STATEMENT OF ORIGINALITY

The experimental work in this thesis was carried out in the Department of Chemistry at Loughborough University by Adrian R. Young between September 1992 and September 1995. This work has not previously been presented for any other degree.

Adrian R. Young

March 1996

FREE RADICAL CYCLISATION OF IMINES

by

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A Doctoral Thesis

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March 1996

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Abstract.

Free Radical Cyclisation of Imines.

Introduction.

The free radical cyclisation reaction onto an unsaturated bond is a well known synthetic pathway, where a wide range of cyclic compounds can be produced form acyclic starting materials. Up until recent years, free radical addition to multiple bonds other than carbon-carbon had been little studied. Nowadays there is much information available of radical addition to carbonyl, thiocarbonyl, nitrile and oxime ether (C=NOR) functional groups. However there has been surprisingly little detailed study of similar reactions involving imines (C=NR) or hydrazones (C=NNHR).

Monocyclisation.

In the early phase of the research, different types of imine were synthesised and subjected to the standard free radical cyclisation procedure (tributyl-tin hydride / AIBN, added by syringe pump to refluxing solvent) to determination of the regiochemistry of cyclisation onto imines and to assess the synthetic potential of the reaction. The results of this investigative study show that a variety of five and six-membered ring compounds can be synthesised in good yield. A similar study of hydrazones showed that five-membered rings can be formed under the same reaction conditions.

Tandem Reactions.

In the next phase, the aim was to extend the methodology to produce more complex structures from acyclic starting materials. If a radical adds to the carbon atom of an imine, a nitrogen-centred (aminyl) radical is generated which can undergo subsequent addition to a suitably positioned double bond to yield a bicyclic amine. This type of reaction is known as tandem or cascade cyclisation. By this method, compounds could be synthesised which have similar structures to natural products. A range of suitably designed imines was prepared and underwent cyclisation, producing many different types of bicyclic amine in yields varying from moderate to good.

The Synthesis of Natural Products.

After the successful formation of key bicyclic structures, the third phase of the research aimed at the synthesis of one or more of target natural products. The synthetic strategy used in the tandem reactions outline above was adapted for these purposes. However the synthesis of the desired compounds could not be achieved in the time, but progress towards their formation was achieved.

Acknowledgements.

I wish to thank Messrs. Alistair Daley, Paul Hartopp and John Kershaw of the Technical Staff of the Loughborough University Chemistry Department for their assistance. I also wish to thank my colleagues in laboratory F0.01 for their patient endurance during countless bad-smelling work-up procedures.

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Contents.

Free Radical Cyclisation Reactions of Imines

1. Introduction.

1.1. General Information.

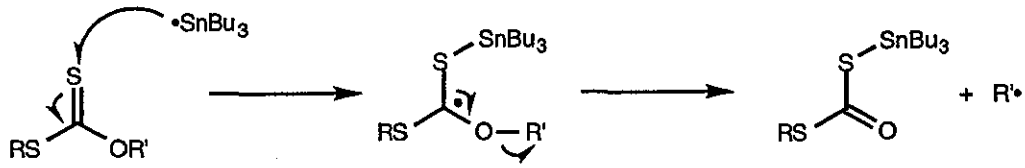
Organic free radical chemistry continues to grow rapidly and there is an increasingly wide scope of synthetic transformations that occur involving free radical intermediates.[1] Free radical reactions all proceed according to the same principles. Initiation of the reaction takes place by the thermal or photochemical decomposition of a free radical initiator present in the reaction mixture. The first radicals so formed then react with a substrate, for example an alkene or a metal hydride producing a second radical which undergoes further reaction, producing more radicals in a chain reaction. The chain reaction is terminated by intermolecular or intramolecular abstraction of hydrogen or by reaction with a radical trap such as diphenylpicrylhydrazyl (DPPH). One of the first free radical procedures to find widespread use was the polymerisation of alkenes. However in recent years, free radical procedures have been used in other areas of synthesis e.g. the reduction of a carbon-halogen bond to a carbon-hydrogen bond using a metal hydride. In reactions of this type, the halogen reacts with the radical produced from the hydride forming a carbon radical which abstracts a hydrogen from a second molecule of the metal hydride, thus propagating the chain reaction. The halogen atom in this reaction is called the radical leaving group or radicophile.

The most common free radical initiator is *N,N'*-azobis(isobutyronitrile) (AIBN) which has almost completely replaced dibenzoyl peroxide in radical reactions. AIBN decomposes thermally to nitrogen gas and two equivalents of initiating radicals. Other initiators include alternative peroxides, e.g. di-*t*-butyl peroxide but increasingly metal salts are being employed as initiators. The metal salt which has been used the most is samarium (II) iodide, which in solution in THF, is a highly reactive electron donor which forms radicals by the transferring of one electron to a carbonyl group or any similar electron acceptor.[2]

The metal hydride with the most widespread use is tri-*n*-butyltin hydride (Bu_3SnH) but in some reactions alkyl mercury hydrides, formed by the *in situ* reaction of alkyl mercury halides with sodium borohydride, have proved to be a suitable alternative.[3]

Bromine and iodine are the most common radical leaving groups in reactions with Bu_3SnH, though chlorine can be used but is generally not suitable. Other useful leaving groups include benzenesulfenyl (PhS) and benzeneselenyl (PhSe) and various thiocarbonyl groups e.g. xanthate esters.[4] The "soft" metal atom (i.e. Sn) reacts with the "soft" halogen or group (VI) element which undergoes scission to form a stable addition product and alkyl radical. An example showing the addition of the Bu_3Sn radical to the xanthate ester functional group is shown in Scheme 1.

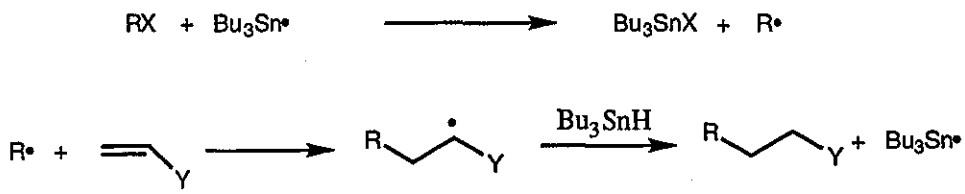
Scheme 1



1.2. Intermolecular Free Radical Reactions.

Intermolecular radical reactions such as the polymerisation of alkenes have been known for many years, but the reactions tend to be of low selectivity and a variety of products can be formed for just one reaction mixture. Synthetically useful intermolecular reactions (Scheme 2) must fit a number of selectivity requirements.

Scheme 2



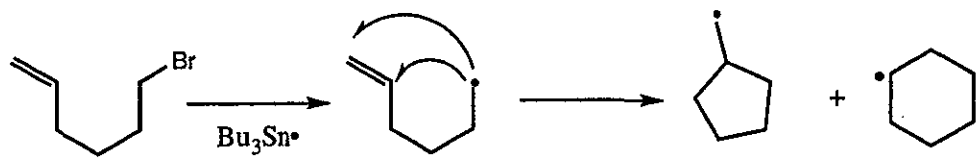
The alkyl radical R• must react with the alkene faster than with Bu_3SnH or RX. The radical formed after the addition of R• with the alkene must react only with Bu_3SnH and the Bu_3Sn• must only react with RX. (Radical recombinations are not considered to be a likely reaction pathway owing to their very low concentrations in the reaction mixture.) These criteria are met if the alkene has an electron withdrawing substituent (Y = CN, COR, CO_2R) and the alkyl halide electron releasing substituents (e.g. alkyl, aryl, alkoxy, amino). An electron-deficient radical can also react with an electron-rich alkene and fulfil the above requirements. However other combinations of reagents including intermolecular reactions of unactivated alkenes produce many products including polymers and alkylated tin products. Therefore intermolecular radical reactions have fairly limited synthetic scope and proceed well only if the radical and the alkene have the appropriate electronic properties.

1.3. Intramolecular Free Radical Reactions.

Intramolecular radical addition reactions, otherwise known as cyclisation reactions, have been developed over recent years and represent a breakthrough in synthetic radical chemistry. Cyclic molecules can be produced with high regioselectivity and stereo-selectivity. Since the activation entropies of intramolecular reactions are much less negative than those of intermolecular reactions[5] (brought about by the inherent close proximity of radical and the unsaturated bond), reactions occur on a much wider range of substrates. Not only do the electronic properties of radical and alkene cease to be a decisive factor in selectivity, enabling unactivated alkenes and alkynes to react,

unsaturated bonds other than carbon-carbon undergo radical addition including carbon-nitrogen and even carbon-oxygen bonds. A typical radical cyclisation reaction is shown in Scheme 3:

Scheme 3



(1) (2) (3)

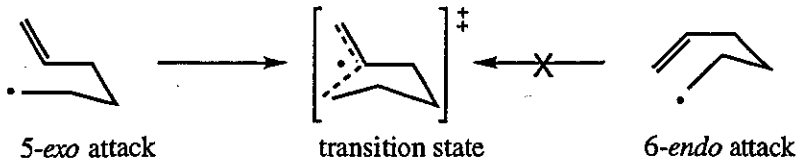
Ratio: 98 2

Although the initial radical (**1**) and the product radicals (**2, 3**) have the same nucleophilicity, the selectivity requirements for intermolecular addition are also fulfilled because the former reacts intramolecularly and the latter react intermolecularly with Bu_3SnH. Since the reactivity and the selectivity requirements for chain reactions are fulfilled, radical cyclisations are generally synthetically useful. There are however a few limitations. Three- and four-membered rings cannot normally be synthesised as the acyclic radicals analogous to 5-hexenyl above are more stable than the cyclised radicals,[6] unless the cyclised radical can be stabilised.[7] Also the formation of medium sized rings (7-12 members) is not a synthetically useful route. As the radical and the multiple bond become more remote, the activation entropy of cyclisation become more negative and reaction becomes more difficult.[8] The formation of large rings (14 and above) have been achieved by radical cyclisation under conditions of high dilution.[9] In these reactions, the two ends are so far apart the reaction is effectively intermolecular and so the selectivity requirements outlined in Section *1.2* need to be observed, e.g. the double bond must be electron deficient for a nucleophilic carbon radical to interact.

Most of the radical cyclisation work has led to the synthesis of five and six membered rings and much is known about the regioselectivity of these transformations. 5-Hexenyl radicals (**1**) cyclise to form predominantly the cyclopentylmethyl radical (**2**), and only a trace amount of the more stable cyclohexyl radical (**3**). According to Baldwin's rules,[10] radical addition resulting in the formation of the cyclopentane ring is named 5-*exo* addition or cyclisation, the product being the 5-*exo* product. Similarly the formation of the secondary radical (**3**) occurs by 6-*endo* cyclisation forming the 6-*endo* product. The reason why 5-*exo* cyclisation is favoured can be explained in terms of the angle of approach of the radical to the double bond. In the transition state of an intermolecular reaction, the radical has been calculated to approach the alkene at an angle of around 100°.[11] In the case of the 5-hexenyl radical (**1**) this is approximately the same angle of *exo*-attack of the radical to the double bond, thus intermolecular and 5-*exo* attack are geometrically compatible. This contrasts with *endo*-attack where the radical

can only approach the carbon atom at an unfavourable angle of around 70-80°.

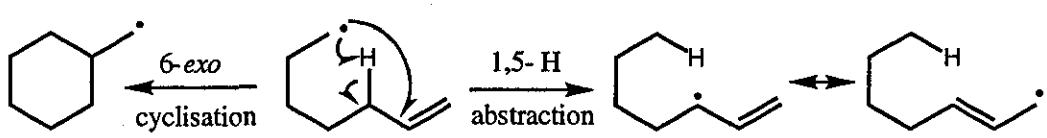
Another factor which can be taken into account in explaining the preference for *exo* attack is the arrangement of the atoms in the transition state.



The 5-*exo* transition state takes the chair form whereas the 6-*endo* transition state must take the more strained boat form for the radical to approach close enough to react and other steric factors such as 1,3-diaxial interactions can impede 6-*endo* attack.[12] In most reactions 5-*exo* adducts are produced as the result of kinetic control but wherever conditions exist for thermodynamic control (e.g. reversible cyclisations), it is possible to increase the yield of the 6-*endo* adduct since the secondary radical formed is more stable.[13] Some cyclisation reactions preferentially produce the 6-*endo* adduct, e.g. chains containing a silicon or an amide group.[14] If 5-*exo* addition is sterically impeded, e.g. by a di-substituted *exo*-carbon, then 6-*endo* addition becomes more favoured.

The formation of cyclohexane rings by cyclisation of the analogous 6-heptenyl radicals (**4**) also occur for similar reasons to those outlined above (Scheme 4). Though 6-*exo* products (**5**) are formed in the largest amounts, 7-*endo* cyclisation are generally more unfavourable than for 6-*endo* reactions. There is a potential third reaction pathway, where the acyclic radical (**4**) abstracts the hydrogen atom shown, by a 1,5-hydrogen shift, via a geometrically favourable six membered ring transition state. The driving force for this pathway is the formation of the allylic radical (**6**), stabilised by resonance. For the simple 6-heptenyl radical, the amount of product reulting from 1,5-hydrogen abstraction is only 10%. However the proportion of acyclic products can be dramatically increased if the allylic radical (**6**) is further stabilised by conjugation with for example an aromatic ring. Hence the substituents on the alkene bond can affect the synthetic utility of 6-*exo* cyclisation reactions.

Scheme 4



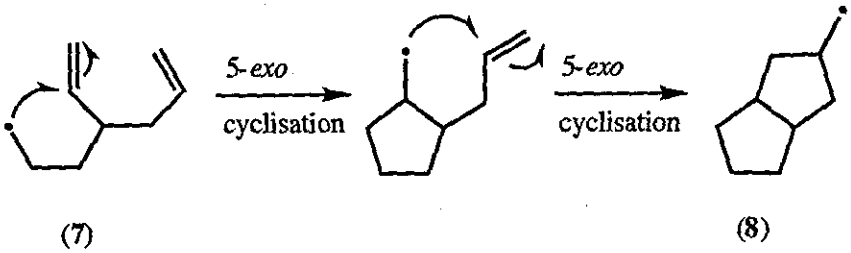
(**5**) (**4**) (**6**)

1.4. Tandem Cyclisation Reactions.

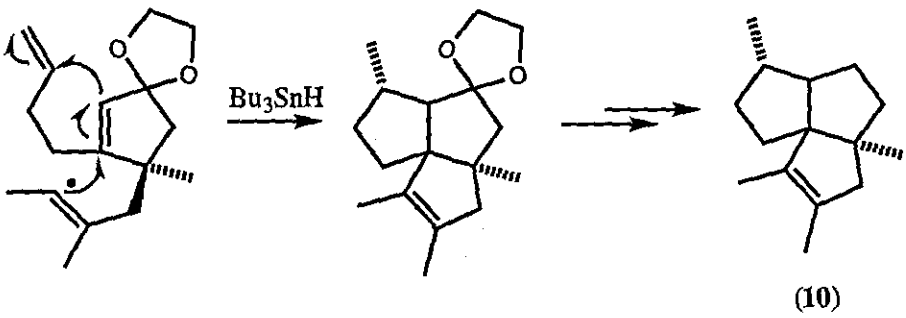
A tandem cyclisation occurs when two or more rings are formed in a single radical reaction. The radical formed by the first cyclisation is trapped by a second double bond suitably positioned forming a second radical (which could react further if other double

bonds were available to react). Polycyclic structures can be formed from acyclic starting materials. Scheme 5 shows a general tandem reaction where a bicyclo[3.3.0]octane (**8**) is formed by two successive 5-*exo* cyclisations from the acyclic radical (**7**).

Scheme 5



If the starting material is designed such that successive 5- and 6-*exo* additions occur then there is a large variety of possible structures that can be produced. Since many natural products contain fused cyclopentyl and cyclohexyl rings, tandem cyclisations provide a useful route to their synthesis. Curran et al have prepared the tricyclic sesquiterpenes hirsutene (**9**) and silphiperfolene (**10**) by tandem cyclisation using monocyclic starting materials.[18]



2. Addition of Radicals onto Multiple Bonds other than Carbon-Carbon.

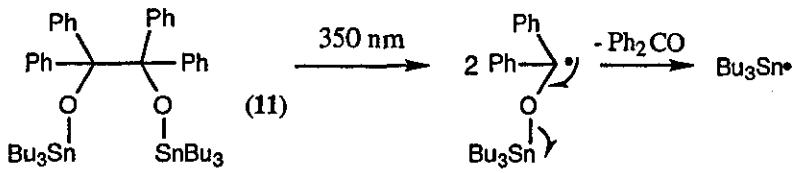
Intramolecular addition of alkyl, aryl and vinyl radicals onto alkene or alkyne bonds constitutes a well understood procedure of widespread synthetic utility. Recently, the reactions of other radical centres have been explored notably nitrogen radicals, both sp^3 (aminyl)[16,17] and sp^2 (iminyl)[18]. The reactions of protonated aminyl radicals has also been studied.[19] However, before the early 1980's, little information had been published regarding the behaviour of radicals towards carbon-hetero and hetero-hetero multiple bonds. The following two chapters give details on many of the considerable variety of reactions carried out on the common and easily accessible functional groups as published in the journals, showing that addition to bonds other than carbon-carbon provides potentially useful synthetic transformations. Chapter 2 reviews addition onto carbonyl, thiocarbonyl, azide and diazene functional groups. Chapter 3 reviews reactions of nitriles and the C=N double bond.

2.1. Addition to the Carbonyl Bond.

For many years, the carbonyl group was thought to be too stable to undergo radical addition, but in recent times, reactions carried out on a variety of substrates have shown that nucleophilic carbon radicals add relatively efficiently to the electrophilic carbonyl carbon to yield interesting results. Addition of silicon and tin radicals to the carbonyl oxygen is well known and has been used to produce carbon radicals for further synthesis. Successful reactions of carbonyl compounds are by and large restricted to the reactive aldehyde and ketone functionalities, the more stabilised carbonyl groups of esters, amides and acid anhydrides being inert.

