePh (623.0 mg, 1.98 mmol) in THF (10.0 mL). The suspension was refluxed for 1 h, and then cooled down to room temperature. HMPA (0.3 mL, 1.73 mmol) was added, followed by a solution of dioxolanone **233** (280.0 mg, 2.64 mmol) in THF (1 mL plus 1 mL as a rinse). The resulting mixture was refluxed for 6 h. Water (2 mL) and 6 N HCl (2 mL) were added, and the solution was extracted with CH_2Cl_2 (3 x 15 mL). The organic layer was washed with brine (3 x 10 mL), dried ($MgSO_4$) and evaporated. The residue was re-dissolved in MeOH (40 mL), concentrated H_2SO_4 (five drops) was added, and the solution was refluxed overnight. The solvent was evaporated and the residue was dissolved in EtOAc (40 mL), washed with saturated aqueous $NaHCO_3$ (3 x 20 mL) and brine (2 x 20 mL), and dried (Na_2SO_4). Evaporation of the solvent and flash chromatograph of the residue over silica gel (2 x 20 cm), using 1:10 EtOAc-hexane, gave **240** (547.0 mg, 80%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR ($CHCl_3$, cast) 2951, 1754 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.78 (s, 3 H), 4.29 (s, 2 H), 5.4 (t, J = 9.7 Hz, 2 H), 7.2-7.35 (m, 3 H), 7.5-7.7 (m, 2 H); ^{13}C NMR

($CDCl_3$, 50.3 MHz), δ 51.98 (q'), 65.51 (t'), 72.52 (t'), 127.43 (d'), 129.21 (d'), 129.99 (s'), 132.91 (d'), 169.85 (s'); exact mass *m/z* calcd for $C_{10}H_{12}O_3{}^{80}Se$ 259.99518, found 259.99503.

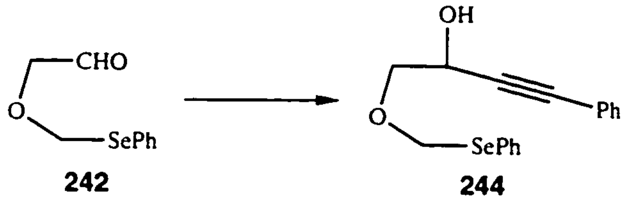
[(Phenylseleno)methoxy]acetaldehyde (242).



240 242

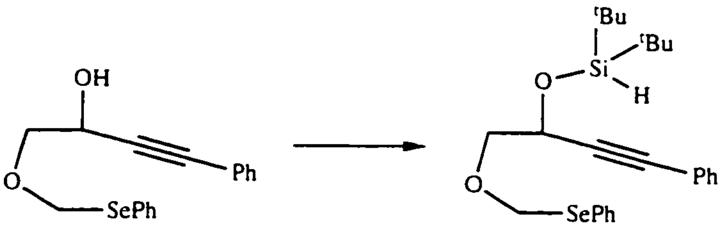
DIBAL-H (0.80 mL, 1.0 M in CH_2Cl_2) was added dropwise to a stirred and cooled (-78 °C) solution of **240** (130.0 mg, 0.5 mmol) in CH_2Cl_2 (20 mL). The solution was stirred for another 1.5 h at -78 °C after the addition. Water (1 mL) was added and the cold bath was removed. After 1 h the solvent was evaporated and the residue was dissolved in Et_2O (30 mL), washed with 3 N HCl (3 x 20 mL), saturated aqueous Na_2CO_3 (2 x 20 mL) and dried (Na_2SO_4). Evaporation of the solvent and flash chromatograph of the residue over silica gel (2 x 20 cm), using 1:4 EtOAc-hexane, gave **242** (91.0 mg, 80%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2, cast) 3051, 2987, 2814, 1736 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 4.21 (s, 2 H), 5.35 (s, 2 H), 7.25-7.35 (m, 3 H), 7.55-7.65 (m, 2 H), 9.71 (s, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 72.92 (t'), 74.20 (t'), 127.58 (d'), 129.18 (d'), 129.73 (s'), 132.93 (d'), 203.87 (s'); exact mass *m/z* calcd for $C_9H_{10}O_2{}^{80}Se$ 229.98460, found 229.98376.

4-Phenyl-1-[(phenylseleno)methoxy]-3-butyn-2-ol (244).



n-BuLi (1.6 M solution in hexanes, 0.20 mL, 0.32 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of phenylacetylene (40.0 mg, 0.38 mmol) in THF (15.0 mL). The mixture was stirred for 30 min, and a solution of aldehyde **242** (72.5 mg 0.32 mmol) in THF (4.0 mL plus 1.0 mL as a rinse) was then added at a fast dropwise rate (*ca* 2 min). The mixture was stirred at -78 °C for 1 h and then the cold bath was removed. When the temperature had reached 0 °C, saturated aqueous NH_4Cl (10.0 mL) was added, and the mixture was extracted with Et_2O (3 x 20 mL). The combined organic extracts were washed with brine (2 x 15 mL), dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (20 cm x 2 cm), using 1:4 EtOAc-hexane, gave **244** (92.0 mg, 87%) as a pure (^{1}H NMR, 300 MHz), colorless oil: FTIR ($CHCl_3$, cast) 3422, 3055, 2232 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.46 (d, J = 5.4 Hz, 1 H), 3.81 (dd, J = 9.8, 6.9 Hz, 1 H), 3.89 (dd, J = 9.8, 3.6 Hz, 1 H), 4.80 (m, 1 H), 5.39 (dd, J = 11.3, 10.0 Hz, 2 H), 7.19-7.70 (m, 10 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 61.90 (d'), 72.85 (t'), 72.89 (t'), 85.85 (s'), 86.47 (s'), 122.2 (s'), 127.44 (d'), 127.8 (d'), 127.27 (d'), 128.6 (d'), 129.17 (d'), 130.0 (s'), 131.82 (d'), 133.30 (d'); exact mass *m/z* calcd for $C_{17}H_{16}O_2{}^{80}Se$ 332.03156, found 332.03159.

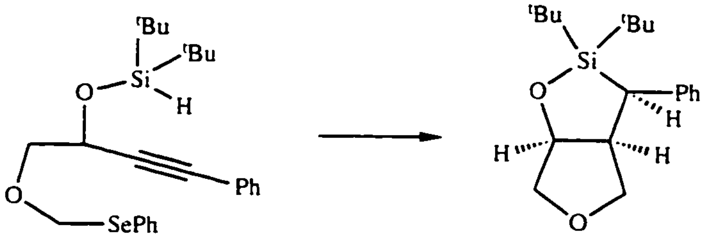
Bis(1,1-dimethylethyl)[[3-phenyl-1-[[(phenylseleno)methoxy]-methyl]-2-propynyl]oxy]silane (246).



244
246

t-Bu_2SiHCl (16.0 mg, 0.089 mmol) was added in one portion to a stirred solution of **244** (20.4 mg, 0.06 mmol) and Et_3N (0.1 mL, 0.09 mmol) in CH_2Cl_2 (1.5 mL), followed by a small crystal of DMAP. The mixture was refluxed for 2 h, cooled, and evaporated. Flash chromatograph of the residue over silica gel (1 x 10 cm), using 1:10 EtOAc-hexane, gave **246** (28.5 mg, 95%) as a pure (^{1}H NMR, 300 MHz), colorless oil: FTIR ($CHCl_3$, cast) 2104 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.05 (s, 9 H), 1.10 (s, 9 H), 3.79-3.92 (m, 2 H), 4.20 (s, 1 H), 4.90 (dd, *J* = 6.5, 4.9 Hz, 1 H), 5.20 (d, *J* = 9.9 Hz, 1 H), 5.31 (d, *J* = 9.9 Hz, 1 H), 7.20-7.34 (m, 6 H), 7.40-7.45 (m, 2 H), 7.60-7.70 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz); δ 19.82 (s'), 20.17 (s'), 27.27 (q'), 65.93 (d'), 73.05 (t'), 73.46 (t'), 85.80 (s'), 87.65 (s'), 127.13 (d'), 128.21 (d'), 128.34 (d'), 129.02 (d'), 131.66 (d'), 133.07 (d'); exact mass *m/z* calcd for $C_{17}H_{16}O_2{}^{80}Se$ 332.03156, found 332.03154.

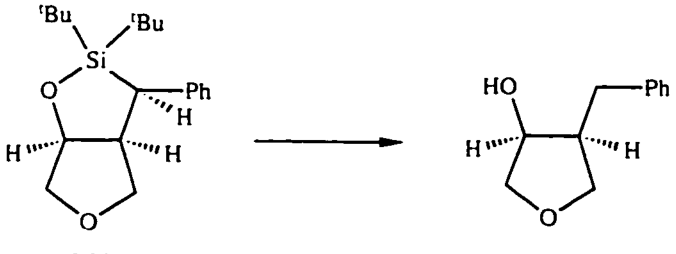
(3α,3aβ,6aβ)-2,2-Bis(1,1-dimethylethyl)hexahydro-3-phenylfuro[3,4-d]-1,2-oxasilole (248).



246 **248**

Solutions of Ph_3SnH (90.9 mg, 0.25 mmol) in PhH (4.0 mL) and of AIBN (5.0 mg, 0.03 mmol) in PhH (4.0 mL) were added simultaneously by syringe pump over 6 h to a stirred and refluxing solution of **246** (64.3 mg, 0.135 mmol) in PhH (25 mL). Refluxing was continued for 1 h after the end of the addition, and the mixture was then cooled to room temperature and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 1:3 EtOAc-hexane, gave the bicyclic product **248** (36.0 mg, 85%) as a pure (^1H NMR 300 MHz), white solid: mp 106-108 °C; FTIR ($CHCl_3$, cast) 2965, 2931, 1600 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.05 (s, 9 H), 1.14 (s, 9 H), 3.33 (m, 1 H), 3.47 (d, J = 7.9 Hz, 1 H), 3.85 (dd, J = 9.8, 3.2 Hz, 1 H), 3.92 (dd, J = 9.2, 7.45 Hz, 1 H), 4.05 (t, J = 9.3 Hz, 2 H), 4.65 (m, 1 H), 7.10-7.30 (m, 5 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 21.15 (s'), 22.31 (s'), 28.20 (q'), 28.41 (q'), 35.14 (d'), 46.79 (d'), 70.20 (t'), 75.60 (t'), 81.87 (d'), 125.15 (d'), 128.40 (d'), 128.76 (d'), 140.94 (s'); exact mass *m/z* calcd for $C_{19}H_{30}O_2Si$ 318.20151, found 318.20106.

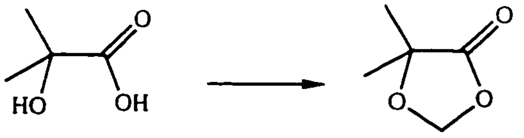
(3*RS*, 4*RS*)-*cis*-4-Benzyl-3-hydroxytetrahydrofuran (250).



248 **250**

TBAF (1.0 M in THF, 0.75 mL, 0.75 mmol) was added to a stirred solution of **248** (20.0 mg, 0.063 mmol) in DMF (1.0 mL), and stirring was continued for 2 h. Evaporation of the solvent and chromatography of the residue over silica gel (2 x 10 cm), using AcOH, gave **250** (8.0 mg, 71%) as a pure (^{1}H NMR, 360 MHz), colorless oil: FTIR ($CHCl_3$, cast) 3387, 3083 cm^{-1}; ^{1}H NMR ($CDCl_3$, 360 MHz) δ 1.59 (d, *J* = 1.9 Hz, 1 H), 2.51 (m, 1 H), 2.75 (dd, *J* = 13.9, 7.27 Hz, 1 H), 2.95 (dd, *J* = 13.9, 8.3 Hz, 1 H), 3.65 (dd, *J* = 10.3, 8.1 Hz, 1 H), 3.82 (dd, *J* = 10.0, 0.9 Hz, 1 H), 3.90-4.00 (m, 2 H), 4.24 (dd, *J* = 8.6, 4.1 Hz, 1 H), 7.18-7.36 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 31.84 (t'), 46.55 (d'), 71.16 (t'), 72.60 (d'), 76.27 (t'), 126.25 (d'), 128.59 (d'), 140.39 (s'); exact mass *m/z* calcd for $C_{11}H_{14}O_2$ 178.09938, found 178.09902.

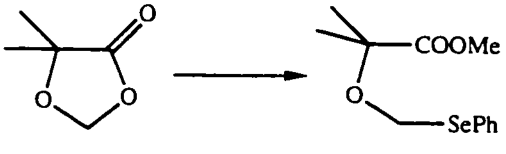
5,5-Dimethyl-1,3-dioxolan-4-one (239).



238 **239**

The literature method[103] was followed with some modifications. Hydroxy acid **238** (10.4 g, 100 mmol), *s*-trioxane (3.5 g, 38.5 mmol), PhH (200 mL), and *p*-TsOH.H_2O (1.0 g, 5.7 mmol) were stirred and refluxed for 30 h in a flask fitted with a Soxhlet apparatus containing a thimble packed with CaH_2 (*ca* 2.0 g) for removal of water (Ar atmosphere). The reaction mixture was cooled, washed with 5% aqueous $NaHCO_3$ (20 mL), water (50 mL) and brine (20 mL), and dried (Na_2SO_4). Evaporation of the solvent, gave **239** (9.50 g, 82%) as a pure (^{1}H NMR, 300 MHz), colorless oil: FTIR ($CHCl_3$, cast) 1738, 1478 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.45 (s, 6 H), 5.45 (s, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 22.31 (q'), 75.31 (s), 91.97 (t'), 175.43 (s'). The ^{1}H NMR and ^{13}C NMR data are identical to those reported in the literature.

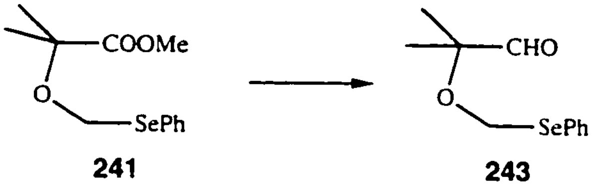
Methyl 2-Methyl-2-[(phenylseleno)methoxy]propanoate (241).



239 **241**

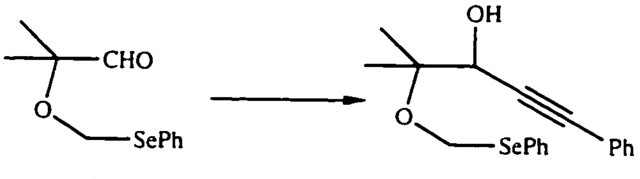
NaH (80% dispersion in mineral oil, 1.0 g, 33.3 mmol) was added in portions to a stirred solution of PhSePh (5.80 g, 18.55 mmol) in THF (100.0 mL). The mixture was refluxed for 1 h, and then cooled to room temperature. HMPA (2.5 mL, 14.38 mmol) was added, followed by a solution of dioxolanone **239** (2.8728 g, 24.74 mmol) in THF (3 mL plus 3 mL as a rinse). Refluxing was resumed and continued overnight. The solution was cooled to room temperature, and MeOH (2.0 mL) added. The solvent was evaporated and the residue was partitioned between water (50 mL) and Et_2O (50 mL). The aqueous layer was acidified (3 N HCl) and extracted with Et_2O (2 x 50 mL). The combined organic extracts were washed with brine (2 x 50 mL) and dried ($MgSO_4$). The solvent was evaporated and the residue was re-dissolved in MeOH (50 mL). Concentrated H_2SO_4 (five drops) were added and the mixture was refluxed overnight. Most of the solvent was evaporated and the residue was dissolved in Et_2O (50 mL). The solution was then washed with saturated aqueous $NaHCO_3$ (3 x 20 mL), brine (30 mL) and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 30 cm), using 1:5 EtOAc-hexane, gave ester **241** (5.0 g, 70%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR ($CHCl_3$, cast) 1738, 1478 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 6 H), 3.68 (s, 3 H), 5.20 (s, 2 H), 7.23-7.32 (m, 3 H), 7.55-7.65 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 24.59 (q'), 52.17 (q'), 65.64 (s'), 78.96 (t'), 127.15 (d'), 128.97 (d'), 130.85 (s'), 132.83 (d'), 174.51 (s'); exact mass *m/z* calcd for $C_{12}H_{16}O_3{}^{80}Se$ 288.02646, found 288.02598.

2-Methyl-2-[(phenylseleno)methoxy]propanal (243).



DIBAL-H (1.0 M in CH_2Cl_2, 12.0 mL, 0.012 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of ester **241** (3.45 g, 11.9 mmol) in CH_2Cl_2 (100 mL). The solution was stirred at -78 °C for 4 h, and 2 N HCl (20 mL) was then added. The aqueous phase was extracted with CH_2Cl_2 (3 x 20 mL), and the combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatograph of the residue over silica gel (3 x 30 cm), using 1:3 EtOAc-hexane, gave **243** (2.78 g, 90%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR ($CHCl_3$, cast) 3071, 3057, 2983, 2804, 1735 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.30 (s, 6 H), 5.29 (s, 2 H), 7.25-7.35 (m, 3 H), 7.58-7.70 (m, 2 H), 9.65 (s, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 20.97 (q'), 65.61 (s'), 81.85 (t'), 127.45 (d'), 129.25 (d'), 130.20 (s'), 132.66 (d'), 203.39 (d'); exact mass *m/z* calcd for $C_{11}H_{14}O_2{}^{80}Se$ 258.01590, found 258.01589.

4-Methyl-4-[(phenylseleno)methoxy]-1-phenyl-1-pentyn-3-ol (245).

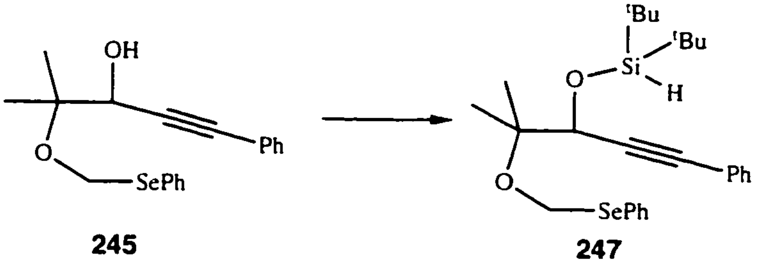


243 **245**

n-BuLi (1.6 M solution in hexanes, 4.20 mL, 6.72 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of phenylacetylene (842.8 mg, 8.25 mmol) in THF (20 mL). The solution was stirred for 30 min, and a solution of aldehyde **243** (1.4148 g, 5.48 mmol) in THF (4.0 mL plus 1.0 mL as a rinse) was added at a fast dropwise rate. The mixture was stirred at -78 °C for 2 h, saturated aqueous NH_4Cl (15.0 mL) was added. The mixture was extracted with Et_2O (3 x 20 mL) and the combined organic extracts were washed with brine (2 x 15 mL), dried (Na_2SO_4), and evaporated. Flash chromatography of the residue over silica gel (20 x 2 cm), using 1:4 EtOAc-hexane, gave **245** (1.79 g, 90%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR ($CHCl_3$, cast) 3442, 3055, 1464 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.39 (s, 3 H), 1.48 (s, 3 H), 3.02 (d, *J* = 5.1 Hz, 1 H), 4.55 (d, *J* = 5.2 Hz, 1 H), 5.26 (d, *J* = 14.6 Hz, 1 H), 5.31 (d, *J* = 14.6 Hz, 1 H), 7.25-7.40 (m, 6 H), 7.41-7.60) (m, 2 H), 7.61-7.76 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 20.59 (q'), 22.33 (q'), 64.30 (t'), 69.47 (d'), 80.71 (s'), 86.10 (s'), 87.34 (s'), 122.61 (s'), 127.50 (d'), 128.36 (d'), 128.58 (d'), 129.22 (d'), 130.54 (s'), 131.83

(d'), 133.31 (d'); exact mass *m/z* calcd for $C_{11}H_{20}O_2{}^{80}Se$ 360.06284, found 360.06191.

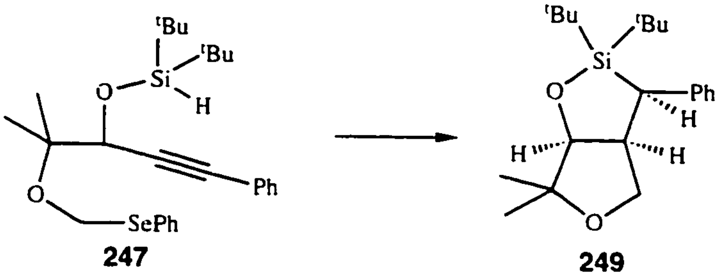
Bis(1,1-dimethylethyl)[[1-[1-methyl-1-[(phenylseleno)methoxy]ethyl]-3-phenyl-2-propynyl]oxy]silane (247).



t-Bu_2SiHCl (500.0 mg, 2.5 mmol) in THF (1 mL plus 0.5 mL as a rinse) was added to a solution of **245** (820.0 mg, 2.28 mmol) in THF (10 mL). Imidazole (205.0 mg, 3.0 mmol) was added to the mixture and the solution was refluxed for 6 h, and cooled to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:10 EtOAc-hexane, gave **247** (1.20 g, 90%) as a pure (^1H NMR, 300 MHz), colorless oil: FTIR ($CHCl_3$, cast) 2105 cm^{-1} (Si-H); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.03 (s, 9 H), 1.15 (s, 9 H), 1.45 (s, 6 H), 4.30 (s, 1 H), 4.68 (s, 1 H), 5.33 (d, J = 11.2 Hz, 2 H), 5.36 (d, J = 11.2 Hz, 2 H), 7.16-7.28 (m, 3 H), 7.30-7.40 (m, 3 H), 7.40-7.50 (m, 2 H), 7.63-7.73 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 19.87 (s'), 20.60 (s'), 21.59 (q'), 21.93 (q'), 27.50 (q'), 27.56 (q'), 64.69 (s'), 73.24 (d'), 80.90 (t'), 86.46 (s'), 88.30 (s'), 123.07

(s'), 126.98 (d'), 128.30 (d'), 128.99 (d'), 131.51 (s'), 131.65 (d'), 132.93 (d'); exact mass *m/z* calcd for $C_{17}H_{25}O_2Si$ (M^+ - PhSe - C_4H_9) 289.16238, found 289.16292.

(3α,3aβ,6aβ)-2,2-Bis(1,1-dimethylethyl)hexahydro-6,6-dimethyl-3-phenylfuro[3,4-d]-1,2-oxasilole (249).

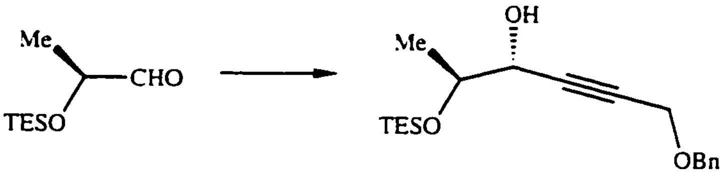


247 **249**

Solutions of Ph_3SnH (191.0 mg, 0.54 mmol) in PhH (5.0 mL) and of AIBN (5.0 mg, 0.03 mmol) in PhH (5.0 mL) were added simultaneously over 6 h by syringe pump to a stirred and refluxing solution of **247** (182.5 mg, 0.363 mmol) in PhH (50.0 mL). Refluxing was continued for 1 h, and the mixture was then cooled to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:3 EtOAc-hexane, gave **249** (106.0 mg, 85%) as a pure (^{1}H NMR, 300 MHz), colorless oil: FTIR ($CHCl_3$, cast) 3038, 1496 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.09 (s, 9 H), 1.15 (s, 9 H), 1.21 (s, 3 H), 1.40 (s, 3 H), 3.44 (d, *J* = 7.5 Hz, 1 H), 3.60 (m, 1 H), 3.90 (dd, *J* = 9.9, 8.1 Hz, 1 H), 4.15 (dd, *J* = 12.1, 7.5 Hz, 2 H), 7.17-7.32 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 21.31 (s'), 22.30 (s'), 22.60 (q'), 24.66 (q'), 28.18 (q'), 28.36 (q'), 35.48 (d'), 46.17 (d'), 68.38

(t'), 84.18 (s'), 86.71 (d'), 125.07 (d'), 128.36 (d'), 128.81 (d'), 141.06 (s'); exact mass *m/z* calcd for $C_{21}H_{34}O_2Si$ 346.23282, found 346.23295.

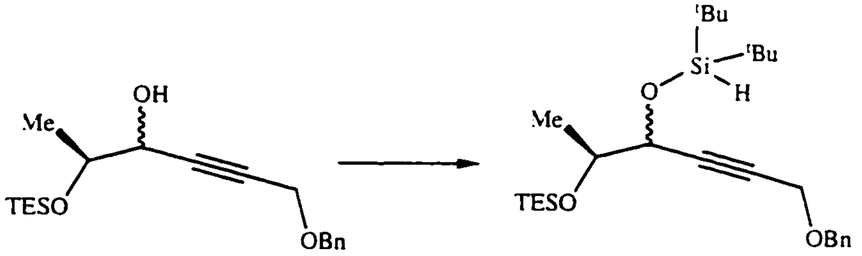
(2*S*,3*R*)-6-(Phenylmethoxy)-2-[(triethylsilyl)oxy]hex-4-yn-3-ol (275).



274 **275**

n-BuLi (1.6 M solution in hexanes, 10.0 mL, 16.0 mmol) was added slowly to a cooled (-78 °C) solution of acetylene (2.45 g, 16.78 mmol) in THF (30 mL). The cold bath was removed and, when the mixture had reached -30 °C (*ca* 30 min), the solution was cooled down again to -78 °C. A solution of aldehyde **274** (2.743 g, 14.5 mmol) in THF (3 mL plus 1 mL as a rinse) was added dropwise to the acetylide solution, and the mixture was stirred for another 3 h at -78 °C. Saturated aqueous NH_4Cl (2.0 mL) was then added. Most of the solvent was evaporated and the residue was mixed with EtOAc (60 mL). The organic phase was washed with brine (2 x 40 mL), and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:3 EtOAc-hexane, gave **275** (3.88 g, 80%) as a mixture of two isomers which were used directly for the next step.

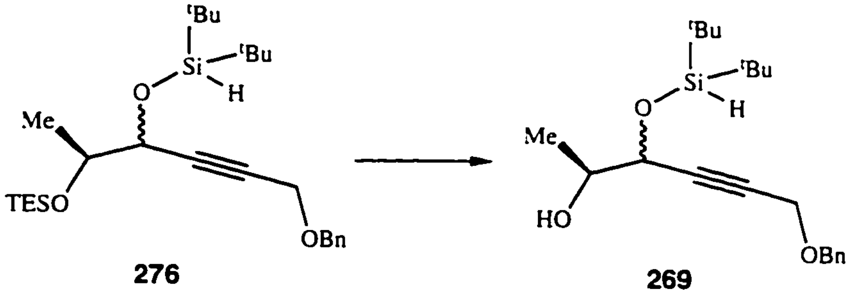
(*R**,*S**)-3-(1,1-Dimethylethyl)-8,8-diethyl-2,2,6-trimethyl-5-[3-(phenylmethoxy)-1-propynyl]-4,7-dioxa-3,8-disiladecane (276).



275 **276**

t-Bu$_2$SiHCl (1.65 g, 9.22 mmol) was added in one portion to a stirred solution of **275** (2.60 g, 7.77 mmol) in CH$_2$Cl$_2$ (5.0 mL). Et$_3$N (2.50 mL, 10 mmol) was then added, followed by DMAP (*ca* 120 mg), and the solution was refluxed for 2 h (tlc control, silica, 1:10 EtOAc-hexane). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 30 cm), using increasing amounts of EtOAc in hexane (100% hexane to 1:10 EtOAc-hexane), gave crude **276** (3.32 g,), which were taken directly to the next step.

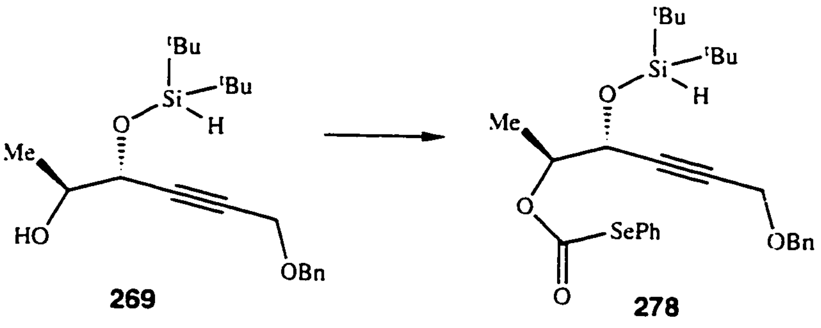
2-[[Bis(1,1-dimethylethyl)silyl]oxy]-6-(phenylmethoxy)hex-4-yn-2-ol (269).



276 **269**

Water (0.5 mL) and glacial AcOH (4.0 mL) were added to a stirred solution of **276** (100.0 mg, 0.21 mmol) in THF (4.0 mL). Stirring at room temperature was continued for *ca* 7 h (tlc control, silica, 1:3 EtOAc-hexane). Water (10 mL) was then added, and the mixture was extracted with CH_2Cl_2 (3 x 20 mL). The combined organic extracts were washed with saturated aqueous Na_2CO_3 (2 x 20 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (20 cm x 2 cm), using 1:5 EtOAc-hexane, gave two isomers (85.0, 72%). The major (less polar) isomer **269** (41.2 mg, 54%) was fully characterized and used in the next step: FTIR ($CHCl_3$, cast) 3431, 3032, 2100 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.02 (s, 9 H), 1.04 (s, 9 H), 1.29 (d, *J* = 6.3 Hz, 3 H), 2.32 (d, *J* = 4.7, 1 H), 3.84-3.90 (m, 1 H), 4.20 (s, 1 H), 4.25 (d, *J* = 1.6 Hz, 1 H), 4.47 (m, 1 H), 4.62 (s, 2 H), 7.30-7.42 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) δ 17.78 (q'), 19.83 (s'), 20.22 (s'), 27.23 (q'), 27.33 (q'), 57.28 (t'), 70.63 (d'), 71.12 (d'), 71.44 (t'), 82.90 (s'), 83.99 (s'), 127.86 (d'), 128.10 (d'), 128.42 (d'), 137.45 (s'); exact mass *m/z* calcd for $C_{20}H_{30}O_3Si$ ($M^+ - C_4H_9$) 330.20151, found 330.20129. The polar isomer had: ^1H NMR ($CDCl_3$, 300 MHz) δ 1.02 (s, 18 H), 1.33 (d, *J* = 6.4 Hz, 3 H), 2.50 (d, *J* = 4.7, 1 H), 4.05-4.15 (m, 2 H), 4.25 (s, 2 H), 4.40-4.45 (m, 1 H), 4.60 (s, 2 H), 7.30-7.42 (m, 5 H).

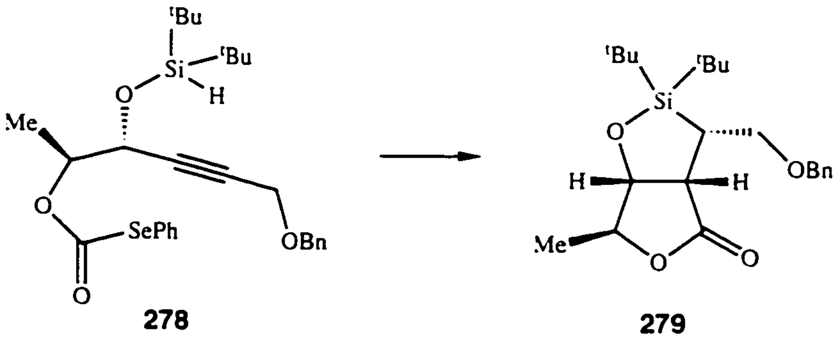
Phenyl (*R**,*S**)-*O*-[2-[[Bis(1,1-dimethylethyl)silyl]oxy]-1-methyl-5-(phenylmethoxy)-3-pentynyl]carbonoselenoate (278).



A solution of $COCl_2$ in PhMe (*ca* 1:1 v/v) was added by pipette in small portions to a stirred solution of **269** (300.0 mg, 0.82 mmol) in THF (5.0 mL) until all the starting material had reacted (several min) (tlc control, silica, 1:10 EtOAc-hexane). The solution was then concentrated to half of its original volume, using a rotary evaporator in which the receiving flask contained aqueous $NaHCO_3$ solution. A freshly prepared solution of PhSeNa [from PhSeSePh (256.0 mg, 0.82 mmol) and $NaBH_4$ (65.0 mg, 1.72 mmol) in EtOH (10 mL)] was added, and stirring was continued for 4 h (tlc control, silica, 1:10 EtOAc-hexane). The mixture was then diluted with Et_2O (30 mL) and washed with water (2 x 20 mL) and brine (20 mL). The organic phase was dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (20 cm x 2 cm), using 1:10 EtOAc-hexane, gave **278** (358.0 mg, 80%) as a pure (^1H NMR, 200 MHz), slightly yellowish oil: FTIR ($CHCl_3$, cast) 2963, 2097 (Si-H), 1728 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ

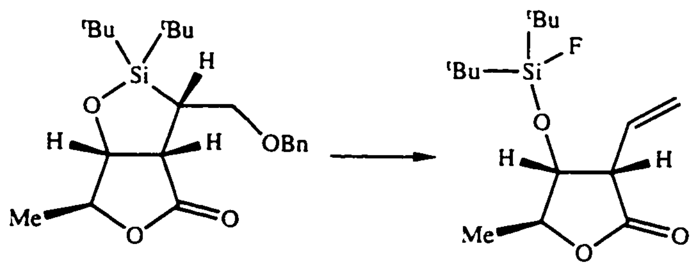
1.06-1.11 (two close s, 18 H), 1.45 (d, J = 6.4 Hz, 3 H), 4.18 (s, 1 H), 4.24 (d, J = 1.6 Hz, 2 H), 4.61 (s, 2 H), 4.75 (m, 1 H), 5.09-5.21 (m, 1 H), 7.25-7.45 (m, 8 H), 7.59-7.72 (m, 2 H); ^{13}C NMR (CDCl$_3$, 50.3 MHz) δ 14.47 (q'), 19.99 (s'), 20.31 (s'), 27.24 (q'), 27.35 (q'), 57.18 (t'), 67.97 (d'), 71.41 (t'), 77.40 (d'), 82.59 (s'), 83.70 (s'), 126.10 (s'), 127.91 (d'), 128.19 (d'), 128.48 (d'), 129.09 (d'), 129.28 (d'), 135.77 (d'), 137.39 (s'), 166.60 (s'); exact mass *m/z* calcd for $C_{24}H_{29}O_4{}^{80}SeSi$ ($M^+ - C_4H_9$) 489.10004, found 489.09938. Anal. Calcd for $C_{28}H_{38}O_4{}^{80}SeSi$: C 61.63, H 7.02. Found: C 61.56, H 6.76.

