Selenium Mediated Cyclizations and Reactions of Selenones

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by
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‘Look with all your eyes, look’

Jules Verne, “Michael Strogoff”

‘What is the use of a book’, thought Alice, ‘without pictures or conversations?’

Lewis Carrol, “Alice in Wonderland”
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Abstract

An investigation of stereoselective selenium mediated cyclizations of allylic alcohols was carried out. Cyclizations of N-protected 4-hydroxy-5-pentenylamines occurred under kinetic control with cis-stereoselectivity to afford N-protected phenylselenomethyl hydroxypyrrolidines in high yield. Selenium induced cyclizations of N-protected 5-hydroxy-6-hexenylamines occurred under thermodynamic control with trans-stereoselectivity to afford N-protected phenylselenomethyl hydroxy piperidines in high yield. A mechanism to account for these contrasting reactivities is proposed. Some of the piperidines formed stable hydrates and exhibited through space coupling to water in the 1H n.m.r. spectra. Some of the pyrrolidines were elaborated to biologically important diols via intramolecular substitution of the corresponding selenones with hydroxide ion.

The conditions required for formation of alkyl phenyl selenones from alkyl phenyl selenides using MCPBA were investigated using 77Se n.m.r. analysis. Several intermolecular substitution reactions of alkyl phenyl selenones by soft nucleophiles such as water, methanol and chloride ion were demonstrated to occur under mild conditions and in high yield. Treatment of β-benzamidoselenides with MCPBA and base at room temperature afforded cis-fused 2-oxazolines, whereas treatment with excess phenylselenenyl bromide at 120°C afforded previously unreported trans-fused 2-oxazolines. Treatment of β-acetamidoselenides with MCPBA gave lactones or esters.

Hydroxyselenations of allylic alcohols generally occurred with high regioselectivity to afford β,β'-dihydroxyselenides, which could be transformed to β-hydroxy epoxides upon treatment with MCPBA and base. The formation of trans-β-hydroxy epoxides from allylic alcohols using this methodology is in contrast to established methods which give cis-β-hydroxy epoxides.

Hydroxyselenation of crotyl acetate or 2-acetoxy cyclohexene was regio- and stereo-catholic, in contrast to the regio- and stereo-specific addition of phenylselenenyl chloride to these compounds. Additions of phenylselenenyl chloride in the presence of zinc chloride to these compounds was also regio- and stereo-catholic. A mechanism to account for these differing reactivities is proposed.

Attempts to induce radical, reductive or oxidative cyclizations of N-acryloyl and N-alkyl 2-phenylselenomethyl pyrrolidines were unsuccessful, however N-acrylated or N-alkylated β-amidoselenides could be cyclized to form five and six membered ring nitrogen heterocycles via radical abstraction of selenium.
Statement of originality

I give consent to this copy of my thesis, when deposited in the University Library, being available for photocopying and loan.

This thesis contains no material previously submitted for a degree or diploma in any University and to the best of my knowledge contains no material written or published by any other person except where due reference is made in the text.

Matthew Cooper

23rd December 1994
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For the casual reader, pretty pictures may be found on pages 25, 39 and 225. For the discerning researcher I hope some of the work detailed in this thesis may be of use to you and I wish you all the best for your studies.
Abbreviations

Ac     acetyl
AIBN   azobisisobutyronitrile
Boc    tertbutoxycarbonyl
BOC-ON 2-(tertbutoxycarbonyloxyimino)-2-phenylacetonitrile
DBN    1,5-diazabicyclo[4.3.0]non-5-ene
DBU    1,9-diazabicyclo[5.4.0]undec-7-ene
DCC    dicyclohexylcarbodiimide
DEAD   diethyl azodicarboxylate
DMAP   dimethylaminopyridine
DMF    N,N-dimethylformamide
DMSO   dimethylsulfoxide
EDC    1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
HMPA   hexamethylphosphoramide
HPLC   high performance liquid chromatography
LDA    lithium diisopropylamide
MCPBA  meta chloroperbenzoic acid
N.m.r.  nuclear magnetic resonance
NBS    N-bromosuccinimide
Phth   phthaloyl
TBDMS  tertbutyldimethylsilyl
TBDPS  tertbutyldiphenylsilyl
TFA    trifluoroacetic acid
TFAA   trifluoroacetic anhydride
THF    tetrahydrofuran
Ts     p-toluenesulfonyl
TTMSS  tris(trimethylsilyl)silane

* Near the completion of this thesis the IUPAC committee replaced the term “phenylselenenyl” with “phenylselanyl” for compounds such as PhSeCl, however due to time constraints the former term is still used throughout this thesis.
Some of this thesis has been presented in the following publications;


Chapter 1

An introduction to the chemistry of organoselenium compounds

Selenium was discovered in 1878 by the Swedish chemist J. J. Berzelius in the lead chamber deposits of his sulphuric acid plant. He named the element after Selena, the greek goddess of the moon because of its association with the element Tellurium, which was named after the Roman god of the earth, Tellus. For the next century, organoselenium chemistry was a neglected field and as late as the 1960’s there were only two organoselenium reagents generally employed by organic chemists. Selenium metal was used for dehydrogenations of hydrocarbons and isomerization of alkenes and selenium dioxide was used for oxygenation of a variety of organic compounds, most notably alkenes and ketones.¹ Selenium compounds had a bad reputation with synthetic chemists because of their toxicity and a tendency to produce malodourous mixtures that were hard to purify. However in 1970 Jones and co-workers² reported that several steroidal selenoxides decomposed rapidly at room temperature to give the corresponding alkenes. In 1973 Sharpless³ reported a mild method for the conversion of epoxides to allylic alcohols using phenylselenide anion and within months Reich,⁴ Clive⁵ and Sharpless⁶,⁷ independently reported the conversion of alkenes to allylic alcohols by addition of various selenium reagents to the double bond and subsequent elimination of the selenoxide. The discovery of the selenoxide syn elimination as a mild, general method for the formation of alkenes paved the way for a renaissance in organoselenium chemistry. Over a thousand publications utilizing organoselenium reagents or intermediates appeared in the next ten years and the field has since become the subject of some excellent books⁸,⁹ and reviews.¹⁰-¹³
Chapter 1

The inherent versatility of selenium compounds lies in their ability to act as both an electrophile and as a nucleophile. Phenylselenide anion, generated from the reaction of diphenyldiselenide with sodium borohydride\(^3\) or N-acetylcysteine sodium salt,\(^14\) is a potent nucleophile and has been used to open epoxides,\(^3\) displace halide and sulfonate anions,\(^15\) and cleave esters and lactones.\(^16\) Phenylselenide anion also undergoes conjugate addition to \(\alpha\beta\)-unsaturated carbonyl compounds\(^17\) and, with tributyl phosphine, converts alcohols directly to alkyl phenyl selenides.\(^18\) In marked contrast, organoselenium species containing a good leaving group (e.g. Cl, Br, I, O\(_2\)CCF\(_3\), phth) can serve as extremely reactive, soft nucleophiles.\(^4,7,19-24\) Organoselenium moieties can thus be introduced into a variety of organic substrates as nucleophiles or as electrophiles, using very mild conditions and usually in high yield. Since the phenylseleno moiety is a poor leaving group,\(^25\) a variety of synthetic transformations may be effected without disturbing the selenium residue. This group can ultimately be removed by reduction with triphenyltin hydride\(^26-28\) or nickel boride,\(^29,30\) or by oxidation to the alkene\(^6,31-33\) (scheme 1.0). Selenides may also be oxidatively substituted with halides using a number of reagents under a variety of conditions,\(^34-38\) or stannylated using tributylallylstannane in the presence of AIBN.\(^39\)

![Scheme 1.0](https://via.placeholder.com/150)

Addition of selenium to an organic compound is usually carried out using the commercially available phenylselenenyl halides, phenylselenenyl phthalimide, phenylseleninic acid or diphenyldiselenide. Phenylselenenyl halides react instantaneously with double bonds to give anti-Markovnikov adducts, which
isomerize rapidly at room temperature in polar solvents,\textsuperscript{40} or slowly at low temperatures in non-polar solvents,\textsuperscript{41} to the thermodynamically more stable Markovnikov adducts.\textsuperscript{21} This isomerization involves the reversible formation of an episelenonium ion and is dependent upon the solvent, temperature and nature of the counter anion of the selenium reagent used\textsuperscript{42} (scheme 1.1). Addition of selenium to alkenes has also been effected using phenylselenenyl fluoride,\textsuperscript{43} phenylselenenyl trifluoroacetate,\textsuperscript{20,23} phenylselenenyl sulfonates,\textsuperscript{44,45} phenylselenenyl triflate,\textsuperscript{46} benezeneseleninic anhydride,\textsuperscript{47,48} diphenyldiselenide and peroxydisulfate,\textsuperscript{49} diphenyldiselenide and ceric ammonium nitrate,\textsuperscript{50} diphenyldiselenide and stannic chloride,\textsuperscript{51} and by photon electron transfer from 1,4-dicyanonaphthalene to diphenyldiselenide.\textsuperscript{52-54} These additions generally occur in high yield and with high regioselectivity.

![Scheme 1.1](image)

The intermediate episelenonium ion may also be trapped by solvent. Hydroxyselenation\textsuperscript{22,55,56} of alkenes has been effected with phenylselenenyl halides using aqueous acetonitrile as solvent, methoxyselenation\textsuperscript{57} using methanol as solvent and acetoxysele

\textsuperscript{19} using sodium acetate and acetic acid as solvent. Reaction of an alkene with phenylselenenyl chloride and aqueous triflic acid in a nitrile containing solvent leads to amidoselenated\textsuperscript{19,58-60} products arising from a Ritter type reaction (scheme 1.2).
If there is a nucleophilic group present in an unsaturated molecule then addition of electrophilic selenium to the double bond is followed by cyclization. This process has been termed "cyclofunctionalization" by Clive, as cyclization results in the concomitant incorporation of the synthetically useful phenylseleno group (scheme 1.3). Phenylselenenyl halides have effected cyclization of alcohols and phenols to cyclic ethers, carboxylic acids to lactones, and thiols and thioacetates to cyclic thioethers. Clive and co-workers have extended this methodology to the synthesis of nitrogen heterocycles. It was found that whilst unsaturated amines do not cyclize readily, their carbamate derivatives do so in the presence of silica gel. Selenium induced cyclizations of unsaturated amides and transannular cyclizations of unsaturated aza-4-cyclooctenes have also been reported.
Reaction of a diene with a phenylselenenyl halide enables participation of one double bond as a nucleophile in an intramolecular attack on the intermediate episelenonium ion. This results in a transannular cyclization\textsuperscript{72,73} and formation of a carbocation, which can be captured by another nucleophile or by solvent. When the reaction is carried out in the presence of water a bicyclic ether is formed\textsuperscript{22,55,56,74} (scheme 1.4).
Selenium, like its chalcogen relative sulfur, is able to stabilise carbanions. \(\alpha\)-Lithioselenides\(^{34}\) are formed by cleavage of selenoacetals and selenoketals with n-butyl lithium\(^{75}\) or by deprotonation of alkyl selenides with LDA\(^{76}\) and react readily with alkyl halides, epoxides, carbonyl compounds and disulfides\(^{8}\) (scheme 1.5). This methodology lacks generality as deprotonation of alkyl selenides occurs only if there is an electron withdrawing group adjacent to the selenium. The greater acidity of selenoxides as compared to selenides allows ready deprotonation of these species with LDA to form \(\alpha\)-lithioselenoxides, which also react with a wide variety of electrophiles.\(^{77}\) The products formed may either fragment upon workup to form alkenes, or can be reduced to selenides with trimethyl phosphite or sodium iodide and sodium bisulfite\(^{78}\) (scheme 1.6).
Phenylselenenyl halides react spontaneously with the enol form of ketones,\textsuperscript{79} or with ketone enolate anions,\textsuperscript{31} enol acetates\textsuperscript{80,81} and silyl enol ethers\textsuperscript{82} to give α-phenylseleno carbonyl compounds (scheme 1.7). These compounds may then be transformed to their α,β-unsaturated derivatives \textit{via} elimination of the corresponding selenoxide.

The addition of selenium to a molecule followed by elimination of the selenoxide has been employed in a number of synthetically useful transformations. Two of the better known examples are the conversion of ketones to enones,\textsuperscript{31} and the conversion of epoxides and alkenes to allylic alcohols.\textsuperscript{3,83} In a similar manner alkenes may be converted to allylic ethers and acetates,\textsuperscript{6,19} lactones converted to unsaturated esters,\textsuperscript{84} and enones undergo a 1,3 transposition\textsuperscript{11,85,86} (scheme 1.8).
These examples illustrate the considerable versatility and varied reactivity of organoselenium compounds.
Chapter 2

Selenium induced cyclizations of unsaturated N-protected hydroxyamines

2.0 An introduction to polyhydroxylated pyrrolidine and indolizidine alkaloids and their bioactivity

Polyhydroxylated nitrogen heterocycles are found abundantly in nature and constitute a major class of glucosidase inhibitors (fig. 2.0.1). Compounds such as detoxinine\textsuperscript{87} (1), the triol (2), anisomycin\textsuperscript{88} (3), retronecin\textsuperscript{89} (4), slaframine\textsuperscript{90-92} (5), swainsonine\textsuperscript{93-96} (6) and castanospermine\textsuperscript{97-100} (7) effect highly specific inhibition of a variety of trimming glucosidases and show little cytotoxicity \textit{in vitro} or \textit{in vivo}.\textsuperscript{101} They have been used, or implicated for use, as antihyperglycemic compounds, inhibitors of tumour metastasis, antiobesity drugs, fungistatic compounds, insect antifeedants and antivirals.\textsuperscript{124}

![Chemical structures](Fig. 2.0.1)
Castanospermine was first isolated\textsuperscript{102} from the Australian legume \textit{Castanospermum australae} in 1981 and has attracted particular attention due to its significant anti-HIV activity both \textit{in vitro}\textsuperscript{103} and \textit{in vivo}\textsuperscript{104}. Castanospermine interferes with processing of the HIV glycoprotein gp120\textsuperscript{105}, a heavily glycosylated viral outer envelope protein that binds to the CD-4 receptor of the human T lymphocyte. As interaction of gp120 with the CD-4 receptor is required for viral syncytium formation\textsuperscript{101}, castanospermine consequently reduces viral infectivity and replication.

The potent and varied biological activity of these pyrrolidine and indolizidine alkaloids has attracted the attention of many synthetic organic chemists. Most syntheses of the indolizidines have involved elaboration of modified sugars\textsuperscript{93,98,100,105,106}, whilst others have employed cycloaddition reactions\textsuperscript{107,108}, iminium ion cyclizations\textsuperscript{109}, radical cyclizations\textsuperscript{92,94}, epoxide openings\textsuperscript{91,97}, and biomimetic strategies\textsuperscript{110}. Most syntheses of the pyrrolidines have utilized a diastereoselective electrophilic addition to the double bond of an allylic alcohol. Additions to allylic alcohols have been widely used in the synthesis of heterocyclic compounds with defined stereochemistry\textsuperscript{111,112} however most reports have been confined to cyclization with oxygen nucleophiles such as 3-hydroxy-4-pentenoic acid\textsuperscript{113,114} and 3-hydroxy-4-pentenol\textsuperscript{115,116}. The few reported cases of cyclization with a nitrogen nucleophile have employed a palladium catalyst\textsuperscript{117}, mercuric acetate\textsuperscript{90,118-120} and halogens\textsuperscript{121,122} to effect cyclization. These syntheses exploit the \textit{syn} directing effect of the allylic hydroxyl group to give the \textit{cis} stereochemistry of the substituents at C\textsubscript{2} and C\textsubscript{3} possessed by the alkaloids depicted in figure 2.0.1.

Polyhydroxylated piperidines with \textit{trans} substituents at C\textsubscript{2} and C\textsubscript{3}, such as the acetamide\textsuperscript{123} (8), deoxymannojirimycin\textsuperscript{124} (9) and the prosopis alkaloids prosopinine (10a) and prosopine\textsuperscript{125} (10b) (fig. 2.0.2) also possess potent biological activity.
The cyclization of unsaturated carbamates\textsuperscript{68,69} and amides\textsuperscript{70,126} using phenylselenenyl halides is known to afford pyrrolidines and piperidines in high yield. The use of selenium reagents as mediators of stereoselective cyclization of these substrates however, has received little attention. Nino\textsuperscript{i}\textsuperscript{126} has reported that cyclization of an optically active pentenyl amide with phenylselenenyl chloride gave a pyrrolidine with 25\% enantiomeric excess and Clive\textsuperscript{69} has reported that cyclization of a 5-hexenyl carbamate with phenylselenenyl chloride gave only a cis 2,6 disubstituted piperidine (scheme 2.0.3).

It was thought that selenium induced cyclization of an unsaturated N-protected amine possessing an allylic hydroxy group may afford products with defined stereochemistry at C\textsubscript{2} and C\textsubscript{3} arising from an asymmetric induction (scheme 2.0.4). The concomitant incorporation of the synthetically useful phenylseleno group could then enable further elaboration of these cyclized products to some of the compounds depicted in figure 2.0.1.
Hence the aims of the work presented in this chapter were to:

i) develop an efficient, expeditious synthesis of a variety of N-protected unsaturated 3-hydroxy-4-pentenylamines and 4-hydroxy-5-hexenylamines,

ii) investigate the stereoselectivity of selenium induced cyclizations of these compounds, and

iii) develop a methodology to effect substitution of the phenylselenenyl group and elaboration of the cyclized products to biologically active compounds.
2.1 Synthesis and cyclizations of N-protected 4-hydroxy-5-pentenylamines

2.1.1 Synthesis of starting materials

Synthesis of the amine (12), precursor to required starting materials, was accomplished by the literature procedure\textsuperscript{121} outlined in scheme 2.1.1.

\[
\begin{align*}
\text{CH}_3\text{CN, nBuLi} & \xrightarrow{-78^\circ\text{C}} \text{N} \equiv \text{CH} & (11) \\
\text{LiAlH}_4 & \xrightarrow{} \text{N} \equiv \text{CH} \equiv \text{CH} \equiv \text{CH}_2 \equiv \text{CH}_2 \equiv \text{CH}_2 \equiv \text{NH}_2 & (12)
\end{align*}
\]

Scheme 2.1.1

Mixed aldol condensation of the lithium salt of acetonitrile with acrolein at -78°C occurred regioselectively to give the nitrile (11) in high yield. The nitrile was reduced with lithium aluminium hydride to give the amine (12), three equivalents of the reducing agent in dilute, ethereal solution being required to drive the reaction to completion. The amine was purified by distillation from a small amount of hydroquinone, and when stored in a freezer was stable for several months.

As unsaturated amines are known\textsuperscript{15,127} to react directly upon nitrogen with selenium electrophiles, it was necessary to synthesise the N-protected analogues of (12) for the cyclization studies. A variety of different N-protecting groups, conferring differing degrees of nucleophilicity and differing steric environments to the nitrogen atom were employed (scheme 2.1.2).
The ethyl carbamate (13) was prepared using standard Schotten-Bauman conditions.\(^1\) Reaction of (12) with ethyl chloroformate and sodium hydroxide in aqueous media proved superior to a similar reaction using either pyridine or triethylamine as base in organic solvents. The carbamoylation was high yielding and the carbamate (13) could be used without further purification. The tert-butyl carbamate (14) was also best prepared under Schotten-Bauman conditions and reaction of (12) with BOC-ON\(^{128}\) gave (14) in good yield. The sulfonamide (15) was prepared by reaction of (12) with tosyl chloride in pyridine.

Attempts to synthesise the acetamide (17) did not meet with such immediate success. Reaction of (12) with acetyl chloride using a variety of bases and solvents gave a 1:1 mixture of the required amide (17) and the diacetylated (16) (scheme 2.1.3) as evidenced by t.l.c. and the \(^1\)H n.m.r. spectrum, which showed singlets at 2.09 and 1.98 ppm corresponding to the acetate and acetamide methyl resonances respectively. A similar product mixture was obtained using acetyl chloride under Schotten-Bauman conditions, or when reaction was attempted
using DCC or EDC and acetic acid in the presence of a catalytic amount of DMAP.\textsuperscript{129} Attempts to induce clean formation of (17) using DMAP in acetic anhydride also proved fruitless. Kisfaludy has reported\textsuperscript{130} the use of pentafluorophenol acetate as a reagent for the selective formation of acetamides from aminoalcohols. However when (12) was reacted with this reagent, formed from reaction of pentafluorophenol with acetyl bromide, only starting materials were recovered.

\[
\begin{align*}
\text{NH}_2 & \quad \text{OH} & \text{CH}_3\text{COCl} & \quad \text{Et}_3\text{N}, \text{THF} & \quad \text{NH} \quad \text{Ac} \\
(12) & & & & (17) \quad + \quad (16)
\end{align*}
\]

Scheme 2.1.3

Competition between the primary amine and a relatively less reactive secondary, allylic alcohol for an electrophile was quite suprising. However, formation of the acetate could possibly be facilitated \textit{via} an intramolecular trans-acetylation reaction (scheme 2.1.4).

\[
\begin{align*}
\text{HN} & \quad \text{C}=\text{O} & \quad \text{OH} & \quad \rightarrow & \quad \left[ \begin{array}{c}
\text{NH}_2 \\
\text{Ac}
\end{array} \right] \quad \rightarrow & \quad \text{NH} \quad \text{Ac} \\
& & & & & \quad \text{OAc}
\end{align*}
\]

Scheme 2.1.4

As all attempts to produce the acetamide were accompanied by formation of the diacetate, it was decided that a more suitable approach was to deliberately form (16), then selectively hydrolyse the more labile ester moiety. Reaction of (12) with excess acetyl chloride resulted in formation of (16) only, in good yield. Subsequent hydrolysis of (16) in methanolic potassium hydroxide however, gave only low yields of the desired amide. It was thought that much of the highly polar amide was being lost in the aqueous phase upon workup. Methanolic barium hydroxide has been employed\textsuperscript{131} in the selective hydrolysis of acetates, the barium...
acetate formed as a result of reaction being insoluble in methanol and easily removed by filtration. Reaction of (16) with one equivalent of barium hydroxide in methanol at room temperature for one hour afforded (17) in quantitative yield.

2.1.2 Cyclization studies

Cyclization reactions were routinely carried out using a slight excess of the phenylselenenyl halide (PhSeX) in the presence of dry silica gel as catalyst,\textsuperscript{69} and anhydrous potassium carbonate as a non-nucleophilic acid scavenger. As addition of phenylselenenyl halides is a reversible process,\textsuperscript{10,69} an acid trap was required to prevent competing addition of HX, formed as an adjunct to cyclization, to the free alkene. Under these conditions the orange colour of phenylselenenyl chloride was discharged immediately upon addition to a solution of (14) in dichloromethane at -78°C. Examination of the reaction mixture by reverse phase HPLC also revealed the rapid conversion of starting material to a distinct, UV-active product. Reactions were followed by reverse phase HPLC as the acyclic, selenium containing intermediates tended to streak on silica t.l.c. plates, and HPLC analysis also enabled rapid and accurate determination of diastereomeric product ratios.

The reaction mixture was stirred at -78°C for 10 minutes then at room temperature for 3 hours. Chromatography of the mixture to remove the diphenyldiselenide by-product yielded a mixture of diastereomers (18a) and (18b) in the ratio 64:36 in 83% yield (scheme 2.1.5). The product ratios did not change with time or when the isolated product mixture was resubjected to the reaction conditions described above. This result, and the fact that cis isomers are generally less stable than trans isomers suggested that the reaction was under kinetic control. The diastereomers could not be separated by chromatography on silica or alumina, however repeated fractional recrystallization gave a crystalline product of high diastereomeric purity. The supernatant of recrystallization was concentrated to give the minor diastereomer as a white solid, which when recrystallized also showed high diastereomeric purity.
Chapter 2.1

Scheme 2.1.5

The $^1$H n.m.r. spectra of the major diastereomer (fig. 2.1.6a) showed no NH resonance and the protons H$_{4a}$ and H$_{4b}$ appeared as distinct multiplets at 1.69 and 1.24 ppm. This suggested that the molecule was conformationally rigid and that cyclization had occurred. The proton H$_3$ appeared as a multiplet at 4.37 ppm, the protons H$_{5a}$, H$_{5b}$ and H$_2$ as complex multiplets at 3.4 ppm, and the diastereotopic protons adjacent to selenium as doublets of doublets at 3.71 and 3.17 ppm. The major diastereomer (18a) was assigned the cis stereochemistry initially on the basis of the $^{13}$C n.m.r. spectra, resonances being assigned by analogy with literature values$^{122}$ and by a HETCOR$^{132}$ experiment. The CSe resonance of (18a) was 2 ppm further upfield than that of (18b). This is attributed to a $\gamma$-gauche effect$^{133}$ which is a good indication of the relative stereochemistry of substituted small ring systems.

Fig. 2.1.6a
Fig. 2.1.6b

A nOE difference experiment would provide collaborating evidence for this assignment, but it was first necessary to identify the exact location of the resonance for H₂. This was determined from the DQF-COSY\textsuperscript{134} spectra (fig 2.1.6b) which enabled complete characterization of the couplings of (18a). The longitudinal relaxation time (T\textsubscript{1}) of (18a) was determined to be 1.08 seconds and the delay time for the nOE experiment was set at 8 seconds. A 4.1\% enhancement was observed between H₂ and H₃ of (18a) and a 0.5\% enhancement for the same protons of (18b) (fig. 2.1.7).

Fig. 2.1.7
While these experiments were being carried out (18a) was obtained in crystalline form suitable for X-ray analysis, which clearly depicts the cis relationship of the substituents at C2 and C3 (Appendix fig. 6.0).

2.1.3 Solvent effects

The effect of solvent on the rate and stereoselectivity of reaction was examined. As the reaction was occurring exclusively via a 1,5 exo process,\textsuperscript{135} it was likely that cyclization would be facilitated by the rapid formation of the intermediate selenonium ion (23) from the initial anti-Markovnikov adduct (22) (scheme 2.1.8). This should occur more rapidly in polar solvents\textsuperscript{42,48} and at higher temperatures.\textsuperscript{63}

![Scheme 2.1.8](image)

The carbamate (13) was subjected to the reaction conditions described in section 2.1.2 in dichloromethane for 4 hours to give a 3:1 mixture of (19a) and (19b) in high yield (table 2.1.9). Reaction initiated at 0\textdegree C using chloroform as solvent gave a 5:1 mixture of (19a) and (19b). Reaction using dioxane as solvent gave a similar yield and product ratio to that obtained using dichloromethane as solvent. When acetonitrile was used as solvent only starting materials were recovered. HPLC and t.l.c. analysis indicated that addition of phenylselenenyl chloride to the double bond had occurred, but as no cyclization ensued, the adducts formed had reverted to starting materials upon chromatography. Mercurinium and selenonium species such as (23) are known\textsuperscript{136} to chelate to nitriles, which may result in a less electrophilic carbon adjacent to selenium and hence a less reactive intermediate.
2.1.4 Effect of the selenium reagent

The effect of a number of different selenium reagents on the mode of cyclization was investigated. When phenylselenenyl bromide was used in place of phenylselenenyl chloride the rate and stereoselectivity of reaction was enhanced (table 2.1.9). This result suggests that in polar solvents, better leaving group ability of the anion of the selenating reagent results in the rapid formation of the intermediate episelenonium ion (23), which presages stereoselective cyclization.

Table 2.1.9: Cyclizations of ethyl 4-hydroxy-5-pentenylcarbamte (13)

<table>
<thead>
<tr>
<th>Substrate</th>
<th>PhSeX</th>
<th>Reaction conditions</th>
<th>Product ratio 19a/19b (%) yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>X = Cl</td>
<td>CH₂Cl₂, a, 4h</td>
<td>75/25 (88)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CHCl₃, b, 30 min</td>
<td>85/15 (88)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>dioxane, b, 40 min</td>
<td>76/24 (83)</td>
</tr>
<tr>
<td>Br</td>
<td></td>
<td>CH₂Cl₂, a, 2 h</td>
<td>79/21 (95)</td>
</tr>
<tr>
<td>SO₄</td>
<td></td>
<td>CHCl₃, b, 20 min</td>
<td>87/13 (95)</td>
</tr>
<tr>
<td>Phth</td>
<td></td>
<td>CH₂Cl₂, a, 4 h</td>
<td>72/28 (84)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CH₂Cl₂, a, 48 h</td>
<td>No reaction</td>
</tr>
</tbody>
</table>

a = -78°C 10 min then to RT, b = 0°C 10 min then to RT.

Tiecco et al has reported⁴⁹ that the presence of nucleophilic halide ions is sometimes responsible for a decrease in stereoselectivity of selenium induced cyclizations. Alkyl phenyl selenides may also react with phenylselenenyl halides⁵⁷,¹³⁷ affording deselenation products and complex mixtures. It was thought the reagents phenylselenenyl sulfate⁴⁹ and phenylselenenyl phthalimide,²² which do not suffer from these complications may effect a greater stereoselectivity. However, when (13) was reacted with phenylselenenyl sulfate no increase in stereoselectivity was observed. Reaction with phenylselenenyl phthalimide gave only starting materials, although HPLC and t.l.c. analysis indicated that selenium containing intermediates had formed. It is possible that
the phthalimido group is too bulky to allow the approach of the neighbouring phenylseleno moiety, thus formation of the selenonium ion (23) is sterically hindered and cyclization cannot occur (scheme 2.1.10).

![Scheme 2.1.10](image)

2.1.5 Effect of hydrogen Bonding

The allylic hydroxyl group plays an important role in the stereoselective cis cyclization of 3-hydroxy-4-pentenamides,121,122 3-hydroxy-4-pentenoic acids114 and 4-pentene-1,3-diols.116 It has been proposed115,116 that a transition state characterized by an intramolecular hydrogen bonded six membered ring directs attack of the electrophile to the syn face of the double bond (scheme 2.1.11). Prohibition of this hydrogen bonding by protection of the allylic alcohol as an acetate116 or a benzyl ether138 resulted in a marked decrease in stereoselectivity.

![Scheme 2.1.11](image)

To determine if hydrogen bonding played a similar role in the selenium induced cyclizations, O-protected derivatives of (13) were synthesised. The acetate (24) was formed from reaction of (13) with acetyl chloride and the tert-butyldimethylsilyl ether (25) by reaction139 of (13) with tert-butyldimethylsilyl chloride. Reaction of the acetate (24) with phenylselenenyl bromide required two days and gave a 1:1 mixture of the diastereomers (27a cis) and (27b trans) (scheme 2.1.12). Clearly the rate and stereoselectivity of cyclization is considerably depressed upon protection of the allylic alcohol.
When the silyl ether (25) was reacted with phenylseleneny1 bromide a mixture of (19a) and (19b) in the ratio 2:1 was recovered. The presence of these alcohols suggested that the silyl ether (25) was being cleaved by hydrogen bromide formed as an adjunct to cyclization to the alcohol (13), despite the presence of potassium carbonate. The more robust \( t \)-butyldiphenylsilyl ether (26) was synthesised, as the TBDPS group is \( \sim 100 \) times more stable to acid hydrolysis than the TBDMS group.\(^{140}\) Reaction of (26) with phenylseleneny1 bromide for one hour gave a mixture of (28a \( cis \)) and (28b \( trans \)) in the ratio 3:2 in moderate yield (scheme 2.1.12). The greatly enhanced rate of cyclization of (26) compared to (24) may be attributed to the greater steric bulk of the TBDPS group which can induce the intermediate selenonium ion adduct to adopt the chair-like conformation required for cyclization.\(^{115,116}\)

2.1.5 Effect of the N-protecting group

The effect of various nitrogen protecting groups on the mode of cyclization was investigated (table 2.1.13).
Table 2.1.13: Selenium induced cyclization of N-protected 4-hydroxy-5-pentenylamines

<table>
<thead>
<tr>
<th>Substrate</th>
<th>PhSeX</th>
<th>Reaction conditions</th>
<th>Product ratio (yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>13</td>
<td>Cl</td>
<td>CH$_2$Cl$_2$, a, 4h</td>
<td>19a/19b 75/25 (88)</td>
</tr>
<tr>
<td></td>
<td>Br</td>
<td>CHCl$_3$, b, 20 min</td>
<td>87/13 (95)</td>
</tr>
<tr>
<td>15</td>
<td>Cl</td>
<td>CH$_2$Cl$_2$, a, 3 h</td>
<td>18a/18b 64/36 (83)</td>
</tr>
<tr>
<td></td>
<td>Br</td>
<td>CHCl$_3$, b, 20 min</td>
<td>72/28 (84)</td>
</tr>
<tr>
<td>14</td>
<td>Cl</td>
<td>CH$_2$Cl$_2$, a, 4 h</td>
<td>20a/20b 74/26 (56)</td>
</tr>
<tr>
<td></td>
<td>Br</td>
<td>CHCl$_3$, b, 20 min</td>
<td>88/12 (70)</td>
</tr>
<tr>
<td>17</td>
<td>Cl</td>
<td>CH$_2$Cl$_2$, a, 24 h</td>
<td>21a/21b 90/10c (21)</td>
</tr>
<tr>
<td></td>
<td>Br</td>
<td>CHCl$_3$, b, 1 h</td>
<td>&gt;99/&lt;1 (40)</td>
</tr>
</tbody>
</table>

a = -78°C 10 min then to RT, b = 0°C 10 min then to RT, c = determined by HPLC. none of the trans isomer could be isolated.

The carbamates (13) and (14) and the sulfonamide (15) were of comparable reactivity, the carbamates exhibiting slightly greater stereoselectivity of cyclization. Reaction of the amide (17) with phenylselenenyl chloride however, resulted in a much greater diastereomeric excess. When (17) was subjected to reaction with phenylselenenyl bromide in chloroform none of the trans isomer could be detected by HPLC or $^1$H n.m.r. analysis. The diasteromeric purity of the product (21a) was confirmed upon examination of the $^{19}$F n.m.r. spectrum of the trifluoroacetate derivative (29), formed by reaction of the crude isolate with trifluoroacetic anhydride (scheme 2.1.14). The spectrum showed only one peak at -0.63 ppm, corresponding to a single diastereomer. The trifluoroacetates (30a) and (30b), formed in an analogous manner from (20a) and (20b) were clearly resolvable by $^{19}$F n.m.r. at -0.32 and 2.34 ppm.
The reactivity towards selenium induced cyclization of the sulfonamides, carbamates and amides shows two general tendencies: the less acidic the NH the greater the yield and the greater the double bond character of the C-N bond of the protecting group the greater the stereoselectivity. The observed stereoselectivity may be attributed to the carbonyl of the protecting group influencing which face of the double bond is attacked by selenium. This hypothesis is proposed on the basis of molecular modelling studies using PC Model on the substrates (13), (15) and (17) and on their phenylseleno adducts (fig. 2.1.16). In all cases there is strong hydrogen bonding depicted between the hydroxyl proton and the nitrogen atom to form a six-membered ring. This interaction results in the protecting group on nitrogen shielding one face of the double bond and directs the subsequent selective stereofacial attack of selenium to this bond (scheme 2.1.15).
Molecular modelling of (17) and its reaction intermediate

Fig. 2.1.16

The dramatic stereospecific cyclization of the amide (17) is a consequence of restricted rotation about the C-N bond. The minimised energy profile from a dihedral drive about the C-N bond for (13), (14), (15) and (17) also gives insight into the rationale for the stereoselectivity (fig. 2.2.17). Compounds (13), (14) and (15) have a similar energy profile, however that of (17) is of much higher energy, reflecting the greater double bond character of this bond\(^{141}\), and there is a significant local minimum in which hydrogen bonding is seen between the hydroxyl proton and the oxygen atom of the amide. The calculations are not of sufficiently high order to discriminate between hydrogen bonding to the \(\pi\)-bond or
to the lone pair electrons of the carbonyl oxygen atom. However, given the dramatic difference in stereoselectivity between the carbamates, sulfonamide and amide, it is more likely this interaction is occurring through the $\pi$ electrons of the C-O bond, as the lone pair electrons of the oxygen atom are equally available for coordination in all these groups.

**Dihedral Drive About the C-N bond of (13),(14),(15) and (17)**

![Graph showing dihedral angle vs relative energy for compounds (13), (14), (15), and (17).](image)

**Fig. 2.1.17**

### 2.1.6 Attempted cyclization of amino $\alpha\beta$-unsaturated ketones

Phenylselenenyl chloride is known\(^{24}\) to add to $\alpha\beta$-unsaturated ketones. It was of interest to see if such adducts would undergo cyclization in the presence of an internal nucleophile. $\alpha\beta$- Unsaturated ketones such as (31) were best prepared via a Swern oxidation\(^{142}\) of the alcohol (13), other methods\(^{143,144}\) resulting in low
yields. Reaction of (31) with phenylselenenyl chloride or phenylselenenyl bromide in different solvents for several days gave only low yields of starting materials. HPLC and t.l.c. analysis indicated that addition of the selenium reagent to the double bond had occurred, but as no cyclization ensued, these adducts reverted to starting materials upon chromatography (scheme 2.1.18).

![Scheme 2.1.18](image-url)
2.2 Synthesis and cyclizations of N-protected 4-hydroxy-5-hexenylamines

2.2.1 Introduction and synthesis of starting materials

Whilst there have been many examples of the cyclization of N-substituted-3-hydroxy-4-pentenylamines using a variety of electrophilic reagents,\textsuperscript{90,117,118,121,122,138} 4-hydroxy-5-hexenylamines have proved comparatively unreactive.\textsuperscript{117,122} In the few cases in which cyclization has occurred\textsuperscript{117} product mixtures were obtained or the reaction occurred non-stereoselectively (scheme 2.2.1). Despite the fact that Tamaru\textsuperscript{122} has reported that N-protected 4-hydroxy-5-hexenylamines are unreactive towards phenylselenenyl chloride and phenylselenenyl phthalimide it was thought that cyclization of these compounds could be facilitated using the methodology established in Chapter 2.1.

\begin{equation}
\text{NBS or NIS or Br}_2 \quad \text{PhSePhth or Hg(OAc)}_2
\end{equation}

\begin{equation}
PdCl_2, CuCl, CO, AcOH
\end{equation}

\begin{equation}
\text{Hg(OAc)}_2, \text{NaBH}_4
\end{equation}

\begin{Scheme}
\text{Scheme 2.2.1}
\end{Scheme}
Synthesis of the amine (33) was accomplished following the literature procedure\textsuperscript{122} outlined in scheme 2.2.2.

\[
\text{CH}_3\text{CN, nBuLi} \xrightarrow{-78^\circ\text{C}} \text{N}
\]

Scheme 2.2.2

Mixed aldol condensation of the lithium salt of acetonitrile with butadiene monoxide at -78\(^\circ\)C occurred regioselectively to give the nitrile (32) in high yield. The nitrile was reduced with lithium aluminium hydride to give the amine (33), which was purified by distillation from a small amount of hydroquinone. The hexenylamine (33) was less stable and less reactive to nitrogen protection than the pentenylamine (12).

The carboxamides (35) and (36) were synthesised in a manner analogous to (13) and (14) by reaction of (33) under Schotten-Bauman conditions\textsuperscript{1} with ethyl chloroformate and BOC-ON respectively. The sulfonamide (37) was synthesised by reaction of (33) with tosyl chloride in pyridine. The amide (38) was synthesised via barium hydroxide mediated hydrolysis of the diacetate (39), formed from reaction of (33) with excess acetyl chloride (scheme 2.2.3).

2.2.2 Cyclization studies

When the sulfonamide (37) was subjected to reaction with phenylselenenyl chloride under standard conditions (\textit{vide supra}) the cyclization was shown by HPLC analysis to be extremely slow in comparison with the sulfonamide (15). Reaction for 48 hours gave a moderate yield of a mixture of the trans- and cis-substituted hydroxypiperidines (41a) and (41b) in the ratio 3:1 (scheme 2.2.4).
Reaction with phenylselenenyl bromide resulted in a similar yield of (41a) and (41b) in the ratio 5:1. The reaction appears to be under thermodynamic control and is slow because no hydrogen bonding between the hydroxyl proton and the nitrogen atom occurs. Such hydrogen bonding would require the formation of a thermodynamically unfavourable seven-membered ring.

The relative stereochemistry of these diastereomers was assigned on the basis of the coupling constants between $H_2$ and $H_3$. In the cis isomer (41b) $H_2$ appeared at 3.56 ppm (ddd) and $H_3$ at 4.09 ppm (dt) with $J_{2,3}$ of 3.7 Hz. In the trans isomer (41a)
H₂ appeared at 3.87 ppm (ddd) and H₃ at 4.43 ppm (dt) with J₂,₃ of 9.5 Hz. These coupling constants compare favourably with the values calculated by application of the Karplus equation to the energy minimised structures of (41b): H₂H₃ 3.7Hz and (41a): H₂H₃ 8.7Hz. The assigned stereochemistry was confirmed by a series of nOE experiments in which a 13.7% enhancement was seen between the protons H₂ and H₃ of (41b), and only a 2.6% enhancement for the same protons of (41a).

Treatment of the carbamate (35) with phenylselenenyl chloride gave a mixture of (40a) and (40b) in the ratio 3:1 in moderate yield (scheme 2.2.5).

![Scheme 2.2.5](image)

Attempts to induce cyclization of the tert-butylcarbamate (36) with phenylselenenyl bromide or phenylselenenyl chloride in a variety of solvents proved fruitless. Selenium containing intermediates could be isolated but none of the desired cyclized product was observed. Phenylselenenyl phthalimide has been reported to cyclize tert-butyl carbamates with no complications, however reaction of (36) with this reagent gave none of the cyclized product.

### 2.2.3 Structure elucidation of stable hydrates

Upon extended reaction times formation of (40a) and (40b) was accompanied by the appearance of a more polar, crystalline solid. The solid was formed over a period of days upon exposure of the isolated selenides (40a) and (40b) to THF/water, and within hours upon addition of silica gel to this reaction medium. Mass spectral analysis of this product revealed a molecular ion at 361 m/z, corresponding to (40) [343 m/z] plus water. The ¹H n.m.r. spectra of the solid showed it to be a 3:1 mixture of two diastereomers, hence the solid was recrystallized to give a product of high diasteromeric purity (48). The ¹³C n.m.r. of (48) was similar to that of (40a); the corresponding resonances lying within 0-4 ppm of each other. The original
diastereomeric mixture was converted to the 2-methyl piperidines (45a) and (45b) by reduction with nickel boride²⁹ (scheme 2.2.6), a more efficient method than reduction with tributyltin hydride.⁵⁹

\[
\text{unknown solid} \xrightarrow{\text{NiCl}_2, \text{NaBH}_4, \text{THF, MeOH}} (45a), (45b)
\]

Scheme 2.2.6

This result, and the similarity of the \(^{13}\text{C}\) n.m.r. spectra of (48) and (40a) suggested that the water was not covalently bound to the carbon skeleton of the hydroxypiperidine and that (48) was in fact a stable hydrate. Three possible structures for this hydrate were considered (fig. 2.2.8). It could result from inclusion of water between the hydroxyl group and the selenium atom (46), between the selenium atom and the carbonyl of the carbamate (47), or between the hydroxyl group and the carbonyl of the carbamate (48).

![Fig. 2.2.8](image)

Tomoda¹⁴⁶ has cited a significant through space coupling between \(^{77}\text{Se}\) and the benzylic protons of diselenocin (49) as evidence for a H...Se hydrogen bond.

Although the H...O hydrogen bond occurs widely in organic compounds in both the solid state¹⁴⁷ and in solution,¹⁴⁸ diselenocin is the only case in which a H...Se hydrogen bond has been observed. If the water molecule of the hydrate was bonded to the selenium atom as depicted in structures (46) and (47) then it should
be possible to observe through space coupling between a proton of the water molecule and selenium in the $^77\text{Se}$ spectrum of (48). The $^77\text{Se}$ spectrum of (48), run without $^1\text{H}$ broad band decoupling, gave a poorly resolved signal at 260 ppm with a width at half height ($\omega_{1/2}$) of 28 Hz; typical for a selenium atom bonded to a methylene group.\textsuperscript{149} Attempts to improve the resolution of the spectrum by running the n.m.r. at -50°C with increased digitization were unsuccessful. When the $^77\text{Se}$ n.m.r. was acquired with $^1\text{H}$ broad band decoupling $\omega_{1/2}$ narrowed to 8 Hz. However, this is most likely due to the loss of through bond $^2J$ coupling to the methylene protons adjacent to selenium and does not constitute unequivocal evidence for any through space coupling to a proton of water.

The $^1\text{H}$ n.m.r. spectra of (48) (fig. 2.2.9, table 2.2.11) showed hydroxyl protons at 4.86ppm as a triplet, 3.00ppm as a triplet and 1.9ppm as a triplet. None of these resonances correlated with any carbon atom in the HETCORR spectrum of (48) and all disappeared when the $^1\text{H}$ n.m.r. spectrum was run in d$_4$-methanol (fig. 2.2.10). The $^1\text{H}$ n.m.r. spectrum run in deuterochloroform showed the protons H$_{7a}$ and H$_{7b}$ at 3.92 ppm as the AB portion of an ABMX system. This resonance collapsed to the AB portion of an ABX system upon irradiation of the hydroxyl at 3.00 ppm (table 2.2.12). The COSY45 spectrum of (48) (fig. 2.2.13) showed coupling between this hydroxyl resonance and both H$_{7a}$H$_{7b}$ and H$_3$. These couplings implied that resonance at 3.00 ppm was due to the hydroxyl proton at C$_3$ (ROH) and that H$_{7a}$ or H$_{7b}$ was coupled to ROH either through space, or long range through five $\sigma$-bonds and a hetero-atom! The protons H$_{6a}$ and H$_{6b}$ appeared as a broad doublet of triplets which collapsed to a broad triplet upon irradiation of the hydroxyl at 4.86 ppm (OH$_a$). As the water molecule was not covalently bound to the piperidine skeleton this implied that there was scalar through space coupling between OH$_a$ and either H$_{6a}$ or H$_{6b}$. Upon D$_2$O exchange OH$_a$ remained unchanged, the resonance at 1.9 ppm (OH$_b$) disappeared and ROH shifted ~2 ppm downfield. This result, and the relative chemical shifts of the hydroxyl resonances (OH$_a$>ROH>OH$_b$), suggested that OH$_a$ and to a lesser degree ROH were strongly hydrogen bonded\textsuperscript{211} to the piperidine, and OH$_b$ only weakly so.
Chapter 2.2

The d$_4$-methanol spectrum of (48) gave great insights into the nature of hydrogen bonding in the hydrate. In d$_4$-methanol, H$_7$$_a$ and H$_7$$_b$ appeared as the AB portion of an ABX system at 3.89 and 3.77 ppm respectively and H$_6$$_a$ and H$_6$$_b$ appeared as a broad triplet at 3.10 ppm. This spectrum, when compared to the spectrum run in deuterochloroform confirmed the existence of coupling between H$_6$$_a$ or H$_6$$_b$ and OH$_a$, and between H$_7$$_a$ or H$_7$$_b$ and ROH. These couplings could be clearly seen in the COSY45 spectrum of (48) (fig. 2.2.13). An expansion of the OH$_a$H$_6$$_a$H$_6$$_b$ cross peak in the DQF-COSY spectrum of (48), revealed that OH$_a$ was coupled to H$_6$$_a$, but not to H$_6$$_b$ (fig. 2.2.14).
Table 2.2.11: $^1$H N.m.r. data for (48)

<table>
<thead>
<tr>
<th></th>
<th>CDCl$_3$</th>
<th>CD$_3$OD</th>
<th>Correlation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\delta$</td>
<td>mult</td>
<td>J (Hz)</td>
</tr>
<tr>
<td>H$_2$</td>
<td>3.28</td>
<td>ddd</td>
<td>3.3, 5.0, 1.4</td>
</tr>
<tr>
<td>H$_3$</td>
<td>3.97</td>
<td>m</td>
<td>—</td>
</tr>
<tr>
<td>H$_6$a</td>
<td>3.20</td>
<td>m*</td>
<td>—</td>
</tr>
<tr>
<td>H$_6$b</td>
<td>3.20</td>
<td>m*</td>
<td>—</td>
</tr>
<tr>
<td>H$_7$a</td>
<td>3.92</td>
<td>m#</td>
<td>—</td>
</tr>
<tr>
<td>H$_7$b</td>
<td>3.92</td>
<td>m#</td>
<td>—</td>
</tr>
<tr>
<td>ROH</td>
<td>3.00</td>
<td>t</td>
<td>6.1</td>
</tr>
<tr>
<td>OH$_a$</td>
<td>4.86</td>
<td>t</td>
<td>6.3</td>
</tr>
<tr>
<td>OH$_b$</td>
<td>1.9</td>
<td>s</td>
<td>—</td>
</tr>
</tbody>
</table>

* H$_6$a H$_6$b appear as broad dt (6.3, 6.9Hz)  # AB portion of ABMX system

Table 2.2.12: $^1$H decoupling and resultant multiplicities for protons of (48)

<table>
<thead>
<tr>
<th>proton</th>
<th>irradiation @ H$_x$: multiplicity, J (Hz)</th>
<th>proton</th>
<th>irradiation @ H$_x$: multiplicity, J (Hz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>H$_2$</td>
<td>H$_7$a H$_7$b: d, 1.4</td>
<td>H$_7$a</td>
<td>ROH: dd, 11.3, 9.3</td>
</tr>
<tr>
<td>H$_3$</td>
<td>m</td>
<td>H$_7$b</td>
<td>ROH: dd, 11.3, 5.0</td>
</tr>
<tr>
<td>H$_6$a H$_6$b</td>
<td>OH$_a$: br t, 6.9</td>
<td>OH$_a$</td>
<td>H$_6$a: s</td>
</tr>
</tbody>
</table>
Fig 2.2.13: COSY45 spectrum for (48)
Fig. 2.2.14: DQF-COSY spectrum for (48)
The NOESY spectrum of (48) indicated spatial proximity between OH₁ and H₆, but none between ROH and H₇ (fig. 2.2.15). This result, together with molecular modelling studies of the hydrate suggested that the scalar coupling between OH₁ and H₆ was through space and that between OH and H₇ was through bond. From an energy minimisation of the proposed structure for the hydrate (fig. 2.2.16) in which the water molecule is hydrogen bonded to the carbonyl oxygen and the hydroxyl oxygen it can be seen that OH₁ is in close proximity to H₆, but OH is spatially distant from H₇ and H₇b.
During the course of these studies the tert-butyldiphenylsilyl ether (43) was synthesised\textsuperscript{139} from the alcohol (37) in an attempt to increase the amount of \textit{trans} isomer formed from a cyclization under thermodynamic control. Reaction of (43) with phenylselenyld chloride however, gave an inseparable mixture of the hydrates (44a) and (44b) in low yield in the ratio 3:1 (scheme 2.2.17). It is possible that the silyl ethers (44a) and (44b) can form stable hydrates, whereas the alcohols (41a) and (41b) cannot, because the steric bulk of the TBDPS group induces some kind of conformational change in the molecule enabling water to hydrogen bond effectively to both the oxygen and selenium atoms. The $^1$H n.m.r., COSY 45 and HETCORR spectra of (44a) provided corroborating evidence for the general
structure for the hydrates proposed above. The hydroxyl proton, OH_\text{a} of (44a) appeared as a triplet (6.2Hz) at 4.44ppm and OH_\text{b} as a singlet at 2.03ppm. These multiplicities and chemical shifts are comparable to those observed for the same protons of (48). The protons H_7\text{a} and H_7\text{b} of (44a) appeared as the AB portion of a simple ABX system at 3.90 and 3.82ppm as in the case of this silyl ether, they are not further split by a hydroxyl proton at C_3. The fact that (44a) and (44b) can form stable hydrates indicates that hydrogen bonding of the water molecule is occurring to the oxygen atom and not the proton of the hydroxyl group.

\[
\begin{align*}
\text{NH} \quad \text{SO}_2\text{Tol} & \quad \text{OTDBPS} \\
\text{PhSeCl} & \quad \text{PhSe} \\
\text{(43)} & \quad \text{(44a)} + \text{(44b)}
\end{align*}
\]

**Scheme 2.2.17**

Reaction of the amide (38) with phenylselenenyl chloride gave a mixture of the hydrates (42a) and (42b) in moderate yield in the ratio 3:1 (scheme 2.2.18). The mixture could be recrystallized to give (42a) as a single diastereomer. The formation of a stable hydrate was most facile with the amide (38), slow with the carbamate (35) and did not occur with the sulfonamide (37). The ability of these compounds to include water follows a general trend in accordance with the rotational barrier about the C-N and SO_2-N bonds.\(^{141}\) The more double bond character the C-N bond of the protecting group possesses, the more likely it is that the compound will include water. This observation supports the hypothesis that the inclusion of water involves hydrogen bonding to the carbonyl or sulfonyl moiety of the protecting group. Although all of the hydrates were solids none were suitable for X-ray crystallographic analysis, however all gave microanalytical data consistant with the structures proposed.
When the substituted hydroxypyrrolidines (18a) and (19a) were reacted with THF/water in the presence of silica gel only starting materials were recovered (scheme 2.2.19). Molecular modelling studies of (18a) and (19a) suggest that the interatomic distance between the hydroxyl group and the oxygen of the carbonyl group is too small in these cases to allow coordination of water to both atoms, thus no hydrates are formed.