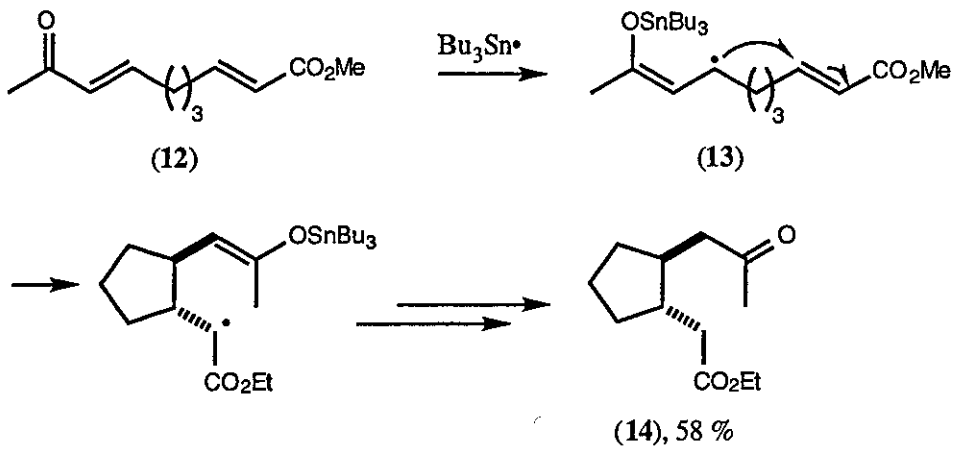
2.1.1. Intermolecular Addition.

There are several isolated examples of intermolecular addition to the carbonyl bond. Alkyl radicals produced by the thermal decomposition of diazenes (e.g. AIBN) have been shown to add to the carbonyl carbon of 2,6-di-*t*-butyl-*p*-benzoquinone.[20] Alkyl radicals add to carbon monoxide (at 25 atmospheres) to form acyl radicals which are trapped by acrylonitrile or methyl vinyl ketone, the products isolated in yields in the range 57-74%.[21] Trialkyltin radicals add to the oxygen atom of ketones.[22-24] The addition of $Bu_3Sn\bullet$ to benzophenone yields, on dimerisation, bis-(*O*-stannyl) pinnacolates.[24] The bis(tributytin) derivative (**11**) is relatively stable and can be synthesised and used in radical reactions as a photolytic source of Bu_3Sn radicals.[25]



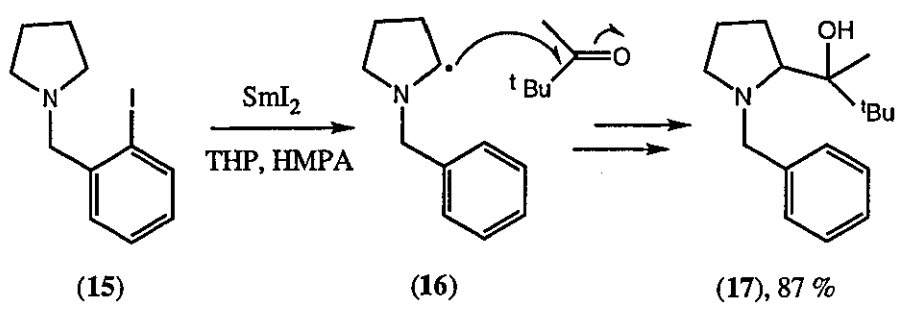
Trialkylsilicon radicals[26,27] also add to the carbonyl oxygen as does samarium diiodide,[28] though the latter is not strictly speaking a radical, but a 4f[1] salt which behaves like a radical in certain reactions. Thus, the carbonyl group can be utilised as a radical precursor in cyclisation reactions (Scheme 6). The doubly unsaturated keto-ester (**12**), reacts with $Bu_3Sn\bullet$ to form the allylic radical (**13**) which cyclises by 5-*exo* addition to form the keto-ester (**14**) to give one diasteromer.[29]

Scheme 6



A novel intermolecular reaction sequence is shown in Scheme 7.[30] *N*-(2-Iodo-benzyl)pyrrolidine (**15**), when reacted with samarium diiodide, yields an aryl radical which rapidly abstracts a hydrogen from the pyrrolidine ring to form the radical (**16**), via a 1,5-hydrogen atom shift. The radical (**16**) reacts with a variety of ketones, e.g. *t*-butyl methyl ketone, to give the adduct (**17**).

Scheme 7

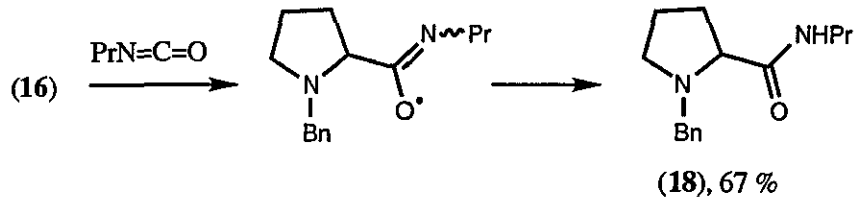


This reaction has been adapted to include other functional groups besides ketones. Radical (**16**) adds across the isocyanate group (Scheme 8) yielding the amide (**18**). This reaction is the only example of radical addition to the isocyanate functional group.

2.1.2. Intramolecular Addition.

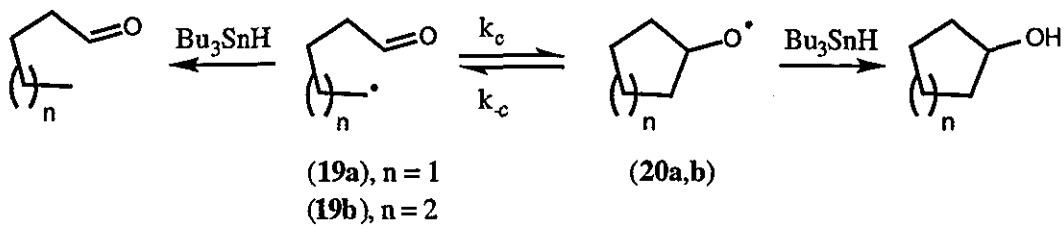
Kinetic studies[31] carried out on cylisations of carbon-centred radicals onto aldehydes and ketones show such reactions to be reversible. Though the rate constants at

Scheme 8



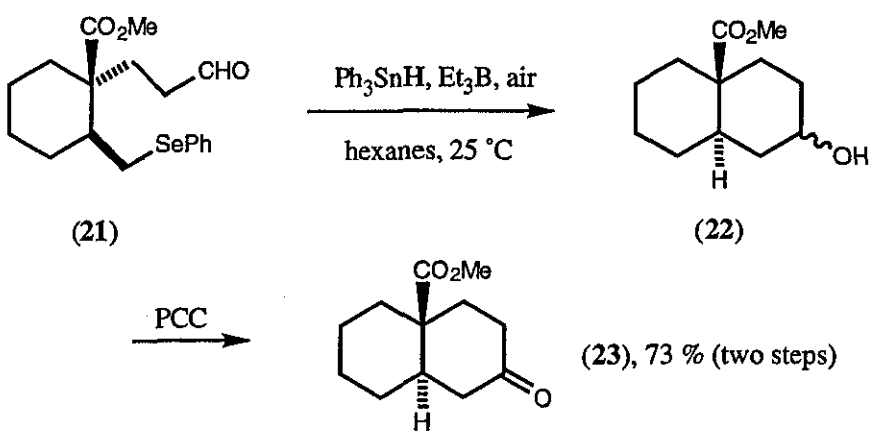
80°C, for both 5-*exo* cyclisation ($k_c = 8.7 \times 10^5\ s^{-1}$) and 6-*exo* cyclisation ($k_c = 1.0 \times 10^6\ s^{-1}$) onto the aldehyde carbon of the simple radicals (**19a,b**) shown in Scheme 9, both exceed the cyclisations of the corresponding alkenes at the same temperature ($2.3 \times 10^5\ s^{-1}$ and $5.4 \times 10^3\ s^{-1}$ respectively), the β-scission reaction of the cycloalkyloxy radical (**20a,b**), resulting in ring opening, occurs at a faster rate at 80°C ($k_{-c} = 4.7 \times 10^8\ s^{-1}$ and $1.1 \times 10^7\ s^{-1}$ respectively). 5-*exo* Cyclisation of radical (**19a**) is 540 times slower than the ring opening reaction and therefore would only occur if, for example, the abstraction of hydrogen by the cyclised radical (**20a**) proceeded at an even faster rate. In such a case a successful cyclisation would depend largely on the radical reagent used.

Scheme 9



6-*exo* Cyclisation of radical (**19b**) is only 11 times slower than the opening of the cyclohexyloxy radical (**20b**) and even the simple case shown in Scheme 9 (n = 2) would be predicted to yield a small amount of cyclised product. It would also be predicted from this kinetic data that 6-*exo* cyclisations would proceed better than analogous 5-*exo*

Scheme 10

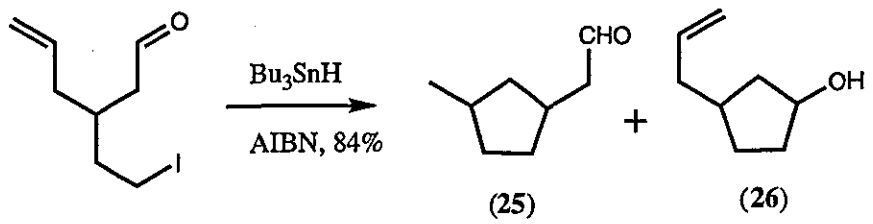


reactions, which is generally what has been found to occur. An example of this cyclisation from work carried out by Clive is shown in Scheme 10.[32] Cyclisation of the aldehyde (**21**) using Ph_3SnH at room temperature in the presence of triethylborane and air gave only the 6-*exo* adduct (**22**), which was oxidised to the ketone (**23**) in 73% yield over the two steps.

2.1.2.1. Competition Studies.

Fraser-Reid and co-workers have studied reactions where radicals cyclise onto either an alkene or a carbonyl group in the same molecule.[33,34] In a reaction where 5-*exo* addition onto an alkene competes with 5-*exo* addition onto an aldehyde (Scheme 11),[33] the unsaturated aldehyde (**24**) was cyclised under standard conditions (Bu_3SnH, AIBN, refluxing toluene) yielding the aldehyde (**25**) as the major product, with 25% of the alcohol (**26**). All the kinetic factors outlined above combine to bring about the observed result, the prevailing of 5-*exo* onto the alkene, despite the slightly slower reaction rate.

Scheme 11

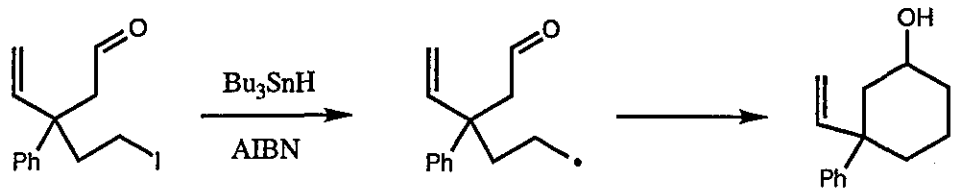


(**24**) (**25**) (**26**)

Ratio (**25**) : (**26**) = 3 : 1

Conversely if 5-*exo* addition to an alkene competes with 6-*exo* onto an aldehyde,[34] the latter prevails. In the reaction shown in Scheme 12, cyclisation of the aldehyde (**27**) yields only the cyclohexanol (**28**).

Scheme 12



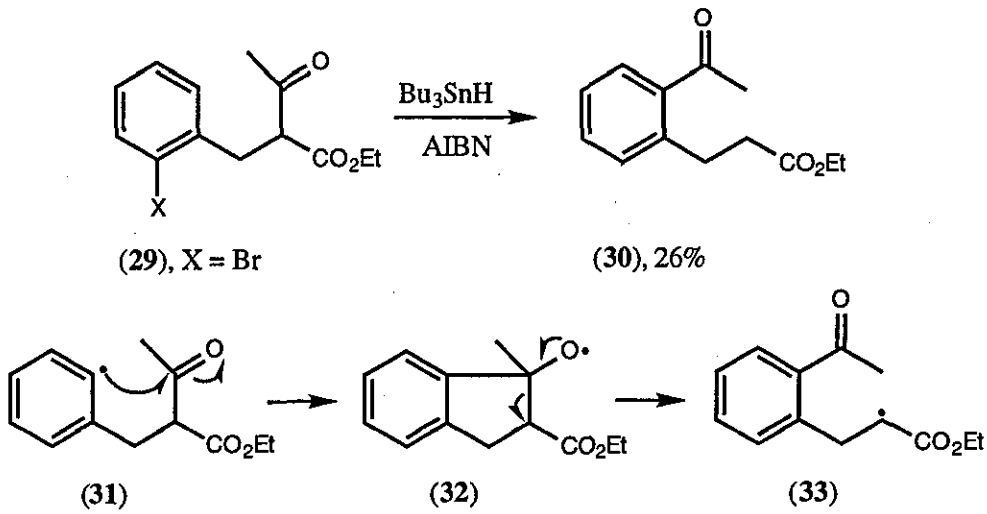
(**27**) (**28**), 85 %

2.1.2.2. Carbonyl Group Migration.

In order to use the unfavourable 5-*exo* cyclisation to synthetic advantage, reactions were carried out where after 5-*exo* cyclisation, β-scission occurs by breaking a different bond to that which was formed to yield a rearranged product. One example of such a reaction is shown in Scheme 13.[35] The reaction of the keto-ester (**29**, X = Br) yields 26% of rearranged product (**30**), with the reduced starting ester (**29**, X = H) being the

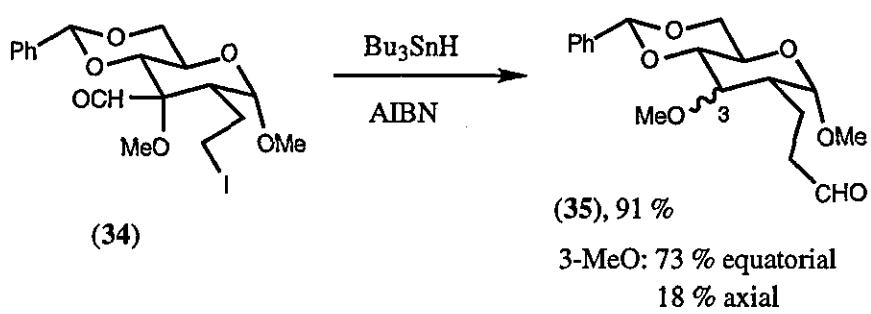
major product. The aryl radical (**31**) adds by 5-*exo* cyclisation to the ketone, yielding the alkoxy radical (**32**), which on reforming the carbonyl bond, breaks the bond leading to the radical (**33**), stabilised by its position α to the ester group. The formation of the carbonyl group and the stabilised radical (**33**) are driving forces for the rearrangement. Abstraction of hydrogen leads to the product (**30**). This illustrates that 5-*exo* cyclisation onto the carbonyl group even by the highly reactive aryl radical proceeds with difficulty.

Scheme 13



Greater success has been achieved with the rearrangement shown in Scheme 14.[36] The aldehyde (**34**) was cyclised under standard conditions to give the aldehyde (**35**) in 91% yield, via 5-*exo* cyclisation. In this case the driving force for rearrangement is the formation of the stabilised α-methoxy radical, which abstracts hydrogen from Bu_3SnH at a slow enough rate to give the observed regioselectivity at the 3-position.

Scheme 14

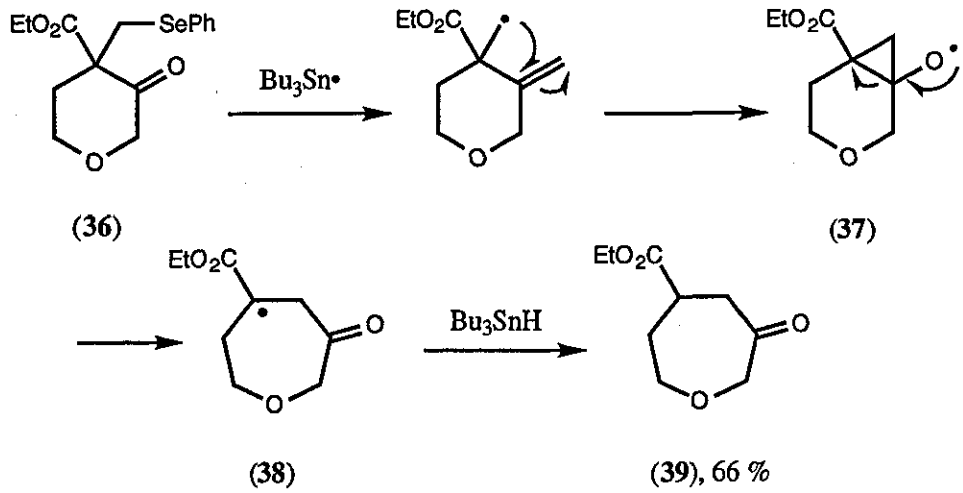


2.1.2.3. Ring Expansions.

An alternative way to capitalise on the ease of formation of the carbonyl bond after cyclisation involve ring expansion reactions.[37,38] Many examples are known where the ring size is increased by one atom, an example of which is given in Scheme 15.[37] Cyclisation of the ketone (**36**), via 3-*exo* addition to the carbonyl group, results in the formation of the 7-ring ketone (**39**) as the major product. The driving force for the

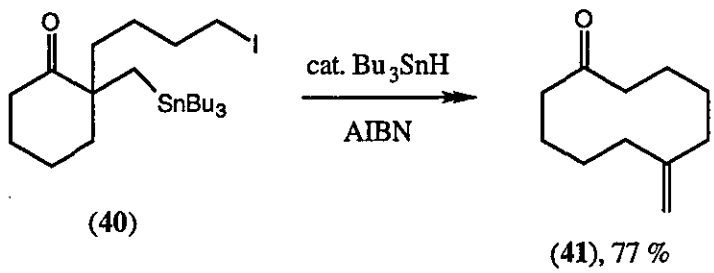
reaction is the facile ring opening of the cyclopropyloxy radical (**37**) with the simultaneous formation of the stabilised radical (**38**).