(3α,3aβ,6β,6aβ)-2,2-Bis(1,1-dimethylethyl)tetrahydro-6-methyl-3-[(phenylmethoxy)methyl]furo[3,4-d]-1,2-oxasilol-4(2*H*)-one (279).



Solutions of Ph$_3$SnH (256.0 mg, 0.73 mmol) and of AIBN (10.0 mg, 0.06 mmol), both in PhH (8.0 mL), were added simultaneously over 6 h by syringe pump to a stirred and refluxing solution of **278** (268.0 mg, 0.49 mmol) in PhH (60 mL). Refluxing was continued for 1 h after the end of the addition and the mixture was then cooled to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:9 EtOAc-hexane, gave **279** (169.0 mg, 85%) as a pure (^{1}H NMR, 300 MHz) oil: FTIR (CHCl$_3$, cast) 3087, 1769 cm^{-1}; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.05 (two close s, 18 H), 1.30 (d, *J* = 6.9 Hz, 3 H), 2.23 (m, 1 H), 3.38 (dd, *J* = 9.9, 5.3 Hz, 1 H), 3.95 (dd, *J* = 9.1, 6.4 Hz, 1 H), 4.29 (d, *J* = 5.3 Hz, 1 H), 4.40 (dd, *J* = 10.2, 9.1 Hz, 1 H), 4.54 (d, *J* = 11.5 Hz, 1 H), 4.65 (d, *J* = 11.5 Hz, 1 H; q, *J* = 6.8 Hz, 1 H), 7.19-7.42 (m, 5 H); ^{13}C NMR (CDCl$_3$, 75.5 MHz) 18.88 (q'), 20.37 (s'), 21.43 (s'), 25.17 (d'), 26.90 (q'), 27.65 (q'), 43.73 (d'), 66.69 (t'), 73.20 (t'), 82.13 (d'), 82.62 (d'), 127.51 (d'), 127.95 (d'), 128.31 (d'), 138.58 (s'), 175.73 (s'); exact mass *m/z* calcd for C$_{22}$H$_{34}$O$_4$Si 390.22263, found 390.22092.

(3*R,4*R**,5*R**)-4-[[Bis(1,1-dimethylethyl)fluorosilyl]oxy]-3-ethenyldihydro-5-methyl-2(3*H*)-furanone (280).**



279 **280**

$BF_3.OEt_2$ (0.34 mL, 2.73 mmol) was added to a stirred solution of **279** (88.0 mg, 0.225 mmol) in CH_2Cl_2 (10.0 mL). The mixture was stirred for 8 h, transferred to a separatory funnel, washed with brine (2 x 10 mL), and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 10 cm), using 1:3 EtOAc-hexane, gave **280** (51.0 mg, 75 %) as a pure (^1H NMR, 400 MHz), colorless oil: FTIR ($CHCl_3$, cast) 3066, 1765 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 18 H), 1.40 (d, J = 6.8 Hz, 3 H), 3.40 (dd, J = 7.9, 5.7 Hz, 1 H), 4.50 (dd, J = 5.6, 2.0 Hz, 1 H), 4.56 (d of q, J = 6.7, 2.0 Hz, 1 H), 5.34-5.45 (m, 2 H), 5.70-5.86 (m, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 17.80 (q'), 19.62, 19.87 (two s', J_{C-F} = 12.8 Hz), 20.54, 20.85 (two s', J_{C-F} = 15.9 Hz), 26.68 (q'), 26.86 (q'), 48.91 (d'), 77.24 (d'), 82.27 (d'), 121.87 (t'), 128.25 (d'), 174.95 (s'); exact mass m/z calcd for $C_{11}H_{18}FO_3Si$ ($M^+ - C_4H_9$) 245.10092, found 245.10098.

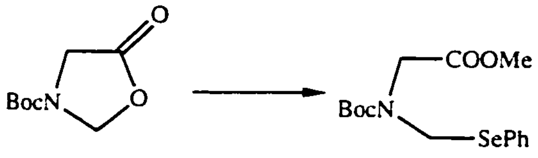
(1,1-Dimethylethyl 5-Oxo-3-oxazolidinecarboxylate (290).

290

N-Boc glycine (4.38 g, 25.0 mmol) and paraformaldehyde (1.0 g, 28.0 mmol) were dissolved in PhH (120 mL). *p*-

$TsOH.H_2O$ (250.0 mg, 1.5 mmol) was added, and the mixture was refluxed for 1 h, using a Dean-Stark apparatus, and then cooled to room temperature. Evaporation of the solvent and flash chromatograph of the residue over silica gel (2 x 20 cm), using 1:3 EtOAc-hexane, gave **290** (2.85 g, 61%) as a pure (^{1}H NMR, 400 MHz), colorless oil. Upon standing, the liquid solidified: mp. 39.0-40.0 °C; FTIR ($CHCl_3$, cast) 2979, 1809, 1759, 1712 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.36 (s, 9 H), 3.88 (s, 2 H), 5.24 (s, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 28.35 (q'), 43.99 (t'), 78.69 (s'), 82.17 (t'), 151.94 (s'), 170.13 (s'); exact mass *m/z* calcd for $C_8H_{13}O_4N$ 187.08446, found 187.08414.

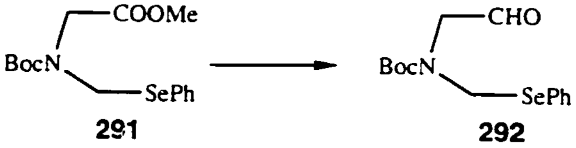
Methyl *N*-[(1,1-Dimethylethoxy)carbonyl]-*N*-[(phenylseleno)-methyl]glycinate (291).



290 **291**

NaH (80% dispersion in mineral oil, 190.0 mg, 6.3 mmol) was added in small portions to a stirred solution of PhSeSePh (1.10 g, 3.50 mmol) in THF (10.0 mL). The suspension was then refluxed for 2 h, and then cooled to room temperature. HMPA (0.56 mL, 3.22 mmol) was added in one portion, followed by a solution of **290** (871.4 mg, 4.65 mmol) in THF (2 mL plus 1 mL as a rinse). The solution was refluxed for 5 h (tlc control, silica, 1:3 EtOAc-hexane), cooled to room temperature, and diluted with water (1.0 mL). The THF was evaporated under water pump vacuum, and the residue was partitioned between water (20 mL) and Et_2O (20 mL). The organic extract was washed with water (3 x 10 mL) and the combined aqueous extracts were acidified with 3 N HCl to *ca* pH 2. The acidic solution was extracted with EtOAc (3 x 20 mL), and the combined organic extracts were washed with water (2 x 20 mL), brine (2 x 20 mL), and filtered through a column [4.0 (diameter) x 7.0 cm] of anhydrous $MgSO_4$. The filtrate was evaporated and the residue was redissolved in Et_2O (10 mL), and cooled to 0 °C in an ice-water bath. Ethereal diazomethane was added dropwise until all the acid had been esterified (tlc control, silica, 1:3 EtOAc-hexane). Evaporation of the solvent and flash chromatography of the residue over silica gel (30 x 3 cm), using 1:3 EtOAc-hexane, gave **291** (1.33 g, 80%) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR ($CHCl_3$, cast), 1753, 1703 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.3 (two s, 9 H), δ 3.69 (two s, 3 H), δ 3.99 (two s, 2 H), δ 4.90 (two s, 2 H), δ 7.2-7.32 (m, 3 H), δ 7.53-7.65 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) δ 28.13 (three q' from rotamers), 47.46 (four t' from rotamers), 52.07 (d'), 81.19 (t'), 127.90 (two d' from rotamers), 128.40 (two s' from rotamers), 129.12 (d'), 135.03 (two d' from rotamers), δ 154.06 (two s' from rotamers), 169.84 (s'); exact mass *m/z* calcd for $C_{15}H_{21}O_4NSe$ 359.06357, found 359.06256.

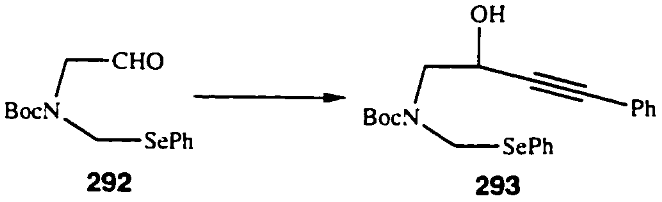
***N*-[(1,1-Dimethylethoxy)carbonyl]-*N*-[(phenylseleno)-methyl]glycinal (292).**



DIBAL-H (1.0 M solution in CH_2Cl_2, 3.0 mL, 3.0 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of **291** (510.0 mg, 1.42 mmol) in dry Et_2O (20 mL). After 30 min. little starting material remained (tlc control, silica, 1:5 EtOAc-hexane). More DIBAL-H (1.0 M solution in CH_2Cl_2, 1.5 mL, 1.5 mmol) was added, and stirring was continued for 15 min. MeOH (1.0 mL) was then added, and the solution was poured into saturated aqueous potassium sodium tartrate (30 mL). The solution was extracted with Et_2O (3 x 20 mL) and the combined organic extracts were washed with water (20 mL), brine (20 mL) and dried ($MgSO_4$). Evaporation of the solvent and flash chromatography of the residue over silica gel (3.0 x 20 cm), using 1:5 EtOAc-hexane, gave **292** (279.0 mg, 83%) as a pure (^{1}H NMR, 400 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3071, 3057, 2977, 2931, 2872, 2819, 2720, 1735, 1698, 1579 cm^{-1}; ^{1}H NMR (CD_2Cl_2, 400 MHz) δ 1.30 (two close s, 9 H), 3.92 (two close s, 2 H), 4.92 (two close s, 2 H), 7.21-7.39 (br m, 3 H), 7.55-7.65 (br m, 2 H), 9.45-9.50 (two close s, 1 H); ^{13}C NMR (CD_2Cl_2, 100.6 MHz) δ 28.00 (q'), 28.11 (q'), 47.89 (t'), 48.48 (t'), 56.56 (t'), 57.15 (t'), 81.63 (s'), 81.80 (s'), 128.14 (d'), 128.51 (d'), 128.59 (s'), 128.73 (s'), 129.51

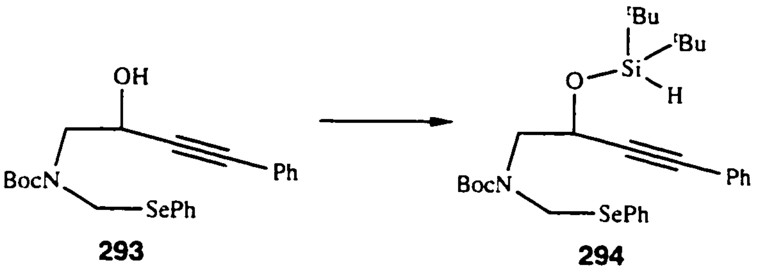
(d'), 129.58 (d'), 134.89 (d'), 135.79 (d'), 154.23 (s'), 154.71 (s'), 198.45 (d'), 198.51 (d'); exact mass (HR electrospray) *m/z* calcd for $C_{14}H_{20}NO_3{}^{80}Se$ (M + H) 330.060839, found 330.059420.

1,1-Dimethylethyl (2-Hydroxy-4-phenyl-3-butynyl)[(phenylseleno)methyl]carbamate (293).



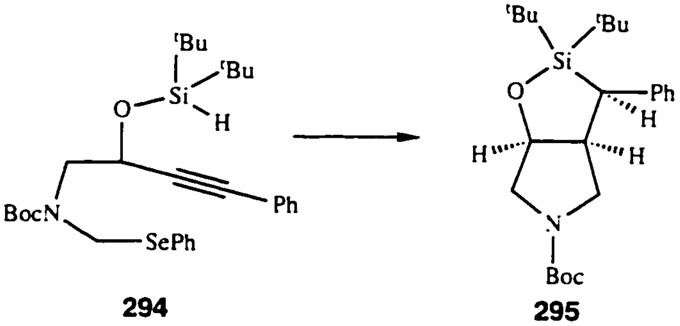
n-BuLi (1.6 M in hexanes, 1.3 mL, 2.08 mmol) was added to a stirred and cooled (-78 °C) solution of phenylacetylene (224.0 mg, 2.19 mmol) in THF (10.0 mL). After 10 min, a solution of aldehyde **292** in THF (2.0 mL plus 1.0 mL as a rinse) was added in two portions. Stirring was continued for 3 h. Several drops of saturated aqueous NH_4Cl were then added, the THF was evaporated, and the residue was dissolved in CH_2Cl_2 and dried ($MgSO_4$). Evaporation of the solvent gave the crude alcohol **293**, which was used directly in the next step.

1,1-Dimethylethyl [2-[[Bis(1,1-dimethylethyl)silyl]oxy]-4-phenyl-3-butynyl][(phenylseleno)methyl]carbamate (294).



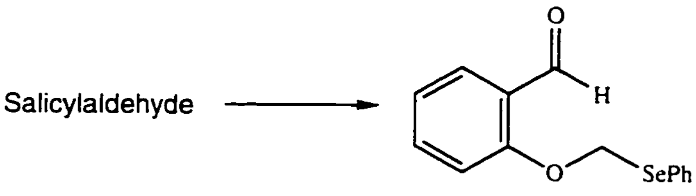
Imidazole (118.0 mg, 1.70 mmol) and t-Bu_2SiHCl (193.5 mg, 1.10 mmol) were added successively to a stirred solution of crude **293** in THF (10.0 mL), and stirring was continued for 3 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 30 cm), using increasing amounts of EtOAc in hexane (from 1:10 to 1:3), gave **294** (503.0 mg, 82%) as a pure (^1H NMR, 300 MHz) oil: FTIR ($CHCl_3$, cast), 2101 (Si-H), 1703 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 0.99 (s, 9 H), 1.03 (s, 9 H), δ 1.29 (s, 4.6 H), 1.39 (s, 4.4 H), 3.48-3.70 (m, 2 H), 4.10-4.20 (m, 1 H), 4.80-5.23 (m, 3 H), 7.18-7.36 (m, 6 H), 7.37-7.42 (m, 2 H), 7.55-7.70 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) (mixture of rotamers) 19.59 (s'), 20.26 (s'), 27.31 (q'), 28.06 (q'), 28.32 (q'), 48.14 (t'), 49.91 (t'), 52.49 (s'), 65.19 (d'), 65.41 (d'), 80.63 (t'), 80.83 (t'), 86.41 (s'), 88.22 (s'), 127.65 (d'), 127.97 (d'), 128.33 (d'), 128.77 (s'), 131.58 (d'), 135.03 (d'), 135.75 (d'), 154.38 (s'); exact mass m/z calcd for $C_{20}H_{29}NO_3Si$ (M^+ - PhSe - C_4H_9) 360.19949, found 360.19932.

1,1-Dimethylethyl (3α,3aβ,6aβ)-2,2-Bis(1,1-dimethylethyl)-hexahydro-3-phenyl-5*H*-1,2-oxasilolo[4,5-c]pyrrole-5-carboxylate (295).



Solutions of Ph_3SnH (140.0 mg, 0.40 mmol) in PhH (8.0 mL) and of AIBN (5.0 mg, 0.03 mmol) in PhH (8.0 mL) were added simultaneously by syringe pump over 8 h to a stirred and refluxing solution of **294** (150.0 mg, 0.262 mmol) in PhH (40.0 mL). Refluxing was continued for 1 h after the end of the addition, and the mixture was then cooled to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 30 cm), using 1:3 EtOAc-hexane, gave **295** (105.0 mg, 95%) as a pure (^{1}H NMR, 200 MHz), white solid: mp 126.0-128.0 °C; FTIR ($CHCl_3$, cast) 2971, 2895, 1697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz, 55 °C) δ 1.05 (s, 9 H), 1.16 (s, 9 H), 1.43 (s, 9 H), 3.15-3.32 (br m, 1 H), 3.39 (d, *J* = 7.3 Hz, 1 H), 3.51 (dd, *J* = 7.5, 4.3 Hz, 2 H), 3.59-3.90 (br m, 2 H), 4.55 (t, 4.2 Hz), δ 7.05-7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 20.96 (s'), 22.52 (s'), 23.44 (q'), 25.17 (q'), 28.38 (q'), 28.50 (q'), 28.67 (q'), 35.89 (d'), 36.08 (d'), 45.03 (d'), 45.84 (d'), 48.25 (t'), 53.70 (s'), 54.03 (s'), 79.21 (t'), 79.86 (d'), 80.79 (d'), 125.26 (d'), 128.43 (d'), 128.78 (d'), 140.30 (s'), 140.54 (s'), 154.46 (s'); exact mass *m/z* calcd for $C_{24}H_{39}NO_3Si$ 417.26993, found 417.26881.

2-[(Phenylseleno)methoxy]benzaldehyde (257).

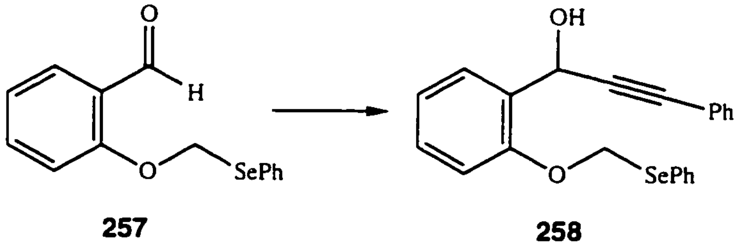


257

Dry acetone (20 mL) was added to $PhSeCH_2Cl$[89] (3.16 g, 15.4 mmol) and NaI (11.52 g, 76.9 mmol), and the mixture was stirred and refluxed for 3 h, cooled to room temperature, and evaporated. Et_2O (20 mL) was added and the solid was filtered off, and washed with Et_2O (20 mL). The combined washings were evaporated to give crude $PhSeCH_2I$, which was used directly for the next step.

Salicylaldehyde (1.22 g, 10.0 mmol) in THF (2.0 mL) was added by cannula over *ca* 1 min to a stirred and cooled (0 °C) suspension of NaH (60% dispersion in mineral oil, 0.45 g, 12 mmol) in THF (40.0 mL). The mixture was stirred at 0 °C for 20 min, and then a solution of crude $PhSeCH_2I$ in THF (5 mL) was added by cannula over *ca* 1 min. The mixture was refluxed for 4 h, and then cooled to room temperature. Water (10 mL) was added, and the mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated. Flash chromatography of the residue over silica gel (3 x 25 cm), using increasing amounts of EtOAc in hexane (from 5% to 15%), gave **257** (650.0 mg, 22%) as a pure (^{1}H NMR, 400 MHz), colorless oil: FTIR (CH_2Cl_2 cast) 3072, 3057, 2859, 2759, 1689, 1598 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 5.80 (t, $J_{C\text{-}Se}$ = 8.7 Hz, 2 H), 7.02 (d, J = 8.4 Hz, 1 H), 7.11 (t, J = 7.5 Hz, 1 H), 7.21-7.40 (m, 3 H), 7.49-7.64 (m, 3 H), 7.86 (dd, J = 7.7, 1.8 Hz, 1 H), 10.38 (d, J = 0.5 Hz, 1 H); ^{13}C NMR (CD_2Cl_2, 75.5 MHz) 68.60 (t'), 114.84 (d'), 122.43 (d'), 126.72 (s'), 128.29 (d'), 128.72 (d'), 129.03 (s'), 129.71 (d'), 133.84 (d'), 135.85 (d'), 159.55 (s'), 189.47 (d'); exact mass m/z calcd for $C_{14}H_{12}O_2{}^{80}Se$ 292.00024, found 292.00048. Anal. Calcd for $C_{14}H_{12}O_2{}^{80}Se$: C 57.96, H 3.92. Found C 57.74, H 4.15.

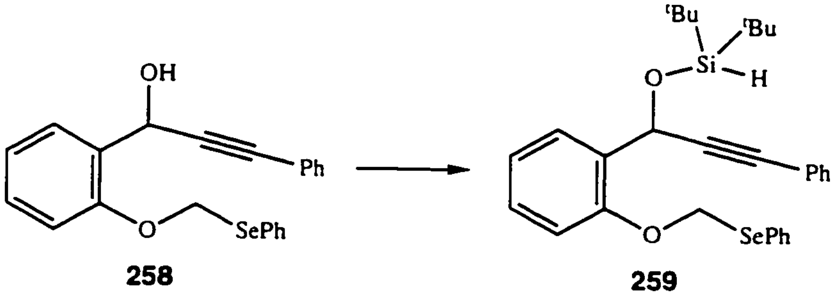
1-[2-[(Phenylseleno)methoxy]phenyl]-3-phenyl-2-propyn-1-ol (258).



n-BuLi (1.6 M in hexanes, 0.46 mL, 0.747 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of phenylacetylene (100.0 mg, 0.98 mmol) in THF (10.0 mL).

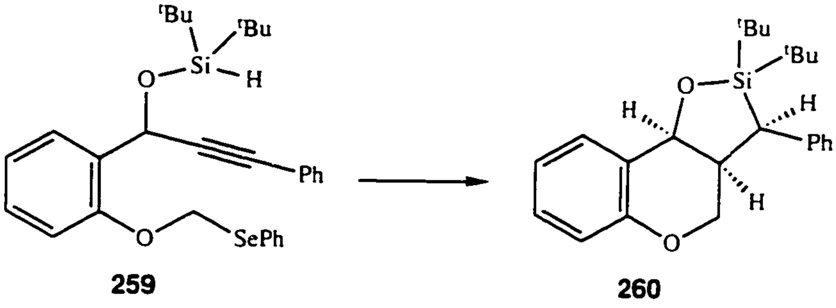
Stirring was continued for 15 min, and then a solution of aldehyde **257** (94.8 mg, 0.498 mmol) in THF (2.0 mL plus 1 mL as a rinse) was added by syringe. The cold bath was removed and, after *ca* 1 h, by which time the mixture had attained room temperature, the reaction was quenched by addition several drops of water. The THF was evaporated, the residue was dissolved in CH_2Cl_2 (30 mL), and the solution was dried ($MgSO_4$) and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 1:3 EtOAc-hexane, gave **258** as a pure (^1H NMR, 300 MHz), colorless oil (110.0 mg, 80%). FTIR ($CHCl_3$, cast) 3419, 3056, 2926, 1951, 1599, 1588 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.80 (d, J = 5.4 Hz, 1 H), 5.76 (s, 2 H), 5.90 (d, J = 5.5 Hz, 1 H), 6.91-7.80 (m, 14 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 61.12 (d'), 68.22 (t'), 86.29 (s'), 88.37 (s'), 113.45 (d'), 122.36 (d'), 122.72 (s'), 128.03 (d'), 128.31 (d'), 128.51 (d'), 129.42 (d'), 129.61 (d'), 130.37 (s'), 131.86 (d'), 133.83 (d'), 154.17 (s'); exact mass *m/z* calcd for $C_{22}H_{18}O_2{}^{80}Se$ 394.04721, found 394.04789.

Bis(1,1-dimethylethyl)[[3-phenyl-1-[2-[(phenylseleno)methoxy]phenyl]-2-propynyl]oxy]silane (259).



t-Bu_2SiHCl (96.0 mg, 0.536 mmol) was added in one portion by syringe to a stirred solution of **258** (78.5 mg, 0.268 mmol) and Et_3N (0.2 mL) in CH_2Cl_2 (2.0 mL). A small crystal of DMAP (*ca* 2 mg) was added after 10 min. Reaction was complete after 30 min (tlc control, silica, 1:10 EtOAc-hexane). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:10 EtOAc-hexane, gave **259** as a pure (^{1}H NMR, 300 MHz), colorless oil (110.0 mg, 95%). FTIR ($CHCl_3$, cast) 3059, 2960, 2097, 1599, 1589 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.95 (s, 1 H), 1.12 (s, 1 H), 4.28 (s, 1 H), 5.79 (s, 2 H), 6.11 (s, 1 H), 6.88-7.50 (m, 11 H), 7.60-7.90 (m, 3 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 19.94 (s'), 20.21 (s'), 27.21 (q'), 27.43 (q'), 62.75 (d'), 68.23 (t'), 84.92 (s'), 90.04 (s'), 112.94 (d'), 122.19 (d'), 123.22 (s'), 127.63 (d'), 128.11 (d'), 128.18 (d'), 128.71 (d'), 129.22 (d'), 130.16 (s'), 131.58 (s'), 131.67 (d'), 133.52 (d'), 153.07 (s'); exact mass *m/z* calcd for $C_{30}H_{36}O_2Si^{80}Se$ 536.16496, found 536.16498.

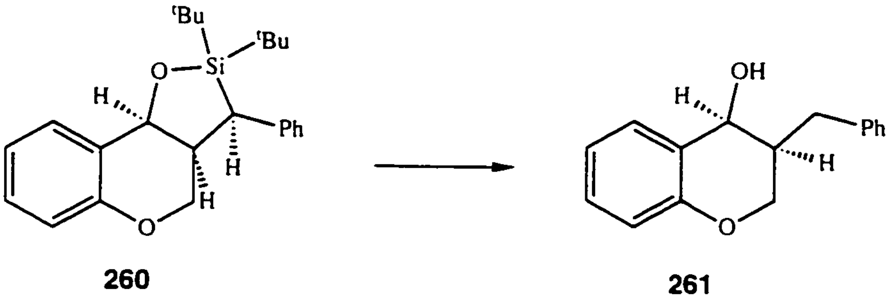
(3α,3aβ,9bβ)-2,2-Bis(1,1-dimethylethyl)-2,3,3a,9b-tetrahydro-3-phenyl-4*H*-1,2-oxasilolo[4,5-c][1]benzopyran (260).



Solutions of Ph_3SnH (116.0 mg, 0.328 mmol) in PhH (5.0 mL) and of AIBN (5.0 mg, 0.03 mmol) in PhH (5.0 mL) were added simultaneously by syringe pump over 4.5 h to a stirred and refluxing solution of **259** (110.0 mg, 0.252 mmol) in PhH (40 mL). Refluxing was continued for 1 h after the end of the addition, and the mixture was then cooled to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:10 CH_2Cl_2-hexane, gave **260** (60.0 mg, 85%) as a pure (^1H NMR, 200 MHz), white solid: mp 128.0-131.0 °C; FTIR ($CHCl_3$, cast) 3035, 1610, 1586 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 1.10 (s, 9.98 H), 1.20 (s, 8.2 H), 2.90-3.09 (m, 1 H), 3.49 (d, *J* = 7.4 Hz, 1 H), 3.95 (dd, *J* = 12.4, 11.0 Hz, 1 H), 4.25 (dd, *J* = 10.7, 3.2 Hz, 1 H), 4.85 (d, *J* = 4.1 Hz, 1 H), 6.88 (d, *J* = 8.2 Hz, 1 H), 6.99 (dd, *J* = 7.5, 1.0 Hz, 1 H), 7.16-7.40 (m, 6 H), 7.47 (dd, *J* = 7.6, 1.5 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 22.95 (s'), 28.74 (q'), 29.12 (q'), 35.27

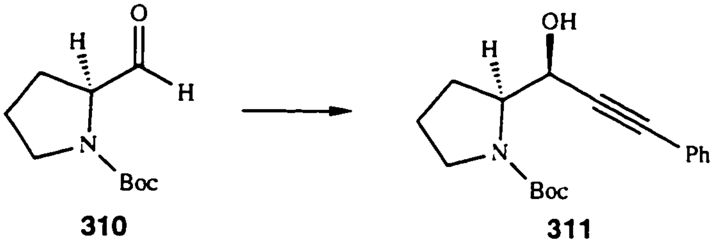
(d'), 42.07 (d'), 64.69 (t'), 71.61 (d'), 116.65 (d'), 120.74 (d'), 123.71 (s'), 125.64 (d'), 128.47 (d'), 129.10 (d'), 130.15 (d'), 131.73 (d'), 138.84 (s'), 154.89 (s'); exact mass *m/z* calcd for $C_{24}H_{32}O_2Si$ 380.21716, found 380.21579.

Cis-3,4-Dihydro-3-(phenylmethyl)-2*H*-1-benzopyran-4-ol (261).



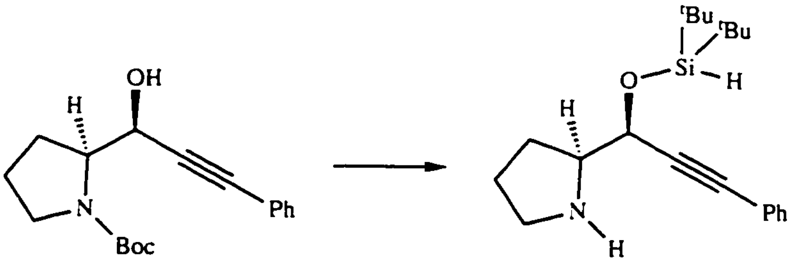
TBAF (1.0 M in THF, 1.0 mL, 1.0 mmol) was injected in one portion into a stirred solution of **260** (40.0 mg, 0.10 mmol) in DMF (3.0 mL). The color of the solution quickly changed to brownish red. Stirring was continued for 30 min, and then Et_2O (20 mL) and water (10 mL) were added. The organic phase was separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with water (2 x 20 mL) and brine (2 x 20 mL), dried ($MgSO_4$), and evaporated. Flash chromatography of the residue over silica gel (2 x 20 cm), using 1:3 EtOAc-hexane, gave **261** (21.5 mg, 90%) as a pure (^1H NMR, 400 MHz), white solid: mp 103.0-105.0 °C; FTIR ($CHCl_3$ cast) 3439, 3061, 3026, 772 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.70 (s, 1 H), 2.29-2.41 (m, 1 H), δ 2.68 (dd, J = 13.7, 7.3, 1 H), 2.90 (dd, J = 13.7, 8.4, 1 H), δ 4.05-4.15 (m, 2 H), 4.52 (d, J = 2.0, 1 H), δ 6.82-6.94 (m, 2 H), δ 7.17-7.41 (m, 7 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 32.88 (t'), 40.03 (d'), 64.97 (d'), 65.00 (t'), 116.96 (d'), 120.55 (d'), 124.22 (s'), 126.36 (d'), 128.61 (d'), 129.14 (d'), 129.97 (d'), 130.17 (d'), 139.20 (s'), 154.38 (s'); exact mass m/z calcd for $C_{16}H_{16}O_2$ 240.11504, found 240.11534.

1,1-Dimethylethyl [*S*-(*R**,*R**)]-2-(1-Hydroxy-3-phenyl-2-propynyl)-1-pyrrolidinecarboxylate (311).



n-BuLi (1.6 M in hexane, 1.90 mL, 3.04 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of phenylacetylene (320.0 mg, 3.13 mmol) in THF (10.0 mL). Stirring at -78 °C was continued for another 15 min after the addition, and a solution of freshly prepared aldehyde **310** (292.9 mg, 1.56 mmol) in THF (4.0 mL plus 1.0 mL as a rinse) was then added in one portion. Stirring at -78 °C was continued for 2 h, at which point water (five drops) was added. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:3 EtOAc-hexane, gave equal amounts of two isomers (^{1}H NMR, 300 MHz). The less polar diastereomer **311** (192.0 mg, 41%) was carried on to the next step. The isomer has: FTIR ($CHCl_3$, cast) 3380, 2976, 1737, 1693 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.50 (s, 9 H), 1.70-2.20 (m, 4 H), 3.30-3.60 (m, 2 H), 4.10 (dd, *J* = 12.6 Hz, 6.0 Hz, 1 H), 4.62 (d, *J* = 5.9 Hz, 1 H), 7.21-7.33 (m, 3 H), 7.34-7.50 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 23.86 (t'), 28.45 (q'), 28.68 (t'), 47.67 (t'), 62.79 (d'), 67.39 (d'), 80.66 (s'), 85.08 (s'), 88.66 (s'), 122.75 (s'), 128.24 (d'), 128.33 (d'), 131.71 (d'), 157.52 (s'); exact mass *m/z* calcd for $C_{14}H_{15}NO_3$ ($M^+ - C_4H_9$) 245.10519, found 245.10452. The polar isomer has the following spectra data: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.49 (s, 9 H), 1.70-2.19 (m, 4 H), 3.29-3.60 (m, 2 H), 4.01-4.19 (t, *J* = 6.81 Hz, 1 H), 4.54-4.70 (br s, 1 H), 7.21-7.31 (m, 3 H), 7.32-7.47 (m, 2 H).