2.2.4 Cyclization of 4-hydroxy-4-methylhex-5-enamines

Substitution at the allylic position of compounds such as (36) has been reported\textsuperscript{122} to increase the efficacy of cyclization reactions. Accordingly the tert-butylcarbamate (53) was synthesised following the procedure outlined in scheme 2.2.20. Reaction\textsuperscript{150} of isoprene with N-bromosuccinimide gave a mixture of bromohydrins which were converted directly to the epoxide (50) upon treatment with aqueous base. The epoxide (50) was selectively opened at the least hindered
position with the lithium salt of acetonitrile at -78°C to give the nitrile (51) which was reduced with lithium aluminium hydride to give the amine (52) in good yield. Reaction of (52) with BOC-ON and triethylamine in dioxane/water gave the tert-butylcarbamate (53); a method superior to reaction under Schotten-Bauman conditions\textsuperscript{1} or reaction with diterbutylidicarbonate.\textsuperscript{151}

The carbamate (53) underwent clean cyclization with phenylselenenyl chloride to give a mixture of (54a) and (54b) in the ratio 3:1 in good yield (scheme 2.2.21). The relative stereochemistry of the major diastereomer in this case was assigned on the basis of a series of nOE experiments in which a 0.5% enhancement was seen between the methyl protons and H2. Enhancements of 5.2% and 5.6% were seen between the methyl protons and the diastereotopic protons H7\textsubscript{a} and H7\textsubscript{b}. Energy minimizations of the structures (54a) and (54b) using PC Model confirmed that the major, trans isomer, (54a) was more stable than the minor, cis isomer, (54b) which is consistent with the reaction being under thermodynamic control.

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure}
\caption{Scheme 2.2.20}
\end{figure}

\begin{figure}
\centering
\includegraphics[width=\textwidth]{figure}
\caption{Scheme 2.2.21}
\end{figure}
2.3 Conversion of alkylphenyl selenides to alcohols.

2.3.1 Substitution reactions of alkyl phenyl selenides

Elaboration of the selenides described in sections 2.1 and 2.2 to the biologically active compounds depicted in section 2.0 required a methodology to convert the primary phenylseleno residue to a primary alcohol. Only one example of such a transformation, via an intermediate selenone, has been reported\textsuperscript{152} in the literature, and the general applicability of this reaction has not been investigated (scheme 2.3.1).

\[
\text{CH}_3(\text{CH}_2)_8\text{CH}_2\text{Se-Ph} \xrightarrow{\text{THF, KOH, } \Delta} \text{CH}_3(\text{CH}_2)_8\text{CH}_2\text{-OH}
\]

Scheme 2.3.1

The conversion of alkylphenylselenides to alkyl halides however, has been widely studied. Selenonium halides, formed from the corresponding selenides by the action of alkyating or oxidizing agents\textsuperscript{153,154,158} have been known since the late 19th century. Recently Krief\textsuperscript{34,35} and others\textsuperscript{36-38,155} have reported a number of procedures which convert selenides to the corresponding halides via the intermediacy of selenonium halides under mild conditions (scheme 2.3.2).

\[
\begin{align*}
\text{R} \quad \text{R'} \quad \text{SePh} & \quad \xrightarrow{\text{R, R', R''}} \quad \text{[R \quad R' \quad \text{SePh}]} \\
& \quad \xrightarrow{\text{X}} \quad \text{[R \quad R' \quad \text{X}]} \\
& \quad \xrightarrow{\text{R''}} \quad \text{R \quad R' \quad X}
\end{align*}
\]

Scheme 2.3.2

It was thought that the selenide (63), used as a model compound for these studies, may be converted via a selenonium halide to the bromide (66), which could be hydrolysed to the alcohol (67) (scheme 2.3.3).
Synthesis of the selenide (63) was initially accomplished starting with 5-bromopentene (scheme 2.3.4). Reaction\(^\text{266}\) of this bromide with freshly prepared\(^\text{156}\) potassium phthalimide gave a good yield of the phthalimide (60), which was deprotected\(^\text{157}\) with hydrazine hydrate in refluxing ethanol. The ethereal extracts containing the amine (61) were reacted directly with ethyl chloroformate in the presence of triethylamine to give the carbamate (62) which was cyclized\(^\text{69}\) with phenylselenenyl chloride to afford the selenide (63) in good yield.

A more efficent synthesis was achieved from the commercially available S-(+)-hydroxymethylpyrrolidine (scheme 2.3.5). Whilst awaiting delivery of this reagent, trial reactions for this route were carried out on the inexpensive racemic hydroxymethylpiperidine. Reaction\(^\text{158}\) of this amino alcohol with gaseous hydrogen bromide and thionyl chloride to give the chloride (70) proved superior to other methods.\(^\text{159}\) The chloride (70) was reacted with phenylselenide anion to give the selenide (71), which was treated with ethyl chloroformate under Schotten-Bauman conditions to give the carbamate (72). Hydroxymethylpiperidine could be
converted directly to the selenide (71) by reaction with phenylselenenyl phthalimide and tributylphosphine (scheme 2.3.5). In an analogous manner S-(+)-hydroxymethylpyrrolidine was protected as the ethyl carbamate (68) then converted to the selenide (69).

\[ \text{PhthSePh} + \text{nBu}_3\text{P} \rightarrow \text{EtOCOCl} + \text{NaOH}_{(aq)} \rightarrow \text{CO}_2\text{Et} \]

(71) (72)

When (63) was reacted under the conditions of Morella\(^{38}\) using bromine and tetrabutylammonium bromide only low yields of the desired alkybromide (66) were obtained, despite numerous variations to the reaction conditions. Morella has reported\(^{160}\) the formation of the trifluoroacetate (73) from reaction of the selenide (72) with hydrogen peroxide and trifluoroacetic acid in refluxing carbon tetrachloride. It was thought the desired alcohol (67) could be formed from hydrolysis of such an acetate (scheme 2.3.6). However reaction of the selenide (63) using the conditions described above gave only the unstable selenoxide (64) (\textit{vide infra}) and the starting selenide. The hydrogen peroxide used in this reaction was quite old and it is possible that with fresh hydrogen peroxide under the vigorous conditions employed by Morella the selenide (72) was, at least in part, being oxidized to the corresponding selenone, which then underwent substitution with trifluoroacetic acid. Sharpless has proposed\(^{32}\) the intermediacy of a selenone in the conversion of the lauryl phenyl selenide to lauryl acetate using hydrogen peroxide in refluxing acetic acid (scheme 2.3.6).
2.3.2 Substitution reactions of alkyl phenyl selenones

Formation of alkyl phenyl selenones from oxidation of the corresponding selenides has been achieved using pertrifluoroacetic acid\textsuperscript{161,162} or MCPBA.\textsuperscript{162} Krief has reported\textsuperscript{162} the conversion of decyl phenyl selenide to decyl alcohol by reaction with MCPBA and potassium hydroxide in refluxing THF. When (63) was subjected to these reaction conditions the alcohol (67) was formed, but in only 40\% yield (scheme 2.3.7).
Reaction using tetrabutylammonium hydroxide in place of potassium hydroxide also gave low yields of (67) and reaction using water gave a mixture of the alkene (75) and the ring opened ketone (76) resulting from elimination of the intermediate selenoxide (64) (scheme 2.3.8). Reaction in a mixture of acetic acid and water also gave low yields of (67), accompanied by starting material.

![Scheme 2.3.8](image)

As the yield of (67) was dependent upon the yield of the selenone (65), the conditions for the formation of (65) were optimized by using $^{77}\text{Se}$ n.m.r. analysis. When the oxidation of (63) with MCPBA was carried out in an n.m.r. tube using a number of different solvents it was possible to determine the rate of formation of (65) by examination of the timed $^{77}\text{Se}$ n.m.r. spectra. Using THF as solvent the starting selenide (63), which appeared at 267 ppm, oxidized rapidly to the selenoxide (64), at 850 ppm, which then slowly oxidized to the selenone (65), at 988 ppm (scheme 2.3.9). These resonances were assigned by comparison with literature values$^{9,163,149,164}$ and from the $^{77}\text{Se}$ n.m.r. spectra of the isolated compounds.

![Scheme 2.3.9](image)
$^{1}$H n.m.r. studies of the oxidation of the selenide (18a) to the selenone (99) using MCPBA in deuterochloroform also showed rapid conversion of the selenide to the corresponding selenoxide, then slow conversion over a period of 24 hours to the selenone. The diastereotopic protons of (99) were shifted 0.5-1.2 ppm downfield relative to those of (18a) (fig. 2.3.9) due to deshielding by the adjacent oxygen atoms of the selenonyl group.

The type of solvent employed in the oxidations of (63) had a marked effect upon the rate of formation of the selenone. Generally the rate was much slower in aprotic solvents compared to protic solvents. When log of the time taken for complete conversion of (63) to (65) (log t) was plotted against the dielectric constant of the solvent (a crude measure of solvent polarity) an almost log linear relationship was seen for the protic solvents (fig. 2.3.10).
Fig. 2.3.10: Log (t_min) vs dielectric constant for the formation of (65) from (63) using MCPBA in various solvents

When the oxidation was carried out using an alcohol as solvent a peak at 1215 ppm appeared after formation of the selenone(65). This resonance formed most rapidly with methanol or ethanol as solvent, and slowly with isopropyl alcohol or tert-butanol. It did not appear at all with non-nucleophilic solvents. Examination of the products formed from these reactions revealed that substitution of the selenonyl moiety with the alcohols was occurring to afford alkyl ethers. This was most facile when methanol was used as solvent. The resonance at 1215 ppm corresponds\textsuperscript{9,165} to that of benzeneseleninic acid, which is formed upon substitution of the selenonyl moiety. Reaction of the selenide and excess
MCPBA in methanol at room temperature for 90 minutes afforded a 87% yield of the methoxy ether (77). Similar reaction in ethanol gave the ethoxy ether (78) in 60% yield. It is possible that this substitution was being effected via anchimeric assistance of the neighbouring carboxy group (scheme 2.3.11).

\[
\begin{align*}
\text{NCO}_2\text{Et} & \xrightarrow{\text{MCPBA}} \text{NCO}_2\text{Et} \quad \text{PhSeO}_2\text{H} \\
\text{NCO}_2\text{Et} & \xrightarrow{\text{ROH}} \text{NCO}_2\text{Et} + \text{PhSeO}_2\text{H}
\end{align*}
\]

(63) (77) R=Me (78) R=Et

Scheme 2.3.11

Alternatively Uemura\textsuperscript{166} has proposed that MCBA or MCPBA itself catalyses the formation of species such as (79) in which the phenylselenenium group acts as a much better leaving group than the phenylselenonyl group, due to the electron withdrawing ability of the aryl ester (scheme 2.3.12). This mechanism is in accordance with the observation of Krief\textsuperscript{152} that decyl phenyl selenone reacts with methanol to give decyl methyl ether only upon the addition of MCPBA to the reaction media. The sulfonamide (80), prepared from reaction of the amine (252) with tosyl chloride in pyridine, was also converted cleanly to a methoxy ether (81) upon treatment with MCPBA in methanol. This result clearly discredits the hypothesis that the substitution is being effected by anchimeric assistance of the protecting group as this is unlikely in the case of the sulfonamide due to the geometry of the S=O bonds.
From the $^{77}\text{Se}$ n.m.r. studies the optimum conditions for oxidation of (63) alkyl phenyl selenide to (65) were found to be reaction with three equivalents of MCPBA in isopropyl alcohol or DMF for 1-2 hours at room temperature. Attempted formation of the selenone (65) using OXONE® in ethanol/water gave only the selenoxide (64) and a small amount of the alcohol (67). The alcohol (67) could be obtained in 78% yield from reaction of (63) with MCPBA for one hour, followed by treatment with aqueous sodium hydroxide for four hours at room temperature. If the base and MCPBA were added simultaneously, lower yields of (67) were accompanied by formation of the alkene (75) and ketone (76) resulting from elimination of the intermediate selenoxide. Using these conditions the optically active selenide (69) was converted cleanly back to the alcohol (68) without any loss of optical activity. The alcohol (67) could also be formed in good yield by reaction with MCPBA in DMF at room temperature for 2 hours, then heating the mixture with water at 80°C for two hours.

When the selenide (63) was treated only with MCPBA using isopropyl alcohol or DMF as solvent the selenone (65) could be isolated as a crystalline solid suitable for X-ray analysis (Appendix fig. 6.4). The diastereotopic protons $H_{6a}$ and $H_{6b}$ of (65) appeared as doublets of doublets at 4.10 and 3.69 ppm in the $^1\text{H}$ n.m.r. spectra, as compared to 3.21 and 3.03 ppm for the same protons of (64) and 2.88 and 2.73 ppm for those of (63). The infrared spectrum of (65) showed characteristic Se=O absorptions$^{167}$ at 910 and 890 cm$^{-1}$. The selenone (65) gave a molecular ion...
under fast atom bombardment conditions and a fragmentation corresponding to loss of PhSeO₂.

Formation of (65) was accompanied by significant amounts of the alcohol (67), and the ester (82) if extended reaction times were employed (scheme 2.3.13). It is not clear if (67) arises from direct attack of adventitious water on the selenonyl group or if a selenone-seleninate rearrangement takes place. Commercial MCPBA contains 3-5% water, however yields of the alcohol of up to 32% were obtained using recrystallized MCPBA and dry DMF in the presence of 4 Å sieves under argon. This suggests that the rearrangement process is more likely.

![Scheme 2.3.13](image)

**Scheme 2.3.13**

It was also possible to isolate small amounts of the vinyl selenone (84) from reactions involving the oxidation of (63) (scheme 2.3.14). The structural identification of (84) was not straight-forward as the compound was only isolated in minute amounts and gave no molecular ion under conditions of electron impact or fast atom bombardment. Fragmentations were seen corresponding to M-O (weak), M-O₂ (weak), M-Se(O)₂Ph and PhthCH₂. The ¹H n.m.r. resonances of (84) were assigned by a COSY 90 experiment. The protons H₁aH₁b appeared at 3.72 ppm (t) coupled to H₂aH₂b, which appeared at 1.91 ppm (quintet). H₃aH₃b appeared at 2.42 ppm (dt), H₄ at 7.20 ppm (dt) and H₅ at 6.72 ppm (d). Significantly the olefinic protons further from the selenium atom appeared downfield from those adjacent to selenium. The ¹³C n.m.r. spectra, interpreted with the aid of a HETCORR experiment, showed a similar effect for the carbons attached to these protons. This observation supported a vinyl selenone structure, as deshielding of the β-position occurs in αβ-unsaturated systems in which the α-position is substituted with oxygen. The ortho protons of the phenyl ring were also shifted.
downfield and showed splitting characteristic of a phenylselenone and the infrared spectrum showed a characteristic Se=O absorption at 900 cm$^{-1}$.$^{167}$ The vinyl selenone (84) was probably formed by oxidative elimination of the selenide (83), which resulted from addition of phenylselenenyl chloride to contaminating residual amounts of the alkene (60). Reaction of the alkene (60) with phenylselenenyl chloride followed by oxidation with MCPBA in the presence of base gave material identical to (84) (scheme 2.3.14).

![Scheme 2.3.14](image-url)
Chapter 2.4

2.4 Synthesis of polyhydroxylated alkaloids via nucleophilic displacement of the phenylselenonyl moiety

With an efficient methodology for the transformation of a phenylseleno moiety to an alcohol established, the selenides formed in sections 2.1 and 2.2 could be elaborated to a wide variety of biologically active compounds. The cis pyrrolidine (20a) was converted to the cis diol (85) in good yield by reaction with MCPBA and sodium hydroxide. The diol (85) was protected as its disilyl ether (86) by reaction with tertbutyldimethylsilyl chloride (scheme 2.4.1).

![Scheme 2.4.1](image)

Compounds such as (85) and (86) are useful templates for the synthesis of a variety of alkaloids. The disilyl ether (86) has been oxidized with platinum under oxygen to β-hydroxyproline, and converted via an aldol condensation of a chiral enolate ester on the aldehyde (87) to (-) detoxinine. The aldehyde (87) has also been elaborated to a hydroxyindolizidine. The disilyl ether (86) has been oxidized with ruthenium(VIII) oxide to the lactam (88), which was converted to 3-hydroxyglutamic acid, an amino acid component of the peptide antibiotic S-520 (scheme 2.4.2).
Reaction of the trans piperidine (41a) with MCPBA and sodium hydroxide gave good yield of a solid which was at first assumed to be the diol (89). However mass spectral and microanalytical data indicated the compound had the molecular formula C_{13}H_{17}NSO_{3}, equivalent to the diol (89) minus water. The protons and carbons adjacent to oxygen appeared further downfield in the n.m.r. than the values expected by analogy with compounds similar to (89) in the literature.\textsuperscript{123} These observations are consistent with the bicyclic structure (91) in which the
selenonyl moiety has been displaced by intramolecular attack of the hydroxyl group to form an oxetane ring (scheme 2.4.3). The solid was obtained in crystalline form suitable for X-ray analysis, which depicts the cis-fused [4.2.0] bicyclic structure proposed for (91).

Scheme 2.4.3

The formation of a cis-fused oxetane from a trans-substituted hydroxypiperidine was most unusual. Intramolecular attack of the alcohol on the selenonyl moiety is possible for the trans-piperidine (41a) if the ring adopts a boat conformation, however this would lead to a highly strained trans fused product and the X-ray structure of (91) clearly shows a cis-fused ring junction. It is possible that following oxidation of the selenide (41a) to the corresponding selenone, attack of the hydroxy group on selenenium had resulted in the formation of a trans-fused [4.3.0] bicyclic intermediate (scheme 2.4.4). Attack of hydroxide ion at the position α to the selenium would then give a primary alcohol and result in transfer of the selenonyl moiety to the secondary hydroxyl group. Intramolecular attack of the primary hydroxyl at C3 can then occur with inversion of configuration to give the oxetane (91).
Alternatively, the trans-piperidine may interconvert to the cis-piperidine via a base catalysed ring opening. Sulfonylmethyl substituted tetrahydropyrans are known\textsuperscript{172,173} to undergo isomerization in the presence of base by an elimination-addition sequence (scheme 2.4.5).

In an analogous manner it is possible that removal of the acidic proton adjacent to the selenonyl moiety would give a vinyl selenone with a negative charge stabilized by the electron deficient nitrogen of the sulfonamide (scheme 2.4.6). This species can then cyclize onto the vinyl selenone to give both the cis and trans piperidines (90b) and (90a). The cis piperidine (90b) can convert irreversibly to the oxetane (91) via an intramolecular substitution, whereas the trans piperidine (90a) can only react to interconvert back to a mixture of the cis and trans isomers once again. In this manner the trans-seleno piperidine (41a) is converted completely to the oxetane (91).
To test which of these hypotheses was correct, attempts were made to synthesise the selenides (92a) and (92b). It was thought that (92b) could be readily formed from reaction of the anion of bis-phenylselenomethane (94) with cyclohexene oxide (scheme 2.4.7), however this gave only phenylselenobutane and toluene, indicating that the anion was not sufficiently reactive to open the epoxide.

\[
\begin{align*}
\text{CH}_2\text{C}_2 & \xrightarrow{\text{NaBH}_4, (\text{PhSe})_2} \text{EtOH} \quad (\text{PhSe})_2\text{CH}_2 \\
& \xrightarrow{\text{i) } \text{nBuLi, } -78^\circ \text{C} \quad \text{ii) } \text{cyclohexene ox}} \\
& \quad \text{(94)} \quad \text{(92b)}
\end{align*}
\]

Scheme 2.4.7

An alternative synthesis involved reduction of the ketone (96) prepared by reaction of the silyl enol ether (95) with phenylselenochloromethane (97) and titanium (IV) chloride at low temperature. These conditions proved superior to those using bis-phenylselenomethane as the selenating reagent, or with zinc bromide or stannic chloride as the Lewis acid. Reduction of (96) with lithium aluminium hydride was carried out at low temperature to prevent deselenation occurring, and gave a mixture of the alcohols (92a) and (92b) in the ratio 9:1 (scheme 2.4.8). Reductions of α-seleno carbonyl compounds with lithium...
aluminium hydride are generally cis-stereoselective as the organometallic reagent approaches the carbonyl centre from the least hindered face opposite the phenylseleno moiety. The relative stereochemistry of the two alcohols was assigned on the basis of nOe experiments in which a 10.9% enhancement was seen between the protons H₁ and H₂ of (92a), and only a 1.6% enhancement between the same protons of (92b). Reaction of (92a) with MCPBA for one hour, then with 10% sodium hydroxide for one hour gave a modest yield of the oxetane (98). In stark contrast similar reaction of (92b) and MCPBA and base gave the diol (93). These results suggest that formation of the cis-fused oxetane (91) from the trans-selenide (41a) was in fact occurring via the mechanism outlined in scheme 2.4.6. If formation of this oxetane was occurring via transfer of the selenonyl group as suggested in scheme 2.4.4 then both (92a) and (92b) would be expected to afford oxetanes upon treatment with MCPBA and base. Only the cis-selenide (92a) forms an oxetane because there is no electron acceptor present in the six-membered ring of (92b) to facilitate a base catalysed isomerization of a trans selenone to the cis selenone as was the case with the piperidin (41a).

\[
\text{Me}_3\text{SiCl TiCl}_4, \text{PhSeCH}_2\text{Cl} \xrightarrow{\text{CH}_2\text{Cl}_2, -23\degree\text{C}} \text{OSiMe}_3
\]

(95)  (96)

\[
\text{LiAlH}_4, \text{Et}_2\text{O, -15\degreeC} \xrightarrow{} \text{OH} \text{SePh}
\]

(96)  (92a)  (92b)

\[
\text{H} \xrightarrow{i) \text{MCPBA}} \text{H}
\]

(98)  (93)

Scheme 2.4.8
Chapter 3

Intemolecular and intramolecular substitution reactions of alkyl phenyl selenones

3.0 An introduction to the chemistry of selenones

Although sulfones have been widely studied and proven very useful in organic synthesis, relatively little is known\textsuperscript{12,159} about their chalcogen relatives, the selenones. A few papers, most of them belonging to the older literature, have described the synthesis and isolation of diaryl\textsuperscript{177-179} aryl alkyl\textsuperscript{180,161} and dialkyl selenones\textsuperscript{181}. However, access to these compounds is often limited to specific cases dictated by the high reactivity of the corresponding selenoxides\textsuperscript{182}. Recently selenones have been postulated as intermediates in a number of valuable synthetic transformations (scheme 3.0). Alkyl phenyl selenides have been converted to dialkyl ethers upon treatment with MCPBA in alcoholic solvents\textsuperscript{166} and treatment of primary \( \beta \)-hydroxy alkyl phenyl selenides with excess MCPBA afforded epoxides in good yield\textsuperscript{183a}. Low yields of epoxides were obtained upon addition of potassium hydroxide to an aryl vinyl selenone\textsuperscript{184}. Oxidation of the ethylene acetals of aryl 1-phenylselenoethyl ketones was accompanied by aryl migration to yield 2-aryl propanoic acids\textsuperscript{183b}. Vinyl selenones have been converted to cyclopropylcarbonyl compounds \textit{via} reaction with enolate anions\textsuperscript{185} and cyclopropanecarboxylates have been prepared from reaction of vinylselenones with \( \alpha \beta \)-unsaturated esters\textsuperscript{186} and metallomalonates\textsuperscript{187}. Acyclic 3-hydroxyvinyl selenones undergo addition reactions with alkoxides followed by an internal substitution with the hydroxy group to give 3-alkoxyoxetanes\textsuperscript{188,189}. Cyclic 3-hydroxyvinyl selenones afford acetylenic ketones \textit{via} an addition-fragmentation reaction\textsuperscript{189,190}. Intramolecular substitution of the phenylselenonyl group by nitrogen gives cyclic amides\textsuperscript{191} and has been shown to occur with inversion of configuration\textsuperscript{192}. In all of these cases the selenonyl moiety behaves as an excellent leaving group, an attribute not possessed by the sulfonyl group.
\[
\begin{align*}
C_{11}H_{23}CH_2-SePh & \xrightarrow{\text{MCPBA, ROH}} C_{11}H_{23}CH_2-OR \quad \text{Ref 166} \\
\text{Ph} & \xrightarrow{\text{KOH(aq), THF}} \text{Ph} \quad \text{Ref 184} \\
\text{OH} & \xrightarrow{\text{MCPBA, MeOH}} \quad \text{Ref 183a} \\
\text{O} & \xrightarrow{\text{MCPBA, MeOH}} \quad \text{Ref 183b} \\
\text{Se(O)Ph} & \xrightarrow{\text{CH}_2=\text{CHCO}_2\text{Me}, \text{tBuOK}} \quad \text{Ref 185} \\
\text{OH} & \xrightarrow{\text{NaOH, MeOH, H}_2\text{O}} \quad \text{Ref 188} \\
\text{HO Bu} & \xrightarrow{\text{NaOH, MeOH}} \quad \text{Ref 189} \\
\text{NH Ts} & \xrightarrow{\text{MCPBA, KOH, iPrOH}} \quad \text{Ref 191}
\end{align*}
\]

Scheme 3.0
Krief has published comprehensive studies of the formation\textsuperscript{162} and reactivity\textsuperscript{152} of simple primary alky phenyl selenones. Oxidation of methyl phenyl selenide or dimethyl selenide, which cannot undergo a selenoxide syn-elimination, to the corresponding selenones was best achieved using ozone at 0°C\textsuperscript{181} or potassium permanganate at room temperature.\textsuperscript{179,180} Long chain primary alky phenyl selenones were best formed using trifluoroperacetic acid\textsuperscript{161} or excess MCPBA. Krief found that decyl phenyl selenone could be substituted with a variety of nucleophiles including hydroxide, methoxide, phenylsulfide, cyanide, iodide and azide. Competition experiments in ethanolic solution showed that the phenyl selenonyl group was a better leaving group than bromide or iodide. As these studies were carried out only on a simple, primary selenone it would be of considerable interest to determine if the excellent leaving group ability of the phenylselenonyl group could be exploited in transformations of more complicated organic molecules.

Thus the aims of the work presented in this chapter were to

i) determine if the facile intermolecular substitution of selenones described in chapter 2.3 would occur in other systems and

ii) exploit the excellent leaving group ability of the selenonyl group in intramolecular substitution reactions with a neighbouring group to form cyclized products.
3.1 Intermolecular substitution reactions of selenones.

As the work of Krief\textsuperscript{152} had focused solely on the nucleophilic displacement of a primary selenone, it was of interest to determine if a secondary selenone, such as (101), would exhibit similar reactivity. Oxidation of (100), formed from reaction of bromocyclohexane with phenylselenide anion, with excess MCPBA however, gave no recoverable materials (scheme 3.1.1).

Scheme 3.1.1

Introduction of a second functional group to the cyclohexylselenide (100) would enable easier isolation and visualization by t.l.c. of any substitution products. Reaction of the \(\beta\)-methoxy selenide (102), formed by methoxyselenation\textsuperscript{57} of cyclohexene, with excess MCPBA in methanol for one hour at room temperature gave not the expected dimethoxycyclohexane (103), but the ring contracted acetal (104) in quantitative yield (scheme 3.1.2).

Scheme 3.1.2
The substituted styrene (105) also gave a product (106) arising from a 1,2-shift in quantitative yield upon reaction with MCPBA in methanol. Both (104) and (106) could be formed in one step by reaction of the respective alkene with phenylselenenyl chloride and MCPBA in methanol. These products resulted from a 1,2-alkyl shift leading to a stabilized carbocation, which was quenched by methanol (scheme 3.1.3). The acetal (106) was identical in all respects to a sample synthesised independently from reaction of phenylacetaldehyde and p-toluenesulfonic acid in methanol. These 1,2 alkyl and aryl shifts of selenones had been observed previously by Uemura.166

![Scheme 3.1.3](image)

In an attempt to form the aldehyde (108) from a similar 1,2 shift, the selenide (107), formed from hydroxyselenation22,55 of cyclohexene, was reacted with MCPBA in methanol (scheme 3.1.4). Although the $^1$H n.m.r. of the crude product showed aldehydic resonances at 9.60 and 9.36 ppm, yields of isolated product were low and these products rapidly decomposed to complex mixtures.

![Scheme 3.1.4](image)
Substitution of the selenonyl moiety could be effected by nucleophiles other than methanol. Reaction of styrene with phenylselenenyl chloride\textsuperscript{21} in DMF, followed by oxidation with MCPBA in the presence of tetrabutylammonium chloride at room temperature gave only the vinyl chloride (110), resulting from elimination of the intermediate selenoxide. However, if the reaction was carried out at 0°C a 1:1 mixture of the 1,2-dichloride (111) and the 2,2-dichloride (112) could be isolated (scheme 3.1.5). In this case direct substitution of the intermediate selenone competed with the 1,2-aryl shift as the intermediate carbocation leading to formation of (112) was no longer stabilized by an adjacent oxygen, as was the case with reaction in methanol.

![Scheme 3.1.5](image)

The facile 1,2-shifts observed for the compounds depicted in this section limits the synthetic utility of the phenylselenonyl moiety as a good leaving group. Intermolecular substitutions of alkyl phenyl selenones need to be more thoroughly investigated.
3.2 Hydroxyselenation of allylic alcohols and their conversion to epoxides

3.2.1. Hydroxyselenation of allylic alcohols

Krief and co-workers have reported several preparative methods for the formation of epoxides from β-hydroxy selenides involving the conversion of selenides to selenonium salts, followed by treatment with strong alkali. Epoxides have also been synthesised by treatment of selenides with dichlorocarbene. It should also be possible to form epoxides from β-hydroxy selenides via the intermediacy of a selenone (scheme 3.2.1).

![Scheme 3.2.1](image)

The required β-hydroxyselenides are readily formed from reaction of an alkene with phenylselenenyl chloride or phenylselenenyl phthalimide in the presence of water. The hydroxyselenation of allylic alcohols using such methods however, has not been investigated. Liotta has reported that phenylselenenyl chloride adds in a regio- and stereospecific manner to 2-cyclohexenol, but that reaction with compounds such as crotyl alcohol or 2-cyclopentenol gave regioisomeric or stereoisomeric mixtures (scheme 3.2.2). It was of interest to determine if addition of "PhSeOH" to allylic alcohols showed any regio- or stereoselectivity, and if the products formed from such reactions could be elaborated to β-hydroxy epoxides.
Initial studies were carried out on acyclic allylic alcohols to determine the regioselectivity of the hydroxyselenation reaction. Reaction of 3-methylbut-2-en-1-ol with phenylselenenyl chloride in aqueous acetonitrile at room temperature for 18 hours gave only the single regioisomer (120), in high yield (scheme 3.2.3). $H_{1a}$ and $H_{1b}$ of (120) appeared as a multiplet at 3.95 ppm and $H_2$ as a triplet at 3.30 ppm in the $^1H$ n.m.r. spectrum. Formation of this regioisomer, the Markovnikov adduct, could be explained on the basis of its greater thermodynamic stability, or by a directing effect of the hydroxyl group. The formation of the anti-Markovnikov adduct (120) upon reaction of 2-methylbut-3-en-2-ol under the same conditions suggested that the allylic hydroxyl group did indeed exhibit a strong directing effect on the addition of “PhSeOH”. Reaction using methylallyl alcohol gave only the anti-Markovnikov adduct (121). Hydroxyselenation of trans-2-hexenol gave a mixture of the erythro isomers (122a) and (122b) in the ratio 98:2 as determined by $^1H$ n.m.r and hydroxyselenation of cis 2-hexenol gave a mixture of the threo isomers (123a) and (123b) in the ratio 92:8. The formation of the erythro isomers from trans-hexenol and the threo isomers from cis-hexenol indicates that the addition of “PhSeOH” to the double bond proceeds with trans-stereospecificity. The isomers (122a) and (123b) both showed $^2J$ coupling for the hydroxyl protons in the $^1H$ n.m.r. spectra, the primary hydroxyl protons appearing as triplets and the secondary hydroxyl protons as doublets. The appearance of this coupling is probably due to intramolecular hydrogen bonding between the two adjacent hydroxy groups resulting in restricted conformational mobility of these molecules.
It was not known if the regioselectivity of the hydroxyselenations described above was due to the directing effect of the hydroxyl group on the attack by water of the intermediate episelenonium ion (124), or from selective delivery of the phenylseleno group to the α-carbon of the double bond via an intermediate seleno-oxonium intermediate (125).

The reactivity of the substrates linalool (126) and geraniol (128), which contain both an allylic and an isolated double bond, towards hydroxyselenation was examined. Reaction of linalool with phenylselenenyl chloride in aqueous acetonitrile gave rise to only one regioisomer
(127), as a pair of diastereomers, resulting from addition of "PhSeOH" to the more substituted double bond. The olefinic protons of (127a) appeared as ABX doublets of doublets at 6.80, 5.22 and 5.03 ppm and the proton under selenium as a multiplet at 3.35 ppm in the $^1$H n.m.r. spectrum. Hydroxyselenation of geraniol gave a mixture of the two regioisomers (129b) and (129a) in the ratio 7:5, resulting from addition of "PhSeOH" to both double bonds (scheme 3.2.4). The $^1$H n.m.r. spectrum of the mixture showed the olefinic proton of (129b) as a triplet at 5.20ppm and that of (129a) as a doublet of triplets at 5.46 ppm. The proton under selenium of (129b) appeared as a multiplet at 3.07 ppm and that of (129a) as a multiplet at 3.62 ppm. These results suggest that delivery of the phenylseleno moiety from complexation with the hydroxyl group does not occur, as were this the case, addition would be expected to occur to a large extent at the allylic double bond and not the isolated double bond of linalool and geraniol.

(126) $\rightarrow$ (127a) + (127b)

(128) $\rightarrow$ (129a) + (129b)

Scheme 3.2.4
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Hydroxyselenation of crotyl alcohol* gave the regioisomers (130a) and (130b) in the ratio 7:4 (scheme 3.2.5). This result was not surprising as the two carbons of the episelenonium ion intermediate in this case are sterically and electronically similar. The observed ratio of regioisomers is similar to that observed for the addition of phenylselenenyl chloride to crotyl alcohol.85,86

\[
\text{OH} \quad \text{PhSeCl} \quad \text{CH}_3\text{CN}, \text{H}_2\text{O} \quad \begin{array}{c}
\text{OH} \\
\text{SePh}
\end{array} + \begin{array}{c}
\text{OH} \\
\text{SePh}
\end{array} \\
(130\text{a}) \quad (130\text{b})
\]

Scheme 3.2.5

Hydroxyselenation of cinnamyl alcohol gave a complex mixture of products. Although it was possible to isolate the hydroxyselenide (131), this soon decomposed to a complex mixture containing starting materials (scheme 3.2.6a). Attempts to isolate the major product as its acetonide derivative (132) by the addition of 2,2-dimethoxypropane and a catalytic amount of p-toluenesulfonic acid or camphorsulfonic acid to the reaction mixture gave only the starting alkene (scheme 3.2.6b). It appeared the addition of “PhSeOH” to the benzylic double bond was reversible and this process was catalysed by acid. This facile reversible addition may be due to the inherent stability of the intermediate benzylic carbocation formed from solvation of the hydroxyselenide (131).

\[
\text{Ph} \quad \text{OH} \quad \begin{array}{c}
\text{Ph} \\
\text{Se}^+
\end{array} \quad \text{H}_2\text{O} \quad \begin{array}{c}
\text{OH} \\
\text{SePh}
\end{array} \\
(131)
\]

Scheme 3.2.6a

* As commercially available crotyl alcohol consists of a 70:30 mixture of trans:cis isomers, reactions using crotyl alchol or crotyl acetate gave a corresponding mixture of erythro and threo isomers. For clarity only the major erythro isomers are quoted.
Reaction of 2-cyclohexen-1-ol with phenylselenenyi chloride in aqueous acetonitrile gave a 10:1 mixture of the diastereomers (133a) and (133b) (scheme 3.2.7). In the major isomer H$_1$ appeared at 4.11 ppm (m), H$_2$ at 3.22 ppm (dd 2.7, 9.7Hz) and H$_3$ at 3.94 (dt 4.2, 9.7Hz) in the $^1$H n.m.r. spectrum. In the minor isomer, the isosteric and isoelectronic protons H$_1$ and H$_3$ appeared at 3.28 ppm (dt, 4.2, 10.1Hz) and H$_3$ appeared at 2.77 ppm (t, 10.1Hz). 2-Cyclohexene-1-ol exists almost exclusively as the pseudoaxial conformer due to an anomeric effect$^{195}$ as there is greater orbital overlap between the $\pi$ orbital of the double bond and the $\sigma^*$ orbital of the C-O bond in the pseudoaxial conformer than in the pseudoequatorial conformer. The major diastereomer (133a) arises from addition of selenium to the double bond directed to the syn-face by the axial hydroxyl group. Axial attack of water on the intermediate episelenonium ion thus formed then leads to the cis-trans geometry of (133a) (scheme 3.2.7).
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Hydroxyselenation of more substituted cyclic allylic alcohols gave complex product mixtures. Reaction of isophorol (134)\textsuperscript{197}, formed by lithium aluminium hydride reduction of isophorone, with phenylselenenyl chloride in aqueous acetonitrile gave a mixture of (135a), (135b) and the starting material (134) in the ratio 40:35:21 (scheme 3.2.8). Fortuitously, the major isomer (135a) crystallized upon standing. The regio- and stereochemistry of (135a) was assigned from examination of the \textsuperscript{1}H n.m.r., DEPT 135, DEPT 90, COSY and NOESY spectra, and by conversion to the epoxide (167b) \textit{vide infra}. \(\text{H}1\) appeared as a triplet of triplets (J 11.3, 3.8Hz) at 4.28 ppm, which collapsed to a doublet of triplets (J 11.3, 3.8Hz) at 4.27 ppm upon D\textsubscript{2}O exchange. Thus \(\text{H}1\) was coupled to both the \(\text{C}1\) hydroxyl proton and \(\text{H}6\) a 11.3Hz and to \(\text{H}2\) and \(\text{H}6\) at 3.8Hz. \(\text{H}2\) appeared as a doublet of triplets (J 3.8, 1.8Hz) at 3.40 ppm, the 1.8Hz splitting arising from a \(^4\)J coupling\textsuperscript{169} to \(\text{H}6\), and the \(\text{C}1\) hydroxyl proton appeared as a doublet (J 11.3Hz) at 2.49 ppm.

\[
\begin{align*}
\text{LiAlH}_4 & \rightarrow \text{PhSeCl} \\
\text{CH}_3\text{CN}, \text{H}_2\text{O} & \rightarrow \text{SePh} \\
\text{(134)} & \rightarrow \text{(135a)}, \text{(135b)}
\end{align*}
\]

\textbf{Scheme 3.2.8}

Hydroxyselenation of myrtenol (136) gave a complex mixture from which it was possible to isolate a low yield of the anti-Markovnikov adduct (137). Reaction using pulegol (138), formed by reduction\textsuperscript{255} of pulegone with sodium borohydride in the presence of ceric chloride, also gave a complex mixture of products (scheme 3.2.9). These observations suggest that addition of “PhSeOH” to highly substituted cyclic double bonds is reversible, which leads to mixtures of isomers.
3.2.2 Hydroxyselenation of allylic acetates

Liotta has found that addition of phenylselenenyl chloride to allylic acetates proceeds with a higher degree of regio- and stereoselectivity than addition to the corresponding allylic alcohols. Reaction of crotyl acetate with phenylselenenyl chloride, for example, was thought to proceed via an episelenonium ion intermediate in which interaction of the carbonyl group with the electron deficient selenium atom results in differing charge densities at the $\alpha$ and $\beta$ carbons (scheme 3.2.10).

In contrast to these regioselective additions, hydroxyselenation of crotyl acetate (140), formed by reaction of crotyl alcohol with acetyl chloride, gave a mixture of (141a) and (141b) in the ratio 57:43. Formation of (141a) and (141b) was accompanied by formation of the diols (130a) and (130b) in the ratio 4:1 (scheme
3.2.11). The diols result from \textit{in situ} hydrolysis of the corresponding acetates, a process which was probably enhanced by anchimeric assistance from the neighbouring phenylseleno group.

When acetoxycyclohexene (143), formed from reaction of 2-cyclohexene-1-ol with acetyl chloride, was reacted with phenylselenenyl chloride in aqueous acetonitrile a mixture of (144a) and (144b) in the ratio 55:45 was isolated. This result implies that under the conditions of hydroxyselenation there is no neighbouring group participation by the acetyl group and the selenonium ions (145a) and (145b) are equally likely to be formed (scheme 3.2.12).
It was perplexing that addition of phenylselenenyl chloride to allylic acetates proceeded in a regiospecific manner, but hydroxyselenation of these compounds occurred in a non-regioselective manner. During the writing of this thesis Haughan\textsuperscript{196} reported that hydroxyselenation of (143) with phenylselenenyl phthalimide also proceeded in a regiocatholic manner. Haughan proposed that the diastereospecific addition of phenylselenenyl chloride to (143) may be due to the formation of a seleno-oxonium ion (146) which constrains the delivery of selenium to the \textit{syn} face of the double bond. He further proposed that the hydroxyselenation of (143) is regiocatholic because (146) cannot be formed when using phenylselenenyl phthalimide as a selenating reagent, due to the inferior leaving group ability of the counter anion. This proposal is not consistent with the observation that an identical product mixture to that reported by Haughan was obtained when hydroxyselenation of (143) was carried out using phenylselenenyl chloride in place of phenylselenenyl phthalimide.

It is more likely that the interaction of the carbonyl group with the electron deficient selenium centre is disrupted by water, which may hydrogen bond to the carbonyl group. This hypothesis was supported by the observation that reaction of crotyl acetate with phenylselenenyl chloride in methanol, a much less effective hydrogen bond donor than water, gave only the single regioisomer (147), and reaction of crotyl acetate with phenylselenenyl chloride and sodium acetate in acetic acid gave only the diacetate (149) accompanied by the alcohol (141b) (scheme 3.2.13).

If the carbonyl group of crotyl acetate is indeed interacting with the intermediate episelenonium ion, the use of a more electron withdrawing acetate, or the addition of a Lewis acid to complex with the the carbonyl group, should disrupt this interaction and hence reduce the regioselectivity of addition.
However, reaction of the trifluoroacetate (150), formed by reaction of crotyl alcohol with trifluoroacetic anhydride and a catalytic amount of DMAP, with phenylselenenyl chloride in methanol gave only the single regioisomer (151), along with hydrolysis product (148a) (scheme 3.2.14). Addition of phenylselenenyl chloride to a deuterochloroform solution of (150) gave only (152) as detected by $^1$H n.m.r. spectroscopy. Thus no loss of regioselectivity occurred with the more electron withdrawing trifluoroacetate. Reaction of crotyl acetate with phenylselenenyl chloride and one equivalent of titanium (IV) chloride in deuterochloroform resulted in hydrolysis of the acetyl group and the resultant formation of a 7:3 mixture of (119a) and (119b) as evidenced by $^1$H n.m.r. Reaction using one equivalent of zinc chloride however, gave a mixture of the regioisomers (153a) and (153b) in the ratio 2:1. As a check of Liotta’s work, reaction of crotyl acetate with phenylselenenyl chloride alone in deuterochloroform gave only (153a) as detected by $^1$H n.m.r. analysis. Complexation of the oxygen atom of the carbonyl group with zinc had resulted in the loss of stereoselectivity of addition to (140). Methoxyselenation of (140) in the presence of zinc chloride gave a mixture of (147a) and (147b) in the ratio 7:3, and the alcohols (148a) and (148b) in the ratio 7:3. Integration of the methoxy peaks in the $^1$H n.m.r. spectrum enabled accurate determination of these product ratios.
Liotta\textsuperscript{85} has proposed that the dramatic increase observed in regioselectivity of addition of phenylselenenyl chloride to allylic acetates over allylic alcohols can be qualitatively understood in terms of the relative charge densities of the $\alpha$ and $\beta$ carbons of the intermediate episelenonium ion (scheme 3.2.10). He argued that the acetoxyalkyl substituent of crotyl acetate was a weaker inductive donor than the hydroxyalkyl substituent of crotyl alcohol, resulting in a greater difference between the charge densities at $C_\alpha$ and $C_\beta$, and hence a greater regioselectivity of addition for crotyl acetate than for crotyl alcohol. If this were the case, then complexation of a Lewis acid to the carbonyl group of the acetate (140) should further increase the regioselectivity of addition. The results presented above suggest that this hypothesis is incorrect and that it is the interaction between the carbonyl group and the electron deficient selenium of the episelenoniumion intermediate that is responsible for the regioselective addition. When this interaction is disrupted by complexation of the carbonyl group to a Lewis acid or by
hydrogen bonding of the carbonyl group to water the regioselectivity of addition is lost.

The effect of a Lewis acid on the stereochemistry of the addition of phenylselenenyl chloride to allylic acetates was investigated using acetoxy cyclohex-2-ene (143). Reaction of (143) with phenylselenenyl chloride in deuterochloroform did not result in the exclusive formation of (155a), as reported by Liotta, but a mixture of the stereoisomers (155a) and (155b) in the ratio 9 : 1 (scheme 3.2.16). This result suggested that acetoxy cyclohex-2-ene reacts with phenylselenenyl chloride predominately at the syn face of the double bond as the pseudoequatorial conformer, and to a limited extent at the anti face of this conformer (scheme 3.2.15). The regioisomeric purity of this mixture was confirmed by an oxidative elimination of the phenylseleno group to give the vinyl chloride (157). Reaction of the trifluoroacetate (160), formed from reaction of 2-cyclohexenol with trifluoroacetic anhydride and DMAP, with phenylselenenyl chloride also gave a regioisomerically pure mixture of (161a) and (161b) in the ratio 20:1. When reaction was carried out in the presence of zinc chloride a mixture of the four possible stereoisomers (155a), (155b), (156a) and (156b) was formed, initially in the ratio 2 : 1 : 0.4 : 0.1. After one hour at room temperature a mixture of (155a), (155b), (156a) and (156b) in the ratio 2 : 1 : 1 : 0.15 was detected by $^1$H n.m.r. Oxidative elimination of this mixture gave a mixture of the alkenes (157), (158), (159a), and (159b) in the ratio 3 : 1 : 0.3 : 0.2 (scheme 3.2.16).

![Scheme 3.2.15](image-url)
These results suggest that in the presence of zinc chloride there is no interaction between the neighbouring acetate group and the selenonium ion formed from addition of phenylselenenyl chloride to (143), thus the syn and anti adducts depicted in scheme 3.2.12 are equally likely to be formed.

3.2.3 Formation of epoxides from β-hydroxyselenides

Reaction of the selenide (133a) with five equivalents of MCPBA in isopropyl alcohol for one hour to form the corresponding selenone, followed by treatment with 10% aqueous sodium hydroxide for one hour gave a moderate yield of the trans epoxide (165a) and a small amount of the isopropyl ether (166) (scheme 3.2.17).
The ether (166) resulted from displacement of the intermediate selenone by solvent, as it was not formed upon exposure of the epoxide (165a) to aqueous sodium hydroxide in isopropyl alcohol. The epoxide (165a) could be formed in good yield, without concomitant formation of (166) if the selenide (133a) were reacted with MCPBA and 10% aqueous potassium hydroxide in one pot. The stereochemistry of the epoxide (165a) was assigned as trans by comparison of the $^1$H n.m.r. spectrum, in which H$_2$ appeared as a doublet coupled to H$_3$ only, with that reported in the literature.$^{197}$ Reaction of a β-dihydroxy selenone with base to give a trans-hydroxy epoxide complements established methodologies$^{197-199}$ which give cis-hydroxy epoxides. Epoxidation$^{197}$ of 2-cyclohexene-1-ol with MCPBA gave a mixture of the cis (165b) and trans (165a) epoxides in the ratio 96:4 (scheme 3.2.18).

![Scheme 3.2.18](image)

Reaction of the hydroxyselenide (135a) with MCPBA and aqueous potassium hydroxide for one hour gave the trans epoxide (167a) in good yield. The proton H$_1$ appeared at 4.17 ppm, (dd, 7.2, 5.8Hz) and H$_2$ at 2.97 ppm (s) in the $^1$H n.m.r. spectrum. The $^{13}$C n.m.r. spectrum showed the carbons C$_1$, C$_2$ and C$_3$ at 65.9, 62.9 and 59.4 ppm respectively. This product has complementary stereochemistry to the epoxide (167b) obtained from reaction$^{197}$ of isophorol with MCPBA, in which H$_1$ appeared as a doublet of doublets of doublets (J 11.1, 6.1, 2.0Hz) at 4.00 ppm, H$_2$ as a doublet (J 2.0Hz) at 3.08 ppm and the carbons C$_1$, C$_2$ and C$_3$ at 65.4, 62.2 and 61.0 ppm respectively (scheme 3.2.19).
The acetate (144a) could be converted to the trans-epoxide (168a) and the acetate (144b) to the cis-epoxide (168b) by reaction with MCPBA and sodium hydroxide for 40 minutes. The acetates (144a) and (144b) could be converted to the epoxy alcohols (165a) and (165b) respectively by reaction with MCPBA and aqueous potassium hydroxide for six hours (scheme 3.2.20).