Scheme 15



The synthesis of medium rings (8-10 members)[39-42] has also been achieved by mechanisms analogous to that shown in Scheme 15. For these reactions 5-*exo* and 6-*exo* addition precede ring opening. In the reaction illustrated below, the formation of the stable Bu_3Sn radical is the driving force for the formation of the ten membered ring unsaturated ketone (**41**) from the iodo-stannane (**40**) (Scheme 16).[42]

Scheme 16

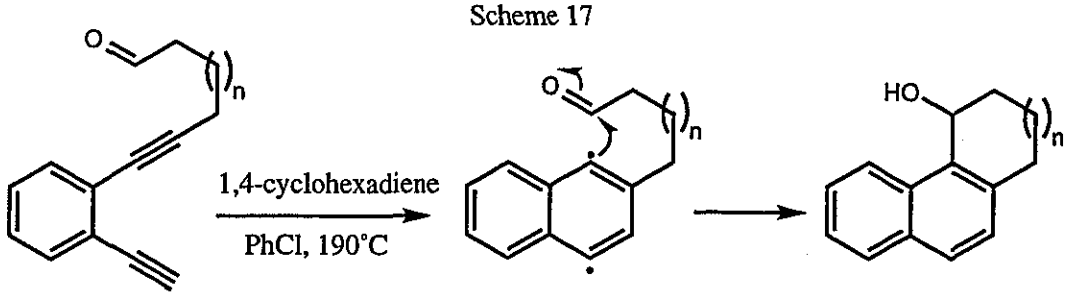


2.1.2.4. Irreversible Cyclisations.

There are several unique cases where cyclisation onto the carbonyl group is irreversible. Cyclisation of aldehydes by both 5-*exo* and 6-*exo* addition have been successfully achieved by the reaction sequence shown in Scheme 17.[43] The 6-*exo* reaction is illustrated (n = 1), though the 5-*exo* reaction (n = 0) gives an analogous product but in lower yield (26%). Thermal cyclisation and aromatisation of the 1,2-dialkynylbenzene (**42**) leads to the aromatic diradical (**43**) which then adds by one of the radical centres to the aldehyde group which on abstraction of two hydrogen atoms yields the alcohol (**44**). This alcohol dehydrates under the reaction conditions yielding the corresponding conjugated alkene as the major product isolated (57%), with a small

amount of the uncyclised aldehyde (20%) formed from the direct reduction of the diradical (**43**) by 1,4-cyclohexadiene. (See also Section *3.2* - Oxime Ethers.)

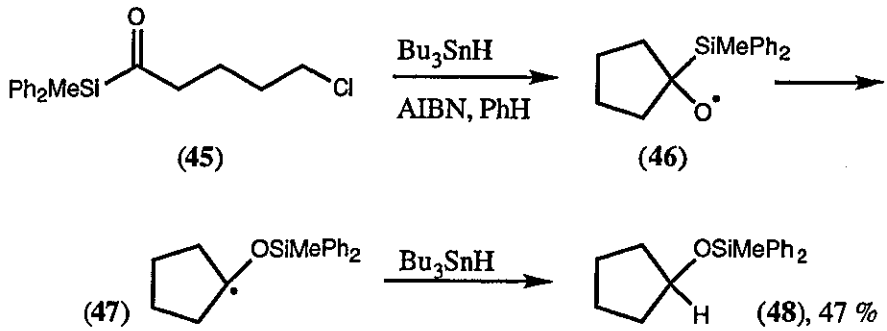
Scheme 17



(**42**), n = 0,1 (**43**) (**44**)

5-*exo* Cyclisations of acylsilanes such as (**45**) have been shown to cyclise irreversibly,[31,44] an example of which is given in Scheme 18.[31] Reaction under standard conditions yields the cyclopentyloxy radical (**46**) which rapidly rearranges to form the more stable α-silyloxy radical (**47**) which upon abstraction of hydrogen yields the silyl ether (**48**) as the only cyclised product.

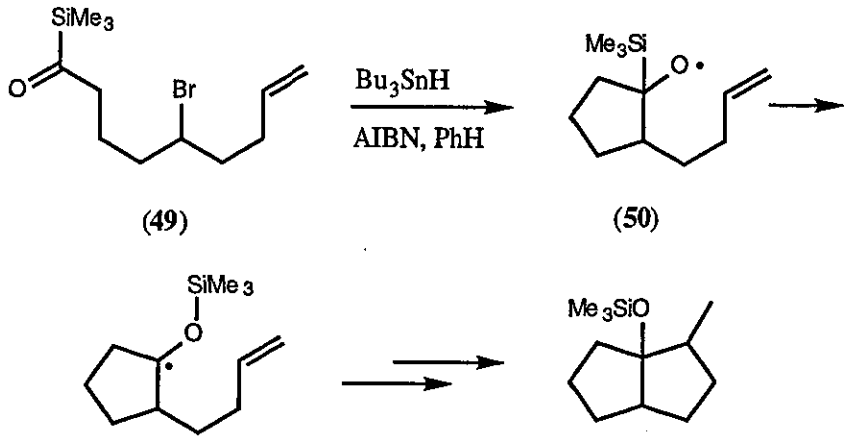
Scheme 18



(**45**) (**46**)

(**47**) (**48**), 47 %

Scheme 19



(**49**) (**50**)

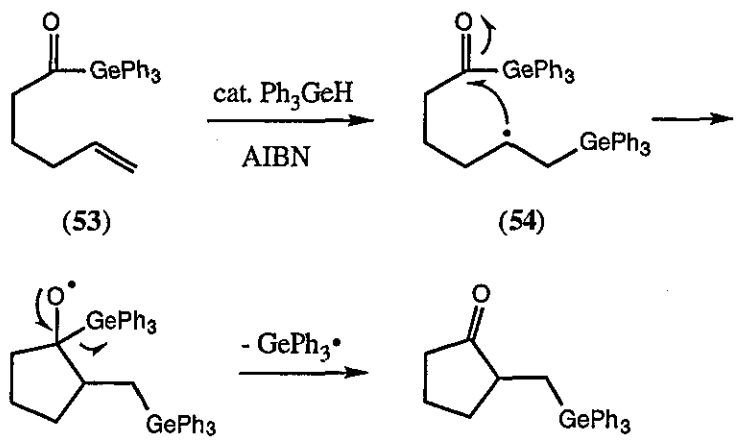
(**51**) (**52**), 70 %

This methodology has been extended in the double cyclisation reaction shown in Scheme 19.[44] The acylsilane (**49**) cyclises in the same way to yield, after rearrangement

of the radical (**50**) to the α-silyloxy radical (**51**) which cyclises further, by subsequent 5-*exo* addition, yielding the bicyclic silyl ether (**52**). This reaction is not strictly speaking a tandem radical reaction, as radical (**50**) is not trapped by 6-*exo* addition to the alkene but rearranges to radical (**51**) before further reaction takes place.

Analogous reactions of acylgermanes also give rise to irreversible 5-*exo* addition onto the ketone group.[45] An example of this work by Curran and co-workers is illustrated in Scheme 20. Reaction of the acylgermane (**53**) with catalytic triphenylgermane commences with the addition of the Ph_3Ge radicals with the alkene group yielding the secondary radical (**54**) which adds to the ketone, the resulting alkoxy radical (**55**) eliminating $Ph_3Ge\bullet$ on reforming the carbonyl group in the product (**56**).

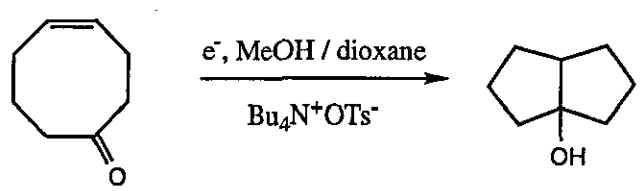
Scheme 20



(**53**) (**54**) (**55**) (**56**), 88 %

Shono and co-workers have successfully synthesised a variety of cyclic compounds by electrochemically initiated cyclisation reactions.[46] Both 5-*exo* and 6-*exo* cyclisations of a range of unsaturated ketones yield tertiary alcohols some of which are hard to access by other methods. In the example shown in Scheme 21, cyclooct-4-enone (**57**) cyclises under the given conditions to yield the bridgehead alcohol (**58**) in 69% yield.

Scheme 21



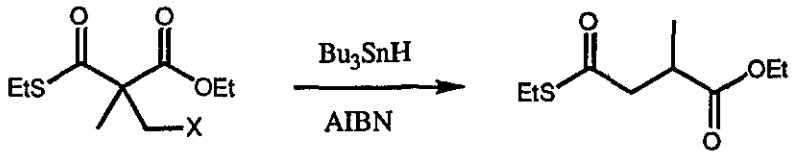
(**57**) (**58**), 69 %

2.1.3. Addition to other Carbonyl Functional Groups.

Though esters, amides and similar functional groups are largely inert to radical addition, one reaction has been reported of a reaction involving the addition to the more reactive thioester group (Scheme 22).[35] The mechanism for the formation of chain lengthened diester (**60**) from the dialkyl malonate analogue (**59**) is similar to that of

radical ring expansion (Scheme 15), proceeding via a cyclopropyloxy radical. The yield for the formation of the diester (**60**) is less than 10% indicating that even for the relatively reactive thioester group, radical addition is an unfavourable reaction.

Scheme 22

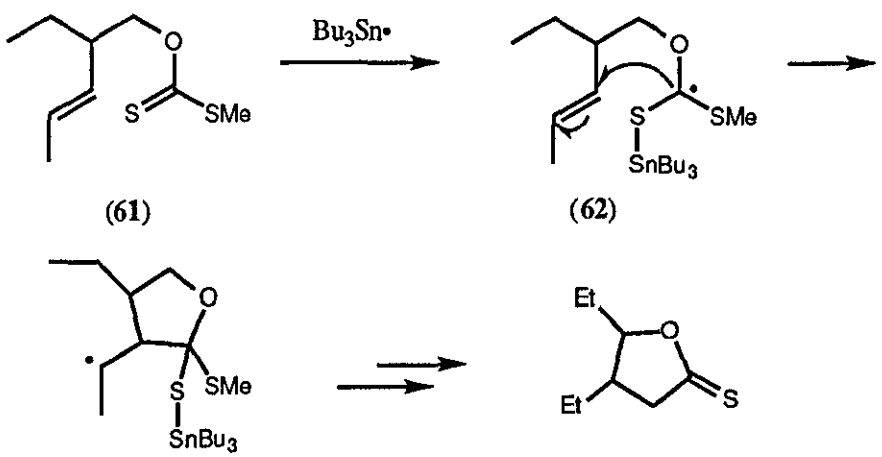


(**59**), X = Br, I (**60**), 3 - 8 %

2.2. Addition to the Thiocarbonyl Bond.

The addition of trialkylsilyl and trialkylsytannyl radicals to the 'soft' sulfur atom of the C=S bond has been thoroughly studied,[47] Barton and co-workers having developed a series of reagents containing the thionocarbonate (ROC(=S)OR'), thionocarbamate (RR'NC(=S)OR") and xanthate (ROC(=S)SR') groups all of which have found extensive use in synthetic chemistry. The use of xanthate esters[48,49] has received the most attention owing to the relative ease of formation. One reaction is illustrated in Scheme 23.[49] This is one of only a few examples of cyclisations where the thiocarbonyl group is retained in the product. The Bu_3Sn radical adds to the thiocarbonyl sulphur atom of the ester (**61**), forming a carbon-centred radical (**62**) which then adds to the alkene to form initially the dithioketal moiety (**63**). The product isolated from this reaction is the thionolactone (**64**) which is formed by the elimination of the neutral species (Bu_3SnSMe).

Scheme 23

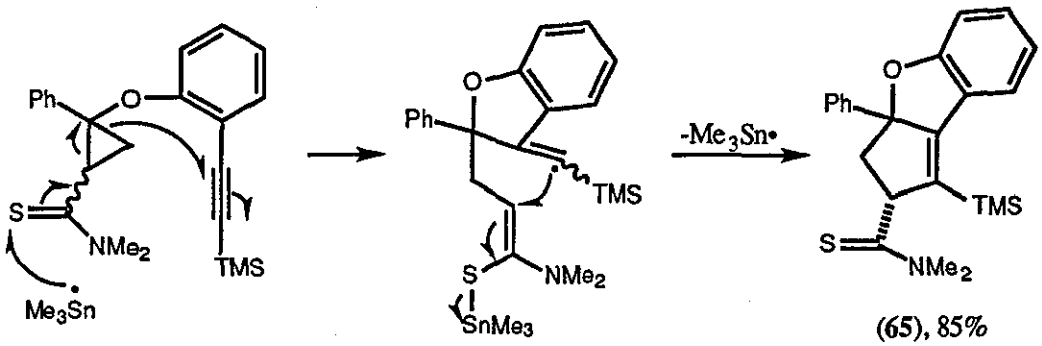


(**61**) (**62**) (**63**) (**64**), 80%

Of the other functional groups in use, thionocarbamates formed by condensing a carboxylic acid with commercially available 1,1'-thiocarbonyldiimidazole, have also been widely employed (for an example see Section *3.1*). Successful radical reactions of

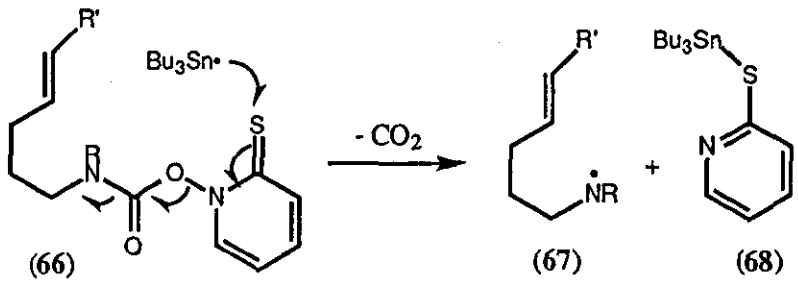
thioamides have also been reported.[50,51] In the example shown in Scheme 24, the simple thioamide group is the radicophilic centre in a tandem cyclisation reaction which yields the product (**65**) with retention of the thioamide group.[51]

Scheme 24



One of the most efficient and widely employed radical leaving groups is formed by condensing an acid chloride with *N*-hydroxypyridine-2-thione, forming compounds known as 'Barton esters'.[47] In the example shown in Scheme 25, which indicates that functional groups other than carboxylic acids can be used to form the radical precursors,[16] the $Bu_3Sn\bullet$ adds to the sulphur atom of the radical precursor (**66**) and the resulting radical undergoes rapid decomposition eliminating carbon dioxide and forming, in this case, the aminyl radical (**67**) which then adds to the alkene. The driving force for the decomposition is the formation of the aromatic by-product (**68**). These compounds are often so labile, that Bu_3SnH is not usually employed, ultraviolet light being sufficient to initiate the radical reaction.

Scheme 25



2.3. Addition to the Diazene Bond.

The addtion of radicals to nitrogen containing multiple bonds has been a more recent development in synthetic chemistry, with the exception of the nitroso (RN=O) and nitrile groups. The former have been studied over a long period as radical traps for EPR studies as radicals add to the nitrogen atom to yield stable nitroxyl radicals ($R_2N\text{-}O\bullet$).[52] The relatively long history of radical reactions of nitriles is reviewed in Section *3.1*.

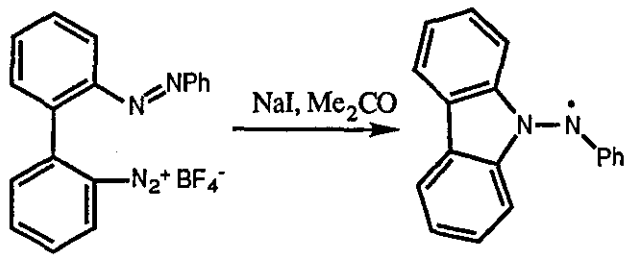
Compounds with the N=N linkage are called diazenes, though they are often known as 'azo' or 'diazo' compounds. In radical chemistry, by far the most well known

diazene is the radical initiator AIBN, and radical reactions could not proceed without making use of the thermal instability of aliphatically substituted diazenes. The radical addition reactions of this class of compounds has been less studied. There are now several scattered examples of syntheses involving addition to the N=N bond. Hillgartner successfully added Me_3Sn radicals to AIBN and some of its analogues[24] and in a separate mechanistic study Görgényl added methyl radicals to diethyldiazene (EtN=NEt) and analysing the products discovered a complex mechanism involving mono- and polyalkylation.[53]

2.3.1. Cyclisation Reactions.

By far the largest study of cyclisation reactions has been carried out on aromatically substituted diazenes owing to their relative stability and ease of formation. 5-*exo* Cyclisation of aryl radicals onto such compounds yields functionalised *N*-amino carbazoles.[54-56] Though bromine and iodine are the usual radical leaving groups in these reactions, in the example illustrated in Scheme 26,[56] the aryl radical is generated by *in situ* reduction of the diazonium ion (**69**) by iodide, and cyclises to form the stablised radical (**70**) which dimerises to give the isolated hydrazine product in 70% yield.

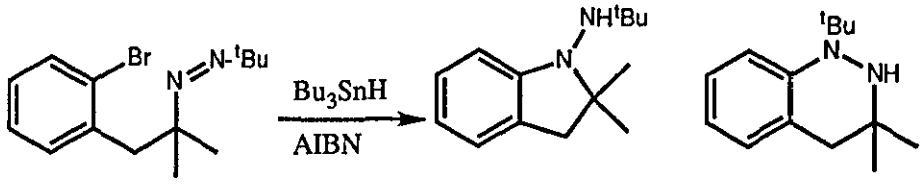
Scheme 26



(**69**) (**70**) 80 %

The cyclisation of diazene (**71**) under standard conditions[57] (Scheme 27) yielded only 28% of the product resulting from 5-*exo* addition (**72**) and 54% of that resulting from 6-*endo* addition (**73**). This result, where the stereoelectronically unfavourable 6-*endo* cyclisation [(**71**) to (**73**)] prevails over the more favoured 5-*exo* [(**71**) to (**72**)] is probably due to the increased strain of the transition state caused by the approach of the sterically hindered 5-*exo* nitrogen by the aryl radical. The 6-*endo* nitrogen is sterically less crowded and can react.