[*S*-(*R,*R**)]-2-[1-[[Bis(1,1-dimethylethyl)silyl]oxy]-3-phenyl-2-propynyl]pyrrolidine (313).**

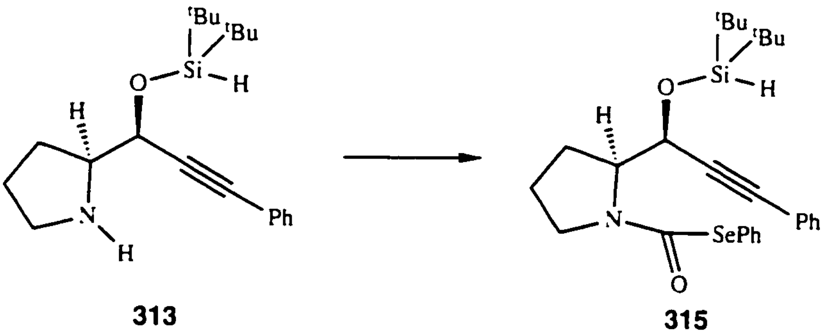


311 **313**

TFA (3.0 mL) was added to a stirred solution of **311** (181.0 mg, 0.60 mmol) in CH_2Cl_2 (5.0 mL) at room temperature.

Stirring was continued for 1 h, the mixture was diluted with CH_2Cl_2 (30 mL), and washed with saturated aqueous $NaHCO_3$ (3 x 10 mL), and dried (Na_2SO_4). The solvent was evaporated and the residue was redissolved in THF (5.0 mL). Imidazole (43.0 mg, 0.63 mmol) was added, followed by *t*-Bu_2SiHCl (112.8 mg, 0.63 mmol), and the solution was refluxed overnight. The mixture was cooled and evaporated, flash chromatography of the residue over silica gel (2 x 20 cm), using 1:4 EtOAc-hexane, gave **313** (122.0 mg, 60 %) as a pure (^1H NMR, 200 MHz) slightly yellowish oil: FTIR ($CHCl_3$, cast) 3336, 3179, 3081, 2103 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.02 (s, 4.5 H), 1.05 (s, 4.5 H), 1.70-2.09 (m, 4 H), 2.60 (broad s, 1 H), 2.85-3.21 (m, 2 H), 3.40 (dd, J = 12.0 Hz, 6.0 Hz, 2 H), 4.22 (s, 1 H), 4.64 (d, J = 6.1 Hz, 1 H), 7.25-7.36 (m, 3 H), 7.37-7.50 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 19.82 (s'), 20.33 (s'), 25.28 (t'), 27.36 (t'), 27.45 (q'), 46.51 (t'), 63.98 (d'), 69.93 (d'), 85.86 (s'), 88.60 (s'), 122.95 (s'), 128.25 (d'), 131.63 (d'); exact mass m/z calcd for $C_{17}H_{24}NOSi$ ($M^+ - C_4H_9$) 286.16268, found 286.16249.

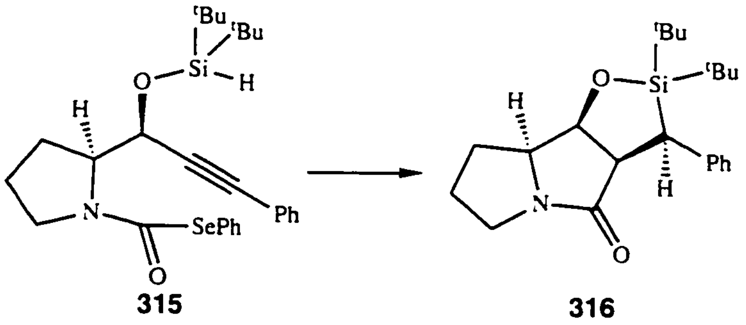
***Se*-Phenyl [*S*-(*R**,*R**)]-2-[1-[[Bis(1,1-dimethylethyl)silyl]-oxy]-3-phenyl-2-propynyl]-1-pyrrolidineselenocarboxylate (315).**



A solution of $COCl_2$ in PhMe (*ca* 1:1 v/v) was added dropwise to a stirred solution of **313** (120.0 mg, 0.35 mmol) in THF (4.0 mL). Acylation was complete in 10 min (tlc control, silica, 1:10 EtOAc-hexane). Evaporation of the solvent, using a rotary evaporator in which the receiving flask contained aqueous $NaHCO_3$, and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:20 EtOAc-hexane, gave the carbamoyl chloride **314**. This compound was dissolved in THF (2.0 mL plus 1.0 mL as a rinse) and added by syringe to a stirred solution of freshly prepared PhSeNa [from PhSeSePh (244.0 mg, 0.78 mmol) and $NaBH_4$ (59.0 mg, 1.56 mmol) in EtOH (10.0 mL)]. Stirring was continued for 6 h at room temperature. The mixture was then diluted with EtOAc (30 mL), washed with brine (2 x 15 mL), and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:10 EtOAc-hexane, gave selenide **315** (154.4 mg, 84 %) as a pure (^1H NMR, 400

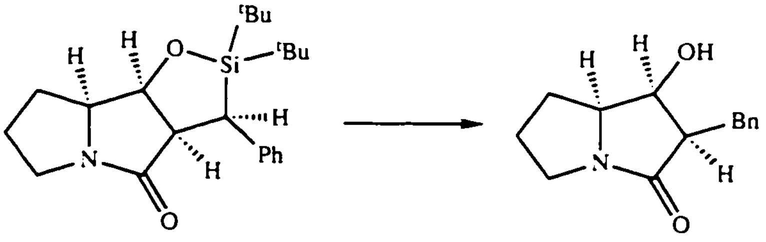
MHz), slightly yellowish solid: mp. 94.5-95.5 °C; FTIR ($CHCl_3$, cast) 3059, 2961, 2098, 1732 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 1.01 (s, 7.5 H), 1.09 (s, 7.5 H), 1.14 (two close s, 3 H), 1.88-2.02 (m, 1 H), 2.05-2.21 (m, 1 H), 2.26-2.51 (m, 2 H), 3.52-3.70 (m, 2 H), 4.15 (s, 1 H), 4.29-4.39 (m, 1 H), 5.20 (d, *J* = 5.4 Hz, 0.17 H), 5.40 (d, *J* = 4.9 Hz, 0.83 H), 7.30-7.49 (m, 8 H), 7.60-7.70 (m, 2 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 19.87 (s'), 20.02 (s'), 24.01 (t'), 26.18 (t'), 27.30 (q'), 47.96 (t'), 62.99 (d'), 65.99 (d'), 85.78 (s'), 88.05 (s'), 122.92 (s'), 126.73 (s'), 128.36 (d'), 128.84 (d'), 129.17 (d'), 131.52 (d'), 136.53 (d'), 162.90 (s'); exact mass *m/z* calcd for $C_{28}H_{37}NO_2Si^{80}Se$ 527.17590, found 527.17611.

Compound (316).



Solutions of Ph_3SnH (60.0 mg, 0.17 mmol) in PhH (5.0 mL) and of AIBN (5.0 mg, 0.03 mmol) in PhH (5.0 mL) were added simultaneously over 6 h by syringe pump to a stirred and refluxing solution of **315** (43.0 mg, 0.082 mmol) in PhH (30 mL). Refluxing was continued for 1 h after the addition, and solution was then cooled to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:1 EtOAc-hexane, gave **316** (22.8 mg, 75%) as a pure (^{1}H NMR, 400 MHz), colorless oil: FTIR (CH_2Cl_2, cast) 3056, 2933, 1692, 1495 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.06 (s, 9 H), 1.12 (s, 9 H), 1.80-1.90 (m, 1 H), 1.99-2.23 (m, 3 H), 2.98-3.10 (m, 1 H), 3.36 (d, *J* = 8.1 Hz, 1 H), 3.41-3.50 (m, 1 H), 3.80 (dd, *J* = 8.1, 4.2 Hz, 1 H), 3.90-3.99 (m, 1 H), 4.54 (t, *J* = 4.1 Hz, 1 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 20.93 (s'), 22.28 (s'), 23.68 (t'), 26.73 (t'), 27.11 (d'), 28.24 (q'), 28.45 (q'), 34.48 (d'), 41.32 (t'), 53.09 (d'), 63.56 (d'), 125.19 (d'), 127.49 (d'), 130.28 (d'), 137.94 (s'), 172.13 (s'); exact mass *m/z* calcd for $C_{22}H_{33}NO_2Si$ 371.22806, found 371.22862.

1*S*-(1α,2α,7aα)-Hexahydro-1-hydroxy-2-phenylmethyl-3-oxo-1*H*-pyrrolizine (317).

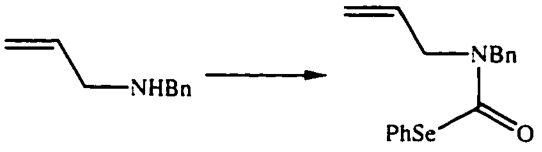


316 **317**

TBAF (1.0 M in THF, 0.10 mL, 0.10 mmol) was added to a stirred solution of **316** (14.0 mg, 0.037 mmol) in DMF (1.0 mL), and stirring was continued for 2 h. Evaporation of the solvent and chromatography of the residue over silica gel (2 x 10 cm), using AcOH, gave **317** (6.62 mg, 76%) as a pure (^{1}H

NMR, 300 MHz), colorless oil: FTIR ($CHCl_3$, cast) 3334, 3085, 1680, 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.55 (s, 1 H), 1.69-1.80 (m, 1 H), 1.90-2.10 (m, 3 H), 2.87 (dd, *J* = 14.0, 11.4 Hz, 1 H), 2.99-3.10 (m, 2 H), 3.22 (dd, *J* = 14.1, 3.80 Hz, 1 H), 3.56-3.70 (m, 1 H), 3.80-3.90 (m, 1 H), 4.20 (dd, *J* = 7.6, 3.5 Hz, 1 H), 7.20-7.36 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.6 MHz) 23.21 (t'), 26.80 (t'), 29.44 (t'), 41.83 (t'), 53.82 (d'), 64.19 (d'), 70.16 (d'), 126.22 (d'), 128.64 (d'), 128.71 (d'), 140.03 (s'), 177.22 (s'); exact mass *m/z* calcd for $C_{14}H_{17}NO_2$ 231.12593, found 231.12594.

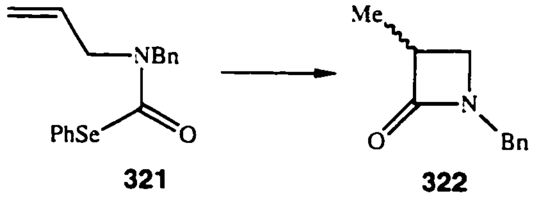
Se-Phenyl (Phenylmethyl)(2-propenyl)selenocarbamate (321).



320 321

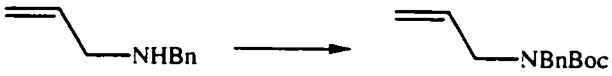
A solution of $COCl_2$ in PhMe (*ca* 1:1 v/v) was added dropwise to a stirred solution of amine **320** (670.0 mg, 4.55 mmol) in THF (15.0 mL). When the reaction was complete (*ca* 10 min, tlc control, silica, 1:10 EtOAc-hexane), the solvent was evaporated, using a rotary evaporator in which the receiving flask contained aqueous $NaHCO_3$. Flash chromatography of the residue over silica gel (3 x 20 cm), using 1:20 EtOAc-hexane, gave the carbamoyl chloride, which was dissolved in THF (10.0 mL plus 2.0 mL as a rinse) and added by syringe to a stirred solution of freshly prepared PhSeNa [from PhSeSePh (1.85 g, 6.00 mmol) and $NaBH_4$ (*ca* 450 mg, 12.0 mmol) in EtOH (20.0 mL)]. Stirring was continued for 6 h at room temperature. The mixture was then diluted with EtOAc (50 mL), washed with water (2 x 30 mL), brine (2 x 30 mL), and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:10 EtOAc-hexane, gave selenide **321** (1.25 g, 84 %) as a pure (^1H NMR, 400 MHz), yellowish oil: FTIR (CH_2Cl_2, cast) 3061, 3029, 1672, 1578, 1495 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 3.90 (two br s, 2 H), 4.65 (two br s, 2 H), 5.09-5.50 (m, 2 H), 5.67-6.02 (m, 1 H), 7.18-7.60 (m, 8 H), 7.61-7.85 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 49.41 (t'), 49.99 (t'), 50.16 (t'), 51.46 (t'), 118.51 (t'), 126.77 (s'), 127.47 (d'), 127.69 (d'), 128.41 (d'), 128.73 (d'), 128.93 (d'), 129.11 (d'), 132.05 (d'), 136.73 (d'), 168.00 (s'); exact mass *m/z* calcd for $C_{17}H_{17}NO^{80}Se$ 331.04755, found 331.04799.

3-Methyl-1-(phenylmethyl)-2-azetidinone (322).



Solutions of Ph_3SnH (574.0 mg, 1.6 mmol) in PhH (10.0 mL) and of AIBN (5.0 mg, 0.03 mmol) in PhH (10.0 mL) were added simultaneously by syringe pump over 8 h to a stirred and refluxing solution of **321** (270.0 mg, 0.817 mmol) in PhH (100 mL). Refluxing was continued for 1 h after the addition and the mixture was then cooled to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:2 EtOAc-hexane, gave **322** (45.7 mg, 32%) as an oil containing slight impurities (^{1}H NMR, 300 MHz): FTIR (CH_2Cl_2, cast) 3063, 3030, 1747, 1693, 1604 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.30 (d, J = 7.3, 3 H), 2.76 (dd, J = 5.4, 2.3 Hz, 1 H), 3.12-3.25 (m, 1 H), 3.30 (t, J = 5.2 Hz), 4.32 (d, J = 15.1 Hz, 1 H), 4.40 (d, J = 15.1, 1 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 13.66 (q'), 44.64 (d'), 46.69 (t'), 49.55 (t'), 126.77 (d'), 127.65 (d'), 128.11 (d'), 155.82 (s'), 171.15 (s'); exact mass *m/z* calcd for $C_{11}H_{13}NO$ 175.09972, found 175.09949. The ^{1}H NMR spectra data correspond to those given[118] in the literature.

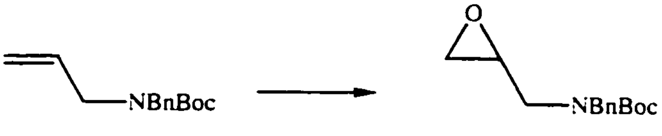
1,1-Dimethylethyl Phenylmethyl-2-propenylcarbamate (327).



320 **327**

A solution of $(Boc)_2O$ (873.0 mg, 4.00 mmol) in CH_2Cl_2 (10.0 mL plus 2.0 mL as a rinse) was added to a stirred solution of **320** (570.0 mg, 3.88 mmol) and Et_3N (1.1 mL, 7.7 mmol) in CH_2Cl_2 (15.0 mL). After *ca* 5 min, a small crystal of DMAP (*ca* 10 mg) was added and the solution was refluxed overnight, and then cooled to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:3 EtOAc-hexane, gave **327** (861.0 mg, 90%) as a pure (^{1}H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2, cast) 3065, 2976, 1696, 1644, 1605 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.48 (s, 9 H), 3.70 (br s, 2 H), 4.40 (s, 2 H), 5.00-5.21 (br m, 2 H), 5.60-5.90 (br m, 1 H), 7.10-7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 28.42 (q'), 48.69 (t'), 49.37 (t'), 79.71 (s'), 116.70 (t'), 127.13 (d'), 127.60 (d'), 128.64 (d'), 133.75 (d'), 138.32 (s'), 155.66 (s'); exact mass *m/z* calcd for $C_{15}H_{21}NO_2$ 247.15723, found 247.15662.

1,1-Dimethylethyl Phenylmethyl-(2,3-epoxypropyl)carbamate (328).

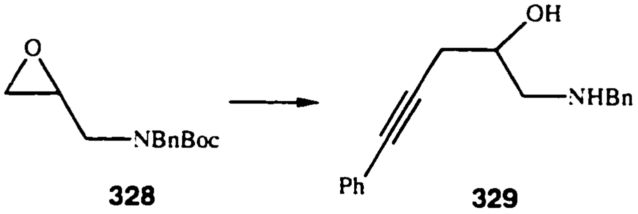


327 **328**

m-CPBA (57-86% from Aldrich, 1.90 g, *ca* 7 mmol) was added in small portions to a stirred solution of **327** (683.7 mg, 2.76 mmol) in EtOAc (20.0 mL), and stirring was continued overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:3 EtOAc-hexane, gave **328** (363.9 mg, 50%) as a pure (^{1}H NMR, 300 MHz), colorless oil. FTIR (CH_2Cl_2, cast) 2970, 1695, 1634 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.45 (s, 9 H), 2.35

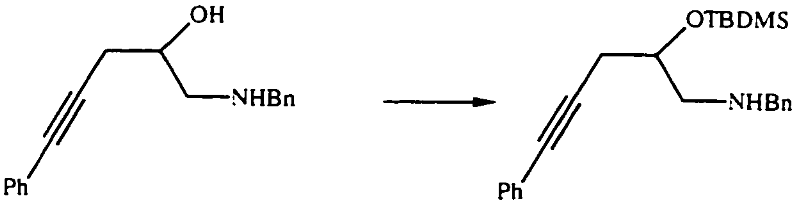
(br s, 1 H), 2.65 (t, *J* = 4.5 Hz, 1 H), 2.85-3.21 (br m, 2 H), 3.34 (br s, 0.5 H), 3.65 (br s, 0.5 H), 4.43 (d, *J* = 18.0 Hz, 1 H), 4.51-4.70 (br m, 1 H), 7.10-7.38 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 28.39 (q'), 45.00 (t'), 45.37 (t'), 48.38 (t'), 50.64 (d'), 50.88 (t'), 51.44 (t'), 80.17 (s'), 127.23 (d'), 127.82 (d'), 128.49 (d'), 138.17 (s'), 155.66 (s'); exact mass *m/z* calcd for $C_{15}H_{21}NO_3$ 263.15213, found 263.15119.

5-Phenyl-1-[(phenylmethyl)amino]pent-4-yn-2-ol (329).



n-BuLi (1.6 M in hexanes, 2.0 mL, 3.20 mmol) was added dropwise to a stirred and cooled (-78 °C) solution of phenylacetylene (410.0 mg, 4.0 mmol) in THF (10.0 mL). The solution was stirred at -78 °C for another 15 min and $BF_3 \cdot .OEt_2$ (0.40 mL, 3.20 mmol) was then added in one portion, followed by a solution of **328** (422.0 mg, 1.60 mmol) in THF (2.0 mL plus 1.0 mL as a rinse), which was added at a fast dropwise rate. Stirring was continued at -78 °C for 30 min, and the mixture was then diluted with Et_2O (40 mL) and water (20 mL). The organic layer was separated and the aqueous layer was extracted with Et_2O (2 x 10 mL). The combined organic extracts were washed with water (2 x 20 mL) and brine (2 x 20 mL), dried ($MgSO_4$), and evaporated. The residue was redissolved in CH_2Cl_2 (3.0 mL), TFA (3.0 mL) was added, and the mixture was stirred at room temperature for 2 h. The solvent was evaporated and the residue was dissolved in EtOAc (20 mL), washed with saturated aqueous Na_2CO_3 (10 mL x 2) and brine (20 mL), and dried (Na_2SO_4). Evaporation of the solvent afforded crude **329**, which was used directly in the next step.

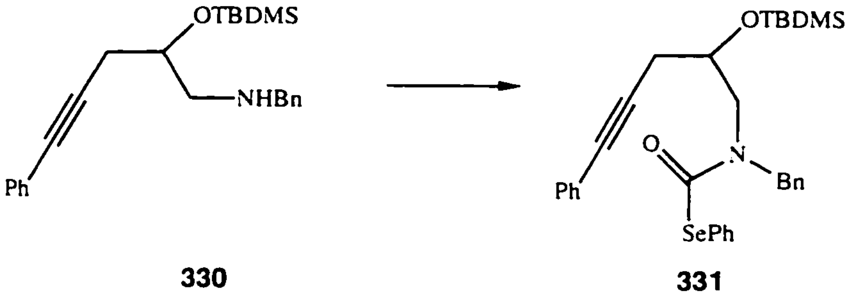
N-(Phenylmethyl)-2-[[1,1-Dimethylethyl)dimethylsilyl]oxy]-5-phenyl-4-butynamine (330).



329 **330**

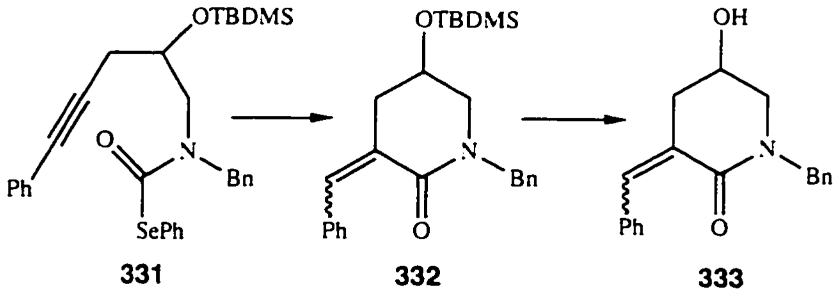
t-BuMe$_2$SiCl (367.7 mg, 2.44 mmol) was added in one portion to a stirred solution of **329** and imidazole (166.0 mg, 2.44 mmol) in THF (10.0 mL), and stirring was continued overnight. The THF was evaporated, and the residue was dissolved in EtOAc (20 mL). The solution was washed with saturated aqueous NH_4Cl (10.0 mL), water (10.0 mL) and brine (15.0 mL), and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:3 EtOAc-hexane, gave **330** (370.3 mg, 61 % from **328**) as a pure (^{1}H NMR, 300 MHz), yellowish oil: FTIR (CH_2Cl_2, cast) 3062, 3027, 1598 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.12 (s, 3 H), 0.18 (s, 3 H), 0.95 (s, 9 H), 1.80 (br s, 1 H), 2.59-2.77 (m, 2 H), 2.78-2.94 (m, 2 H), 3.82 (d, *J* = 13.5 Hz, 1 H), 3.89 (d, *J* = 13.5 Hz, 1 H), 4.05-4.15 (m, 1 H), 7.22-7.41 (m, 10 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) -4.62 (q'), -4.43 (q'), 18.10 (s'), 25.86 (q'), 26.54 (t'), 53.85 (t'), 54.35 (t'), 70.92 (d'), 82.25 (s'), 89.28 (s'), 123.83 (s'), 126.85 (d'), 127.65 (d'), 127.97 (d'), 128.19 (d'), 128.38 (d'), 131.57 (d'), 140.48 (s'); exact mass *m/z* calcd for $C_{24}H_{33}NOSi$ 379.23315, found 379.23263.

Se-Phenyl 2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-5-phenyl-4-pentynyl)(phenylmethyl)seloncarbamate (331).



A solution of $COCl_2$ in PhMe (*ca* 1:1 v/v) was added dropwise to a stirred solution of amine **330** (157.5 mg, 0.415 mmol) and pyridine (0.35 mL, 0.43 mmol) in THF (10.0 mL). When the reaction was over (*ca* 10 min, tlc control, silica, 1:10 EtOAc-hexane), the solvent was evaporated, using a rotary evaporator in which the receiving flask contained aqueous $NaHCO_3$ solution. Flash chromatography of the residue over silica gel (2 x 20 cm), using 1:10 EtOAc-hexane, gave the carbamoyl chloride which was redissolved in THF (3.0 mL plus 1.0 mL as a rinse) and added by syringe to a stirred solution of freshly prepared PhSeNa [from PhSeSePh (262.0 mg, 0.84 mmol) and $NaBH_4$ (*ca* 60 mg, 0.85 mmol) in EtOH (10.0 mL)]. Stirring was continued for 6 h at room temperature. The mixture was then diluted with EtOAc (40 mL), washed with brine (2 x 20 mL) and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using first hexane (to remove selenium species), and then 1:3 EtOAc-hexane, gave **331** containing slight impurities (^1H NMR, 400 MHz): FTIR(CH_2Cl_2, cast) 3060, 3030, 2953, 1672, 1490 cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz) δ 0.15-0.29 (m, 6 H), 1.05 (two s, 9 H), 2.55-2.80 (m, 2 H), 3.25 (dd, J = 13.7, 8.6 Hz, 0.5 H), 3.41 (dd, J = 15.2, 9.0 Hz, 0.5 H), 3.71 (dd, J = 13.6, 3.4 Hz, 0.5 H), 3.86 (dd, J = 13.6, 3.5 Hz, 0.5 H), 4.31-4.50 (br m, 1 H), 4.66 (d, J = 16.2 Hz, 1 H), 4.81 (d, J = 16.9 Hz, 0.5 H), 4.90 (d, J = 14.7 Hz, 0.5 H), 7.20-7.50 (m, 8 H), 7.61-7.75 (m, 2 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) -4.69 (q'), -4.42 (s'), 25.90 (q'), 26.66 (t'), 26.83 (t'), 51.97 (t'), 52.91 (t'), 53.24 (t'), 54.50 (t'), 68.85 (d'), 69.79 (d'), 82.79 (s'), 83.37 (s'), 85.25 (s'), 85.82 (s'), 123.63 (s'), 126.77 (s'), 127.40 (d'), 127.60 (d'), 127.70 (d'), 127.90 (d'), 128.20 (d'), 128.31 (d'), 128.43 (d'), 128.75 (d'), 128.83 (d'), 128.90 (d'), 129.11 (d'), 131.61 (d'), 135.98 (s'), 136.66 (d'), 136.83 (d'), 165.21 (s'); exact mass *m/z* calcd for $C_{31}H_{37}NO_2Si^{80}Se$ 563.17590, found 563,17530.

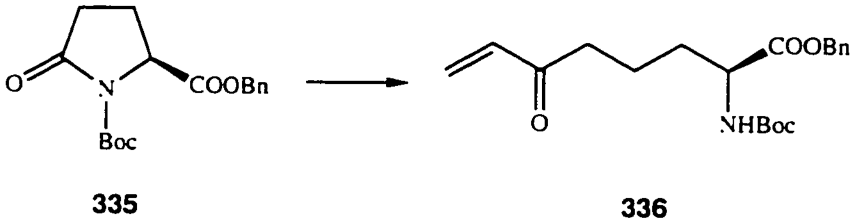
5-Hydroxy-1-(phenylmethyl)-2-(phenylmethylidene)-2-oxopiperidine (333).



Solutions of Ph_3SnH (280.0 mg, 0.80 mmol) and of AIBN (5.0 mg, 0.03 mmol), each in dry PhH (15.0 mL), were added simultaneously by syringe pump over 8 h to a stirred and refluxing solution of **331** in PhH (80 mL). Refluxing was continued for 1 h after the addition, and the solution was then cooled to room temperature. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:3 EtOAc-hexane, gave crude **332**, together with inseparable reduction product. The crude material was dissolved in THF (2.0 mL), and TBAF (1.0 M in THF, 0.50 mL, 0.50 mmol) was added, and the mixture was stirred at room temperature for 1 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 3:1 EtOAc-hexane, gave **333** (81.0 mg, 66.5 % from **331**) as a pure (^{1}H NMR, 200 MHz), colorless oil: FTIR (CH_2Cl_2, cast) 3373, 2918, 1648, 1593 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.85-3.12 (m, 2 H), 5.32 (dd, J = 12.4, 6.1 Hz, 1 H), 3.48 (dd, J = 12.4, 3.6 Hz, 1 H), 4.02-4.19 (m, 1 H), 4.51 (d, J = 14.6 Hz, 1 H), 4.79 (d, J = 14.6 Hz, 1 H), 7.20-7.49 (m, 10

H), 7.98 (t, J = 1.9 Hz, 1 H); ^{13}C NMR (CDCl$_3$, 50.3 MHz) 34.64 (t'), 51.24 (t'), 53.14 (t'), 63.72 (d'), 126.24 (s'), 127.53 (d'), 128.10 (d'), 128.26 (d'), 128.36 (d'), 128.69 (d'), 129.69 (d'), 135.70 (s'), 136.81 (s'), 138.58 (d'), 164.63 (s'); exact mass m/z calcd for $C_{19}H_{19}NO_2$ 293.14157, found 293.14151.

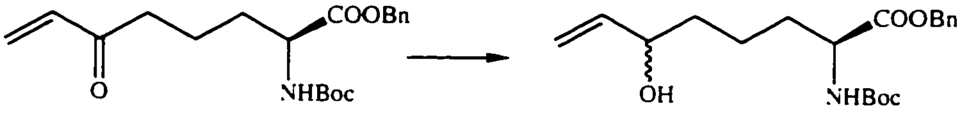
Benzyl (2*S*)-2-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-oxo-7-octenoate (336).



Vinylmagnesium bromide (1.0 M in THF, 1.55 mL, 1.55 mmol) was added dropwise to a stirred and cooled (-40 °C) solution of lactam **335** (410.0 mg, 1.28 mmol) in THF (7.0 mL). Stirring was continued at -40 °C for 1 h, and then 1 N HCl (1.0 mL) was added. The cold bath was removed and, when the mixture had attained room temperature, it was diluted with EtOAc (40.0 mL). The solution was washed with 1 N HCl (20 mL), water (20 mL) and brine (20 mL), and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 20 cm), using 1:3 EtOAc-hexane, gave ketone **336** (400.0 mg, 90%) as a pure (^{1}H NMR, 360 MHz), colorless oil: ^{1}H NMR (CDCl$_3$, 360 MHz) δ 1.42 (s, 9 H), 1.95-2.08 (m, 1 H), 2.10-2.28 (m, 1 H), 2.58-2.79 (m, 2 H), 4.30-

4.40 (br m, 1 H), 5.10-5.22 (m, 3 H), 5.72-5.80 (m, 1 H), 6.08-6.18 (m, 1 H), 6.19-6.32 (m, 1 H), 7.21-7.40 (m, 5 H). The ^{1}H NMR data are identical to those reported[122] in the literature.

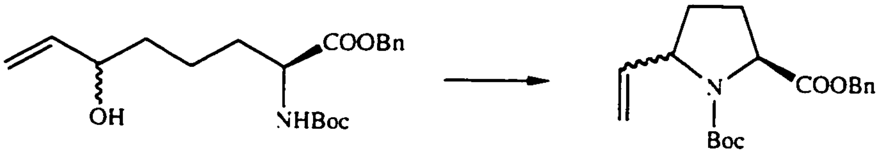
Benzyl (2*S*)-2-[[(1,1-Dimethylethoxy)carbonyl]amino]-5-hydroxy-7-octenoate (337).



336 **337**

NaBH$_4$ (162.0 mg, 4.28 mmol) was added in small portions to a stirred and cooled (-20 °C) solution of ketone **336** (1.4960 g, 4.29 mmol) and CeCl$_3$·.7H$_2$O (1.60 g, 4.30 mmol) in bench MeOH (20.0 mL). When the reaction was complete (*ca* 2 h, tlc control, 1:1 EtOAc-hexane), the mixture was quenched by addition of saturated aqueous NH$_4$Cl (10.0 mL). Most of the MeOH was removed *in vacuo* and the residue dissolved in EtOAc (50.0 mL). The solution was washed with 1 N HCl (20 mL), water (20 mL) and brine (30 mL), and dried (Na$_2$SO$_4$). Evaporation of the solvent gave **337** as a oil, which was used without further purification. The material had: ^{1}H NMR (CDCl$_3$, 300 MHz) δ 1.39-2.02 (m, 13 H), 4.07 (dd, J = 9.9 Hz, 7.2 Hz, 1 H), 4.38 (s, 1 H), 5.02-5.25 (m, 5 H), 5.72-5.85 (m, 1 H), 7.30-7.40 (m, 5 H).

Benzyl 1-[(1,1-Dimethylethoxy)carbonyl]-5-ethenylprolinate (338).

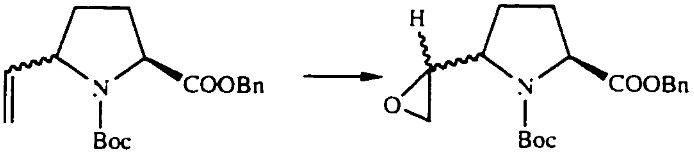


337 **338**

MsCl (0.27 mL, 3.42 mmol) was added to a stirred and cooled (-50 °C) solution of crude **337** (1.09 g, 2.85 mmol) in CH_2Cl_2 (20 mL), followed by Et_3N (0.8 mL, 5.70 mmol). The cold bath was removed, and the mixture was allowed to warm to room temperature. A condenser was fitted onto the flask and the solution was refluxed (Ar atmosphere) until reaction was complete (*ca* 2 days, tlc control, silica, 1:3 EtOAc-hexane). Most of the solvent was evaporated, and the residue was redissolved in EtOAc (30 mL), washed with water (2 x 15 mL) and brine (30 mL), and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 20 cm), using 1:3 EtOAc-hexane, gave **338** (804.9 mg, 85%) as a mixture of isomers (^1H NMR 360 MHz): FTIR (CH_2Cl_2, cast) 3022, 2932, 1745, 1695 cm^{-1}; ^1H NMR ($CDCl_3$, 360 MHz) δ 1.13 (s, 4 H), 1.22 (two close s, 5 H), 1.60-2.30 (m, 4 H), 4.20-4.38 (m, 1 H), 4.39-4.42 (m, 0.7 H), 4.50-4.70 (m, 0.3 H), 5.0-5.30 (m, 4 H), 5.70-5.90 (m, 1 H), 7.20-7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 25.87 (t'), 27.27 (t'), 27.84 (q'), 28.19 (q'), 29.29 (t'), 29.54 (t'), 59.33 (d'), 59.63 (d'), 60.66 (d'), 62.02 (d'), 66.61 (t'), 67.04 (t'), 79.84

(s'), 79.93 (s'), 113.86 (t'), 114.03 (t'), 128.38 (d'), 128.47 (d'), 128.60 (d'), 128.51 (d'), 128.55 (d'), 135.41 (s'), 135.65 (s'), 137.89 (d'), 138.22 (d'), 153.40 (s'), 154.31 (s'), 172.34 (s'), 172.48 (s'); exact mass *m/z* calcd for $C_{19}H_{25}NO_4$ 331.17834, found 331.17795.