The hydroxyselenides (120), (121), (122a), (123a), (130) and (141) could all be converted smoothly to the corresponding epoxides (170), (171), (172), (173), (174) and (175) by reaction with MCPBA and aqueous potassium hydroxide in isopropyl alcohol for one hour (table 3.2.21).
Table 3.2.21: Hydroxyselenation of allylic alcohols and their conversion to epoxides

<table>
<thead>
<tr>
<th>Alkene</th>
<th>Addition Product</th>
<th>% Yield</th>
<th>Epoxide</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\text{CH}_2\text{OH})</td>
<td>+ (\text{HO}-\text{SePh}) (130a)</td>
<td>100</td>
<td>(\text{HO}-\text{O}-\text{SePh}) (174)</td>
<td>66</td>
</tr>
<tr>
<td>(\text{HO}-\text{CH}=(\text{CH})_2\text{OH})</td>
<td>(130b)</td>
<td>100</td>
<td>(170)</td>
<td>74</td>
</tr>
<tr>
<td>(\text{HO}-\text{CH}=(\text{CH})=\text{CH}_2\text{OH})</td>
<td>(120)</td>
<td>86</td>
<td>(170)</td>
<td>74</td>
</tr>
<tr>
<td>(\text{HO}-\text{C(CH}=\text{CH}_2\text{OH})</td>
<td>(121)</td>
<td>85</td>
<td>(171)</td>
<td>78</td>
</tr>
<tr>
<td>(\text{HO}-\text{CH}=(\text{CH})=\text{CH}-\text{CH}_2\text{OH})</td>
<td>+ (\text{PhSeOH}) (122a) 98 : 2 (122b)</td>
<td>91</td>
<td>(\text{HO}-\text{O}-\text{PhSePh}) (172)</td>
<td>70</td>
</tr>
<tr>
<td>(\text{HO}-\text{CH}=(\text{CH})=\text{CH}-\text{CH}=(\text{CH})\text{OH})</td>
<td>(123a) 92 : 8 (123b)</td>
<td>72</td>
<td>(\text{HO}-\text{O}-\text{SePh}) (173)</td>
<td>65</td>
</tr>
<tr>
<td>(\text{HO}-\text{CH}=(\text{CH})=\text{CH}-\text{CH}_2\text{OH})</td>
<td>+ (\text{HO}-\text{SePh}) (133a) 10 : 1 (133b)</td>
<td>91</td>
<td>(\text{HO}-\text{O}-\text{SePh}) (165a)</td>
<td>68</td>
</tr>
<tr>
<td>(\text{HO}-\text{CH}=(\text{CH})=\text{CH}-\text{CH}_2\text{OH})</td>
<td>(135a)</td>
<td>60</td>
<td>(167a)</td>
<td>72</td>
</tr>
</tbody>
</table>
Hydroxyselenation of allylic alcohols and allylic acetates, followed by treatment of the resultant selenides with MCPBA and aqueous potassium hydroxide thus provides β-hydroxy epoxides in good yield, with complementary stereochemistry to that obtained using established methods.
3.3 Reactions of β-amido selenides

3.3.1 Formation of cis-substituted oxazolines

2-Substituted oxazolines are useful intermediates in the synthesis of a variety of biologically active compounds, including α-aminoalkanols and α-amino acids. Whilst there are many examples in the literature of the conversion of β-hydroxy- and β-haloamides to oxazolines, only a few examples of the conversion of a β-amidoselenide to an oxazoline have been reported. β-Amidoselenides can be formed in high yield by a Ritter type reaction of phenylselenenyl chloride and an alkene in a nitrile containing solvent. Oxidation of a β-amidoselenide to the corresponding selenone with MCPBA, and treatment with base should result in intramolecular displacement of the selenonyl group and formation of a 2-substituted oxazoline (scheme 3.3.1). As the amidoselenation of alkenes occurs with trans-stereospecificity and nucleophilic displacement of the selenonyl group occurs with inversion of configuration, this route should provide an expeditious synthesis of cis-substituted 2-substituted oxazolines from alkenes.

\[ \text{Reactions of } \beta\text{-amido selenides} \]

![Scheme 3.3.1](image)

Reaction of cyclopentene with phenylselenenyl chloride, benzonitrile and aqueous triflic acid at 90°C for one hour gave an excellent yield of the β-amidoselenide (180). Treatment of (180) with 3 equivalents of MCPBA and 4.5 equivalents of powdered potassium hydroxide in isopropyl alcohol afforded the 2-phenyloxazoline (186a) in 93% yield (scheme 3.3.2), and small amounts of two unidentified compounds. H7a of (186a) appeared as a doublet of triplets (J 8.3, 5.3Hz) at 4.68 ppm, and H3a as a doublet of triplets (J 8.3, 7.0Hz) at 4.13 ppm in the
$^{1}$H n.m.r. spectrum. A 4.1% nOЕ enhancement between these two protons at the ring junction provided good evidence for the cis-fused stereochemistry assigned to (186a).

Scheme 3.3.2

Reaction of the β-amidoselenide (181), formed in high yield by amidoselenation of cyclohexene, under the conditions described above gave a 90% yield of the oxazoline (187a). Amidoselenation of cycloheptene and cyclooctene with benzonitrile was more problematical, and low yields of (182) and (183) were obtained. Conversion of these β-amidoselenides to the oxazolines (188) and (189) however, proceeded in high yield (scheme 3.3.3). Attempted amidoselenation of 1-hexene with benzonitrile was unsuccessful, with no evidence for the formation of an amide obtained by infrared or $^{1}$H n.m.r. analysis of the crude reaction product. Attempted amidoselenation of styrene with benzonitrile also proved fruitless. Amidoselenation of cis-2-butene with benzonitrile gave a 5:1 mixture of the threo and erythro selenides (184) and (185). The formation of a mixture of isomers was unexpected as amidoselenation of cis-2-butene$^{192}$ with acetonitrile afforded only the threo isomer. The major isomer (184) could be isolated isomerically pure upon recrystallization of this product mixture. Reaction of (184) with MCPBA and potassium hydroxide gave only the cis-oxazoline (190) in good yield. Reaction of (185), formed by amidoselenation of trans-2-butene, under the same conditions gave only the trans-oxazoline (191) in good yield.
As amidoselenation of alkenes occurs with trans stereoselectivity,\textsuperscript{58} these results suggest that the intramolecular substitution of the phenylselenenonyl group occurs with inversion of configuration. Thus the overall transformation of alkenes to 2-substituted oxazolines is cis stereoselective.

3.3.2 Formation of trans-substituted oxazolines

When phenylselenenyl bromide was used in place of phenylselenenyl chloride and the mixture heated at 120°C, instead of 90°C, in the amidoselenation of cyclopentene, a mixture of the expected amide (180) and the trans-fused oxazoline (186b) was isolated. Formation of trans-oxazolines such as (186b) has not
been reported in the literature. Reaction of cyclopentene with two equivalents of phenylselenenyl bromide and aqueous triflic acid in benzonitrile at 120°C gave only the oxazoline (186b) in 52% yield (scheme 3.3.4). The oxazoline (186b) hydrolysed upon standing in air over a period of weeks to the β-hydroxyamide (192). Analysis of the \(^1\)H n.m.r., \(^{13}\)C n.m.r. and mass spectra of (186b) showed it to be isomeric with the cis-fused oxazoline (186a). H\(_{6a}\) of (186b) appeared as a triplet (J 6.9Hz) at 5.11 ppm and H\(_{3a}\) as a triplet (J 7.1Hz) at 4.73 ppm. No coupling was seen between these two ring junction protons, probably as the dihedral angle between them approaches 90°, and no nOES enhancement could be detected between the ring junction protons upon irradiation at either 5.11 ppm or 4.74 ppm.

\[
\text{Cyclopentene} \xrightarrow{\text{PhSeBr, PhCN, CF}_3\text{SO}_2\text{H, H}_2\text{O}} \text{SePh} \quad \text{NHCOPh} + \quad \text{Ph} \quad \text{OH} \quad \text{NHCOPh}
\]

 Scheme 3.3.4

Alkyl phenylselenides can be converted to alkyl bromides by reaction with phenylselenenyl bromide.\(^{38,160}\) The selenide reacts with phenylselenenyl bromide to form an intermediate selenonium ion, which is displaced, with inversion of configuration,\(^{35}\) by bromide ion. It is possible that the β-selenoamide (180) formed from amidoselenation of cyclopentene was reacting with the second equivalent of phenylselenenyl bromide to give an intermediate β-bromoamide (scheme 3.3.5). Steric repulsion between the two cis substituents of the cyclopentyl ring then forces the carbonyl group of the amide above the plane of the ring into a position in which \(\text{SN}_2\) attack of the bromide by the oxygen atom can occur.
Reaction of the *trans* β-selenoamide involving two successive nucleophilic substitutions thus occurs with net retention of configuration and leads to the *trans* stereochemistry of the isolated product. Reaction of cyclohexene under the conditions described above gave the *trans*-oxazoline (187b) in 57% yield.

If the reaction was occurring *via* a β-bromoamide intermediate, then the use of phenylselenenyl iodide in place of phenylselenenyl bromide should result in the formation of a more reactive intermediate and increased yields of cyclized product. Accordingly, cyclopentene was reacted with two equivalents of phenylselenenyl iodide under the conditions described above to give (186b) in 75% yield. Attempts to form *trans* 2-methyl oxazolines in one pot from alkenes were unsuccessful. Reaction of cyclohexene with two equivalents of phenylselenenyl bromide and triflic acid in acetonitrile under reflux gave only the acetamide (195) (*vide infra*). It is likely that the differing reactivities of the acetamide (195) and benzamide (180) towards cyclization were due to the temperature achievable using acetonitrile or benzonitrile as solvent during the reaction. The boiling point of acetonitrile (82°C) was not sufficiently high to overcome the energy barrier to a reaction involving the strained intermediate depicted in scheme 3.3.5. Amidoselenation of cyclopentene with excess phenylselenenyl bromide and benzonitrile at 80°C gave only the amide (180).

The work presented in this section demonstrates the utility of β-amido
selenides as useful precursors for the stereospecific synthesis of both cis- and trans-2-substituted oxazolines.

3.3.3 Reactions of β-selenoacetamides with MCPBA

The acetamide (195) was synthesised in an analogous manner to (181), using acetonitrile instead of benzonitrile. Reaction of (195) with three equivalents of MCPBA and potassium hydroxide in isopropyl alcohol gave not the expected 2-methyloxazoline (196), but an 87% yield of the lactone (197), a 12% yield of the β-hydroxyamide (198) and a trace of (199) (scheme 3.3.6).

The lactone (197) and the alcohol (198) were also formed when reaction was carried out without potassium hydroxide or when dry DMF was used as solvent. The hemiaminal (199) most likely results from attack by solvent on the stabilized carbocation formed by a 1,2-alkyl shift (scheme 3.3.7).
Structural identification of (197) was not straightforward. The $^1$H n.m.r. spectrum of (197) showed a broad singlet (1H) at 7.56 ppm and a singlet (3H) at 2.11 ppm corresponding to the NH and methyl resonances of the acetamide group. The proton $\alpha$ to the amide appeared as a doublet of doublets (1H) at 5.35 ppm. This splitting pattern implied that there were only two protons at the $\beta$ positions of (197) (there was no coupling seen in the COSY spectrum between this proton and the NH of the amide). This meant that one of the $\beta$ positions was a fully substituted carbon or a heteroatom. Two multiplets (1H) at 2.63 and 2.50 ppm were indicative of the protons $\alpha$ to a cyclic ketone (fig. 3.3.8).

![NMR spectrum of (197)](image)

**Fig 3.3.8**

The $^{13}$C n.m.r. spectrum of (197) provided corroborative evidence for the proposed structure. The resonance at 170.3 ppm corresponded to the carbonyl group of the lactone and the resonance at 157.5 ppm appeared in the region expected for an amide.$^{133,169}$ The lactone (197) gave a (M+H) ion under conditions of fast atom bombardment and fragmentations corresponding to the loss of CH$_3$ and NHCOCH$_3$. Peaks were seen at 3250, 1720 and 1655 cm$^{-1}$ in the infrared spectrum. Combustion analysis confirmed the empirical formula C$_8$H$_{13}$NO$_3$ of (197). By analogy with the above structures, the two minor products observed from reaction of the benzamide (181) with MCPBA and potassium hydroxide were assigned the structures (200) and (201) (scheme 3.3.9).

![Scheme 3.3.9](image)
Chapter 3.3

The formation of the lactone (197) from the selenide (195) was surprising and exciting. Any mechanism proposed for the formation of (197) must account for the differing reactivity of the acetamide (195) and the benzamide (181): i.e. that the acetamide forms the lactone and the benzamide cyclizes to the oxazoline. It is possible that whilst both (195) and (181) were cyclizing to form oxazolines, the methyl oxazoline (196) was readily hydrolysed by adventitious water to give the hydroxyamide (198) (scheme 3.3.1). Compounds such as (196) have been employed as precursors to amino acids and ketones\textsuperscript{202,203} and are susceptible to hydrolysis. As the ability of an amide residue to behave as a leaving group during hydrolysis of an oxazoline is dictated by its acidity, hydrolysis occurs much more readily for (196) than for (187a) because the acetamide group is some 100 times more acidic than the benzamide \(\text{pKa(acetamide)} = 0.37, \text{pKa(benzamide)} = -2.16\)\textsuperscript{168}. Attack of water at the 2-position is also more sterically hindered for (187a) than for (196) and in (187a) occurs at a less reactive, conjugated double bond. It is possible the hydroxyamide (198) thus formed reacts with benzeneseleninic acid to form a seleninate species which is oxidized to a selenonate by the excess MCPBA present. The selenonate is then oxidized to a $\beta$-keto amide, which undergoes a Baeyer-Villiger rearrangement\textsuperscript{204} to give the lactone (197). The intermediacy of a selenonate in this reaction is invoked as there have been no reported examples of the oxidation of a secondary alcohol being effected by MCPBA, and reaction of (198) with MCPBA in isopropyl alcohol gave only starting materials. Unfortunately, benzeneseleninic acid could not be obtained in time to be used in a reaction with MCPBA and (198), however it is likely that this will result in formation of the lactone (196). The generality of this type of transformation and the utility of benzeneselenonates as mediators for the oxidation of alcohols under extremely mild conditions warrants further investigation.
It is also possible that the hydroxy amide (198) was being formed from nucleophilic displacement of the selenonyl group by significant amounts of adventitious water. If this were the case then compounds such as the β-seleno acetate (202) should also give rise to lactones upon treatment with MCPBA. Oxidation of the acetate (202), formed from reaction\(^7\) of cyclohexene with phenylselenenyl bromide and sodium acetate in glacial acetic acid however, gave only the selenone (203) (scheme 3.3.11). Attempts to induce cyclization of (203) to the lactone (204) by treatment with butyl lithium at -78°C proved fruitless and complex mixtures were obtained. It is likely that deprotonation was occurring not at the methyl group, but at the more acidic position adjacent to the selenonyl group. The reaction of (203) with more sterically hindered bases such as LDA warrants further investigation.
When the acetamide (205), formed from reaction of styrene with phenylselenenyl chloride under Ritter conditions, was reacted with MCPBA in the presence of potassium hydroxide only phenacyl acetate (206) was obtained (scheme 3.3.12). Identification of (206) was difficult as this product bore little structural similarity to the starting amide or the expected 2-methyl oxazoline (207). The $^1$H n.m.r. of (206) showed aromatic resonances at 7.90 and 7.6-7.3 ppm indicative of a benzoyl substituent, a methylene singlet at 5.35 ppm and a methyl singlet at 2.23 ppm. The $^{13}$C n.m.r. spectrum showed peaks at 192 and 170 ppm for the two carbonyls, and at 66 and 20 ppm for the methylene and methyl carbons respectively. The mass spectrum showed a molecular ion at 178 m/z and fragmentations corresponding to acetyl, phenyl and benzoyl. The infrared spectrum showed peaks at 1750 and 1700 cm$^{-1}$ for the ester and ketone carbonyls respectively. Structural elucidation was achieved by the use of a relay HETCORR experiment employing a 3.45 ms delay before the $^{13}$C-$^1$H mixing time. This experiment enabled determination of $^2$J C-C-H couplings and showed that the methylene protons were coupled long range to the ketone carbonyl and the methyl protons were coupled long range to the ester carbonyl. The $^1$H n.m.r. data for (206) was consistent with that reported in the literature$^{205}$ for phenacyl acetate.
It is suggested that the acetate (206) results from hydrolysis of the oxazoline (207) to the benzylic amine (208), which is oxidized by benzeneselenonic acid or MCPBA to the corresponding imine, then hydrolysed to the ketone (206) (scheme 3.3.12). Secondary amines such as (208) are readily converted to ketones by a variety of oxidizing agents including peracids and diphenylseleninic anhydride.

3.3.4 Reactions of cyclo-octadiene with phenylselenenyl chloride

As part of the studies on the formation of oxazolines from β-amidoselenides it was considered that reaction of an amide such as (210) may afford products in which a transannular cyclization had competed with oxazoline formation (scheme 3.3.13).

Accordingly, cyclo-octadiene was reacted with two equivalents of phenylselenenyl chloride and aqueous triflic acid in benzonitrile at 90°C for four
hours. This gave not the expected product (210), but a moderate yield of bicyclic ether (211) and an inseparable mixture of (212a) and (212b) in the ratio 1:7:3 (scheme 3.3.14).

\[
\text{PhCN} \quad \begin{array}{c} 2 \text{PhSeCl}, \text{PhCN} \\ \text{CF}_3\text{SO}_3\text{H}, \text{H}_2\text{O} \end{array} \rightarrow \begin{array}{c} \text{PhSe}^- \text{Ph} \\ \text{O} \end{array} + \begin{array}{c} \text{SePh} \\ \text{NH} \\ \text{Bz} \end{array} \quad (211) \quad \begin{array}{c} \text{H} \\ \text{H} \\ \text{H} \end{array} + \begin{array}{c} \text{SePh} \\ \text{NH} \\ \text{Bz} \\ \text{H} \end{array} \quad (212a) + (212b)
\]

Scheme 3.3.14

[3.3.1] Bicyclic ethers such as (211) have been formed by hydroxyselenation of dienes with phenylselenenyl chloride\(^{55}\) and by oxyselenation of dienes with phenylselenocyanate and copper (II) chloride.\(^{74}\) By analogy with these reports, it is likely that (211) was formed by transannular attack of an intermediate hydroxyselenide on the episelenonium ion formed at the other double bond. The bicyclic amides (212a) and (212b) are formed as a result of transannular attack of the double bond on the episelenonium ion to give an intermediate carbocation. Attack of benzonitrile at either face of this carbocation and subsequent hydrolysis gives the diastereomers (212a) and (212b) (scheme 3.3.15).

\[
\begin{array}{c} \text{PhCN} \\ \text{H}_2\text{O}^- \end{array} \rightarrow \begin{array}{c} \text{SePh} \\ \text{PhCN} \end{array} \rightarrow \begin{array}{c} \text{H} \\ \text{H} \end{array} \rightarrow (212a) + (212b)
\]

Scheme 3.3.15

The structures (212a) and (212b) were assigned by comparison of their \(^1\text{H}\) n.m.r. and \(^{13}\text{C}\) n.m.r. spectra with those values reported for similar [3.3.1] bicyclic systems in the literature.\(^{73,208,209}\) The \(^{13}\text{C}\) n.m.r. resonances were assigned by a combination of DEPT 135, DEPT 90 and DEPT 45 experiments. The bridgehead carbons (C\(_1\),C\(_5\)) of the major isomer (212a) appeared at 47.1 and 45.9 ppm, C\(_6\) at 50.1
ppm and C₂ at 58.8 ppm. The bridgehead carbons (C₁,C₅) of the minor isomer (212b) appeared at 46.6 and 45.9 ppm, C₆ at 48.6 ppm and C₂ at 53.9 ppm. The carbons C₂ and C₆ of an exo-endo disubstituted [3.3.1] bicyclo-octane are shifted upfield relative to the same carbons of an exo-exo disubstituted [3.3.1] bicyclo-octane.²⁰⁸

The ¹H n.m.r. resonances of (212a) (table 3.3.16) were assigned by examination of the DQF-COSY spectrum. The NOESY spectrum of (212a) and (212b) (fig. 3.3.17) showed enhancements for (212a) between the amide proton and both H₂ and H₁. nOE enhancement between the amide and the bridgehead proton H₁ of (212a) confirmed the exo configuration of the benzamide substituent. Enhancements were also seen between the bridgehead protons H₁ and H₅, and between H₅ and H₆ of (212a), which confirmed the endo configuration.

Table 3.3.16: ¹H n.m.r. resonances and correlations for (212a)

<table>
<thead>
<tr>
<th>proton</th>
<th>resonance δ, m (J Hz)</th>
<th>COSY</th>
<th>NOESY</th>
</tr>
</thead>
<tbody>
<tr>
<td>NH</td>
<td>6.18, d (6.8)</td>
<td>H₂</td>
<td>H₂, H₁</td>
</tr>
<tr>
<td>H₂</td>
<td>4.06, dddd (6.8, 8.1, 56, 7.0)</td>
<td>NH, H₃₃b, H₁</td>
<td>NH, H₅</td>
</tr>
<tr>
<td>H₆</td>
<td>3.47, ddd (6.3, 5.4, 8.7)</td>
<td>H₇₇b, H₅</td>
<td>H₅</td>
</tr>
<tr>
<td>H₅</td>
<td>2.79, dt (8.7, 8.4)</td>
<td>H₆, H₁, H₄₄b</td>
<td>H₁, H₆</td>
</tr>
<tr>
<td>H₁</td>
<td>2.33, dt (8.4, 7.0)</td>
<td>H₂, H₅, H₈₈b</td>
<td>H₅</td>
</tr>
</tbody>
</table>
Attempted transannular cyclization of cyclo-octadiene with phenylselenenyl chloride in dichloromethane gave only the addition product (213). If cyclization was occurring via a carbocation intermediate then cyclization should be facilitated by the use of polar, ionizing solvents. Reaction of cyclo-octadiene with phenylselenenyl chloride in acetic acid at room temperature gave only the addition product (214), however reaction at reflux for 18 hours gave a moderate yield of the [3.3.1] bicycles (215a) and (215b) in the ratio 52:48 (scheme 3.3.18). Formation of a carbon-carbon bond by selenium induced transannular cyclization of a diene has been previously reported by Clive\cite{73} and others.\cite{44,72,210}
Scheme 3.3.18
3.4 Miscellaneous reactions of selenones and proposals for future research

3.4.1 Reactions of β-selenonyl ethers and β-selenonyl ketones

Alcohols react with alkenes in the presence of phenylselenenyl halides to afford β-alkoxy selenides.\(^{57}\) It was thought that in a similar manner treatment of an alkene with phenylselenenyl chloride and a 1,2 diol followed by oxidation of the resultant selenide to the selenone, could result in the formation of a dioxane (scheme 3.4.1).

![Scheme 3.4.1]

Accordingly, styrene was treated with phenylselenenyl chloride and ethylene glycol for 18 hours, then oxidized in situ with excess MCPBA. This resulted only in the formation of the selenone (216), and none of the expected cyclized product. X-ray diffraction analysis of (216) (Appendix fig. 6.12) revealed the interatomic distance between the hydroxyl proton and the selenonyl oxygen to be 2.1 Å, which is indicative of a hydrogen bond.\(^{211}\) This hydrogen bonding accounts for the stability and consequential lack of reactivity of this reaction intermediate. Attempts to induce cyclization of (216) by treatment with potassium hydroxide or sodium hydride gave only the vinyl selenone (217), resulting from β-elimination of benzeneselenonic acid.

Reaction of cyclohexene with phenylselenenyl chloride and ethylene glycol followed by oxidation with MCPBA gave only the ester (218) (scheme 3.4.2). The protons adjacent to oxygen appeared as AA'XX' multiplets at 4.20 and 3.81 ppm, and the proton α to the carbonyl group as a quintet at 2.77 ppm in the \(^1\)H n.m.r. spectrum. The isolated material was identical to that synthesised from a Mitsunobo coupling\(^{212}\) of cyclopentane carboxylic acid with ethylene glycol, a method superior to reaction of cyclopentane carboxylic acid with thionyl chloride and ethylene glycol.
Small amounts of the hydroxyselenone (219) were also isolated from this reaction. It was possible that (219) was undergoing a 1,2 shift then being attacked by ethylene glycol in an analogous manner to scheme 3.1.2 to give the ester (218). However reaction of (107) with excess MCPBA in methanol gave none of the expected ester (220) (scheme 3.4.3). This suggests that (219) was not a reaction intermediate, but a minor product resulting from attack of adventitious water on the intitial cyclohexeneselenonium ion adduct and subsequent oxidation with MCPBA.

3.4.2 Proposals for further research

During the final year of work for this Ph.D. thesis the serendipitous discovery of the excellent leaving group ability of the phenylselenonyl moiety revealed a promising and relatively unexplored area of research in organoselenium chemistry. Due to the finite time available however, it was not possible to pursue many of the ideas put forward for study. The following discussion represents a brief summary of some of these ideas that are considered appropriate for further research.
Substitution reactions of secondary and tertiary selenones have not been investigated. A systematic study of the reactivity of such compounds towards substitutions with water, halides, cyanides, azides, alcohols, thiols, Grignard reagents as well as transition metal mediated couplings of these compounds should be undertaken (scheme 3.4.4).

Cyclization of functionalized alkenes with selenium reagents results in the concomitant incorporation of a selenium residue.\textsuperscript{40} Oxidation of this residue to a selenone, which may be displaced by an internal nucleophile could enable access to a wide variety of heterocycles. In this manner treatment of an alkene with phenylselenenyl halides in the presence of a molecule containing two nucleophilic groups, followed by oxidation of the resultant selenide with MCPBA, could lead to cyclized products with defined regio- and stereo-chemistry. Similarly, treatment of an alkene using a molecule containing a nucleophilic and an electron withdrawing group followed by oxidation to the selenone and treatment with a sterically hindered base may give heterocyclic products (scheme 3.4.4).

![Scheme 3.4.4](image-url)
The high electrophilicity of the central carbonyl of ninhydrin has been exploited in the synthesis of fused and spirocyclic ring systems.\textsuperscript{213} Is it possible that treatment of a $\beta$-hydroxyselelenide with ninhydrin followed by oxidation of the resultant adduct to a selenone could lead to an intermediate which may be hydrolysed to a diol (scheme 3.4.5). This methodology may provide a cheap, expeditious synthesis of cis 1,2 diols from alkenes.

Scheme 3.4.5

The facile formation of oxetanes via intramolecular displacement of selenones warrants further investigation. Treatment of the Grignard reagent derived from a $\beta$-bromo selenide with an aldehyde, followed by oxidation of the resultant hydroxy selenide with MCPBA, should afford a substituted oxetane. Alternatively, these compounds may be formed via alkylation of a hydroxy selenide with ethyl bromoacetate followed by oxidation and treatment with base. This methodology could be applied to the synthesis of the cancer therapy drug taxol.\textsuperscript{214} Addition of phenylselenenyl acetate to an allylic alcohol should result in the formation of an anti-
Markovnikov adduct with the phenylseleno group *syn* to the hydroxy group.\textsuperscript{85} Subsequent treatment with MCPBA would then result in cyclization and give the C-D rings of taxol (scheme 3.4.5).

Ketones may be able to be converted to epoxides by successive treatment with phenylselenenyl chloride, Grignard reagents then MCPBA (scheme 3.4.6).

![Scheme 3.4.6](image)

The previously unreported formation of *trans*-fused oxazolines from β-amido selenides warrants further investigation. The possible intermediacy of the β-bromoamide depicted in scheme 3.3.5 in the conversion of (180) to (186b) needs to be established. If the mechanism outlined in scheme 3.3.5 is correct then treatment of this bromoamide with phenylselenenyl chloride under reflux should afford the *trans*-oxazoline (186b).

The potential of benzeneselenonic acid as an efficient, mild oxidizing agent for the conversion of alcohols to aldehydes, ketones, and possibly even esters and lactones needs to be evaluated. In order to determine if this reagent is effecting transformation of the hydroxyamide (198) to the lactone (197), oxidations of (198) should be carried out with MCPBA alone, MCPBA and benzeneseleninic acid, and with benzeneselenonic acid and the reaction products monitored by $^{77}\text{Se}$ n.m.r. spectroscopy.
Chapter 4

Selenium induced radical cyclizations of unsaturated amines and amides

4.0 Introduction to radical cyclizations of organoselenium compounds

Free radicals have come to be recognised as important reactive intermediates in organic synthesis. This has been due mainly to an increased understanding of free radical processes\(^{215-217}\) and the ready availability of precursors and reagents designed specifically for radical-based synthesis.\(^{218}\) Work on the subject of organoselenium radicals was reviewed in 1973 by Shine,\(^{219}\) who commented on the paucity of well documented reactions of such species compared to the extensive literature on organosulfur radicals. It was not until 1976 that the \(\text{S}_2\text{H}2\) cleavage of alkyl phenyl selenides with tributyltin hydride was first investigated by Ingold and co-workers.\(^{220}\) Clive\(^{26,27,68,73}\) and Corey\(^{28}\) subsequently demonstrated the smooth reduction of a large variety of alkyl phenyl selenides with triphenyltin hydride and AIBN as a radical initiator. This reaction is initiated by homolysis of the tin hydride, which proceeds at elevated temperatures even in the absence of added initiator. Reduction products are formed via the radical chain mechanism outlined in scheme 4.0.1. The reactivity of phenyl selenides towards radical abstraction was determined\(^{220}\) to lie between chlorides and phenyl sulfides [I > Br > Cl > SePh > SPh > xanthate] and phenyl selenides have been selectively reduced in the presence of sulfides.\(^{27}\) The reductive cleavage of arylseleno groups with tin hydrides has been exploited in the synthesis of steroids, penicillins, macrolides and many other natural products.\(^{253}\) Selenium abstraction has also been effected by tris(trimethylsilylsilyl)silane,\(^{221}\) triphenyltin hydride in the presence of triethylborane and air,\(^{222}\) and by photolysis in the presence of phosphines.\(^{223}\)
The use of the phenylseleno group as a mediator of free radical cyclizations has only recently gained acceptance. Clive\textsuperscript{27} first reported the 1,5 exo cyclization of an unsaturated selenide with triphenyltin hydride in 1980 (scheme 4.0.1). In the last decade phenyl selenides have been employed as radical precursors in the synthesis of spiro compounds,\textsuperscript{224,225} macrocycles,\textsuperscript{226} pyrrolidines,\textsuperscript{227} and indolizidines.\textsuperscript{92,228,110} Phenylseleno esters\textsuperscript{229} and phenylseleno lactams\textsuperscript{110} have been employed as precursors to acylamino radicals, which undergo a wide variety of intermolecular and intramolecular alkene addition reactions.

Selenium induced cyclizations result in the concomitant incorporation of the phenylseleno moiety, a precursor to a free radical. It was envisaged that cyclization of a substrate such as the amide (230) with phenylselenenyl chloride and subsequent free radical cyclization of the resultant selenide (231) may provide an elegant, expeditious route to pyrrolizidines and indolizidines (scheme 4.0.2).
The cyclization of acetamides\textsuperscript{70} and benzamides\textsuperscript{126} has been effected by phenylselenenyl halides, however the resultant selenide in both cases was simply reduced to the alkane. The methodology for the free radical cyclization of nitrogen heterocycles is well established. Amides,\textsuperscript{230-232} lactams,\textsuperscript{92,228,232} sulfonamides\textsuperscript{233,234} and conjugated enamines\textsuperscript{235} have been utilized as key intermediates for free radical cyclization in the synthesis of a variety of pyrrolidine, indolizidine and indole alkaloids (scheme 4.0.3).

![Scheme 4.0.3](image)

The aims of the work presented in this chapter were to investigate the selenium induced cyclization of compounds such as (231) and to determine if such products could be elaborated to nitrogen containing bicyclic systems.
4.1 Attempted cyclizations of N-acryloyl 2-phenylselenomethylpyrrolidine

4.1.1 Synthesis of starting materials

The amide (230) was synthesised from 1-bromopent-4-ene via the Gabriel sequence\textsuperscript{157} (scheme 4.1.1). Reaction of this bromide with freshly prepared potassium phthalimide\textsuperscript{156} gave the phthalimide (60), which was deprotected\textsuperscript{157} with hydrazine hydrate in refluxing ethanol. The ethereal extracts containing the amine (61) were reacted directly with acryloyl chloride, prepared from reaction\textsuperscript{236} of acrylic acid and benzoyl chloride, under Schotten-Bauman conditions\textsuperscript{1} to give the amide (230) in good yield. This method proved superior to a similar reaction using acryloyl chloride and triethylamine, or attempted coupling of the amine with acrylic acid using DCC, or a direct synthesis from reaction of 1-bromopent-4-ene with acrylamide and sodium hydride.

\begin{center}
\begin{tikzpicture}
\node at (0,0) {\text{Br}};
\node at (1,0) {\text{C}_5\text{H}_{10}\text{Br}};
\node at (3,0) {\text{PhthK}};
\node at (4,0) {\text{DMF, } \Delta};
\node at (5,0) {\text{Phth}};
\node at (6,0) {\text{C}_5\text{H}_{10} \text{SePh}};
\node at (8,0) {\text{NH}_2\text{NH}_2};
\node at (9,0) {\text{EtOH}};
\node at (10,0) {\text{H}_2\text{N}};
\node at (11,0) {\text{C}_5\text{H}_{10} \text{SePh}};
\node at (12,0) {\text{EtOCOC}_2\text{H}_5 \text{NaOH}_{\text{aq}}};
\node at (13,0) {\text{C}_5\text{H}_{10} \text{NH}};
\end{tikzpicture}
\end{center}

Scheme 4.1.1

Toshimitsu has reported\textsuperscript{70} the cyclization of unsaturated acetamides with phenylselenenyl bromide in acetonitrile. Reaction of the amide (230) under these conditions however, gave only starting material. It is possible that the intermediate selenonium ion, formed from addition of phenylselenenyl bromide to the isolated double bond, was chelating to acetonitrile,\textsuperscript{136} as was the case with
the carbamate (13) in section 2.1.3. This would result in a less electrophilic carbon adjacent to selenium and hence a less reactive intermediate to be attacked by the acrylamide nitrogen. The acetamide (233), formed from reaction of the amine (252) (vide infra) with acetyl chloride, did undergo clean cyclization with phenylselenenyl bromide in acetonitrile to give the selenide (234), which reflects the greater nucleophilicity of the acetamide (233) compared to the acrylamide (230).

\[
\text{NH} \quad \text{COCH}_3 \\
\text{PhSeBr, CH}_3\text{CN} \\
\text{(233)} \rightarrow \text{COCH}_3 \\
\text{SePh} \\
\text{(234)}
\]

Scheme 4.1.2

Cyclization of (230) was effected by phenylselenenyl chloride or phenylselenenyl bromide when dichloromethane was used as solvent (scheme 4.1.2). The amide (231) could also be prepared in quantitative yield from the selenide (252) by reaction with acryloyl chloride and triethylamine. Initial interpretation of the $^1$H n.m.r. spectrum of (231) was difficult as the molecule existed as two rotamers on the n.m.r. time scale at room temperature. The olefinic protons appeared as doublets of doublets at 6.53, 6.24 and 5.49 ppm for one rotamer and at 6.35, 5.97 and 5.44 ppm for the other. These resonances were resolved to a single ABX splitting pattern when the n.m.r. was acquired in deuterated toluene at 60°C, or upon addition of a drop of titanium (IV) chloride to the sample.

4.1.2 Cyclization studies of 2-phenylselenomethyl-1-acryloylpyrrolidine (231)

Reaction of (231) with 1.2 equivalents of tributyltin hydride and 0.05 equivalents of AIBN as a radical initiator in degassed, refluxing benzene at 0.05M concentration gave only the reduction product (235), contaminated by significant amounts of tin by-products. These by-products were largely absent if an ethereal solution of the product was treated with DBU and an ethereal solution of iodine prior to chromatography. The reduction product (235) was obtained even if reaction was carried out at higher dilution and the tributyltin hydride and AIBN were added slowly to a refluxing solution of the selenide (231) and AIBN over four
hours. Tris(trimethylsilyl)silane (TTMSS) is an effective reducing agent for alkyl phenyl selenides$^{221,238}$ and often gives higher yields of cyclized products compared to oraganostannane reagents. This is because the Si-H bond is of higher energy than the Sn-H bond$^{239}$ and thus TTMSS does not quench an intermediate radical by donation of hydrogen as readily as tributyltin hydride. It was thought the use of this reagent may reduce the extent of direct reduction of the selenide (231) and expedite cyclization. Reaction of (231) with TTMSS and AIBN in either refluxing benzene, toluene or xylene however, gave only the addition products (238a) and (238b) (scheme 4.1.3). Addition of silyl radicals to double bonds is generally a very fast process$^{240}$ and the rate constants for these additions are comparable to the abstraction of the phenylseleno group by TTMSS [addition to CH$_2$=CHCO$_2$Et = (9.67±0.94) x 10$^7$ M$^{-1}$s$^{-1}$, abstraction of PhSeC$_{10}$H$_{21}$ = (9.63±1.26) x 10$^7$ M$^{-1}$s$^{-1}$]$^{221}$ The bis-silylmethylated products arise from further attack of silyl radical on the initial tris-silylmethylated addition products (scheme 4.1.4).

Scheme 4.1.3
Danishefsky has reported\textsuperscript{241} the reductive cyclization of organomercurials using sodium borohydride. However from reaction of (231) with sodium borohydride only starting materials were recovered. Alkyl phenyl selenides are known to be rapidly reduced by the more reactive nickel boride,\textsuperscript{29,30} formed \textit{in situ} from nickel chloride and sodium borohydride. Reaction of (231) with one equivalent of nickel boride gave not the expected indolizidine (240), but a mixture of the selenide (236) and the deselenated (237) (scheme 4.1.3). Nickel borohydride has recently been shown to be an effective agent for the 1,4-reduction of αβ-unsaturated aldehydes and ketones.\textsuperscript{242} It was likely that the products (236) and (237) arose from 1,4-reduction of the αβ-unsaturated amide competing with reductive deselenation. As the αβ-unsaturated system was destroyed by this facile reduction, no cyclization could occur.

Since all attempts to effect reductive cyclization of (231) were unsuccessful it was thought the desired product (240) may be formed instead \textit{via} an oxidative process. Elimination\textsuperscript{10,12,32,83} of the selenoxide (241) should yield the enamide (242), which may be induced thermally, or by Lewis acid, to cyclize to (240) (scheme 4.1.5).

Oxidation\textsuperscript{31} of the selenide (231) to the selenoxide (241) with MCPBA in dichloromethane at 0°C proved superior to oxidation with hydrogen peroxide\textsuperscript{6,31,32} or with sodium periodate.\textsuperscript{31} The selenoxide (241) decomposed upon standing over
several weeks to a mixture of (231), (245) and (246) (scheme 4.1.6), hence it was
generally used on the same day of preparation. Thermolysis\textsuperscript{160} of (241) in
refluxing carbon tetrachloride in the presence of anhydrous potassium carbonate
for one hour followed by chromatography gave a mixture of the selenide (231), the
alcohol (244) and the ring opened ketones (245) and (246) (scheme 4.1.6, table 4.1.7).

\[
\begin{align*}
(243) & \xrightarrow{H_2O} (244) \\
(241) & \xrightarrow{MCPBA} (242) \\
(241) & \xrightarrow{K_2CO_3, CCl_4, \Delta} (242) \\
(242) & \xrightarrow{H_2O} (245) \\
(242) & \xrightarrow{PhSe-OH} (246)
\end{align*}
\]

\textbf{Scheme 4.1.6}

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|c|c|c|}
\hline
\textbf{Conditions} & \textbf{(231)} & \textbf{(242)} & \textbf{(244)} & \textbf{(245)} & \textbf{(246)} \\
\hline
R.T. 4 weeks & 20\% & - & - & 56\% & 11\% \\
\hline
K_2CO_3, CCl_4, \Delta & 3\% & - & 10\% & 16\% & 7\% \\
\hline
DBU, CCl_4, \Delta & 3\% & 50\% & - & - & - \\
\hline
\end{tabular}
\caption{Reactions of the selenoxide (241)}
\end{table}
The alcohol (244) probably arose from the selenone (243) formed by oxidation\(^3\) of the selenoxide by MCPBA, and the selenide (231) from reduction\(^2\) of the selenoxide by phenylseleninic acid. Alternatively it is possible that (241) was disproportionating to a mixture of (243) and (231). The ketones (245) and (246) arose from hydrolysis of the enamide (242) and the corresponding phenylseleninic acid adduct respectively (scheme 4.1.6). Similar additions of phenylseleninic acid have been reported to occur with vinyl ethers\(^2\) and enamines\(^3\) to give \(\beta\)-selenoketones. The presence of the ketones (245) and (246) indicated that the desired enamide (242) was being formed, but that hydrolysis was occurring upon chromatography.

When the thermolysis of (241) was carried out in dry xylene in the presence of DBN and the crude reaction product was passed rapidly through a short column of dry silica it was possible to isolate the enamide (242), accompanied by some of the selenide (231). Attempts to induce cyclization of (242) by pyrolysis gave an intractable tar. Reaction with boron trifluoride etherate in refluxing ether or refluxing xylene gave only starting materials.

\(\alpha\)-Lithio selenoxides, prepared\(^1\) by an \textit{in situ} oxidation, deprotonation sequence from alkyl selenides, are known to react with aldehydes and ketones to afford allylic alcohols.\(^7\) Addition to \(\alpha\beta\)-unsaturated aldehydes and ketones generally occurs with 1,2 regioselectivity,\(^7\) however 1,4 addition predominates in the presence of HMPA.\(^2\) The product selenoxide is generally converted to the alkene upon workup,\(^3\) but may also be reduced back to a selenide with trimethyl phosphite.\(^8\) It was thought that an intramolecular reaction of the \(\alpha\)-lithio selenoxide (247) with a Michael acceptor may lead to the cyclized product (248) (scheme 4.1.8). However, reaction of (231) with 1.1 equivalents of MCPBA in dry THF at \(-78^\circ\)C, followed by 2.5 equivalents of LDA in the presence of HMPA and reductive workup with trimethylphosphite gave only starting material.
These results suggested that the acrylamido group of (231) and (242) most likely adopts a conformation in which there is little or no orbital overlap between the $\pi$ bond of the alkene and the methyl or methylene substituent bond at C₆. Modelling studies revealed that the rotamer (231b) is thermodynamically more stable than the rotamer (231a). As interconversion of (231b) to the desired precursor to cyclization (231a) is restricted by the double bond character of the C-N bond of the amide, there is little opportunity for a radical or a developing negative charge at C₆ to be captured by the double bond to precipitate cyclization (scheme 4.1.9).
4.2 Attempted cyclizations of N-alkylated 2-phenylselenomethylpyrrolidines

4.2.1 Synthesis of N-substituted 2-phenylselenomethylpyrrolidines

Since all attempts to cyclize the amide (231) were unsuccessful, it was thought that a substrate in which there was free rotation about the C-N bond of the N-substituent would be more suitable for cyclization. Accordingly, a variety of N-substituted pyrrolidines which lacked the exo carbonyl group were synthesised. Reaction of the amine (61) with BOC-ON and DMAP in dichloromethane gave the carbamate (250) in good yield. Reaction of (250) with phenylselenenyl phthalimide in dichloromethane for 18 hours gave yields of the selenide (251) superior to similar reaction with phenylselenenyl chloride or phenylselenenyl bromide. The selenide (251) was converted quantitatively to 2-phenylselenomethylpyrrolidine (232) by treatment with trifluoroacetic acid in dichloromethane for two hours (scheme 4.2.1).

N-alkylation was initially attempted using pyrrolidine as a model compound and 2-(bromomethyl)acrylate as an alkylating agent. It was thought over alkylation may occur in the reaction of this secondary amine with the alkyl
bromide, leading to formation of a quaternary, water soluble ammonium salt. Addition of the bromide to a solution of pyrrolidine and triethylamine in ethanol was thus carried out over four hours using a perfusor, then the reaction mixture was stirred at room temperature for 24 hours. This resulted in only a 21% yield of the desired alkylated product (253). T.l.c. examination of the reaction mixture indicated that a significant amount of starting material remained, even after reaction at room temperature for three days. When a mixture of 2-(bromomethyl)acrylate, pyrrolidine and triethylamine in dichloromethane was heated under reflux for two hours however, (253) could be obtained in 93% yield.

Scheme 4.2.2
Reaction of the selenide (252) under these conditions afforded the acrylate (254) in 89% yield. The alkyne (255) and the ester (256) were synthesised in a similar manner in high yield by reaction with propargyl bromide and ethyl bromoacetate respectively (scheme 4.2.2).

4.2.2 Cyclization studies of N-substituted 2-phenylselenomethylpyrrolidines

Reaction of the alkyne (255) with 1.2 equivalents of tributyltin hydride and 0.05 equivalents of AIBN in degassed, refluxing benzene at 0.05M concentration gave only starting materials accompanied by a very low yield of the stannane (257) (scheme 4.2.3). The $^1$H n.m.r. spectrum of (257) showed resonances corresponding to a butyl group, but none for the acetylenic proton. The two protons adjacent to the triple bond, which in (255) appeared at 3.51 ppm as doublets weakly coupled to the acetylenic proton, appeared at 3.90 ppm as a singlet in (257). A weak molecular ion and fragmentations corresponding to the loss one and three butyl moieties from the molecular ion were detected under conditions of fast atom bombardment. Stannylation at the terminal position of the alkyne was unexpected as any interaction of tributyltin radical with an alkyne normally results in the formation of a vinylstannane.\textsuperscript{247} It is possible that (257) arises from deprotonation of the alkyne, followed by nucleophilic attack of the resultant anion on tributyltin oxide, a common contaminant of tributyltin hydride. Starting materials were obtained upon slow addition of the reagents to the alkyne in high dilution [0.02M] using between two to four equivalents of tributyltin hydride with either benzene, toluene or xylene as solvent. Reaction of (255) with TTMSS or freshly prepared\textsuperscript{248} triphenyltin hydride under these conditions also gave only starting materials (scheme 4.2.3).
Reaction of the acrylate (254) with tributyltin hydride or freshly prepared triphenyltin hydride under the above conditions gave only starting materials. Reaction using TTMSS gave starting materials accompanied by the silane (258), formed from competing addition of the silyl radical to the double bond\(^2\) (scheme 4.2.3). Upon extended reaction times it was also possible to isolate a small amount of the amine (252) resulting from homolysis of the C-N bond of the N-substituent.

Despite numerous attempts using a variety of radical inducers and reaction conditions, the selenides (254) and (255) could not be induced to cyclize. The absence of any direct reduction product indicated that selenium abstraction to form a carbon centered radical at C\(_6\) was not occurring. Although 1,5 exo dig and 1,6 endo trig free radical cyclizations have been widely utilised in the formation of pyrrolidines and piperidines,\(^92,94,110,228,230-233,235\) only two such cyclizations have been reported in which there was no electron withdrawing group adjacent to nitrogen. Danishefsky\(^227\) has utilized the free radical cyclization of the stannyl selenide (260) in the synthesis of 3-demethoxyerythratidinone (261) and
Watanabe\textsuperscript{249} has induced cyclization of the highly reactive trichloromethylamine (262) to form the pyrrolidine (263) (scheme 4.2.4).

In the few cases in which unsuccessful attempts at free radical cyclization of free amines have been reported in the literature,\textsuperscript{233,234} the formation of an $\alpha$-amino radical has been invoked to account for the absence of cyclized product. It is likely that in the case of the alkyne (255) and the acrylate (254), abstraction of the allylic or propargylic hydrogen, leading to a stabilized captodative radical,\textsuperscript{250,251,252} is more facile than abstraction of selenium. Cyclization of (260) can occur as the protons $\alpha$ to nitrogen are not allylic and cyclization of (262) occurs as generation of the dichloromethane radical is much faster\textsuperscript{253} than abstraction of the allylic proton. It is also possible that the tertiary amine was reacting directly with tributyltin radical or an intermediate radical to form an anion and an aminium radical cation,\textsuperscript{252} effectively disrupting propagation of the radical chain reaction (scheme 4.2.5).
In an attempt to induce cyclization of the acrylate (254) via the enamine (259), (254) was treated with hydrogen peroxide in dichloromethane, followed by thermolysis in refluxing carbon tetrachloride with anhydrous potassium chloride (scheme 4.2.6). Unfortunately this gave a complex mixture of unidentifiable products.

Attempts to induce cyclization of the acrylate (256) via an α-lithioselenoxide, as described in section 4.1.2, also gave a mixture of unidentifiable products. It was possible that the selenoxide was being converted to an enamine via β-elimination of “PhSeOH” with LDA (scheme 4.2.7). Decomposition of the enamine then lead to the complex product mixture.
observed.

Scheme 4.2.7
4.3.1 Free radical cyclization of β-acrylamido selenides

Attempted cyclizations of the amide (231) were unsuccessful due to the rigid amide bond obstructing formation of the geometry required for cyclization. Attempted cyclizations of the amines (254) and 255) were unsuccessful due to the assistance of the electron rich nitrogen stabilising an α-amino radical. These results suggested that a compound in which the electron donating ability of the nitrogen atom was reduced, but rotation of the electron acceptor towards a radical centre was not constrained, would prove more suitable for study. The acrylamide (265), in common with (231), possesses an exo carbonyl bond, however the vinyl bond may still freely rotate towards a radical centre, which should predispose it towards radical induced cyclization.

The acrylamide (265) was synthesised from the hydroxyselenide (107) by reaction with aqueous triflic acid in refluxing acrylonitrile (scheme 4.3.1). This amide was then cyclized cleanly to the lactam (266) by reaction with tributyltin hydride and AIBN in refluxing benzene at [0.05M] for six hours.

![Scheme 4.3.1](image-url)
In a similar manner, the alkyne (267), synthesised by alkylation of (107) with propargyl bromide and sodium hydride, gave a mixture of the alkene (268) and the bis-trimethylsilyl adduct (269) upon treatment with TTMSS and AIBN in refluxing benzene (scheme 4.3.2).

\[
\text{(107)} \xrightarrow{\text{SePh}} \xrightarrow{\text{Br}} \xrightarrow{\text{NaH, THF}} \text{(267)} \xrightarrow{\text{TTMSS, AIBN}} \xrightarrow{\text{PhH, } \Delta} \text{(268)} \xrightarrow{\text{Si(SiMe}_3)_2} \quad \text{(269)}
\]

Scheme 4.3.2

The work presented in this chapter has shown that the easily accesible selenides (265) and (267) undergo facile radical induced cyclization by abstraction of a phenylseleno group. Much time and effort was spent attempting to induce radical cyclizations of N-alkylated pyrrolidines to no avail, however the succesful cyclization of N-alkylated \( \beta \)-amido selenides was a gratifying, if belatedly successful result. Ahh, the joys of research, the laughter, the tears, the inspiration, the near lethal concentration of caffeine in my system .... at last it is finished. Think I’ll go have a beer - if you’ve just read this tome from end to end have one for me too!
Chapter 5

Experimental

5.1 General experimental

Infrared spectra were recorded on a Jasco A-102 spectrometer as nujol mulls or liquid films, or as solutions where indicated. $^1$H n.m.r., $^{13}$C n.m.r. and all two dimensional n.m.r. spectra were obtained at 300 MHz on a Brucker ACP-300 spectrometer. DQFCOSY, NOESY, HETCORR and RLCOSY spectra were recorded at a constant 20°C in phase sensitive mode using time proportional phase incrementation to give quadrature detection in $f_1$. Routinely 2048 data points were recorded in $f_1$ and 512 in $f_2$, with 64 transients at each value of $t_1$. nOE samples were degassed by freeze-pump-thawing (4 cycles) and run at a constant 20°C. NOESY spectra were recorded with mixing times between 5 and 200ms and a z-filter was employed to suppress zero quantum artefacts. $^1$H n.m.r. spectra were recorded as solutions in deuterochloroform, using tetramethylsilane as an internal standard unless otherwise specified. $^{77}$Se n.m.r. spectra were obtained at 300 MHz on a Brucker CXP-300 spectrometer with a spectral width of 100kHz and a digital resolution of 6 Hz/point using diphenyldiselenide ($\delta = 463$ppm) as an external standard. $^{19}$F n.m.r. spectra were obtained at 300 MHz on a Brucker CXP-300 spectrometer using trifluoroacetic acid ($\delta = 0$ppm) as an external standard. Electron impact mass spectra were recorded at 70 eV on an AEI 3074 mass spectrometer. Fast atom bombardment mass spectra and CA-MIKES spectra were recorded on a V.G. ZAB 2HF mass spectrometer. Optical rotations were carried out in ethanol with a 5 cm cell using a Perkin Elmer 141 spectropolarimeter. Melting points were recorded on a Kofler hot-stage apparatus equipped with a Reichert microscope, and are uncorrected. Microanalyses were performed by the Australian Microanalytical Service, Melbourne.
Preparative chromatography was performed using Merck Kieselgel PF254 silica using, unless otherwise stated, a Chromatotron 7924T (Harrison Research, Palo Alto/TC Research, California), eluting with a gradient of light petroleum/ethyl acetate. Flash chromatography was performed using Merck Kieselgel 60 (230-400 mesh) eluting with a gradient of light petroleum/ethyl acetate. High performance liquid chromatography (HPLC) was carried out using a Waters Model 501 solvent delivery system and a U6K injector with a Waters Model 481 absorbance detector. Analyses were performed using a Waters Z-module with a Waters Radial-PAK™ C18 reverse phase cartridge (10cm x 8mm) eluting with a methanol/water gradient.