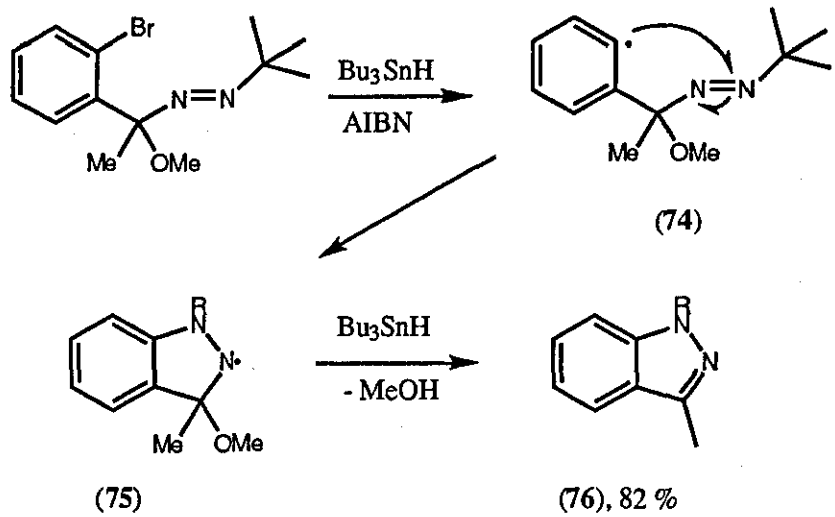
Scheme 27



(**71**) (**72**) 28 % (**73**) 54 %

Scheme 28 illustrates another stereoelectronically unfavourable reaction that of 5-*endo* cyclisation.[58] The radical (**74**) does not add by 4-*exo* cyclisation onto the nearest nitrogen, as such reactions are very rare. In this reaction, the driving force for the unfavourable 5-*endo* cyclisation is the formation of the stabilised hydrazinyl radical (**75**) which forms the indazole (**76**) by hydrogen atom abstraction and elimination of MeOH, thus aromatising the five membered ring.

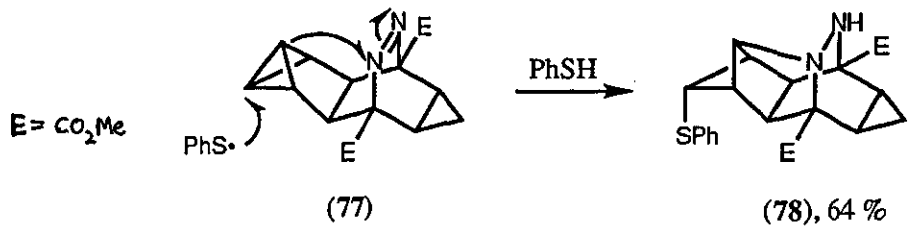
Scheme 28



2.3.2. Cyclisation by Relief of Ring Strain.

A highly novel reaction of this type is illustrated in Scheme 29.[59] The treatment of the highly strained diazene (**77**) with benzenethiol and AIBN, yields PhS radicals which attack the compound at the point shown, where the largest amount of strain energy would be released, forming a cyclobutyl radical which adds by 5-*exo* addition (or 6-*endo*) to the diazene nitrogen and the hexacyclic hydrazine product (**78**) is isolated after abstraction of hydrogen from PhSH.

Scheme 29

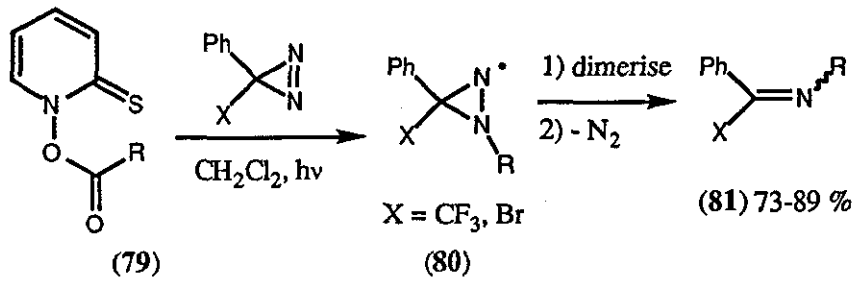


2.3.3. Addition of Radicals to Diazirines.

Diazirines are three membered ring diazenes, isomeric to linear diazoalkanes, which have found use as synthetic intermediates in radical reactions (Scheme 30).[60] Photolysis of the 'Barton esters' (**79**) of a wide range of alkanecarboxylic acids (R = 2-phenylethyl, cyclohexyl, 1-adamantyl) produce alkyl radicals which add to the 3,3-disubstituted diazirines. The diaziridinyl radicals (**80**) are formed which dimerise and

then extrude nitrogen gas to form the imines (**81**) as the initial products in yields of over 70%. .

Scheme 30



These imines are hydrolysed to give nitrogenous products depending on the group X. If X is trifluoromethyl, then the product is an amine and if X is bromine, the product is an *N*-benzoyl amide. These reactions produce in 'one pot', the unusual synthetic transformations:

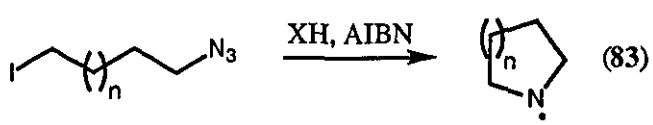
2.4. Addition to the Azide Functional Group.

Radical reactions of the azide group constitute the only detailed study of addition to heterocumulene or 1,3-dipolar functional groups, except the one example of addition to RN=C=O outlined in Section *2.1.1*. Much of the study of the reactions of azides has been carried out by Sunggak Kim and co-workers[61] with only isolated examples from other work.[62-66]

2.4.1. Monocyclisation.

Simple 5-*exo* and 6-*exo* cyclisation of the ω-iodoazides (**82**), using Bu_3SnH and the alternative reagent tris(trimethylsilyl)silane (TTSS) have been achieved (Scheme 31). The radical derived from (**82**) adds onto the nitrogen atom bonded to carbon, yield the cyclic aminyl radicals (**83**). The yields are comparable to analogous reactions of alkenes indicating that 5-*exo* addition proceeds better than 6-*exo* addition.

Scheme 31



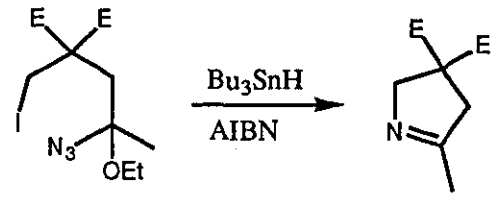
(**82**)

X = Bu_3Sn, n = 1, 88 %

X = $(TMS)_3Si$, n = 2, 50 %

For the cyclisation of the α-ethoxy azide (**84**) (Scheme 32), 5-*exo* cyclisation followed by loss of ethanol yields the cyclic imine (**85**).

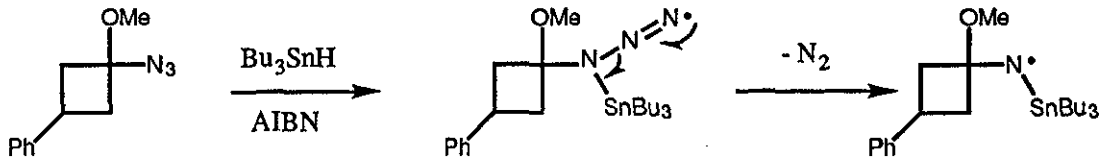
Scheme 32



(84) E = CO_2Me (85) 81 %

The choice of radical reducing agent is also important in these reactions. In both the above examples, iodine is the radical leaving group. If another is used instead, for example a thiocarbonyl functional group, reaction with Bu_3SnH fails altogether. This is because Bu_3Sn radicals add efficiently to the azide group[63] with loss of nitrogen gas as illustrated in Scheme 33a.[61] The tin radicals add to the 'inner' nitrogen atom of the α-methoxy azide (**86**) and after loss of nitrogen, forms the stannylaminyl radical (**87**).

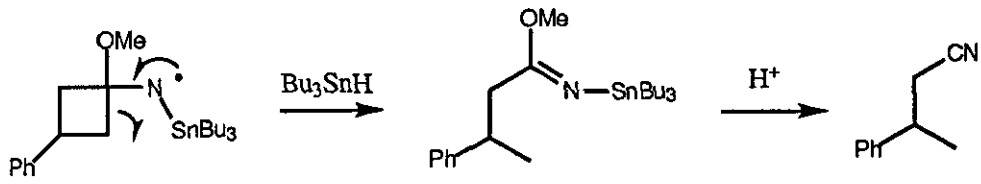
Scheme 33a



(86) (87)

Because the radical (**87**) is also a cyclobutylaminyl radical, ring opening occurs and after abstraction of hydrogen, the imine (**88**) is formed. This is converted to the nitrile (**89**) by acid work-up which is isolated in 94% yield (Scheme 33b).

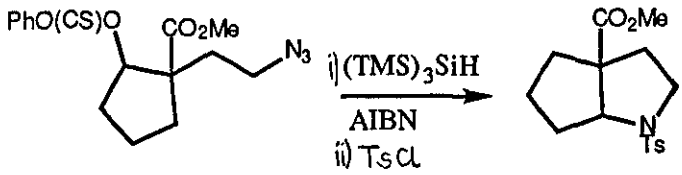
Scheme 33b



(87) (88) (89), 94 %

This is the preferred pathway for the reaction Bu_3Sn radicals with azides, unless the rate for reaction with another group is faster, as is the case for iodine. $(TMS)_3Si$

Scheme 34



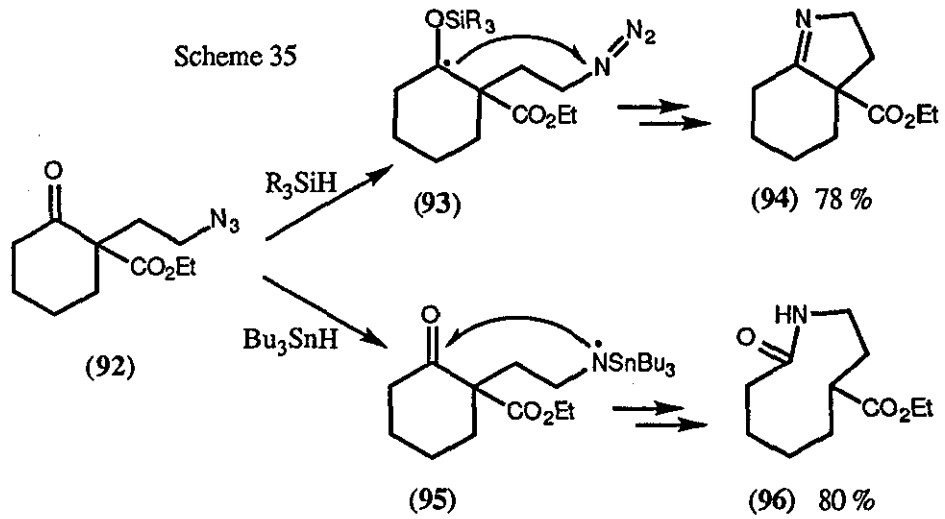
(90) (91) 60 %

radicals do not add to the azide group (unlike Et_3Si or Ph_3Si)[64] and can be used with most radical leaving groups. In Scheme 34, the azido ester (**90**) reacts to yield the cyclised product, isolated as the *N*-tosyl amide (**91**).

2.4.2. Other Reactions.

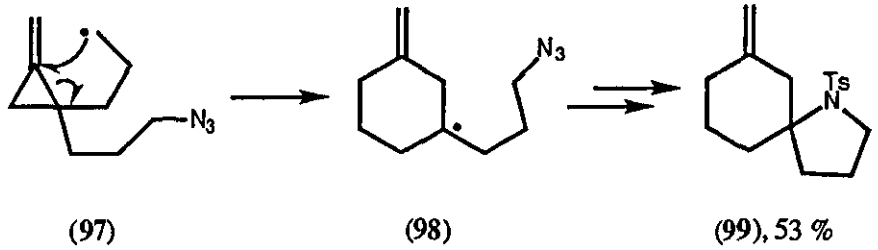
In the reaction of the ketone (**92**), two different products are formed depending on the radical reagent used (Scheme 35). On using TTSS, the R_3Si radical adds to the ketone group forming the α-silyloxy radical (**93**) which cyclises by 5-*exo* addition to the azide group which yields the bicyclic imine (**94**) after acid work up. If Bu_3SnH is used instead, the Bu_3Sn• adds to the azide group which cyclises to yield the 9-ring lactam (**96**), resulting from cyclisation of the aminyl radical (**95**) onto the carbonyl group and ring opening.

Scheme 35



Another example of a tandem reaction of azides is that carried out by Kilburn (Scheme 36).[65] The radical (**97**), generated using TTSS / AIBN, cyclises by way of 5-*exo* cyclisation followed by β-scission to the intermediate tertiary radical (**98**). Cyclisation onto the azide group yields, after hydrogen atom abstraction and sulfonylation, the spirocyclic sulfonamide (**99**).

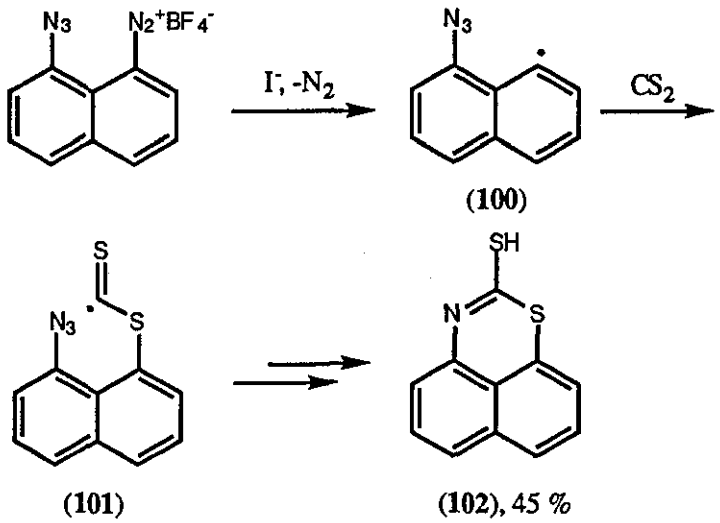
Scheme 36



Benati used aryl radicals generated from the *in situ* reduction of the diazonium salts to bring about reactions of 8-azidonaphth-1-yl radicals.[66] Scheme 37 shows a novel

intermolecular reaction, where the radical (**100**), which cannot cyclise onto the azide group directly owing to the formation of a highly strained intermediate, adds to carbon disulfide, forming the thiocarbonyl radical (**101**) which cyclises by 6-*exo* addition to the azide group yielding the heterocyclic thiol (**102**) as the product.

Scheme 37



In summary, the addition of radicals to carbonyl, diazene and azide groups has been shown, in certain cases, to be of considerable synthetic potential. For analogous reactions of the thiocarbonyl group, few reactions occur where the functionality is retained in the products, but the use of 'Barton esters' and related radical presursors in synthesis is now standard procedure.

3. Addition of Radicals to Carbon-Nitrogen Multiple Bonds.

Up until the early 1990's there were very few details available on the reaction of radicals with carbon-nitrogen multiple bonds with the exception of the nitrile group. The first radical reactions of nitriles were described in the early 1970's. In more recent times there has been considerable interest in the reactions of oxime ethers (RR'C=NOR") and also isolated examples of reactions of hydrazones and imines. This chapter contains examples of these reactions as reported in the literature.

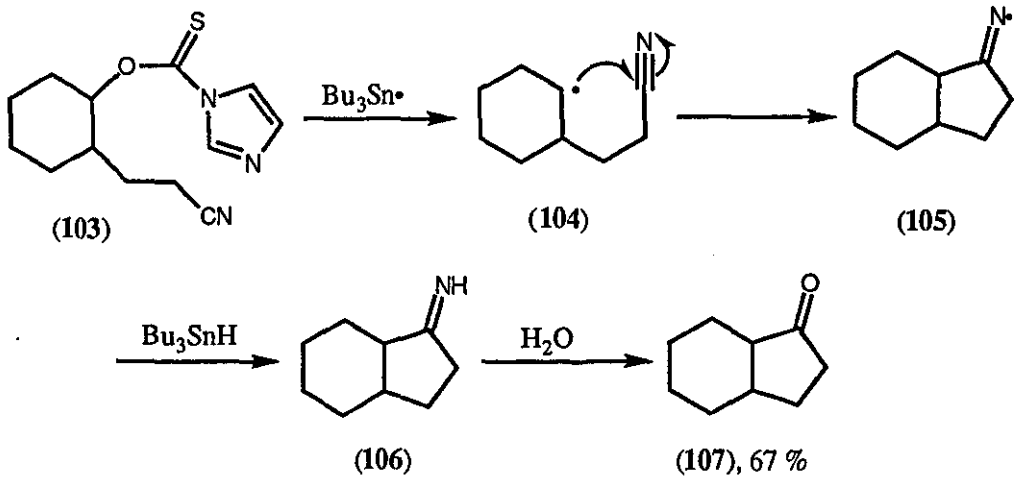
3.1. Addition to the Nitrile Bond.

The first intermolecular radical reaction involing nitriles was published in 1972, where the electrochemically generated acetone radical anions added to cyanamide to produce 5-ring nitrogen heterocycles.[67] Later studies investigated the interaction of hydroxyl radicals with acetonitrile in the atmosphere[68] and the trapping of radicals produced from the photolysis of 'Barton esters' by alkyl- and arylsulfonyl cyanides.[69] The intermolecular rections of nitriles are much better known.