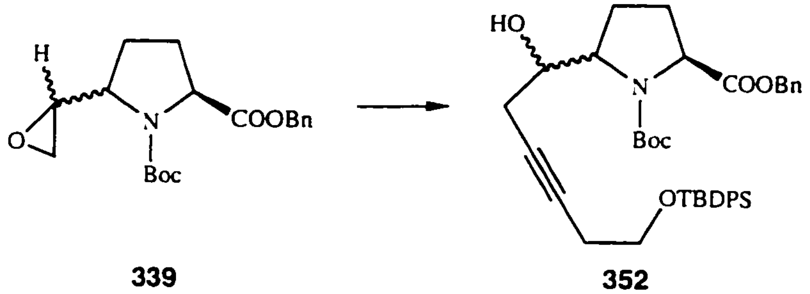
Benzyl 1-[(1,1-Dimethylethoxy)carbonyl]-5-(1,2-epoxyethenyl)-prolinate (339).



338 **339**

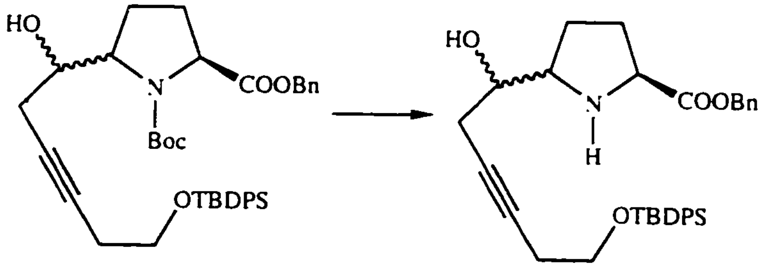
m-CPBA (57%-86% from Aldrich, 3.0 g, *ca.* 11 mmol) was added to a stirred and cooled (0 °C) solution of alkene **338** (1.48 g, 4.45 mmol) in EtOAc (25.0 mL). Stirring was continued for 2-3 days, by which time reaction was over (tlc control, silica, 1:3 EtOAc-hexane). More EtOAc (30.0 mL) was added and the solution was washed with saturated aqueous $Na_2S_2O_3$ (40 mL x 2), saturated aqueous Na_2CO_3 (40 mL x 2) and brine (40 mL), and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 30 cm), using 1:1 EtOAc-Hexane, gave **339** (1.24 g, 80%) as a mixture of isomers (^{1}H NMR, 200 MHz): FTIR (CH_2Cl_2, cast) 2976, 2932, 1746, 1699 cm^{-1}; ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.33 (s, 4.8 H), 1.45 (two close s, 4.2 H), 1.72-1.99(m, 2 H), 2.0-2.48 (m, 2 H), 2.45-2.69 (m, 1 H), 2.70-2.90 (m, 1 H), 3.0-3.11 (m, 1 H), 4.20-4.45 (m, 2 H), 5.05-5.30 (m, 2 H), 7.3-7.42 (m, 5 H); ^{13}C NMR ($CDCl_3$, 75.5 MHz) 28.19 (q'), 28.38 (q'), 36.35 (t'), 36.93 (t'), 37.17 (t'), 37.69 (t'), 58.29 (d'), 58.64 (d'), 66.70 (d'), 66.77 (s'), 73.10 (d'), 74.16 (d'), 80.41 (t'), 117.44 (d'), 128.04 (d'), 128.14 (d'), 128.30 (d'), 128.40 (d'), 128.48 (d'), 128.60 (d'), 135.53 (s'), 153.93 (s'), 154.41 (s'), 172.71 (s'), 173.04 (s'); exact mass *m/z* calcd for $C_{19}H_{25}NO_5$ 347.17328, found 347.17397.

Benzyl 1-[(1,1-Dimethylethoxy)carbonyl]-5-[6-[[(1,1-dimethyl-ethyl)diphenylsilyl]oxy]-1-hydroxy-3-hexynyl]prolinate (352).



A solution of oxirane **339** (473.0 mg, 1.36 mmol) in THF (3.0 mL plus 1.0 mL as a rinse) was added to a stirred and cooled (-78 °C) solution of acetylide **351** [from corresponding acetylene (837.0 mg, 2.72 mmol) and BuLi (1.6 M in hexane, 1.65 mL, 2.64 mmol) in THF (15.0 mL)]. After 10 min, $BF_3 \cdot .OEt_2$ (0.34 mL, 2.76 mmol) was added in one portion. Stirring was continued for 1 h at -78 °C and then saturated aqueous Na_2CO_3 (5.0 mL) was added. Most of the THF was evaporated, and the residue was diluted with EtOAc (40.0 mL) and washed with water (30 mL) and brine (30 mL), and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 30 cm), using 1:3 EtOAc-hexane, gave alcohol **352** (758.0 mg, 84%) as a mixture of isomers (^1H NMR, 200 MHz): FTIR (CH_2Cl_2, cast) 3439, 3069, 1745, 1697, 1498 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.10 (s, 9 H), 1.39 (s, 6.5 H), 1.49 (s, 2.5 H), 1.70-2.15 (m, 3 H), 2.20-2.59 (m, 5 H), 3.05 (br s, 1 H), 3.80 (t, J = 7.0 Hz, 2 H), 3.96-4.29 (m, 2 H), 4.30-4.55 (m, 1 H), 5.05-5.39 (m, 2 H), 7.25-7.54 (m, 11 H), 7.68-7.82 (m, 4 H); ^{13}C NMR ($CDCl_3$, 100.6 MHz) 19.23 (t'), 23.04 (t'), 24.37 (t'), 24.84 (t'), 25.75 (t'), 26.17 (t'), 26.85 (q'), 28.12 (q'), 28.32 (q'), 28.43 (t'), 28.79 (t'), 60.48 (d'), 60.94 (d'), 61.39 (d'), 62.74 (d'), 62.85 (d'), 71.26 (d'), 71.68 (d'), 71.92 (d'), 73.48 (d'), 77.39 (t'), 77.82 (t'), 79.19 (s'), 79.46 (s'), 80.73 (s'), 81.22 (s'), 127.73 (d'), 128.12 (d'), 128.16 (d'), 128.51 (d'), 129.69 (d'), 133.68 (s'), 133.73 (s'), 135.59 (d'), 155.19 (s'), 156.07 (s'), 172.67 (s'), 173.07 (s'); exact mass m/z calcd for $C_{35}H_{40}NO_6Si$ ($M^+ - C_4H_9$) 598.26251, found 598.26323.

Benzyl 5-[6-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-1-hydroxy-3-hexynyl]prolinate (353).

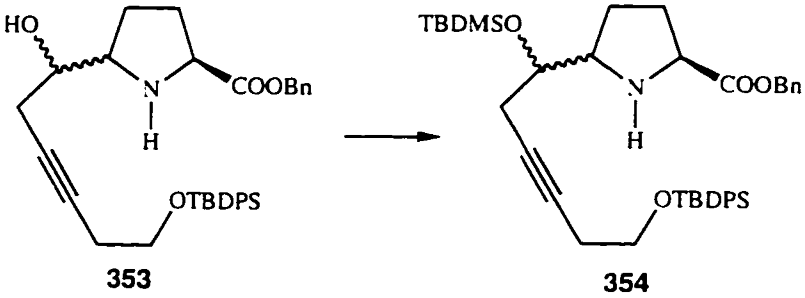


352 **353**

TFA (2.0 mL) was added in one portion to a stirred and cooled (*ca*. -15 °C) solution of alcohols **352** (522.0 mg, 0.79 mmol) in CH_2Cl_2 (2.0 mL). The mixture was stirred at room temperature for *ca* 2 h, by which time reaction was complete (tlc control, silica, 2:1 EtOAc-hexane). The solvent was evaporated and the residue was diluted with EtOAc (40 mL), washed with saturated aqueous Na_2CO_3 (2 x 20 mL) and brine (30 mL), and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 20 cm), using 2:1 EtOAc-hexane, gave amine **353** (345.0 mg, 78%) as a mixture of isomers (^{1}H NMR, 400 MHz): FTIR (CH_2Cl_2, cast) 3500, 1745 cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.05 (s, 9 H), 1.60-1.90 (m, 3 H), 2.12-2.50 (m, 5 H), 2.95 (br s, 2 H), 3.35-3.41 (m, 0.5 H), 3.42-3.54 (m, 1 H), 3.60-3.70 (m, 0.5 H), 3.71-3.80 (m, 2 H), 3.81-3.91 (m, 1 H), 5.15 (s, 2 H), 7.3-7.46 (m, 6 H), 7.62-7.78 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 19.19 (s'), 22.96 (t'), 23.93 (t'), 24.55 (t'), 25.64 (t'), 26.79 (q'), 28.36 (t'), 30.20 (t'), 30.55 (t'), 59.74

(d'), 59.79 (d'), 60.87 (d'), 61.02 (d'), 62.76 (t'), 66.84 (t'), 70.92 (d'), 71.34 (d'), 77.15 (s'), 77.70 (s'), 79.30 (s'), 127.69 (d'), 128.16 (d'), 128.42 (d'), 128.64 (d'), 129.66 (s'), 133.69 (s'), 135.57 (d'), 174.95 (s'), 175.19 (s'); exact mass *m/z* calcd for $C_{34}H_{41}NO_4Si$ 555.28052, found 555.28258.

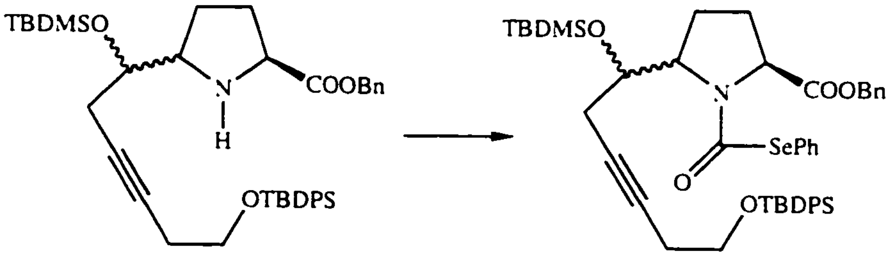
Benzyl 5-[[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-6-[[(1,1-dimethylethyl)diphenylsilyl]oxy]]-3-hexynyl]prolinate (354).



Pyridine (0.10 mL, 1.20 mmol) and *t*-$BuMe_2SiOTf$ (0.245 mL, 1.10 mmol) were added in that order to a stirred and cooled (0 °C) solution of alcohol **353** (198.0 mg, 0.36 mmol) in CH_2Cl_2 (2.0 mL). The reaction was continued for 30 min. and MeOH (*ca* 1.0 mL) was added. The mixture was stirred for another 30 min. and dissolved in EtOAc (20 mL), washed with water (10 mL), brine (20 mL), and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:5 EtOAc-hexane, gave amine **354** (205.2 mg, 85%) as a mixture of isomers (^1H NMR, 400

MHz). This compound was only characterized by its ^{1}H NMR spectrum because of its instability on standing: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 0.05-0.17 (several s, 6 H), 0.90-1.00 (several s, 9 H), 1.15 (s, 9 H), 1.55-2.00 (m, 4 H), 2.11-2.60 (m, 5 H), 3.45-3.55 (m, 1 H), 3.62-3.74 (m, 1 H), 3.75-3.87 (m, 2 H), 3.90-4.00 (m, 1 H), 5.20 (s, 2 H), 7.30-7.50 (m, 11 H), 7.30-7.40 (m, 4 H).

Benzyl 5-[1-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-6-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-3-hexynyl]-1-[(phenylseleno)carbonyl]prolinate (356).



354

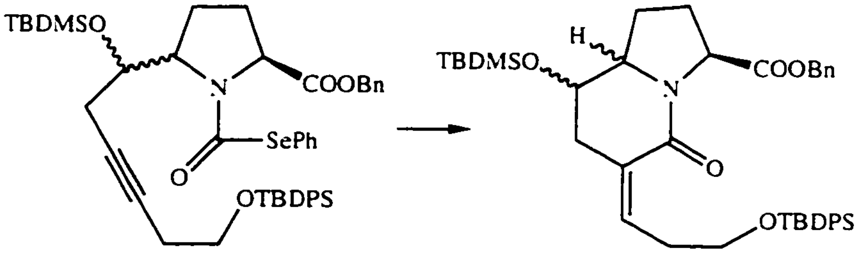
356

A solution of $COCl_2$ in PhMe (1:1 v/v) was added by pipette to a stirred solution of freshly prepared amine **354** (247.1 mg, 0.368 mmol) in THF (4.0 mL). After 30 min the reaction was complete (tlc control, silica, 1:10 EtOAc-hexane). The solution was concentrated to one third of its original volume, using a rotary evaporator in which the receiving flask contained aqueous $NaHCO_3$ solution. Flash chromatography of the residue over silica gel (2 x 20 cm), using 1:10 EtOAc-hexane, gave the carbamoyl chloride **355** as a colorless oil, which was used immediately for next step.

NaH (60% dispersion in mineral oil, 41.0 mg, 1.03 mmol) was added to a stirred solution of PhSeSePh (160.0 mg, 0.51 mmol) in THF (10.0 mL). The solution was refluxed for 1 h and cooled to room temperature. HMPA (0.20 mL, 1.15 mmol) was added, followed by freshly prepared carbamoyl chloride **355** (188.0 mg, 0.256 mmol) in THF (2.0 mL plus 1.0 mL as a rinse). The mixture was stirred for 6 h. Most of the solvent was evaporated and the organic material was dissolved in Et_2O (40 mL) and washed with water (20 mL) and brine (30 mL), and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:10 EtOAc-hexane, gave the carbamoyl selenide **356** (174.0 mg, 80%) as a mixture of isomers (^{1}H NMR, 300 MHz), slightly yellowish oil: FTIR (CH_2Cl_2, cast) 1745, 1730 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.01-0.22 (m, 6 H), 0.75-1.00 (m, 9 H), 1.01-1.11 (m, 9 H), 1.80-2.60 (m, 8 H), 3.68-3.82 (m, 2 H), 4.08-4.35 (m, 1 H), 4.36-4.60 (m, 2 H), 5.01-5.22 (m, 1 H), 5.23-5.38 (m, 1 H), 7.27-7.59 (m, 16 H), 7.60-7.80 (m, 4 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 22.80 (s'), 22.96 (s'), 23.20 (s'), 25.39 (t'), 25.69 (q'), 25.83 (q'), 26.83 (q'), 28.14 (t'), 29.93 (t'), 61.45 (d'), 61.83 (d'), 62.75 (t'), 62.87 (t'), 63.15 (d'), 63.66 (d'), 66.93 (t'), 67.36 (t'), 67.77 (d'), 71.21 (d'), 79.02 (s'), 81.25 (s'), 127.67 (d'), 128.12 (d'), 128.45 (d'), 128.51 (d'), 129.65 (d'), 128.81 (d'), 129.00 (d'), 129.13 (d'), 129.63 (d'), 133.70 (s'), 135.54

(d'), 136.25 (d'), 136.33 (d'), 159.60 (s'), 171.00 (s'); exact mass (HR electrospray) *m/z* calcd for $C_{47}H_{58}NO_5{}^{80}SeSi_2Na$ (M^+ + Na) 876.29947, found 876.30035.

Benzyl (3*S*)-6-[3-[[(1,1-Dimethylethyl)diphenylsilyl]oxy]-propylidene]-8-[[(1,1-dimethylethyl)diphenylsilyl]oxy]-5-oxo-3-indolizidinecarboxylate (357).



356 **357**

Solutions of Ph_3SnH (134.0 mg, 0.38 mmol) in PhMe (5.0 mL) and of AIBN (10.0 mg, 0.06 mmol) in PhMe (5.0 mL) were added simultaneously by syringe pump over 7 h to a stirred and refluxing solution of carbamoyl selenide **356** (163.5 mg, 0.19 mmol) in PhMe (20.0 mL). Refluxing was continued for 2 h after the addition, and the solution was then cooled. Evaporation of the solvent and flash chromatography of the residue over silica gel (2 x 20 cm), using 1:3 EtOAc-hexane, gave a mixture (^1H NMR, 300 MHz) of **357** and the reduction product (117.5 mg, 88%) with a ratio of *ca* 3:1 in favor of the cyclization product as colorless oil: FTIR (CH_2Cl_2 cast) 3069, 2954, 2891, 1747, 1669, 1624 cm^{-1}; ^1H NMR ($CDCl_3$, 300

MHz) showed a clear *dd* at δ 6.90 (J = 8.0, 1.9 Hz) and all the other necessary signals corresponding to **357**; exact mass (HR electrospray) m/z calcd for $C_{41}H_{55}NO_5Si_2N_a$ (M^+ + Na) 720.35165, found 720.35179. The ^{13}C spectra will be obtained once the material is purified.

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Chapter Three

Stereocontrolled α functionalization of pyrrolidines and related systems

Introduction

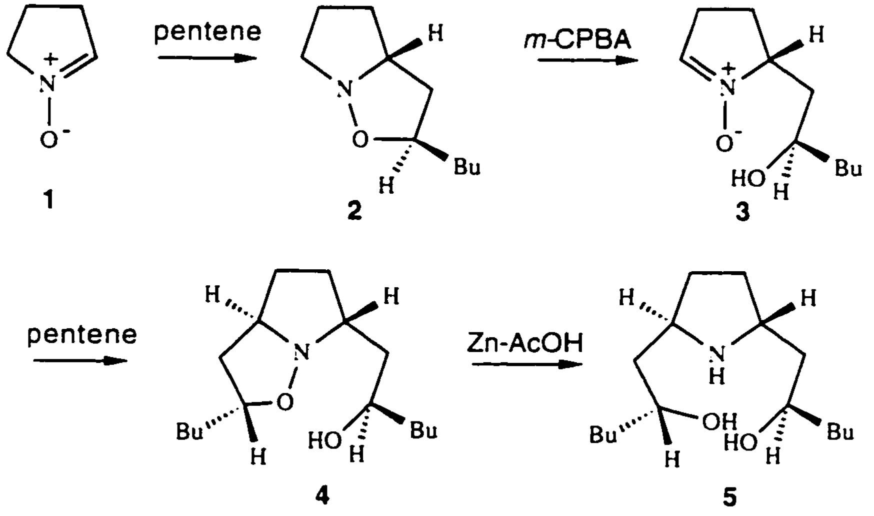
Pyrrolidines have long provided organic chemists with interesting and important synthetic targets.[1] This is mainly due to the remarkable medicinal and biological activities shown by such compounds and the possibility that synthetic work would have applications in the pharmaceutical industry. Most recent efforts in the synthesis of alkaloids have concentrated on the control of stereochemistry, and this aspect has been strongly encouraged by the requirement of the pharmaceutical industry for optically pure drugs.

While a variety of chiral centers may exist in a pyrrolidine structure, one of the most common structural features is the presence of a chiral center adjacent to the ring nitrogen (α position). This position often carries a substituent, or it may be the point of fusion of two rings.

Many methods have been reported for the functionalization of the α position of pyrrolidines, and the following is a brief review of general methods for this transformation.

A. The nitrone approach

An example of the 1,3 dipole cyclization of nitrones is shown in Scheme 1. The addition of 1-pyrroline *N*-oxide **1** to monosubstituted alkenes in the presence of a peracid allowed regiospecific access to aldonitrone **3**.[2] The same reaction can be repeated to afford 2,5 disubstituted pyrrolidines **5**. The N-O bond in intermediate **4** can be cleaved easily by treatment with zinc in acetic acid.



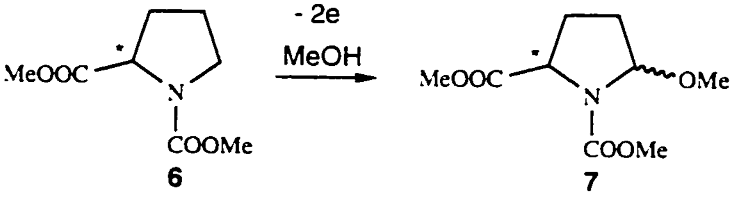
Scheme 1

B. Nucleophilic substitution of *N*-acyliminium ions

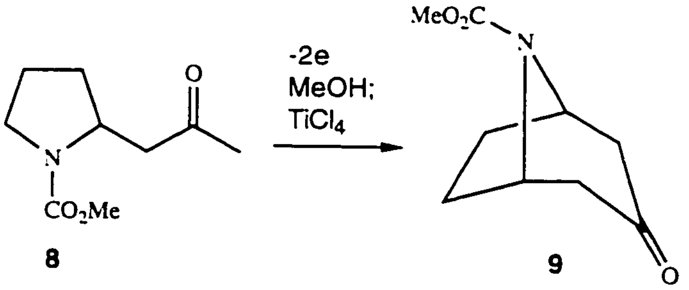
An *N*-acyliminium ion can be generated either electrochemically, or by reduction of a lactam, as described in the following paragraphs.

a. *Electrochemical method.*

Pioneered by Shono, the electrochemical method[3] to functionalize the α position of an amide has been adopted quite frequently for synthesis of various nitrogen containing heterocycles.[3] The regioselectivity of the process is usually such that reaction occurs at the less substituted position α to nitrogen (Scheme 2). The yield is usually around 80%, but no stereocontrol is achievable. Compound **7**, prepared in this way,[3a] is a useful intermediate for many subsequent transformations leading to complex structures, and the same is true of compounds related to **7**. For example, when applied to **8** (Scheme 3), the initial methoxylated product can be cyclized by the action of $TiCl_4$ to afford the bicyclic ketone **9**.[3c]

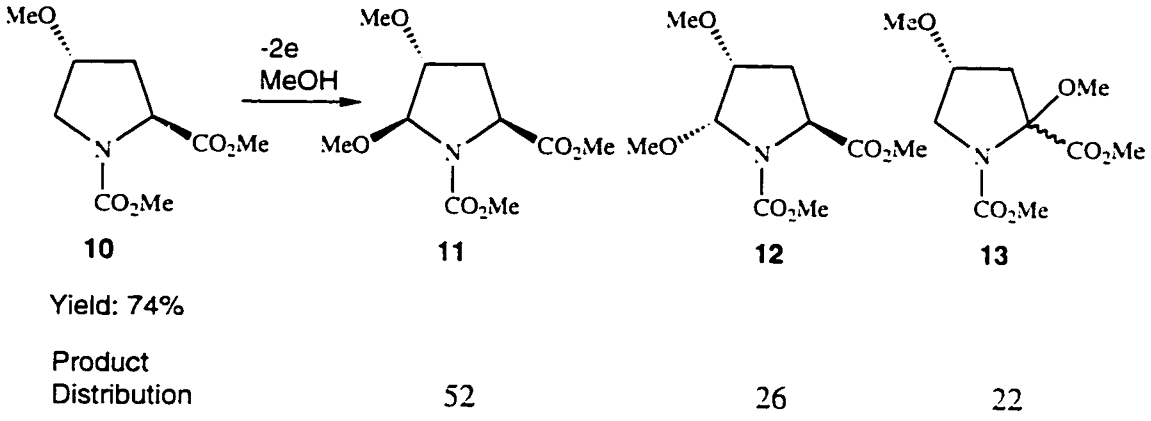


Scheme 2



Scheme 3

However, the outcome of the reaction in more heavily substituted systems is less predictable, as shown by the anodic oxidation of the 4-hydroxyproline derivative **10** (Scheme 4).[3d] In this case, a mixture of products (**11-13**) was obtained in a ratio of 52:26:22. The separation of the minor undesired regioisomer **13** was rather difficult.



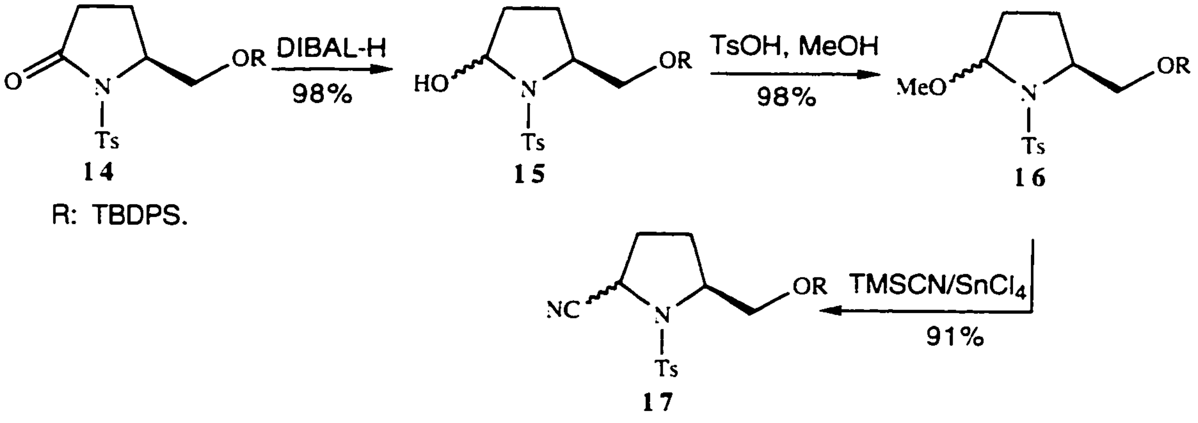
Scheme 4

b. Partial reduction of lactams.

As commonly practiced, partial reduction of a lactam will afford, after treatment with acid, the acyliminium species, and many examples of this procedure have been reported.[4]

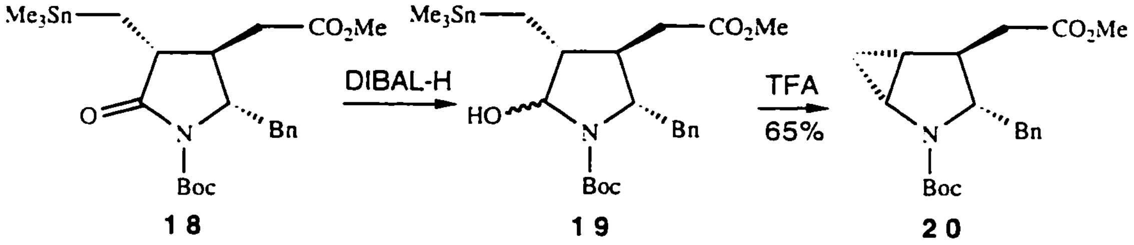
Partial reduction of a pyroglutamic acid derivative, such as **14**, can be accomplished easily by reducing agents, of which DIBAL-H is the most popular (**14** → **15**).[4c,5] Treatment with methanol in the presence of acid, gave the corresponding methoxy compounds (via the intermediacy of an tosyliminium species), and further treatment with Me_3SiCN, in the presence of tin tetrachloride, afforded a mixture of *cis* and *trans* cyanides (**16** → **17**) (Scheme 5), reaction again proceeding via an acyliminium intermediate. The diastereoselectivity depends on both the Lewis acid and the nature of each specific nucleophile involved.[4c] In the illustrated case

(Scheme 5), an 80% d.e. favoring the *trans* isomer was observed.



Scheme 5

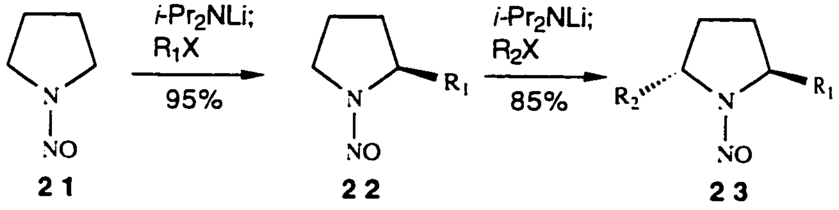
Nucleophilic attack on the acyliminium species may also occur intramolecularly, as shown in a recent report from Hanessian's laboratory (Scheme 6).[5]



Scheme 6

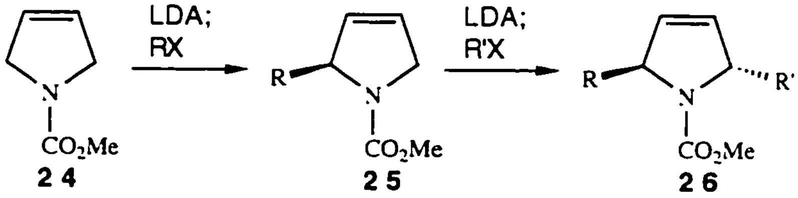
C. Electrophilic substitution reactions

Another way in which the reactivity of the position α to the nitrogen can be utilized, involves electrophilic substitution. Fraser *et al.*[6] first synthesized 2,5 dialkylated pyrrolidines via metallated nitropyrrolidines (Scheme 7). Compound **21** was alkylated twice at the α and α' positions with the regioselectivity of the second step being determined by both the lithium amide species used and the specific alkylating agent. The second alkylation is highly regioselective but the diastereoselectivity was less than 70%, with the *trans* isomer **23** being favored.



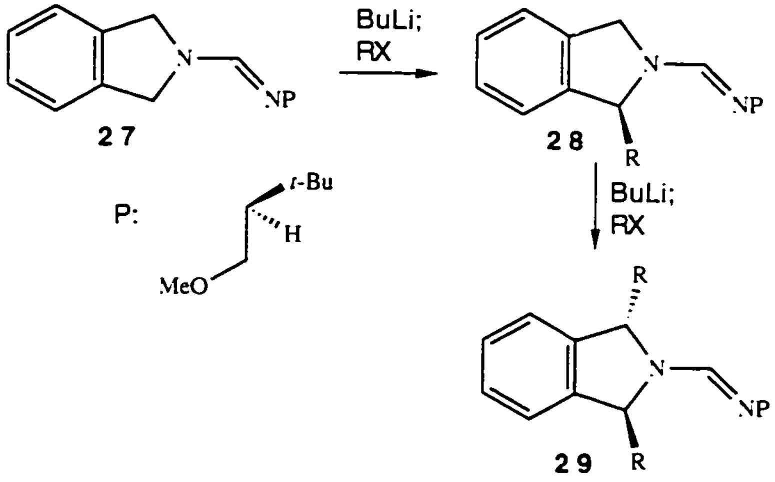
Scheme 7

MacDonald[7] started from a pyrroline derivative (**24**) and carried out a similar reaction sequence (Scheme 8), but achieved both good regio (>97% at α' position) and excellent diastereoselectivity (*trans* >95%).



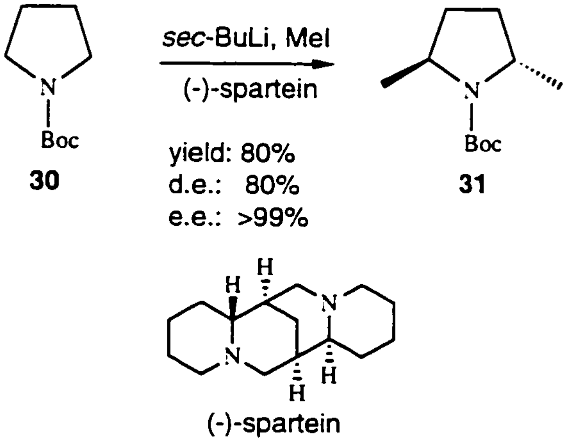
Scheme 8

Recently the synthesis of 1,3 dialkylated isoindolines from chiral formamidines **27** (Scheme 9) has been reported.[8] The level of asymmetric induction was very high, and the reaction afforded products with e.e. from 94 to >99%.



Scheme 9

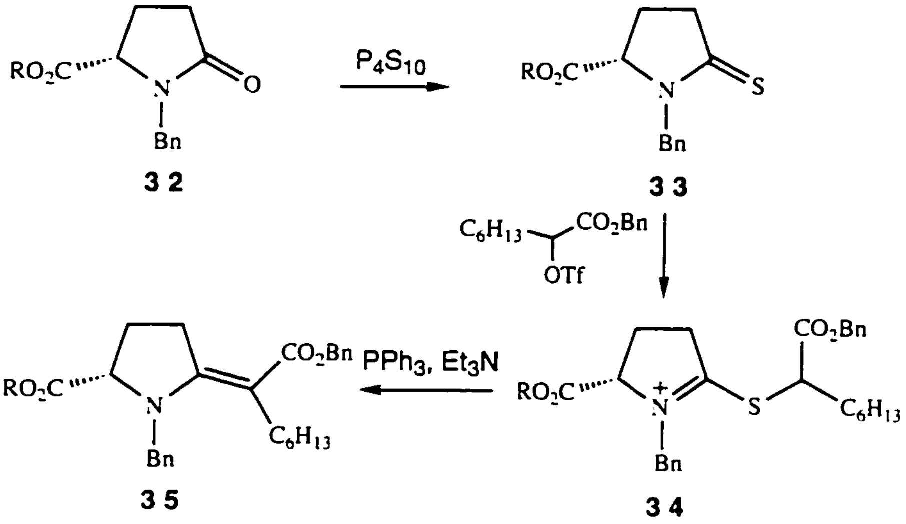
Impressive examples are also found in work from Beak's group.[9] For example, asymmetric deprotonation of pyrrolidines, and subsequent stereoselective alkylation was carried out to give optically active pyrrolidines. In the example shown in Scheme 10, product **31** was obtained with a d.e. of 80% and e.e. of 99%.