All solvents were purified by distillation and dried using standard laboratory procedures. All organic extracts were dried over anhydrous sodium sulphate unless otherwise specified. Light petroleum refers to the fraction with boiling range 66-69°C. Phenylselenenyl chloride, phenylselenenyl bromide and phenylselenenyl iodide were obtained from Aldrich® Australia and were used without further purification. Phenylselenenyl phthalimide was synthesised according to the method of Nicolaou. MCPBA was recrystallized from dichloromethane/light petroleum and was 85% pure as determined by epoxidations of a stoichiometric amount of cyclohexene. Sodium hydride was used as a 60% dispersion in oil. “Block” distillation refers to a short path micro-distillation using a sublimating block.
5.2 Work described in Chapter 2

3-Hydroxypent-4-enonitrile (11)\textsuperscript{122}

To a stirred mixture of acetonitrile (8 ml) in dry THF (120 ml) at -78°C under nitrogen was added a solution of n-butyllithium (44 ml [2.5M solution in hexane], 0.11 mol) dropwise over 10 min. The mixture was stirred at -78°C for 2 h then acrolein (8.0 ml, 0.12 mol) added in one portion. The mixture was stirred at this temperature for a further 3 min. then quenched by the addition of 2N hydrochloric acid (47.5 ml, 0.095 mol). The majority of solvents were removed under reduced pressure, the residue extracted with ether (2x50 ml), the extracts dried and the solvent removed under reduced pressure to give the nitrile (11) (8.44g, 87%) as a light yellow oil. \(^1\)H n.m.r.: 5.87, ddd (J 17.1, 10.6, 6.6Hz), CH\(=\)CH\(_2\); 5.24, dd (J 1.8, 17.1Hz), CH\(_a\)H\(_b\)=CH ; 5.08, dd (J 1.8, 10.6Hz), CH\(_a\)H\(_b\)=CH ; 4.30, m, CHO\(_{OH}\); 3.20, s, OH ; 2.58, d (J 7.2 Hz), CH\(_2\). \(\nu_{\text{max}}\) : 3420, 2250, 1640 cm\(^{-1}\). Mass spectrum: 98 (M+H), 80 (M-OH), 57 (M-C\(_2\)H\(_2\)N).

5-Aminopent-1-ene-3-ol (12)\textsuperscript{122}

To a stirred suspension of lithium aluminium hydride (2.2g, 55mmol) in dry ether (150 ml) under nitrogen was added a solution of the nitrile (11) (3.2g, 33mmol) in dry ether (25 ml) dropwise, maintaining a gentle reflux. The mixture was heated under reflux for a further 2.5 h then quenched by the addition of 15% sodium hydroxide (10 ml). The cooled mixture was filtered, the solid residue washed with THF (50 ml), the filtrate dried and the solvent removed under reduced pressure to give a yellow oil which was purified by distillation to give the amine (12) (2.75g, 83%). b.p. 114-116°C, 0.05mm. \(^1\)H n.m.r.: 5.87, ddd (J 17.1, 10.6, 6.6Hz), CH\(=\)CH\(_2\); 5.24, dd (J 1.8, 17.1Hz), CH\(_a\)H\(_b\)=CH ; 5.08, dd (J 1.8, 10.6Hz), CH\(_a\)H\(_b\)=CH ; 4.15, m, CHO\(_{OH}\); 3.00, m, CH\(_2\)N ; 2.86, br m, NH\(_2\) OH ; 1.66, m, CH\(_2\). \(\nu_{\text{max}}\) : 3350, 3180, 1640, 1600 cm\(^{-1}\). Mass spectrum: 102 (M+H), 84 (M-OH).
Ethyl N-(3-hydroxy-4-pentenyl)carbamate (13)

To an emulsified mixture of the amine (12) (1.01g, 10mmol) in water (30 ml) at 0°C was added ethyl chloroformate (0.65g, 6mmol). The emulsion was stirred at 0°C for 5 min. then a second portion of ethyl chloroformate (0.65g, 6mmol) added, followed immediately by a solution of sodium hydroxide (0.5g, 1.2mmol) in water (5 ml). The mixture was stirred at 0°C for further 1.5 h, and extracted with ethyl acetate (3x20 ml). The combined organic extracts were washed with 1N hydrochloric acid (10 ml), then 10% sodium bicarbonate (10 ml). The organic phase was separated, dried, the solvent removed under reduced pressure and the residue chromatographed to give the carbamate (13) (1.53g, 89%) as a light yellow oil. b.p. 115-118°C, 0.013mm (block). Found: C 55.18% H 8.58% N 8.09%. C₈H₁₈NO₃ requires C 55.47% H 8.73% N 8.09%. ¹H n.m.r.: 5.87, ddd (J 17.1, 10.6, 6.6 Hz), CH=CH₂; 5.79, s, NH; 5.24, dd (J 1.8, 17.1 Hz), CH₃H₁=CH; 5.08, dd (J 1.8, 10.6 Hz), CH₃H₂=CH; 4.19, s, OH; 4.17, m, CHOH; 4.08, q (J 6.9 Hz), CH₂CH₃; 3.29, m, CH₂N; 1.71, m, CH₂; 1.22, t (J 6.9 Hz), CH₃. υ_max : 3600, 3450, 1705, 1510 cm⁻¹. Mass spectrum: 174 (M+H), 156 (M-OH), 102 (M-CO₂Et).

N-(3-Hydroxy-4-pentenyl)-4-toluenesulfonamide (14)

To a stirred mixture of the amine (12) (505mg, 5mmol) in dry pyridine (10 ml) under nitrogen at 0°C was added portionwise tosyl chloride (1.05g, 5.5mmol). The mixture was stirred at this temperature for 4 h, diluted with ethyl acetate (40 ml) and washed with 1N hydrochloric acid (2x40 ml), then 10% sodium bicarbonate (20 ml). The organic phase was separated, dried, the solvent removed under reduced pressure and the residue recrystallized (ethyl acetate/ether/light petroleum) to give the sulfonamide (14) (1.11g, 88%) as white needles, m.p. 70-71.5°C. Found: C 56.38% H 6.68% N 5.46%. C₁₂H₁₇NO₃S requires C 56.45% H 6.71% N 5.49%. ¹H n.m.r.: 7.75, d (J 8.2 Hz), 2H; 7.30, d (J 8.2 Hz), 2H; 6.91, s, NH; 5.79, ddd (J 17.1, 10.6, 6.6 Hz), CH=CH₂; 5.18, dd (J 1.8, 17.1 Hz), CH₃H₁=CH; 5.08, dd (J 1.8, 10.6 Hz), CH₃H₂=CH; 4.24, m, CHOH; 3.80, br s, OH; 3.08, m, CH₂N; 2.42, s, ArCH₃;
**Experimental 5.2.1**

1.71, m, CH$_2$. $\nu_{\text{max}}$ : 3350, 3250, 1160, 815 cm$^{-1}$. Mass spectrum: 256 (M+H), 238 (M-OH), 184 (M-C$_4$H$_6$OH), 155 (M-SO$_2$PhCH$_3$).

$t$-Butyl N-(3-hydroxy-4-pentenyl)carbamate (15)

To an emulsified mixture of the amine (12) (101mg, 1mmol) in water (10 ml) at 0°C was added portionwise BOC-ON (271mg, 1.1mmol) followed by a solution of sodium hydroxide (44mg, 1.1mmol) in water (1 ml). The mixture was warmed to room temperature and stirred for a further 6 h. The mixture was then diluted with ethyl acetate (20 ml) and washed with hydrochloric acid (2x10 ml), then 10% sodium bicarbonate (10 ml). The organic phase was separated, dried, the solvent removed under reduced pressure and the residue chromatographed to give the carbamate (15) (133mg, 68%) as a colourless oil, b.p. 108°C, 0.01mm (block). Found: C 59.36%, H 9.59%, N 6.79%. C$_{10}$H$_{19}$NO$_3$ requires C 59.67%, H 9.52%, N 6.96%. $^1$H n.m.r.: 5.87, ddd (J 17.1, 10.6, 6.6 Hz), CH=CH$_2$; 5.42, br s, NH; 5.24, dd (J 1.8, 17.1 Hz), CH$_a$H$_b$=CH; 5.08, dd (J 1.8, 10.6 Hz), CH$_a$H$_b$=CH; 4.18, m, CH$_2$OH; 4.03, s, OH; 3.32, m, CH$_a$N; 3.15, m, CH$_b$N; 1.64, m, CH$_2$; 1.44, s, 9H. $\nu_{\text{max}}$ : 3340, 1685, 1520 cm$^{-1}$. Mass spectrum: 202 (M+H), 145 (M-tBu), 101 (M-CO$_2$tBu).

N-(3-Acetoxy-4-pentenyl)acetamide (16)

To a mixture of the amine (12) (101mg, 1mmol) and triethylamine (404 mg, 4mmol) in dry THF (10 ml) under nitrogen at 0°C was added acetyl chloride (286 ml, 4mmol) dropwise over 2 min. The resultant solution was warmed to room temperature and stirred overnight. The solvent was then removed under reduced pressure, the residue diluted with ethyl acetate (20 ml), washed with 1N hydrochloric acid (2x10 ml), 10% sodium bicarbonate (10 ml). The organic was phase separated, dried, the solvent removed under reduced pressure and the residue chromatographed to give the acetate (16) (142mg, 77%) as a colourless oil, b.p. 135°C, 0.06mm (block). HRMS: 185.1056 C$_9$H$_{15}$NO$_3$ requires 185.1052. $^1$H n.m.r.: 5.9, s, NH; 5.80, ddd (J 17.1, 10.6, 6.6 Hz), CH=CH$_2$; 5.32, m, 1H; 5.25, dd (J 1.8, 17.1 Hz), CH$_a$H$_b$=CH; 5.19, dd (J 1.8, 10.6 Hz), CH$_a$H$_b$=CH; 3.46, m, CH$_a$N; 3.08, m,
\[ \text{Experimental} \]

CH\(_{12}\)N : 2.09, s, OCOCH\(_3\) ; 1.98, s, NCOCH\(_3\) ; 1.83, m, CH\(_2\). \( \nu_{\text{max}} \) : 3300, 1735, 1650, 1240 cm\(^{-1}\). Mass spectrum: 185 (M\(^+\)), 126 (M-OCOCH\(_3\)).

Table 5.2.1: Selenium induced cyclization of N-protected 3-hydroxy-4-pentenylamines

<table>
<thead>
<tr>
<th>Substrate</th>
<th>PhSeX</th>
<th>Reaction conditions</th>
<th>Product ratio (yield)</th>
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<td>13</td>
<td>Cl</td>
<td>CH(_2)Cl(_2), 2a, 4h</td>
<td>19a/19b 75/25 (88)</td>
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<td>CHCl(_3), 2b, 30 min</td>
<td>85/15 (88)</td>
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<td>dioxane, 2b, 40 min</td>
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<td>Br</td>
<td>CH(_2)Cl(_2), 2a, 2 h</td>
<td>79/21 (95)</td>
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<td>CHCl(_3), 2b, 20 min</td>
<td>87/13 (95)</td>
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<td>SO(_4)</td>
<td>CH(_2)Cl(_2), 2a, 4 h</td>
<td>72/28 (84)</td>
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<td>Phth</td>
<td>CH(_2)Cl(_2), 2a, 48 h</td>
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<td>Cl</td>
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<td>20a/20b 74/26 (56)</td>
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<td>80/20 (60)</td>
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<td>CHCl(_3), 2b, 20 min</td>
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<td>CH(_2)Cl(_2), 2a, 3 h</td>
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<td>72/28 (84)</td>
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<td>Cl</td>
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<td>&gt;99/&lt;1 (23)</td>
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<td>CHCl(_3), 2b, 1 h</td>
<td>&gt;99/&lt;1 (40)</td>
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2a= -78°C 10 min then to RT, 2b= 0°C 10 min then to RT, * determined by HPLC:

none of the trans isomer could be isolated

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N-(3-hydroxy-4-pentenyl)acetamide (17)

A mixture of the acetate (16) (400mg, 2.1mmol) and barium hydroxide (680 mg, 2.1mmol) in methanol (20 ml) was stirred at room temperature for 1 h. The solution was filtered through celite, the celite washed with methanol (10 ml) and the solvent removed under reduced pressure to give the amide (17) (300 mg, 100%) as a colourless oil, b.p. 142°C, 0.02mm (block). Found: C 58.89% H 9.11% N 10.15%

C7H13NO2 requires: C 58.89% H 9.15% N 9.78%. 

1H n.m.r.: 6.45, s, NH; 5.87, ddd (J 17.1, 10.6, 6.6 Hz), CH=CH2; 5.24, dd (J 1.8, 17.1 Hz), CHaHb=CH; 5.08, dd (J 1.8, 10.6 Hz), CHaHb=CH; 4.17, m, CHOH; 3.56, s, OH; 3.24, dt (J 8.3, 1.8 Hz), CHaN; 3.18, dt (J 8.3, 1.8 Hz), CHbN; 1.99, s, CH3; 1.72, m, 1H; 1.62, m, 1H. v max : 3250, 1630, 1540 cm⁻¹. Mass spectrum [FAB]: 144 (M+H), 126 (M-OH).

2-(R*)-Phenylselenomethy-3(R*)-hydroxypyrrolidine-1-tosylate (18a) and 2-(S*)-phenylselenomethy-3(R*)-hydroxypyrrolidine-1-tosylate (18b)

Method 2a: To a stirred mixture of the sulfonamide (14) (254mg, 1mmol), dry silica (250mg), and anhydrous potassium carbonate (250mg) in dry dichloromethane (10 ml) under nitrogen at -78°C was added a solution of phenylselenenyl chloride (230mg, 1.2mmol) in dry dichloromethane (3 ml) dropwise over 5 min. The mixture was stirred at -78°C for 10 min. then at room temperature for 3h. The solution was filtered through celite, the celite washed with ethyl acetate, the filtrate concentrated under reduced pressure and the residue chromatographed to give a mixture of the cis and trans pyrrolidines (18a) and (18b) which was fractionally recrystallized (ethyl acetate/ether/light petroleum) to give (18a) as translucent needles, m.p. 110-112°C. Found: C 52.36% H 5.15% N 3.47%

C18H21NO3SSe requires C 52.68% H 5.16% N 3.41%. 

1H n.m.r.: 7.62, m, 2H; 7.37, m, 3H; 7.44 and 7.37, d (J 8.2 Hz), C6H4; 4.37, m, H3; 3.71, dd (J 12.3, 3.6 Hz), H6a; 3.56, dt (J 5.8, 10.8 Hz), H5a; 3.46, dddd (J 11.8, 3.6, 4.0 Hz), H2; 3.44, dt (J 5.8, 10.8 Hz), H5b; 3.20, dd (J 12.3, 11.8 Hz), H6b; 2.38, s, ArCH3; 2.34, br s, OH; 1.66, m, H4a; 1.17, m, H4b. 

13C n.m.r.: 144.1, 133.9, 129.4, 127.2 (Ar); 71.8 (C3); 63.7 (C7); 47.7 (C2); 32.6 (C5);
Experimental 5.2.1

26.7 (C₄) ; 20.6 (MePh). nOE (% enhancement): H₂H₃ (4.1), H₂H₆a (1.6), H₂H₆b (0.8), H₃OH (2.4), H₃H₄a (3.0), H₃H₄b (1.8), H₄aH₄b (11.0), H₆aH₆b (17.5). vₘₐₓ: 3400, 1660, 1580, 1480 cm⁻¹. Mass spectrum: 411 (M⁺), 255 (M-SePh), 241 (M-CH₂SePh). The supernatant of recrystallization was then concentrated and the residue recrystallized to give (18b) as white crystals, m.p. 139-141°C. ¹H n.m.r.: 7.80, m, 2H ; 7.63, m, 3H ; 7.37 and 7.24, d (J 8.2 Hz), C₆H₄ ; 4.04, dt (J 6.4, 12.9 Hz), H₃ ; 3.73, dd (J 12.3, 8.9 Hz), H₆a ; 3.63, dt (J 6.5, 10.6 Hz), H₅a ; 3.51, ddd (J 6.4, 1.8, 8.9 Hz), H₂ ; 3.43, dd (J 12.3, 1.8 Hz), H₆b ; 3.06, dt (J 6.5, 10.6 Hz), H₅b ; 2.41, s, ArCH₃ ; 2.30, br s, OH ; 1.91, m, H₄a ; 1.61, m, H₄b. ¹³C n.m.r.: 147.2, 131.4, 129.8, 127.4 (Ar) ; 71.1 (C₃) ; 59.7 (C₇) ; 46.9 (C₂) ; 32.4 (C₅) ; 27.7 (C₄) ; 22.0 (MePh). nOE (% enhancement): H₂H₃ (0.5), H₂H₆a (1.5), H₂H₆b (0.8), H₃OH (2.3), H₃H₄a (3.0), H₃H₄b (1.5), H₄aH₄b (10.1), H₆aH₆b (17.0). vₘₐₓ: 3400, 1660, 1580, 1480 cm⁻¹. Mass spectrum: 411 (M⁺), 255 (M-SePh), 241 (M-CH₂SePh).

Ethyl 2(R*)-phenylselenomethyl-3(R*)-hydroxypyrrolidine-1-carboxylate (19a) and ethyl 2(S*)-phenylselenomethyl-3(R*)-hydroxypyrrolidine-1-carboxylate (19b)

Method 2b: To a solution of the carbamate (13) (173mg, 1mmol), dry silica (250mg), and anhydrous potassium carbonate (250mg) in dry chloroform (10 ml) under nitrogen at 0°C was added a solution of phenylselenenyl chloride (230mg, 1.2mmol) in dry chloroform (3 ml) dropwise over 5 min. The mixture was stirred at 0°C for 10 min. then at room temperature for 30 min. The solution was filtered through celite, the celite washed with ethyl acetate, the filtrate concentrated under reduced pressure and the residue chromatographed to give the cis pyrrolidine (19a) as white crystals (272mg, 83%), m.p. 89-90°C. Found: C 51.17% H 5.64% N 4.25% C₁₄H₁₉NO₃Se requires C 51.22% H 5.83% N 4.27%. ¹H n.m.r. (CDCl₃, 50°C): 7.57, m, 2H ; 7.28, m, 3H ; 4.54, m, H₃ ; 4.10, q (J 6.9 Hz), CH₂CH₃ ; 3.69-3.42, m, 3H ; 3.47, dd (J 12.3, 3.6 Hz), H₆a ; 3.08, dd (J 12.3, 10.9 Hz), H₆b ; 2.51, br s, OH ; 1.94, m, H₄aH₄b ; 1.22, t (J 6.9 Hz), CH₃. ¹³C n.m.r. (CDCl₃, 50°C): 155.4 (C=O) ; 132.3, 131.6, 129.1, 126.6 (Ar) ; 72.1 (C₃) ; 61.1 (CH₂O) ; 44.6 (C₆) ; 32.5 (C₂) ; 32.0 (C₅) ; 25.4 (C₄) ; 14.6 (CH₃). vₘₐₓ: 3420, 1670, 1580, 1480 cm⁻¹. Mass spectrum: 329 (M⁺), 172 (M-SePh), 158 (M-
Further elution gave the trans pyrrolidine (19b) as a light yellow oil (41mg, 12%). ¹H n.m.r. (CDCl₃, 50°C): 7.54, m, 2H; 7.24, m, 3H; 4.35, m, H₃; 4.09, q (J 6.9 Hz), CH₂CH₃; 3.85, m, H₂; 3.63-3.40, m, H₅₈H₅₉; 3.30, dd (J 12.3, 3.0 Hz), H₆₈a; 2.63, br s, OH; 2.55, dd (J 12.3, 11.8 Hz), H₆₉b; 2.04, m, H₄₈a; 1.88, m, H₄₉b; 1.24, t (J 6.9 Hz), CH₃. ¹³C n.m.r (CDCl₃, 50°C): 155.8 (C=O); 134.9, 132.1, 130.5, 129.1 (Ar); 74.2 (C₃); 61.1 (CH₂O); 44.6 (C₆); 31.4 (C₂); 30.0 (C₅); 27.9 (C₄); 14.5 (CH₃). v_max: 3350, 1660, 1580, 1480 cm⁻¹. Mass spectrum: 329 (M⁺), 172 (M-SePh), 158 (M-CH₂SePh).

Using method 2b with the carbamate (15) (201mg, 1mmol), dry silica (250mg), anhydrous potassium carbonate (250mg) and phenylselenenyl chloride (230mg, 1.2mmol) gave the cis pyrrolidine (20a) translucent needles (21.9mg, 62%), m.p. 101-103°C. Found: C 54.01% H 6.83% N 4.08% C₁₆H₂₃NO₃Se requires C 53.93% H 6.51% N 3.93%. ¹H n.m.r. (CDCl₃, 50°C): 7.63, m, 2H; 7.10, m, 3H; 4.49, m, H₃; 3.96, m, H₂; 3.51, m, H₅₈H₅₉; 3.38, dd (J 12.3, 3.6 Hz), H₆₈a; 3.02, dd (J 12.3, 11.8 Hz), H₆₉b; 2.09, br s, OH; 1.88, m, H₄₈aH₄₉b; 1.36, s, 9H. ¹³C n.m.r. (CDCl₃, 50°C): 154.6 (C=O); 133.1, 131.5, 129.2, 127.5 (Ar); 88.1 (CMe₃); 74.0 (C₃); 43.3 (C₆); 32.4 (C₂); 30.6 (C₅) 28.7 (C₄); 28.4 (CH₃). v_max: 3410, 1660, 1460 cm⁻¹. Mass spectrum: 355 (M⁺), 138 (M-SePh), 124 (M-CH₂SePh). Further elution gave the trans pyrrolidine (20b) as a light yellow oil (39mg, 8%). ¹H n.m.r. (CDCl₃, 50°C): 7.63, 2H; 7.14, m, 3H; 4.31, m, H₃; 3.73, m, H₂; 3.50, m, H₅₈; 3.32, m, H₅₉; 3.19, dd (J 12.3, 3.2 Hz), H₆₈a; 2.85, br s, OH; 2.51, dd (J 12.3, 11.6 Hz), H₆₉b; 1.95, m, H₄₈a; 1.76, m, H₄₉b; 1.37, s, 9H. ¹³C n.m.r. (CDCl₃, 50°C): 154.4 (C=O); 132.9, 131.9, 129.0, 127.1 (Ar); 87.8 (CMe₃); 75.1 (C₃); 65.3 (CMe₃O); 44.6 (C₆); 30.9 (C₂); 30.2 (C₅); 29.6 (C₄); 28.5 (CH₃). v_max: 3400, 1660, 1460 cm⁻¹. Mass spectrum: 355 (M⁺), 138 (M-SePh), 124 (M-CH₂SePh).
N-Acetyl-2(R*)-phenylselenomethyl-3(R*)-hydroxypyrrolidine (21)

Using method 2b with the amide (17) (143mg, 1mmol), dry silica (250mg), anhydrous potassium carbonate (250mg) and phenylselenenyl chloride (230mg, 1.2mmol) gave the cis pyrrolidine (21) as white crystals, m.p. 150-151°C. Found: C 52.18% H 5.68% N 4.62% C13H17NO2Se requires C 52.35% H 5.75% N 4.70%. \(^1\)H n.m.r.: 7.63, m, 2H; 7.22, m, 3H; 4.50, dt (J 5.1, 5.6 Hz), H, 3.70, dd (J 12.2, 3.5 Hz), H, 3.61, m, 3H; 3.09, dd (J 12.2, 9.9 Hz), H; 3.08, br s, OH; 2.05, m, H, 1.99, s, COCH3. \(^1\)C n.m.r.: 206.5 (C=O); 132.2, 130.0, 128.4, 125.1 (Ar); 69.6 (C3); 60.1 (C6); 45.2 (C2); 32.0 (C5); 28.7 (C4); 21.8 (CH3). \(\nu_{max}\) : 3400, 1630, 1060 cm\(^{-1}\). Mass spectrum: 299 (M\(^+\)), 142 (M-SePh), 128 (M-CH2SePh).

Ethyl N-(3-acetoxy-4-pentenyl)carbamate (24)

To a stirred mixture of the carbamate (13) (692mg, 4mmol) and triethylamine (505mg, 5mmol) in dry THF (20 ml) under nitrogen at 0°C was added acetyl chloride (430ml, 6mmol) dropwise over 2 min. The mixture was warmed to room temperature and stirred for a further 24 h. The solvent was removed under reduced pressure, the residue redissolved in ethyl acetate (50 ml), washed with 1N hydrochloric acid (2x10 ml), then 10% sodium bicarbonate (10 ml). The organic phase was separated, dried, the solvent removed under reduced pressure and the residue chromatographed to give the acetate (24) (688mg, 80%) as a colourless oil, b.p. 101°C, 0.02mm (block). Found: C 71.15% H 8.18% N 2.40% C24H33NO3Si requires C 71.03% H 8.08% N 2.40%. \(^1\)H n.m.r.: 5.80, ddd (J 17.1, 10.6, 6.6 Hz), CH=CH2; 5.34, m, CHOH; 5.22, dd (J 1.8, 17.1 Hz), CHaHb; 5.19, dd (J 1.8, 10.6 Hz), CHaHb=CH; 5.06, br s, NH; 4.10, q (J 6.9 Hz), CH2CH3; 3.31, m, 1H; 3.11, m, 1H; 2.08, s, COCH3; 1.83, m, 2H; 1.23, t (J 6.9 Hz), CH3. \(\nu_{max}\) : 3350, 1730, 1715, 1225 cm\(^{-1}\). Mass spectrum: 216 (M+H), 156 (M-OAc), 102 (M-OAc-Co2Et).
Experimental 5.2.1

Ethyl N-(3-t-butyldimethylsilyloxy-4-pentenyl)carbamate (25)

A mixture of the carbamate (13) (500mg, 2.9mmol), imidazole (450mg, 7.5mmol), dimethylaminopyridine (75mg, 0.5mmol) and t-butyldimethylsilyl chloride (682mg, 4.5mmol) in dry DMF (10ml) was stirred at room temperature for 24 h. The mixture was diluted with ether (10 ml), washed with saturated sodium chloride (10 ml), 5% hydrochloric acid (2x5 ml), 10% sodium bicarbonate (5 ml), and again with saturated sodium chloride (10 ml). The organic phase was separated, dried, and the solvent removed under reduced pressure to give the silyl ether (25) (822mg, 97%) as a colourless oil, b.p. 72-4°C, 0.015mm. Found: C 58.67%, H 10.36%, N 4.67% C11H29NO3Si requires C 58.49% H 10.17% N 4.87%. 1H n.m.r.: 5.80, ddd (J 17.1, 10.6, 6.6 Hz), CH=CH2; 5.29, dd (J 1.8, 17.1 Hz), CHaHb=CH; 5.19, br s, NH; 5.08, dd (J 1.8, 10.6 Hz), CHaHb=CH; 4.27, m, CHOH; 4.08, q (J 6.9 Hz), CH2CH3; 3.26, m, CH2N; 2.93, m, 2H; 1.22, t (J 6.9 Hz), CH3; 0.91, s, 9H; 0.07, s, CH3Si; 0.04, s, CH3Si. v_max : 3480, 1705, 1530 cm⁻¹. Mass spectrum: 287 (weak M¹), 272 (M-CH3), 230 (M-tBu).

Ethyl N-(3-t-butyldiphenylsilyloxy-4-pentenyl)carbamate (26)

A mixture of the carbamate (13) (519mg, 3mmol), imidazole (450mg, 7.5mmol), dimethylaminopyridine (80mg, 0.6mmol) and t-butyldiphenylsilyl chloride (1.24g, 4.5mmol) in dry DMF (10ml) was stirred at room temperature for 24 h. The mixture was diluted with ether (10 ml), washed with saturated sodium chloride (10 ml), 5% hydrochloric acid (2x5 ml), 10% sodium bicarbonate (5 ml), and again with saturated sodium chloride (10 ml). The organic phase was separated, dried, and the solvent removed under reduced pressure to give the silyl ether (26) (1.22g, 99%) as a colourless oil, b.p. 120°C, 0.02mm (block). Found: C 71.15% H 8.18% N 2.40% C24H33NO3Si requires C 71.01% H 8.08% N 2.40%. 1H n.m.r.: 7.7-7.2, m, 10H; 5.80, ddd (J 17.1, 10.6, 6.6 Hz), CH=CH2; 5.19, br s, NH; 5.01, dd (J 1.8, 17.1 Hz), CHaHb=CH; 4.98, dd (J 1.8, 10.6 Hz), CHaHb=CH; 4.27, m, CHOH; 4.03, q (J 6.9 Hz),
\[ \text{CH}_2\text{CH}_3 ; 3.20, \text{m, CH}_2\text{N} ; 1.60, \text{m, 2H ; 1.26, t (J 6.9 Hz), CH}_3 ; 1.06, \text{s, 9H. v}_\text{max} \times 3460, 1700, 1530 \text{ cm}^{-1}. \text{ Mass spectrum: 354 (M-tBu), 200 (M-Ph}_2\text{Bu), 172 (M-SiPh}_2\text{Bu).} \]

**Reaction of (25) with phenylselenenyl bromide**

Using method 2b with the carbamate (287mg, 1mmol), dry silica (500mg), anhydrous potassium carbonate (500mg) and phenylselenenyl bromide (260mg, 1.1mmol) gave the cis hydroxypyrrolidine (19a) (170mg, 54%). Further elution gave the trans hydroxypyrrolidine (19b) (80mg, 26%).

**Ethyl 2'(R*)-phenylselenomethyl-3'(R*)-acetoxyprroloidine-1-carboxylate (27a) and ethyl 2'(S*)-(phenylselenomethyl)-3'(R*)-O-acetoxyprroloidine-1-carboxylate (27b)**

Using method 2b with the carbamate (24) (215mg, 1mmol), dry silica (500mg), anhydrous potassium carbonate (500mg) and phenylselenenyl bromide (283mg, 1.2mmol) gave a 1:1 mixture of the cis and trans pyrrolidines as a viscous yellow oil (220mg, 60%). HRMS: 371.0616 C\textsubscript{16}H\textsubscript{21}NO\textsubscript{4}Se requires 371.0636. \( v_\text{max} \times 1720, 1690, 1520, 1240 \text{ cm}^{-1}. \) Mass spectrum: 371 (M+·), 328 (M-COCH\textsubscript{3}), 200 (M-CH\textsubscript{2}SePh). 1H n.m.r. (CDCl\textsubscript{3}, 50°C) (27a): 7.57, m, 2H ; 7.28, m, 3H ; 5.03, m, H\textsubscript{3} ; 4.10 q (J 6.9 Hz), CH\textsubscript{2}CH\textsubscript{3} ; 3.69-3.42, m, 3H ; 3.47, dd (J 12.3, 3.6 Hz), H\textsubscript{6a} ; 3.08, dd (J 12.3, 10.9 Hz), H\textsubscript{6b} ; 2.02, s, COCH\textsubscript{3} ; 1.94, m, H\textsubscript{4a}H\textsubscript{4b} ; 1.22, t (J 6.9 Hz), CH\textsubscript{3}. (27b): 7.54, m, 2H ; 7.24, m, 3H ; 4.96, m, H\textsubscript{3} ; 4.09, q (J 6.9 Hz), CH\textsubscript{2}CH\textsubscript{3} ; 3.85, m, H\textsubscript{2} ; 3.63-3.40, m, H\textsubscript{5a}H\textsubscript{5b} ; 3.30, dd (J 12.3, 3.0 Hz), H\textsubscript{6a} ; 2.55, dd (J 12.3, 11.8 Hz), H\textsubscript{6b} ; 2.10, s, COCH\textsubscript{3} ; 2.04, m, H\textsubscript{4a} ; 1.88, m, H\textsubscript{4b} ; 1.24, t (J 6.9 Hz), CH\textsubscript{3}.

**Ethyl 2'(R*)-(phenylselenomethyl)-3'(R*)-(t-butyldiphenylsilyloxy)prroloidine-1-carboxylate (28a) and ethyl 2'(S*)-(phenylselenomethyl)-3'(R*)-(t-butyldiphenylsilyloxy)prroloidine-1-carboxylate (28b)**

Using method 2b with the carbamate (26) (205mg, 0.5mmol), dry silica (250mg), anhydrous potassium carbonate (250mg) and phenylselenenyl bromide (130mg, 0.55mmol) gave a 3:2 mixture of the pyrrolidines (28a) and (28b) as a viscous yellow oil (192mg, 68%). HRMS: 567.1707 C\textsubscript{30}H\textsubscript{37}NO\textsubscript{3}SeSi requires
567.1708. \( \nu_{\text{max}} \): 1690, 1580, 1480, 1420, 1100 cm\(^{-1}\). Mass spectrum: 567 (M\(^{+}\)), 490 (M-Ph), 434 (M-tBuPh), 411 (M-SePh). \(^1\)H n.m.r. (CDCl\(_3\), 50°C): 28a: 7.70 and 7.32, m, 10H; 7.57, m, 2H; 7.28, m, 3H; 4.41, m, H\(_3\); 4.10 q (J 6.9 Hz), CH\(_2\)CH\(_3\); 3.69-3.42, m, 3H; 3.47, dd (J 12.3, 3.6 Hz), H\(_{6a}\); 3.08, dd (J 12.3, 10.9 Hz), H\(_{6b}\); 1.94, m, H\(_{4a}\)H\(_{4b}\); 1.22, t (J 6.9 Hz), CH\(_3\); 1.11, s, 9H. 28b: 7.70 and 7.32, m, 10H; 7.54, m, 2H; 7.24, m, 3H; 4.30, m, H\(_3\); 4.09, q (J 6.9 Hz), CH\(_2\)CH\(_3\); 3.85, m, H\(_2\); 3.63-3.40, m, H\(_{5a}\)H\(_{5b}\); 3.30, dd (J 12.3, 3.0 Hz), H\(_{6a}\); 2.55, dd (J 12.3, 11.8 Hz), H\(_{6b}\); 2.04, m, H\(_{4a}\); 1.88, m, H\(_{4b}\); 1.24, t (J 6.9 Hz), CH\(_3\); 1.06, s, 9H.

2(R\(^*\))-Phenylselenomethyl-3(R\(^*\))-trifluoroacetoxypyrrolidine-1-acetate (29)

To a stirred mixture of the alcohol (21) (18mg, 0.06mmol) and triethylamine (9mg, 0.09mmol) in dry dichloromethane (2 ml) under nitrogen was added trifluoroacetic anhydride (15mg, 0.072mmol) and the mixture stirred at room temperature for 24 h. The solution was washed with 10% hydrochloric acid (5 ml), 10% sodium bicarbonate (5 ml), dried, and the solvent removed under reduced pressure to give the trifluoroacetate (29) as a colourless oil (15mg, 63%). HRMS: 395.0249 C\(_{15}\)H\(_{15}\)NO\(_3\)F\(_3\)Se requires 395.0247. \(^1\)H n.m.r.: 7.59, m, 2H; 7.24, m, 3H; 5.68, dt (J 5.0, 4.7Hz), H\(_3\); 4.44, ddd (J 5.0, 10.3, 3.7Hz), H\(_2\); 3.89, dd (J 12.8, 3.7Hz), H\(_{6a}\); 3.65, m, H\(_{5a}\)H\(_{5b}\); 2.93, dd (J 12.8, 10.3Hz), H\(_{6b}\); 2.2-2.0, m, 2H; 2.03, s, CH\(_3\). \(^1\)H n.m.r.: -0.63 ppm. \( \nu_{\text{max}} \): 1770, 1685, 1400, 1150 cm\(^{-1}\). Mass spectrum: 395 (M\(^{+}\)), 298 (M-COF\(_3\)).

t-Butyl 2(R\(^*\))-phenylselenomethyl-3(R\(^*\))-trifluoroacetoxypyrrolidine-1-carboxylate (30a) and t-butyl 2(S\(^*\))-phenylselenomethyl-3(R\(^*\))-trifluoroacetoxypyrrolidine-1-carboxylate (30b)

To a stirred 1:1 mixture of the alcohols (20a) and (20b) (62mg, 0.26mmol) and triethylamine (26mg, 0.26mmol) in dry dichloromethane (2 ml) under nitrogen was added trifluoroacetic anhydride (555mg, 0.26mmol) and the mixture stirred at room temperature for 24 h. The solution was washed with 10% hydrochloric acid (5 ml), 10% sodium bicarbonate (5 ml), dried, and the solvent removed under reduced
pressure to give a 1:1 mixture of the trifluoroacetates (30a) and (30b) as a colourless oil (73mg, 89%). HRMS: 453.0649 C_{18}H_{22}NO_{4}F_{3}Se requires 453.0666. \( \nu_{\text{max}} \) : 1775, 1685, 1390, 1160 cm\(^{-1}\). Mass spectrum: 453 (M\(^+\)), 396 (M-tBu), 380 (M-tBuO), 356 (M-COCF\(_3\)), 240 (M-tBu-SePh). \(^1\)H n.m.r. (30a): 7.56, m, 2H; 7.26, m, 3H; 5.51, m, H\(_3\); 4.02, m, H\(_2\); 3.56, m, H\(_5a\)H\(_5b\); 3.28, dd (J 3.2, 12.8Hz), H\(_6a\); 2.69, dd (J 11.6, 12.8Hz), H\(_6b\); 2.3-1.8, m, 2H; 1.37, s, 9H. (30b): 7.56, m, 2H; 7.26, m, 3H; 4.40, m, H\(_3\); 3.80, m, H\(_2\); 3.6-3.4, m, H\(_5a\)H\(_5b\); 3.30, dd (J 3.2, 12.8Hz), H\(_6a\); 2.60, dd (J 11.6, 12.8Hz), H\(_6b\); 2.3-1.8, m, 2H; 1.36, s, 9H. \(^{19}\)F n.m.r. (30a): -0.32 ppm (30b): 2.14 ppm.

**Ethyl N-(3-oxo-4-pentenyl)carbamate (31)**

To a stirred mixture of oxalyl chloride (560mg, 4.4mmol) in dry dichloromethane (5 ml) at -78°C under nitrogen was added a solution of DMSO (0.17ml, 2.2mmol) in dry dichloromethane (3 ml). The mixture was stirred at -78°C for 2 min. then a solution of the alcohol (13) (690mg, 4mmol) in dry dichloromethane (3 ml) added and the mixture stirred at this temperature for a further 15 min. Triethylamine (2.8 ml, 20mmol) was then added, the mixture stirred at -78°C for 5 min., then allowed to warm to room temperature. The mixture was diluted with water (10 ml), extracted with dichloromethane (2x5 ml) and the combined extracts washed with saturated sodium chloride (2x10 ml), dried and the solvent removed under reduced pressure. Chromatography gave the ketone (31) (446mg, 66%) as a light yellow oil. HRMS: 171.0897 C\(_8\)H\(_{13}\)NO\(_3\) requires 171.0896. \(^1\)H n.m.r.: 6.31, dd (J 17.6, 10.1Hz), CH\(_3\)H\(_b\)=CH; 6.20, dd (J 17.6, 1.4Hz), CH\(_a\)CH\(_b\)=CH; 5.88, dd (J 10.1, 1.4Hz), CH\(_a\)CH\(_b\)=CH; 5.12, s, NH; 4.05, q (J 6.9Hz), CH\(_2\); 3.44, dt (J 5.8, 4.7Hz), CH\(_a\)N; 3.39, dt (J 5.8, 6.0Hz), CH\(_b\); 2.82, t (J 5.7Hz), CH\(_a\)CO; 2.66, t (J 5.6Hz), CH\(_b\)CO; 1.19, t (J 6.9Hz), CH\(_3\). \( \nu_{\text{max}} \) : 3350, 1715, 1700, 1540 cm\(^{-1}\). Mass spectrum: 171 (M\(^+\)), 142 (M-Et), 126 (M-OEt).
Attempted cyclization of (31)

To a stirred mixture of the carbamate (171mg, 1mmol), anhydrous potassium carbonate (0.5g) and dry silica gel (0.5g) in dry chloroform (20 ml) under nitrogen at 0°C was added phenylselenenyl bromide (260mg, 1mmol) in dry chloroform (3 ml). The mixture was stirred at room temperature for 5 days then filtered through a short silica column. The column was washed with ethyl acetate, the filtrate concentrated under reduced pressure and the residue chromatographed to give the starting alkene (31) (134mg, 78%).
4-Hydroxyhex-5-enonitrole (32)

To a stirred mixture of acetonitrile (16 ml) in dry THF (250 ml) at -78°C under nitrogen was added a solution of n-butyl lithium (63 ml, 2.5M solution in hexane, 0.11 mol) dropwise over 10 min. The mixture was stirred at -78°C for 2 h then butadiene monoxide (10 g, 0.14 mol) added in one portion. The mixture was stirred as this temperature for a further 1 min. then at 0°C for 40 min. (until the white precipitate disappeared) then quenched by the addition of 2N hydrochloric acid (65 ml, 0.13 mol). The majority of solvents were removed under reduced pressure, the residue extracted with ether (2x50 ml), the extracts dried, the solvent removed under reduced pressure and the residue distilled to give the nitrile (32) as a light yellow oil (15.07g, 97%). b.p. 85°C, 0.2mm 1H n.m.r.: 5.82, ddd (J 17.1, 10.6, Jaby 6.6 Hz), CH=CH₂; 5.18, dd (J 1.4, 17.1 Hz), CH₃H₄=CH; 5.02, dd (J 1.4, 10.6 Hz), CH₃H₂=CH; 4.52, m, CHO; 2.72, m, CH₂CN; 1.4-1.6, m, 2H. ʋₘₐₓ: 3350, 2200, 1600 cm⁻¹. Mass spectrum: 57 (M-C₃H₇N), 54 (M-C₃H₅O) (McLafferty rearrangement).

6-Aminohex-1-en-3-ol (33)

To a stirred suspension of lithium aluminium hydride (7.2g, 0.18mol) in dry ether (350 ml) under nitrogen was added a solution of the nitrile (32) (9.8g, 0.9mol) dropwise, maintaining a gentle reflux. The mixture was heated under reflux for a further 2.5 h, then quenched by the addition of 15% sodium hydroxide (20 ml). The cooled mixture was filtered, the solid residue washed with THF (50 ml), the solvent removed under reduced pressure and the residue distilled to give the amine (33) as a light yellow oil (6.9g, 67%). b.p. 125°C, 0.07mm (block). 1H n.m.r.: 5.82, ddd (J 17.1, 10.6, 6.6 Hz), CH=CH₂; 5.18, dd (J 1.4, 17.1 Hz), CH₃H₂=CH; 5.02, dd (J 1.4, 10.6 Hz), CH₃H₂=CH; 4.11, m, CHO; 3.57, m, CH₂N; 2.40, br s, NH₂,OH; 1.7-1.5, m, 4H. ʋₘₐₓ: 3330, 1660 cm⁻¹. Mass spectrum (FAB): 116 (M+H)

Ethyl N-(4-hydroxy-5-hexenyl)carbamate (35)

To an emulsified mixture of the amine (33) (690mg, 6mmol) in water (50
Experimental 5.2.2

ml) at 0°C was added ethyl chloroformate (450mg, 4.5mmol). The mixture was stirred at this temperature for 5 min. then 30% sodium hydroxide (1.08g, 9mmol) was added followed immediately by a second portion of ethyl chloroformate (450mg, 4.5mmol). The mixture was stirred at room temperature for 2 h then extracted with ethyl acetate (30 ml). The organic extracts were washed with 1N hydrochloric acid (10 ml), 10% sodium bicarbonate (10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give the carbamate (35) as a yellow oil (765mg, 68%). b.p. 108°C, 0.1mm (block). Found: C 57.97% H 9.36% N 8.66% C₉H₁₇NO₃ requires C 57.93% H 9.15% N 8.48%. ¹H n.m.r.: 5.87, ddd (J 17.1, 10.6, 6.6 Hz), CH=CH₂; 5.79, s, 1H; 5.24, dd (J 1.8, 17.1 Hz), CH₃H₆=CH; 5.08, dd (J 1.8, 10.6 Hz), CH₃H₆=CH; 4.82, s, NH; 4.11, q (J 6.9Hz), CH₂; 3.21, m, CH₂N; 1.91, m, 2H; 1.58, m, 2H; 1.23, t (J 6.9Hz), CH₃. v max : 3340, 1690, 1550, 1260 cm⁻¹. Mass spectrum: 188 (M+H), 170 (M-OH).

⁻Butyl N-(4-hydroxy-5-hexenyl)carbamate (36)

A mixture of the amine (33) (0.92g, 8mmol), triethylamine (1.21g, 12mmol) and BOC-ON (2.21g, 9mmol) in dioxane (20 ml) and water (20 ml) was stirred at room temperature for 24 h. The solution was diluted with ethyl acetate (40 ml) and the organic phase separated, washed with 10% sodium hydroxide solution, the solvent removed under reduced pressure and the residue distilled to give the carbamate (36) as a yellow oil (0.92g, 53%), b.p. 105°C, 0.02mm (block). Found: C 59.66% H 10.01% N 7.22% C₁₁H₂₁NO₃ requires C 59.71% H 9.83% N 7.51%. ¹H n.m.r.: 5.82, ddd (J 17.1, 10.6, 6.6 Hz), CH=CH₂; 5.18, dd (J 1.4, 17.1 Hz), CH₃H₆=CH; 5.02, dd (J 1.4, 10.6 Hz), CH₃H₆=CH; 4.80, br s, NH; 4.11, m, CHOH; 3.15, m, CH₂N; 2.69, br s, OH; 1.6-1.4, m, 4H; 1.43, s, 9H. v max : 3340, 1690, 1525 cm⁻¹. Mass spectrum [FAB]: 215 (M+), 159 (M-tBu), 142 (M-tBu0).

N-(4-Hydroxy-5-hexenyl)-4-toluenesulfonamide (37)

To a stirred mixture of the amine (33) (690mg, 6mmol) in dry pyridine (40 ml) under nitrogen at 0°C was added portionwise tosyl chloride (1.33g, 7mmol).
The mixture was stirred at this temperature for 4 h, diluted with ethyl acetate (40 ml) and washed with 1N hydrochloric acid (2x40 ml), then 10% sodium bicarbonate (20 ml). The organic phase was separated, dried, the solvent removed under reduced pressure and the residue recrystallized (ethyl acetate/ether/light petroleum) to give the sulfonamide (37) as a white solid (1.15g, 71%). m.p. 51-53°C. Found: C 61.24% H 7.16% N 5.33% C₁₃H₁₉NO₃S requires C 57.97% H 7.11% N 5.20%.

**N-4-(Hydroxy-5-hexenyl)acetamide (38)**

A mixture of the acetate (39) (0.92g, 4.6mmol) and barium hydroxide (1.47g, 4.6mmol) in methanol (20 ml) was stirred at room temperature for 1 h. The solution was filtered through celite, the celite washed with methanol (10 ml) and the solvent removed under reduced pressure to give the amide (38) (0.72g, 100%) as a colourless oil. b.p. 145°C, 0.02mm (block). HRMS: 157.1098 C₈H₁₅NO₂ requires 157.1102. ¹H n.m.r.: 6.41, s, NH; 5.80, ddd (J 17.1, 10.6, 6.6 Hz), CH=CH₂; 5.17, dd (J 1.8, 17.1 Hz), CH₃H₂b=CH; 5.12, dd (J 1.8, 10.6 Hz), CH₃H₂b=CH; 4.14, m, CHOH; 3.54, m, OH; 3.28, m, CH₂N; 1.98, s, CH₃; 1.7-1.5, m, 4H. νₓₘₓ: 3320, 1640, 1570 cm⁻¹. Mass spectrum: 157(M⁺), 140 (M-OH).

**N-(4-Acetoxy-5-hexenyl)acetamide (39)**

To a mixture of the amine (33) (0.69g, 6mmol) and triethylamine (1.82g, 4mmol) in dry THF (20 ml) under nitrogen at 0°C was added acetyl chloride (1.28 ml, 18mmol) dropwise over 2 min. The resultant solution was warmed to room temperature and stirred overnight. The solvent was then removed under reduced pressure, the residue diluted with ethyl acetate (40 ml), washed with 1N hydrochloric acid (2x10 ml) and 10% sodium bicarbonate (10 ml). The organic was
phase separated, dried, the solvent removed under reduced pressure and the residue chromatographed to give the acetate (39) (0.926g, 77%) as a colourless oil. HRMS: 199.1208 C_{10}H_{17}NO_3 requires 199.1190. ^1H n.m.r.: 5.72, s, NH ; 5.80, ddd (J 17.1, 10.6, 6.6 Hz), CH=CH_2 ; 5.17, dd (J 1.8, 17.1 Hz), CH_{a}H_{b}=CH ; 5.12, dd (J 1.8, 10.6 Hz), CH_{a}H_{b}=CH ; 4.20, m, CHOAc ; 3.65, m, CH_2N ; 2.40, s, CH_3 ; 2.10, s, CH_3 ; 1.9-1.7, m, 2H ; 1.6-1.5, m, 2H. ν_{max} : 1725, 1700, 1230 cm⁻¹. Mass spectrum: 199 (M⁺), 140 (M-OCOCH₃).

Table 5.2.2: Selenium Induced Cyclizations of Substituted 5-Hexenylamines

<table>
<thead>
<tr>
<th>Substrate</th>
<th>Reaction conditions^a</th>
<th>Product ratio (% yield)</th>
</tr>
</thead>
<tbody>
<tr>
<td>35</td>
<td>a, 48 h</td>
<td>40a/40b 3:1 (57)</td>
</tr>
<tr>
<td></td>
<td>b, 18 h</td>
<td></td>
</tr>
<tr>
<td></td>
<td>a or b, 5 days</td>
<td>No reaction</td>
</tr>
<tr>
<td>36</td>
<td>a, 48 h</td>
<td>41a/41b 3:1 (59)</td>
</tr>
<tr>
<td></td>
<td>b, 18 h</td>
<td>5:1 (58)</td>
</tr>
<tr>
<td>37</td>
<td>a, 48 h</td>
<td>42a/42b 3:1 (41)</td>
</tr>
<tr>
<td></td>
<td>b, 18 h</td>
<td></td>
</tr>
<tr>
<td>38</td>
<td>a, 48 h</td>
<td>44a/44b 3:1 (27)</td>
</tr>
<tr>
<td>43</td>
<td>a, 5 days</td>
<td></td>
</tr>
</tbody>
</table>

^a = PhSeCl, CH₂Cl₂ -78°C 10 min. then to RT,  b = PhSeBr, CHCl₃ 0°C 10 min. then to RT.