3.1.1. Synthesis of Cyclic Ketones.

5-*exo* Cyclisation of alkyl and aryl radicals onto the nitrile bond occurs relatively easily in many reactions,[70] but there some recorded cases of surprising failures. One example of a successful cyclisation is illustrated in Scheme 38.[71] Reaction of Bu_3Sn radicals with the 1-imidazolylthiocarbonyl derivative (**103**) yields the secondary radical (**104**) which cyclises easily onto the nitrile group, yielding the iminyl radical (**105**) which abstracts hydrogen from Bu_3SnH to give the imine (**106**) as the initial product which is hydrolysed to the ketone (**107**).

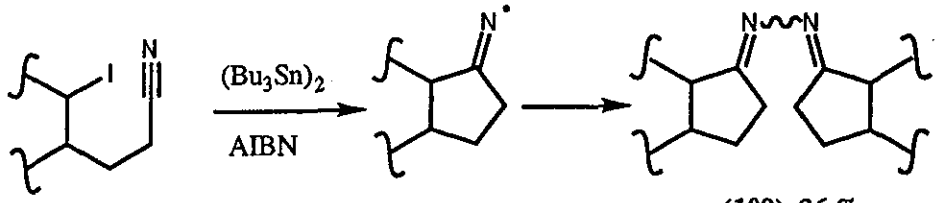
Scheme 38



If the reaction occurs in the absence of a hydrogen atom donor (i.e. using hexa-*n*-butyldistannane), the radicals cyclise forming iminyl radicals analogous to (**105**).

Because no hydrogen atom donor is present, the iminyl radicals dimerise and bis(hydrazones) [e.g. (**108**), Scheme 39] are isolated.[72]

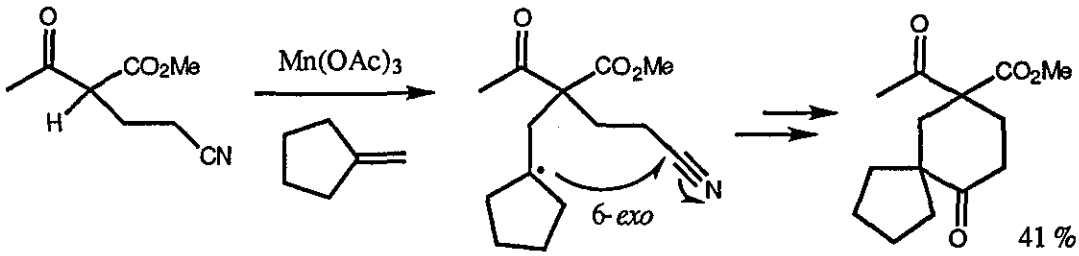
Scheme 39



(**108**), 26 %

The rate of cyclisation of 4-cyanobutyl radicals to form cyclopentylidene iminyl radicals by 5-*exo* addition has been reported to be $1.0 \times 10^4\ s^{-1}$ at 80°C,[73] which is approximately twenty times slower than for the analogous cyclisation of 5-hexenyl radicals. Thus 5-*exo* cyclisation of simple nitriles is a kinetically viable process if the abstraction of hydrogen atoms by the initial radical occurs at a slower rate. For many of the 'failed' reactions, stereochemical factors affecting approach of the radical onto the nitrile group may contribute to the observed reduction in the rate of cyclisation, the result being that direct reduction of the initial radicals are favoured. In contrast to 5-*exo* addition, there are only a few successful 6-*exo* cyclisation reactions reported. There are a number of examples where cyclohexanones have been formed as minor products,[74,75] though the reaction yields are rarely over 10%. However a 41% yield was reported by Snider (Scheme 40).[75]

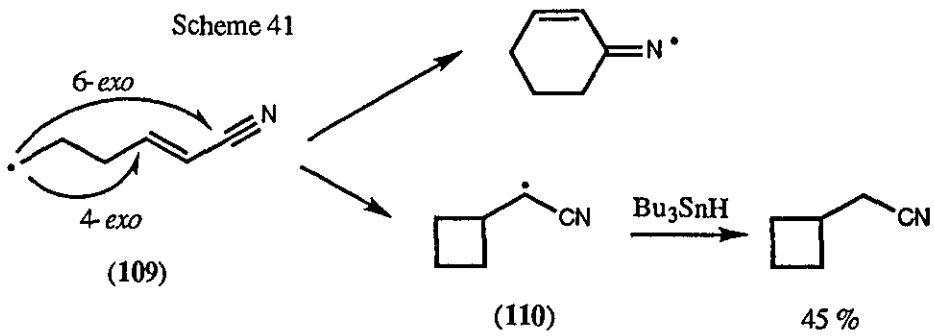
Scheme 40



41 %

For 6-*exo* cyclisation, the slow addition rate has to compete with 1,5-hydrogen abstraction, yielding the stabilised α-cyano radical, in addition to direct reduction by

Scheme 41

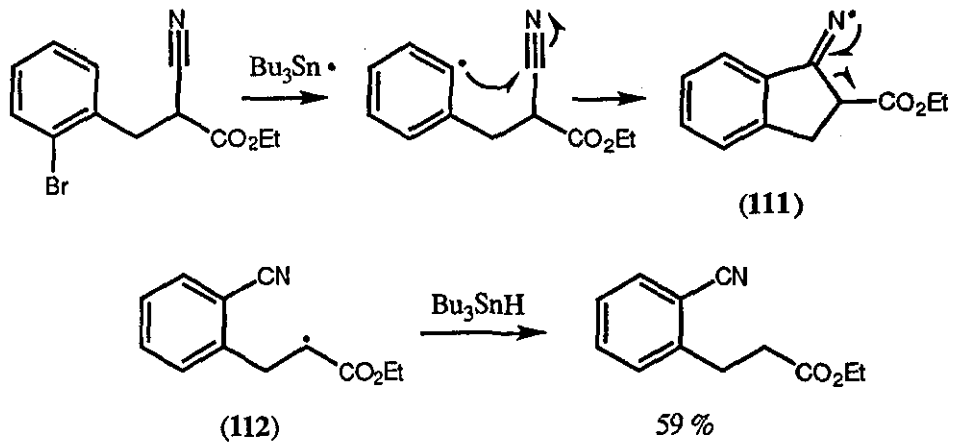


Bu_3SnH. The relative reluctance to cyclise has been demonstrated as illustrated in Scheme 41.[76] In the cyclisation of the 5-cyano-4-pentenyl radical (**109**), there is a competition between 6-*exo* addition onto the nitrile and the normally unfavourable 4-*exo* addition onto the alkene. Not only does the latter reaction prevail with the formation of the stabilised radical (**110**), the rate has been calculated to be greater than $4 \times 10^4\ s^{-1}$ at 80°C, which is the fastest known 4-*exo* cyclisation.

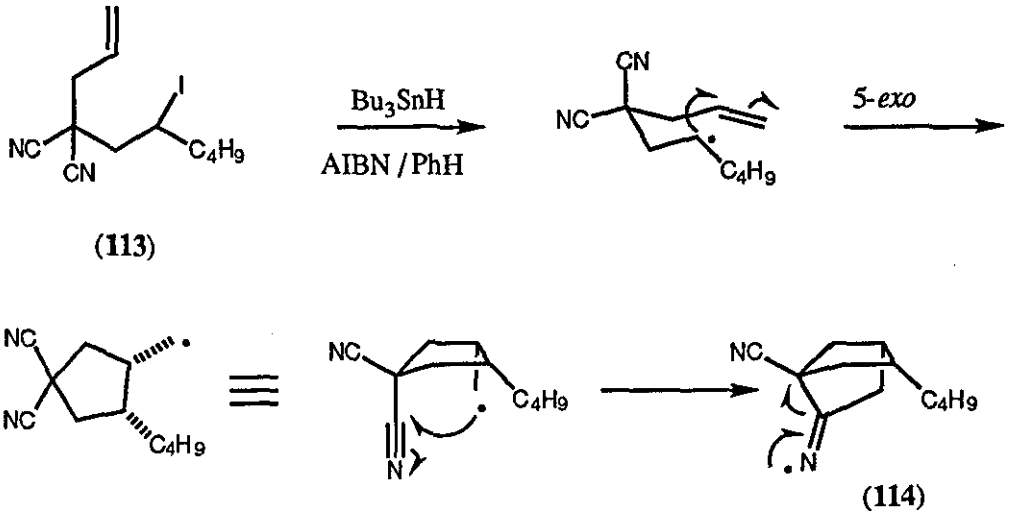
3.1.2. Nitrile Group Migration.

Though simple cyclisation of nitriles has been shown to be irreversible,[73] the process of ring opening can occur under certain circumstances.[35,77] The stable nitrile group can be reformed with a resulting molecular rearrangement. An example from Beckwith's work,[35] analogous to the ketone rearrangement shown in Scheme 13, is illusatrated in Scheme 42, where the driving force for the rearrangement is the formation of the stabilised radical (**112**) from the iminyl radical (**111**).

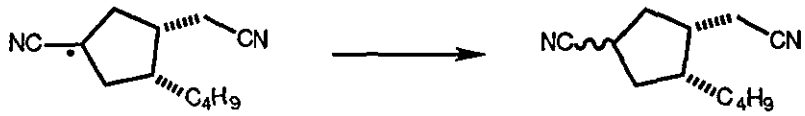
Scheme 42



Scheme 43



Scheme 43 continued



(115) (116), 82 %

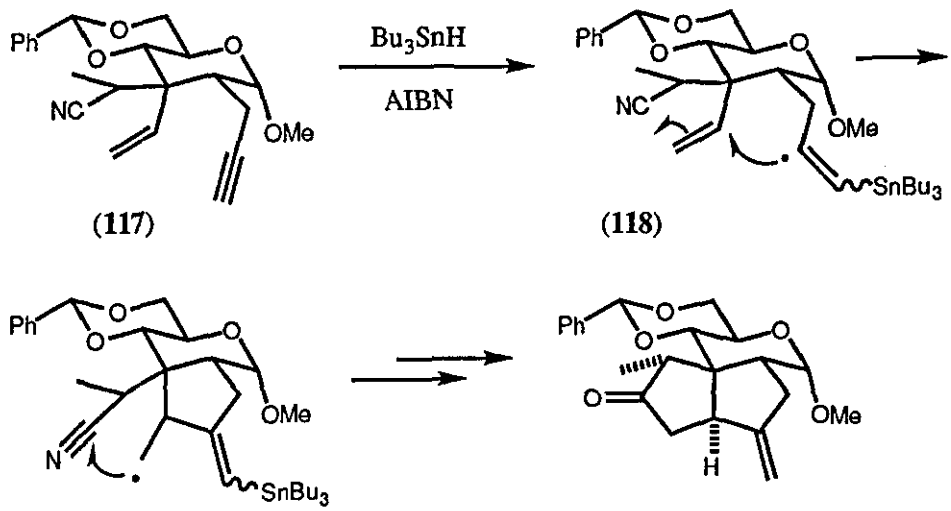
ratio of isomers: 2.9 : 1

In an example of Curran's work on iodomalononitriles (**113**) (Scheme 43),[77] cylisation involves tandem 5-*exo* cyclisations yielding the relatively strained bicyclo[2.2.1]hept-2-ylidene iminyl radical (**114**). In regenerating the nitrile group, the bond breaks leading to the formation of the stabilised radical (**115**), abstracting hydrogen from Bu_3SnH relatively slowly resulting in the observed regioselectivity in the product (**116**).

3.1.3. Tandem Reactions.

Scheme 43, above illustrates a tandem reaction involving nitriles, where the CN bond is the last in the series of unsaturated bonds to be cyclised. Another example (Scheme 44) shows a multiple addition reaction where the vinyl radical (**118**) formed by the addition of $Bu_3Sn\bullet$ to alkyne (**117**), cyclises onto the alkene and then the nitrile forming ultimately the ketone (**119**).[72]

Scheme 44

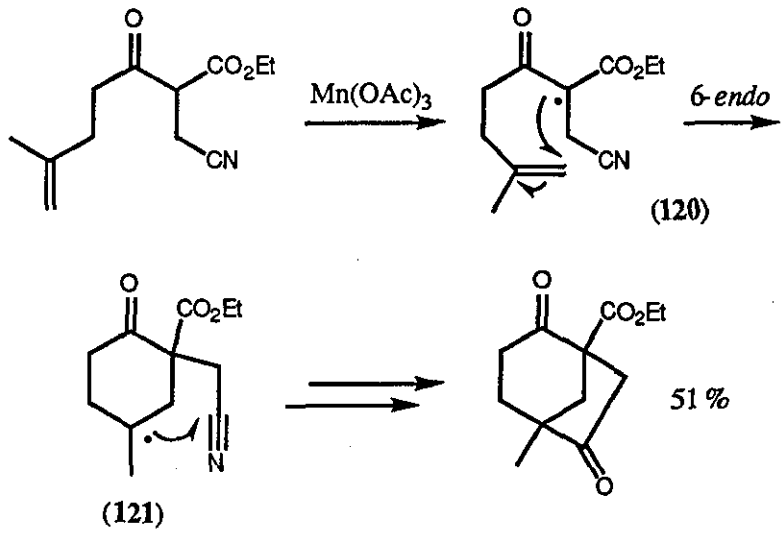


(117) (118)

(119), 65 %

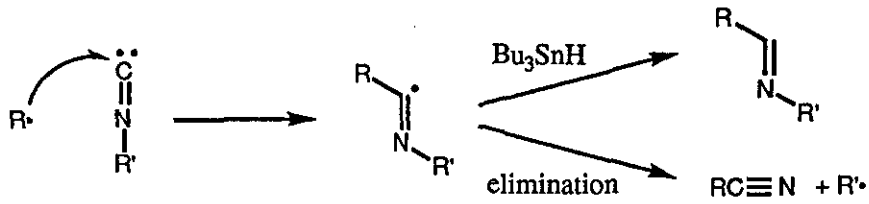
In the reaction shown in Scheme 45,[75] 5-*exo* cyclisation of the radical (**121**) onto the nitrile group follows 6-*endo* cyclisation of the alkene (**120**), producing a tertiary radical. The presence of the methyl group in this alkene prevents any 5-*exo* addition from taking place.

Scheme 45



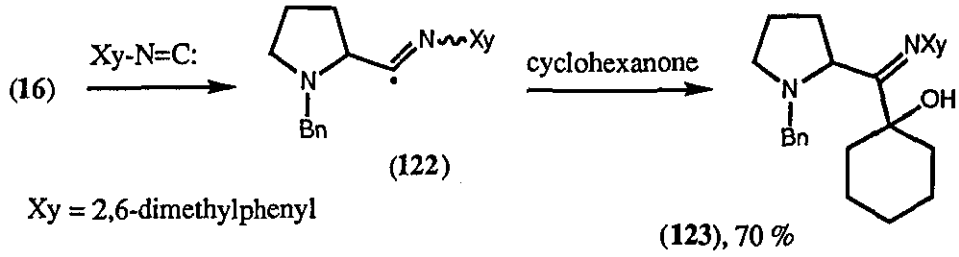
3.1.4. Addition to Isonitriles.

There are many reported instances of isonitriles being used as radical traps,[30,80] where a variety of different radicals (e.g. secondary alkyl, vinyl) add to the unsaturated carbon of the isonitrile bond to yield iminyl radicals (RC•=NR') which cyclise further or eliminate a stabilised radical forming a nitrile.



Ito and co-workers carried out the addition of *N*-benzyl-2-pyrrolidinyl radicals (**16**) to 2,6-dimethylphenyl isocyanide (XyNC), trapping the intermediate radical (**122**) with cyclohexanone to yield the imine (**123**) as the sole product (Scheme 46).[30]

Scheme 46



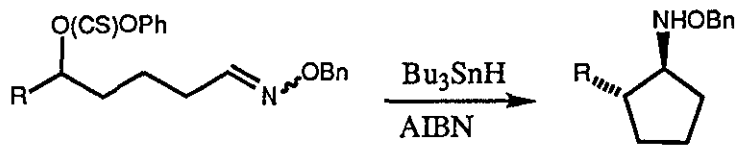
3.2. Cyclisation Reactions of Oxime Ethers.

Of all the common functional groups with a C=N bond, the radical reactions of the oxime ether group (RR'C=NOR") that has received the most attention, and they are all cyclisation reactions. Analogous reactions of oximes have not been reported.

3.2.1. Monocyclisation.

5-*exo* Addition onto the carbon atom has been successfully achieved. Functionalised cyclopentanes [e.g. (**124**), Scheme 47] have been synthesised by additions of alkyl,[65,80,81] aryl[82] and vinyl[83] radicals as well as the allylic radical formed by the addition of $Bu_3Sn\bullet$ to the central carbon of allenes[84] and aldehydes.[85] Radicals formed by the electrochemical reduction of the ketone group by zinc also react with oxime ethers.[86] Oxime ethers have also been employed in place of aldehydes in the thermal rearrangemant and cyclisation of 1,2-dialkynylbenzenes (see Scheme 17).[43] The example below shows that the cyclisation of a relatively simple oxime ether proceeds with high regioselectivity.[82]

Scheme 47

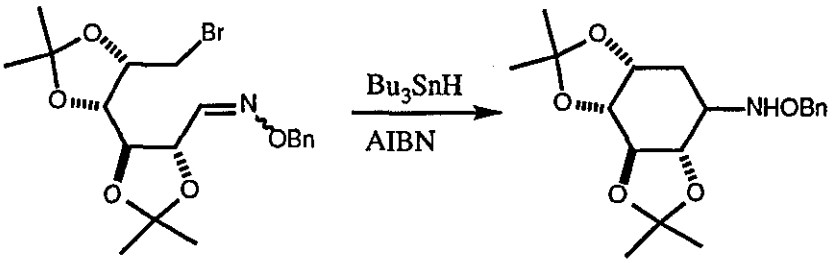


(**124**)

R = *p*-Tol, 32 %; 98 % *trans*

6-*exo* Addition onto the carbon atom also proceedsto yield a variety of functionalised cylohexanes [e.g. (**125**), Scheme 48].[87] The diastereoselectivity of some these reactions has also been demonstrated to be high.

Scheme 48



(**125**), 73 %; 82 % d.e.