Scheme 10

D. Thiolactam pathway

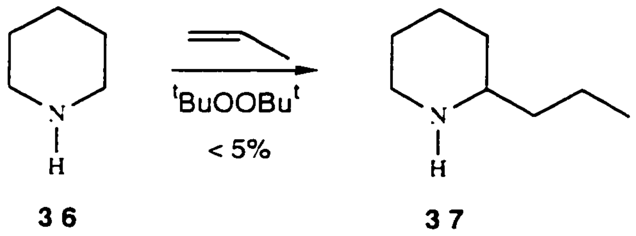
The classical sulfide contraction has been applied to the conversion of lactams into α substituted pyrrolidines. This approach starts from pyroglutamic acid esters, and involves conversion to the corresponding thiolactam (**33**), which are treated with an electrophile and then subject to conditions appropriate for sulfur extrusion (Scheme 11).[10]



Scheme 11

F. α Functionalization by radical reactions

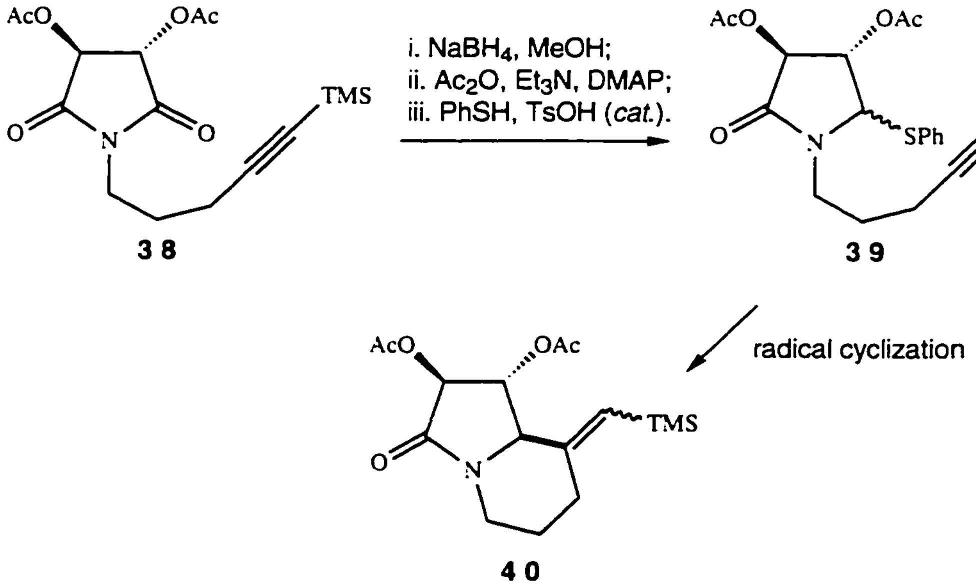
The stability of radicals α to nitrogen has been applied in alkaloid synthesis. A classic example is the work by Urry *et al.*[11] in the one step synthesis of (±)-coniine (Scheme 12). The yield in this case was low, but the experiment served to illustrate the principle.



Scheme 12

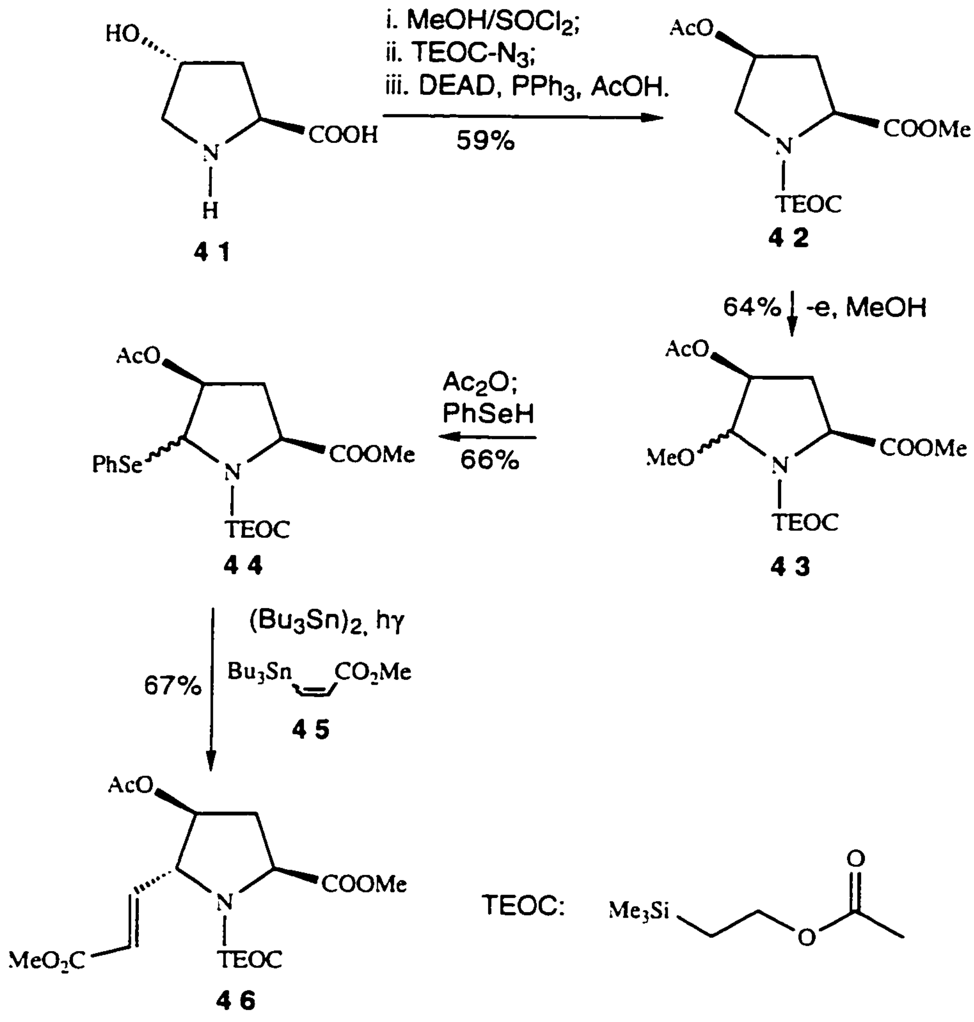
The major problem of intermolecular hydrogen abstraction reactions, however, is the low yield, due, in part to formation of side products by other competing processes.

Many approaches have adopted a pre-functionalization of the α position, followed by installation of a group or atom that can be cleaved homolytically under standard radical conditions. This strategy makes it possible to generate the radical regioselectively in high yields. Examples can be found in many reports[12] and a typical procedure is shown in one of the alkaloid syntheses from the Hart group (Scheme 13).[12c]



Scheme 13

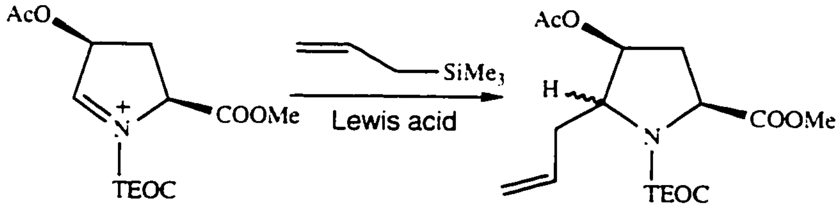
In the total synthesis of bulgecin C from (2*S*,4*R*)-hydroxyproline, Barrett *et al.*[13] used a combination of electrochemical and radical reactions, as illustrated in Scheme 14.



Scheme 14

Compound **42** was obtained by Mitsunobu inversion of the C-4 hydroxyl in commercially available 4-hydroxyproline after esterification and nitrogen protection. In a key step (**42** → **43**), anodic oxidation at C-5 was applied. However, in contrast to reported anodic oxidations of both Boc and Cbz protected proline methyl esters, the corresponding analogs of 4-hydroxyproline produced a complex reaction mixture and gave less than 20 % yield of the desired 5-methoxylated derivatives. Further experimentation eventually led to the adoption of a *O*-(2-(trimethylsilyl)-ethyl)carbamate as the protecting group, and with this form of nitrogen protection, the desired products of electrochemical methoxylation (**43**) were obtained in 80% yield. Direct reaction of the methoxylated derivatives **43** with PhSeH was not satisfactory, but initial replacement by an acetoxy group, followed by treatment with PhSeH, served to install the phenylseleno group. Finally, irradiation of **44** in the presence of **45**, gave the 5 substituted pyrollidine **46** as a single diastereoisomer.

It is interesting to note that the Barrett group had initially attempted to incorporate the C-5 branch of **46** by ionic addition to the appropriate iminium cation with allyltrimethylsilane (Scheme 15). However, it was not possible to control the stereochemical outcome by this ionic reaction, and a mixture of *trans* and *cis* isomers was obtained (Scheme 15). It is not clear why the two approaches show such very different levels of stereoselectivity.



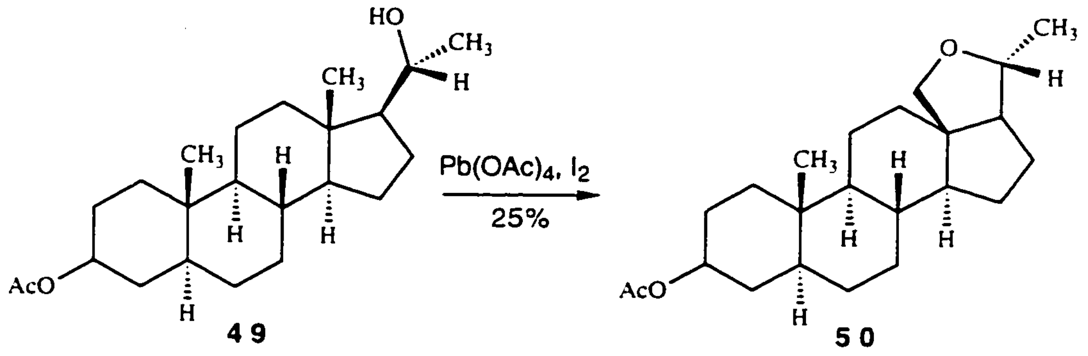
47 48

Scheme 15

An obvious drawback to approaches based on pre-functionalization α to the nitrogen, is the requirement for additional steps to introduce the initial functional group. In more complex structures, conditions for pre-functionalization may be limited by other structural features already present.

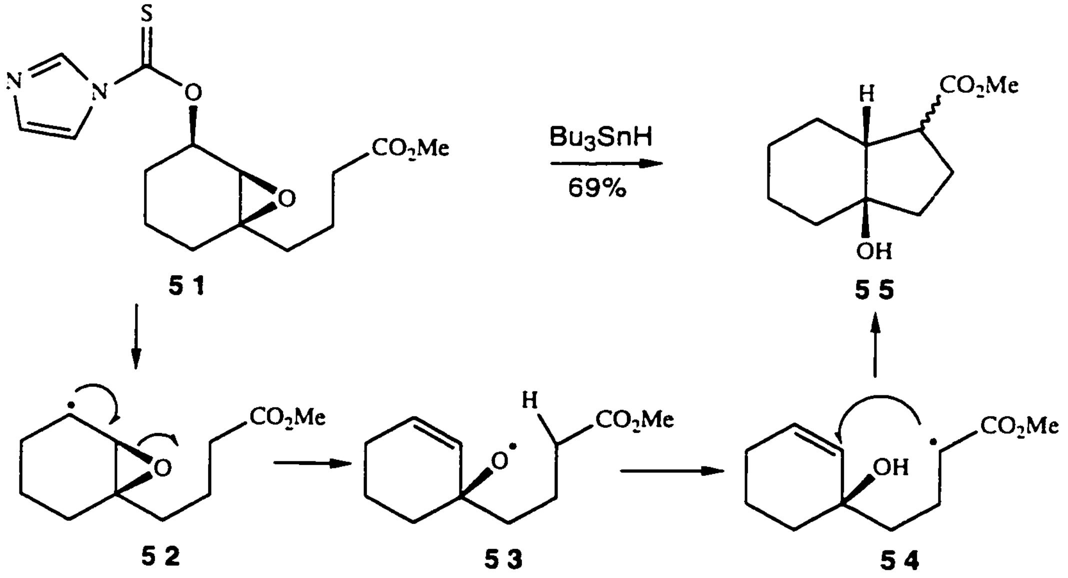
Recently, a novel approach, based on intramolecular hydrogen transfer, has been applied to generate directly radicals α to nitrogen. The net result of such transfer is to switch the radical center from one location to another in the same molecule, a process sometimes termed *radical translocation*. An overview of recent developments in this special area is necessary before a more specific discussion is given of its use in the preparation of pyrrolidines.

While it is true that intramolecular hydrogen transfer reactions initiated by a heteroatom-centered radical (usually N or O) have long been known,[14,15,16] e.g., the Hofmann-Löffler-Freitag reaction, Barton nitrite photolysis, and the hypoiodite reaction (the latter is shown in Scheme 16), these heteroatom-centered radicals have usually been used[14] for remote functionalization, especially of steroids, but the recent development of synthetic radical chemistry has renewed interest in the broader applications of heteroatom-centered radicals.



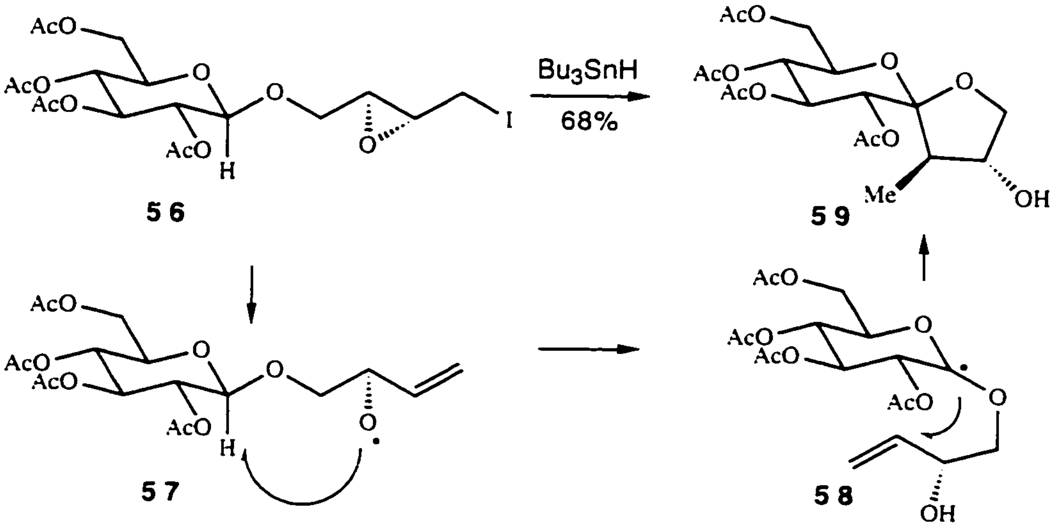
Scheme 16

Rawal *et al* published[17] a unique way to generate an alkoxy radical by opening an oxirane ring through β scission. The alkoxy radical then causes a 1,5 hydrogen transfer (**53** → **54**, Scheme 17). The translocated radical cyclizes back onto the double bond that was generated in the first step, so as to afford the bicyclic product **55**.



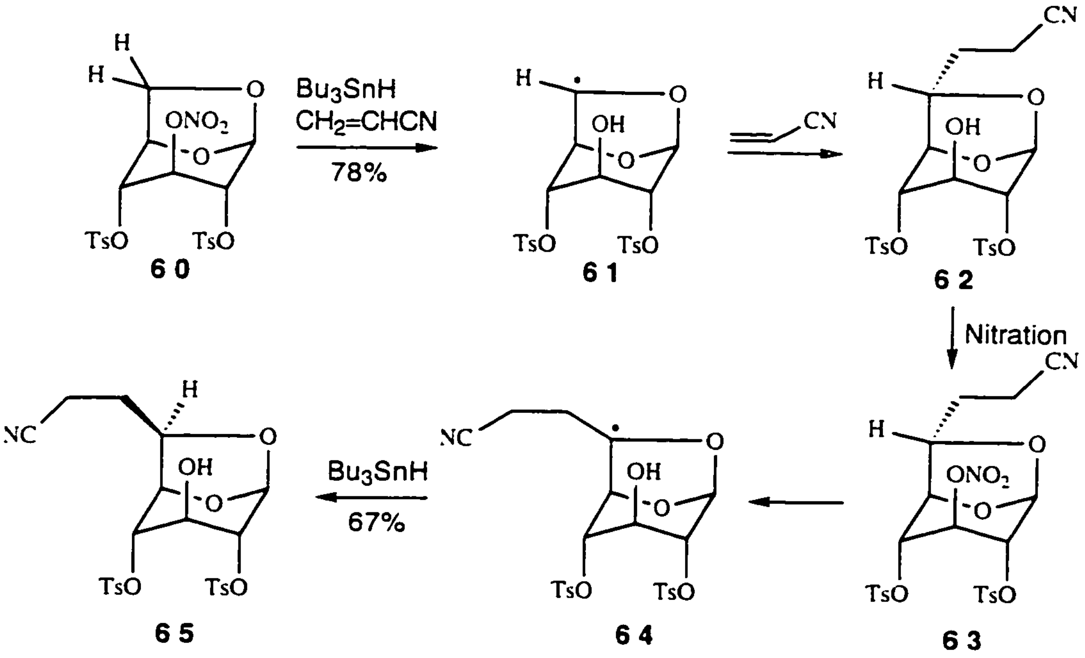
Scheme 17

This strategy has been adopted for constructing a spiro glucoside **59** (Scheme 18).[18] In this case, the oxy radical **56** abstracts the anomeric hydrogen, and the new translocated radical (**58**) cyclizes onto the double bond in the aglycon. The main product (68%) is the spiro sugar **59**.



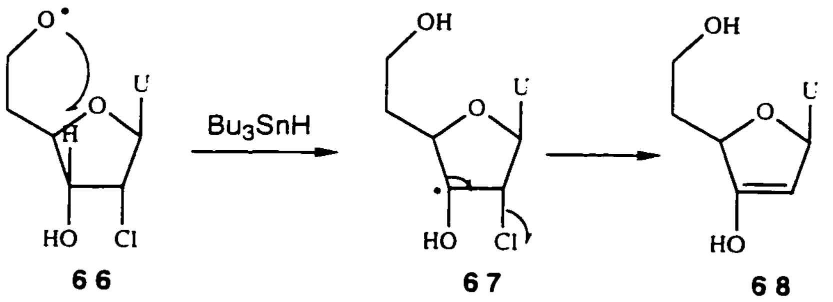
Scheme 18

A process related to the classic Barton reaction has been used in the functionalization of a carbohydrate substrate (Scheme 19).[19]



Scheme 19

The nitrate ester **60** (the Barton reaction involves use of a *nitrite* ester), upon treatment with tin hydride, generates an oxygen centered radical which abstracts the *endo* hydrogen at C-6. This radical reacts intermolecularly with an equivalent of acrylonitrile from the *exo* face of the molecule. The sequence was repeated to generate radical **64**, and in the final step, Bu_3SnH delivers hydrogen from the sterically more accessible *exo* face, to terminate the reaction sequence and produce **65**, with the newly introduced appendage in the C-6 *endo* position.

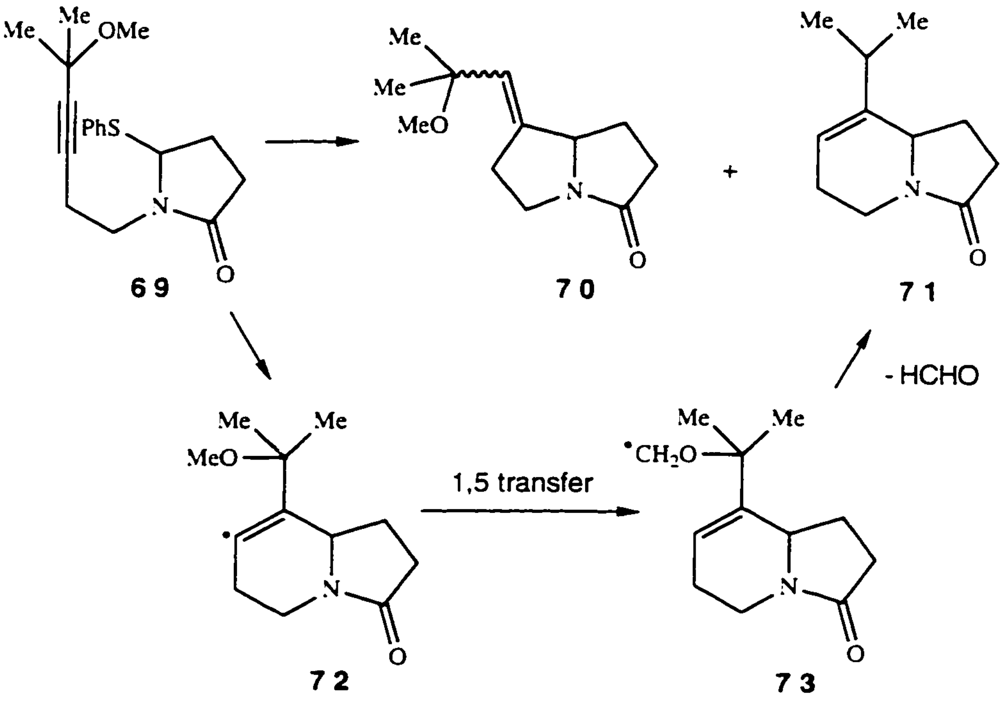


Scheme 20

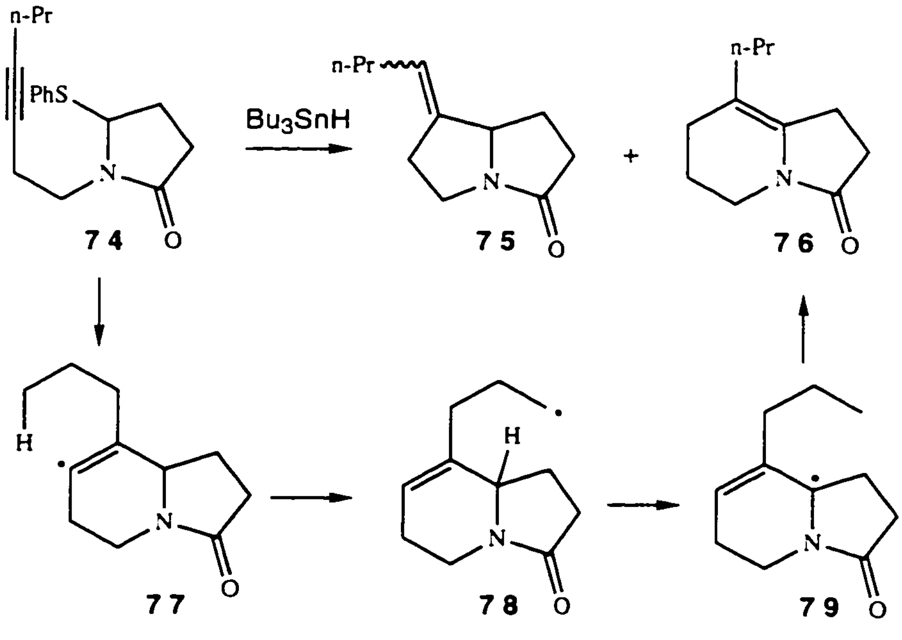
The use of an oxygen centered radical for hydrogen transfer (**66** → **67**) was applied recently[20] in order to cause chlorine displacement by β elimination (**67** → **68**, Scheme 20). This one step sequence accomplished both a dehalogenation and an oxidation of the unprotected secondary alcohol.

In contrast to heteroatom-centered radicals, simple carbon radicals have been developed only recently as synthetic tools for hydrogen transfer. This is puzzling, because isolated cases[21] have been documented since the very early days of synthetic radical chemistry, and these cases were certainly noticed because they usually interrupted the desired processes.

Hart *et al.* reported[12h,12i] two cases of 1,5 hydrogen transfer between carbon radicals in 1985. During studies on the synthesis of (+)-heliotridine and (+)-hastanecine, a systematic study of substituent effects at the triple bond was conducted in order to discriminate between competing 5 *exo* and 6 *endo* cyclization modes. Compounds **71** and **76** were detected in two reactions (Schemes 21 and 22) and their formation could be explained only on the basis of hydrogen transfers, as displayed in the Schemes.

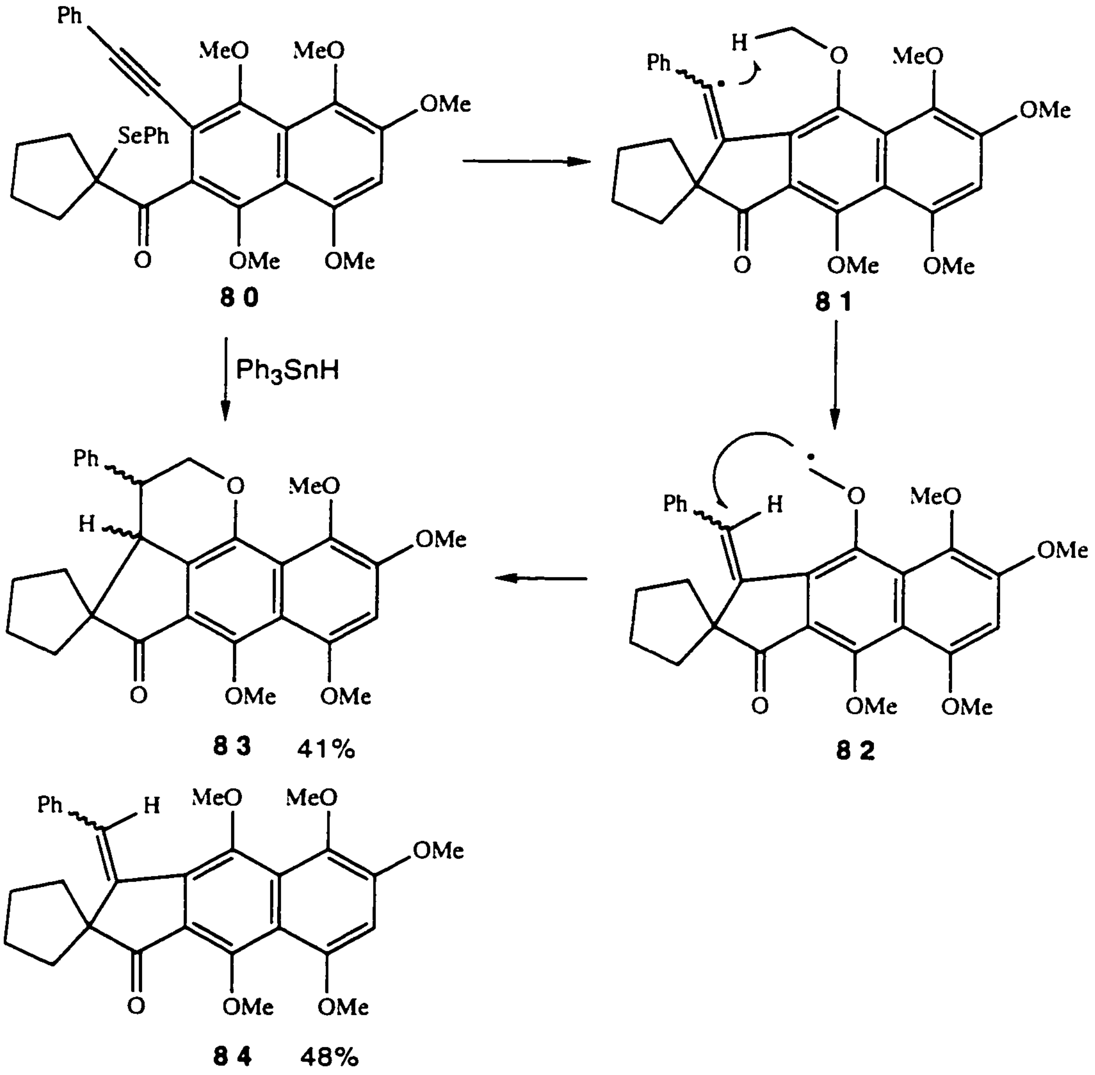


Scheme 21



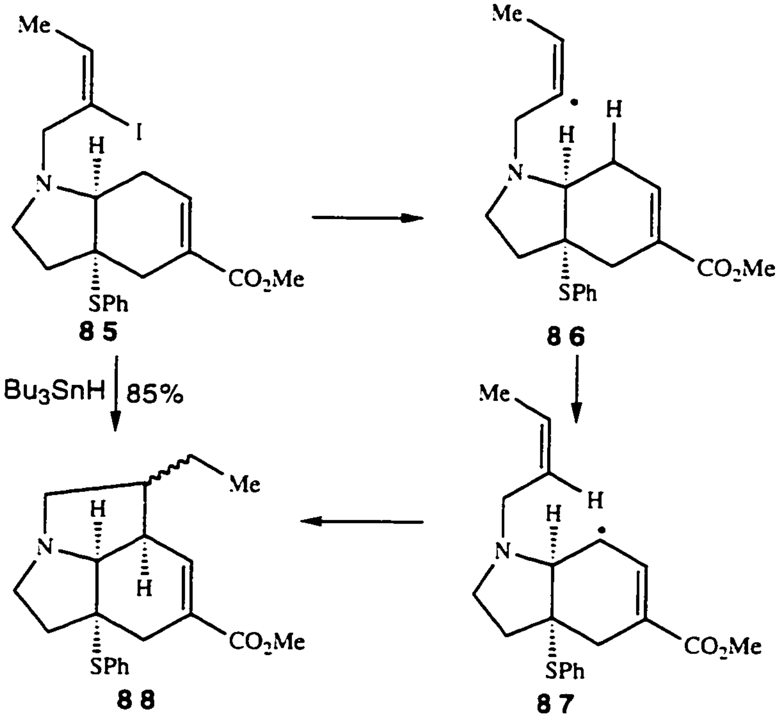
Scheme 22

In model studies[21f] related to the total synthesis of fredericamycin A, carried out in this laboratory, a spiro ketone **84** was constructed (Scheme 23). However, the desired product was accompanied by compound **83**, which was proved to come from a 1,6 hydrogen transfer sequence (**81** → **82** → **83**).



Scheme 23

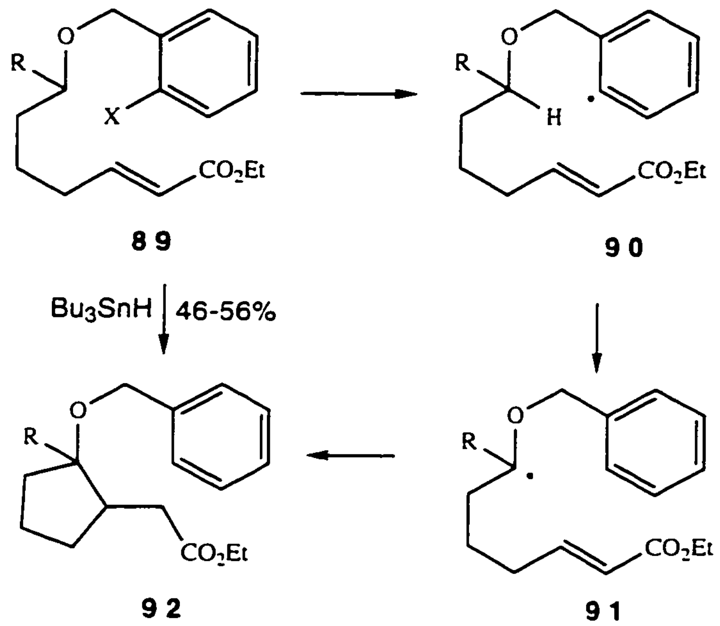
The formation of **83** was an unwanted process, but the deliberate synthetic use of a carbon radical for hydrogen transfer was not reported until 1988, when Parsons *et al.* described[22] a radical translocation sequence from a vinylic position (see **86**) to an allylic position (see **87**), as summarized in Scheme 23.



Scheme 24

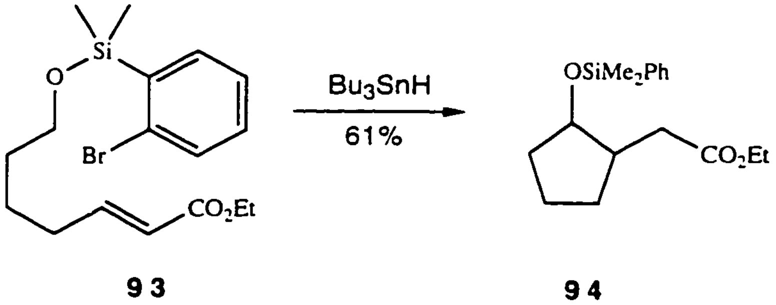
As shown in the Scheme, the thermodynamically more stable allylic radical cyclizes onto the double bond to afford the tricyclic compound **88**. The overall yield in this sequence is 85%.