Ethyl 2(R*)-phenylselenomethyl-3(R*)-hydroxypiperidine-1-carboxylate (40b) and ethyl 2(S*)-phenylselenomethyl-3(R*)-hydroxypiperidine-1-carboxylate (40a)

Using method 2a (see p. 129) with the carbamate (35) (187mg, 1mmol), potassium carbonate (500mg), dry silica (500 mg) and phenylselenenyl chloride (210 mg, 1.1 mmol) gave an inseparable 3:1 mixture of the piperidines (40a) and (40b) (196mg, 57%) as a light yellow oil. Found: C 52.40% H 5.97% N 3.89% C_{15}H_{21}NO_3Se
requires C 52.63% H 6.18% N 4.09%  \( \nu_{\text{max}} \): 3450, 1705, 1295 cm\(^{-1}\). Mass spectrum: 343 (M\(^+\)), 326 (M-OH), 187 (M-SePh), 173 (M-CH\(_2\)SePh). 40a: \(^1\)H n.m.r.: 7.52, m, 2H; 7.22, m, 2H; 4.88, dt (9.6, 5.4Hz), H\(_3\); 4.10, q (6.9Hz), CH\(_2\); 4.02, ddd (9.6, 9.2, 5.5Hz), H\(_2\); 3.44, dd (12.8, 9.2Hz), H\(_7a\); 3.31, dd (12.8, 5.5Hz), H\(_7b\); 3.16, m, H\(_{6a}H_{6b}\); 2.40, s, OH; 1.67, m, H\(_{4a}H_{4b}\); 1.58, m, H\(_5aH_{5b}\); 1.23, t (6.9Hz), CH\(_3\). \(^{13}\)C n.m.r.: 209.1 (C=O), 156.8, 133.3, 129.3, 127.6 (Ar), 70.8 (C\(_3\)), 66.3 (CH\(_2\)O), 61.5 (C\(_7\)), 60.7 (C\(_6\)), 40.4 (C\(_5\)), 31.7 (C\(_4\)), 27.4 (C\(_7\)), 14.6 (CH\(_3\)). \(^{77}\)Se n.m.r.: 306.6. 40b: 7.52, m, 2H; 7.22, m, 3H; 4.68, m, H\(_3\); 4.10, q (6.9Hz), CH\(_2\); 3.89, m, 2H; 3.29, dd (13.3, 3.5Hz), H\(_7a\); 2.64, dd (13.3, 12.7Hz), H\(_7b\); 3.16, m, H\(_{6a}H_{6b}\); 2.40, s, OH; 1.67, m, H\(_{4a}H_{4b}\); 1.58, m, H\(_{5a}H_{5b}\); 1.23, t (6.9Hz), CH\(_3\). \(^{13}\)C n.m.r.: 209.1 (C=O), 156.8, 133.3, 129.3, 127.6 (Ar), 73.4 (C\(_3\)), 66.6 (C\(_7\)), 60.8 (CH\(_2\)O), 37.4 (C\(_2\)), 32.0 (C\(_6\)), 27.5 (C\(_5\)), 24.1 (C\(_4\)), 14.5 (CH\(_3\)). \(^{77}\)Se n.m.r.: 306.8.

2(R\(^\dagger\))-Phenylselenomethyl-3(R\(^\dagger\))-hydroxypiperidine-1-p-toluenesulfonate (41b) and 2(S\(^\dagger\))-phenylselenomethyl-3(R\(^\dagger\))-hydroxypiperidine-1-p-toluenesulfonate (41a)

Using method 2a with the sulfonamide (37) (269mg, 1mmol), potassium carbonate (500mg), dry silica (500mg) and phenylselenenyl chloride (21.0mg, 1.1mmol) gave the cis piperidine (41b) as a colourless oil (63mg, 15%). Found: C 53.62% H 5.35% N 3.16% C\(_{19}\)H\(_{23}\)NO\(_3\)SSe requires C 53.64% H 5.45% N 3.29%.  \( \nu_{\text{max}} \): 3450, 1600, 1580, 1500, 1150 cm\(^{-1}\). Mass spectrum: 425 (M\(^+\)), 408 (M-OH), 268 (M-SePh), 254 (M-CH\(_2\)SePh). \(^1\)H n.m.r.: 7.62 and 7.22, d (J 8.3Hz), C\(_6\)H\(_4\); 7.45, m, 2H; 7.24, m, 3H; 4.09, dt (J 3.7, 5.6Hz), H\(_3\); 3.78, dd (J 3.4, 14.4Hz), H\(_7a\); 3.58, m, H\(_{6a}\); 3.56, ddd (J 11.2, 3.4, 3.7Hz), H\(_2\); 3.10, dd (J 11.2, 14.4Hz), H\(_7b\); 2.95, m, H\(_{6b}\); 2.41, s, ArCH\(_3\); 2.29, s, OH; 2.05, m, 2H; 1.75, m, 2H. \(^{13}\)C n.m.r.: 143.2 133.5 132.9 130.0 129.6 129.0 127.6 127.0 (Ar), 68.8 (C\(_3\)), 52.6 (C\(_7\)), 47.5 (C\(_2\)), 25.4 (C\(_6\)), 23.3 (C\(_4\)), 21.4 (C\(_5\)), 19.6 (ArCH\(_3\)). nOE (% enhancement): H\(_2\)H\(_3\) (13.7) Further elution gave the trans piperidine (41a) as a colourless oil (196mg, 46%). \(^1\)H n.m.r.: 7.62 and 7.22, d (J 8.3Hz), C\(_6\)H\(_4\); 7.45, m, 2H; 7.24, m, 3H; 4.43, dt (J 9.5, 4.8Hz), H\(_3\); 4.13, s, OH; 3.87, dt (J 9.5, 5.0Hz), H\(_2\); 3.65, m, H\(_{6a}\); 3.23, dd (J 12.3, 5.1Hz), H\(_7a\); 2.98, dd (J 12.3, 9.6Hz), H\(_7b\); 2.92, m, H\(_{6b}\); 2.42, s, ArCH\(_3\); 1.8-1.4, m, 4H. \(^{13}\)C n.m.r.: 143.2 133.5 132.9 130.0 129.6 129.0 127.6 127.0 (Ar), 68.9 (C\(_3\)), 57.3 (C\(_7\)), 39.5 (C\(_2\)), 27.2 (C\(_6\)), 23.9 (C\(_4\)), 23.3 (C\(_5\)), 21.5
Experimental 5.2.2

(ArCH₃). nOE (% enhancement): H₂H₃ (2.6). Other spectral data as for (41b).

2(R*)-Phenylselenomethyl-3(R*)-hydroxypiperidine-1-acetate mono hydrate (42b) and 2(S*)-phenylselenomethyl-3(R*)-hydroxypiperidine-1-acetate mono hydrate (42a)

Using method 2a with the amide (38) (157mg, 1mmol), potassium carbonate (500mg), dry silica (500 mg) and phenylselenenyl chloride (210 mg, 1.1 mmol) gave a 3:1 mixture of (42a) and (42b) as a white solid which was recrystallied from ether/light petroleum to give (42a) as white needles (127mg, 41%). m.p. 130-132°C. Found: C 49.93% H 5.93% N 3.96% C₄₁H₂¹NO₅Se requires C 50.01% H 6.41% N 4.24% ¹H n.m.r.: 7.58, m, 2H ; 7.27, m, 3H ; 4.80, m, H₃ ; 3.95, m, H₂ ; 3.87, dd (J 5.0, 4.8Hz), H₇a ; 3.23, dd (J 5.0, 2.6Hz), H₇b ; 3.18, m, H₆aH₆b ; 1.97, s, CH₃ ; 1.78, m, H₄aH₄b ; 1.62, m, H₅aH₅b. ¹³C n.m.r.: 206.4 (C=O), 141.4 134.6 129.3 127.9 (Ar), 72.9 (C₃), 64.6 (C₇), 56.9 (C₂), 39.2 (C₆), 32.4 (C₄), 26.1 (CH₃C=CO), 20.1 (C₅). ᵥ₊: 3280, 1655, 1475 cm⁻¹. Mass spectrum [FAB]: 333 (M₊), 315 (M-H₂O), 297 (M-OH-OH₂).

N-(4-t-Butyldiphenylsilyloxy-5-hexenylsulfonyl)-4-toluenesulfonamide (43)

A mixture of the alcohol (37) (269mg, 1mmol), imidazole (150mg, 2.5mmol), dimethylaminopyridine (27mg, 0.2mmol) and t-butyldiphenylsilyl chloride (413mg, 1.5mmol) in dry DMF (5 ml) was stirred at room temperature for 24 h. The solution was diluted with ether (5 ml), washed with saturated sodium chloride (3 ml), 10% hydrochloric acid (5 ml), 10% sodium bicarbonate (5 ml) and saturated sodium chloride again (3 ml). The organic phase was separated, dried, the solvent removed under reduced pressure and the residue chromatographed to give the silyl ether (43) as a colourless oil (504mg, 99%). ¹H n.m.r.: 7.72 and 7.36, m, 10H ; 7.61 and 7.21, d (J 8.2Hz), 4H ; 5.64, dddd (Jax 17.1, Jbx 10.6, Jay 6.6 Hz), CH=CH₂ ; 4.95, dd (Jab 1.8, Jax 17.1 Hz), CH₄aH₄b=CH ; 4.92, s, NH ; 4.90, dd (Jab 1.8, Jbx 10.6 Hz), CH₄H₅b=CH ; 4.08, m, CHOSi ; 3.46, m, CH₂N ; 2.73, m, 2H ; 2.36, s, ArCH₃ ; 1.35, m, 2H ; 1.04, s, 9H. ᵥ₊: 1740, 1600, 1500, 1160 cm⁻¹. Mass spectrum [FAB]: 507 (weak M₊), 450 (M-tBu), 374 (M-tBu-Ph), 296 (M-(Ph)₂tBu).
2(R*)-Phenylselenomethyl-3(R*)-(t-butyldiphenylsilyloxy)pyrrolidine-1-p-toluenesulfonate mono hydrate (44b) and 2(S*)-phenylselenomethyl-3(R*)-(t-butyldiphenylsilyloxy)-pyrrolidine-1-p-toluenesulfonate mono hydrate (44a)

Using method 2a with the sulfonamide (507mg, 1mmol), potassium carbonate (500mg), dry silica (500 mg) and phenylselenenyl chloride (210 mg, 1.1 mmol) gave the a 3:1 mixture of the hydrates (44a) and (44b) as white crystals (216mg, 32%). m.p. 108-113°C. Found: C 61.36% H 6.55% N 1.70% \( \text{C}_{35}\text{H}_{41}\text{NO}_{3}\text{SSeSi} \) requires C 61.74% H 6.37% N 2.00%

\( (44a): \quad ^1\text{H n.m.r.:} \quad 7.7-7.2, \ m, \ 19\text{H} ; \ 4.44, \ t (J 6.2\text{Hz}), \ \text{OH}_a ; \ 4.00, \ dt (J 1.9, 6.4\text{Hz}), \ \text{H}_3 ; \ 3.90, \ dd (J 11.4, 8.4\text{Hz}), \ \text{H}_7a ; \ 3.82, \ dd (J 11.4, 6.2\text{Hz}), \ \text{H}_7b ; \ 3.27, \ ddd (J 1.9, 6.2, 8.4\text{Hz}), \ \text{H}_2 ; \ 2.55, \ dt (J 6.2, 6.9\text{Hz}), \ \text{H}_{6a}\text{H}_{6b} ; \ 2.39, \ s, \ \text{ArCH}_3 ; \ 2.03, \ s, \ \text{OH}_b ; \ 1.82, \ m, \ \text{H}_4a ; \ 1.47, \ m, \ \text{H}_4b ; \ 1.20, \ m, \ \text{H}_{5a}\text{H}_{5b} ; \ 1.03, \ s, \ 9\text{H}. \quad ^1\text{C n.m.r.:} \quad 143.2 \ 136.0 \ 135.8 \ 129.9 \ 129.4 \ 127.7 \ 127.6 \ 126.9 \ (\text{Ar}), \ 72.5 \ (\text{C}_3), \ 63.0 \ (\text{C}_7), \ 54.6 \ (\text{C}_2), \ 42.5 \ (\text{C}_6), \ 31.9 \ (\text{C}_4), \ 26.8 \ (\text{CH}_3), \ 25.9 \ (\text{CMe}_3), \ 21.4 \ (\text{ArCH}_3), \ 19.4 \ (\text{C}_5). \quad ^{77}\text{Se n.m.r.:} \quad 281. \quad v_{\text{max}} : \ 1760, \ 1600, \ 1500, \ 1175 \ \text{cm}^{-1}. \quad \text{Mass spectrum:} \quad 663 (\text{M}^+), \ 607 (\text{M-tBu}), \ 450 (\text{M-Ph)\text{tBu}}) \quad (44b): \quad ^1\text{H n.m.r.:} \quad 7.7-7.2, \ m, \ 19\text{H} ; \ 4.40, \ t (J 6.2\text{Hz}), \ \text{OH}_a ; \ 4.09, \ dt (J 4.8, 7.2\text{Hz}), \ \text{H}_3 ; \ 3.84, \ dd (J 4.5, 5.4\text{Hz}), \ \text{H}_7a ; \ 3.83, \ dd (J 4.5, 5.6\text{Hz}), \ \text{H}_7b ; \ 3.35, \ ddd (J 4.8, 5.4, 5.6\text{Hz}), \ \text{H}_2 ; \ 2.41, \ dt (J 6.2, 6.8\text{Hz}), \ \text{H}_{6a}\text{H}_{6b} ; \ 2.40, \ s, \ \text{ArCH}_3 ; \ 2.61, \ s, \ \text{OH}_b ; \ 1.82, \ m, \ \text{H}_4a ; \ 1.47, \ m, \ \text{H}_4b ; \ 1.20, \ m, \ \text{H}_{5a}\text{H}_{5b} ; \ 1.03, \ s, \ 9\text{H}. \quad ^1\text{C n.m.r.:} \quad 143.2 \ 136.0 \ 135.8 \ 129.9 \ 129.4 \ 127.7 \ 127.6 \ 126.9 \ (\text{Ar}), \ 74.1 \ (\text{C}_3), \ 62.4 \ (\text{C}_7), \ 53.6 \ (\text{C}_2), \ 42.2 \ (\text{C}_6), \ 31.4 \ (\text{C}_4), \ 26.9 \ (\text{CH}_3), \ 25.9 \ (\text{CMe}_3), \ 21.4 \ (\text{ArCH}_3), \ 19.4 \ (\text{C}_5). \quad ^{77}\text{Se n.m.r.:} \quad 305.

Ethyl 2(S*)-methyl-3(R*)-hydroxypiperidine-1-carboxylate (45a) and ethyl 2(S*)-methyl-3(R*)-hydroxypiperidine-1-carboxylate (45b)

To a stirred 3:1 mixture of the hydrated selenides (40a) and (40b) (30mg, 0.08mmol) and nickel chloride hexahydrate (59mg, 0.25mmol) in THF (3 ml) and methanol (1 ml) at 0°C was added sodium borohydride (28 mg, 0.72mmol). The mixture was stirred at 0°C for 15 min., filtered through celite and the celite washed with methanol (10 ml). The filtrate was concentrated under reduced pressure and the residue chromatographed to give a 3:1 mixture of (45a) and (45b) as a clear oil
Experiment

5.2.2

(13mg, 84%). HRMS: 187.1202 C9H17NO3 requires 187.1208. νmax: 3400, 1705, 1510 cm⁻¹. Mass spectrum: 187 (M⁺), 172 (M-CH₃). (45a): ¹H n.m.r.: 4.80, m, H₃ ; 4.10, q (J 6.9Hz), CH₂CH₃ ; 3.55, dq (J 8.7, 7.3Hz), H₂ ; 3.20, m, H₆aH₆b ; 1.78, s, OH ; 1.7-1.4, m, 4H ; 1.28, d (J 8.7Hz), CH₃ ; 0.94, t (J 6.9Hz), CH₂CH₃. (45b): ¹H n.m.r.: 4.85, m, H₃ ; 4.10, q (J 6.9Hz), CH₂CH₃ ; 3.63, dq (f 4.3, 7.3Hz), H₂; 3.20, m, H₅¿H₅,6 ; 'l'.70, s, OH ; 'l'-'4, m, 4H ; '1.28, d (J 7.2Hz), CH₃ ; 0.94, t (J 6.9Hz), CH₂CH₃.

Ethyl 2(S*)-phenylselenomethyl-3(R*)-hydroxypiperidine-1-carboxylate mono hydrate (48)

A mixture of the trans-selenide (40a) (23mg, 0.067mmol) and silica (10mg) in THF (2 ml) and water (1 ml) was stirred at room temperature for 2 h. The solution was diluted with saturated sodium chloride and extracted with ethyl acetate (2 x 5 ml). The combined organic extracts were dried and the solvent removed under reduced pressure yielding a solid which was recrystallized (ethyl acetate/ether/light petroleum) to give the hydrate (48) as white crystals (24mg, 100%). m.p. 90-91°C. Found: C 51.28% H 6.38% N 3.64% C₁₅H₂₃NO₄Se requires C 50.91% H 6.43% N 3.88% ¹H n.m.r. (CDCl₃): 7.58, m, 2H ; 7.27, m, 3H ; 4.86, t (J 6.3Hz) (collapses to singlet upon irradiation@3.2ppm), OHₐ ; 4.09, q (J 6.9Hz), CH₂ ; 3.97, m, H₃ ; 3.92, m [collapses to AB of an ABX system upon irradiation@3.0ppm], H₇aH₇b ; 3.28, ddd (J 3.3, 5.0, 1.4Hz) [collapses to d, 1.4Hz upon irradiation@3.9ppm], H₂ ; 3.20, br dt (J 6.3, 6.9Hz) [collapses to br t, 6.9Hz upon irradiation@4.9ppm], H₆aH₆b; 3.00, t (J 6.1Hz) , ROH ; 1.7-1.5, m, 4H ; 1.45, s, OHₐ ; 1.23, t (J 6.9Hz), CH₃. ¹H n.m.r. (CD₂OD): 7.58, m, 2H ; 7.25, m, 3H ; 4.05, q (J 7.0Hz), CH₂O ; 3.99, m, H₃ ; 3.89, dd (J 11.3, 9.3Hz), H₇a ; 3.77, dd (J 11.3, 5.0Hz), H₇b ; 3.19, ddd (J 1.9, 5.0, 9.3Hz), H₂ ; 3.10, t (J 6.9Hz), H₆aH₆b ; 1.8-1.4, m, 4H ; 1.21, t (J 7.0Hz), CH₃. ¹³C n.m.r. (CDCl₃): 218.6 (C=O), 156.9 134.5 129.3 127.8 (Ar), 72.4 (C₃), 64.4 (OCH₂), 60.8 (C₇), 56.3 (C₂), 40.5 (C₆), 32.5 (C₄), 26.5 (C₅), 14.6 (CH₃). ¹³C n.m.r. (CD₃OD): 216.4 (C=O), 157.0 135.1 130.1 128.3 (Ar), 70.7 (C₃), 64.1 (C₇), 61.6 (CH₂O), 56.6 (C₂), 41.5 (C₆), 34.0 (C₄), 27.6 (C₅), 15.0 (CH₃). ⁷⁷Se n.m.r. (CDCl₃): 260 ppm. νmax (nujol): 3350, 1705, 1515, 1210 cm⁻¹. Mass spectrum: 361 (M⁺), 343 (M-H₂O).
3-Methyl-3,4-epoxybut-1-ene (50)\textsuperscript{122}

To an emulsified mixture of isoprene (19.0 g, 0.28 mmol) and water (65 ml) at 0°C was added N-bromosuccinimide (50 g, 0.28 mmol) portionwise over 15 min. The mixture was stirred at this temperature for a further 3 h, the organic phase separated, combined with an etheral extract (2x40 ml) of the aqueous phase, dried and the solvent evaporated under reduced pressure to give a mixture of bromohydrins which was not further characterized (40 g, 85%). The total bromohydrin product was then added to a rapidly stirred solution of 30% sodium hydroxide (74.5 g, 0.56 mmol) at 0°C over 10 min. The mixture was stirred at this temperature for a further 2 h, the organic phase separated, combined with an etheral extract (3x40 ml) of the aqueous phase, dried, and fractionally distilled to give the epoxide (50) as a colourless liquid (8.23 g, 35%), b.p. 79-81°C (lit\textsuperscript{122} 78-82°C). \textsuperscript{1}H n.m.r.: 5.80-4.98, m, 3H \((\text{CH}2=\text{CH})\); 2.58, dd (J 10.3, 6.4 Hz), CH\textsubscript{2}; 1.35, s, CH\textsubscript{3}. \(\nu_{\text{max}}\): 3050, 1640 cm\textsuperscript{-1}. Mass Spectrum: 84 (M\textsuperscript{+}).

4-Hydroxy-4-methylhex-5-ene nitrile (51)\textsuperscript{122}

To a stirred solution of dry acetonitrile (16 ml, 290 mmol) and dry tetrahydrofuran (240 ml) at -78°C under nitrogen was added \textit{n}-butyl lithium (42.2 ml of 2.5 M solution in hexane, 105 mmol) dropwise over 10 min. The mixture was stirred at this temperature for 2 h then 3-methyl-3,4-epoxybut-1-ene (50) (8.14 g, 96 mmol) added dropwise to the cloudy mixture over 10 min. The mixture was stirred at -78°C for 1 h, then at 0°C for an additional 2 h. The reaction was quenched by the dropwise addition of 2N hydrochloric acid (47.5 ml, 95 mmol), the solvent removed under reduced pressure and the residue extracted with ether (2x50 ml). The combined extracts were dried and the solvent evaporated under reduced pressure to give the nitrile (51) as a yellow oil (10.93 g, 91%). \textsuperscript{1}H n.m.r.: 5.96, dd (J 9.5, 16.0 Hz), CH=CH\textsubscript{2}; 5.32, dd (J 16.0, 2.1 Hz), CH\textsubscript{a}=CH\textsubscript{2}; 5.14, dd (J 9.5, 2.1 Hz), CH\textsubscript{b}=CH\textsubscript{2}; 3.40, s, OH; 2.36, m, CH\textsubscript{2}CN; 1.95, m, CH\textsubscript{2}; 1.29, s, CH\textsubscript{3}. \(\nu_{\text{max}}\): 3390, 2300, 1640 cm\textsuperscript{-1}. Mass Spectrum: 126 (M+H).
6-Amino-3-methylhex-1-ene-3-ol (52)

To a stirred mixture of lithium aluminium hydride (1.90 g, 50 mmol) in dry ether (40 ml) under nitrogen was added the nitrile (51) (1.25 g, 10 mmol) dropwise, maintaining a gentle reflux. The mixture was refluxed for a further 2.5 h and the cooled solution quenched by the sequential addition of water (2 ml), 15% sodium hydroxide (2 ml), and water (6 ml). The precipitate formed was removed by suction filtration, washed with tetrahydrofuran (10 ml), the filtrate concentrated and the residue distilled from a small amount of quinoline to give the amine (52) as a yellow oil (1.04 g, 81%). b.p. 140°C, 0.05 mm (block). $^1$H n.m.r.: 5.98, dd (J 9.5, 16.0 Hz), $\text{CH}=\text{CH}_2$; 5.38, dd (J 16.0, 2.1 Hz), $\text{CH}_3=\text{CH}_2$; 5.13, dd (J 9.5, 2.1 Hz), $\text{CH}_3=\text{CH}_2$; 2.96, s, $\text{NH}_2$, OH; 2.79, m, $\text{CH}_2\text{N}$; 1.64, m, 4H; 1.30, s, $\text{CH}_3$. $\nu_{\text{max}}$: 3380, 3300, 3220, 1600 cm$^{-1}$. Mass Spectrum: 130 (M+H).

$t$-Butyl-(4-methylhex-5-en-4-ol)carbamate (53)

A mixture of the amine (52) (1.29 g, 10 mmol), triethylamine (1.52 g, 15 mmol) and BOC-ON (2.71 g, 11 mmol) in dioxane (20 ml) and water (20 ml) was stirred at room temperature for 24 h. The solution was washed with 10% aqueous sodium hydroxide (2x20 ml) and the organic phase separated, dried, the solvent removed under reduced pressure and the residue chromatographed to give the carbamate (53) as a yellow oil (1.47 g, 63%). b.p. 128-130°C, 0.20 mm. Found: C 62.29% H 9.93% N 6.26% $\text{C}_{12}\text{H}_{23}\text{NO}_3$ requires C 62.85% H 9.93% N 6.26%. $^1$H n.m.r.: 5.85, dd (J 12.1, 17.4 Hz), $\text{CH}=\text{CH}_2$; 5.19, dd (J 16.0, 1.6 Hz), $\text{CH}_3=\text{CH}_2$; 5.07, dd (J 12.1, 1.6 Hz), $\text{CH}_3=\text{CH}_2$; 3.47, s, OH; 3.08, m, $\text{CH}_2\text{N}$; 1.53, m, 4H; 1.42, s, 9H; 1.26, s, $\text{CH}_3$. $^{13}$C n.m.r.: 156.06 (C=O); 144.67 ($\text{CH}=\text{CH}_2$); 111.69 ($\text{CH}=\text{CH}_2$); 78.99 ($\text{CO}_2\text{C}$); 72.79 ($\text{C(OH)}$); 40.72 ($\text{CH}_2\text{N}$); 38.96 ($\text{C(OH)}\text{CH}_2$); 28.53 (($\text{CH}_3$)$_3$); 27.63 ($\text{CH}_3$); 24.60 ($\text{CH}_2\text{CH}_2\text{N}$). $\nu_{\text{max}}$ (CCl$_4$): 3640, 3500, 3430, 1735, 1650, 1180 cm$^{-1}$. Mass Spectrum: 230 (M+H), 212 (M-$\text{H}_2\text{O}$), 173 (M-$t$Bu), 129 (M-$\text{CO}_2$tBu).
Using method 2a with the carbamate (53) (229 mg, 1 mmol), potassium carbonate (500 mg) dry silica (500 mg) and phenylselenenyl chloride (210 mg, 1.1 mmol) gave a 3:1 mixture of (54a) and (54b) as a white solid which was recrystallized (light petroleum/ether) to give the piperidine (54a) as white needles (289 mg, 75%). m.p. 116-117°C. Found: C 56.24% H 7.05% N 3.70% \( \text{C}_{18}\text{H}_{27}\text{NO}_3\text{Se} \) requires C 56.24% H 7.08% N 3.64%. \( \nu\text{max} \) (CDCl\(_3\)) : 3420, 1680, 1575, 1510 cm\(^{-1}\). Mass Spectrum : 385 (M\(^+\)), 170 (M-CH\(_3\)), 367 (M-OH), 308 (M-Ph). \(^1\)H n.m.r. (CDCl\(_3\), 50°C): 7.62, m, 2H; 7.26, m, 3H; 3.99, dd (J 14.3, 2.5 Hz), H\(_2\); 3.77, m, H\(_{6a}\); 3.31, dd (J 11.5, 14.3 Hz), H\(_{7a}\); 3.15, dd (J 11.5, 2.5 Hz), H\(_{7b}\); 3.02, m, H\(_{6b}\); 2.22, br s OH; 2.02, m, H\(_{5a}\); 1.94, m, H\(_{5b}\); 1.67, m, H\(_{4a}\); 1.23, m, H\(_{4b}\); 1.46, s, CH\(_3\); 1.25, s, 9H. \(^{13}\)C n.m.r. (CDCl\(_3\), 50°C): 210.1 (C=O); 155.6 134.25 129.08 127.65 (Ar); 79.59 (CO\(_2\)C); 72.48 (C\(_3\)); 58.90 (C\(_7\)); 47.30 (C\(_2\)); 45.02 (C\(_6\)); 37.86 (C\(_4\)); 32.10 (CH\(_3\)); 28.29 ((CH\(_3\))\(_3\)); 19.55 (C\(_5\)). nOE (% enhancement): H\(_2\)CH\(_3\) (<0.5), H\(_{7a}\)CH\(_3\) (5.2), H\(_{7b}\)CH\(_3\) (5.6).
N-(4-pentenyl)phthalimide (60)\textsuperscript{266}

A mixture of 5-bromopentene (3g, 20mmol) and freshly prepared\textsuperscript{156} potassium phthalimide (6.45g, 30mmol) in dry DMF (60 ml) under nitrogen was heated under reflux for 2.5 h. The cooled solution was filtered, poured onto water (60 ml) and extracted with dichloromethane (3x40 ml). The combined organic extracts were washed with 10% sodium hydroxide (30 ml), water (2x30 ml), the organic phase separated, dried, the solvent removed under reduced pressure and the residue recrystallized (dichloromethane/light petroleum) to give the phthalimide (60) (4.02g, 93%) as light brown crystals, m.p. 40-41°C. \textsuperscript{1}H n.m.r.: 7.71, m, 2H ; 7.72, m, 2H ; 5.80, ddt (J 17.1, 10.2, 6.6 Hz), CH=CH\textsubscript{2} ; 5.05, dd (J 1.8, 17.1 Hz), CH\textsubscript{a}H\textsubscript{b}=CH ; 4.98, dd (J 1.8, 10.2 Hz), CH\textsubscript{a}H\textsubscript{b}=CH ; 3.69 t (J 7.3 Hz), CH\textsubscript{2}N ; 2.13, m, 2H ; 1.79, m, 2H. \(\nu_{\text{max}}\) : 2970, 1780, 1718, 1616 cm\textsuperscript{-1}. Mass spectrum: 215 (M\textsuperscript{+}), 160 (M-C\textsubscript{4}H\textsubscript{7}).

Ethyl N-(4-pentenyl)carbamate (62)\textsuperscript{69}

A mixture of the phthalimide (60) (4.3g, 20mmol) and hydrazine hydrate (1.2g, 22mmol) in ethanol (100 ml) under nitrogen was heated under reflux for 3.5 h. The cooled solution was acidified with concentrated hydrochloric acid, the solvent evaporated, the residue dissolved in 10% sodium hydroxide (40 ml) and extracted with ether (3x30 ml). To the dried combined organic extracts at 0°C was added ethyl chloroformate (1.2g, 12mmol). The mixture was stirred at this temperature for 5 min. then a second portion of ethyl chloroformate (1.2g, 12mmol) added, followed immediately by triethylamine (2.4g, 25mmol). The mixture was stirred at room temperature for a further 2 h, then washed with 1N hydrochloric acid (10 ml), then 10% sodium bicarbonate (10 ml). The organic phase was separated, dried, the solvent removed under reduced pressure and the residue chromatographed to give the carbamate (62) (2.97g, 95%) as a light yellow oil. \textsuperscript{1}H n.m.r.: 5.80, ddt (J 17.1, 10.2, 6.6 Hz), CH=CH\textsubscript{2} ; 5.05, dd (J 1.8, 17.1 Hz), CH\textsubscript{a}H\textsubscript{b}=CH ; 4.98, dd (J 1.8, 10.2 Hz), CH\textsubscript{a}H\textsubscript{b}=CH ; 4.78, s, NH ; 4.11 q (J 6.9Hz), CH\textsubscript{2} ; 3.18, m, CH\textsubscript{2}N.
Experimental 5.2.3

; 2.05 ,m, 2H ; 1.60, m, 2H ; 1.26, t (J 6.9Hz), CH₃. \( \nu_{\text{max}} \) : 3340, 1705, 1530, 1255 cm\(^{-1}\).
Mass spectrum: 157 (M\(^+\)), 84 (M-CO₂Et).

**Ethyl 2-(phenylselenomethyl)pyrrolidine-1-carboxylate (63)**

To a stirred mixture of the carbamate (62) (1.57g, 10mmol), dry silica gel (1g), and anhydrous potassium carbonate (0.5g) in dry dichloromethane (20 ml) at -78°C under nitrogen was added a solution of phenylselenenyl chloride (2.1g, 1.1mmol) in dry dichloromethane (5 ml) dropwise over 5 min. The mixture was stirred at -78°C for 10 min. then at room temperature for 40 h. The solution was filtered, the solvent removed under reduced pressure and the residue chromatographed to give the selenide (63) as a light yellow oil (2.44g, 78%). \(^1\)H n.m.r.: 7.54, m, 2H ; 7.23, m, 3H ; 4.07, q (J 6.9Hz), CH₂ ; 4.01, m, CHN ; 3.50-3.29, m, CH₂N ; 2.88, dd (J 6.8, 7.2Hz), CH₃Se ; 2.73, dd (J 6.8, 7.2Hz), CH₃Se ; 2.02-1.75, m, 4H ; 1.22, t (J 6.9Hz), CH₃. \(^{77}\)Se n.m.r.: 267. \( \nu_{\text{max}} \) : 1685, 1405, 1105 cm\(^{-1}\). Mass spectrum: 313 (M\(^+\)), 157 (M-SePh), 143 (M-CH₂SePh).

**t-Butyl 2-bromomethylpyrrolidine-1-carboxylate (66)**

To a stirred mixture of the selenide (63) (70mg, 0.2mmol) and tetrabutylammonium bromide (71mg, 0.22mmol) in acetonitrile (10 ml) was added a solution of bromine (2.3M in carbon tetrachloride, 0.10 ml, 0.24mmol) and the mixture heated under reflux for 20 min. To the cooled reaction mixture was added hydrogen peroxide (0.1 ml, 1mmol) then 10% sodium bicarbonate (5 ml). The mixture was extracted with dichloromethane (2 x 10 ml), the extracts washed with water (10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give the bromide as a yellow oil (4 mg, 7%). \(^1\)H n.m.r.: 4.72, m, H₂ ; 3.90, dd (J 10.3, 3.6Hz), H₆a ; 3.73, dd (J 10.3, 7.8Hz), H₆b ; 3.57, m, H₅aH₅b ; 2.4-1.8, m, 4H ; 1.22, s, 9H. \( \nu_{\text{max}} \) : 1680, 1400, 1170 cm\(^{-1}\). Mass spectrum: 263/265 (M\(^+\)), 190/192 (M-tBuO), 162/164 (M-CO₂tBu).
**Ethyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (67)**

To a solution of the selenide (63) (313mg, 1mmol) in isopropyl alcohol (10 ml) was added MCPBA (608mg, 3mmol) and the mixture stirred at room temperature for 1 h. Sodium hydroxide (10%, 10 ml) was then added and the mixture stirred for a further 4 h. The solvent was removed under reduced pressure and the residue redissolved in ethyl acetate (10 ml). This solution was washed with saturated sodium bicarbonate (2x10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give the alcohol (67) as a colourless oil (135mg, 78%). \(^1H\) n.m.r.: 4.58, m, \(H_{6a}\); 4.15, q (J 7.0Hz), \(C_2\); 4.00, m, \(H_{6b}\); 3.64, m, \(H_2\); 3.61, s, OH; 3.51, m, \(H_{5a}\); 3.34, m, \(H_{5b}\); 2.04, m, 1H; 1.85, m, 2H; 1.58, m, 1H; 1.28, t (J 7.0Hz), \(CH_3\). \(\nu_{max}\): 3390, 1680, 1430, 1380, 1080 cm\(^{-1}\). Mass spectrum: 173 (M\(^+\)), 155 (M-H\(_2\)O), 142 (M-CH\(_2\)OH).

**(S)-(+)Ethyl 2-(hydroxymethyl)pyrrolidine-1-carboxylate (68)**

**i) from \(S-(+)-hydroxymethylpyrrolidine\)**

To an emulsified mixture of \(S-(+)\)-hydroxymethylpyrrolidine (5.05g, 50mmol) in water (100 ml) at 0°C was added ethyl chloroformate (3.29g, 30mmol). The mixture was stirred at this temperature for 5 min. then a second portion of ethyl chloroformate (3.29g, 30mmol) added, followed immediately by a solution of sodium hydroxide (2.4g, 60mmol) in water (5 ml). The mixture was stirred at 0°C for a further 4 h, then washed with 1N hydrochloric acid (10 ml), and 10% sodium bicarbonate (10 ml). The organic phase was separated, dried, the solvent removed under reduced pressure and the residue chromatographed to give the carbamate (68) (7.51g, 87%) as a light yellow oil. \([\alpha]^{D}_{25} = -17.80^\circ\) \(^1H\) n.m.r.: 4.58, m, \(H_{6a}\); 4.15, q (J 7.0Hz), \(CH_2\); 4.00, m, \(H_{6b}\); 3.64, m, \(H_2\); 3.61, s, OH; 3.51, m, \(H_{5a}\); 3.34, m, \(H_{5b}\); 2.04, m, 1H; 1.85, m, 2H; 1.58, m, 1H; 1.28, t (J 7.0Hz), \(CH_3\). \(\nu_{max}\): 3385, 1680, 1430, 1385, 1085 cm\(^{-1}\). Mass spectrum: 173 (M\(^+\)), 155 (M-H\(_2\)O), 142 (M-CH\(_2\)OH).
ii) from the selenide (69)

To a solution of the selenide (69) (313mg, 1mmol) in isopropyl alcohol (10 ml) was added MCPBA (608mg, 3mmol) and the mixture stirred at room temperature for 1 h. 10% sodium hydroxide (5 ml) was then added and the mixture stirred for a further 4 h. The solvent was removed under reduced pressure and the residue redissolved in ethyl acetate (10 ml). This solution was washed with saturated sodium bicarbonate (2x10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed (ethyl acetate/light petroleum) to give the alcohol (68) as a colourless oil (130mg, 75%). [α]D25 = -17.21°. Other spectral data as above.

S (+) Ethyl 2-(phenylselenomethyl)pyrrolidine-1-carboxylate (69)

To a stirred mixture of (68) (3.46g, 20mmol) and tributylphosphine (6.07g, 30mmol) in dry THF (100 ml) at 0°C was added N-(phenylseleno)phthalimide (9.06g, 30mmol). The mixture was stirred at this temperature for 2 h., the solvent removed under reduced pressure and the residue chromatographed to give the selenide (69) as a yellow oil (5.84g, 93%). [α]D25 = -5.63°. Other spectral data as for the racemic material.

Reactions of ethyl 2-(phenylselenomethyl)pyrrolidine-1-carboxylate (63)

i) with OXONE ® (64)

To a vigorously stirred mixture of the selenide (63) (105mg, 0.33mmol) at 0°C in dry ethanol (10 ml) was added a solution of OXONE (1.02g, 1.66mmol) in water (5 ml). The mixture was warmed to room temperature, stirred for a further 5 days then diluted with water (10 ml), extracted with chloroform (2x10 ml), the combined organic extracts were dried, the solvent removed under reduced pressure and the residue chromatographed to give the alcohol (67) (2mg, 3%). Further elution gave ethyl 2-(phenylseleninylmethyl)pyrrolidine-1-carboxylate (64) as a pale yellow oil (111mg, 97%). HRMS: 329.0532 C14H19NO3Se requires 329.0529. 1H
Experimental  5.2.3

n.m.r.: 7.99, d (J 8.0Hz), 2H ; 7.67, m, 3H ; 4.17, m, H₂ ; 3.68, q (J 7.0Hz), CH₂O ; 3.42, m, H₅aH₅b ; 3.21, dd (J 12.0, 9.0Hz), H₆a ; 3.03, dd (J 12.0, 2.6Hz), H₆b ; 2.0-1.7, m, 4H ; 1.21, t (J 7.0Hz), CH₃. ¹⁷⁷Se n.m.r.: 850. ʋₚᵥᵥ: 1700, 1580, 1420, 1260, 830 cm⁻¹. Mass spectrum: 329 (weak M⁺), 313 (M-O), 156 (M-Se(O)Ph), 142 (M-CH₂Se(O)Ph).

ii) with MCPBA in iPrOH (65), (82)

A mixture of the selenide (63) (313mg, 1mmol) and MCPBA (608mg, 3mmol) in isopropyl alcohol (10 ml) was stirred at room temperature for 4 h. The solvent was removed under reduced pressure and the residue redissolved in ethyl acetate (10 ml). The solution was washed with saturated sodium bicarbonate (2x10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give ethyl 1-ethoxycarbonyl-2-pyrrolidinylmethyl 3-chlorobenzoate (82) (12 mg, 4%) as a yellow oil. HRMS: 311.0975 C₁₅H₁₆NO₄Cl requires 311.0924. ¹H n.m.r.: 8.09, t (J 1.8Hz), H₂ ; 8.01, dt (J 7.7, 1.3Hz), H₆ ; 7.53, ddd (J 7.7, 1.8, 1.3Hz), H₄ ; 7.42, t (J 7.7Hz), H₅ ; 4.95, m, H₆aH₆b ; 4.21, m, H₂ ; 4.16, q (J 7.0Hz), CH₂O ; 3.6-3.4, m, H₅aH₅b ; 2.0-1.8, m, H₄aH₄b ; 1.26, t (J 7.0Hz), CH₃. ¹³C n.m.r.: 170.6 (OC=O), 160.3 (NC=O), 134.4, 133.8, 130.2, 129.8, 128.3, 123.7 (Ar), 67.7 (C₆), 47.2 (C₂), 43.9 (C₅), 29.0 (C₃), 14.6 (C₄). ʋₚᵥᵥ: 1725, 1705, 1560, 1175 cm⁻¹. Mass spectrum: 311/313 (M⁺), 266/288 (M-EtO), 238/240 (M-CO₂Et), 155 (M-C₆H₄ClCO₂H), 111 (C₆H₄Cl). Further elution gave the alcohol (67) (35mg, 20%) as a yellow oil followed by ethyl 2-(phenylselenonylmethyl)pyrrolidine-1-carboxylate (65) as transluscent crystals (220mg, 64%). m.p. 103-104°C. ¹H n.m.r.: 8.00, d (J 8.2Hz), 2H ; 7.69, m, 3H ; 4.30, m, H₂ ; 4.10, dd (J 12.2, 2.3Hz), H₆a ; 3.95, m, H₅aH₅b ; 3.69, dd (J 12.2, 9.6), H₆b ; 3.39, q (J 6.8Hz), CH₂ ; 2.44, m, 1H ; 2.22, m, 1H ; 1.93, m, 2H ; 1.99, t (J 6.8Hz), CH₃. ⁷⁷Se n.m.r.: 988. ʋₚᵥᵥ: 1710, 1255, 910, 890 cm⁻¹. Mass spectrum[FAB]: 345 (M⁺), 156 (M-SeO₂Ph).

iii) with MCPBA and H₂O in DMF (75), (76)

To a solution of the selenide (63) (313mg, 1mmol) in isopropyl alcohol (10 ml) was added MCPBA (608mg, 3mmol) and the mixture stirred at room
temperature for 2 h. The solvent was removed under reduced pressure and the residue redissolved in ethyl acetate (10 ml). This solution was washed with saturated sodium bicarbonate (2x10 ml), the solvent removed under reduced pressure and the residue redissolved in DMF (4 ml) and water (1 ml) and the mixture heated at 80°C for 2 h. The cooled mixture was diluted with ether (10 ml), washed with saturated sodium chloride (5 ml), saturated sodium bicarbonate (5 ml), then with saturated sodium chloride again (5 ml). The organic phase was separated, dried, the solvent removed under reduced pressure and the residue chromatographed to give the alcohol (67) (125 mg, 72%).

iv) with MCPBA in water/THF (76)

A mixture of the selenide (63) (195 mg, 0.33 mmol) and MCPBA (288 mg, 1.66 mmol) in THF (5 ml) and water (1 ml) was stirred at room temperature for 6 h. The mixture was diluted with saturated sodium chloride (5 ml), the organic phase separated, washed with saturated sodium bicarbonate (5 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give ethyl 2-methylenepyrrrolidine-1-carboxylate (75) as a light yellow oil (10 mg, 20%). $^1$H n.m.r.: 5.65, s, H$_{6a}$; 5.63, s, H$_{6b}$; 4.11, q (J 6.9 Hz), CH$_2$; 3.37, m, CH$_2$N; 2.0-1.67, m, 4H; 1.25, t (J 6.9 Hz), CH$_3$. $\nu_{max}$: 1710, 1640, 1530 cm$^{-1}$. Mass spectrum: 155 (M$^+$).

Further elution gave ethyl N-(5-oxopentyl)carbamate (76) as a light yellow oil (20 mg, 34%). $^1$H n.m.r.: 4.78, s, NH; 4.11, q (J 6.9 Hz), CH$_2$; 3.16, m, CH$_2$N; 2.50, t (J 7.0 Hz), CH$_2$CO; 2.15, s, CH$_3$; 1.77, m, 2H; 1.23, t (J 6.9 Hz), CH$_3$. $\nu_{max}$: 3380, 1715, 1530 cm$^{-1}$. Mass spectrum: 173 (M$^+$), 119 (M-CH$_2$COCH$_3$).

v) with MCPBA in acetic acid

A mixture of the selenide (63) (62 mg, 0.2 mmol) and MCPBA (103 mg, 0.6 mmol) in acetic acid (2 ml) was stirred at room temperature for 24 h. The solvent was removed under reduced pressure and residue redissolved in dichloromethane (5 ml). The solution was washed with saturated sodium bicarbonate (5 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to
give starting materials (15mg, 24%). Further elution gave the alcohol (67) (12mg, 34%).

vi) with MCPBA in methanol (77)

A mixture of the selenide (63) (105mg, 0.33mmol) and MCPBA (174mg, 1mmol) in methanol (10 ml) was stirred at room temperature for 90 min. The mixture was diluted with chloroform (20 ml) and washed with saturated sodium bicarbonate (10 ml). The organic phase was separated, dried, the solvent removed under reduced pressure and the residue chromatographed to give ethyl 2-methoxymethylpyrrolidine-1-carboxylate (77) (50mg, 87%) as a colourless oil. $^1$H n.m.r.: 4.13, m, H$_6$a; 4.13, q(J 6.9Hz), CH$_2$; 3.78, m, H$_6$b; 3.57, m, H$_2$; 3.38, s, OCH$_3$; 3.19, m, H$_5$ab; 1.90, m, H$_3$a; 1.74, m, H$_3$b; 1.17, m, H$_4$ab; 1.26, t(J 6.9Hz), CH$_3$. $\nu_{max}$: 1735, 1475, 940 cm$^{-1}$. Mass spectrum: 187 (M$^+$), 155 (M-MeOH), 142 (M-CH$_2$OMe).

vii) with MCPBA in ethanol (78)

A mixture of the selenide (63) (313mg, 1mmol) and MCPBA (608mg, 3mmol) in dry ethanol (10 ml) was stirred at room temperature for 2 h. The solvent was removed under reduced pressure and the residue redissolved in ethyl acetate (20 ml). The solution was washed with saturated sodium bicarbonate solution (10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give ethyl 2-methoxymethylpyrrolidine-1-carboxylate (78) (121mg, 60%) as a colourless oil. $^1$H n.m.r.: 4.37, q (J 7.0Hz), CH$_2$O; 4.20, m, H$_6$a; 4.14, q (J 6.9Hz), CH$_2$O; 4.07, m, H$_6$b; 3.8-3.3, m, 3H; 1.9-1.5, m, 4H; 1.25, t (J 6.9Hz), CH$_3$; 1.19, t (J 7.0Hz), CH$_3$. $\nu_{max}$: 1730, 1460 cm$^{-1}$. Mass spectrum: 201 (M$^+$), 155 (M-EtOH), 142 (M-CH$_2$OEt).

2-Chloromethylpiperidine hydrobromide (70)$^{158}$

A mixture of hydroxymethylpiperidine (2.4g, 20mmol) in chloroform (80 ml) was saturated with hydrogen bromide then thionyl chloride (5.4g, 24mmol) added dropwise over 5 min. The mixture was heated under reflux for 2.5 h, then
diluted with water (20 ml) and extracted with 10% hydrochloric acid (3x20 ml). The combined aqueous extracts were concentrated under reduced pressure to give the hydrobromide salt (70) as a dark brown solid (3.2g, 90%). m.p. 185-190°C lit.158 m.p. 189-190°C.

2-Phenylselenomethylpiperidine (71)

i) from the chloride (70)

To a stirred solution of diphenyldiselenide (1.05g, 3.4mmol) in dry ethanol (60 ml) was added portionwise sodium borohydride (260mg, 7mmol). A solution of hydrobromide salt (70) (1.07g, 5mmol) in dry ethanol (5 ml) was then added and the mixture heated under reflux for 2.5 h. The cooled mixture was filtered, diluted with water (20 ml) and extracted with chloroform (3x20 ml). The combined organic extracts were dried, the solvent removed under reduced pressure, and the residue chromatographed (dichloromethane/methanol) to give the selenide (71) as a dark yellow oil (1.21g, 94%). 1H n.m.r.: 7.50, m, 2H; 7.25, m, 3H; 3.11, m, H2; 3.05, dd (J 12.0, 4.0Hz), H7a; 2.80, dd (J 12.0, 8.9Hz), H7b; 2.60, dt (J 2.8, 8.9Hz), H6aH6b; 2.34, s, NH; 1.8-1.2, m, 6H. vmax: 3315, 1480, 1430 cm⁻¹. Mass spectrum: 255 (M⁺), 84 (M-CH2SePh).

ii) from hydroxymethylpiperidine

To a stirred mixture of hydroxymethylpiperidine (230mg, 2mmol) and tributylphosphine (607mg, 3mmol) in dry THF (100 ml) at 0°C was added N-(phenylseleno)phthalimide (906mg, 3mmol). The mixture was stirred at this temperature for 2 h, the solvent removed under reduced pressure and the residue chromatographed to give the selenide (71) as a yellow oil (229mg, 90%).

2-Phenylselenomethylpyrrolidine-1-p-toluenesulfonate (80)

A mixture of the amine (252) (239mg, 1mmol) and p-toluenesulfonyl chloride (290mg, 1.5mmol) in pyridine (10 ml) was stirred at room temperature for 4
h. The mixture was diluted with ethyl acetate (20 ml), washed with 10% hydrochloric acid (10 ml), 10% sodium bicarbonate (10 ml), dried, the solvent removed under reduced pressure and the residue distilled to give the sulfonamide (80) as a yellow oil (316mg, 80%). b.p. 210°C, 0.04mm [block]. Found: C 55.39% H 5.52% N 3.597%. C18H21NO2SSe requires C 54.72% H 5.37% N 3.557%. 1H n.m.r.: 7.58, m, 2H; 7.49, d (J 8.0Hz), 2H; 7.31, m, 3H; 7.21, d (J 8.0Hz), 2H; 3.60, m, 2H; 3.46, m, 1H; 3.10, dt (J 10.1, 6.7Hz), 1H; 2.82, dd (J 11.4, 13.0Hz), 1H; 2.38, s, CH3; 1.8-1.4, m, 4H. v<sub>max</sub>: 1600, 1580, 1500, 1480, 1345, 1200, 1150, 1090, 810, 735 cm<sup>-1</sup>. Mass spectrum: 395 (M<sup>+</sup>), 238 (M-SePh), 224 (M-CH2SePh).

2-Methoxymethylpyrrolidine-1-p-toluenesulphonate (81)

To a stirred mixture of the selenide (63) (200mg, 0.5mmol) in methanol (20 ml) was added MCPBA (540mg, 2.5mmol) and the mixture stirred at room temperature for 1 h. The solvent was removed under reduced pressure, the residue redissolved in dichloromethane (10 ml), washed with 10% sodium hydroxide (10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give the ether (81) as a colourless oil (80mg, 60%). 1H n.m.r.: 7.64, d (J 8.2Hz), 2H; 7.31, d (J 8.2Hz), 2H; 3.61, m, H<sub>6a</sub>; 3.37, s, OMe; 3.35, m, H<sub>6b</sub>; 3.33, m, H<sub>2</sub>; 2.45, m, H<sub>5a</sub>; 2.43, s, ArCH=; 2.36, m, H<sub>5b</sub>; 1.8-1.2, m, 4H. v<sub>max</sub>: 1600, 1500, 1340, 1160, 910 cm<sup>-1</sup>. Mass spectrum:[FAB]: 270 (M+H), 238 (M-OMe), 155 (Ts), 91 (C<sub>6</sub>H<sub>4</sub>CH<sub>2</sub>).