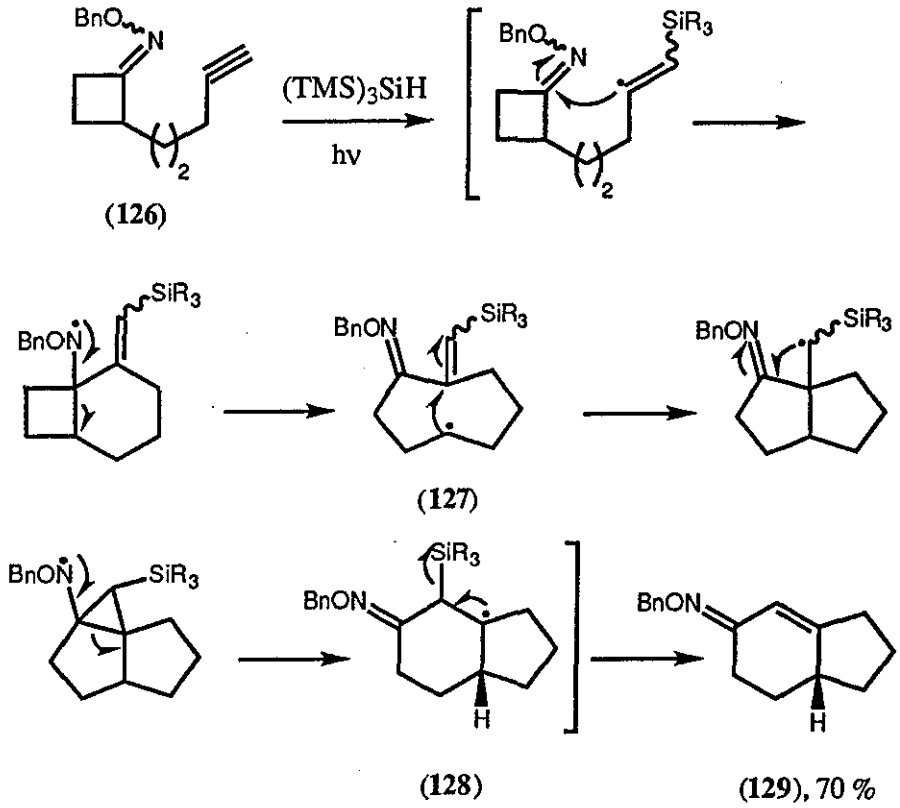
There is one example of 7-*exo* addition to the oxime ether bond among the reactions carried out by Naito,[85] the only reported such addition to any carbon-hetero multiple bond. There are as yet no reported examples of additions to the nitrogen atom of the oxime ether group.

3.2.2. Tandem Reactions.

The only reported tandem or cascade cyclisation involving oxime ethers is the novel reaction carried out by Pattenden and co-workers where the cyclobutanone oxime

(**126**) is converted to α,β-unsaturated oxime ether (**129**) in a 'one pot' synthesis, as illustrated in Scheme 49.[88]

Scheme 49



The oxime ether (**126**) was cyclised using TTSS and ultraviolet light. The $(TMS)_3Si$ radicals initially added to the alkyne group, and the resulting vinyl radical reacted by a series of steps involving 6-*exo* addition to the C=N bond, β-scission, 5-*exo* addition to the alkene group of the intermediate (**127**), 3-*exo* addition to the C=N bond, and β-scission to form the tertiary radical (**128**) which eliminated the trialkylsilyl radical to yield the product (**129**). This reaction is unique in that the unsaturated bond is attacked twice in the same reaction, with the oxime ether bond subsequently reforming from the opening of the strained rings.

3.3. Cyclisation Reactions of Hydrazones.

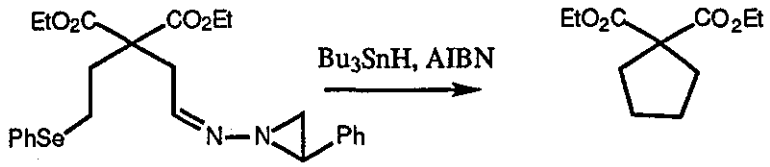
Much of the work carried out on hydrazones has been carried out by Sunggak Kim and co-workers on *N*-aziridinyl imines,[89,90] though since 1993, more examples of cyclisations have been reported.[91,92]

3.3.1. Reactions of N-Aziridinyl Imines.

5-*exo* and 6-*exo* Cyclisations onto the hydrazone bond have been achieved using a variety of free radical precursors. Scheme 50 shows a cyclisation starting with the

benzeneselenyl precursor (**130**), though similar examples use bromine, iodine, carbonyl groups and alkynes.

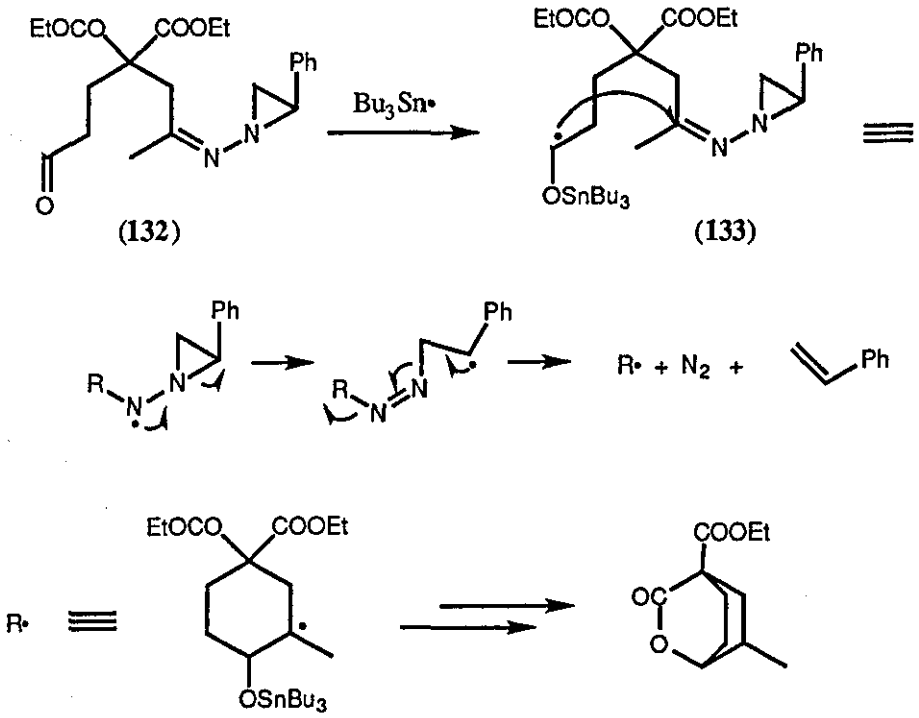
Scheme 50



(**130**) (**131**), 75 %

The mechanism for the formation of products analogous to the cyclic product (**131**) is illustrated in Scheme 51. In the reaction between Bu_3SnH and the hydrazone (**132**) the Bu_3Sn radicals add to the ketone oxygen yielding the carbon-centred radical (**133**) which adds, in this case, by 6-*exo* addition to the hydrazone carbon, yielding initially an *N*-aziridinylaminyl radical which rapidly fragments liberating nitrogen and styrene, producing the tertiary radical (**134**) which abstracts hydrogen from Bu_3SnH. Work up yields the bicyclic lactone (**135**) in 58% yield.

Scheme 51



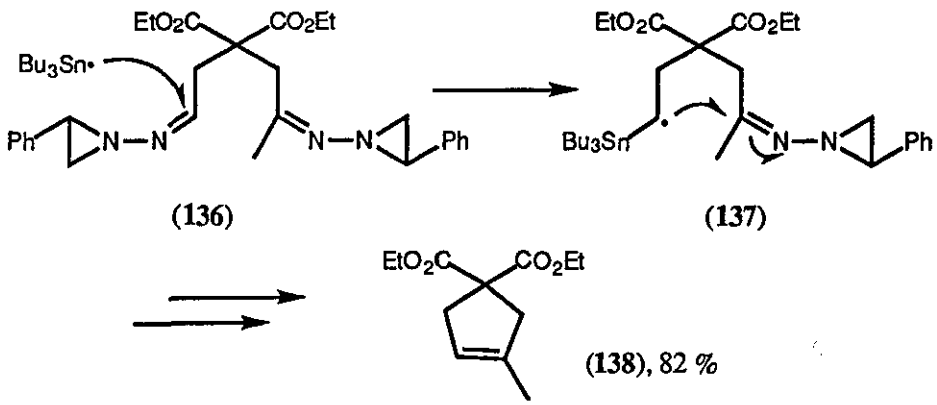
(**132**) (**133**)

(**134**) (**135**), 58 %

The novel reaction, illustrated in Scheme 52, shows the *N*-azridinyl imine functional group as the precursor to the carbon centered radicals used to cyclise onto the second hydrazone group of the bis(hydrazone) (**136**). The Bu_3Sn radicals add to the less sterically hindered aldehyde hydrazone of (**136**), which fragments to form the radical

(137) which cyclises with the same fragmentation pattern to form the diester product (138). This example also shows that ketone hydrazones also undergo radical addition despite the relatively sterically hindered unsaturated centre.

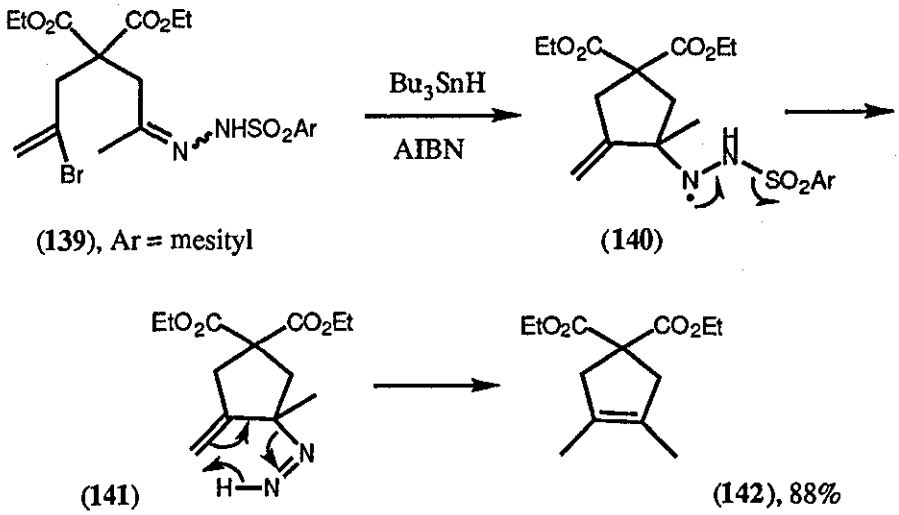
Scheme 52



3.3.2. Other Reaction of Hydrazones.

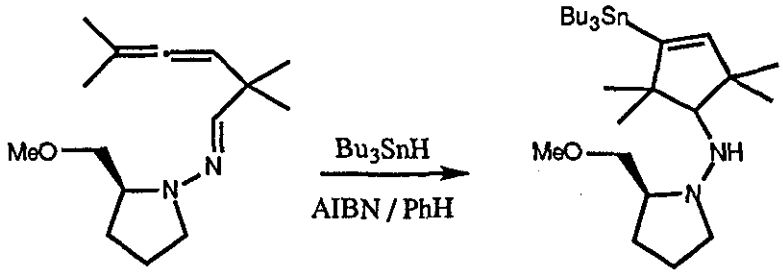
Scheme 53 illustrates the cyclisation of an arenesulfonylhydrazone.[90] The vinyl radical formed from the hydrazone (**139**) adds efficiently to the C=N bond forming the intermediate (**140**). The formation of the product (**142**) arises, first from the elimination of the arenesulfonyl radical leaving group from the radical (**140**) to form the diazene intermediate (**141**), which on liberating nitrogen through a 1,5-hydrogen shift, leads to the diester (**142**).

Scheme 53



Hatem and co-workers successfully cyclised the allylic radical formed by the addtion of Bu_3Sn radicals to the allene group, by 5-*exo* addition to the SAMP hydrazone (**143**),[91] to yield the functionalised hydrazine (**144**) (Scheme 54). This reaction also shows that a limited level of stereoselectivity can be achieved by addition to hydrazones, the bulky Bu_3Sn group influencing the stereochemistry in this case. (See Section *6.1.2*

Scheme 54

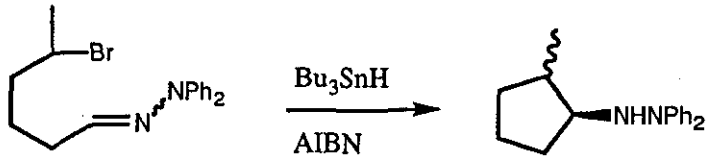


(143) (144), 78 %, 50 % d.e.

for additional work on stereoselective addition to hydrazones.)

In an extensive kinetic study into the cyclisation reactions of simple *N,N*-diphenylhydrazones, carried out by Fallis,[92] the rate of 5-*exo* cyclisation onto the hydrazone carbon has been calculated to be greater than 10^8 s^{-1} at 80°C, which are among the fastest cyclisations known, as a result of the formation of stabilised hydrazinyl radicals. Scheme 55 illustrates just one of the many reactions investigated. For this reaction, cyclisation of the hydrazone (**145**) produces the substituted hydrazines (**146**) with a *cis-trans* ratio of 2.5, with only a trace amount of uncyclised material. The rate constant for the formation of the *cis*-2-methylcyclopentylhydrazine is calculated to be 1.1 x 10^8 s^{-1} at 80°C whereas that for the *trans* isomer is 4.6 x 10^8 s^{-1} at 80°C, both very fast cyclisations. The corresponding 6-*exo* cyclisations proceed with a rate of 9.4 x 10^5 s^{-1} at 80°C, a fast reaction but with little regioselectivity as *cis* and *trans* 2-methylcyclohexylhydrazines are formed in roughly equal amounts.

Scheme 55



(145) (146), 91 %

cis : *trans* 2.5 : 1

As with oxime ethers, there are as yet no reported cyclisations where radical addition to the nitrogen atom takes place for hydrazones.

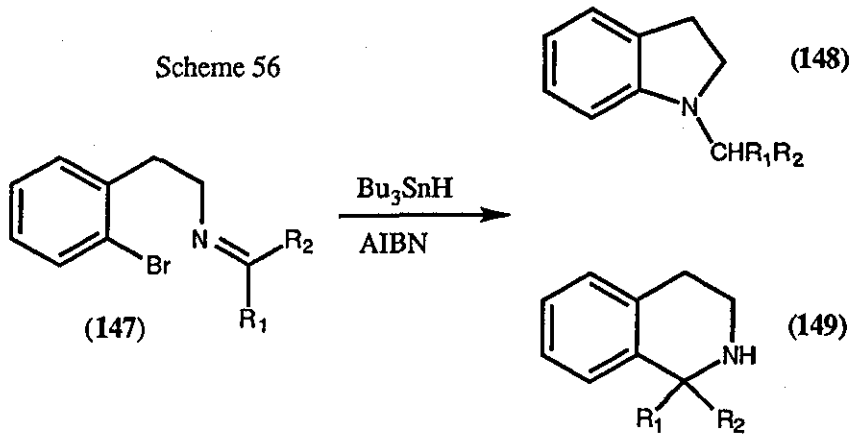
3.4. Addition to the Imine Bond.

Until 1994, there had been very little information published regarding the radical reactions of imines. Much of the initial study was carried out by Warkentin in which aryl radicals were added to a variety of imines to yield tetrahydroisoquinolines.[93] In this study the rate constants were measured for the cyclisations as well as information on regio- and stereoselectivity.

3.4.1. Cyclisation of Aryl Radicals.

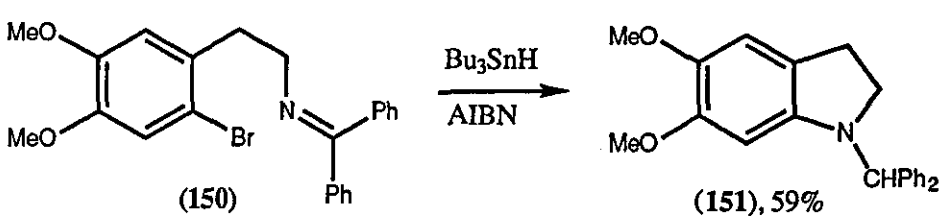
A general reaction illustrating Warkentin's work is illustrated in Scheme 56. The reaction of the imine (**147**) under standard conditions yields radicals which can either cyclise by 5-*exo* addition to the imine nitrogen or 6-*endo* onto the carbon atom. The 6-*endo*-product (**149**) is formed almost exclusively in these reactions, with only trace amounts of the 5-*exo* product (**148**). [If R_1 = H, R_2 = ^iPr, the ratio (**149**) : (**148**) is 55 : 1.] If an aromatic imine is used (R_1 = H, R_2 = Ph), the preference for *endo*-attack is much less marked (*endo* : *exo* ratio - 12 : 1).

Scheme 56



The cyclisations were found to be irreversible, as attempts were made to convert authentic samples of the *exo* products to the *endo* products but without success. Kinetic studies of both *C*-alkyl and *C*-aryl aldimines show that 5-*exo* cyclisation is around four to five times slower than 6-*endo*. The rate constants (R_1 = D, R_2 = Ph) for 5-*exo* and 6-*endo* cyclisations are $3.8 \times 10^7\ s^{-1}$ at 80°C and $1.6 \times 10^8\ s^{-1}$ at 80°C respectively, both very fast cyclisations. There are several reasons for this selectivity:- the aryl radical reacts with the electrophilic imine carbon, resulting in the formation of a C-C bond rather than a C-N bond; the formation of a less strained cyclised product; and steric factors where the transition state for the *endo* approach of the bulky aryl radical is less strained than for the *exo* approach. Steric hindrance around the imine carbon contributes to the stereoselectivity. Cyclisation of a ketimine (R_1 = R_2 = Et) gave mainly reduced acyclic starting material but the cyclised minor products were found to contain a ratio of 6-*endo* to 5-*exo* of 1 : 2.5 showing that radical addition to the ketimine carbon is sterically impeded.