Shortly afterwards Curran's group published[23] a series of experiments in which an *o*-iodobenzyl- or an iodomethylsilyl-protected alcohol was shown to undergo similar hydrogen transfer (Schemes 24 and 25). The new feature in these studies is the adoption of aryl as opposed to vinyl radicals as the species to abstract hydrogen. The aryl group in both cases becomes part of an ordinary protecting group after the transfer process (benzyl for **89** and (dimethyl)phenylsilyl for **93**).



X= Br, I. R: H, Me.

Scheme 25

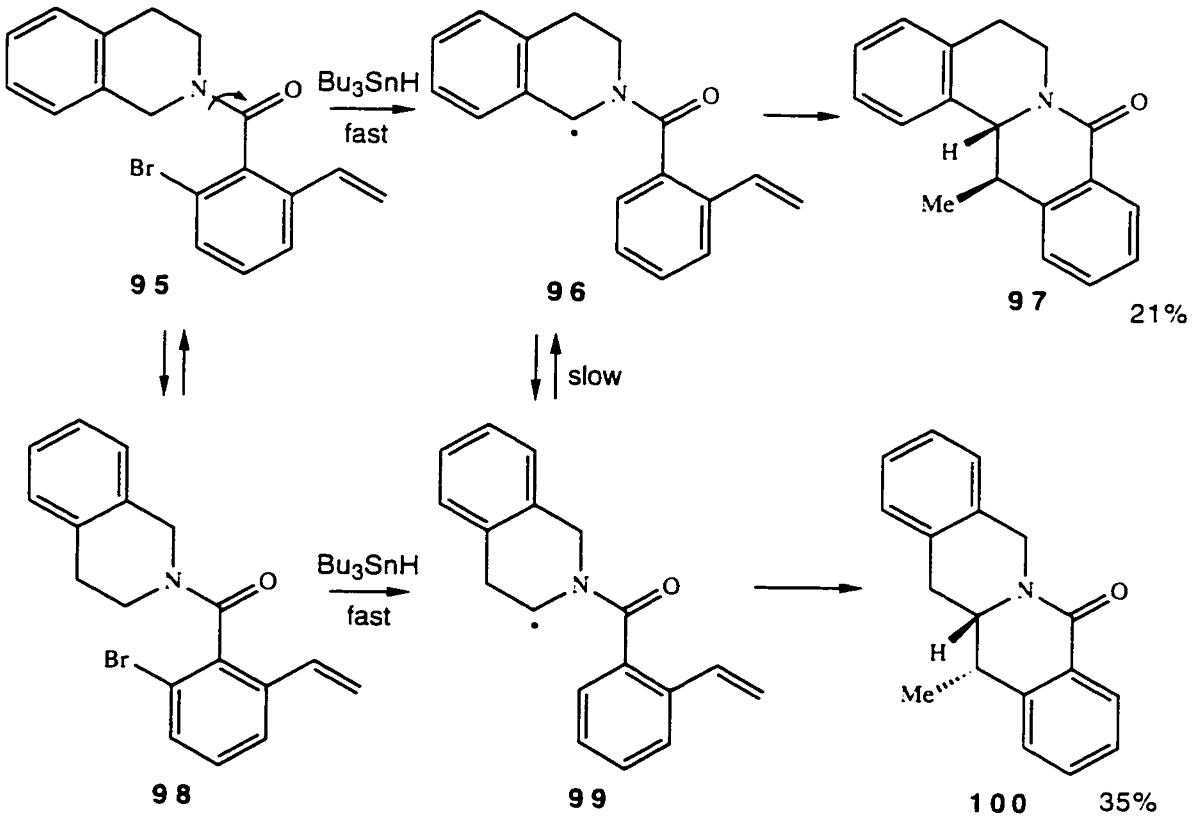


Scheme 26

These radical translocation reactions using vinyl or aryl radicals rather than the more reactive heteroatom-centered radicals showed that vinyl and aryl radicals were sufficiently reactive to abstract hydrogen at least from those carbons that would afford a stabilized radical.

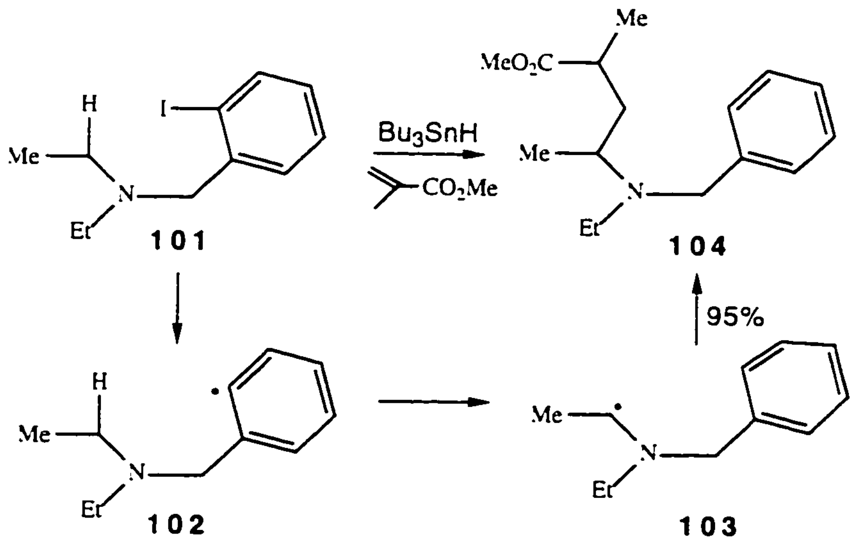
The so called PRT strategy (PRT stands for *protective radical translocating groups*), originally suggested (Schemes 24 and 25) by Curran, was expanded[24] by the development of an *o*-iodobenzamide protecting group for amines.

In one representative application[24] to amines (Scheme 27), an *o*-bromobenzoyl group was used to protect a substituted amine (see **95** and **98**). Following the hydrogen transfer (**95** → **96** and **98** → **99**), the bromobenzamide **95** was converted into the angular and linear dibenzoquinolizidinones **97** and **100** in 21% and 35% yield, respectively. It is interesting that the yield of **97** is lower than that of **100**, even though the former is produced via a more stabilized (benzylic) radical. This result is attributed to slow rotation about the amide C-N bond. The equilibrium between **95** and **98** is much slower than the 1,5 hydrogen transfer. This suggestion is supported by modern knowledge of lifetimes of aryl radicals and rates of amide bond rotation. The values[24] indicate that the geometry of a typical C-N bond will be fixed during the entire lifetime of an aryl radical. Amide rotamers such as **95** and **98** interconvert in solution with a typical lifetime of 10^{-3} s. At the same time, the maximum solution lifetime of an aryl radical does exceed 10^{-5} s. Thus, the different yields of cyclization products in this case simply reflect the percentage of the each rotamer in the starting compound **95**.



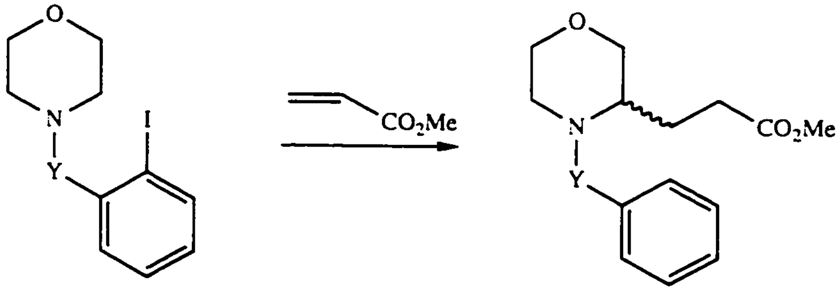
Scheme 27

Undheim's group have studied[25] radical translocation for both o-iodobenzyl-protected amines (such as **101**) (Scheme 27), and it was found that radical translocation could take place on an alkyl amine substrate with high efficiency.



Scheme 28

A comparison[25] between the α amino and α amidoyl radicals is interesting (Scheme 29). Compound **105** requires 3 equivalents of acrylate to afford a yield of 46% of the adduct **107**, while **106** affords 66% yield of **108** with *ca.* 1 equivalent of the reagent. Again, an unfavorable conformation of the amide accounts for the lower coupling yield.

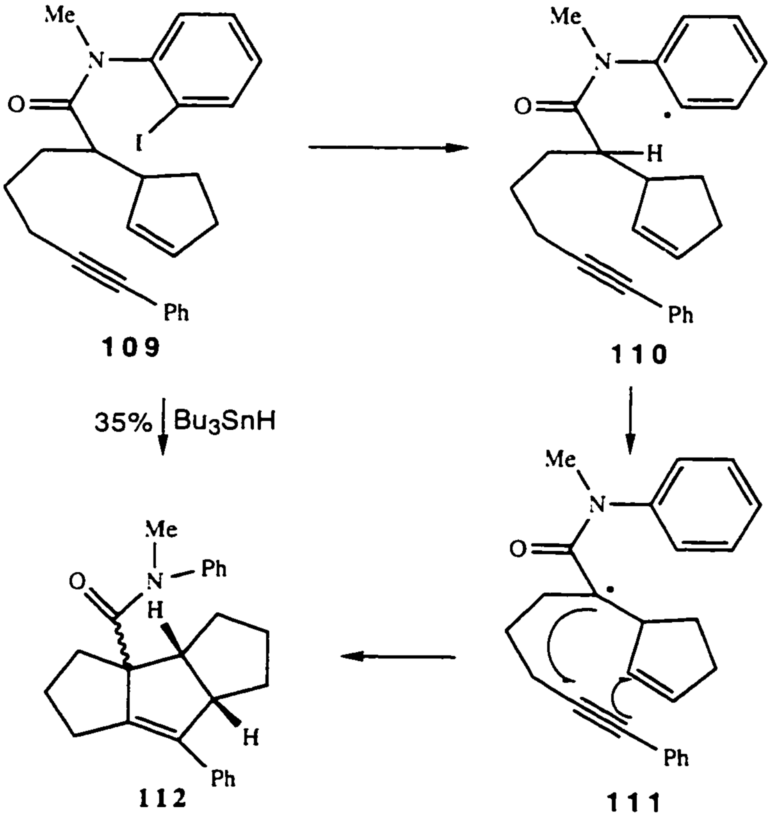


105 Y= CO, 3 equiv. acrylate, 46% **107**
106 Y= CH_2, 1.1 equiv. acrylate, 66% **108**

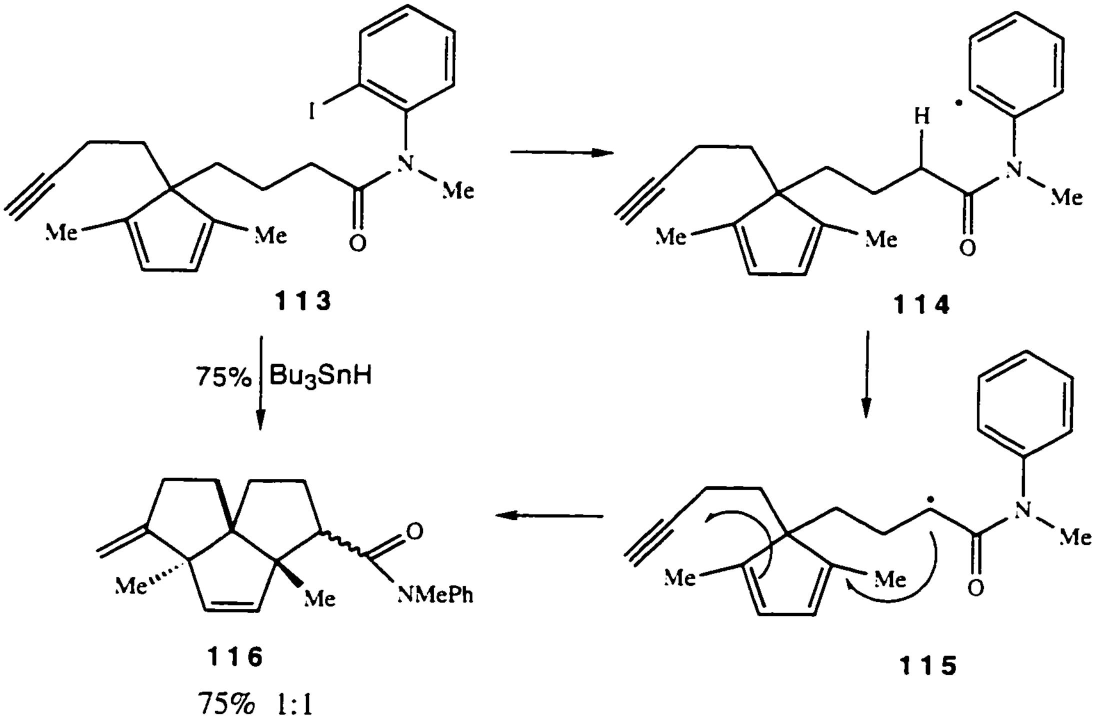
Scheme 29

These recent systematic studies showing efficient 1,5 hydrogen transfer by vinylic and aryl radicals have made the process into a potentially useful tool in organic synthesis.

Schemes **30**[26] and **31**[26] show two remarkable examples of processes triggered by intramolecular hydrogen transfer. In both cases, a radical translocation to the position α to the carbonyl was used to construct linear (**112**) and angular (**116**) polyquinane skeletons. In the first example,[26] compound **112** was obtained in 35% yield. These two cases are clearly based on the increased stability of radicals α to carbonyl groups, relative to the aryl radical species.

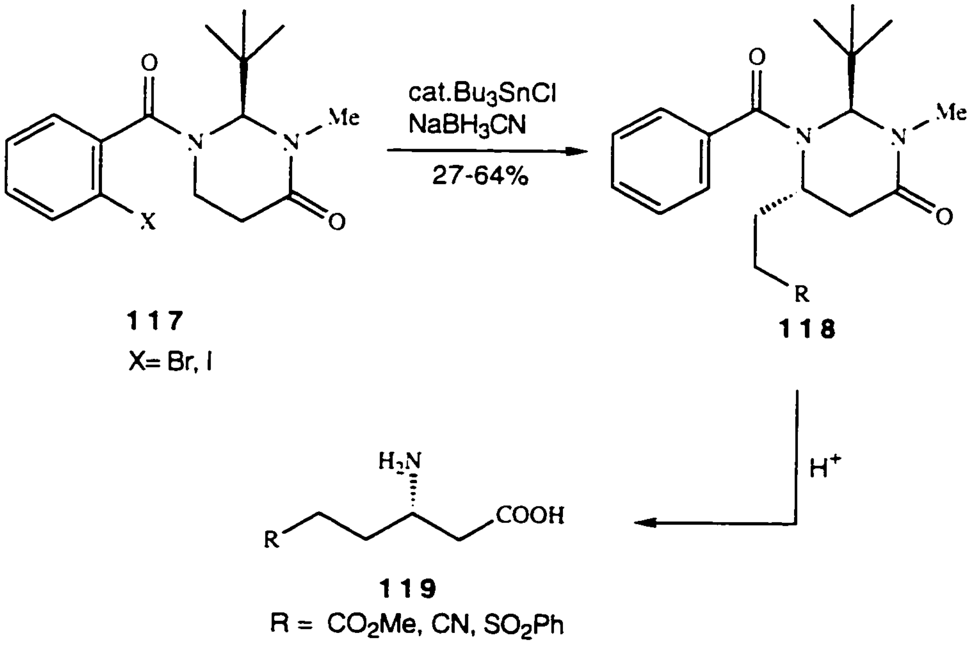


Scheme 30



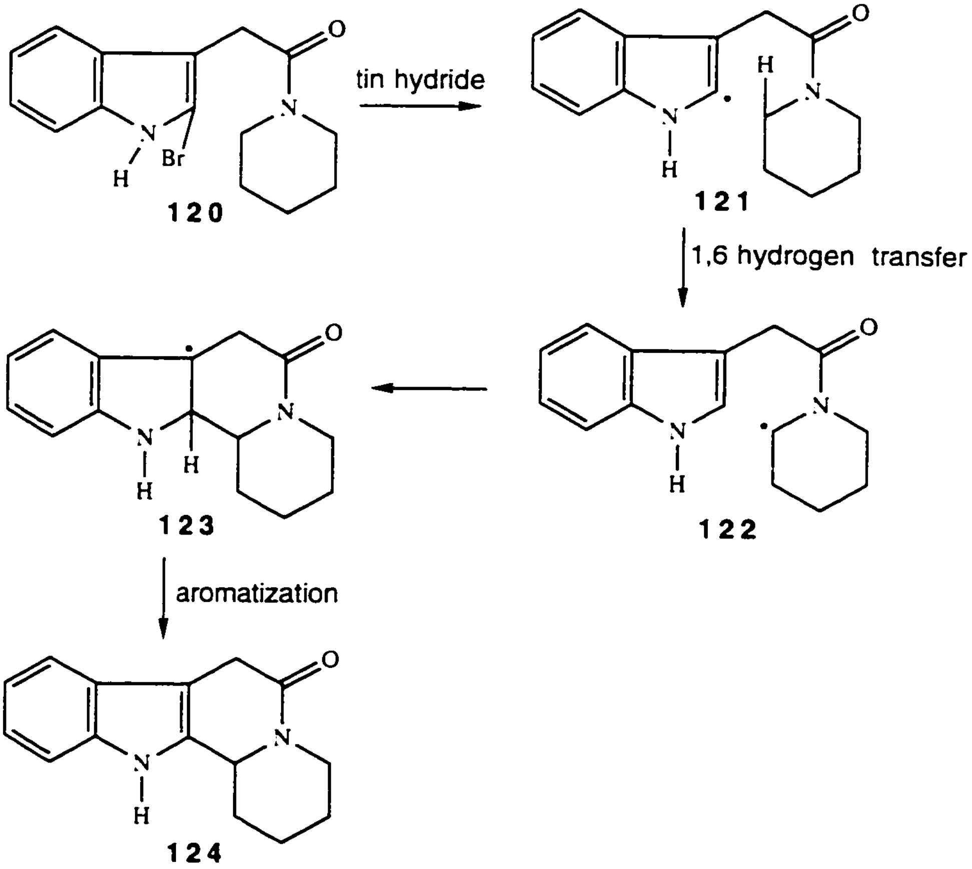
Scheme 31

Snieckus and his colleagues recently reported[27] an asymmetric synthesis of β aminoacids, using the sequence shown in Scheme 32. Stereoselectivity was achieved through the adoption of a chiral template. One interesting feature of these reaction is the somewhat better yields achieved with bromo compounds over the iodo analogs.



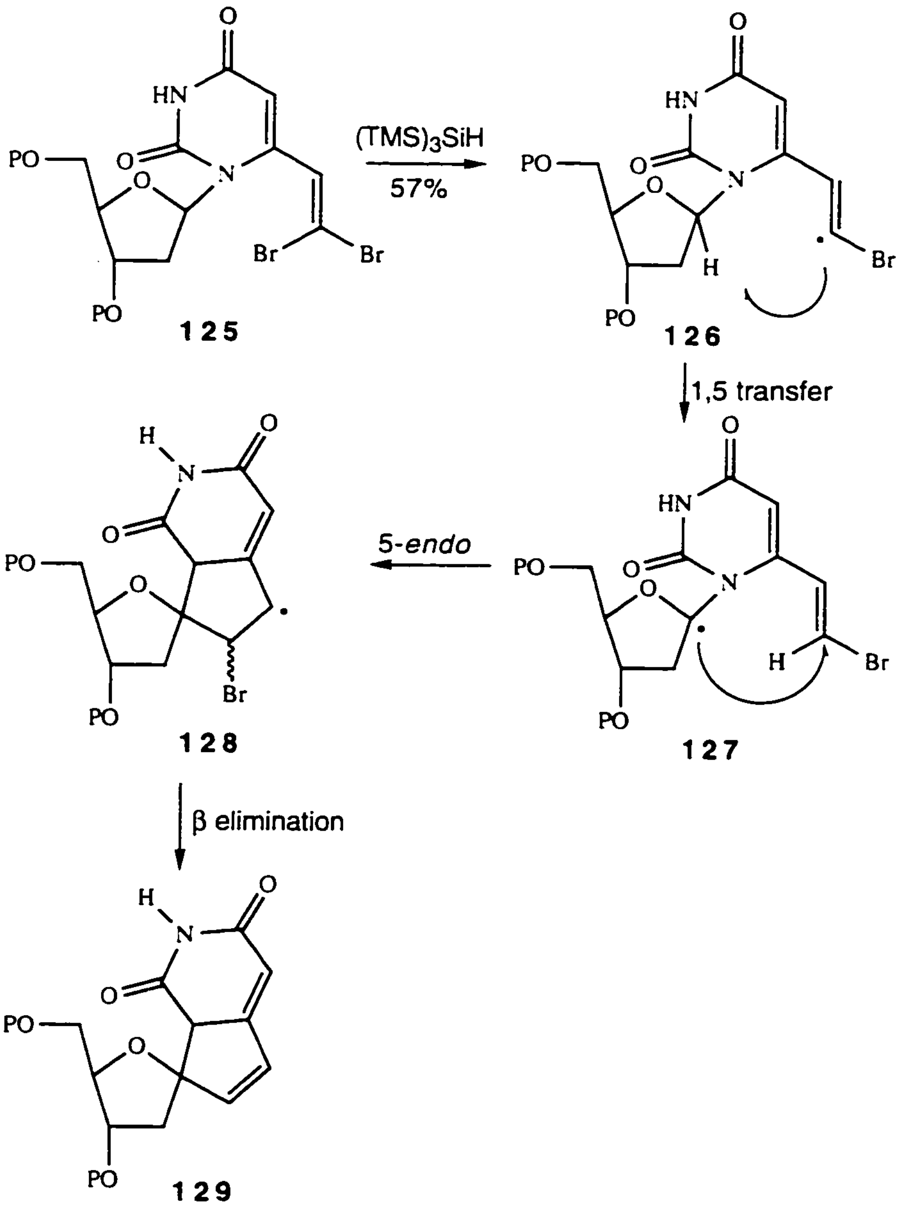
Scheme 32

Radical transfers other than those of the 1,5 type are also possible under certain conditions. For example, in the construction of substituted indoles shown in Scheme 33,[28] radical **121** abstracts hydrogen via a 1,6 transfer (**121** → **122**), and the new radical **122** cyclizes onto the aromatic double bond, interestingly, via a 6- *exdo* process. Rearomatization then restores the indole system.



Scheme 33

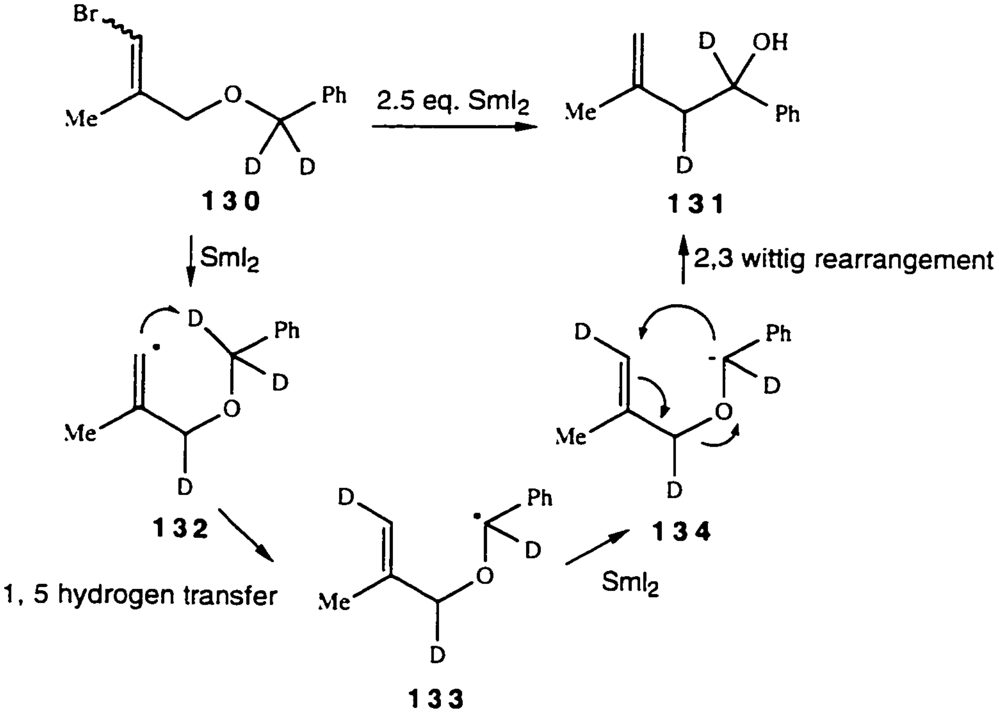
An interesting radical translocation with the nucleoside substrate **125** was reported recently from Chatgilialoglu's laboratory (Scheme 34).[29] The final 5 *endo* cyclization (**127** → **128**) in this tandem sequence is unusual, but was made possible in this case by the reactive nature of the (conjugated) double bond. The resulting radical (**128**) then underwent β elimination. (Scheme 34).



Scheme 34

Hydrogen transfer through metal mediated reactions is also possible, and the results of a recent study[30] are shown in Scheme 35. Reduction of bromides **130** gave the vinylic radical **132**, which abstracts a deuterium by 1,5 hydrogen transfer. The resulting benzyloxy radical was reduced by the second equivalent SmI_2, and afforded the anionic species **134**.

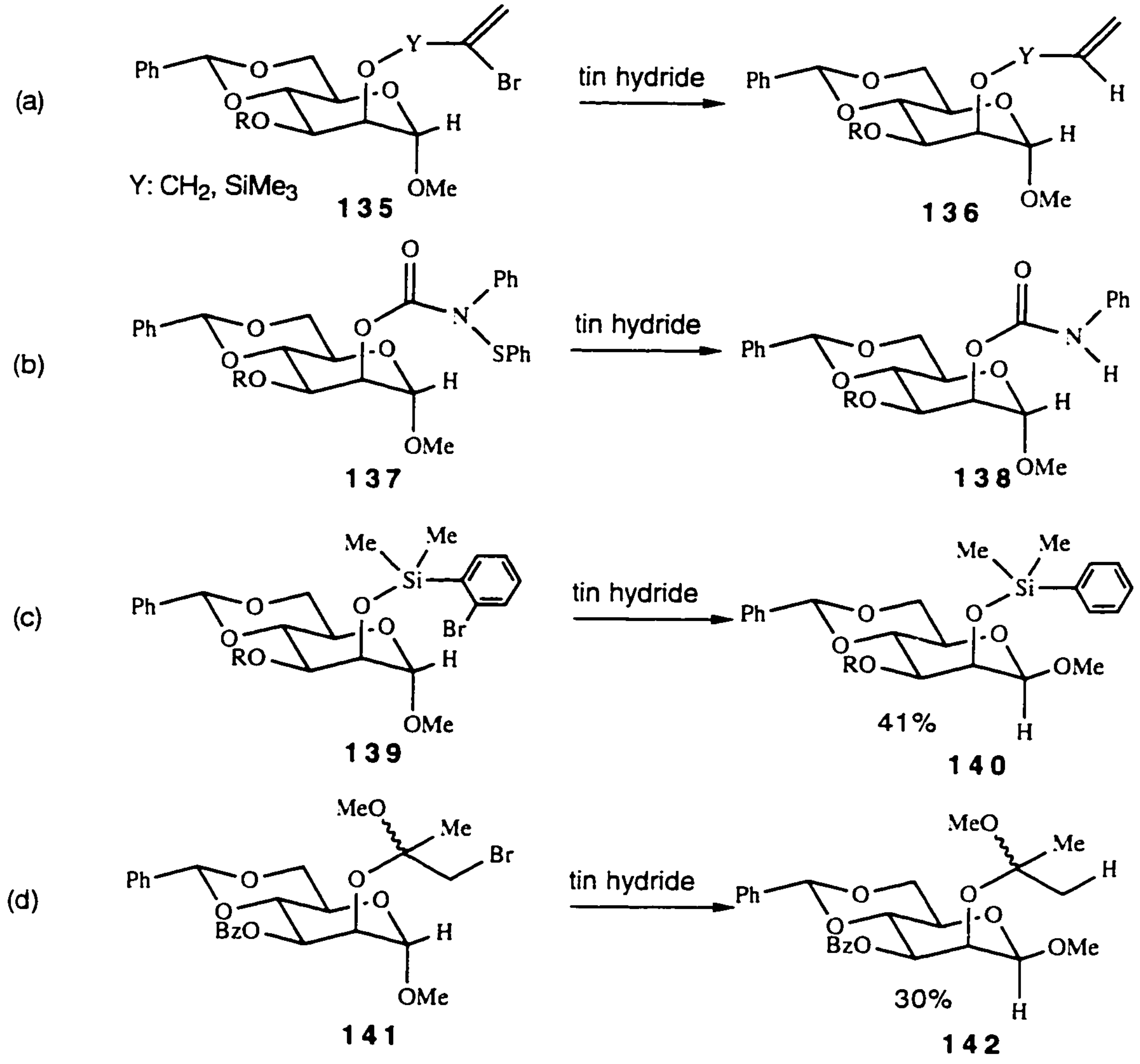
A [2,3] Wittig rearrangement then takes place, and the final product is alcohol **131**.



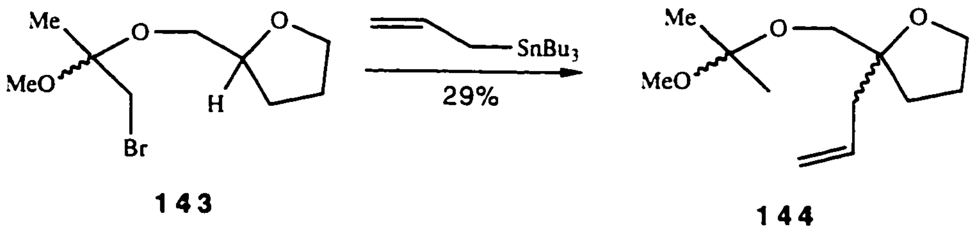
Scheme 35

Crich[31] and Curran,[32] and their collaborators, independently reported hydrogen transfer processes that achieve inversion of an α-manopyranoside to the β-anomer. The Curran group reported two examples (a, b in Scheme 36) in which the required 1,5 hydrogen transfer did not occur, for reasons that are unclear, and so a 1,6 transfer sequence (c in Scheme 36) was examined, and found to produce the required anomeric inversion (**139** → **140**).

In contrast, Crich *et al.* succeeded in applying a 1,5 hydrogen transfer process by adopting an acetal tether, as shown in entry d of Scheme 36. The same protocol was also shown[31] to work with other systems such as that shown in Scheme 37.



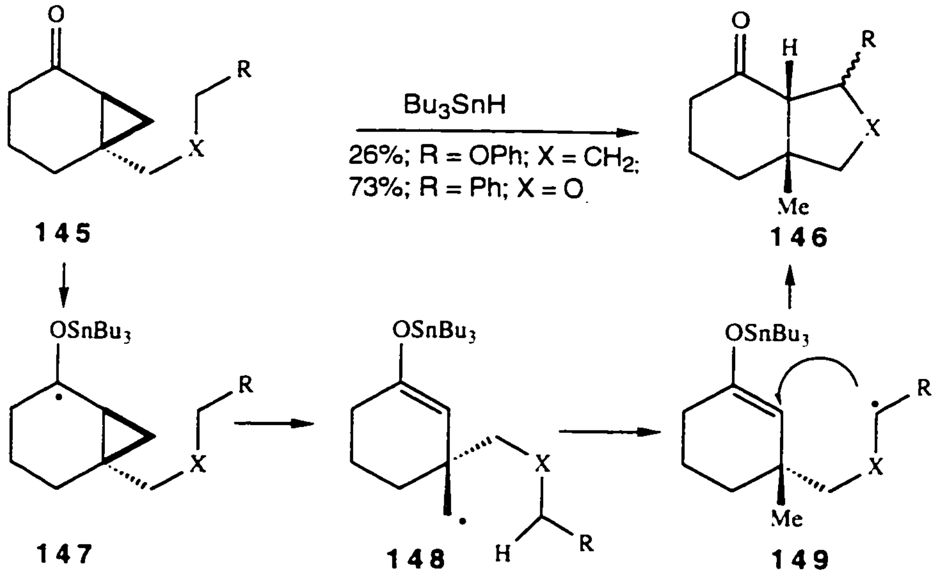
Scheme 36



Scheme 37

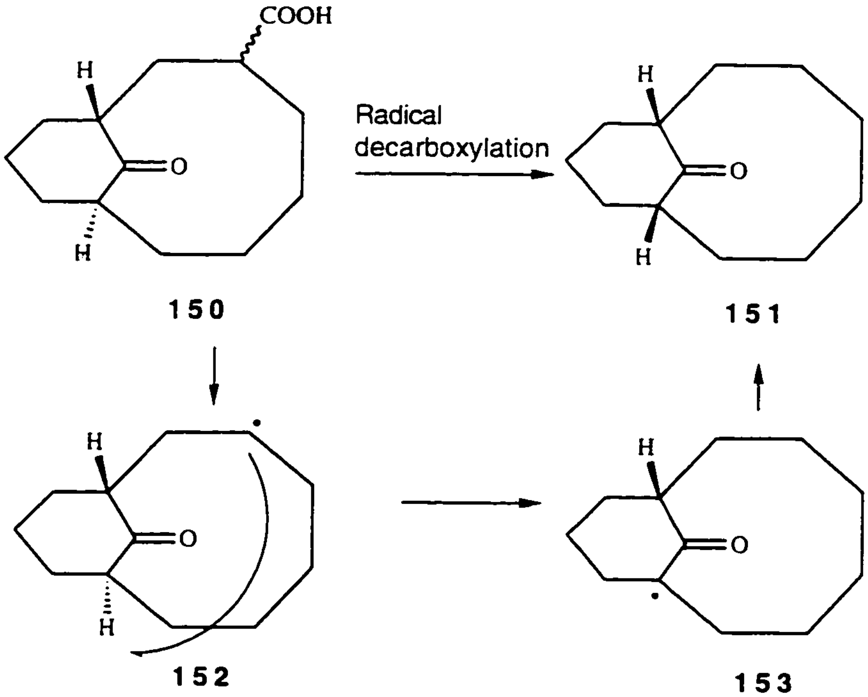
The special feature in Crich's approach is that the abstraction/transfer process results from first generating an alkyl radical, rather than a heteroatom or an olefinic radical. This is rather unusual, since it *was* generally accepted that the hydrogen abstraction by alkyl radicals is less likely because of the weakly exothermic nature of the process and the intervention of competing intermolecular sequences. However, the successful transfers in these cases is the result of the weakness of the C-H bond involved. This bond is flanked by two oxygens, which would serve to stabilize the resulting radical.