N-(4-Chloro-5-phenylselenopentyl)phthalimide (83)

A mixture of the phthalimide (60) (30mg, 0.14mmol) and phenylselenenyl chloride (30mg, 0.15mmol) in dry dichloromethane (5 ml) was stirred under nitrogen for 24 h. The solvent was removed under reduced pressure and the residue chromatographed to give the selenide (83) as a yellow oil (51mg, 92%). 1H n.m.r.: 7.82, dd (J 5.4, 3.1Hz), 2H; 7.70, dd (J 5.4, 3.1Hz), 2H; 7.54, m, 2H; 7.24, m, 3H; 3.68, tt (J 4.1, 7.2Hz), CHCl; 3.70, t (J 7.3Hz), CH<sub>2</sub>N; 3.22, dd (J 11.1, 4.1Hz), CH<sub>2</sub>Se; 2.20, m, CH<sub>2</sub>; 1.79, m, CH<sub>2</sub>. v<sub>max</sub>(CH<sub>2</sub>Cl<sub>2</sub>): 1775, 1720, 1600 cm<sup>-1</sup>. Mass spectrum:
N-(5-Phenylselenyl-3-pentenyl)phthalimide (84)

To a stirred mixture of the selenide (83) (406 mg, 1 mmol) in isopropyl alcohol was added MCPBA (608 mg, 3 mmol) and potassium hydroxide (252 mg, 4.5 mmol) and the mixture stirred at room temperature for 4 h. The solvent was evaporated under reduced pressure and the residue redissolved in ethyl acetate (20 ml). The solution was washed with 10% sodium hydroxide (20 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give the vinylselenone (84) as white needles (330 mg, 82%). ¹H n.m.r.: 7.95, dt (J 6.9, 1.4 Hz), H₂H₆; 7.83, dd (J 3.1, 5.4 Hz), H₄H₇; 7.71, dd (J 3.1, 5.4 Hz), H₅H₆; 7.68, m, H₄; 7.64, tt (J 6.3, 1.6 Hz), H₅; 7.61, tt (J 6.9, 1.6 Hz), H₃; 7.20, dt (J 15.1, 6.8 Hz), H₁₃; 6.72, dt (J 15.1, 1.5 Hz), H₁₄; 3.72, t (J 6.9 Hz), H₁₀a,b; 2.42, dt (J 6.9, 6.8 Hz), H₁₂a,b; 1.91, qn (J 6.9 Hz), H₁₁a,b. ¹³C n.m.r.: 162.9 (C=O), 131.9 (C₃C₈), 142.1 (C₁), 148.3 (C₁₃), 134.1 (C₄C₇), 131.8 (C₄'), 130.8 (C₁₄), 130.2 (C₃C₅), 126.8 (C₂C₆'), 123.3 (C₅C₆), 36.8 (C₁₀), 29.3 (C₁₂), 26.3 (C₁₁). υₘₐₓ(CCl₄): 1760, 1700, 1030, 900 cm⁻¹. Mass spectrum: 387 (M-O), 371 (M-O₂), 214 (M-Se(O)₂Ph), 160 (PhthCH₂).

2-(R*)-Phenylselenylmethyl-3(R*)-hydroxypyrrolidine-1-tosylate (99)

A mixture of the selenide (18a) (41 mg, 0.1 mmol) and MCPBA (100 mg, 0.5 mmol) in deuterochloroform (1 ml) was reacted in a n.m.r. tube over a period of 24 h. ¹H n.m.r. showed the gradual appearance of the selenone (99) after 4 h., and no further change after 24 h. ¹H n.m.r.: 8.02, d (J 8.0 Hz), 2H; 7.28, m, 3H; 4.42, dd (J 12.3, 10.4 Hz), H₆b; 4.34, dt (J 6.2, 5.0 Hz), H₃; 4.16, dd (J 12.3, 2.4 Hz), H₆a; 3.83, ddd (J 10.4, 2.4, 6.2 Hz), H₂; 3.45, m, H₅aH₅b; 2.36, s, ArCH₃; 2.20, br s, OH; 1.69, m, H₄a; 1.20, m, H₄b.
Experimental 5.2.4

t-Butyl 2(R*)-(hydroxymethyl)-3(R*)-hydroxypyrrolidine-1-carboxylate (85)\(^{118}\)

To the selenide (20a) (178mg, 0.5mmol) in isopropyl alcohol (40 ml) was added MCPBA (407mg, 2mmol) and the mixture stirred at room temperature for 1 h. 10% sodium hydroxide (5 ml) was then added and the mixture stirred at room temperature for a further 4 h. The solution was diluted with saturated sodium bicarbonate (10 ml) and extracted with chloroform (2x20 ml). The combined organic extracts were washed with saturated sodium chloride (10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give the diol (85) as a light yellow oil (64mg, 59%). \(^1\)H n.m.r.: 3.85, br s, 1H; 3.75, br s, 1H; 3.6-3.4, m, 3H; 3.29, m, 1H; 3.05, br s, 1H; 1.95, m, 1H; 1.63, m, 1H; 1.46, s, 9H. \(^{13}\)C n.m.r.: 156.3 (C=O), 80.3 (OCMe\(_3\)), 72.6 (C\(_3\)), 67.9 (C\(_6\)), 63.8 (C\(_2\)), 44.9 (C\(_5\)), 31.5 (C\(_4\)), 28.3 (CH\(_3\)). \(v_{max}: 3400, 1695, 1670\) cm\(^{-1}\). Mass spectrum [FAB]: 219 (M+H\(_2\)), 217 (M\(^+\)), 186 (M-CH\(_2\)OH), 162 (M+H\(_2\)-tBu), 144 (M-tBuO).

t-Butyl 2(R*)-(t-butyldimethylsilyloxy)methyl)-3(R*)-((t-butyldimethylsilyloxy)methyl)pyrrolidine-1-carboxylate (86)\(^{118}\)

A mixture of the diol (85) (44mg, 0.2mmol), imidazole (86mg, 1.4mmol), t-butyldimethylsilyl chloride (80 mg, 0.5mmol) and DMAP (6mg, 0.05mmol) in dry DMF (2 ml) under nitrogen was stirred at room temperature for 24 h. The mixture was diluted with ether (3 ml), washed with saturated sodium chloride (2 ml), 10% hydrochloric acid, 10% sodium bicarbonate (2 ml) and saturated sodium chloride (2 ml) again. The organic phase was separated, dried, the solvent removed under reduced pressure and the residue chromatographed to give the silyl ether (86) as a light yellow oil (50 mg, 76%). \(^1\)H n.m.r.: 4.34, br m, H\(_3\); 3.70, m, H\(_{6a}\); 3.66, m, H\(_{6b}\); 3.54-3.26, m, 3H; 2.15-1.94, m, H\(_{4a}\); 1.70-1.80, m, H\(_{4b}\); 1.43, s, 9H; 0.88, s, 9H; 0.06-0.01, m, 12H. \(v_{max}: 1695\) cm\(^{-1}\). Mass spectrum [FAB]: 445 (M\(^+\)), 388 (M-tBu), 373 (M-tBu-Me).
N-Tosyl-2-aza-7-oxobicyclo[4.2.0]octane (91)

To a solution of the selenides (41a) and (41b) (260mg, 0.61mmol) in isopropanol (10 ml) was added MCPBA (420mg 85%, 2.4mmol) and the mixture stirred at room temperature for 1 h. 10% sodium hydroxide (5 ml) was then added and the mixture stirred for a further 2 h. The solution was diluted with saturated sodium thiosulfate (5 ml) and extracted with chloroform (2x20 ml). The combined organic extracts were washed with saturated sodium bicarbonate (10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give a solid that was recrystallized (Et2O/light petroleum) to give the oxetane (91) as rhombic transluscent crystals (120mg, 74%). m.p. 92-94°C. Found: C 58.44% H 6.44% N 5.26% C13H17NSO3 requires C 58.41% H 6.41% N 5.24%. "H n.m.r.: 7.63, d (J 8.2Hz), 2H; 7.32, d (J 8.2Hz), 2H; 5.05, m, H5; 4.79, dd (J 7.1, 6.1Hz), H3a; 4.42, m, H3b; 4.38, m, H2; 3.64, dt (J 11.2, 4.6Hz), H8a; 2.80, dt (J 11.2, 4.0Hz), H8b; 2.43, s, ArCH3; 2.2-1.4, m, 4H. 13C n.m.r: 143.7 134.5 129.7 127.2 (Ar), 79.5 (C5), 76.1 (C3), 50.1 (C2), 42.7 (C8), 27.0 (C7), 21.5 (ArCH3), 19.2 (C6). νmax(CCl4): 1580, 1480, 1040 cm⁻¹. Mass spectrum: 267 (M⁺), 236 (M-CH2OH), 155, 91 (PhCH3).

cis-2-Phenylselenomethylcyclohexanol (92a) and trans-2-phenylselenomethylcyclohexanol (92b)

A solution of the ketone (96) (268mg, 1mmol) in dry ether (5 ml) was added slowly to a stirred solution of lithium aluminium hydride (76mg, 2mmol) in ether (5 ml) at -15°C. The mixture was stirred at -15°C for 2 h., then at room temperature for 1 h. The mixture was quenched by the addition of 6 drops of 50% potassium hydroxide then diluted with ether (10 ml), filtered through celite and washed with saturated brine (5 ml). The organic phase was separated, dried, the solvent removed under reduced pressure and the residue chromatographed to give the alcohol (92a) as a yellow oil (30mg, 11%). "H n.m.r.: 7.48, m, 2H; 7.25, m, 3H; 3.38, m, H1; 3.37, dd (J 12.0, 4.0Hz), H7a; 2.89, dd (J 12.0, 7.6Hz), H7b; 1.96, m, 2H; 1.73, br s, OH; 1.7-1.2, m, 7H. 13C n.m.r.: 132.1 131.2 129.0 126.5 (Ar), 74.4 (C1), 45.7 (C7), 35.6 (C6), 32.1,
Experimental 5.2.4

31.1, 25.4, 24.9. nOE (enhancement): $H_1H_2$ (10.9%). $\nu_{\text{max}}$ : 3340, 1580, 1480, 1440, 1040 cm$^{-1}$. Mass spectrum: 270 (M$^+$), 113 (M-SePh). Further elution gave the alcohol (92b) as a yellow oil (130mg, 48%). $^1H$ n.m.r.: 7.48, m, 2H; 7.25, m, 3H; 4.09, m, $H_1$; 3.06, dd (J 12.0, 7.8Hz), $H_{7a}$; 2.89, dd (J 12.0, 6.4Hz), $H_{7b}$; 1.9-1.1, m, 10H. $^{13}C$ n.m.r.: 132.1 131.2 129.0 126.5 (Ar), 68.5 (C1), 41.7 (C7), 33.0 (C6), 31.0, 27.2, 25.1, 20.1 nOE (enhancement): $H_1H_2$ (1.6%). Other spectral data as for (92a)

**Attempted synthesis of (92a) with bis-phenylselenomethane and cyclohexene oxide**

To a stirred solution of bis-phenylselenomethane (94) (0.2g, 0.6mmol) in dry THF (10 ml) at -78°C under nitrogen was added n-butyl lithium (1.63M, 0.56 ml, 0.9mmol) and the mixture stirred at this temperature for 2 h. Cyclohexene oxide (66µl, 0.65mmol) was then added, the solution stirred at -78°C for 5 min. then quenched by the addition of 10% hydrochloric acid (1 ml). The mixture was warmed to room temperature, diluted with ether and washed with saturated sodium chloride (10 ml). The etheral extracts were dried (MgSO$_4$) and the solvent evaporated to give 1-phenylselenobutane as a yellow oil (120mg, 94%). $^1H$ n.m.r.: 7.48, m, 2H; 7.26, m, 3H; 2.93, dd (J 7.2, 7.5Hz), $CH_2Se$; 1.7-1.3, m, 4H; 0.92, t (J 7.2Hz), $CH_3$. $^{13}C$ n.m.r.: 132.9 132.3 129.1 126.0 (Ar), 32.7 (CSe), 27.5, 23.0, 13.5.

**trans-2-Hydroxymethylcyclohexanol (93)**

A mixture of the selenide (92b) (200mg, 0.7mmol) and MCPBA (608mg, 3mmol) in isopropyl alcohol (20ml) was stirred at room temperature for 1 h then 10% sodium hydroxide (5 ml) added. The mixture was stirred for a further 2 h, the solvent removed under reduced pressure and the residue redissolved in ethyl acetate (10 ml). The solution was washed with 10% sodium hydroxide (10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give the oxetane as a colourless oil (23mg, 18%). $^1H$ n.m.r.: 4.16, m, $H_1$; 3.76, d (J 4.1Hz), $H_{7a}H_{7b}$; 2.17, br s, 2OH; 1.8-1.2, m, 9H. $\nu_{\text{max}}$ : 3480, 3400, 1260, 1030 cm$^{-1}$. Mass spectrum: 130 (M$^+$), 112 (M-H$_2$O), 99 (M-CH$_2$OH).
Experiment 5.2.4

**bis-Phenylselenomethane (94)**

To a stirred mixture of diphenyldiselenide (1.0g, 3.2mmol) in ethanol (50 ml) under nitrogen was added sodium borohydride in small portions until the solution turned colourless. Diiodomethane (0.85g, 3.2mmol) was then added and the mixture heated under reflux for 1 h. The solvent was removed under reduced pressure and the residue diluted with water (20 ml). The solution was extracted with ether (2x30 ml), the combined etheral extracts washed with 10% sodium hydroxide (20 ml), water (20 ml), dried (K₂CO₃) and the solvent removed under reduced pressure to give (94) as a yellow oil (0.85g, 81%). ¹H n.m.r.: 7.55, m, 4H; 7.29, m, 6H; 4.24, s, CH₂Se. νmax : 1580, 1480, 740 cm⁻¹. Mass spectrum: 328 (M⁺), 171 (M-SePh).

**1-Cyclohexenylxytrimethylsilane (95)**

To a stirred solution of cyclohexanone (8.2g, 0.08mol) and triethylamine (20.3g, 0.2mol) in dry DMF (200 ml) under nitrogen was added chlorotrimethylsilane (10.9g, 0.2mol) and the mixture refluxed for 6 h. The cooled solution was diluted with hexane (100 ml) and the solution filtered to removed the precipitated triethylamine hydrochloride. The filtrate was washed with cold 10% sodium bicarbonate (2x50 ml), cold 5% hydrochloric acid (50 ml), then cold 10% sodium bicarbonate (50 ml) again. The organic extracts were dried, the solvent removed under reduced pressure and the residue distilled to give the silyl enol ether (95) as a colourless liquid (10.7g, 74%). b.p. 79-81°C, 24mm [lit 74-75°C, 20mm]. ¹H n.m.r.: 4.87, m, CH= ; 1.99, m, 4H ; 1.6-1.4, m, 4H ; 0.18, s, 9H. νmax : 2960, 1680, 1200 cm⁻¹. Mass spectrum: 170 (M⁺), 155 (M-Me), 127, 75 (Me₃Si).

**2-Phenylselenomethylcyclohexanone (96)**

To a stirred solution of phenylselenochloromethane (97) (6g, 29mmol) and the silyl ether (95) (5.65 ml, 29mmol) in dry dichloromethane (40 ml) at -23°C under nitrogen was added titanic chloride (3.5 ml, 32mmol). The solution was stirred at
-23°C for 1h. then the solution poured into saturated sodium bicarbonate (100 ml). The mixture was extracted with ether (3x20 ml), the combined etheral extracts dried, the solvent removed under reduced pressure and the residue chromatographed to give the ketone (96) as a yellow oil. \(^1\)H n.m.r.: 7.48, m, 2H ; 7.25, m, 3H ; 3.33, dd (J 12.3, 5.3Hz), H\(_7\)a ; 2.73, dd (J 12.3, 7.3Hz), H\(_7\)b ; 2.35, m, CH\(_2\)CO ; 2.2-1.1, m, 6H. \(\nu_{\text{max}}\) : 1700, 1565, 1465 cm\(^{-1}\). Mass spectrum: 268 (M\(^+\)), 157 (SePh), 110 (M-SePh), 83, 54.

**Phenylselenochloromethane (97)**\(^{267}\)

To a stirred solution of diphenyldiselenide (1.56g, 5mmol) in ethanol (25 ml) was added sodium borohydride (0.5g, 13.2mmol) portionwise over 5 min. The solution was then added dropwise over 5 min. to a refluxing solution of dichloromethane (100 ml) and the mixture refluxed for a further 1 h. The cooled solution was acidified with 10% hydrochloric acid, washed with water (20 ml), dried, the solvent removed under reduced pressure and the residue distilled to give (97) as a yellow oil (1.8g, 88%). b.p. 58-62°C, 0.5mm. \(^1\)H n.m.r.: 7.58, m, 2H ; 7.24, m, 3H ; 4.93, s, 2H. \(\nu_{\text{max}}\) : 1600, 1500 cm\(^{-1}\). Mass spectrum: 206 (M\(^+\)).

**cis-7-Oxabicyclo[4.2.0]octane (98)**

A mixture of the selenide (92a) (200mg, 0.7mmol) and MCPBA (608mg, 3mmol) in isopropyl alcohol (20ml) was stirred at room temperature for 1 h then 10% sodium hydroxide (5 ml) added. The mixture was stirred for a further hour, the solvent removed under reduced pressure and the residue redissolved in ethyl acetate (10 ml). The solution was washed with 10% sodium hydroxide (10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give the oxetane as a colourless oil (71mg, 64%). \(^1\)H n.m.r.: 4.71, dd (J 6.3, 8.3Hz), 1H ; 4.47, dd (J 6.9, 9.0Hz), 1H ; 4.33, t (J 6.3Hz), 1H ; 2.0-1.2, m, 9H. \(\nu_{\text{max}}\) : 1580, 1480, 1030 cm\(^{-1}\). Mass spectrum: 110 (M\(^+\)), 95 (M-O), 81, 69, 55, 41.
5.3 Work described in Chapter 3

Phenylselenocyclohexane \((\text{100})^{10}\)

To a stirred solution of diphenylselenide (937mg, 3mmol) in ethanol (10 ml) was added sodium borohydride portionwise until the solution was colourless. Bromocyclohexane (370µl, 3mmol) was then added and the mixture heated under reflux for 3 h. The solvent was removed under reduced pressure and the residue redissolved in isopropyl alcohol to precipitate any remaining diphenylselenide. The mixture was filtered and this process repeated. The filtrate was concentrated under reduced pressure and the residue chromatographed to give the selenide \((\text{100})\) as a yellow oil (638mg, 89%). $^1$H n.m.r.: 7.53 and 7.24, m, 5H; 3.25, tt (J 10.7, 3.6Hz), CHSe; 2.00, m, 2H; 1.70, m, 2H; 1.6-1.2, m, 6H. $\nu_{\text{max}}$: 1580, 1680, 790 cm$^{-1}$. Mass spectrum: 240 (M$^+$), 83 (M-SePh).

Attempted formation of phenylselenonylvlcyclohexane \((\text{101})\)

A mixture of the selenide (240mg, 1mmol) and MCPBA (608mg, 3mmol) in dry DMF (20 ml) under nitrogen was stirred at room temperature for 18 h. The solution was diluted with saturated sodium bicarbonate (20 ml) and extracted with ether (2x20 ml). When the combined etheral extracts were washed with saturated sodium chloride (10 ml), dried and the solvent removed under reduced pressure no organic material was recovered.

Trans-1-Methoxy-2-phenylselenocyclohexane \((\text{102})^{57}\)

Phenylselenenyl chloride (1.95g, 10mmol) was added to a solution of cyclohexene (0.82g, 10mmol) in methanol (50 ml) and the solution stirred at room temperature for 1 h. The solution was diluted with water (10 ml), extracted with ether (2x20 ml), the combined organic extracts dried and the solvent removed under reduced pressure to give the selenide \((\text{102})\) (2.70g, 100%) as a yellow oil. $^1$H n.m.r.: 7.61, m, 2H; 7.27, m, 3H; 3.40, s, OCH$_3$; 3.27, dt (J 3.7, 8.7Hz), CHO; 3.17, dt (J 3.7, 8.3Hz), CHSe;
2.32-2.09, m, 2H; 1.78-1.50, m, 2H; 1.29, m, 4H. \( \nu_{\text{max}} \) : 2960, 1600, 1550, 1500, 1100, 750 cm\(^{-1} \). Mass spectrum: 270 (M\(^{+}\)), 113 (M-SePh), 82 (M-SePh-OMe).

**Cyclopentylaldehyde dimethyl acetal (104)**\(^{166} \)

A mixture of the selenide (102) (270mg, 1mmol) and MCPBA (1.01g 85%, 5mmol) in dry methanol (10 ml) was stirred at room temperature for 1 h. The solution was diluted with saturated brine (10 ml) and extracted with ether (2x10 ml). The combined organic extracts were washed with saturated sodium thiosulfate (10 ml), 10% sodium hydroxide (10 ml), dried and the solvent removed under reduced pressure to give the acetal (104) as a colourless liquid (138mg, 96%). \( ^{1}H \) n.m.r.: 4.11, d (J 7.8Hz), CHO; 3.33, s, OCH\(_{3} \); 2.21, sextet (J 7.8Hz), 1H; 1.7-1.3, m, 8H. \( \nu_{\text{max}} \) : 1450, 1350 cm\(^{-1} \). Mass spectrum: 112 (M-MeOH).

**1-Methoxy-1-phenyl-2-phenylselenopropane (105)**\(^{57} \)

Phenylselenenyl chloride (1.95g, 10mmol) was added to a solution of styrene (1.04g, 10 mmol) in methanol (50 ml) and the solution stirred at room temperature for 1 h. The solution was diluted with water (10 ml), extracted with ether (2x20 ml), the combined organic extracts dried and the solvent removed under reduced pressure to give the selenide (105) (2.87g, 98%) as a yellow oil. \( ^{1}H \) n.m.r.: 7.48, m, 2H; 7.22, m, 3H; 7.33, m, 5H; 4.34, dd (J 8.4, 5.0Hz), CHO; 3.32, dd (J 8.4, 12.2Hz), CH\(_{3}\)Se; 3.24, s, OCH\(_{3} \); 3.09, dd (J 5.0, 12.2Hz), CH\(_{2}\)Se. \( \nu_{\text{max}} \) : 3010, 1600, 1500, 1550, 1110 cm\(^{-1} \). Mass spectrum: 292 (M\(^{+}\)), 121 (M-CH\(_{2}\)SePh).

**Phenylacetaldehyde dimethyl acetal (106)**\(^{166} \)

To a stirred mixture of the selenide (105) (292mg, 1mmol) in methanol (10 ml) was added MCPBA (1.01g 85%, 5mmol). The mixture was stirred at room temperature for 1 h, diluted with saturated brine (5 ml) and extracted with ether (2x10 ml). The combined organic extracts were washed with sodium thiosulfate (10 ml), 10% sodium hydroxide (10 ml), dried, and the solvent removed under reduced pressure to give the acetal (106) as a colourless liquid (161mg, 97%). b.p. 220°C. \( ^{1}H \) n.m.r.: 7.25, m, 5H;
4.55, t (J 5.5Hz), 1H; 3.32, s, 6H; 2.91, d (J 5.5Hz), 2H. \( \nu_{\text{max}} \): 1600, 1500, 1450, 1365 cm\(^{-1}\). Mass spectrum: 134 (M-MeOH), 81 (PhCH\(_2\)).

An authentic sample was prepared as follows: A mixture of phenylacetaldehyde (360mg, 3mmol) and p-toluenesulfonic acid (20 mg) in dry methanol (10 ml) was stirred at room temperature for 1 h. The solvent was removed under reduced pressure and the residue chromatographed to give the acetal (106) (470mg, 95%) identical in all respects with the material obtained above.

*trans*-2-Phenylselenocyclohexanol (107)\(^{22}\)

Phenylselenenyl chloride (0.96g, 5mmol) was added to a solution of cyclohexene (0.41g, 5mmol) in acetonitrile (15 ml) and water (3 ml) and the solution stirred at room temperature for 24 h. The solution was diluted with saturated sodium bicarbonate (10 ml), extracted with dichloromethane (2x20 ml), the combined organic extracts dried and the solvent removed under reduced pressure to give the selenide (107) (1.23g, 96%) as a yellow oil. \(^1\)H n.m.r.: 7.59, m, 2H; 7.26, m, 3H; 3.32, dt (J 4.3, 10.1Hz), CHO; 2.97, s, OH; 2.89, ddd (J 3.9, 10.1, 12.2Hz), CHSe; 2.12, m, 2H; 1.65, m, 2H; 1.6-1.2, m, 4H. \( \nu_{\text{max}} \): 3420, 1055, 735 cm\(^{-1}\). Mass spectrum: 256 (M\(^+\)), 239 (M-OH), 99 (M-SePh).

1-Chloro-1-phenyl-2-chloropropane (111) and 1,1-dichloro-2-phenylpropane (112)

To a stirred mixture of styrene (104mg, 1mmol) in dry DMF (10 ml) at 0°C under nitrogen was added phenylselenenyl chloride (191.5mg, 1mmol). The mixture was stirred at 0°C for 2 min. then MCPBA (608mg 85%, 3mmol) and tetrabutylammonium chloride (278mg, 1mmol) added. The resultant solution was stirred at 0°C for 1 h. diluted with saturated sodium bicarbonate (10 ml) and extracted with ether (2x10 ml). The combined etheral extracts were washed with saturated brine (10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give a mixture of several unidentified compounds as a yellow oil (38mg). Further elution gave a mixture of (111) and (112) in the ratio 1:1 as a yellow oil.
(82mg, 47%). $^1$H n.m.r. (111): 7.23, m, 5H; 4.73, dd (J 9.2, 3.8Hz), 1H; 3.27, dd (J 12.7, 3.8Hz), 1H; 3.13, dd (J 12.7, 9.2Hz), 1H. (112): 7.33, m, 5H; 6.06, dd (J 8.1, 4.4Hz), 1H; 3.81, dd (J 11.8, 8.1Hz), 1H; 3.72, dd (J 11.8, 4.4Hz), 1H. $\nu_{\text{max}}$: 1490, 1450 cm$^{-1}$. When the above reaction was carried out at room temperature chromatography gave only the vinyl chloride (110) as a colourless oil (138mg, 98%). $^1$H n.m.r.: 7.60, m, 5H; 5.73, d (J 1.8Hz), 1H; 5.49, d (J 1.8Hz), 1H.
For (119a) and (119b) see p. 176

3-Methyl-2-phenylseleno-1,3-butanediol (120)

**Method 3a:** To a stirred mixture of 3-methyl-2-butene-1-ol (430mg, 5mmol) in acetonitrile (20 ml) and water (4 ml) at 0°C was added phenylselenenyl chloride (960mg, 5mmol). The solution was stirred at 0°C for 1 h., then at room temperature for 24 h. The mixture was diluted with saturated sodium bicarbonate (10 ml) and extracted with chloroform (2x30 ml). The combined organic extracts were dried, the solvent removed under reduced pressure and the residue chromatographed to give the diol (120) as a colourless oil (1.30g, 100%). b.p. 150°C, 0.05mm (block). Found: C 50.84% H 6.47% C11H16O2Se requires C 50.97% H 6.22%. \(^1\)H n.m.r.: 7.59, m, 3H ; 7.28, m, 3H ; 3.95, m, CH2O ; 3.30, t (J 5.5Hz), CHSe ; 2.88, br s, 2OH ; 1.43, s, CH3 ; 1.41, s, CH3. \(\nu_{\text{max}}\) : 3300, 1580 cm\(^{-1}\). Mass spectrum: 260 (M\(^+\)), 243 (M-OH), 185 (M-CH\(_3\)CHSePh).

Using method 3a but with 2-methyl-3-butene-2-ol (430mg, 5mmol) gave the diol (1.12g, 86%).

2-Methyl-2-phenylseleno-propane-1,3-diol (121)

Using method 3a but with methylallyl alcohol (360mg, 5mmol) gave the hydroxy selenide (121) (1.04g, 85%) as a colourless oil. b.p. 138-140°C, 0.05mm [block]. Found: C 49.30% H 6.02% C\(_{10}\)H\(_{14}\)O\(_2\)Se requires C 48.99% H 5.76%. \(^1\)H n.m.r.: 7.53, m, 2H ; 7.23, m, 3H ; 3.54, dd (J 11.1, 5.0Hz), H\(_{1a}\) ; 3.47, dd (J 11.1, 4.5Hz), H\(_{1b}\) ; 3.21, d (J 12.5Hz), H\(_{3a}\) ; 3.07, d (J 12.5Hz), H\(_{3b}\) ; 3.03, s, OH ; 2.81, br dd (J 5.0, 4.5Hz), OH ; 1.22, s, CH3. \(\nu_{\text{max}}\) : 3350, 1570, 1470 cm\(^{-1}\).

erthro 2-Phenylselenohexane-1,3-diol (122a) and erythro-3-Phenylselenohexane-1,2-diol (122b)

Using method 3a but with trans-2-hexene-1-ol (500mg, 5mmol) gave an inseparable mixture of (122a) and (122b) in the ratio 98:2 (1.25g, 91%) as a yellow oil.
b.p. 150°C, 0.06mm (block). Found: C 52.81% H 6.70% C12H18O2Se requires C 52.75% H 6.64%. 1H n.m.r.: (122a): 7.58, m, 2H ; 7.27, m, 3H ; 4.04, ddd (11.9, 5.7, 4.5Hz), H3 ; 3.88, m, H1aH1b ; 3.29, dt (J 4.5, 5.2Hz), H2 ; 2.86, t (J 6.1 Hz), OH ; 2.77, d (J 5.8Hz), OH ; 1.7-1.3, m, 4H ; 0.92, t (J 7.3Hz), CH3. v_max : 3400, 1575, 1475, 1060, 1020 cm⁻¹. Mass spectrum: 274 (M⁺), 257 (M-OH), 184 (PhSeCHCH2), 157 (PhSe).

394 threeo-2-Phenylesselenohexane-1,3-diol (123a) and threeo-3-phenylselenohexane-1,2-diol (123b)

Using method 3a but with cis 2-hexene-1-ol (500mg, 5mmol) gave a white solid which was recrystallized (ether/light petroleum) to give the selenide (123a) as white needles (990mg, 72%). m.p. 90-91°C. Found: C 52.77% H 6.57% C12H18O2Se requires C 52.75% H 6.64%. 1H n.m.r.: 7.58, m, 2H ; 7.25, m, 3H ; 3.91, m, 3H ; 3.30, dt (J 3.0, 5.3Hz), H2 ; 2.95, br s, 2OH ; 1.7-1.3, m, 4H ; 0.90, t (J 7.2Hz), CH3. v_max (nujol): 3360, 3300, 1580, 1475 cm⁻¹. Mass spectrum: 274 (M⁺), 257 (M-OH), 184 (PhSeCHCH2), 157 (PhSe). Further elution gave (123b) as a colourless oil (88mg, 6%). 1H n.m.r.: 7.57, m, 2H ; 7.27, m, 3H ; 3.76, ddt (J 2.9, 5.3, 7.6Hz), H2 ; 3.63, m, H1aH1b ; 3.21, m, H3 ; 3.06, br d (J 2.9Hz), OH ; 2.25, br t (J 5.3Hz), OH ; 1.68, m, 2H ; 1.50, m, 2H ; 0.91, t (J 6.7Hz), CH3.

2.6(S*)(3(R*)-phenylselenoct-7-ene-2,6-diol (127a) and 2.6(S*)(dimethyl-3(S*)-phenylselenoct-7-ene-2,6-diol (127b)

Using method 3a but with linalool (308mg, 2mmol) gave a complex mixture of products. Chromatography gave an inseparable mixture of (127a) and (127b) in the ratio 1:1 as a yellow oil (140mg, 42%). HRMS: 328.0963 C16H24SeO2 requires 328.0942. 1H n.m.r. [tentative assignments] (127a): 7.57, m, 2H ; 7.26, m, 3H ; 6.8, dd (J 17.4, 10.7Hz), Hx ; 5.22, dd (J 17.4, 1.2Hz), Ha ; 5.03, dd (J 10.7, 1.2Hz), Hb ; 3.35, m, CHSe ; 2.2-1.4, m, 4H ; 1.39, s, CH3 ; 1.31, s, CH3 ; 1.27, s, CH3. (127b): 7.57, m, 2H ; 7.26, m, 3H ; 5.90, dd (J 17.4, 10.7Hz), Hx ; 5.14, dd (J 17.4, 1.2Hz), Ha ; 4.99, dd (J 10.7, 1.2Hz), Hb ; 2.65, m, CHSe ; 2.2-1.4, m, 4H ; 1.37, s, CH3 ; 1.33, s, CH3 ; 1.28, s, CH3.
Experimental 5.3.2

$\nu_{\max}(CCl_4): 3360, 1580, 1480, 1370, 1040 \text{ cm}^{-1}$. Mass spectrum: 328 (M$^+$), 171 (M-SePh-OH), 127 (M-SePh-OH-CH=CH$_2$).

3(S$^*$),7-Dimethyl-2(S$^*$)-phenylselenooct-6-ene-1,3-diol (129b) 3,7-dimethyl-6-phenylselenooct-2-ene-1,7-diol (129a)

Using method 3a but with geraniol (308mg, 2mmol) gave an inseparable mixture of (129b) and (129a) in the ratio 7:5 as a yellow oil (400mg, 62%). HRMS: 328.0938 C$_{16}$H$_{24}$O$_2$Se requires 328.0941. $\nu_{\max}$: 3350, 1580, 1480, 1040 cm$^{-1}$. Mass spectrum: 328 (M$^+$), 154 (M-SePh-OH). $^1$H n.m.r.: (129b): 7.60, m, 2H; 7.25, m, 3H; 5.20, t (J 6.7Hz), H$_6$; 4.03, m, H$_{1a}$; 4.02, m, H$_{1b}$; 3.07, m, H$_2$; 2.76, s, 2OH; 2.43, m, H$_{5a}$; 2.20, m, H$_{5b}$; 1.8-1.6, m, 2H; 1.51, s, CH$_3$; 1.35, s, CH$_3$; 1.24, s, CH$_3$. (129a): 7.57, m, 2H; 7.24, m, 3H; 5.09, t (J 6.8Hz), H$_2$; 4.10, dd (J 15.0, 6.8Hz), H$_{1a}$H$_{1b}$; 3.60, m, 2OH; 2.47, br s, 2OH; 2.1-1.9, m, 4H; 1.67, s, CH$_3$; 1.59, s, CH$_3$; 1.27, s, CH$_3$.

trans-2-Phenylseleno-1,3-butanediol (130a) and trans-3-phenylseleno-1,2-butanediol (130b)

Using method 3a but with crotyl alcohol (360mg, 5mmol) gave an inseparable mixture of the selenides (130a) and (130b) as a yellow oil (1.23g, 100%). b.p. 135°C, 0.03mm. Found: C 48.74% H 6.01% C$_{10}$H$_{14}$O$_2$Se requires C 48.78% H 5.74%. $^1$H n.m.r. (130a): 7.55, m, 2H; 7.24, m, 3H; 4.04, dq (J 7.2, 6.3Hz), H$_3$; 3.97, dd (J 11.7, 4.5Hz), H$_{1a}$; 3.80, dd (J 11.7, 6.5Hz), H$_{1b}$; 3.57, br s, 2OH; 3.20, ddd (J 7.2, 6.5, 4.5Hz), H$_2$; 1.34, d (J 6.3Hz), CH$_3$. (130b): 7.55, m, 2H; 7.24, m, 3H; 4.13, m, H$_2$; 4.01, dd (J 11.7, 4.5Hz), H$_{1a}$; 3.85, dd (J 11.7, 6.5Hz), H$_{1b}$; 3.57, s, 2OH; 3.22, dq (J 3.3, 6.3Hz), H$_3$; 1.33, d (J 6.3Hz), CH$_3$. $\nu_{\max}$: 3360, 1050 cm$^{-1}$. Mass spectrum: 246 (M$^+$), 184 (M-CH$_3$CHOH-OH), 157 (M-SePh).
trans-1-Phenyl-2-phenylselenopropane-1,3-diol (131)

To a stirred mixture of cinnamyl alcohol (134mg, 1mmol) in dichloromethane (10 ml) and water (0.2 ml) was added phenylselenenyl phthalimide (362mg, 1.2mmol) and the mixture stirred at room temperature for 18 h. The solution was filtered, the solvent removed under reduced pressure and the residue chromatographed to give the selenide (131) as a yellow oil (100 mg, 32%) which rapidly decomposed to a complex mixture of products upon standing. ¹H n.m.r.: 7.4-7.1, m, 10H; 4.93, d (J 6.1Hz), H₁; 4.60, br s, 2OH; 3.87, dd (J 11.7, 3.3Hz), H₃a; 3.70, dd (J 11.0, 5.7Hz), H₃b; 3.41, m, H₂. Mass spectrum: 308 (M⁺), 290 (M-OH), 260 (M-OH-CHOH).

Attempted formation of the acetonide (132)

To a stirred mixture of cinnamyl alcohol (134mg, 1mmol) in dichloromethane (10 ml) and water (0.2 ml) was added phenylselenenyl phthalimide (362mg, 1.2mmol), p-toluenesulfonic acid (20 mg) and 2,2-dimethoxypropane (1.04g, 10mmol) and the mixture stirred at room temperature for 18 h. The solution was filtered, the solvent removed under reduced pressure and the residue chromatographed to give only starting materials (107mg, 80%).

Reaction as above but using phenylselenenyl chloride (210mg, 1.1mmol), 2,2-dimethoxypropane (1.04g, 10mmol) and camphor sulfonic acid (20mg) in acetonitrile (10 ml) and water (2 ml) also gave only starting materials (110mg, 82%).

r-2-Phenylseleno-cis-1,trans-3-cyclohexanediol (133)

To a stirred mixture of 2-cyclohexenol (98mg, 1mmol) in acetonitrile (20 ml) and water (4 ml) was added phenylselenenyl chloride (192mg, 1mmol). The mixture was stirred at room temperature for 2 h, diluted with 10% sodium bicarbonate (10 ml) and extracted with chloroform (2x15 ml). The combined organic extracts dried, the solvent removed under reduced pressure and the residue chromatographed to give a 10:1 mixture of the selenides (133a) and (133b) as a
yellow oil (248mg, 91%). b.p. 165°C, 0.03mm (block). Found: C 53.38% H 6.06%
C_{12}H_{16}O_2Se requires C 53.14% H 5.95%.

1H n.m.r.: (133a): 7.62, m, 2H ; 7.27, m, 3H ; 4.11, m, H_1 ; 3.94, dt (J 4.2, 9.7Hz), H_3 ; 3.22, dd (J 2.7, 9.7Hz), H_2 ; 2.67, s, 2OH ; 1.80, m, 2H ; 1.60, m, 2H ; 1.40, m, 2H. (133b): 7.62, m, 2H ; 7.27, m, 3H ; 3.28, dt (J 4.2, 10.1Hz), H_1H_3 ; 3.03, s, 2OH ; 2.77, t (J 10.1Hz), H_2 ; 1.6-1.2, m, 6H. v_{max} : 3400, 1600, 1500, 1095 cm^{-1}. Mass spectrum: 272 (M^+), 158 (M-Ph -2OH), 97 (M-SePh -OH).

Isophorol (134)^{197}

To a stirred mixture of lithium aluminium hydride (40mg, 10mmol) in dry ether (50 ml) under nitrogen was added a solution of isophorone (1.38g, 10mmol) in dry ether (50 ml) dropwise over 5 min. The mixture was stirred at room temperature for 1 h, then cooled and quenched by the addition of 10% hydrochloric acid (10 ml). The organic phase was separated, washed with 10% sodium bicarbonate solution (10 ml), dried and the solvent removed under reduced pressure to give the alcohol (134) as a colourless liquid (1.38g, 99%). b.p. 78-80°C, 9 mm.

1H n.m.r.: 5.42, m, CH=CH-C ; 4.23, m, CHO; 1.96, br s, OH ; 1.84, br d (J 17.5Hz), 1H ; 1.76, ddd (J 12.6, 6.3, 1.4Hz), 1H ; 1.67, s, CH_3 ; 1.60, br d (J 17.5Hz), 1H ; 1.22, dd (J 12.6, 9.1Hz), 1H ; 0.99, s, CH_3 ; 0.88, s, CH_3. v_{max} : 3300, 1665, 1430, 1010 cm^{-1}. Mass spectrum: 140 (M^+), 125 (M-CH_3), 105 (M-CH_3-OH).

r-2-Phenylseleno-3,5,5-trimethylcyclohexane-cis-1,trans -3-diol (135a)

Using method 3a but with isophorol (700mg, 5mmol) gave a mixture of (135a) and (135b) and (134) in the ratio 40:35:21 as a yellow oil (960mg, 60%). b.p. 160°C, 0.02mm (block). Upon standing white crystals of (135a) formed spontaneously (670mg, 42%). m.p. 103-105°C. Found: C 57.72% H 7.13%
C_{15}H_{22}O_2Se requires C 57.51% H 7.08%.

1H n.m.r.: 7.61, m, 2H ; 7.25, m, 3H ; 4.28, tt (J 11.3, 3.8Hz), H_1 [4.27, dt (11.3, 3.8Hz), H_1 upon D_2O shake] ; 3.40, dt (J 3.8, 1.8Hz), H_2 ; 2.49, d (J 11.3Hz), OH ; 1.65, ddt (J 11.4, 3.8, 1.8Hz), H_{6e} ; 1.52, d (J 14.6Hz), H_{4a} ; 1.48, s, CH_3 ; 1.38, dt (J 14.6, 1.8Hz), H_{4e} ; 1.32, s, OH ; 1.14, s, CH_3 ; 1.13, dd (J 11.4, 11.3Hz), H_{6a} ; 0.95, s, CH_3. 13C n.m.r.: 143.8, 134.0, 129.3, 127.6 (Ar), 76.4 (C_3), 68.1 (C_1), 65.6

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Experimental 5.3.2

(C₂), 46.8 (C₄), 45.8 (C₆), 33.6 (CH₃), 31.8 (CH₃), 28.2 (CH₃). ν maxi(CCl₄) : 3500, 3460, 1475, 1365, 1040 cm⁻¹. Mass spectrum: 314 (M⁺), 297 (M-OH), 139 (M-SePh-H₂O), 121 (M-SePh-2H₂O).

2(R⁺)-Hydroxymethyl-2-phenylseleno-3-(R⁺)-hydroxy-6,6-dimethylbicyclo[3.3.1]
heptane (137)

Using method 3a but with (-) myrtenol (136) (760mg, 5mmol) gave a complex mixture from which it was possible to isolate the selenide (137) by chromatography (216mg, 13%). HRMS: 326.0796 C₁₅H₂₂O₂Se requires 326.0785. ¹H n.m.r.: 7.61, m, 2H ; 7.28, m, 3H ; 4.36, d (J 12.6Hz), CH₃OH ; 4.10, m, CHO OH ; 4.19, d (J 12.6Hz), CH₂OH ; 2.2-1.6, m, 6H ; 2.0, br s, 2OH ; 1.20, s, CH₃ ; 1.18, s, CH₃. ν max : 3360, 1580, 1480, 1375, 1160, 1020, 740 cm⁻¹. Mass spectrum: 326 (M⁺), 309 (M-OH), 232 (M-OH-Ph), 151 (M-OH-SePh), 42 (CMe₂).

cis-Pulegol (138)

cis-Pulegol was prepared according to the method of Gemal²⁵⁵ using pulegone (1.52g, 10mmol) and gave cis pulegol (138) as white crystals (1.45g, 94%). m.p. 29-30°C lit.²⁵⁵ m.p. 31.5°C. ¹H n.m.r.: 5.69, m, CHO OH ; 3.01, br s, OH ; 2.1-0.9, m, 6H ; 1.31, s, CH₃ ; 1.30, s, CH₃ ; 0.94, d (J 6.2Hz), CH₃. ν max : 3340, 1665, 1030 cm⁻¹. Mass spectrum: 154 (M⁺), 139 (M-CH₃), 120 (M-CH₃-OH), 42 (Me₂C).

Hydroxyselenation of (138)

Using method 3a, but with cis-pulegol (138) (154mg, 1mmol) gave a complex product mixture that was not characterised as a yellow oil (200mg).

Crotyl acetate (140)

To a stirred mixture of crotyl alcohol (0.72g, 10mmol) and triethylamine (1.21g, 12mmol) in dry dichloromethane (20 ml) at 0°C was added acetyl chloride (0.840g, 12mmol) in dry dichloromethane (5 ml) dropwise over 2 min. The mixture was stirred at room temperature for 1 h., washed with 10% hydrochloric acid (10
ml), then 10% sodium bicarbonate (10 ml), the organic phase separated, dried and the solvent removed under reduced pressure to give the acetate (140) as a colourless oil (1.06g, 93%). $^1$H n.m.r.: 5.78, m, 1H; 5.30, m, 1H; 4.49, dt (J 6.8, 1.2Hz), 2H; 2.06, s, COCH$_3$; 1.72, m, 3H. $\nu_{\text{max}}$ : 1740, 1225 cm$^{-1}$. Mass spectrum: 114 (M$^+$), 71 (M-COCH$_3$), 43 (COCH$_3$).

**trans-3-Hydroxy-2-phenylselenobutyl acetate (141a) and trans-2-hydroxy-3-phenylselenobutyl acetate (141b)**

Using method 3a but with crotyl acetate (570mg, 5mmol) gave an inseparable mixture of the acetates (141a) and (141b) in the ratio 57:43 as a yellow oil (460mg, 32%). b.p. 145°C, 0.05mm (block). HRMS: 288.0253 C$_{12}$H$_{15}$O$_3$Se requires 288.0264. (141b): $^1$H n.m.r.: 7.59, m, 2H; 7.27, m, 3H; 4.19, m, CH$_2$OAc; 3.87, m, CHOH; 3.44, dq (J 4.7, 7.0Hz), CHSe; 2.60, br d (J 4.1Hz), OH; 2.05, s, CH$_3$CO; 1.43, d (J 7.0Hz), CH$_3$. $\nu_{\text{max}}$ : 3350, 1720, 1560, 1030 cm$^{-1}$. Mass spectrum: 288 (M$^+$), 245 (M-Ac), 131 (M-SePh). (141a): $^1$H n.m.r.: 7.59, m, 2H; 7.27, m, 3H; 4.20, m, CH$_2$OAc; 3.68, m, CHOH, 3.55, m, CHSe; 2.74, br s, OH; 2.06, s, CH$_3$CO; 1.46, d (J 6.8Hz), CH$_3$. Other spectral data as above. Further elution gave a mixture of (130a) and (130b) in the ratio 4:1 as a colourless oil (455mg, 37%). Spectral data as above.

**Acetoxy cyclohex-2-ene (143)**

To a stirred mixture of 2-cyclohexenol (686mg, 7mmol) and triethylamine (1.06g, 10.5mmol) in dry dichloromethane (10 ml) at 0°C under nitrogen was added acetyl chloride (750µl, 10.5mmol) dropwise over 5 min. The solution was stirred at room temperature for 12 h, washed with 10% hydrochloric acid (5 ml), 10% sodium bicarbonate (5 ml), dried and the solvent removed under reduced pressure to give the acetate (143) as a colourless liquid (900mg, 92%). $^1$H n.m.r.: 5.95, m, H$_2$; 5.71, m, H$_3$; 5.24, m, H$_2$; 2.1-1.6, m, 6H; 2.06, s, CH$_3$. $\nu_{\text{max}}$ : 1720, 1375, 1240 cm$^{-1}$. Mass spectrum: 97 (M-COCH$_3$), 81 (M-OCOCH$_3$).
r-2-Phenylseleno-trans-3-hydroxycyclohexane-cis-1-acetate (144a) and r-2-hydroxy-
trans-3-phenylselenocyclohexane-cis-1-acetate (144b)

To a stirred mixture of the acetate (143) (910mg, 6.5mmol) in acetonitrile (20 ml) and water (5 ml) at 0°C was added a solution of phenylselenenyl chloride (1.25g, 6.5mmol) in acetonitrile (3 ml). The mixture was stirred at 0°C for 1 h, then at room temperature for 24 h. The solution was then diluted with saturated sodium bicarbonate (10 ml) and extracted with chloroform (3x20ml). The combined organic extracts were washed with saturated sodium chloride (10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give the selenide (144a) (955mg, 47%) as a yellow oil. b.p. 150°C, 0.05mm (block). 1H n.m.r.: 7.60, m, 2H ; 7.28, m, 3H ; 5.43, m, CHOAc ; 4.12, m, CHOH ; 3.47, dd (J 7.7, 3.3Hz), CHSe ; 2.84, br s, OH ; 1.90, s, CH3 ; 2.1-1.4, m, 6H. 13C n.m.r: 170.1 (C=O), 135.0 134.7 129.8 123.7 (Ar), 73.6 (COAc), 70.8 (COH), 55.6 (CSe), 33.0, 21.5, 20.8, 19.7. v_max: 3350, 1720, 1580, 1480 cm⁻¹. Mass spectrum: 314 (M+), 271 (M-Ac), 157 (M-SePh), 147, 104, 76. Further elution gave the selenide (144b) (775mg, 38%) as a yellow oil. 1H n.m.r.: 7.60, m, 2H ; 7.28, m, 3H ; 5.30, m, CHOAc ; 3.52, dd (J 9.5, 2.7Hz), CHOH ; 3.39, dt (J 9.6, 3.7Hz), CHSe ; 2.61, br s, OH ; 2.11, s, CH3 ; 2.1-1.4, m, 6H. 13C n.m.r: 170.7 (C=O), 136.2 134.2 129.0 128.3 (Ar), 72.3 (COAc), 71.8 (COH), 46.3 (CSe), 31.4, 28.2, 21.2, 20.9.