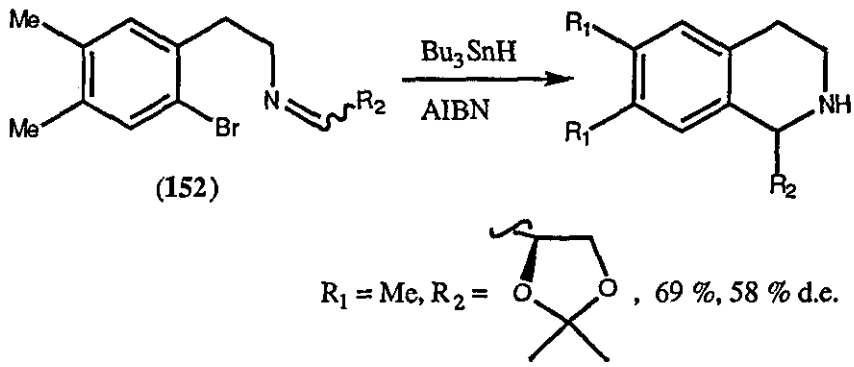
Scheme 57



The cyclisation of the more nucleophilic 3,4-dimethoxy radical derived from imine (**150**) (Scheme 57), onto ketimines has been reported by Takano[94] as part of work paralleling that of Warkentin. The formation of the indoline (**151**) as the sole product results from 5-*exo* cyclisation onto the nitrogen atom with the formation of a highly stablised diphenylmethyl radical.

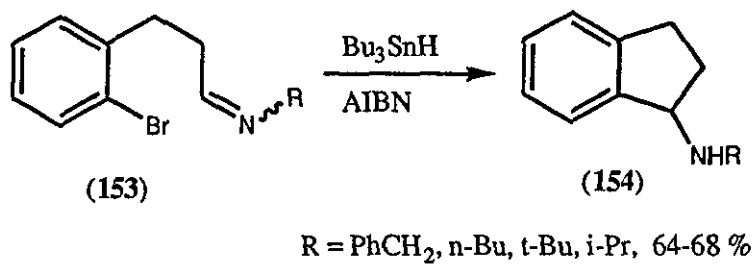
The cyclisation reaction of aryl radicals also shows some degree of stereo-selectivity (Scheme 58). A diasteromeric excess of 58% was achieved by cyclising the imine derived from glyceraldehyde (**152**).[95]

Scheme 58



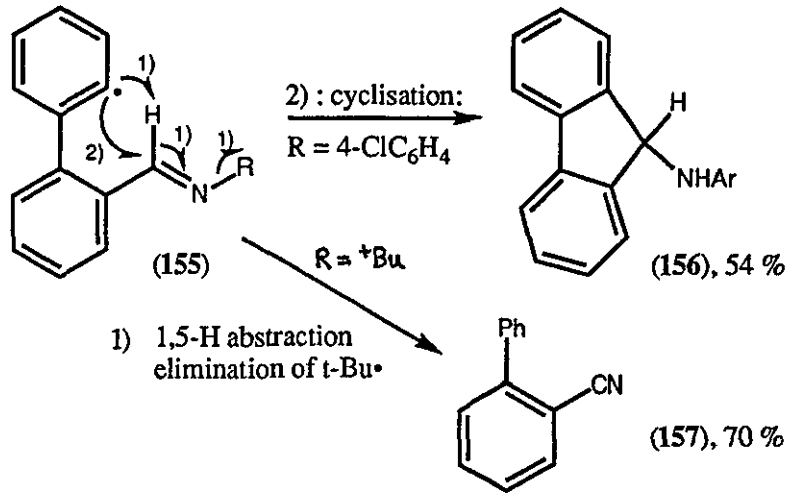
Warkentin also investigated cyclisation reactions of imines of the type shown in Scheme 59.[96] Cyclisation of the imines (**153**) yielded the *N*-alkylindolines (**154**) as the only reaction products. For the reaction where R = benzyl, the rate constant was calculated to be 3.9 x 10^8 s^{-1} at 80°C, the fastest reported cyclisation then reported.

Scheme 59



A modification to Warkentin's work was carried out by Leardini (Scheme 60).[97] The biphenyl-2-yl radicals (**155**) react with aldimine group to yield products depending on the group R. Successful 5-*exo* addition was achieved with an aromatic substituent on the imine nitrogen (R = 4-chlorophenyl), and the 9-aminofluorene derivative (**156**) was isolated. In the reaction of the *N*-alkyl imine (**155**, R = ^{t}Bu), abstraction of the aldimine hydrogen by 1,5-abstraction, followed by β-elimination of the stabilised tertiary radical resulted in the formation of 2-phenylbenzonitrile (**157**).

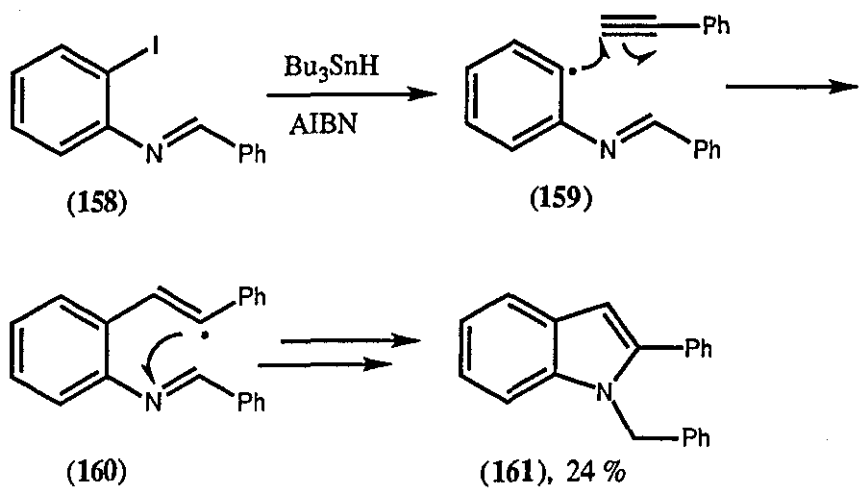
Scheme 60



3.4.2. Other Radical Reactions of Imines.

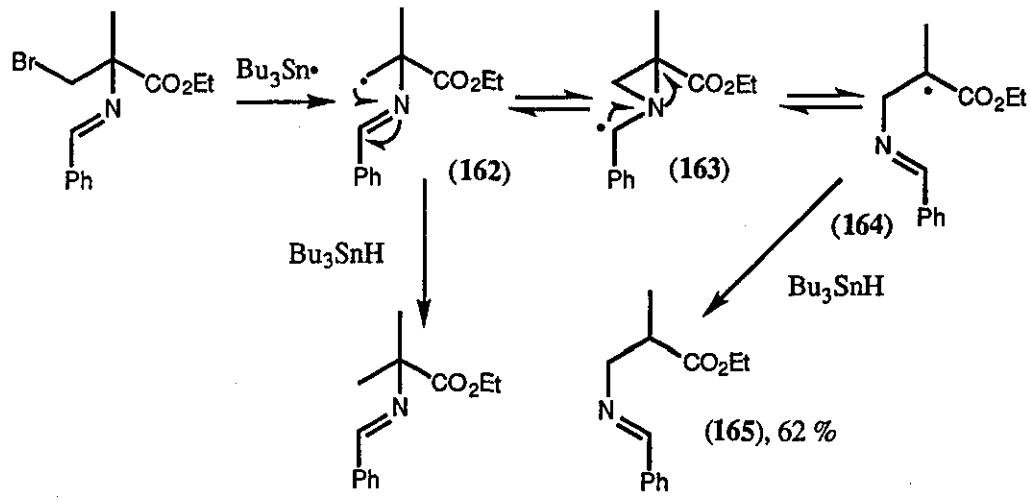
Only a few intermolecular radical addition reactions of imines have been described.[97,98] A novel cyclisation reaction is illustrated in Scheme 61.[97] The aryl radical (**159**) resulting from the abstraction of iodine from the imine (**158**) does not cyclise onto the imine bond. Instead intermolecular addition to phenylacetylene produces the vinyl radical (**160**) which cyclises by 5-*exo* addition to the imine nitrogen to give the indole (**161**) as the product. The yield (24%) may be low, but this reaction illustrates that vinyl radicals add to imines.

Scheme 61



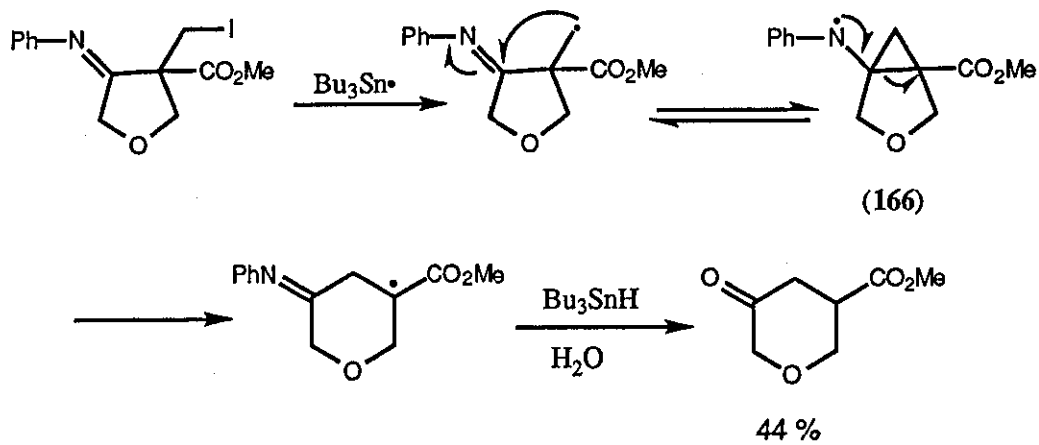
Radical cyclisation of an aliphatic radical onto an imine has been reported on several occasions both proceeding by 3-*exo* cyclisation followed by ring opening.[99,100] In the first example (Scheme 62),[99] the attack of the radical (**162**) onto the nitrogen of the imine forms the aziridine intermediate (**163**) which opens to form the radical (**164**) stabilised by the adjacent ester group. In the major product, which is a β-amino acid derivative (**165**), the imine group moves one carbon further from the ester group and the reaction could be described as a 1,2 amine shift.

Scheme 62



Another example forms part of Dowd's work on free radical ring expansion (Scheme 63)[37] and shows that one-carbon ring expansion via the cyclopropylaminyl intermediate (**166**) procedes for an imine in much the same way as for a ketone.

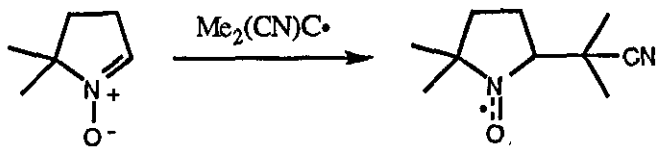
Scheme 63



3.4.3. Addition to Iminium Salts and Related Compounds.

As for imines, there are relatively few reported reactions of addition to moieties with a formal positive charge on the nitrogen atom, as iminium ions, protonated aromatic bases and nitrones. Addition to the carbon atom of nitrones is relatively well known,[101,102] forming highly stabilised nitroxyl radicals, and such compounds are used as radical traps in the same way as nitroso compounds.[52] In a pioneering study of the late 1960's, addition of 2-cyanoisopropyl radicals (from the thermolysis of AIBN) to the nitrone (**167**) yielded nitroxyl radicals (**168**), isolated as red crystals though only in 6% yield (Scheme 64).[101] Nowadays radicals analogous to (**168**) are not isolated but are generated and reacted *in situ* as part of EPR spectroscopic studies.[102]

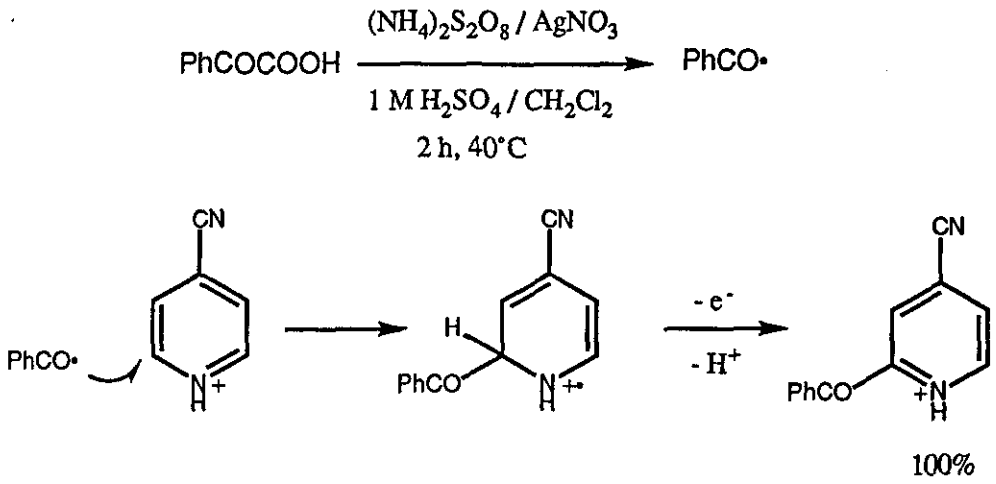
Scheme 64



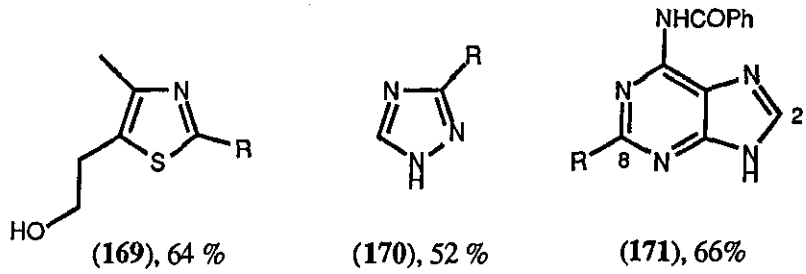
(167) (168), 6 % isolated yield

Intermolecular radical addition to protonated aromatic bases has been successfully employed in the synthesis of substituted heteroarenes, including the addition of benzoyl radicals to the 2-position of 4-substituted pyridines (Scheme 65).[103]

Scheme 65



In the synthesis of novel nucleosides, radicals generated from protected sugars added to the 2-position of a range of pyridines.[104] These reactions were carried out in the presence of one equivalent of acid (usually camphor-10-sulfonic acid). Barton demonstrated that radicals add selectively to other protonated heterocycles including thiazoles (**169**), 1,2,4-triazoles (**170**) and purines (**171**).[105] Radicals add to the 2-position of the imidazole ring of caffeine.

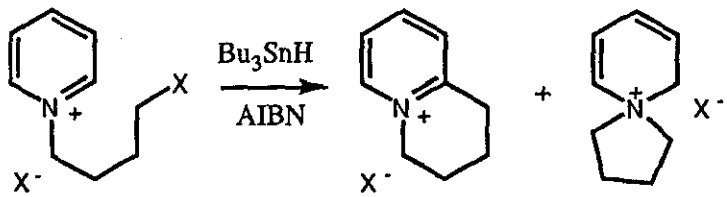


(**169**), 64 % (**170**), 52 % (**171**), 66%

There are fewer examples of cyclisation onto alkylated aromatic bases.[106-7] One example from Murphy's work is illustrated in Scheme 66.[106] Radicals formed from reaction of $Bu_3Sn\bullet$ with iminium salt (**172**) gave rise to two products, salts (**173**) and

(**174**). Bicyclic iminium salt (**173**) is formed by a radical pathway analogous to the intermolecular reactions, but is the minor product. The spirocyclic salt (**174**) is not formed by a radical pathway as reactions carried out in the absence of AIBN or where X is the *p*-toluenesulfonyl group (which is not abstracted by $Bu_3Sn\bullet$), yield only this product which is formed by a polar reaction pathway.

Scheme 66



(**172**) (**173**) (**174**)

X = I or Br, ratio (**173**) : (**174**) = 1 : 2

X = OTs (**174**) only

To conclude, there is an increasing amount of information on free radical reactions of the common carbon-nitrogen multiply bonded functional groups and kinetic studies carried out on the cyclisation onto hydrazones, and also by aryl radicals onto imines, indicate that these reactions proceed at a very fast rate. The study of sp^3 carbon-centred radical cyclisations of imines had not been reported up to the commencement of the research. Chapter 4 deals with the synthesis of simple imine systems, and Chapter 5 and Chapter 6 discuss the monocyclisation reactions carried out on imines and hydrazones.

4. Initial Studies - Preparation of Simple Imines for Cyclisation.

4.1. Introduction.

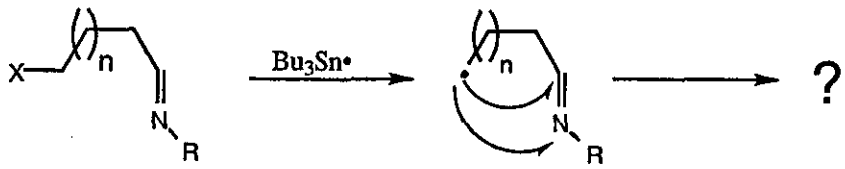
The aim of the research was to develop new methods for the synthesis of nitrogen heterocycles by cyclisation of carbon-centered radicals onto imines thereby generating aminyl radicals.[108] These intermediates may be directly reduced to form monocyclic amines or used in tandem cyclisations to yield bicyclic compounds. The various stages leading up to the synthesis of a variety of imines for monocyclisation are discussed in this chapter. Chapter 5 deals with the cyclisation reactions themselves and in Chapter 6, monocyclisation reactions arising from the findings of the initial work are discussed. Among these reactions are the cyclisation reactions of hydrazones and the attempts made at stereoselective cyclisations.