Another recent report[33] has also described a series of reactions where alkyl radicals – in this case formed through opening of a cyclopropane ring – are capable of abstracting hydrogen by the 1,5 mode. The new radical was shown to cyclize further, as summarized in Scheme 38. The higher yield in one case shows that the benzylic hydrogen was more efficiently abstracted than the hydrogen activated only by an oxygen (and not *also* by a phenyl group).



Scheme 38

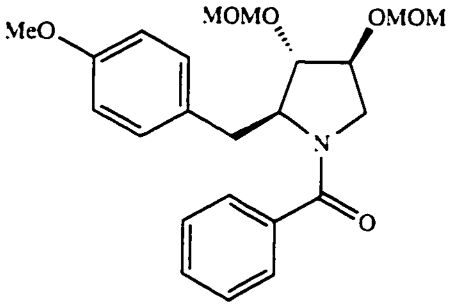
Alkyl radicals can also abstract hydrogen α to a ketone carbonyl. For example, an unexpected isomerization was found[34] when a Barton decarboxylation was carried out on compound **150** (Scheme 39), and the overall process can be interpreted by the hydrogen transfer shown.



Scheme 39

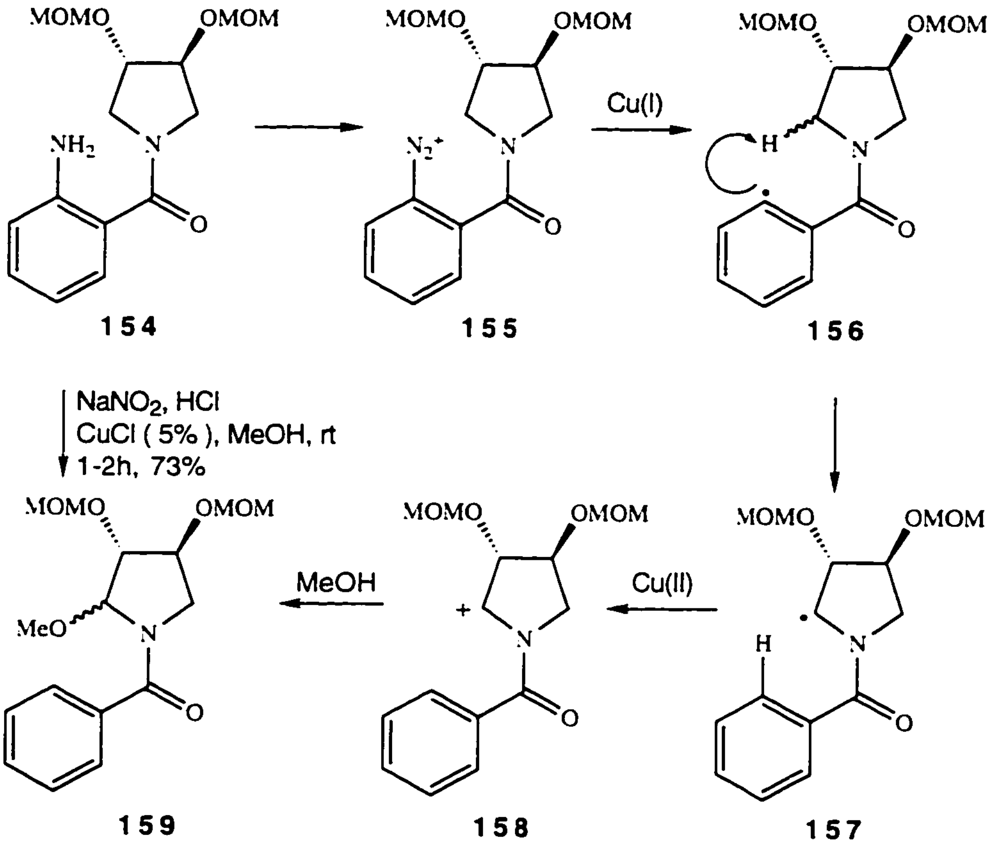
The above examples show that abstraction by alkyl radicals *is* possible if the translocated radical is sufficiently stable, the process being thermodynamically favored in these cases.

The adoption of 1,5 hydrogen transfer for the functionalization of a pyrrolidine system has been reported several times. In an approach to the antibiotic anisomycin (figure 1), Weinreb[35] *et al.* used a classic method to generate an aryl radical (**155** → **156**). This aryl radical then abstracted hydrogen from the α position of the pyrollidine, to form a stabilized secondary radical (**156** → **157**, Scheme 40). Oxidation of this new species by Cu(II) led to an acyliminium ion that was captured by methanol (**158** → **159**). The detailed mechanism of this sequence was investigated.[35]



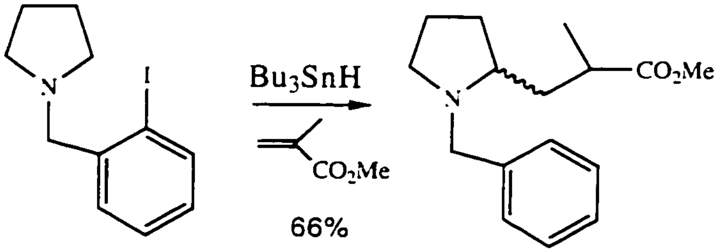
Anisomycin

Figure 1



Scheme 40

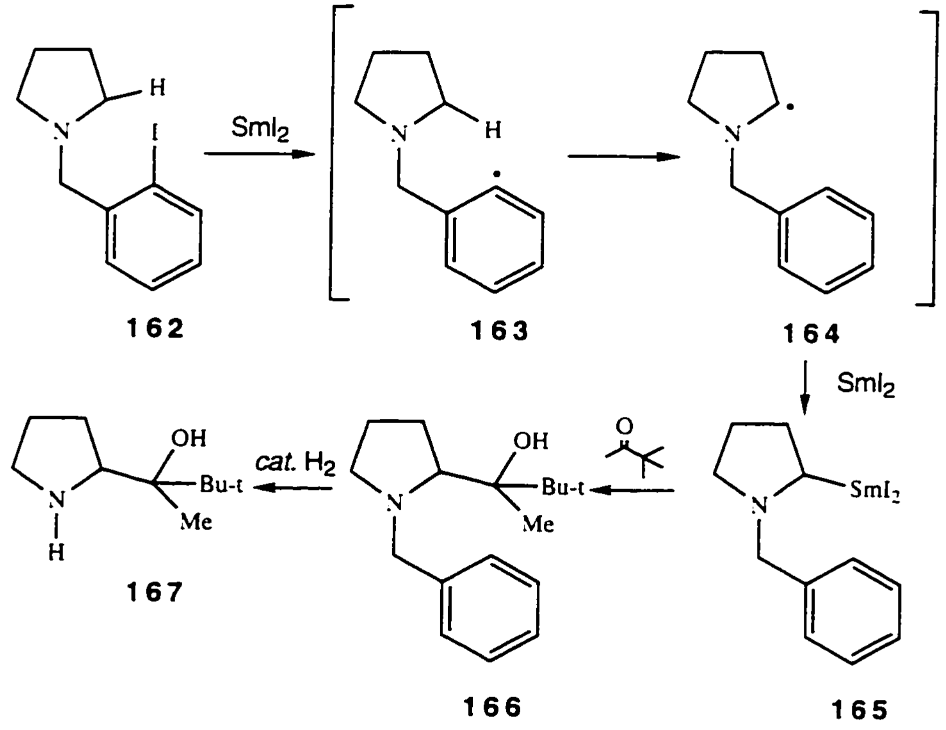
Simple pyrrolidine systems were prepared through 1,5 hydrogen transfer in several methodology studies, as in the report[25] from Undheim's laboratory to the effect that the PRT strategy (*protective radical translocating groups*) can be used efficiently to afford pyrrolidines **161** (Scheme 41).



160 **161**

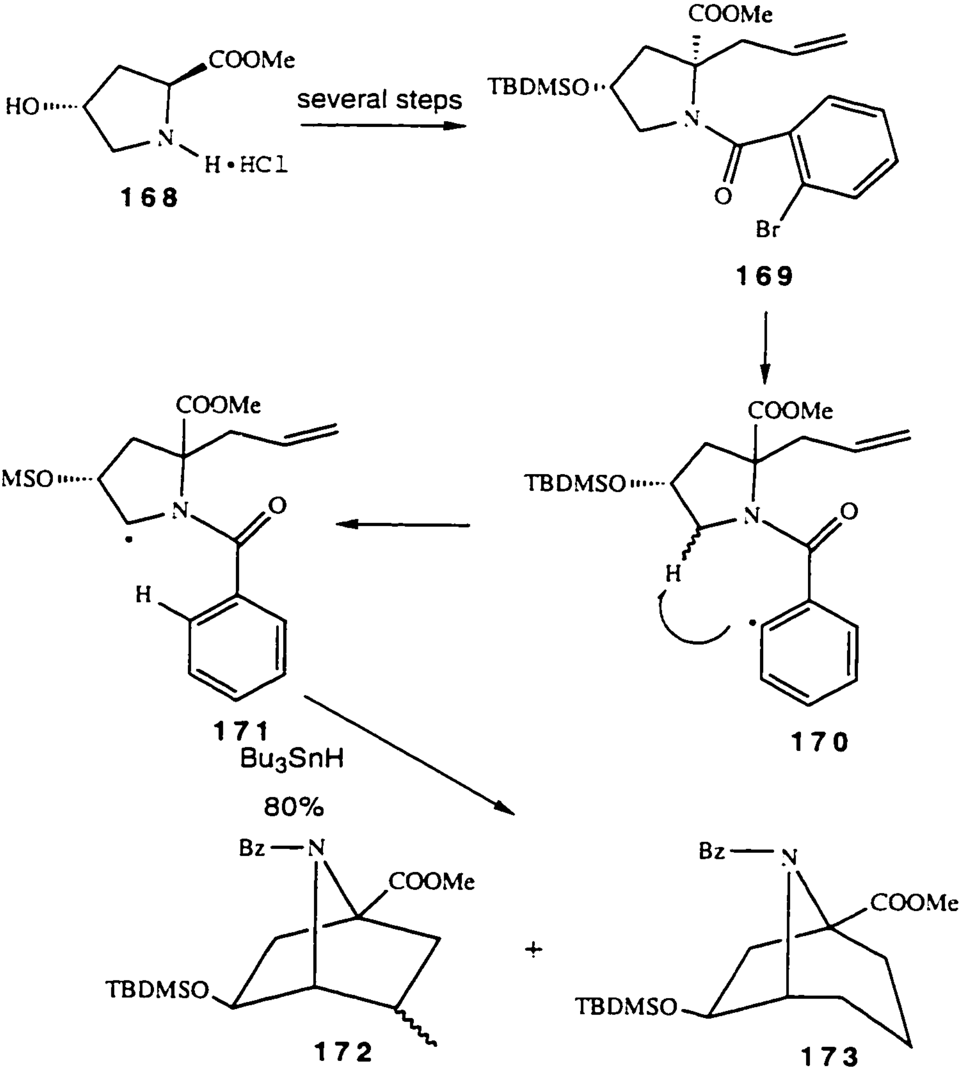
Scheme 41

Another example was reported by Ito *et al.*[36] Here a SmI_2 mediated process was again shown to effect the same hydrogen transfer chemistry as the stannane mediated processes. The translocated radical **164** was further reduced by SmI_2 via single electron transfer and the resulting carbanion was trapped by various electrophiles (Scheme 42).



Scheme 42

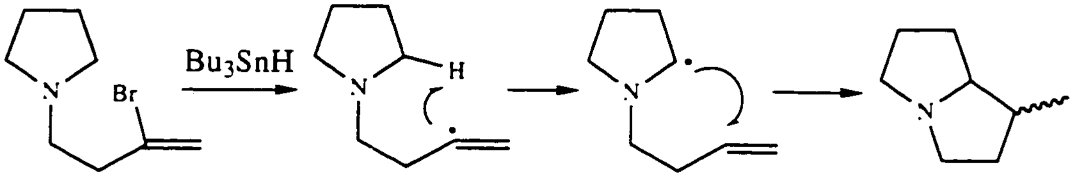
The previously established *o*-halobenzamide sequence has been used in the proline system,[37] as shown in Scheme 43. An aryl radical, generated under standard conditions, abstracted hydrogen from the α position of the heterocycle, and formed the secondary radical **171**. The latter then formed different bridgehead ring systems **172** and **173**.



Scheme 43

It is quite apparent in this example that the authors used a quaternary center at C-2 in compound **169** in order to avoid indiscriminate abstraction of hydrogen atoms from both the α and α' positions of the pyrrolidine ring.

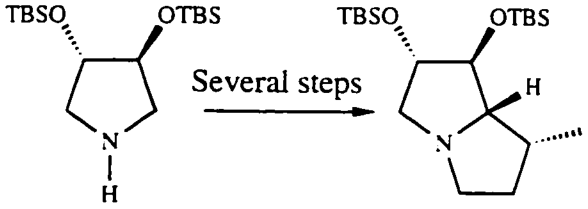
In a more recent report[38] (Scheme 44) a similar strategy was followed, although instead of an o-bromobenzamide, a vinylic bromide was used. Again, the initial radical abstracted hydrogen from the α position of the heterocycle, and the new radical further cyclized onto the pendant double bond.



174 175 176 177

Scheme 44

To circumvent the problem of two possible sites of abstraction, the sequence was applied[38] to a compound with C_2 symmetry; in his case only one radical would be formed, as implied by Scheme 45.



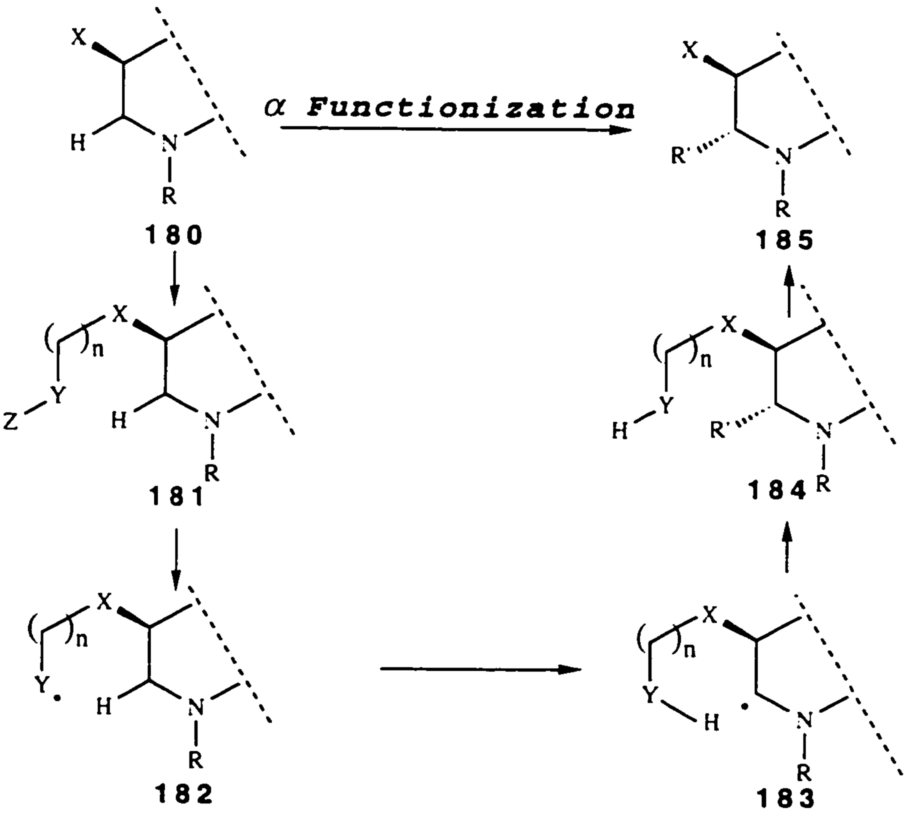
178 179

Scheme 45

The above survey shows that hydrogen abstraction from the position α to nitrogen occurs readily when the attacking radical is aryl or vinyl, but the experiments described in the next section show that the process is of much broader scope, and even alkyl radicals can be used to initiate the sequence.

Preliminary Results and discussion

We were interested in developing a general method to functionalize the α position of cyclic amines in a manner that might be relevant to the synthesis of alkaloids. We wanted to effect regioselective hydrogen transfer by using a tether that was both easy to install, and to remove – after it had served its purpose. This strategy is shown in Scheme 46.

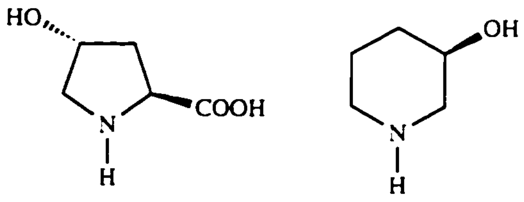


Scheme 46

In this scheme, R could be any common nitrogen protection group, X is carbon or any heteroatom, and the length of the tether would be tailored to ensure efficient hydrogen abstraction. Although 1,4 to 1,7 radical translocations of hydrogen have been observed, the 1,5 process, which is takes place via a thermodynamically favored six membered transition state, is frequently the most reliable type. Thus, we expected that n = 1 would represent the optimum situation. The net result of the process as illustrated will be the substitution of a C-H bond in the original molecule by a new C-C bond. The orientation of this new C-C bond ought generally to be controlled by the stereochemistry at the point of attachment of the neighboring tether.

A. *The choice of starting material.*

In order to test the above idea, we needed a substrate that would enable us to install a tether for the subsequent hydrogen transfer. *Trans*-4-Hydroxyproline (**186**) and (*R*)-3-hydroxypiperidine (in the form of its hydrogen chloride salt, **187**) were obviously suitable (Figure 2). Both compounds are commercially available and



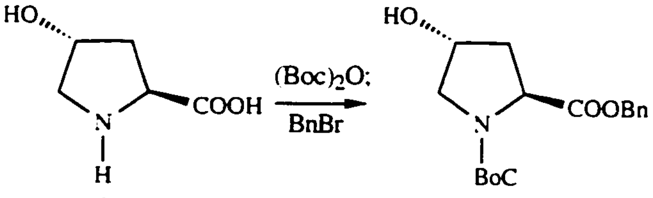
186 **187**

Figure 2

inexpensive (under $3 per gram). Secondly, the stereochemically defined hydroxyl groups onto which the tether would be attached, could eventually be removed by radical deoxygenation sequences, if that were desired.

Thirdly, these two compounds are structurally rather simple, and so they would not unnecessarily complicate the experiments to test the idea.

In the event, we based our investigation on *trans* 4-hydroxyproline, and the carboxylate and amine functionalities were first masked by standard reactions to obtain compound **189** (Scheme 47).

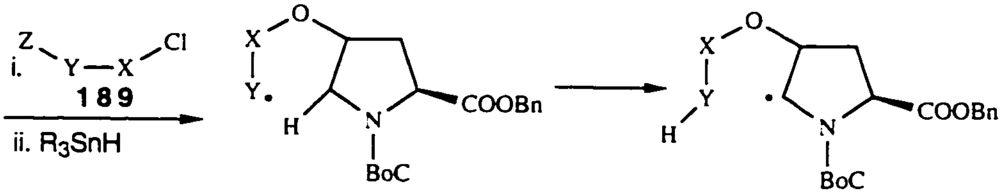


186 **188**

Scheme 47

B. The installation of the tether.

As out aim was to carry out 1,5 hydrogen transfers, a two carbon unit (**189**) had to be attached to the hydroxy group (Scheme 48).



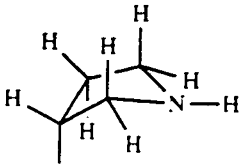
188 **190** **191**

X, Y = carbon
Z = any atom that may afford cleavage of Z-Y bond under radical conditions.

Scheme 48

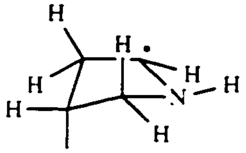
Setting Y to be an oxygen or nitrogen atom might at first be regarded as a suitable choice because these heteroatom-centered radicals are good abstractors of hydrogen, but generating such systems would not be easy, and might require a multistep sequence. We were forced, therefore, to look for other suitable tethers, and we wondered if a simple alkyl radical (i.e., Y = C) might be suitable, on the basis of the following considerations.

A dependable hydrogen transfer usually involves the generation of a stabilized carbon centered radical. These radicals are frequently allylic or benzylic, or are stabilized by attached heteroatoms such as oxygen or nitrogen. For the nitrogen case, a theoretical study has been published,[39] and it is now accepted that a three-electron two-orbital π-like interaction exists in the amino-methyl radical. This effect is responsible for the special stabilization, and is maximized when the singly occupied sp^n orbital of C and the non bonded doubly occupied sp^n orbital of nitrogen are anti-coplanar to each other. For the five-membered pyrrolidine system, the radical was believed to adopt an envelope conformation with C-5 at the vertex. This conformation accommodates a favorable alignment of the orbitals and has no C-H eclipsing interactions which are present in the parent ring (figure 3).



192

pyrrolidine



193

pyrrolidine radical

Figure 3

A comparison of bond dissociation energies (BDE) can also be used to predict the possibility of a bond breaking/bond forming sequence.

Bond Dissociation Energies

$$RH \longrightarrow R\cdot + H\cdot$$

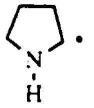
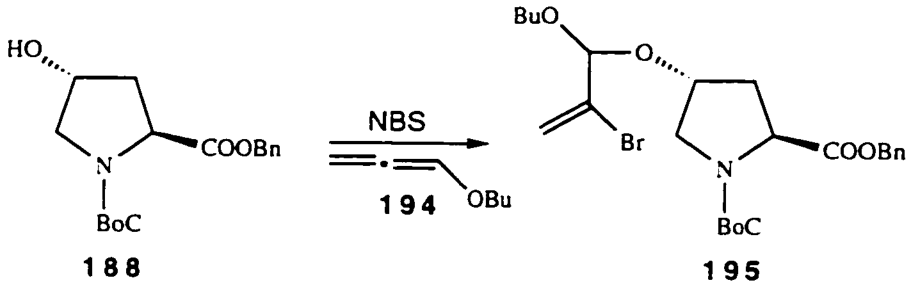
R•	BDE (kJ/mol)
Ph •	464
$H_2C{=}CH\cdot$	444
$CH_3\cdot$	438
Et •	419
$Me_2CH\cdot$	401
	377

Table 1

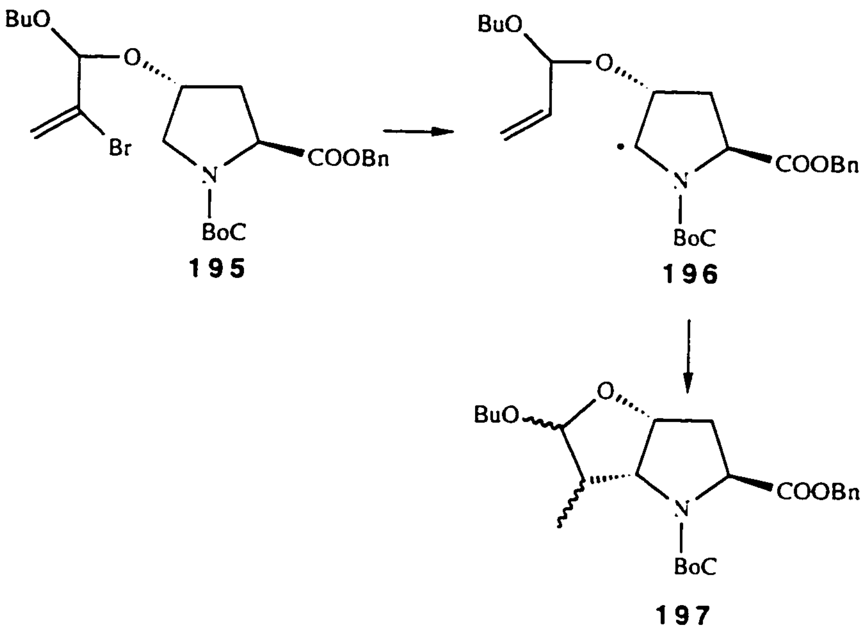
As listed in Table 1,[39,40] the BDE for a C-H bond α to nitrogen in a simple pyrrolidine system is about 377 kJ/mole, while the values for aryl and vinyl C-H bonds are 464 and 444 kJ/mole, respectively. This substantial difference in BDE permits a thermodynamically favorable abstraction of hydrogen from the position α to nitrogen, as described in the review section of this thesis. At the same time, the BDE of the alkyl C-H bond is in the range 401-438 KJ/mole – a value that is significantly different from that of the amino C-H bond. This difference in BDE should allow efficient hydrogen transfer.

We briefly considered the possibility of using a vinyl bromide tether, as shown in Scheme 49.

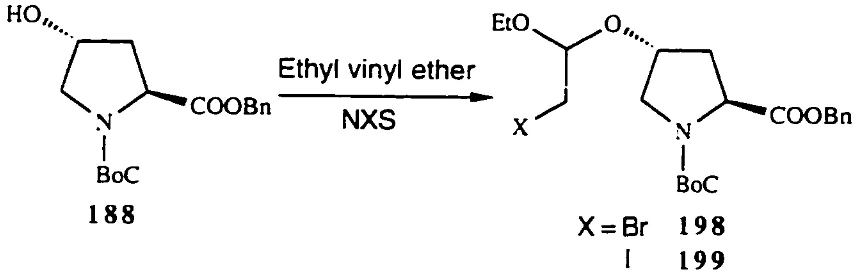


Scheme 49

The vinyl bromide **195**, which could, in principle, be made from an allenic ether according to a literature method,[41] would be a fine choice and, in addition, the transferred radical should be able to cyclize in a 5 exo fashion onto the double. Such a process would give a *cis* fused ring (Scheme 50). However, we have not yet examined this possibility, as we thought of a simpler alternative, which is illustrated in Scheme 51.



Scheme 50

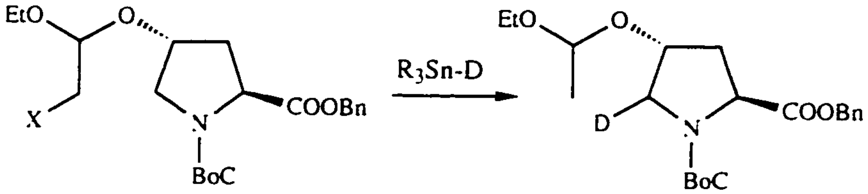


Scheme 51

This approach followed the well established Stork protocol for making bromoacetals,[42] and installation of the pendant was accomplished with ease for both the bromo (**198**) and the iodo (**199**) series.

C. *Demonstration of the idea.*

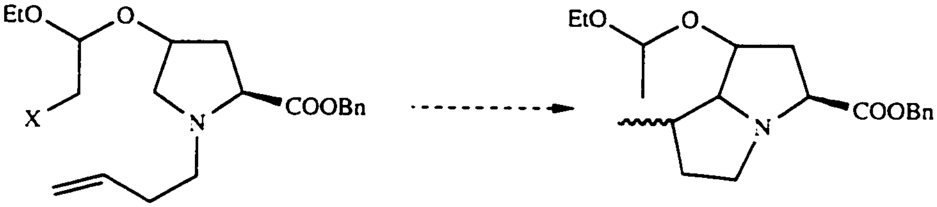
There are several general ways to monitor a radical translocation process. One can treat the compound in benzene with a deuterated tin hydride and proceed to determine the percentage of deuteride in the product by ^{2}H NMR (Scheme 52).



198/199 **200**

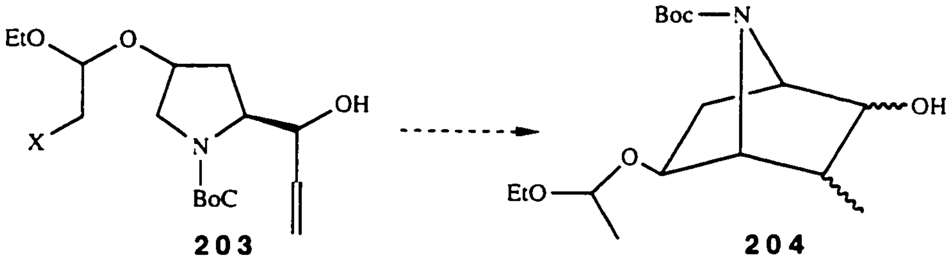
Scheme 52

Alternatively, one can attach an alkenyl pendant in a suitable location to trap the translocated radical (Schemes 53 and 54). The detection and isolation of cyclized products would provide evidence of reaction of translocated radicals.



201 **202**

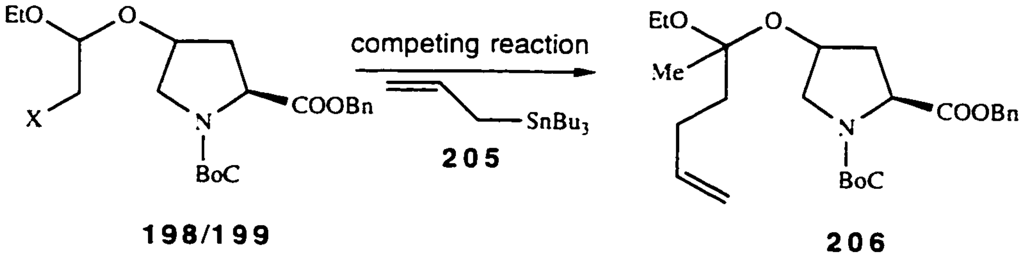
Scheme 53



203 **204**

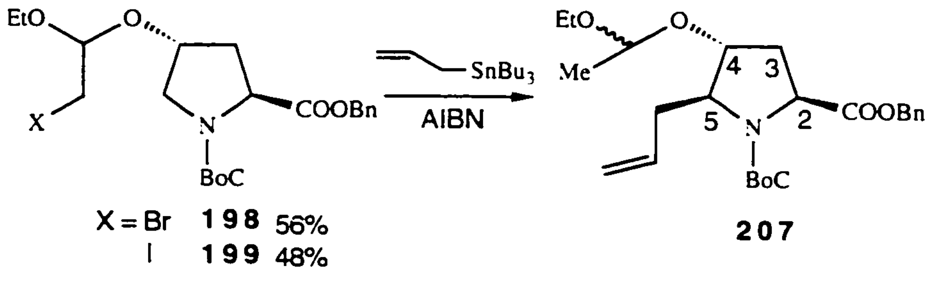
Scheme 54

We decided to use the allylation method developed a few years ago by Keck.[43] This intermolecular trapping approach would offer useful insight into the process since the allylation allows equal opportunity for both radicals to react with the allylstannane. Only a highly efficient 1,5 hydrogen transfer would lead to substantial allylation at the new radical center, and this approach would subject the plan to a demanding test: if the translocation were not efficient, then reaction would proceed as shown in Scheme 55.



Scheme 55

We tested (Scheme 56) both bromide **198** and iodide **199**. The reaction was conducted under normal allylation conditions [43] and continuous addition of AIBN was found to be necessary, as in many similar reported reactions.[43]

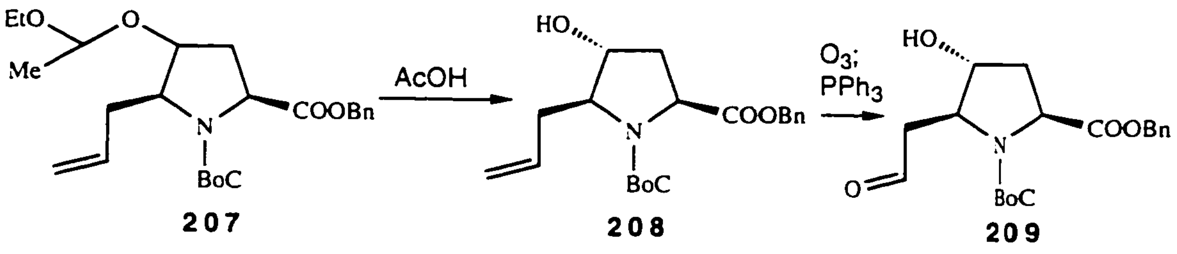


Scheme 56

Compounds **207** were isolated in 56% and 48% yield from **199** and **200**, respectively as single isomers (Scheme 56), together with compound **206** (*ca.*30-40%). Although we have not yet optimized this process, the result not only showed strict stereochemical control in attachment of the C-5 group by the neighboring C-4 substituent, but also proved a relatively unimportant role of the C-2 branch over the reaction outcome. The observed stereocontrol stands in contrast to the ionic process in Barrett's report,[13] where nucleophilic attack on an acyliminium species at C-5 resulted in two isomers.