Reactions of crotyl acetate (140)

i) with phenylselenenyl chloride (153a)

To a solution of crotyl acetate (11.4mg, 0.1mmol) in deuterochloroform (0.5 ml) was added phenylselenenyl chloride (19.1mg, 0.1mmol) and the reaction followed by 1H n.m.r. Only the adduct trans-3-chloro-2-phenylselenobutyl acetate (153a) was detected. 1H n.m.r.: 7.61, m, 2H ; 7.30, m, 3H ; 4.49, d (J 5.6Hz), CH2O ; 4.37, m, CHCl ; 3.47, dt (J 6.8, 5.5Hz), CHSe ; 2.03, s, CH3 ; 1.67, d (J 6.6Hz), CH3.
ii) with phenylselenenyl chloride and zinc chloride (153a),(153b)

To a stirred mixture of crotyl acetate (114mg, 1mmol) and anhydrous zinc chloride (136mg, 1mmol) in dry deuterochloroform (2 ml) under nitrogen was added phenylselenenyl chloride (191mg, 1mmol) in deuterochloroform (1 ml). $^1$H n.m.r. showed a mixture of the adducts (153a) and (153b) in the ratio 2:1. $^1$H n.m.r. (153b): 7.61, m, 2H; 7.30, m, 3H; 4.43, d (J 5.8Hz), CH$_2$OAc; 4.31, m, CHCl; 3.23, m, CHSe; 2.10, s, CH$_3$CO; 1.58, d (J 7.2Hz), CH$_3$.

iii) with phenylselenenyl chloride and titanic chloride (119a),(119b)

To a stirred mixture of crotyl acetate (57mg, 0.5mmol) and titanic chloride (55µl, 0.51mmol) in dry deuterochloroform (2 ml) under nitrogen was added phenylselenenyl chloride (96mg, 0.5mmol) in deuterochloroform (1 ml). $^1$H n.m.r. showed a mixture of the adducts (119a) and (119b) in the ratio 7:3. $^1$H n.m.r. (119a): 7.58, m, 2H; 7.30, m, 3H; 4.20, d (J 5.6Hz), CH$_2$O; 4.35, m, CHCl; 3.40, dt (J 6.8, 5.5Hz), CHSe; 2.60, s, OH; 1.70, d (J 6.6Hz), CH$_3$. (119b): 7.58, m, 2H; 7.30, m, 3H; 4.26, d (J 5.8Hz), CH$_2$O; 4.22, m, CHCl; 3.23, m, CHSe; 2.60, s, OH; 1.63, d (J 7.2Hz), CH$_3$.

iv) with phenylselenenyl chloride in methanol (147a)

To crotyl acetate (114mg, 1mmol) in dry methanol (10 ml) under nitrogen was added phenylselenenyl chloride (191mg, 1mmol) and the reaction stirred at room temperature for 18 h. The solvent was removed under reduced pressure and the residue chromatographed to give trans-3-methoxy-2-phenylselenobutyl acetate (147a) as a light yellow oil (260mg, 86%). HRMS: 302.0423 C$_{13}$H$_{18}$O$_3$Se requires 302.0421. $^1$H n.m.r.: 7.57, m, 2H; 7.25, m, 3H; 4.43, dd (J 11.7, 4.5Hz), H$_1$a; 4.36, dd (J 11.7, 6.4Hz), H$_1$b; 3.62, qn (J 6.1Hz), H$_3$; 3.49, dt (J 4.6, 6.1Hz), H$_2$; 3.35, s, OMe; 1.97, s, COCH$_3$; 1.34, d (J 6.1Hz), CH$_3$. $\nu_{\text{max}}$: 1730, 1580, 1480, 1125, 1100, 700 cm$^{-1}$. Mass spectrum: 302 (M$^+$), 242 (M-OAc), 184 (M-OAc-CH$_3$CH(OMe)), 157 (SePh), 85.
v) with phenylselenenyl chloride and zinc chloride in methanol  \((148a), (148b)\)

To a stirred mixture of crotyl acetate (114mg, 1mmol) and zinc chloride (136mg, 1mmol) in dry methanol (10 ml) under nitrogen was added phenylselenenyl chloride (191mg, 1mmol). The mixture was stirred at room temperature for 18 h, the solvent removed under reduced pressure and the residue chromatographed to give a mixture of trans-3-methoxy-2-phenylselenobutyl acetate \((147a)\) and trans-2-methoxy-3-phenylselenobutyl acetate \((147b)\) in the ratio 7:3 as a yellow oil (83mg, 27%). \(^1\)H n.m.r. \((147a)\): As above. \((147b)\): 7.60, m, 2H ; 7.26, m, 3H ; 4.39, m, \text{H}_1\text{aH}_1\text{b} ; 3.64, dt (J 6.3, 6.1Hz), \text{H}_2 ; 3.47, m, \text{H}_3 ; 3.33, s, \text{OMe} ; 1.98, s, \text{COCH}_3 ; 1.37, d (J 6.1Hz), \text{CH}_3 . Further elution gave a mixture of \((148a)\) and \((148b)\) in the ratio 7:3 as a yellow oil (66mg, 25%). HRMS: 260.0305 \(\text{C}_{11}\text{H}_{15}\text{O}_{2}\text{Se}\) requires 260.0314. \(^1\)H n.m.r. \((148a)\): 7.57, m, 2H ; 7.25, m, 3H ; 3.89, dd (J 11.7, 4.5Hz), \text{H}_{1\text{a}} ; 3.89, dd (J 11.7, 6.4Hz), \text{H}_{1\text{b}} ; 3.62, \text{qn} (J 6.1Hz), \text{H}_3 ; 3.35, s, \text{OMe} ; 3.25, dt (J 4.7, 6.6Hz), \text{H}_2 ; 2.68, s, \text{OH} ; 1.34, d (J 6.1Hz), \text{CH}_3 . \((148b)\): 7.57, m, 2H ; 7.25, m, 3H ; 3.74, dd (J 11.7, 4.5Hz), \text{H}_{1\text{a}} ; 3.67, dd (J 11.7, 4.1Hz), \text{H}_{1\text{b}} ; 3.86, m, \text{H}_2 ; 3.41, \text{qn} (J 6.2Hz), \text{H}_3 ; 2.87, s, \text{OH} ; 3.36, s, \text{OMe} ; 1.46, d (J 6.1Hz), \text{CH}_3 . \nu_{max} : 3500, 1580, 1480, 1365, 1090, 700 cm\(^{-1}\). Mass spectrum: 260 (\(M^+\)), 184 (M-OH-\text{CH}_3\text{CH(OMe)}), 157 (SePh), 59 (\text{CH}_3\text{CH(OMe)}).  

v) with phenylselenenyl chloride in acetic acid \((149)\)

A mixture of crotyl acetate (114mg, 1mmol), phenylselenenyl bromide (236mg, 1mmol) and anyhydrous sodium acetate (330mg, 4mmol) in glacial acetic acid (10 ml) was stirred at room temperature for 24 h. The solution was diluted with water (20 ml) then extracted with ethyl acetate (2x20 ml). The combined organic extracts were washed with water (20 ml), 10% sodium bicarbonate, dried, the solvent removed under reduced pressure and the residue chromatographed to give the selenide \((149)\) as a yellow oil (170mg, 52%). HRMS: 330.0363 \(\text{C}_{14}\text{H}_{18}\text{O}_{4}\text{Se}\) requires 330.0369. \(^1\)H n.m.r.: 7.59, m, 2H ; 7.27, m, 3H ; 5.19, \text{qn} (J 5.9Hz), \text{CHOAc} ; 4.41, dd (J 11.7, 5.7Hz), \text{CH}_3\text{OAc} ; 4.29, dd (J 11.7, 7.1Hz), \text{CH}_2\text{OAc} ; 3.51, dt (J 7.1, 5.7Hz), \text{CHSe} ; 2.02, s, \text{CH}_3 ; 1.96, s, \text{CH}_3 ; 1.37, d (J 6.0Hz), \text{CH}_3 . \nu_{max} : 1740, 1375, 1220,
1020, 690 cm$^{-1}$. Mass spectrum: 330 (M$^+$), 271 (M-OAc), 173 (M-SePh). Further elution gave the alcohol (141a) as a yellow oil (34mg, 12%).

**Crotyl trifluoroacetate (150)**

To a stirred mixture of crotyl alcohol (720mg, 10mmol) and DMAP (20 mg) in dry dichloromethane (20 ml) was added trifluoroacetic anhydride (1.41 ml, 10mmol) dropwise over 1 min. The mixture was stirred at room temperature overnight then washed with 10 hydrochloric acid (10 ml), 10 % sodium bicarbonate (10 ml), dried, the solvent removed under reduced pressure and the residue distilled under nitrogen to give the acetate (150) as a colourless liquid (1.45g, 86%). b.p. 105-108$^\circ$C. $^1$H n.m.r.: 5.93, m, H$_2$; 5.62, m, H$_3$; 4.76, d (J 6.7Hz), H$_{1a}$H$_{1b}$; 1.75, m, CH$_3$. $\nu_{\text{max}}$: 1790, 1225, 1160 cm$^{-1}$. Mass spectrum: 126 (M-COCF$_3$), 110 (M-OCOCF$_3$).

**trans-3-Methoxy-2-phenylselenobutyl trifluoroacetate (151)**

To a stirred mixture of the acetate (150) (169mg, 1mmol) in dry methanol (10 ml) under nitrogen was added phenylselenenyl chloride (191mg, 1mmol). The mixture was stirred at room temperature overnight, the solvent removed under reduced pressure and the residue chromatographed to give the selenide (151) as a yellow oil (140mg, 78%). $^1$H n.m.r.: 7.58, m, 2H; 7.28, m, 3H; 5.12, d (J 5.8Hz), CH$_2$O; 4.30, m, CHCl; 3.58, dt (J 7.0, 5.6Hz), CHSe; 1.63, d (J 6.3Hz), CH$_3$. $\nu_{\text{max}}$: 1750, 1580, 1440, 1100, 695 cm$^{-1}$. Mass spectrum: 274 (M-COCF$_3$), 184 (PhSeCH), 85 (COCF$_3$). Further elution gave the alcohol (148a) (10mg, 6%).

**trans-3-Chloro-2-phenylselenobutyl trifluoroacetate (152)**

To crotyl trifluoroacetate (85mg, 0.5mmol) in deuterochloroform (2 ml) under nitrogen was added phenylselenenyl chloride (96mg, 0.5mmol) and the mixture followed by $^1$H n.m.r. Only the adduct (152) could be detected. $^1$H n.m.r.: 7.58, m, 2H; 7.28, m, 3H; 5.12, d (J 5.8Hz), CH$_2$O; 4.30, m, CHCl; 3.58, dt (J 7.0, 5.6Hz), CHSe; 1.63, d (J 6.7Hz), CH$_3$. 178
Reactions of Acetoxy-1-cyclohex-2-ene (143)

i) with phenylselenenyl chloride (155a), (155b)

To a stirred mixture of the acetate (143) (70mg, 0.5mmol) in deuterochloroform (2 ml) under nitrogen was added phenylselenenyl chloride (96mg, 0.5mmol) and the mixture stirred at room temperature for 2 h. ¹H n.m.r. showed a mixture of (155a) and (155b) in the ratio 9:1. ¹H n.m.r. (155a): 7.58, m, 2H; 7.28, m, 3H; 5.33, dt (4.1, 7.8Hz) (collapses to dd (J 4.1, 7.8Hz) upon irradiation @ 3.8 ppm), CHO; 4.50, m (collapses to t (J 4.1Hz) upon irradiation @ 3.8 ppm), CHCl; 3.81, m (collapses to d (2.4 Hz) upon irradiation @ 5.3 and to d (J 4.1 Hz) upon irradiation @ 4.5 ppm), CHSe; 2.26, m, 2H; 1.98, s, CH₃; 1.75, m, 4H. (155b): 7.58, m, 2H; 7.28, m, 3H; 4.83, ddd (9.4, 9.4, 4.4Hz) (collapses to dd (J 4.4, 9.4) upon irradiation @ 3.2 ppm), CHO; 3.70, m, CHCl; 3.20, t (J 9.4Hz) (collapses to d (J 9.4Hz) upon irradiation @ 4.8 or 3.7 ppm), CHSe; 2.26, m, 2H; 2.06, s, CH₃; 1.75, m, 4H.

ii) with phenylselenenyl chloride and zinc chloride (156a), (156b)

To a stirred mixture of the acetate (143) (70mg, 0.5mmol) and anyhydrous zinc chloride (68mg, 0.5mmol) in deuterochloroform (2 ml) under nitrogen was added phenylselenenyl chloride (96mg, 0.5mmol) and the mixture stirred at room temperature for 2 h. ¹H n.m.r. showed a mixture of (155a), (155b), (156a) and (156b) in the ratio 4:2:2:1. ¹H n.m.r. (156a): 7.58, m, 2H; 7.28, m, 3H; 5.57, ddd (J 9.4, 3.1, 3.1), CHO; 4.36, m, CHCl; 3.68, m, H₃; 2.26, m, 2H; 2.10, s, CH₃; 1.75, m, 4H. (156b): 7.58, m, 2H; 7.28, m, 3H; 4.64, dt (J 4.1, 8.0Hz), CHO; 4.58, m, CHCl; 3.67, m, CHSe; 2.26, m, 2H; 2.11, s, CH₃; 1.75, m, 4H.

Acetoxy-3-chlorocyclohex-2-ene (157)

A mixture of the acetate (280mg, 2mmol) and phenylselenenyl chloride (420mg, 4.2mmol) in dry chloroform (20 ml) was stirred at room temperature for 1 h. Hydrogen peroxide (34% v/v, 5 ml) was then added and the mixture stirred vigorously for a further 20 min. The solution was washed with water (10 ml), dried
and the solvent removed under reduced pressure. The residue was redissolved in carbon tetrachloride (5 ml) and added to a refluxing mixture of DBN (620mg, 5mmol) in carbon tetrachloride (20 ml) under nitrogen. The mixture was refluxed for 15 min. then the cooled solution was washed with 10% hydrochloric acid (10 ml), water (10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give the alkene (157) as a colourless liquid (150mg, 43%). \(^1\)H n.m.r.: 5.90, dt (J 4.3, 1.6Hz), H\(_2\); 5.27, m, H\(_1\); 2.33, m, 2H; 2.03, s, CH\(_3\); 1.8-1.7, m, 4H. \(\nu_{\text{max}}\) (CCl\(_4\)): 1735, 1650, 1240 cm\(^{-1}\). Mass spectrum: 175 (weak M\(^+\)), 138 (M-Cl), 114 (M-OAc), 97 (M-Cl-Ac), 79 (M-Cl-OAc).

**Acetoxy-3-chlorocyclohex-2-ene (157) and acetoxy-2-chlorocyclohex-2-ene and (158)**

Reaction was carried out as for (157) above except anhydrous zinc chloride (272mg, 2mmol) was added to the initial reaction mixture. Chromatography gave an inseparable mixture of (157), (158), (159a) and (159b) in the ratio 3 : 1 : 0.3 : 0.2. \(^1\)H n.m.r. (158): 7.58, m, 2H; 7.24, m, 3H; 6.11, dd (J 3.3, 4.9Hz), H\(_3\); 5.35, m, H\(_1\); 2.33, m, 2H; 2.10, s, CH\(_3\); 1.8-1.7, m, 4H. (159a): 7.58, m, 2H; 7.24, m, 3H; 5.9-5.7, m, 2H; 5.02, dt (J 11.6, 3.7Hz), H\(_1\); 4.78, m, H\(_2\); 2.33, m, 2H; 2.12, s, CH\(_3\); 1.8-1.7, m, 4H. (159b): 7.58, m, 2H; 7.24, m, 3H; 5.9-5.7, m, 2H; 5.10, ddt (J 3.0, 3.5, 8.0Hz), H\(_1\); 4.68, m, H\(_2\); 2.33, m, 2H; 2.08, s, CH\(_3\); 1.8-1.7, m, 4H.

**Trifluoroacetoxycyclohex-2-ene (160)**

To a stirred mixture of 2-cyclohexenol (490mg, 5mmol) and DMAP (20 mg) in dry dichloromethane (20 ml) under nitrogen was added trifluoroacetic anhydride (0.705 ml, 5mmol) dropwise and the mixture stirred at room temperature for 24 h. The solution was washed with 10% hydrochloric acid (20 ml), 10% sodium bicarbonate (20 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give the acetate (160) as a colourless liquid (460mg, 48%). \(^1\)H n.m.r.: 6.09, ddt (J 9.9, 4.1, 0.8Hz), H\(_2\); 5.76, ddt (J 9.9, 4.1, 2.1Hz), H\(_3\); 5.43, m, H\(_1\); 2.1-1.2, m, 6H. \(\nu_{\text{max}}\) : 1720, 1375, 1240 cm\(^{-1}\). Mass spectrum: 97 (M-COCF\(_3\)), 81 (M-OCOCF\(_3\)).
Experimental 5.3.2

r-Trifluoroacetoxy-trans-3-chloro-cis-2-phenylselenocyclohexane (161a)

To a stirred mixture of the trifluoroacetate (195mg, 1mmol) in deuterochloroform (5 ml) under nitrogen was added phenylselenenyl chloride (191mg, 1mmol). \(^1\text{H n.m.r.} \) showed a 20:1 mixture of (161a) and (161b). \(^1\text{H n.m.r.}: \) (161a): 7.58, m, 2H; 7.29, m, 3H; 5.48, dt (J 3.8, 6.8Hz), \( \text{H}_1 \); 4.53, ddd (J 3.8, 3.8, 5.8Hz), \( \text{H}_3 \); 3.72, dd (J 3.8, 5.8Hz), \( \text{H}_2 \); 2.3-1.2, m, 6H. (161b): 7.58, m, 2H; 7.29, m, 3H; 4.95, ddd (9.4, 9.4, 4.4Hz), \( \text{H}_1 \); 3.60, m, \( \text{H}_3 \); 3.20, t (J 9.4Hz), \( \text{H}_2 \); 2.3-1.2, m, 6H.

trans-2,3-Epoxycyclohexan-1-ol (165a)

i) from the selenide (133a)

**Method 3b:** A mixture of the selenide (133a) (272mg, 1mmol), MCPBA (1.01g 85%, 5mmol) and 10% potassium hydroxide (2 ml) in isopropyl alcohol (20 ml) was stirred at room temperature for 1 h. The solution was diluted with saturated sodium thiosulfate (10 ml) and extracted with chloroform (2x20 ml). The combined organic extracts were washed with 10% sodium hydroxide (10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give the trans epoxide (165a) as a colourless oil (79mg, 70%). \(^1\text{H n.m.r.}: \) 4.02, m, \( \text{H}_1 \); 3.24, m, \( \text{H}_3 \); 3.08, d (J 3.0Hz), \( \text{H}_2 \); 2.19, br d (J 4.3Hz), \( \text{H}_4a \); 2.0-1.7, m, 3H; 1.5-1.2, m, 3H. \( \nu_{\text{max}} \) (CCl\(_4\)): 3620, 1230, 825 cm\(^{-1}\). Mass spectrum: 97 (M-OH), 70 (M-C\(_2\)H\(_4\)O), 57 (M-C\(_2\)H\(_5\)O\(_2\)). If the reaction was carried out as above with the potassium hydroxide added 1 h after the MCPBA further elution gave \( r \)-2-isopropoxy-trans-1-cis-3-cyclohexanediol (166) (10mg, 6%) as white crystals. m.p. 95-98°C. HRMS: 174.1257 C\(_9\)H\(_{13}\)O\(_3\) requires 174.1256. \(^1\text{H n.m.r.}: \) 3.72, septet (J 6.1Hz), CHO\(_2\)\( \text{Pr} \); 3.50, dt (J 8.8, 4.4Hz), \( \text{H}_1 \); 3.23, t (J 8.8Hz), \( \text{H}_2 \); 3.12, ddd (J 9.1, 8.8, 4.2Hz), \( \text{H}_3 \); 2.74, s, OH; 2.58, s, OH; 1.95, m, 2H; 1.72, dt (J 9.1, 3.0Hz), \( \text{H}_1 \); 1.4-1.2, m, 3H; 1.17, d (J 6.1Hz), \( \text{CH}_3 \); 1.15, d (J 6.1Hz), \( \text{CH}_3 \). \( \nu_{\text{max}}\) (CH\(_2\)Cl\(_2\)): 3620, 1230, 825 cm\(^{-1}\). Mass spectrum: 174 (M\(^+\)), 114 (M-iPrOH).
ii) from cyclohex-2-enol

To a mixture of 2-cyclohexenol (98mg, 1mmol) in acetonitrile (20 ml) and water (4 ml) was added phenylselenenyl chloride (191mg, 1mmol) and the mixture stirred at room temperature for 18 h. A solution of MCPBA (1.01g, 5mmol) in isopropyl alcohol (10 ml) and 10% aqueous potassium hydroxide (2 ml) was then added and the mixture stirred at room temperature for a further hour. The mixture was diluted with saturated sodium bicarbonate (10 ml) and extracted with chloroform (2x20 ml). The combined organic extracts were dried, the solvent removed under reduced pressure and the residue chromatographed to give the epoxide (165a) (70 mg, 62%).

cis-2,3-Epoxy-cyclohexan-1-ol (165b)

To a stirred solution of the 2-cyclohexenol (196mg, 2mmol) in dichloromethane (10 ml) at 0°C was added a solution of MCPBA (405mg 85%, 2mmol) in dichloromethane (5 ml) dropwise over 10 min. The mixture was stirred at room temperature for a further 24 h, filtered, washed with 10% sodium thiosulfate (5 ml), 10% sodium bicarbonate (5 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give the epoxide (165b) (155mg, 68%) as a colourless liquid. $^1$H n.m.r.: 4.01, dddd (J 8.0, 5.2, 2.4Hz), H$_1$; 3.46, m, H$_2$; 3.45, br s, OH; 3.33, m, H$_3$; 1.8-1.2, m, 6H. $\nu_{\text{max}}$ (CCl$_4$): 3590, 1230, 820 cm$^{-1}$. Further elution gave the epoxide (165a) (4 mg, 2%).

trans-2,3-Epoxy-3,5,5-trimethyl-cyclohexan-1-ol (167a)

Using method 3b but with the selenide (135a) (31mg, 0.1mmol), MCPBA (108mg, 0.5mmol) and 10% potassium hydroxide (0.2 ml) in isopropyl alcohol (5 ml) gave the trans epoxide (167a) as a colourless oil (11mg, 72%). $^1$H n.m.r.: 4.17, dd (J 7.2, 5.8Hz), H$_1$; 2.97, s, H$_2$; 2.15, br s, OH; 1.71, d (J 15.1Hz), H$_{4a}$; 1.64, dd (J 13.4, 5.8Hz), H$_{6a}$; 1.52, d (J 15.1Hz), H$_{4b}$; 1.34, s, CH$_3$; 1.17, dd (J 13.4, 7.2Hz), H$_{6b}$; 0.97, s,
cis-2,3-Epoxy-3,5,5-trimethylcyclohexan-1-ol (167b)

To a stirred solution of isophorol (134) (140mg, 1mmol) in dichloromethane (10 ml) at 0°C was added a solution of MCPBA (202mg 85%, 1mmol) in dichloromethane (5 ml) dropwise over 10 min. The mixture was stirred 0°C for a further 2 h, filtered, washed with 10% sodium thiosulfate (5 ml), 10% sodium bicarbonate (5 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give the cis epoxide (167b) (154mg, 99%) as a colourless liquid. ¹H n.m.r.: 4.00, ddd (J 1.1, 6.1, 2.0Hz), H₁; 3.08, d (J 2.0Hz), H₂; 1.57, d (J 15.0Hz), H₄a; 1.37, ddd (J 12.1, 2.2, 6.1Hz), H₆a; 1.27, s, CH₃; 1.13, dd (J 12.1, 11.1Hz), H₆b; 0.82, s, CH₃; 0.78, s, CH₃. ¹³C n.m.r.: 65.4 (C₁), 62.2 (C₂), 61.0 (C₃), 42.2 (C₄), 39.8 (C₆), 31.2 (C₅), 31.1 (CH₃), 26.3 (CH₃), 24.6 (CH₃). \( \nu_{\text{max}}(\text{CCl}_4) : 3325, 1360, 1040 \text{ cm}^{-1} \).

Reaction of the selenide (144a)

i) with MCPBA and NaOH (168a)

A mixture of the selenide (144a) (157mg, 0.5mmol), 10% sodium hydroxide (1 ml) and MCPBA (505mg, 2.5mmol) in isopropyl alcohol (10 ml) was stirred at room temperature for 40 min. The solvent was removed under reduced pressure, the residue redissolved in ether (20 ml). The solution was washed with saturated sodium bicarbonate (10 ml), dried, the solvent was removed under reduced pressure and the residue chromatographed to give the trans 2,3-epoxycyclohexane-1-acetate (168a) (52mg, 67%) as a colourless liquid. ¹H n.m.r.: 5.04, dt (J 1.2, 6.8Hz), H₁; 3.29, m, H₃; 3.23, m, H₂; 2.11, s, CH₃; 1.8-1.3, m, 6H. \( \nu_{\text{max}} : 1725, 1370, 1245 \text{ cm}^{-1} \).

ii) with MCPBA and KOH

As above but with 10% potassium hydroxide (1 ml) for 4 h. gave the trans epoxyalcohol (165a) (45mg, 79%).
Reaction of the selenide (144b)

i) with MCPBA and NaOH (168b)

As above but with the selenide (144b) (157mg, 0.5mmol) gave the cis-2,3-epoxycyclohexane-1-acetate (168b) (57mg, 73%) as a colourless oil. $^1$H n.m.r.: 5.12, dt (J 1.4 5.2Hz), H$_1$ ; 3.29, m, H$_3$ ; 3.07, d (J 3.6Hz), H$_2$ ; 2.10, s, CH$_3$ ; 1.8-1.3, m, 6H. $v_{\text{max}}$: 1725, 1370, 1240 cm$^{-1}$.

ii) with MCPBA and KOH

As above but with the selenide (144b) (157mg, 0.5mmol) and (10% potassium hydroxide (1 ml) for 6 h gave the cis epoxyalcohol (165b) (38mg, 67%).

3,4-Epoxy-2-methyl-butanol-2-ol (170)

Using method 3b but with the selenide (120) (260mg, 1mmol) gave the epoxide (170) as a colourless liquid (75mg, 74%). $^1$H n.m.r.: 3.98, br s, OH ; 3.86, dd (J 12.2, 4.2Hz), H$_{1a}$ ; 3.68, dd (J 12.2, 6.9Hz), H$_{1b}$ ; 3.01, dd (J 6.9, 4.2Hz), 1H ; 1.36, s, CH$_3$ ; 1.32, s, CH$_3$. $v_{\text{max}}$: 3320, 1580, 1030 cm$^{-1}$.

385 2,3-Epoxy-2-methylpropan-1-ol (171)

Using method 3b but with the selenide (121) (246mg, 1mmol) gave the epoxide (171) as a colourless liquid (69mg, 78%). $^1$H n.m.r.: 3.73, d (J 12.3Hz), H$_{1a}$ ; 3.62, d (J 12.3Hz), H$_{1b}$ ; 2.92, d (J 4.8Hz), H$_{3a}$ ; 2.66, d (J 4.8Hz), H$_{3b}$ ; 1.37, s, CH$_3$. $v_{\text{max}}$: 3340, 1580, 1030 cm$^{-1}$.

395 erythro-2,3-Epoxyhexan-1-ol (172)

Using method 3b but with the selenide (122a) (274mg, 1mmol) gave the epoxide (172) as a colourless liquid (75mg, 65%). $^1$H n.m.r.: 4.07, br s, OH ; 3.78, dd (J 12.8, 3.0Hz), H$_{1a}$ ; 3.68, dd (J 12.8, 6.7Hz), H$_{1b}$ ; 2.96, m, H$_2$H$_3$ ; 1.6-1.3, m, 4H ; 0.95, t (J 7.5Hz), CH$_3$. $v_{\text{max}}$: 3430, 1255, 1030 cm$^{-1}$.
393 three-2,3-Epoxyhexan-1-ol (173)

Using method 3b but with the selenide (123a) (274mg, 1mmol) gave the epoxide (173) as a colourless liquid (81mg, 70%). $^1$H n.m.r.: 4.09, br s, OH; 3.85, dd (J 12.8, 2.4Hz), H$_{1a}$; 3.53, dd (J 12.8, 4.2Hz), H$_{1b}$; 2.89, m, H$_2$H$_3$; 1.5-1.3, m, 4H; 0.89, t (J 7.3Hz), CH$_3$. $\nu_{\text{max}}$: 3430, 1255, 1030 cm$^{-1}$.

2,3-Epoxybutan-1-ol (174)

Using method 3b but with a mixture of the selenides (130a) and (130b) (246mg, 1mmol) gave the epoxide (174) as a colourless liquid (58mg, 66%). $^1$H n.m.r.: 4.01, br s, OH; 3.94, dd (J 12.7, 2.4Hz), H$_{1a}$; 3.63, dd (J 12.7, 4.4Hz), H$_{1b}$; 3.06, dq (J 2.4, 5.3Hz), H$_3$; 2.93, dt (J 4.5, 2.4Hz), H$_2$; 1.35, d (J 5.3Hz), CH$_3$. $\nu_{\text{max}}$: 3460, 1580, 1440, 1235 cm$^{-1}$.

2,3-Epoxybutane-1-acetate (175)

Using method 3b but with a mixture of the selenides (141a) and (141b) (288mg, 1mmol) gave the epoxide (175) as a colourless liquid (92mg, 71%). $^1$H n.m.r.: 4.37, dd (J 12.2, 3.0Hz), H$_{1a}$; 3.92, dd (J 12.2, 6.1Hz), H$_{1b}$; 2.94, m, 2H; 2.10, s, CH$_3$CO; 1.35, d (J 5.0Hz), CH$_3$. $\nu_{\text{max}}$: 3460, 1720, 1580, 1230, 1030 cm$^{-1}$.
N-(2-Phenylselenocyclopentane)benzamide (180)

Method 3c: To a solution of cyclopentene (0.689, 10 mmol) in benzonitrile (10 ml) was added phenylseleneny chloride (1.91g, 10 mmol) then triflic acid/water (1/5 1.6g). The mixture was heated under reflux for 4 h., cooled, diluted with saturated sodium bicarbonate (10 ml) and extracted with chloroform (2x30 ml). The combined organic extracts were washed with saturated brine (10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give the amide (180) as white crystals (2.38g, 70%). m.p. 110-113°C Found: C 62.92% H 5.60% N 4.00% C₁₈H₁₉NOSe requires C 62.79% H 5.56% N 4.07%. ¹H n.m.r.: 7.6-7.2, m, 10H; 6.23, br d (J 6.5Hz), NH; 4.33, ddt (J 7.6, 6.5, 7.6Hz), CHN; 3.44, dt (J 7.6, 7.9Hz), CHSe; 2.3-1.5, m, 6H. υ_max : 3340, 1620, 1340 cm⁻¹. Mass spectrum: 345 (M⁺), 225 (M-NHCOPh), 188 (M-SePh).

N-(trans-2-Phenylselenocyclohexane)benzamide (181)

Using method 3c but with cyclohexene (0.17g, 2.1mmol) and refluxing for 1 h. gave a white solid which was recrystallized from chloroform/hexane to give the amide (181) (0.59g, 95%) as fine white needles. m.p. 149-150°C lit. 59 m.p. 149-150°C. ¹H n.m.r.: 7.6-7.3, m, 5H; 5.43, d (J 7.1Hz), NH; 3.80, m, CHN; 3.01, dt (J 3.9, 11.5Hz), CHSe; 2.16, m, 2H; 1.90, s, CH₃; 1.66, m, 2H; 1.5-1.1, m, 4H. υ_max (nujol): 3360, 1630, 1520 cm⁻¹. Mass spectrum: 359 (M⁺), 238 (M-NHCOPh), 202 (M-SePh).

N-(trans-2-Phenylselenocycloheptane)acetamide (182)

Using method 3c but using cycloheptene (490mg, 5mmol) and heating under reflux for 18 h gave a white solid which was recrystallized (ether/light petroleum/ethyl acetate) to give the amide (182) as white needles (590mg, 32%). m.p. 126-127°C. Found: C 64.90% H 6.52% N 3.77% C₂₀H₂₃NOSe requires C 64.51% H 6.23% N 3.76%. ¹H n.m.r.: 7.69, d (J 8.6Hz), 2H; 7.54, m, 2H; 7.45, m, 3H; 7.24, m, 3H; 6.32, br d (J 7.4Hz), NH; 4.22, ddt (J 3.3, 7.4, 9.7Hz), CHN; 3.39, dt (J 3.4, 8.8Hz), CHSe;
2.2-1.5, m, 10H. \( \nu_{\text{max}} \) (CCl\(_4\)) : 3340, 1620, 1340 cm\(^{-1}\). Mass spectrum: 373 (M\(^{+}\)), 253 (M-NHCOPh), 216 (M-SePh), 105 (PhCO), 77 (Ph).

**N-(trans-2-Phenylselenocyclooctane)acetamide (183)**

Using method 3c but with cyclooctene (1.12g, 10mmol) gave the amide (183) as yellow crystals (383mg, 10%). m.p. 110-111°C. HRMS: 388.1174 C\(_{21}\)H\(_{26}\)NOSe requires 388.1179. \(^1\)H n.m.r.: 7.79, d (J 10.2Hz), 2H; 7.40, m, 2H; 7.4-7.2, m, 6H; 6.74, d (J 8.0Hz), NH; 4.32, m, CHN; 3.52, dt (J 2.7, 6.9Hz), CHSe; 2.4-1.4, m, 12H. \( \nu_{\text{max}} \): 3340, 1665, 1505, 1480, 1320 cm\(^{-1}\). Mass spectrum: 388 (M\(^{+}\)), 267 (M-NHCOPh), 231 (M-SePh), 105 (PhCO).

**N-(threo-1-Methyl-2-phenylselenopropane)benzamide (184) and N-(erythro-1-methyl-2-phenylselenopropane)benzamide (185)**

* cis-2-Butene was introduced to a dark red solution of phenylselenenyl chloride (0.96g, 5mmol) in benzonitrile (20 ml) until the mixture turned pale yellow. Trifluoromethanesulfonic acid/water 1/5 (1.2g) was then added and the resultant mixture heated under reflux for 4 h. The cooled solution was diluted with saturated sodium bicarbonate solution (10 ml), then extracted with chloroform (2x20 ml). The combined organic extracts were washed with saturated sodium chloride (10 ml), dried, the solvent removed under reduced pressure, and the residue chromatographed to give a mixture of (184) and (185) in the ratio 5:1 (921mg, 68%). Found: C 61.45% H 5.76% N 4.22% C\(_{17}\)H\(_{19}\)NO requires C 61.45% H 5.76% N 4.22% (184): \(^1\)H n.m.r.: 7.71, d (J 8.2Hz), 2H; 7.60, m, 2H; 7.33, m, 3H; 7.22, m, 3H; 6.71, br d (J 8.4Hz), NH; 4.39, m, CHN; 3.56, dq (J 7.4, 4.6Hz), CHSe; 1.42, d (J 7.2Hz), CH\(_3\); 1.26, d (J 6.8Hz), CH\(_3\). \( \nu_{\text{max}} \) (nujol mull): 3300, 1645 cm\(^{-1}\). Mass spectrum: 333 (M\(^{+}\)), 213 (M-NHCOPh), 176 (M-SePh), 105 (PhCO). (185): \(^1\)H n.m.r.: 7.92, d (J 8.2Hz), 2H; 7.59, m, 2H; 7.40, m, 3H; 7.23, m, 3H; 6.71, d (J 8.4Hz), NH; 4.79, dq (J 9.2, 6.5Hz), CHN; 4.28, dq (J 9.2, 7.0), CHSe; 1.29, d (J 6.5Hz), CH\(_3\); 1.20, d (J 7.0Hz), CH\(_3\). \( \nu_{\text{max}} \): 3320, 1645 cm\(^{-1}\). Mass spectrum: 271(M\(^{+}\)), 212 (M-NHCOCH\(_3\)), 114 (M-SePh).
N-(threo-1-Methyl-2-phenylselenopropane)benzamide (185)

trans-2-Butene was introduced to a dark red solution of phenylselenenyl chloride (0.96g, 5mmol) in benzonitrile (20 ml) until the mixture turned pale yellow. Trifluoromethanesulfonic acid/water (1/5 1.2g) was then added and the resultant mixture heated under reflux for 1 h. The cooled solution was diluted with saturated sodium bicarbonate solution (10 ml), then extracted with chloroform (2x20 ml). The combined organic extracts were washed with saturated sodium chloride (10 ml), dried, the solvent removed under reduced pressure, and the residue chromatographed to give the benzamide (185) as a yellow oil (773mg, 57%). Spectral data as above.

cis-2-Phenyl-3a,5,6,6a-tetrahydro-4H-cyclopentoxazole (186a)

Method 3d: A mixture of the selenide (180) (160mg, 0.46mmol), potassium hydroxide (190mg, 3.4mmol) and MCPBA (400mg, 2.3mmol) in isopropyl alcohol (40 ml) was stirred at room temperature for 1 h. The solution was diluted with saturated sodium thiosulfate (10 ml) and extracted with chloroform (2x20 ml). The combined organic extracts were washed with saturated sodium bicarbonate (10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give the cis oxazoline (186a) as a colourless oil (80mg, 93%). 1H n.m.r.: 7.95, d (J 8.0), 2H; 7.40, m, 3H; 4.68, dt (J 8.1, 5.3Hz), CHO; 4.12, dt (J 8.1, 6.1Hz), CHN ; 1.9-1.4, m, 6H. nOE (% enhancement): CHOCHN (4.1%). ν_max: 1640, 1445 cm⁻¹. Mass spectrum: 201 (M⁺), 187 (M-CH₂), 159 (M-(CH₂)₃), 105 (PhCO), 77 (PhCO).

trans-2-Phenyl-3a,5,6,6a-tetrahydro-4H-cyclopentoxazole (186b)

i) with phenylselenenyI bromide

Method 3e: To a solution of cyclopentene (0.16g, 2mmol) in benzonitrile (10 ml) was added phenylselenenyI bromide (944mg, 4mmol) then triflic acid/water (1/5 0.8g). The mixture was heated under reflux for 1 h, cooled, diluted with saturated sodium bicarbonate (10 ml) and extracted with chloroform (2x20 ml). The combined organic extracts were washed with saturated brine (10 ml), dried, the solvent removed
under reduced pressure and the residue chromatographed to give the trans oxazoline (186b) as a dark yellow oil (194mg, 52%). $^1$H n.m.r.: 7.93, d (J 8.0Hz), 2H; 7.40, m, 3H; 5.11, t (J 6.9Hz), CHO; 4.73, t (J 7.1Hz), CHN; 2.04, m, 2H; 1.8-1.5, m, 4H. $^{13}$C n.m.r: 163.7 (C=N), 131.0 128.1 128.0 127.5 (Ar), 84.0 (CHO), 71.7 (CHN), 34.6, 33.8, 22.1. nOЕ (% enhancement): CHOCHN (<0.5%). $\nu_{\text{max}}$: 1640 cm$^{-1}$. Mass spectrum: 201 (M$^+$), 187 (M-CH$_2$), 159 (M-(CH$_2$)$_3$), 105 (PhCO), 77 (PhCO). After standing for 4 weeks (186b) had hydrolysed to N-(cis-2-hydroxycyclohexyl)acetamide (192). $^1$H n.m.r.: 7.93, d (J 8.0Hz), 2H; 7.40, m, 3H; 6.38, br d (J 7.8Hz), NH; 4.31, qn (J 7.8Hz), CHO; 4.73, dt (J 7.8, 8.2Hz), CHN; 2.63, br s, OH; 2.04, m, 2H; 1.8-1.5, m, 4H. $\nu_{\text{max}}$ (nujol): 3300, 1700, 1660, 1240 cm$^{-1}$. Mass spectrum: 142 (M+H), 125 (M-H$_2$O), 100 (M-COCH$_3$).

**ii) with phenylselenenyl iodide**

Using method 3e described above but with phenylselenenyl iodide (2.38g, 4mmol) gave the trans oxazoline (186b) as a yellow oil (280mg, 75%).

cis-3a,4,5,6,7,7a-Hexahydro-2-phenylbenzoxazole (187a)

Using method 3d, but with the benzamide (181) (359mg, 1mmol), gave a mixture of the lactone (200) and the amide (201) (22mg, 9%). (200): $^1$H n.m.r.: 7.41, s, NH; 5.60, dd (J 5.4, 3.0Hz), CHN; 2.90, dt (J 5.4, 4.9Hz), 1H; 2.46, ddd (J 3.0, 5.1, 10.4), 1H; 2.3-1.4, m, 6H. Fractional recrystallization of this mixture gave the amide (201) as translucent needles (15mg, 6%). m.p. 90-100°С. HRMS: 262.1800 C$_{16}$H$_{23}$NO$_2$ requires 262.1806. $^1$H n.m.r.: 7.80, dt (7.7Hz, 0.9Hz), 2H; 7.47, m, 3H; 6.31, d (J 8.6Hz), NH; 5.33, dd (J 8.6, 9.6Hz), CHN; 3.89, qn (J 6.0Hz), CHO; 2.14, m, CH; 2.1-1.4, m, 8H; 1.23, d (J 6.0Hz), CH$_3$; 1.16, d (J 6.0Hz), CH$_3$. $^{13}$C n.m.r.: 167.2 (NCO), 134.3 131.7 128.7 126.9 (Ar), 81.6 (OCO), 69.3 (CO), 45.3, (CN), 28.9, 28.2, 25.7, 23.6, 21.7, 19.0. $\nu_{\text{max}}$: 1640 cm$^{-1}$. Mass spectrum: 262 (M$^+$), 217 (M-iPr), 201 (M-OiPr). Further elution gave the oxazaline (187a) as a yellow oil (180mg, 90%). $^1$H n.m.r.: 8.0-7.2, m, 5H; 4.68, dt (J 8.3, 5.3Hz), CHO; 4.13, dt (J 8.3, 7.0Hz), CHN; 1.8, m, 4H; 1.6-1.4, m, 4H. $\nu_{\text{max}}$: 1640 cm$^{-1}$. Mass spectrum: 201 (M$^+$), 148 (M-C(O)N), 105 (PhCO), 77 (Ph).
**trans-3a,4,5,6,7,7a-Hexahydro-2-phenylbenzoxazole (187b)**

Using method 3e, but with cyclohexene (160mg, 2mmol) gave the *trans* oxazoline (187b) as a yellow oil (228mg, 57%). $^1$H n.m.r.: 7.95, d (J 8.0Hz), 2H; 7.40, m, 3H; 5.11, t (J 7.0Hz), CHO; 4.73, t (J 7.4Hz), CHN; 2.11, m, 2H; 1.8-1.5, m, 4H. $\nu_{max}$: 1640 cm$^{-1}$. Mass spectrum: 201 (M$^+$), 148 (M-C(O)N), 105 (PhCO), 77 (Ph).

**cis-3a,4,5,6,7,8,8a-Heptahydro-4H-2-phenylcycloheptoxazole (188)**

Using method 3d, but with the amide (50mg, 0.14mmol) (182) gave the oxazoline (188) as a colourless oil (25mg, 83%). $^1$H n.m.r.: 7.95, d (J 8.0Hz), 2H; 7.40, m, 3H; 4.70, dt (J 7.0, 5.6Hz), CHO; 4.15, dt (J 7.0, 6.5Hz), CHN; 2.2-1.2, m, 10H. $\nu_{max}$: 1660. Mass spectrum: 215 (M$^+$), 163 (M-C(O)N), 105 (PhCO), 77 (Ph).

**cis-3a,4,5,6,7,8,9,9a-Octahydro-2-phenylcyclo-octoxazole (189)**

Using method 3d, but with the amide (183) (39mg, 0.1mmol) gave the oxazoline (180) as a colourless oil (20mg, 85%). $^1$H n.m.r.: 7.93, d (J 8.0Hz), 2H; 7.40, m, 3H; 4.35, m, CHO; 4.10, m, CHN; 2.2-1.2, m, 12H. $\nu_{max}$: 1680. Mass spectrum: 229 (M$^+$).

**cis-2-Phenyl-4,5-dihydro-4,5-dimethyloxazole (190)**

Using method 3d with the amide (184) (333mg, 1mmol), MCPBA (1.08g, 5mmol) and potassium hydroxide (0.42g, 7.5mmol) in isopropyl alcohol (20 ml) gave the oxazoline (190) (67mg, 77%) as a colourless liquid. $^1$H n.m.r.: 8.05, d (J 7.7Hz), 2H; 7.42, m, 3H; 4.85, dq (J 9.1, 6.6Hz), CHO; 4.35, dq (J 9.1, 7.0Hz), CHN; 1.36, d (J 6.6Hz), CH$_3$; 1.25, d (J J 7.0Hz), CH$_3$. $\nu_{max}$: 1640 cm$^{-1}$. Mass spectrum: 175 (M$^+$), 131 (M-CH$_3$CHO), 103 (M-(CH$_3$)$_2$(CH$_2$)$_2$O), 77 (Ph).

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**trans-2-Phenyl-4,5-dihydro-4,5-dimethyloxazole (191)**

Using method 3d with the amide (185) (167mg, 0.5mol), MCPBA (0.504g, 2.5mmol) and potassium hydroxide (0.21g, 3.7mmol) in isopropyl alcohol (10 ml) gave the oxazoline (191) (40mg, 92%) as a colourless liquid. \(^1\)H n.m.r.: 7.94, d (J 8.2Hz), 2H; 7.40, m, 3H; 4.29, dq (J 6.4, 6.2Hz), CHO; 3.85, dq (J 6.4, 6.8Hz), CHN; 1.41, d (J 6.2Hz), CH\(_3\); 1.33, d (J 6.8Hz), CH\(_3\). \(\nu_{\text{max}}\): 1640, 1445 cm\(^{-1}\). Mass spectrum: 175 (M\(^+\)), 131 (M-CH\(_3\)CHO), 103 (M-(CH\(_3\))\(_2\)(CH\(_2\))\(_2\)O), 77 (Ph).

**N-(trans-2-Phenylselenocyclohexane)acetamide (195)**

To a stirred solution of cyclohexene (0.17g, 2.1mmol) in acetonitrile (20 ml) at room temperature was added phenylselenenyl bromide (0.50g, 2.1mmol). To this solution was added a triflic acid (0.32g, 2.1mmol) and water (0.2 ml) and the mixture heated under reflux for 1 h. The cooled solution was diluted with saturated sodium bicarbonate (10 ml) and extracted with chloroform (2x20 ml). The combined organic extracts were washed with saturated sodium chloride solution (2x10 ml), dried and the solvent removed under reduced pressure to give a white solid which was recrystallized from chloroform/hexane to give the amide (195) (0.68g, 90%) as fine white needles. m.p. 132-133°C lit.\(^5\) m.p. 133-134°C.

**6-Acetamidehexano-6-lactone (197)**

A mixture of the selenide (195) 297mg, 1mmol) and MCPBA (608mg 85%, 3mmol) in isopropyl alcohol (40 ml) was stirred at room temperature for 2 h. The solvent was removed under reduced pressure, and the residue redissolved in ethyl acetate (20 ml). This solution was washed with saturated sodium bicarbonate (10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give (197) as white crystals (150mg, 87%) which were recrystallized from ether/light petroleum. m.p. 100-101°C. Found: C 56.16% H 7.75% N 8.08%. C\(_8\)H\(_{13}\)NO\(_3\) requires C 56.13% H 7.65% N 8.18%. \(^1\)H n.m.r.: 7.56, s, NH; 5.35, dd (J 3.3, 6.6Hz), CHN; 2.64, m, CH\(_3\)CO; 2.56, m, CH\(_3\)CO; 2.11, s, CH\(_3\); 1.9-1.6, m, 6H. \(^{13}\)C n.m.r: 170.4 (CO) 157.5
Experimental 5.3.3

(C=O), 71.9 (CHN) 32.6, 25.4, 22.9, 22.2, 21.5 (CH₃). \( \nu_{\text{max}} \) (CDCl₃) : 3250, 1720, 1655, 1450, 1225 cm⁻¹. Mass spectrum (FAB): 172 (M+H), 112 (M-NHAc), 43 (Ac). Further elution gave a mixture of the N-(cis-2-hydroxycyclohexane)acetamide (198) and N-(1-isopropoxy-1-cyclopentyl)acetamide (199) as a white solid. (199): \(^1\)H n.m.r.: 5.67, d (J 8.4Hz), NH; 5.04, dd (J 8.4, 9.6Hz), CHN; 3.78, q (J 6.0Hz), CHO; 2.14, m, CH; 2.09, s, CH₃; 2.0-1.4, m, 8H; 1.16, d (J 6.0Hz), CH₃; 1.12, d (J 6.0Hz), CH₃. This solid was recrystallized (ethyl acetate/ether/light petroleum) to give (198) as white needles (20mg, 12%) m.p. 137-140°C. \(^1\)H n.m.r.: 5.72, d (J 8.5Hz), NH; 4.88, dt (J 4.5, 10.6Hz), CHOH; 4.10, m, CHN; 2.1-1.2, m, 8H; 1.87, s, CH₃. \( \nu_{\text{max}} \) (nujol) : 3300, 1700, 1660, 1510, 1400, 1250, 880 cm⁻¹. Mass spectrum: 156 (M+H), 139 (M-H₂O), 114 (M-COCH₃).

**trans-2-Phenylselenocyclohexyl acetate (202)**

A mixture of cyclohexene (411mg, 5mmol), phenylselenenyl bromide (1.18g, 5mmol) and anhydrous sodium acetate (1.64g, 20mmol) in glacial acetic acid (50 ml) was stirred at room temperature for 4 h. The solution was diluted with water (50 ml) and extracted with ethyl acetate (2x30 ml). The combined organic extracts were then washed with water (50 ml), 10% sodium carbonate solution (50 ml), dried and the solvent removed under reduced pressure to give the selenide (202) as a yellow oil (1.36g, 81%). \(^1\)H n.m.r.: 7.56, m, 2H; 7.25, m, 3H; 4.83, dt (J 9.3, 4.2Hz), CHO; 3.20, ddd (J 9.3, 4.0, 10.9Hz), CHSe; 2.2-2.0, m, 2H; 1.94, s, CH₃; 1.7-1.3, m, 6H. \( \nu_{\text{max}} \) : 1730, 1575, 1475, 1225, 1030 cm⁻¹. Mass spectrum: 298 (M⁺), 239 (M-OAc), 141 (M-SePh), 99 (M-(CH₂)₃SePh).

**trans-2-Phenylselenonylcyclohexyl acetate (203)**

A mixture of the selenide (202) (298mg, 1mmol) and MCPBA (1.01g, 5mmol) in isopropyl alcohol (20 ml) was stirred at room temperature for 4 h. The solvent was evaporated under reduced pressure, the residue redissolved in ethyl acetate (20 ml), washed with 10% sodium hydroxide solution (10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give the selenone (203) as white needles (270mg, 82%). m.p. 126-126.5°C. Found: C 50.99% H 5.50% C₁₄H₁₈O₄Se
requires C 50.90% H 5.50%. $^1$H n.m.r.: 7.96, d (J 6.8Hz), 2H; 7.67, m, 3H; 5.16, dt (J 4.7, 10.3Hz), CHO; 3.85, ddd (J 4.5, 10.3, 12.8Hz), CHSe; 2.5-1.7, m, 6H; 1.69, s, CH$_3$; 1.4-1.2, m, 2H. $\nu$$_{\text{max}}$ : 1730, 1420, 1260, 900, 705 cm$^{-1}$. Mass spectrum [FAB]: 330 (M$^+$), 298 (M-O$_2$), 239 (M-O$_2$-OAc).

Attempted cyclization of trans-2-phenylselenonylecyclohexyl acetate (203)

To a stirred mixture of the selenone (90mg, 0.27mmol) in dry THF (15 ml) at -78°C under nitrogen was added butyl lithium (2.5M 0.12 ml, 0.3mmol) dropwise over 2 min. The mixture was stirred at -78°C for 1 h. then quenched at this temperature by the addition of 10% hydrochloric acid. The solution was diluted with saturated sodium chloride (20 ml) and extracted with ether (2 x 20 ml). The combined etheral extracts were washed with saturated sodium bicarbonate (20 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give a complex product mixture which was not characterized.

N-(1-Phenyl-2-phenylselenopropane)acetamide (205)$^{58}$

To a mixture of styrene (1.04g, 10mmol) in acetonitrile (20 ml) was added phenylselenenyl chloride (1.91g, 10mmol), followed by triflic acid/water 1/5 (2.6g). The mixture was heated under reflux for 6 h, cooled, filtered, diluted with saturated sodium bicarbonate (10 ml) and extracted with chloroform (2x20 ml). The combined organic extracts were dried, the solvent removed under reduced pressure and the residue chromatographed to give the amide (205) as a yellow oil (1.40g, 43%). $^1$H n.m.r.: 7.47, m, 4H; 7.25, m, 6H; 6.27, br d (J 7.7Hz), NH; 5.23, dt (J 7.3, 6.9Hz), CHN; 3.36, dd (J 12.3, 6.7Hz), CH$_3$Se; 3.26, dd (J 12.3, 6.2Hz), CH$_2$Se; 1.89, s, CH$_3$. $\nu$$_{\text{max}}$ : 3320, 1650 cm$^{-1}$. Mass spectrum: 319 (M$^+$), 157 (SePh), 97.

Phenacyl acetate (206)

To a stirred mixture of the amide (205) (319mg, 1mmol) and potassium hydroxide (280mg, 5mmol) in isopropyl alcohol (40 ml) was added MCPBA (608mg, 3mmol) and the mixture stirred at room temperature for 1 h. The solvent was removed
under reduced pressure and the residue redissolved in dichloromethane. The solution was washed with 10% sodium hydroxide (20 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give the acetate (206) as a colourless liquid (54mg, 34%). ^1H n.m.r.: 7.90, d (J 8.1Hz), 2H; 7.6-7.4, m, 3H; 5.35, s, CH₂; 2.23, s, CH₃. ^13C n.m.r.: 192.1 (C=O); 170.4 (OC=O); 134.1, 133.9, 129.4, 127.7 (Ar); 66.0 (CH₂O); 20.5 (CH₃). ν_max (CCl₄): 1750, 1700, 7365, 1215 cm⁻¹. Mass spectrum: 178 (M⁺), 105 (PhCO), 77 (Ph), 43 (Ac).

exo-2-Benzamido-endo-6-phenylseleno[3.3.0]cyclooctane (212a) and endo-2-benzamido-endo-6-phenylseleno[3.3.0]cyclooctane (212b)

To a stirred mixture of cyclooctadiene (227mg, 2.1mmol) in benzonitrile (20 ml) was added phenylselenenyl chloride (422mg, 2.2mmol) then triflic acid/water (5:1 0.5 ml). The mixture was heated at 100°C for 4 h., then cooled, diluted with saturated sodium bicarbonate (20 ml) and extracted with chloroform (2x20 ml). The combined organic extracts were washed with saturated sodium chloride (20 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give a white solid which was recrystallized (hexane) to give 2,6-bis-(phenylseleno)-9-oxabicyclo[3.3.1]nonane (211) as white needles (66 mg, 7%). m.p. 82-84°C lit. m.p. 84-85°C. ^1H n.m.r.: 7.53, m, 4H; 7.25, m, 6H; 3.93, m, 2H; 3.74, m, 2H; 2.3-1.9, m, 8H. ^13C n.m.r.: 134.3 129.1 128.6 127.5 (Ar), 69.4 (CO), 44.7 (CSe), 27.9, 26.9. ν_max(CCl₄) : 1588, 1485, 1030 cm⁻¹. Mass spectrum: 438 (M⁺), 281 (M-SePh), 157 (SePh). Further elution gave a white solid which was recrystallized (ethyl acetate/ether/light petroleum) to give a mixture of exo-2-acetamido-endo-6-phenylseleno[3.3.0]cyclooctane (212a) and endo-2-acetamido-endo-6-phenylseleno[3.3.0]cyclooctane (212b) as white needles (454mg, 56%). Found: C 65.59% H 5.89% N 3.41% C₂₁H₂₃NSeO requires C 65.62% H 6.03% N 3.64%. ^1H n.m.r. (212a): 7.75, d (J 6.8Hz), 2H; 7.47, m, 5H; 7.25, m, 3H; 6.18, br d (6.8Hz), NH ; 4.07, dddd (J 6.8, 8.1, 5.6, 7.0Hz), H₂ ; 3.47, ddd (J 6.3, 5.4, 8.7Hz), H₆ ; 2.79, dt (J 8.7, 8.4Hz), H₅ ; 2.33, dt (J 8.4, 7.0Hz), H₁ ; 2.3-1.3, m, 8H. (212b): 7.75, d (J 6.8Hz), 2H; 7.47, m, 5H; 7.25, m, 3H; 6.29, br d (6.8Hz), NH ; 4.47, qn (J 7.1Hz), H₂ ; 3.72, ddd (J 6.7, 8.4, 5.4Hz), H₆ ; 2.87, dt (J 6.9, 8.4Hz), H₅ ; 2.38, dt (J 8.4, 7.0Hz), H₁ ; 2.3-
1.3, m, 8H. $^{13}$C n.m.r. (212a): 167.2 (C=O), 134.6 133.3 131.4 131.3 128.9 128.5 128.4 126.8 (Ar), 58.8 (C$_2$), 50.1 (C$_6$), 47.1 (C$_1$), 45.9 (C$_5$), 35.9 (C$_3$), 32.9 (C$_7$), 30.7 (C$_4$), 28.3 (C$_8$). (212b): 167.1 (C=O), 134.6 133.3 131.4 131.3 128.9 128.5 128.4 126.8 (Ar), 53.9 (C$_2$), 48.6 (C$_6$), 46.6 (C$_1$), 45.9 (C$_5$), 34.7 (C$_3$), 32.9 (C$_7$), 26.9 (C$_4$), 25.5 (C$_8$). $\nu_{\text{max}}$: 3300, 1715, 1580, 1480, 1310, 1030 cm$^{-1}$. Mass spectrum: 385 (M$^+$), 265 (M-NHCOPh), 228 (M-SePh), 105 (COPh), 77 (Ph).

trans-1-Phenylseleno-2-chlorocyclooct-5-ene (213)

To a stirred mixture of cyclooctadiene (216mg, 2mmol) in dry dichloromethane (10 ml) under nitrogen was added a solution of phenylselenenyl chloride (383mg, 2mmol) in dichloromethane (3 ml). The solution was stirred at room temperature for 1 h and the solvent removed under reduced pressure to give the selenide (213) as a yellow oil (600mg, 100%). $^1$H n.m.r.: 7.52, m, 2H; 7.22, m, 3H; 5.72, m, 2H; 4.53, dt (J 8.4, 3.2Hz), CHCl; 3.74, m, CHSe; 2.6-2.1, m, 8H. $\nu_{\text{max}}$: 1575, 1485, 900, 735 cm$^{-1}$. Mass spectrum: 300 (M$^+$), 265 (M-Cl), 107 (M-SePh-Cl).

trans-1-Phenylseleno-2-acetoxy-cyclooct-5-ene (214)

To a stirred mixture of cyclooctadiene (216mg, 2mmol) in acetic acid (20 ml) under nitrogen was added a solution of phenylselenenyl chloride (383mg, 2mmol) in acetic acid (3 ml). The solution was stirred at room temperature for 8 h and the solvent removed under reduced pressure to give the selenide (214) as a yellow oil (600mg, 93%). $^1$H n.m.r.: 7.52, m, 2H; 7.22, m, 3H; 5.75, m, 2H; 5.23, dt (J 8.0, 4.8Hz), CHO; 3.84, m, CHSe; 2.6-2.1, m, 8H. $\nu_{\text{max}}$: 1730, 1575, 1485, 900, 735 cm$^{-1}$. Mass spectrum: 324 (M$^+$), 265 (M-OAc), 167 (M-SePh).

exo-2-Acetoxy-endo-6-phenylseleno[3.3.0]cyclooctane (215a) and endo-2-acetoxy-endo-6-phenylseleno[3.3.0]cyclooctane (215b)

To a stirred mixture of the selenide (227mg, 2.1mmol) in acetic acid (20 ml) was added phenylselenenyl chloride (422mg, 2.1mmol) and the mixture heated under reflux for 18 h. The solvent was removed under reduced pressure and the residue
redissolved in dichloromethane (10 ml). The solution was washed with 10% sodium bicarbonate (10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give a mixture of (215a) and (215b) in the ratio 55:45 (295mg, 46%). b.p. 153°C, 0.05mm (block). Found: C 59.19% H 5.98% C_{16}H_{20}O_{2}Se requires C 59.44% H 6.24%. $^1$H n.m.r.: (215a): 7.53, m, 2H; 7.23, m, 3H; 4.82, dt (J 4.0, 5.1Hz), CHOAc; 3.56, m, CHSe; 2.73, m, 1H; 2.42, m, 1H; 2.02, s, CH$_3$; 1.9-1.5, m, 8H. (215b): 7.53, m, 2H; 7.23, m, 3H; 5.23, m, CHOAc; 3.52, m, CHSe; 2.79, m, 1H; 2.38, m, 1H; 2.04, s, CH$_3$; 1.9-1.5, m, 8H. $\nu_{\text{max}}$: 1730, 1575, 1474, 1240, 1020, 730 cm$^{-1}$. Mass spectrum: 324 ($M^+$), 281 (M-Ac), 265 (M-OAc), 108 (M-SePh-OAc).
2-(1-Phenylselenonyl-1-phenylethoxy)ethanol (216)

To a stirred mixture of styrene (104mg, 1mmol) in ethylene glycol (10 ml) and dichloromethane (5 ml) under nitrogen was added phenylselenenyl chloride (191mg, 1mmol) and the mixture stirred at room temperature for 1 h. MCPBA (1.019, 5mmol) was then added to the reaction mixture and the solution stirred at room temperature for a further 1 h. The solution was then washed with 10% sodium hydroxide (20 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give a white solid, which was recrystallized from ether/hexane to give the selenone (216) as translucent prisms (257mg, 73%). m.p. 120-121°C. Found: C 54.47% H 5.37% C₁₅H₁₈O₄Se requires C 54.40% H 5.14%. ¹H n.m.r.: 8.10, d (J 7.9Hz), 2H; 7.69, m, 3H; 7.4-7.2, m, 5H; 5.28, dd (J 11.4, 2.5Hz), CH₃O; 4.74, t (J 5.8Hz), PhCHO; 3.96, dd (J 11.4, 12.6Hz), CH₅O; 3.77, m, CH₃OH; 3.41, m, CH₅OH; 2.98, d (J 5.8Hz), CH₂Se; 2.3, s, OH. ⁷⁷Se n.m.r.: 986. υmax: 3400, 1400, 1340, 1125, 880 cm⁻¹. Mass spectrum[FAB]: 165 (M-SeO₂Ph), 150 (M-SeO₂Ph-OH), 121 (M-SeO₂Ph-C₂H₄OH), 91 (PhCH₂).

trans-β-Phenylselenonystyrene (217)¹⁸⁴

To a stirred mixture of the selenone (217) (100mg, 0.28mmol) in dry THF (10 ml) under nitrogen was added sodium hydride (15mg, 0.35mmol) and the mixture stirred at room temperature for 1 h. The solution was washed with saturated sodium chloride (10 ml), the organic phase separated, dried, the solvent removed under reduced pressure and the residue chromatographed to give a white solid which was recrystallized (ether/light petroleum) to give the vinyl selenone (217) as white needles (60mg, 74%). m.p. 92-94°C. m.p. 92-94°C. ¹H n.m.r.: 8.02, ddd (J 6.9, 1.6, 1.0Hz), 2H; 7.89, d (J 15.1Hz), PhCH⁻CH; 7.65, m, 3H; 7.52, ddd (J 5.8, 1.6, 1.0Hz), 2H; 7.44, m, 3H; 7.22, d (J 15.5Hz), PhCH⁻CH. υmax: 1600, 1585, 1500, 1060, 930, 875 cm⁻¹. Mass spectrum: 293 (M+H), 260 (M-O₂), 183 (M-O₂-Ph).
2-Hydroxyethyl cyclopentanecarboxylate (218)

i) from cyclohexene

To a stirred mixture of cyclohexene (82mg, 1mmol) in ethylene glycol (10 ml) and dry dichloromethane (20 ml) under nitrogen was added phenylselenenyl chloride (191mg, 1mmol) and the mixture stirred at room temperature for 24 h. MCPBA (1.019, 5mmol) was then added and the mixture stirred at room temperature for a further 2 h. The mixture was washed with 10% sodium hydroxide (2x10 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give the ester (218) as a colourless oil (105mg, 66%). $^1$H n.m.r.: 4.20, m, 2H ; 3.81, m, 2H ; 2.77, qn (J 9.6Hz), 1H ; 2.60, br s, OH ; 1.9-1.5, m, 8H. $^{13}$C n.m.r.: 177.2 (C=O), 65.8 (C-O), 60.8 (C-O), 43.6 (CH), 29.9 (CH$_2$), 25.7 (CH$_2$). $\nu_{max}$: 3450, 1740, 1155 cm$^{-1}$. Mass spectrum: 158 (M$^+$), 132 (M-CO), 108 (C$_7$H$_8$O), 72.

ii) from cyclopentane carboxylic acid

A mixture of cyclopentane carboxylic acid (342mg, 3mmol) and diethylazodicarboxylate (522mg, 3mmol) in dry ether (20 ml) under nitrogen was stirred at room temperature for 2 h. Ethylene glycol (2 ml) was then added and the mixture stirred for a further 24 h. The cooled solution was filtered, dried and the solvent removed under reduced pressure to give the ester (218) as a colourless oil (322mg, 68%). Spectral data as above.
Work described in Chapter 4

N-(4-pentenyl)acrylamide (230)

A mixture of the phthalimide (60) (4.3g, 20mmol) and hydrazine hydrate (1.2g, 11mmol) in ethanol (50 ml) under nitrogen was heated under reflux for 3.5 h. The cooled solution was acidified with concentrated hydrochloric acid, the solvent evaporated, the residue dissolved in 10% sodium hydroxide (20 ml) and extracted with ether (3x20 ml). To the dried combined organic extracts at 0°C was added acryloyl chloride (0.87 ml, 11mmol) dropwise over 5 min., followed by a solution of sodium hydroxide (0.44g, 11mmol) in water (1 ml). The solution was warmed to room temperature and stirred for a further 3 h. The mixture was then washed with 1N hydrochloric acid (10 ml), 10% sodium bicarbonate (10 ml), the organic phase separated, dried, the solvent removed under reduced pressure and the residue chromatographed to give the acrylamide (230) (0.98g, 76%) as a colourless oil, b.p. 110°C, 0.02mm (block). Found: C 67.54% H 9.10% N 9.46%. \( \text{C}_8\text{H}_{13}\text{NO} \) requires: C 67.94% H 9.28% N 9.82%. \( ^1\text{H} \text{n.m.r.} \): 7.1, br s, NH ; 6.25, d (J 7.7 Hz), \( \text{CH}_2\text{H}_b=\text{CH} \); 6.22, d (J 4.1 Hz), \( \text{CH}_a\text{H}_b=\text{CH} \); 5.80, ddt (J 17.1, 10.2, 6.6 Hz), COCH ; 5.60, dd (J 7.7, 4.1 Hz), \( \text{CH}=\text{CH} \); 5.05, dd (J 1.6, 17.1 Hz), \( \text{CH}_a\text{H}_b=\text{CH} \); 4.98, dd (J 1.8, 10.2 Hz), \( \text{CH}_a\text{H}_b=\text{CH} \); 3.30, m, \( \text{CH}_2\text{N} \); 2.09, m, 2H ; 1.64, m, 2H. \( \nu_{max} \) : 3260, 3070, 1655, 1620 cm\(^{-1}\). Mass spectrum: 139 (M\(^+\)), 112 (M-C\(_2\text{H}_3\)), 84 (M-COC\(_2\text{H}_3\)).

1-Acryloyl-2-(phenylselenomethyl)pyrrolidine (231)

To a stirred mixture of the amide (230) (140mg, 1mmol), dry silica (400mg) and anhydrous potassium carbonate (400mg) in dry dichloromethane (20 ml) at 0°C under nitrogen was added a solution of phenylselenenyl bromide (260mg, 1.1mmol) in dry dichloromethane (3 ml) dropwise over 5 min. The solution was stirred at 0°C for a further 10 min. then at room temperature for 24 h. The mixture was filtered through a short silica column eluting with ethyl acetate (30 ml), the solvent removed under reduced pressure and the residue chromatographed to give the selenide (231) as a
yellow oil (195mg, 66%). b.p. 126-129°C, 0.02mm (block). HRMS: 295.0461
C_{14}H_{17}NOSe requires 295.0473. \textsuperscript{1}H n.m.r. (C_{6}D_{5}CD_{3}, 60°C): 7.56, m, 2H; 7.27, m, 3H;
6.53, dd (J 16.9, 2.4Hz), CH_{a}H_{b}=CH ; 6.24, dd (J 16.9, 10.3Hz), CH=CH_{2} ; 5.49, dd ( J
10.3, 2.4Hz), CH_{a}H_{b}=CH ; 4.37, m, CHN ; 3.53, dd (J 12.3, 2.2 Hz), CH_{a}Se ; 3.47, m, CH_{2}N ; 2.83, dd (J 12.3, 9.8Hz), CH_{3}Se ; 2.0-1.8, m, 4H. \nu_{\text{max}}: 1635, 1605, 1420 cm\textsuperscript{-1}.
Mass spectrum: 295 (M\textsuperscript{+}), 138 (M-SePh), 124 (M-CH_{2}SePh).

N-(4-Pentenyl)acetamide (233)

A mixture of the phthalimide (60) (645mg, 3mmol) and hydrazine hydrate (225mg, 4.5mmol) in ethanol (25 ml) under nitrogen was heated under reflux for 3.5 h. The cooled solution was acidified with concentrated hydrochloric acid, the solvent evaporated, the residue dissolved in 10% sodium hydroxide (10 ml) and extracted with ether (3x10 ml). To the dried combined organic extracts at 0°C was added acetyl chloride (250ml, 3.3mmol) dropwise over 5 min., followed by a solution of sodium hydroxide (133mg, 3.3mmol) in water (0.5 ml). The solution was warmed to room temperature and stirred for a further 3 h. The mixture was then washed with 1N hydrochloric acid (5 ml), 10% sodium bicarbonate (5 ml), the organic phase separated, dried, the solvent removed under reduced pressure and the residue chromatographed to give the acetamide (233) (260mg, 57%) as a colourless oil. \textsuperscript{1}H n.m.r.: 6.96, br s, NH ;
5.80, ddt (J 17.1, 10.2, 6.6 Hz), CH=CH_{2} ; 5.05, dd (J 1.8, 17.1 Hz), CH_{a}CH_{b}=CH ; 4.98, dd
(J 1.8, 10.2 Hz), CH_{a}CH_{b}=CH ; 3.26, q (J 6.8 Hz), CH_{2}N ; 2.3-1.9, m, 2H ; 1.98, s, COCH_{3} ;
1.60, qn (J 6.8 Hz), 2H. \nu_{\text{max}}: 1650 cm\textsuperscript{-1}. Mass spectrum: 151 (M\textsuperscript{+}), 136 (M-CH_{3}), 108
(M-COCH_{3}).

1-Acetyl-2-(phenylselenomethyl)pyrrolidine (234)

To a stirred mixture of the amide (233) (75mg, 0.5mmol) and dry silica gel (100mg) in acetonitrile (10 ml) at room temperature was added dropwise a solution of phenylselenenyl bromide (142mg, 0.6mmol) in acetonitrile (2 ml). The mixture was stirred at room temperature for 24 h, filtered, the solvent evaporated under pressure and the residue chromatographed to give the pyrrolidine (234) as a colourless oil (40
mg, 26%). ¹H n.m.r.: 7.64, m, 2H; 7.26, m, 3H; 4.32, m, CHN; 3.6-3.3, m, 3H; 3.1-2.6, m, CH₂Se; 2.2-1.8, m, 4H; 1.95, s, COCH₃. ν_max: 1645 cm⁻¹. Mass spectrum: 282 (M⁺), 126 (M-SePh), 112 (M-CH₂SePh).

Reactions of 1-acryloyl-2-(phenylselenomethyl)pyrrolidine (231)

i) with tributyltin hydride (235)

A degassed mixture of the selenide (231) (99mg, 0.33mmol), tributyltin hydride (107µl, 0.4mmol) and AIBN (5 mg, 0.03mmol) in dry benzene (20 ml) was heated under reflux for 6 h. The solvent was removed under reduced pressure and the residue redissolved in ether. DBU (56mg, 0.36mmol) was added and the solution titrated with an ethereal solution of iodine until the iodine colour just persisted. The mixture was filtered through a short silica column eluting with ether (20 ml), the solvent was removed under reduced pressure and the residue chromatographed to give 1-acryloyl-2-methylpyrrolidine (235) as a yellow oil (40mg, 87%). HRMS: 140.1101 C₈H₁₃NO requires 139.0997. ¹H n.m.r.: (C₆D₅CD₃, 60°C): 6.50, dd (16.9, 2.4Hz), CH₃H=CH ; 6.22, dd (J 16.9, 10.3Hz), CH=CH₂ ; 5.80, dd (J 10.3, 2.4Hz), CH₃H=CH ; 4.00, ddq (J 2.6, 6.4, 6.5 Hz), CHN ; 3.23, m, CH₂N ; 1.9-1.7, m, 4H ; 1.18, d (J 6.4) ; CH₃. ν_max: 1640 cm⁻¹. Mass spectrum: 139 (M⁺), 124 (M-CH₃).

ii) with sodium borohydride

To a rapidly stirred solution of the selenide (231) (70mg, 0.24mmol) in dichloromethane (5 ml) was added sodium borohydride (10mg, 0.26mmol) and the mixture stirred at room temperature for 3 h. The solution was washed with 1N hydrochloric acid (5 ml), the organic phase separated, dried and the solvent removed under reduced pressure to give the starting selenide (41mg).

iii) with nickel boride (236), (237)

To a stirred mixture of the selenide (231) (147mg, 0.5mmol) and nickel chloride hexahydrate (238mg, 1.0mmol) in methanol (4 ml) and tetrahydrofuran (2 ml) at 0°C
was added sodium borohydride (114mg, 3mmol) portionwise. The solution was stirred at this temperature for 15 min., filtered through celite, and the solvent removed under reduced pressure. The residue was redissolved in dichloromethane (10 ml), the solution filtered through celite once more, the filtrate concentrated and the residue chromatographed to give 1-propanoyl-2-(phenylselenomethyl)pyrrolidine (236) as a yellow oil (12mg, 15%). HRMS: 297.0631 \( \text{C}_{14}\text{H}_{19}\text{NOSe} \) requires 297.0632. \( ^1\text{H} \) n.m.r.: 7.58, m, 2H; 7.23, m, 3H; 4.34, m, CHN; 3.48, dd (J 12.3, 3.2 Hz), CH\text{a}Se; 3.46, m, CH\text{b}N; 2.91, dd (J 12.3, 9.4 Hz), CH\text{b}Se; 2.15, q (J 7.4 Hz), CH\text{b}CH\text{b}H; 2.0-1.8, m, 4H; 1.09, t (J 7.4 Hz), CH\text{c}CH\text{c}H. \( \nu_{\text{max}} \): 1645 cm\(^{-1}\). Mass spectrum: 297 (M\(^+\)), 140 (M-SePh), 126 (M-CH\text{b}SePh). Further elution gave a mixture of products which was separated by preparative reverse phase HPLC (eluting with \( \text{H}_2\text{O}:\text{MeOH} 35:65 \)) using refractive index detection, to give 1-propanoyl-2-methylpyrrolidine (237) as a colourless oil (64mg, 78%). \( ^1\text{H} \) n.m.r. (CDCl\(_3\), 50\(^\circ\)C): 4.05, ddq (J 2.6, 6.4, 6.5), CHN; 3.23, m, CH\text{b}N; 2.25, q (J 7.3), CH\text{c}CH\text{c}H; 1.9-1.7, m, 4H; 1.18, d (J 6.4); CH\text{c}CH; 1.16, t (J 7.3), CH\text{c}CH\text{c}H. \( \nu_{\text{max}} \): 1645 cm\(^{-1}\). Mass spectrum: 141 (M\(^+\)), 57 (COCH\text{b}CH\text{b}H).

iv) with tris(trimethylsilyl)silane (238a), (238b)

A degassed mixture of the selenide (231) (149mg, 0.5mmol), tris(trimethylsilyl)silane (149mg, 0.6mmol) and azoisobutyronitrile (5mg) in toluene (20 ml) was heated under reflux under an atmosphere of nitrogen for 4 h. The solvent was removed under reduced pressure and the residue chromatographed to give 1-[3-bis(trimethylsilyl)silylpropanoyl]-2-phenylselenomethyly pyrrolidine (238a) as a light yellow oil (117mg, 50%). HRMS: 470.1280 \( \text{C}_{20}\text{H}_{36}\text{NOSi}_{3}\text{Se} \) requires 470.1270. \( ^1\text{H} \) n.m.r.: 7.42, m, 2H; 7.08, m, 3H; 4.15, m, CHN; 3.35, dd (J 12.3, 3.2 Hz), CH\text{a}Se; 3.25, m, CH\text{b}N; 2.65, dd (J 12.3, 9.4 Hz), CH\text{b}Se; 2.02, m, CH\text{c}CO; 1.75, m, 5H; 0.90, m, CH\text{b}Si; -0.17, s, 18H. \( \nu_{\text{max}} \): 1650 cm\(^{-1}\). Mass spectrum[FAB]: 470 (M\(^+\)), 313 (M-SePh). Further elution gave 1-[2-bis(trimethylsilyl)silylpropanoyl]-2-(phenylselenomethyly)pyrrolidine (238b) as a light yellow oil (31 mg, 13%). HRMS: 470.1277 \( \text{C}_{20}\text{H}_{36}\text{NOSi}_{3}\text{Se} \) requires 470.1270. \( ^1\text{H} \) n.m.r.: 7.48, m, 2H; 7.20, m, 3H; 4.13, m, CHN; 3.45, dd (J 12.3, 3.2 Hz), CH\text{a}Se; 3.43, m, CH\text{b}N; 2.81, dd (J 12.3, 9.4 Hz),

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\[ \text{CH}_3\text{Se} ; 2.0-1.7, \text{m}, 6\text{H} ; 0.85, \text{d} \ (J \ 7.1 \ \text{Hz}), \text{CH}_3\text{CHSi} ; -0.16, \text{s}, 18\text{H}. \ v_{\text{max}} : 1650 \ \text{cm}^{-1}. \]

**Mass spectrum:** 470 (M\(^+\)), 313 (M-SePh).

**v) with MCPBA (241)**

To a cooled mixture of the selenide (231) (120 mg, 0.4 mmol) in dichloromethane (10 ml) was added MCPBA (225 mg, 1.1 mmol). The mixture was stirred at 0°C for 10 min., washed with saturated sodium bicarbonate (5 ml), dried and the solvent removed under reduced pressure to give 1-acyloyl-2-phenylseleninylmethylpyrrolidine (241) as a yellow oil (121 mg, 95%). HRMS: 311.0422 C\(_{14}\)H\(_{17}\)NO\(_2\)Se requires 311.0424. \(^1\)H n.m.r.: 8.80, d (J 8.0 Hz), 2H ; 7.52, m, 3H ; 6.37, d (7.7 Hz), CH\(_3\)H\(_b\)=CH ; 6.33, d (J 4.1 Hz), CH\(_3\)H\(_b\)=CH ; 5.65, dd (J 7.7, 4.1 Hz), CH=CH\(_2\) ; 4.12, m, H\(_2\) ; 3.73, m, H\(_{5a}\) ; 3.51, m, H\(_{5b}\) ; 3.28, dd (J 12.1, 9.6 Hz), H\(_{6b}\) ; 3.05, dd (J 12.1, 3.2 Hz), H\(_{6b}\) ; 2.1-1.8, m, 4H. \(v_{\text{max}} : 1640, 1440, 1260, 830 \ \text{cm}^{-1}. \) Mass spectrum: 311 (M\(^+\)), 295 (M-O) 138 (M-Se(O)Ph).

**Reactions of the selenoxide (241)**

**i) thermolysis with DBN (242)**

A mixture of the selenoxide (241) (311 mg, 1 mmol) and DBN (250 mg, 2 mmol) in dry xylene (20 ml) under nitrogen was heated under reflux for 1 h. The solvent was removed under reduced pressure and the residue chromatographed (squat column, light petroleum/ethyl acetate) to give a mixture of the selenide (231) (10 mg, 3%) and 1-acyloyl-2-methylenepepyrrolidine (242) as a light yellow oil (69 mg, 50%). HRMS: 137.0843 C\(_8\)H\(_{11}\)NO requires 137.0841. \(^1\)H n.m.r. (CDCl\(_3\), 50°C): 6.50, dd (16.9, 2.4 Hz), CH\(_{a}\)H\(_b\)=CH ; 6.19, dd (J 16.9, 10.3 Hz), CH=CH\(_2\) ; 5.55, dd (J 10.3, 2.4 Hz), CH\(_{a}\)H\(_b\)=CH ; 4.63, s, H\(_{6a}\) ; 4.61, s, H\(_{6b}\) ; 3.40, m, H\(_{5a}\)H\(_{5b}\) ; 2.32, m, H\(_{3a}\)H\(_{3b}\) ; 1.81, m, H\(_{4a}\)H\(_{4b}\). \(v_{\text{max}} : 1720, 1675, 1610, 1425, 1270, 740 \ \text{cm}^{-1}. \) Mass spectrum: 137 (M\(^+\)), 84 (M-COCH=CH\(_2\)).

**ii) thermolysis with potassium carbonate (244), (245), (246)**

A mixture of the selenoxide (241) (121 mg, 0.33 mmol) and anhydrous potassium carbonate (200 mg), in carbon tetrachloride (10 ml) under nitrogen was
heated under reflux for 1 h. The cooled solution was filtered, the solvent removed under reduced pressure and the residue chromatographed to give the selenide (231) (3 mg, 3%) [spectral data as above]. Further elution gave N-(5-phenylseleno-4-oxopentyl)acrylamide (246) (9mg, 7%) as a yellow oil. HRMS: 311.0410 C_{14}H_{17}NO_{2} requires 311.0424. ¹H n.m.r.: 7.51, m, 2H ; 7.32, m, 3H ; 6.24, dd (J 16.6, 2.1Hz), CHaHb=CHx ; 6.05, dd (J 16.6, 10.3Hz), CHaHb=CHx ; 5.61, dd (J 10.3, 2.1Hz), CHaHb=CHx ; 3.57, s, CH2Se ; 3.29, dt (J 5.9, 6.7Hz), CH2N ; 2.69, t (J 6.7Hz), CH2CO ; 1.81, qn (J 6.7Hz), CH2. v_{max} : 3300, 1715, 1660, 1240, 1190, 800 cm⁻¹. Mass spectrum: 311 (M+¹), 154 (M-SePh), 140 (M-CH2SePh). Further elution gave N-(4-oxopentyl)acrylamide (245) (10mg, 16%) as a yellow oil. HRMS: 156.1024 C_{8}H_{14}NO requires 156.1024. ¹H n.m.r.: 6.27, dd (J 16.6, 1.4Hz), CHaHb=CHx ; 6.08, dd (J 16.6, 10.2Hz), CHaHb=CHx ; 5.61, dd (J 10.2, 1.42Hz), CHaHb=CHx ; 3.34, dt (J 5.9, 6.7Hz), CH2N ; 2.55, t (J 6.8Hz), CH2CO ; 2.16, s, CH3 ; 1.83, qn (J 6.8Hz), CH2. v_{max} : 3300, 1715, 1660, 1200 cm⁻¹. Mass spectrum: 156(M+¹), 90 (M-CH2COCH3), 84 (M-C_{2}H_{4}COCH_{3}), 55 (COCH=CH2). Further elution gave 1-acryloyl-2-(hydroxymethyl)pyrrolidine (244) (5mg, 10%) as a yellow oil. HRMS: 156.1021 C_{8}H_{14}NO_{2} requires 156.1024. ¹H n.m.r.: 6.55, dd (16.9, 2.4Hz), CHaHb=CH ; 6.24, dd (J 16.9, 10.3Hz), CH=CH2 ; 5.65, dd (J 10.3, 2.4Hz), CHaHb=CH ; 5.25, s, OH ; 4.29, m, H_{6a} ; 3.70, m, H_{6b} ; 3.60, m, H_{5a}H_{5b} ; 1.96, m, 2H ; 1.61, m, 2H. v_{max} : 3260, 1705, 1625, 1460, 1365 cm⁻¹. Mass spectrum: 156 (M+¹), 124 (M-CH2OH), 70 (M-CH2OH-CH=CHCO). Further elution gave the starting selenoxide (240) as a colourless oil (25mg, 21%).

iii) attempted formation of the a-lithioselenoxide

To a stirred solution of the selenide (231) (295mg, 1mmol) in dry THF (20 ml) at -15°C under nitrogen was added a solution of MCPBA (260mg, 1.5mmol) in dry THF (5 ml) in one portion. The solution was stirred at -15°C for 15 min. then cooled to -78°C and LDA (2.0M 1.5ml, 3 mmol) added dropwise over 2 min. The solution was stirred at -78°C for a further 20 min. then a mixture of acetic acid/THF (1/5 1.2 ml) added, followed immediately by trimethylphosphite (124 µl, 1mmol). The solution was stirred at this temperature for a further 10 min. then warmed to room temperature, washed
with saturated sodium chloride (10 ml), saturated sodium bicarbonate (10 ml) and sodium chloride (10 ml) again. The organic phase was separated, dried, the solvent removed under reduced pressure and the residue chromatographed to give the starting selenide (53mg, 18%). Further elution gave an intractable mixture.

**Attempted cyclizations of 1-acryloyl-2-methyleneprrolidin (242)**

A mixture of the enamide (242) (10 mg, 0.07mg) and boron trifluoride etherate (1 drop) in dry xylene (5 ml) under nitrogen was heated under reflux for 4 h. The solvent was removed under reduced pressure to give only starting material (5 mg, 50%).

The enamide (242) was heated under vacuum (0.01mm) at 200°C for 20 min. to give an intractable black tar.

**t-Butyl N-(4-pentenyl)carbamate (250)**

A mixture of the phthalimide (60) (2.15g, 10mmol) and hydrazine hydrate (0.6g, 11mmol) in ethanol (60 ml) under nitrogen was heated under reflux for 3.5 h. The cooled solution was acidified with concentrated hydrochloric acid, the solvent evaporated, the residue dissolved in 10% sodium hydroxide (20 ml) and extracted with ether (3x40 ml). To the dried combined organic extracts at room temperature was added BOC-ON (2.21g, 9mmol) and dimethylaminopyridine (0.2g) and the mixture stirred at this temperature for 24 h. The solution was washed with 10% sodium hydroxide (2x20 ml), 1N hydrochloric acid (20 ml), dried and the solvent evaporated to give the carbamate (250) as a colourless oil (1.519g, 75%). b.p.120-123°C, 15mm. Found: C 64.96% H 10.20% N 7.66% C10H19NO2 requires C 64.38% H 10.34% N 7.56%. 1H n.m.r.: 5.80, ddt (J 17.1, 10.2, 6.6 Hz), CH=CH2; 5.05, dd (J 1.8, 17.1 Hz), CHaHb=CH; 5.00, br s, NH; 4.98, dd (J 1.8, 10.2 Hz), CHaCHb; 3.13, dt (J 6.7, 7.4 Hz), CH2N; 2.07, dt (J 6.6, 7.4 Hz), 2H 1.56, qn (J 7.4Hz), 2H; 1.46, s, 9H. vmax: 1700, 1525, 1180 cm⁻¹. Mass spectrum [FAB]: 185 (M⁺), 128 (M-tBu)
t-Butyl 2-(phenylselenomethyl)pyrrolidine-1-carboxylate (251)

To a stirred mixture of the carbamate (250) (1.10g, 6mmol), dry silica gel (1g), and anhydrous potassium carbonate (0.5g) in dry dichloromethane (20 ml) at -78°C under nitrogen was added a solution of phenylselenenyl phthalimide (2.209, 7.2mmol) in dry dichloromethane (5 ml) dropwise over 5 min. The mixture was stirred at -78°C for 10 min. then at room temperature for 18 h. The solution was filtered, the solvent removed under reduced pressure and the residue chromatographed to give the selenide (251) as a light yellow oil (1.78g, 87%). \(^1\)H n.m.r. (CDCl\(_3\), 50°C): 7.53, m, 2H; 7.24, m, 3H; 3.95, m, H\(_2\); 3.4-2.3, m, 3H; 2.75, dd (J 12.3, 11.8Hz), H\(_{6b}\); 2.0-1.7, m, 4H; 1.40, s, 9H. \(\nu_{\text{max}}\) : 1700, 1580, 7495, 1740, 1400, 1180 cm\(^{-1}\). Mass spectrum: 341 (M\(^+\)), 284 (M-tBu), 240 (M-CO\(_2\)tBu), 170 (M-CH\(_2\)SePh).

2-Phenylselenomethylpyrrolidine (252)

A mixture of the carbamate (251) (1.13g, 3.3mmol) and trifluoroacetic acid (5 ml) in dichloromethane (20 ml) was stirred at room temperature for 2 h. The solution was concentrated under reduced pressure, the residue redissolved in dichloromethane and washed with 10% sodium hydroxide (2x20ml). The organic phase was separated, dried and the solvent removed under reduced pressure to give the amine (252) as a light yellow oil (0.79g, 100%). \(^1\)H n.m.r.: 7.50, m, 2H; 7.24, m, 3H; 4.31, m, H\(_2\); 3.65, m, H\(_{5a}\)H\(_{5b}\); 3.33, dd (J 12.0, 5.5Hz), H\(_{6a}\); 3.00, dd (J 12.0, 7.6Hz), H\(_{6b}\); 2.64, m, H\(_{3a}\); 2.51, m, H\(_{3b}\); 2.13, s, NH; 2.08, m, H\(_{4a}\); 1.55, m, H\(_{4b}\). \(\nu_{\text{max}}\) : 3300, 1480, 1435, 1405 cm\(^{-1}\). Mass spectrum: 241 (M\(^+\)), 70 (M-CH\(_2\)SePh).

Methyl 2-(pyrrolidinyl-1-methyl)propenoate (253)

To a stirred mixture of pyrrolidine (142mg, 2mmol) and triethylamine (304mg, 3mmol) in dichloromethane (20 ml) was added methyl 2-(bromomethyl)acrylate (338mg, 2mmol) dropwise over 5 min. The mixture was heated under reflux for 2 h, then the solvent removed under reduced pressure and the residue redissolved in ether (3 ml) to precipitate any salts. The solution was filtered, the filtrate concentrated under
reduced pressure and the residue chromatographed (light petroleum, ethyl acetate) to give the acrylate (253) (315mg, 93%) as a light yellow oil. HRMS: 169.1098 C₉H₁₅NO₂ requires 169.1102 ¹H n.m.r.: 6.26, dd (J 1.4, 1.1Hz), 1H; 5.79, d (1.4, 1.0Hz), 1H; 3.76, s, OCH₃; 3.33, dd (J 1.0, 1.1), 2H; 2.53, m, 4H; 1.77, m, 4H. v_max: 1720, 1630, 1435, 1120 cm⁻¹. Mass spectrum: 169 (M⁺), 154 (M-Me), 84 (M-C(CH₂)CO₂Me).

Methyl 2-(2-phenylselenomethylpyrrolidinyl-1-methyl)propenoate (254)

To a stirred mixture of the amine (252) (239mg, 1mmol) and triethylamine (152mg, 1.5mmol) in dichloromethane (20 ml) was added methyl 2-(bromomethyl)acrylate (179mg, 1mmol) dropwise over 5 min. The mixture was heated under reflux for 2 h, then the solvent removed under reduced pressure and the residue redissolved in ether (5 ml). The solution was filtered, the filtrate concentrated under reduced pressure and the residue chromatographed (light petroleum, ethyl acetate) to give the acrylate (254) (301mg, 89%) as a light yellow oil. b.p. 118°C, 0.2mm (block). Found: C 56.47% H 5.76% N 3.71% C₁₆H₂₁NO₂Se requires C 56.80% H 6.26% N 4.14%. HRMS: 339.0723 C₁₆H₂₁NO₂Se requires 339.0737. ¹H n.m.r.: 7.45, m, 2H; 7.18, m, 3H; 6.01, s, 1H; 5.73, s, 1H; 3.71, s, OCH₃; 3.67, s, 1H; 3.61, s, 1H; 3.12-2.99, m, 4H; 2.74, m, H₅a; 2.15-1.94, m, 2H; 1.76-1.65, m, 2H. v_max: 1715, 1435, 730 cm⁻¹. Mass spectrum: 339 (M⁺), 308 (M-OCH₃), 254 (M-C(CH₂)CO₂CH₃).

1-Propargyl-2-(phenylselenomethyl)pyrrolidine (255)

To a stirred mixture of the amine (252) (1.19g, 5mmol), triethylamine (760mg, 7.5mmol) in dry dichloromethane (40 ml) under nitrogen was added a solution of propargyl bromide (654mg, 5.5mmol) in dry dichloromethane (5 ml) dropwise over 2 min. The mixture was heated under reflux for 2 h, the solvent removed under reduced pressure and the residue redissolved in ether (5 ml). The solution was then filtered, the filtrate concentrated under reduced pressure and the residue chromatographed to give the propargyl amine (255) as a yellow oil (1.05g, 75%). Found: C 60.62% H 5.94% N 4.97% C₁₄H₁₇NSe requires C 60.43% H 6.16% N 5.04%. HRMS: 279.0518 C₁₄H₁₇NSe requires 279.0526. ¹H n.m.r.: 7.8-7.2, m, 5H; 3.52, d (J 2.5Hz), CH₃C≡C; 3.51, d (J
2.5Hz), CH₅C≡C ; 3.58, m, CHN ; 3.21, dd (J 11.3, 3.5Hz), CH₃Se ; 3.1, m, CH₃N ; 2.93, dd (J 11.3, 9.2Hz), CH₅Se ; 2.78, m, CH₅N ; 2.20, d (J 2.3Hz), C≡CH ; 2.1-1.7, m, 4H. νmax : 3250, 1565, 1460, 720 cm⁻¹. Mass spectrum: 279 (M⁺), 122 (M-SePh), 108 (M-CH₂SePh).

**Ethyl 2-(2-phenylselenomethyl-1-pyrrolidinyl)ethanoate (256)**

To a stirred mixture of the amine (252) (1.19g, 5mmol) and triethylamine (760mg, 7.5mmol) in dichloromethane (40 ml) under nitrogen was added a solution of ethyl bromoacetate (1.15g, 5mmol) in dry dichloromethane (5 ml) dropwise over 5 min. The mixture was heated under reflux for 2 h, then the solvent removed under reduced pressure and the residue redissolved in ether (3 ml) to precipitate any salts. The solution was filtered, the filtrate concentrated under reduced pressure and the residue chromatographed (light petroleum, ethyl acetate) to give the ester (256) (1.39g, 85%) as a light yellow oil. b.p. 132°C, 0.09mm (block). Found: C 55.69% H 7.03% N 4.25% C₁₅H₂₁NO₂Se requires C 55.22% H 6.59% N 4.29% HRMS: 327.0727 C₁₅H₂₁NO₂ requires 327.0735. ¹H n.m.r.: 7.46, m, 2H ; 7.22, m, 3H ; 4.14, q (J 7.1Hz), CH₂ ; 3.54, d (J 16.7Hz), CH₃CO ; 3.27, d (J 16.7Hz), CH₅CO ; 3.19, m, H₂ ; 3.07, m, H₆a ; 2.94, m, H₆b ; 2.53, dt (J 8.3, 9.4Hz), H₅aH₅b ; 2.06-1.70, m, 4H ; 1.23, t (J 7.1Hz), CH₃. νmax : 1730, 1190, 730 cm⁻¹. Mass spectrum: 327 (M⁺), 254 (M-CO₂Et), 169 (M-SePh).

**Reactions of methyl 2-(2-phenylselenomethylpyrrolidinyl-1-methyl)propenoate (254)**

**i) with triphenyltin hydride**

A degassed mixture of the selenide (254) (90mg, 0.33mmol), freshly prepared triphenyltin hydride (107mg, 0.37mmol), azoisobutyronitrile (10mg) in benzene (20 ml) under nitrogen was heated under reflux for 12 h. The solvent was removed under reduced pressure and the residue chromatographed to give the starting selenide (60mg, 66%).

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ii) with tris(trimethylsilyl)silane (258)

A degassed mixture of the selenide (254) (225mg, 0.66mmol), tris(trimethylsilyl)silane (200mg, 0.80mol), azoisobutyronitrile (6mg) in benzene (50 ml) under nitrogen was heated under reflux for 12 h. The solvent was removed under reduced pressure and the residue chromatographed to give the starting selenide (160mg, 71%). Further elution gave methyl 3-(2-phenylselenomethyl-1-pyrrolidinyl)-2-bis(trimethylsilyl)silylmethyl)propenoate (258) (64mg, 37%) as a yellow oil. HRMS: 514.1538 C_{22}H_{40}NO_2Si_3Se requires 514.1531. ^1H n.m.r.: 7.63, m, 2H; 7.25, m, 3H; 3.75, m, CH_3N; 3.72, m, CH_3N; 3.71, s, OMe; 3.52, dd (J 12.8, 6.8Hz), H_6a; 3.45-3.41, m, H_2H_5aH_5b; 3.17, dd (J 12.8, 7.8Hz), H_6b; 2.2-1.7, m, 5H; 0.17, s, 27H. v_max(CH_2Cl_2): 1720, 1415, 1260 cm^{-1}. Mass spectrum [FAB]: 514 (M^+), 340 (M-Si(SiMe_3)_2). Upon extended reaction times it was possible also to isolate the amine (252) (10 mg, 6%).

Reactions of 1-propargyl-2-phenylselenomethylpyrrolidine (255)

i) with tris(trimethylsilyl)silane

A degassed mixture of the selenide (255) (140mg, 0.5mmol), tris(trimethylsilyl)silane (137mg, 0.55mol), azoisobutyronitrile (10mg) in benzene (25 ml) under nitrogen was heated under reflux for 12 h. The solvent was removed under reduced pressure and the residue chromatographed to give only the starting selenide (47mg).

ii) with tributyltin hydride (257)

A degassed mixture of the selenide (255) (90mg, 0.33mmol), tributyltin hydride (107mg, 0.37mmol) and azoisobutyronitrile (10mg) in benzene (20 ml) under nitrogen was heated under reflux for 12 h. The solvent was removed under reduced pressure and the residue chromatographed to give 1-(3-tributylstannyl)propargyl-2-phenylselenomethylpyrrolidine (257) (6 mg, 4%). ^1H n.m.r.: 7.8-7.2, m, 5H; 3.90, s, CH_2C=CH; 3.54, m, H_2; 3.12, dd (J 11.3, 3.5Hz), H_6a; 3.1, m, H_5a; 2.93, dd (J 11.3, 9.2Hz), H_6b; 2.78, m, H_5b; 2.20, d (J 2.3Hz), C=CH; 2.1-1.7, m, 4H; 0.88, m, 15H; 1.25, m, 9H; 209
Experimental 5.4

1.70, m, 6H. \( \nu_{\text{max}} : 1560, 1460 \text{ cm}^{-1} \). Mass spectrum [FAB]: 569 (M\(^+\)), 512 (M-Bu), 398 (M-Bu\(_3\)). Further elution gave the starting selenide (33mg, 30%).

iii) \textit{with triphenyltin hydride}

A degassed mixture of the selenide (255) (278mg, 1mmol), freshly prepared\(^{248}\) triphenyltin hydride (107mg, 0.37mmol), azoisobutyronitrile (10mg) in benzene (150 ml) under nitrogen was heated under reflux for 12 h. The solvent was removed under reduced pressure and the residue chromatographed to give only starting materials (166mg, 60%).
N-(trans-2-Phenylselenocyclohexane)acrylamide (265)<sup>60</sup>

To a stirred solution of 1-hydroxy-2-phenylselenocyclohexane (107) (512mg, 2mmol) in acrylonitrile (10 ml) was added trifluoromethanesulfonic acid (0.34g, 2mmol) and the solution stirred at room temperature for 24 h. The mixture was diluted with saturated sodium bicarbonate (10 ml) and extracted with dichloromethane (2x20 ml). The combined organic extracts were washed with saturated sodium chloride solution, dried, the solvent removed under reduced pressure and the residue chromatographed to give the acrylamide (265) as a white needles (556mg, 90%). m.p. 125-127°C lit.<sup>60</sup> m.p. 126-127°C. <sup>1</sup>H n.m.r.: 7.55, m, 2H; 7.27, m, 3H; 6.24, dd (J 17.0, 1.3Hz), CH<sub>H</sub>CH=CH<sub>2</sub>; 5.97, dd (J 17.0, 10.3Hz), CH=CH<sub>2</sub>; 5.61, dd (J 10.3, 1.3Hz), CH<sub>H</sub>=CH=CH<sub>2</sub>; 5.54, m, NH; 3.86, ddt (J 3.8, 7.0, 11.1Hz), CHN; 3.03, dt (J 3.8, 11.0Hz), CHSe; 2.23, m, 1H; 2.15, m, 1H; 1.7-1.2, m, 6H. v<sub>max</sub>: 3335, 1660, 1620, 1550 cm<sup>-1</sup>. Mass spectrum: 309 (M<sup>+</sup>), 238 (M-NHCOCH=CH<sub>2</sub>), 152 (M-SePh), 98 (M-SePh -COCH=CH<sub>2</sub>).

cis-Octahydro-2-quinolone (266)<sup>268</sup>

To a refluxing, degassed mixture of the selenide (265) (309mg, 1mmol) and AIBN (5mg) in benzene (180 ml) under nitrogen was added triphenyltin hydride (386mg, 1.1mmol) and AIBN (10mg) in benzene (20 ml) dropwise over 15 min. The solution was heated under reflux for a further 12 h. then the cooled solution was worked up in the same manner as for (235) to give a white solid which was recrystallized (ether) to give the amide as white crystals (266) (70mg, 46%). m.p. 139-142°C lit.<sup>268</sup> m.p. 144-145°C. <sup>1</sup>H n.m.r.: 5.14, br d (J 7.2Hz), NH; 3.65, m, CHN; 2.50, t (J 7.8Hz), CH<sub>2</sub>CO; 1.8-0.9, m, 11H. v<sub>max</sub>: 1680 cm<sup>-1</sup>. Mass spectrum: 154 (M+H), 125 (M-CO).

N-(Propargyl-N-(trans-2-phenylselenocyclohexyl)acetamide (267)

To a stirred mixture of the amide (195) (594mg, 2mmol) and propargyl bromide (1.19g, 10mmol) in dry THF (40 ml) under nitrogen was added sodium hydride (53mg, 2.2mmol) and the mixture heated under reflux for 2 h. The mixture
was washed with saturated sodium chloride (20 ml), dried, the solvent removed under reduced pressure and the residue chromatographed to give the amide (267) as a yellow oil (533mg, 72%). b.p. 210°C, 0.04mm. Found: C 60.68% H 6.45% N 4.26% C₁₇H₂₁NOSe requires C 61.08% H 6.33% N 4.19%. ¹H n.m.r.: 7.55, m, 2H; 7.28, m, 3H; 3.73, d (J 1.9Hz), CH₂N; 3.64, dt (J 3.7, 11.5Hz), CHN; 3.24, dt (J 3.7, 11.7Hz), CHSe; 2.21, s, CH₃; 2.09, s, C=CH; 1.9-1.2, m, 8H. υₘₐₓ : 3300, 1660, 1400, 930 cm⁻¹. Mass spectrum: 336 (M+H), 238 (M-N(Ac)CH₂C=CH), 178 (M-SePh), 136 (M-SePh-COCH₃).

N-Acetyl-3-methylidenyl-cis-octahydroindole (268) and N-acetyl-3-bis-(trimethylsilyl)silylmethyl-cis-octahydroindole (269)

To a stirred, refluxing mixture of the selenide (267) (210mg, 0.63mmol) and AIBN (5mg) in dry, degassed benzene (120 ml) under nitrogen was added tris(trimethylsilyl)silane (187mg, 0.75mmol) and AIBN (5mg) in dry benzene (5 ml) dropwise over 10 min. The mixture was heated under reflux for 12 h then a second portion of tristrimethylsilylsilane (187mg, 0.75mmol) and AIBN (5mg) in dry benzene (5 ml) was added. The mixture was heated under reflux for a further 12 h, cooled, the solvent removed under reduced pressure and the residue chromatographed to give the silane (269) as a colourless oil (40 mg, 18%). HRMS: 354.2104 C₁₇H₃₆NOSi₃ requires 354.2105. ¹H n.m.r.: 3.87, dt (J 3.2, 6.8Hz), CHN; 3.18, d (J 10.5Hz), CH₃N; 3.09, d (J 10.1Hz), CH₃N; 2.03, s, CH₃; 1.7-1.0, m, 11H; 0.92, dd (J 14.1, 6.4Hz), CH₃Si; 0.74, dd (J 14.1, 8.9Hz), CH₃Si; 0.16, s, 18H. υₘₐₓ : 1650, 1400, 1240, 835 cm⁻¹. Mass spectrum: 354 (M⁺), 280 (M-SiMe₃), 73 (SiMe₃). Further elution gave the alkene (268) as a light yellow oil (80mg, 70%). HRMS: 179.1302 C₁₁H₁₇NO requires 179.1310. ¹H n.m.r.: 5.11, m, CH₃=; 4.96, m, CH₂=; 4.3-3.8, m, 3H; 2.20, m, 1H; 2.01, s, CH₃; 1.7-1.2, m, 8H. υₘₐₓ : 1650, 1640, 1405, 900 cm⁻¹. Mass spectrum: 179 (M⁺), 136 (M-Ac), 94 (M-Ac-C=CH₂), 84, 43 (Ac).
References

References


References

References

References


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References


References

References


Appendices

Fig. 6.0: X-ray crystal structure for (18a)
### Table 6.1 Interatomic bond distances (Å) for (18a)

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Table 6.3: Rates of formation of (65) from (63) using MCPBA in various solvents

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Fig. 6.8: X-ray crystal structure for (91)

![X-ray crystal structure for (91)](image)

Table 6.9: Interatomic bond distances (Å) for (91)
## Appendices

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Fig. 6.12: X-ray structure for (216)
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Molecular Modelling Studies

Molecular modelling was carried out using the modelling package PCModel (v4.41) using the MMX forcefield. Modelling was executed on an Apple Macintosh IIIsi equipped with 5Mb RAM.

Selenium$^+$ is not parameterized in this implementation of the MM2 forcefield so sulfur$^+$ was used as an approximation. Energy minimizations were carried out using a full SCF approach. The dihedral drive routine within PCModel rotates a selected bond several degrees, minimises the resultant structure and calculates the minimised energy of the structure. An energy minimisation profile of the bond rotation is thus produced. Relative minimisations are internally consistent within the program.

Reference

1. MMX Forcefield is derived from the MM2(QCPE-395,1977) forcefield of Allinger, N.L., with the pi-VESCF routines taken from MMP1(QCPE-318), also by Allinger. N.L.