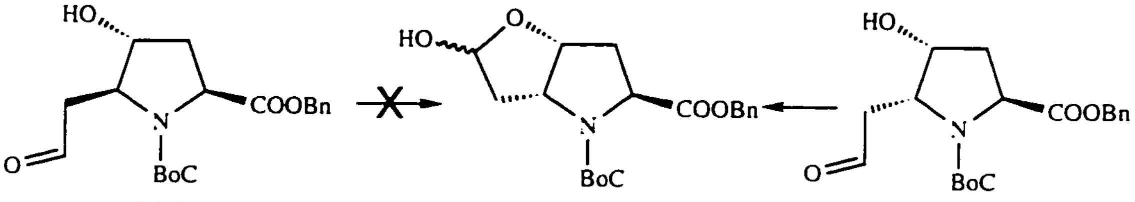
The byproduct, of course, could be reconverted to the starting hydroxyproline (Scheme 57), and this hydrolysis was found to go in 80% yield.

Each reaction (that of **198** and of **199**) was done only once, and the difference between the yields is small. However, if further work shows the difference to be repeatable, the lower yield with the iodo substrate **199** would be surprising, since it has been taken for granted that in most radical reactions, iodo compounds afford better results than corresponding bromo compounds. A recent report by the Snieckus' group, however, described a similar result (see Scheme 32).



Scheme 57

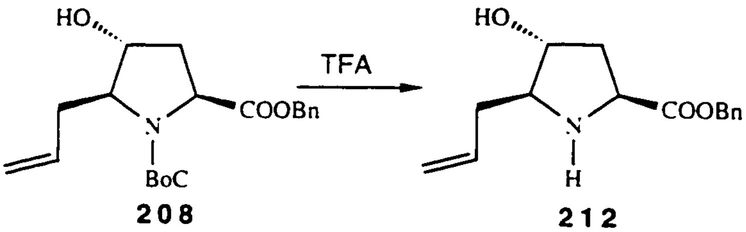
To determine the stereochemistry of the newly formed asymmetrical center, the tether was removed by treating the compound with 50% AcOH-H_2O. Two methods were used to confirm the stereochemistry of **208**. The coupling constant between H-4 and H-5 was found to be 4.7 Hz, which is consistent with values reported[44] for a similar structure. Ozonolysis was also conducted to cleave the double bond. The proton NMR spectrum of the product shows no evidence for the presence of a hemiacetal, only a full one-proton signal, corresponding to the aldehyde hydrogen at 9.75 ppm was observed. It is generally accepted that a hemiacetal will be formed in equilibrium with the open chain isomer if the two substitutes are *cis* to each other (Scheme 58).



209 **210** **211**

Scheme 58

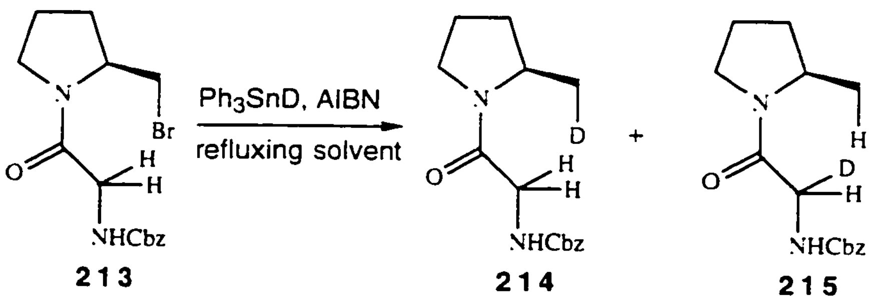
A sample of **208** was hydrolyzed and the Boc group was removed to facilitate NMR analysis. The resulting alcohol **212** (Scheme 59) was obtained crystalline, but, unfortunately, the crystals were too small for X-ray analysis.



Scheme 59

D. Discussion and suggestions for further development of the use of alkyl radical tethers for generation of translocated radicals.

Baldwin *et al.* have investigated[45] the influence of temperature on the rate of hydrogen transfer (Scheme 60). The same reactions were conducted in refluxing benzene, toluene and *p*-xylene. In each case, both the directly deuterated and the transferred product were isolated. From the increasing incorporation of deuterium at C-2 of the glycine residue with increasing temperature, it was concluded that the minor rotamer of the intermediate radical species was required for abstraction. On the same basis, we felt that a higher temperature might improve the yield of our reaction. However, a higher temperature in our allylation would also enhance the rate of competing intermolecular reaction prior to the intramolecular hydrogen abstraction, and we have not yet done the higher temperature reaction.

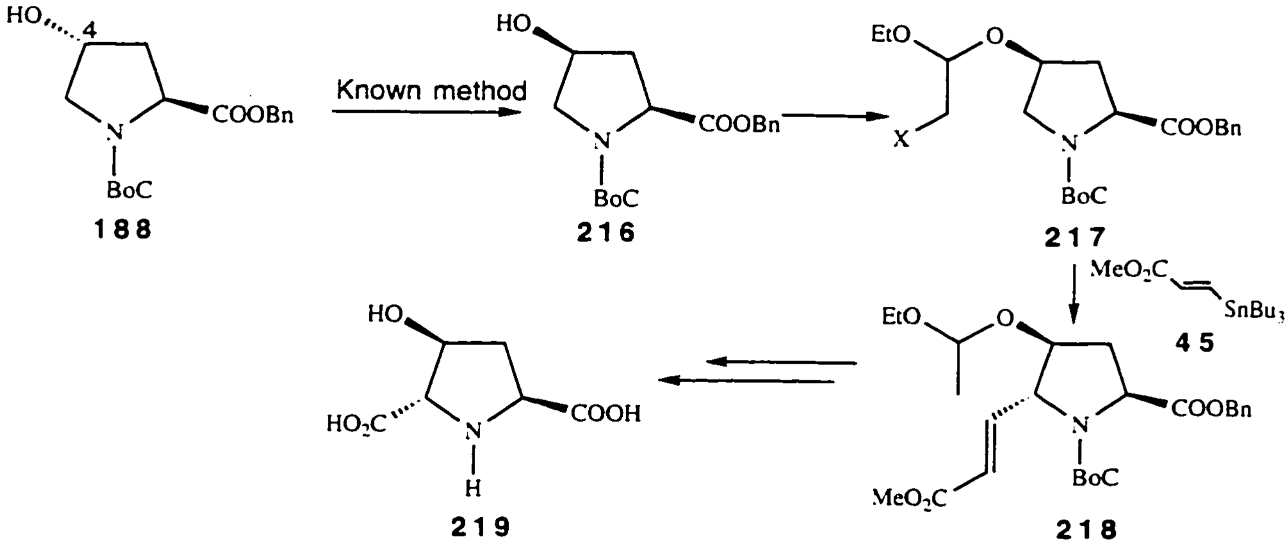


	214	215
benzene:	84%	16%
toluene:	71%	29%
p-xylene:	52%	48%

Scheme 60

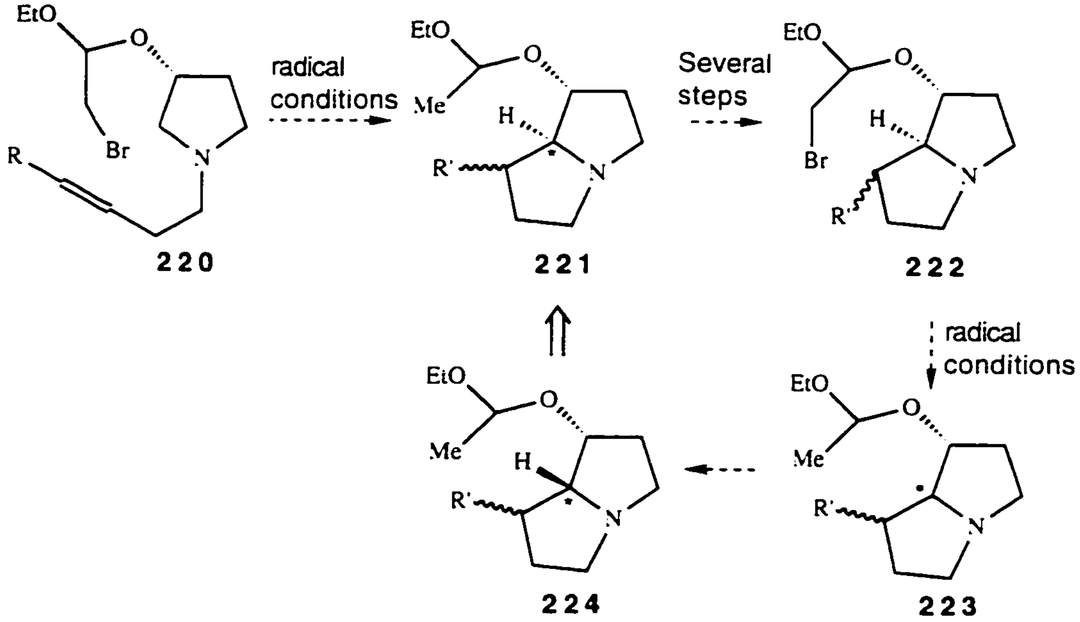
Since the final C-C bond forming step in our sequence is intermolecular, the concentration of the allylstannane and substrate also plays an important role in the process. If the concentration of the tin species is too high, premature allylation will dominate. On the other hand, if the concentration is too low, efficient allylation of the translocated radical will be difficult to achieve. For these reasons, the effect of concentration will be investigated in the future. We note that the initial radical is nucleophilic, but the translocated radical is likely to be less nucleophilic, and so there also exists the possibility of using a substituted allylstannane[43] that discriminates between radicals of different nucleophilicity.

The above methodology could perhaps be applied to the synthesis of (-)-bulgecinine. By following Barret's procedure, it should be possible to convert **188** into **216**, The derived translocated radical should react with reagent **45** to give **218**, from which point straightforward manipulations should afford the natural product **219**.



Scheme 61

The use of a tethered radical for translocation will probably be valuable in the construction of polycyclic alkaloids, as suggested by Scheme 62. As indicated in the Scheme, the initial ring fusion stereochemistry may be amenable to inversion by a second application of hydrogen transfer to a tethered alkyl radical.



Scheme 62

In the case of the proline substrate, the carboxyl group initially present could, of course, be removed - also by radical chemistry. Figure 4 shows a number of commercially

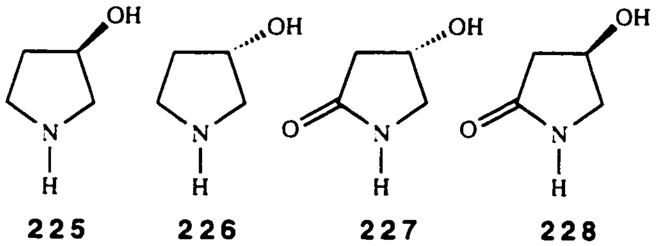
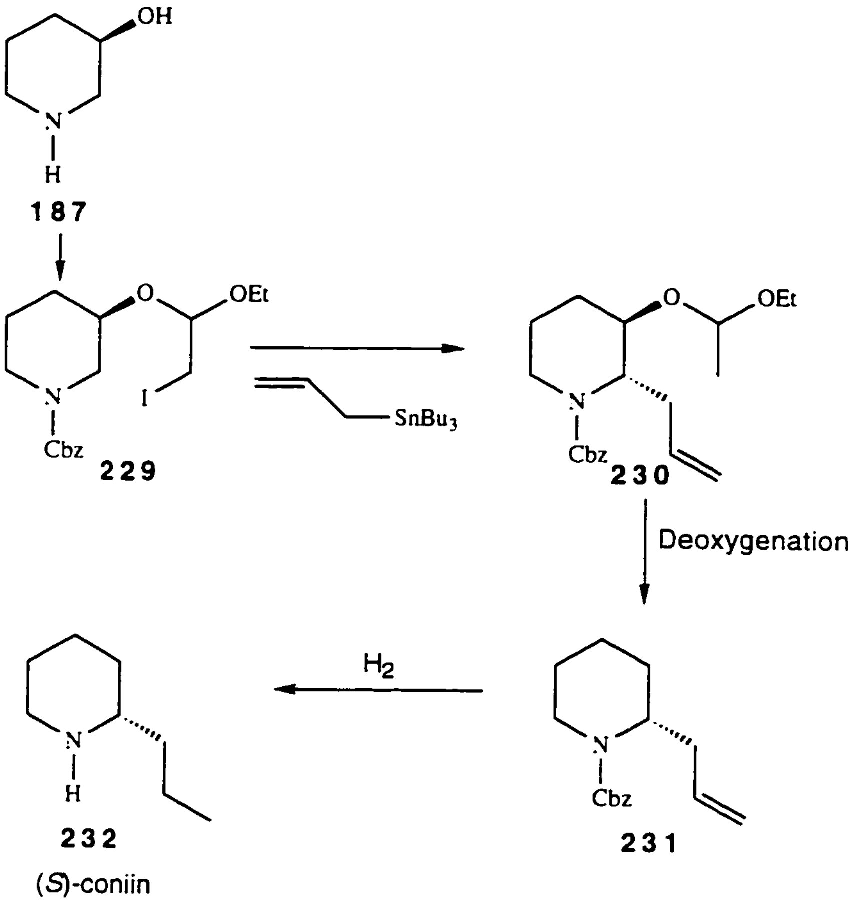
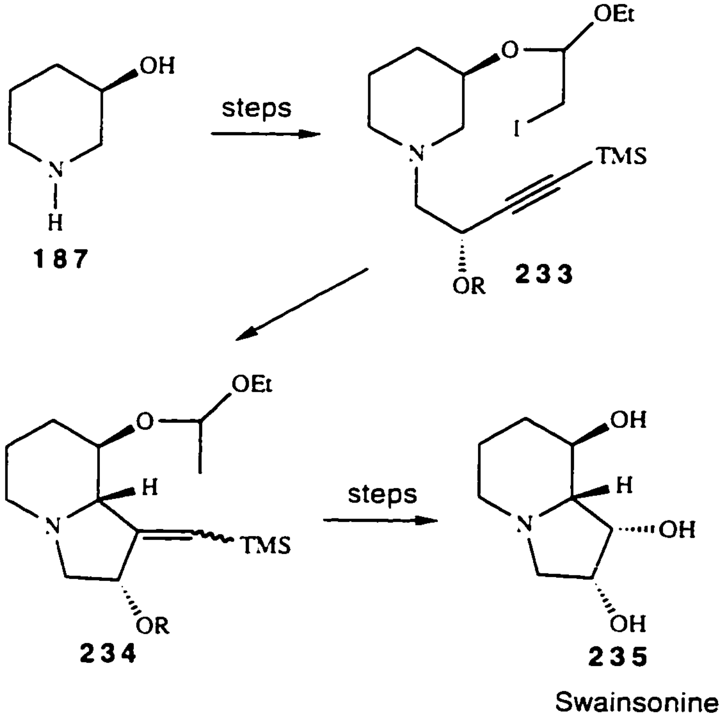


Figure 4

available compounds that would seem to be suitable substrates for the type of hydrogen translocation illustrated above by the conversion of **199** into **208**. The piperidine example is particularly noteworthy, as it could be used for a synthesis of coniine[46] (see Scheme 63) and swainsonine (see Scheme 64), although implementation of the ideas in these cases will depend on the correct stereochemical outcome of the C-C bond forming steps.



Scheme 63



Scheme 64

E. Conclusion.

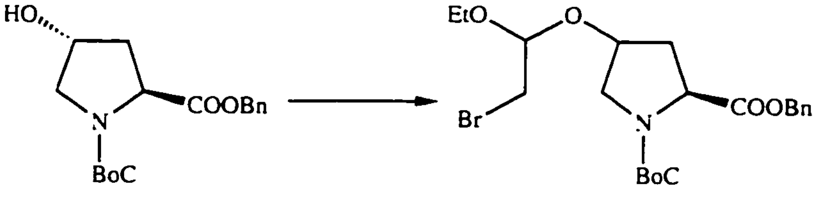
In conclusion, we have illustrated by one example a method to generate a radical α to nitrogen by using a tethered *alkyl* radical. In principle the method can be applied to the synthesis of several alkaloids, and further work in this direction is underway.

III EXPERIMENTAL

General procedures

The same general procedure specified in Chapter 1 apply to the following experiments.

Benzyl (2*S*, 4*R*, 5*S*)-1-[(1, 1-Dimethylethoxy) carbonyl]-4-(2-bromo-1-ethoxyethoxy) prolinate (198).

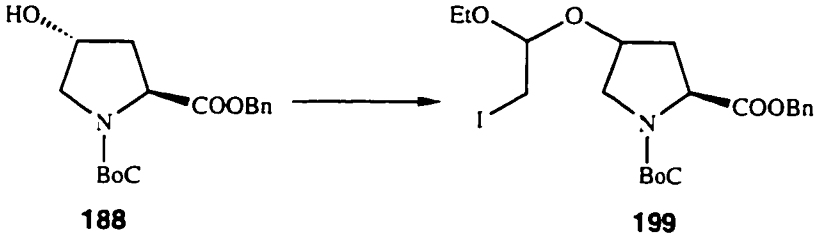


188 **198**

Ethyl vinyl ether (0.29 mL, 3.0 mmol) was added to a stirred solution of alcohol **188** (881.0 mg, 2.74 mmol) in CH_2Cl_2 (10 mL), followed by NBS (321.0 mg, 2.9 mmol). Stirring was continued overnight. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 25 cm), using 1:3 EtOAc-hexane, gave **198** (778.0 g, 60%) as a pure (^{1}H NMR, 300 MHz), colorless oil: FTIR ($CHCl_3$ cast) 1745, 1704, 1495 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.15 (t, *J* = 7.8 Hz, 3 H), 1.30 (s, 5.3 H), 1.41 (s, 3.7 H), 1.96-2.14 (m, 1 H), 2.20-2.42 (m, 1 H), 3.20-3.37 (m, 2 H), 3.42-3.70 (m, 2 H), 4.27-4.50 (m, 2 H), 4.65 (t, *J* = 7.5 Hz, 1 H), 5.01-5.29 (m, 2 H), 7.20-7.40 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 5.18 (t'), 36.53 (s'), 51.24 (t'), 52.20 (t'), 57.52 (q'), 57.75

(q'), 57.85 (q'), 58.07 (q'), 61.23 (t'), 61.96 (t'), 66.73 (t'), 72.97 (d'), 73.58 (d'), 73.98 (d'), 74.37 (d'), 80.21 (t'), 100.77 (d'), 101.18 (d'), 128.03 (d'), 128.17 (d'), 128.36 (d'), 128.43 (d'), 128.60 (d'), 135.45 (s'), 135.70 (s'), 153.65 (s'), 154.21 (s'), 172.43 (s'), 172.69 (s'); exact mass *m/z* calcd for $C_{17}H_{21}NO_4$ (M^+ - $C_4H_8BrO_2$) 303.14706, found 303.14717.

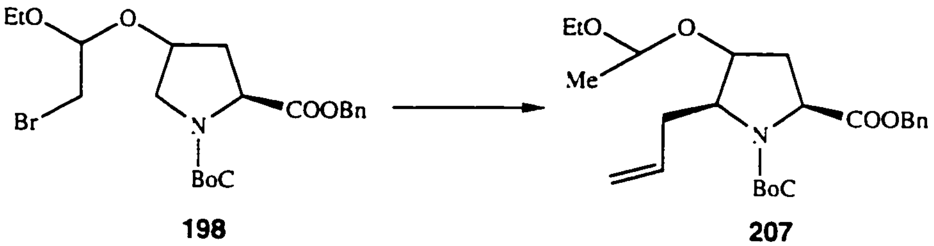
Benzyl (2*S*, 4*R*, 5*S*)-1-[(1, 1-Dimethylethoxy) carbonyl]-4-(1-ethoxy-2-iodoethoxy) prolinate (199).



Ethyl vinyl ether (0.21 mL, 2.24 mmol) was added to a stirred solution of alcohol **188** (720.0 mg, 2.24 mmol) in CH_2Cl_2 (10 mL), followed by NIS (554.5 mg, 2.46 mmol). Stirring was continued for 6 h. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 25 cm), using 1:3 EtOAc-hexane, gave **199** (874.0 mg, 75%) as a pure (^1H NMR, 200 MHz), colorless oil: FTIR ($CHCl_3$ cast) 1747, 1701, 1497, 1477.7 1455; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.19 (t, *J* = 7.0 Hz, 3 H),1.34 (s, 5 H), 1.45 (s, 4 H), 1.95-2.20 (m, 1 H), 2.20-2.50 (m, 1 H), 3.10-3.23 (m, 2 H), 3.41-3.72 (m, 2 H), 4.25-4.55 (m, 2 H), 4.57-4.70 (m, 1 H), 5.02-5.35

(m, 2 H), 7.3-7.4 (m, 5 H); ^{13}C NMR ($CDCl_3$, 50.3 MHz) 5.18 (t'), 36.53 (s'), 51.24 (t'), 52.20 (t'), 57.52 (q'), 57.75 (q'), 57.85 (q'), 58.07 (q'), 61.23 (t'), 61.96 (t'), 66.73 (t'), 72.97 (d'), 73.58 (d'), 73.98 (d'), 74.37 (d'), 80.21 (t'), 100.77 (d'), 101.18 (d'), 128.03 (d'), 128.17 (d'), 128.36 (d'), 128.43 (d'), 128.60 (d'), 135.45 (s'), 135.70 (s'), 153.65 (s'), 154.21 (s'), 172.43 (s'), 172.69 (s'); exact mass *m/z* calcd for $C_{21}H_{30}INO_6$ 519.11182, found 519.11264.

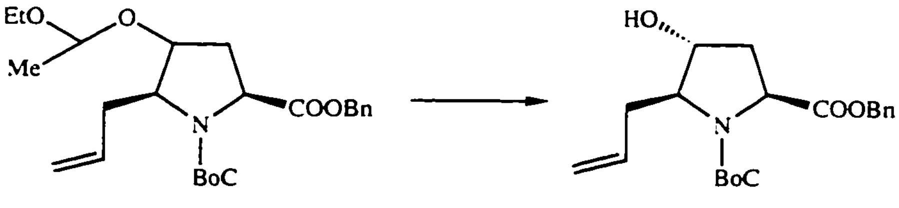
Benzyl (2*S*, 4*R*, 5*S*)-1- [(1, 1-Dimethylethoxy) carbonyl] -4-(1-ethoxyethoxy) -5- (2-propenyl) prolinate (207).



A solution of AIBN (5.0 mg, 0.03 mmol) in PhH (5.0 mL) was added by syringe pump over 6 h to a refluxing solution of **198** (388.0 mg, 0.82 mmol) and allyl stannane (0.51 mL, 1.65 mmol) in PhH (20 mL). Refluxing was continued for 1 h after the end of the addition. Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 25 cm), using 1:3 EtOAc-hexane, gave **207** (200.0 mg, 56%) as a pure (^{1}H NMR, 400 MHz), colorless oil: FTIR (CH_2Cl_2, cast)

3068, 3033, 1750, 1700, 1651 cm^{-1}; ^{1}H NMR (CDCl$_3$, 400 MHz) δ 1.10-1.20 (m, 3 H), 1.21-1.30 (m, 3 H), 1.34 (s, 5 H), 1.45 (s, 4 H), 1.80-2.18 (m, 2 H), 2.20-2.35 (m, 1 H), 2.40-2.55 (m, 0.4 H), 2.60-2.72 (m, 0.6 H), 3.35-3.48 (m, 1 H), 3.50-3.60 (m, 1 H), 3.70-4.05 (m, 1 H), 4.06-4.12 (m, 1 H), 4.34-4.55 (m, 1 H), 4.63-4.74 (m, 1 H), 4.85-5.30 (m, 4 H), 5.70-5.92 (m, 1 H), 7.27-7.42 (m, 5 H); ^{13}C NMR (CDCl$_3$, 75.5 MHz) (mixture of rotamers) 15.14 (q'), 15.20 (q'), 15.32 (q'), 19.94 (q'), 20.22 (q'), 20.36 (q'), 28.17 (q'), 28.38 (q'), 33.95 (t'), 34.85 (t'), 34.99 (t'), 35.85 (t'), 36.38 (t'), 37.04 (t'), 37.24 (t'), 37.76 (t'); exact mass *m/z* calcd for $C_{21}H_{30}NO_6$ (M^+ - C_3H_5) 392.20731, found: 392.20764.

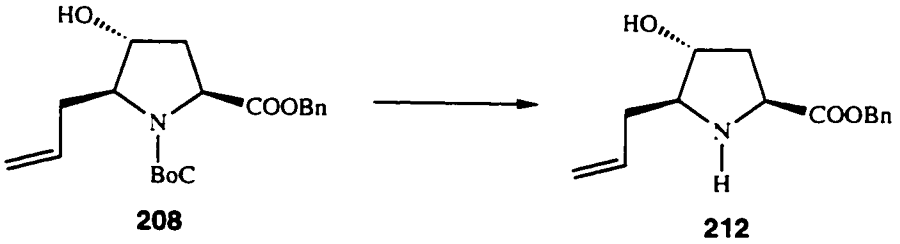
Benzyl (2*S*, 4*R*, 5*S*)-1-[(1, 1-Dimethylethoxy) carbonyl]-4-hydroxy-5-(2-propenyl) prolinate (208).



207 **208**

Compound **207** (200.0 mg, 0.46 mmol) was dissolved in a mixture of AcOH (1.0 mL) and water (1.0 mL) and warmed to *ca* 45 °C for 30 min, by which time hydrolysis was complete (tlc control, silica, 1:3 EtOAc-hexane). EtOAc (20 mL) was added and the solution was washed with saturated aqueous Na_2CO_3 (2 x 10 mL) and brine (20 mL), and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (3 x 20 cm), using increasing amounts of EtOAc in hexane (from 1:3 to 1:1), gave alcohol **208** (130.0 mg, 80%) as a pure (^{1}H NMR, 300 MHz), colorless oil: FTIR (CH_2Cl_2, cast) 3437, 3065, 1746, 1723, 1697 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.27 (s, 5 H), 1.43 (s, 4 H), 1.85-2.15 (m, 3 H), 2.16-2.31 (m, 1 H), 2.4-2.60 (m, 1 H), 3.67-3.82 (m, 1 H), 4.22 (s, 1 H), 4.38-4.60 (m, 1 H), 4.85-5.31 (m, 4 H), 5.70-5.95 (m, 1 H), 7.25-7.41 (m, 5 H); ^{13}C ($CDCl_3$, 75.5 MHz) (mixture of rotamers) 28.19 (q'), 28.38 (q'), 36.35 (t'), 36.94 (t'), 37.17 (t'), 37.70 (t'), 58.29 (d'), 58.64 (d'), 66.70 (d'), 66.78 (s'), 73.10 (d'), 74.16 (d'), 80.41 (t'), 117.44 (t'), 128.04 (d'), 128.14 (d'), 128.30 (d'), 128.40 (d'), 128.48 (d'), 128.60 (d'), 134.62 (d'), 135.53 (s'), 153.93 (s'), 154.41 (s'), 172.70 (s'), 173.04 (s'); exact mass *m/z* calcd for $C_{17}H_{22}NO_5$ (M^+ - C_3H_5) 320.14981, found: 320.15000.

Benzyl (2*S*, 4*R*, 5*S*)-4-hydroxy-5-(2-propenyl) prolinate (212).



TFA (1.0 mL) was added to a stirred solution of **209** (50.0 mg, 0.14 mmol) in CH_2Cl_2 (1 mL) and stirring was continued for 2 h. The solvent was then evaporated and the residue was dissolved in EtOAc (20 mL), washed with saturated aqueous Na_2CO_3 (2 x 10 mL) and brine (15 mL), and dried (Na_2SO_4). Evaporation of the solvent and flash chromatography of the residue over silica gel (1 x 10 cm), using EtOAc, gave amine **213** (29.0 mg, 80%) as a pure (^1H NMR, 200 MHz), white solid: mp 79.5-80.5.5 °C (recrystalized from hexane-EtOAc); $[\alpha]_D^{24}$ -48°C (*c* 0.75, $CHCl_3$); FTIR (CH_2Cl_2, cast) 3228, 3112, 3075, 3031, 1747 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 2.09-2.35 (m, 4 H), 2.43 (s, 2 H), 3.11 (dt, *J* = 7.3, 3.9 Hz, 1 H), 4.00 (dd, *J* = 5.4, 3.9 Hz, 1 H), 4.10 (t, *J* = 8.0 Hz, 1 H), 5.07-5.30 (m, 4 H), 5.75-5.95 (m, 1 H), 7.40 (s, 5 H); ^{13}C ($CDCl_3$, 75.5 MHz) 38.15 (t'), 38.27 (t'), 57.90 (d'), 66.03 (d'), 67.02 (t'), 75.83 (d'), 117.93 (t'), 128.22 (d'), 128.44 (d'), 128.62 (d'), 134.60 (d'), 135.48 (s'), 174.08 (s'); exact mass *m/z* calcd for $C_{12}H_{14}NO_3$ (M^+ - C_3H_5) 220.09737, found 220.09763.

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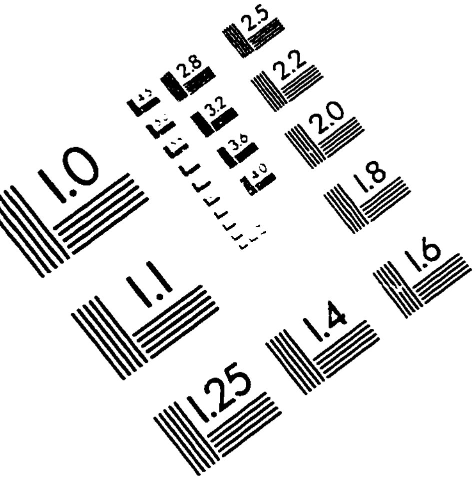

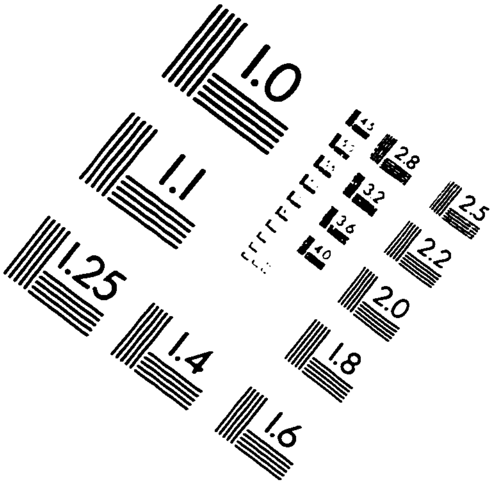

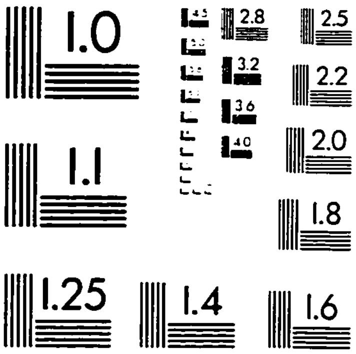

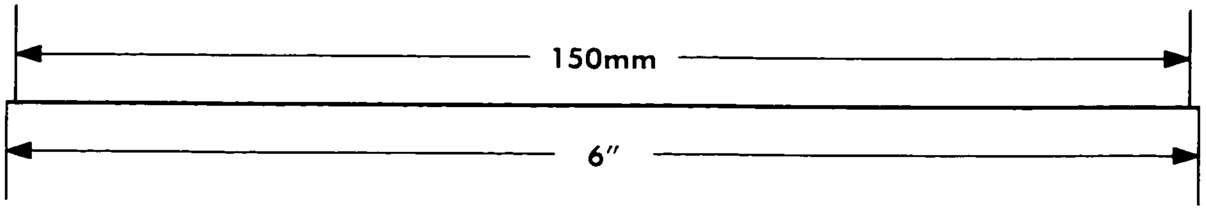

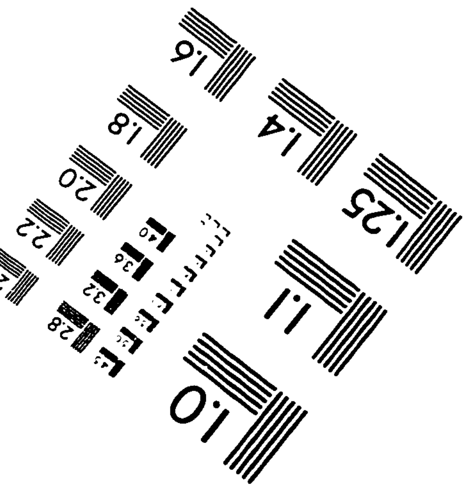

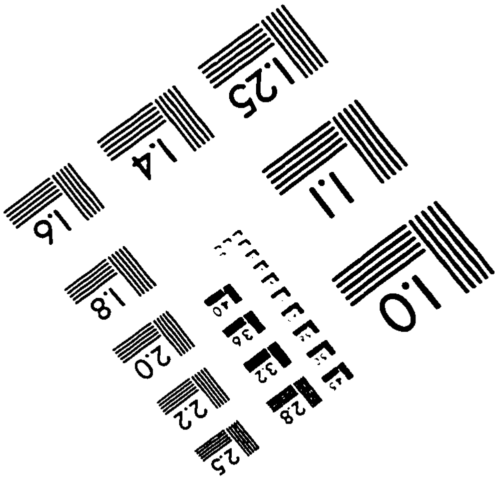

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