4.2. General Synthetic Strategy.

The initial phase of the work was to establish a clear picture of the behaviour of imines towards free radical attack by carbon-centred radicals. As many of the physical and chemical properties of imines are unknown, studies had to be made on whether imines undergo free radical addition and to discern the regiochemistry of the products so formed, i.e. the ratio of *exo* to *endo* products and whether or not the polarisation of the double bond plays a part in biasing the cyclisations towards attack at carbon rather than nitrogen. In the radical addition to aldehydes and ketones, attack is normally at the electrophilic carbon, whereas in the additon to thiocarbonyl bond, attack is normally at the "soft" sulphur atom. (Electronegativity plays little part in these reactions as carbon and sulphur have similar elecronegativities). The C=N bond is a polar bond but not to the same degree as the C=O bond so nitrogen attack could be a possibility if the conditions were suitable.

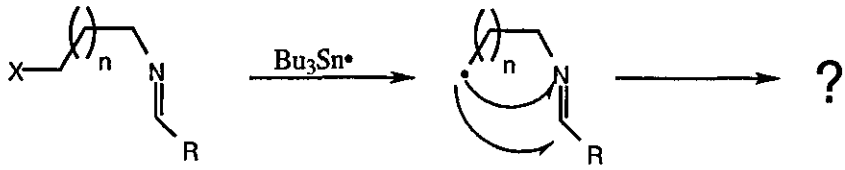
The initial aim was to show that carbon-centered radicals have the the ability to cyclise onto imines. For this purpose, two types of imine were synthesised for cyclisation as shown in Schemes 67 and 68 (R = alkyl or aryl; X = a suitable radical leaving group). Type I imines bear the free radical leaving group on the carbon chain attached to the imine carbon. Type II imines bear the free radical leaving group on the carbon chain attached to the imine nitrogen.

Scheme 67



Type I Imine

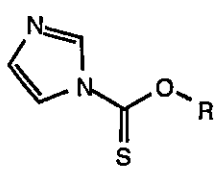
Scheme 68



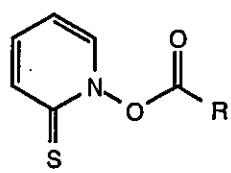
Type II Imine

Simple imines were synthesised to determine the regiochemistry of radical addition, bearing only a radical leaving group in the ω-position of the alkyl chain. Other substituents or functional groups in the alkyl chain were not included, because at this stage stereoselective cyclisation reactions were not being investigated. The two series of imines represent the two possible imine cyclisations that can occur, either *exo* attack on the carbon (Scheme 67) or *exo* attack on the nitrogen (Scheme 68). Studies on the cyclisations of both series of imines would give a broad view of their ability to undergo radical addition.

The use of the common radical generating reagent Bu_3SnH in the cyclisations was chosen and a suitable radical leaving group had to be positioned in the molecule that would be readily abstracted by $Bu_3Sn\bullet$. With the possible problem of the imine displacing the radical leaving group, various groups were considered which were not susceptible to nucleophilic displacement and as a result bromine and iodine were not chosen. The radical leaving groups which were considered included thiocarbamates (**175**) derived from 1,1'-thiocarbonyldiimidazole and *N*-hydroxypyridin-2-thione derivatives (**176**).



(175)



(176)

The latter were not used because of problems of the instability of the derivatives towards light and difficulties of use. The former, despite the expense of the reagent, was considered a useful possible radicophile. Also considered was the use of nitro groups which have many advantages, such as stability to many reaction conditions, but which do not form primary radicals with Bu_3SnH. The formation of primary radicals was preferred in the early work, to keep the cyclisations as simple as possible and the use of nitro groups was placed in reserve. With benzenesulfenyl (PhS) being too unreactive for the formation of carbon radicals, benzeneselenyl (PhSe) was chosen. There are problems associated with this group such as the toxicity of selenium compounds (and their odour), the relative expense of the selenium starting material (diphenyl diselenide) and the ease of oxidation of the benzeneselenyl group. The group is usually placed in a molecule to

produce an alkene by β-elimination under mild oxidising conditions. The ease at which the group was introduced in the preparation of the precursors to the imines outweighed any of the drawbacks.

Imines bearing a stabilising aryl substituent either on the carbon or on the nitrogen were synthesised first, the radical leaving group attached to a carbon chain on the opposite side of the imine bond from the aryl group. These imines were synthesised, because of the substantial stabilisation brought about by the aryl group which would enable isolation and characterisation. Later imines bearing only aliphatic substituents, were not isolated and were generated and reacted in a 'one-pot' reaction.

4.3. Preparation of Imines (Type I).

A series of three imines with a different chain length between the radical leaving group and the imine bond were synthesised for *N*-aryl imines. The chain lengths chosen were those which were the most likely to undergo cyclisation, i.e. chain lengths which would be expected to add to the unsaturated bond by 5-*exo* (6-*endo*) and 6-*exo* (7-*endo*) cyclisation. Imines of shorter chain length were also prepared, not that 4-*exo* cyclisation was at all likely, but 5-*endo* could be envisaged. The aryl group chosen was *p*-tolyl, the reason being that in the crude NMR spectrum each *p*-methyl group would show as a separate singlet and the number of different products could thus be discerned at a glance.

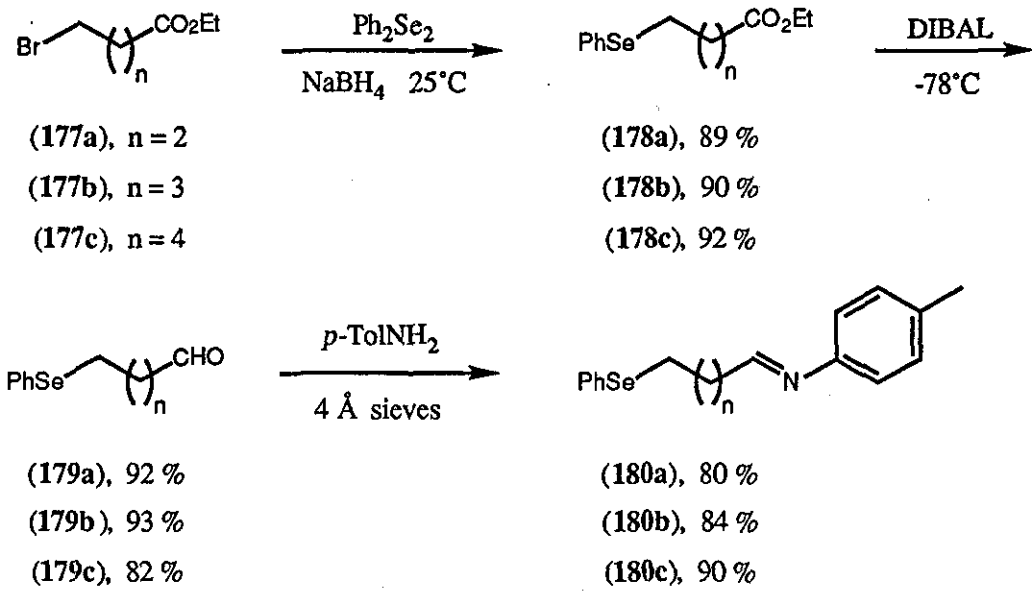
The synthesis of these imines is summarised in Scheme 69. Owing to the lability of the imine bond towards moisture and its relatively unknown reactivity towards electrophiles, a decision was taken to synthesise the imine bond at the end of the synthesis. So the target molecules in the preparation of these imines were the ω-benzeneselenyl aldehydes (**179a-c**).

One route to their preparation was to prepare a suitable substituted ester and to reduce it to the aldehyde using diisobutylaluminium hydride (DIBAL). The first stage was the preparation of the benzeneselenyl substituted esters. There are many methods available to introduce the benzeneselenyl group into a molecule but the one which was chosen has proved to be a useful general method for the preparation of aliphatic benzeneselenyl derivatives, that is the reaction of the ω-bromoesters (**177**) with a benzeneselenide nucleophile generated *in situ* by the borohydride reduction of diphenyl diselenide.[109] The reaction conditions are relatively mild and the yields of the benzeneselenyl esters (**178**) are high. The reaction proceeds by S_N2 substitution and the selenium containing nucleophile is thought to be a complex between the benzeneselenide anion and borane: $[PhSe(BH_3)^-]$.

The reduction of an ester to an aldehyde using DIBAL at first produced problems. The reagent is very air and water sensitive and can fail to react with the substrate if even a trace of water is present. A trial reaction using freshly dried and distilled γ-butyrolactone failed owing to the hygroscopicity of the lactone. However, a literature procedure for the formation of the required aldehydes was found[110] and once the

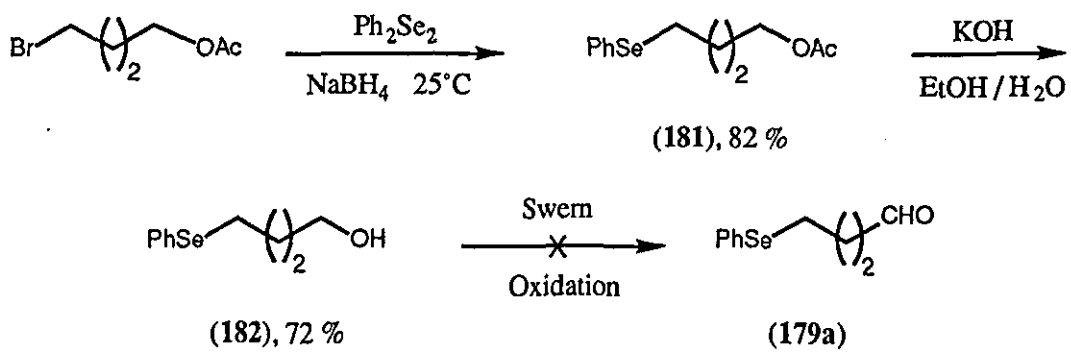
reaction conditions had been mastered, the ω-benzeneselenyl aldehydes (**179a-c**) were prepared in good yield.

Scheme 69



A second route to the aldehydes was attempted (Scheme 70), proceeding via the ω-benzeneselenyl alcohol (**182**). The alcohol was easy to prepare, a two stage synthesis from 4-bromobutyl acetate but the final stage to the aldehyde (**179a**) required oxidation. A reagent that would oxidise the hydroxyl group yet leave the selenium functionality alone, was required. Mild oxidising agents such as hydrogen peroxide and PCC oxidise the selenium, centre[111] and these reagents are used to form alkenes from selenides as mentioned above. The reactivity of activated dimethyl sulphide towards selenium was not known and so the alcohol (**182**) was subjected to Swern oxidation conditions.[112] Unfortunately the aldehyde (**179a**) was not formed in any of the three occasions the reaction was attempted and no identifiable products were obtained. By this stage, the DIBAL reduction of the esters (**178**) were proceeding well so the second route was not followed any further.

Scheme 70



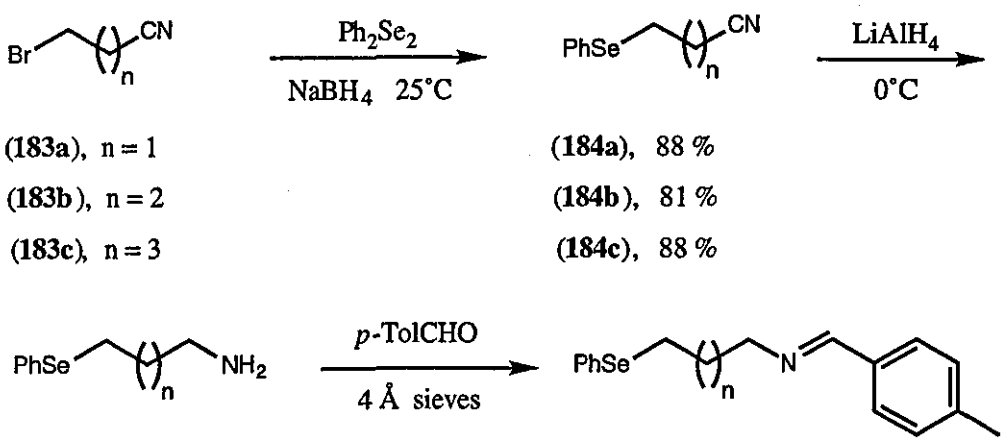
The formation of the imines from the aldehydes was achieved by stirring each aldehyde with *p*-toluidine over molecular sieves. The removal of water by azeotropic distillation was not attempted at first because the stability of the benzeneselenyl functionality towards long periods of refluxing was not clearly understood at the time. The *N*-aryl imines (**180a-c**) were found to be relatively difficult to prepare owing to the low basicity of the aromatic amine, but once formed, they were stable enough to isolate and characterise.

4.4. Preparation of Imines (Type II).

Scheme 71 gives the reaction pathways followed in the preparation of the *C*-aryl imines. As in the case of the type I imines, the imine bond was formed at the end of the synthesis by the coupling of an amine with a *p*-tolualdehyde.

Thus it was required to synthesise primary amines of various chain lengths with the benzeneselenyl group on the terminal carbon. For the introduction of the benzeneselenyl group, the same method was employed as for the esters in Scheme 69. Reaction of a series of ω-bromonitriles (**183**) with diphenyl diselenide / sodium borohydride yielded the ω-benzeneselenyl nitriles (**184a-c**) in very good yield. Reduction of the nitriles with lithium aluminium hydride was thought to be an easy route to the required amines (**185a-c**). However this second step proved to be somewhat troublesome. To start with, only low yields (<40%) of amines were produced and there was extensive decomposition of the benzeneselenyl group giving the bad smelling benzeneselenol (PhSeH) as a by-product. Much time was spent determining the quantity of the hydride needed to reduce the nitrile yet leave the selenium untouched. This was found to be three equivalents of hydride (0.75 equivalents of $LiAlH_4$) per equivalent of nitrile. Using these proportions, the yields for the longer chained amines (**185b,c**) were raised to over 90%.

Scheme 71



(**183a**), n = 1 (**184a**), 88 %

(**183b**), n = 2 (**184b**), 81 %

(**183c**), n = 3 (**184c**), 88 %

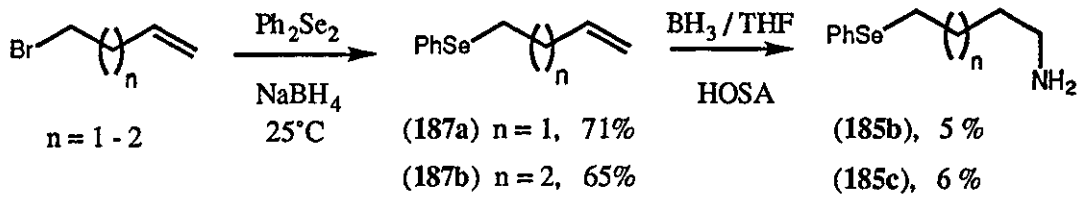
(**185a**), 60 % (**186a**), 75 %

(**185b**), 91 % (**186b**), 90 %

(**185c**), 92 % (**186c**), 91 %

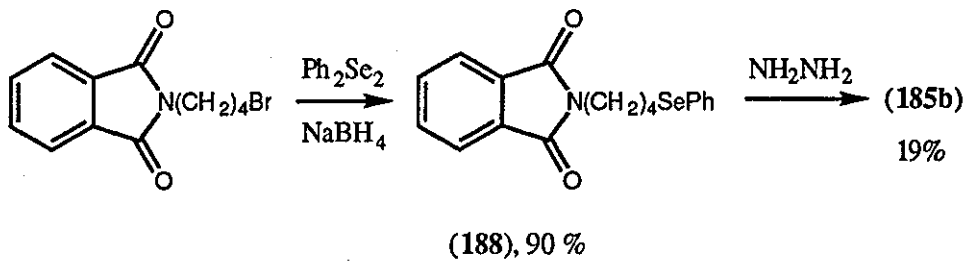
Other methods of producing the amines were briefly explored (Schemes 72-74). The alkenes (**187**) were prepared by the same method as the esters (**178**) and the nitriles (**184**) and then were reacted with borane and hydroxylamine-*O*-sulphonic acid (HOSA).[113] In this reaction the alkene reacts with the borane to give a trialkylborane intermediate which reacts with the HOSA, yielding after hydrolysis the free amine.

Scheme 72



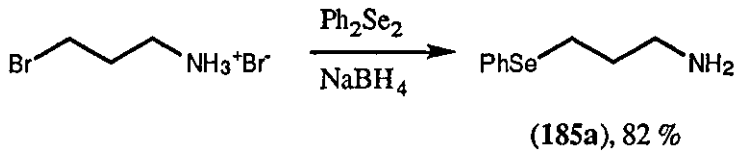
The yields quoted in reference 113 are only around 40%, but it was hoped that the amines could be produced without bad smelling side-products. However these reactions failed all three times attempted and so a new route was explored using a phthalimide intermediate (Scheme 73). Commercially available *N*-(4-bromobutyl)phthalimide was reacted with diphenyl diselenide and sodium borohydride to yield the phthalimide (**188**). Reaction of this compound with hydrazine in ethanol yielded the amine (**185b**) but in poor yield (19%).

Scheme 73



For 3-benzeneselenylpropylamine (**185a**), the yield for reduction of the nitrile (**184a**) never exceeded 60% and an alternative method was used (Scheme 74). Reaction of 3-bromopropylamine hydrobromide with benzeneselenide anions yielded the amine (**185a**) as the only product in 82% yield. This became the standard procedure for the formation of the amine.

Scheme 74



The formation of the *C*-aryl imines was found to be much easier than for the *N*-aryl imines. It proved an opportunity to explore alternative methods for their synthesis. With the concern that molecular sieves are able to adsorb and decompose imines on their surfaces, a milder method of imine synthesis was sought. A search through the literature revealed that imines could be formed using anhydrous potassium carbonate or anhydrous sodium sulphate.[114] Trial reactions were performed on the condensation of cyclohexanone with *n*-propylamine with each of the salts named above and the best result was obtained with sodium sulphate. The imines (**186b**) and (**186c**) were prepared by stirring with sodium sulphate and high yields of imines of high purity were produced. The imine (**186a**) was synthesised by stirring over molecular sieves. The *C*-aryl imines were stable enough for isolation and characterisation but are more easily hydrolysed than *N*-aryl imines, decomposing readily on TLC plates.

4.5. Formation of Imines bearing Aliphatic Substituents.

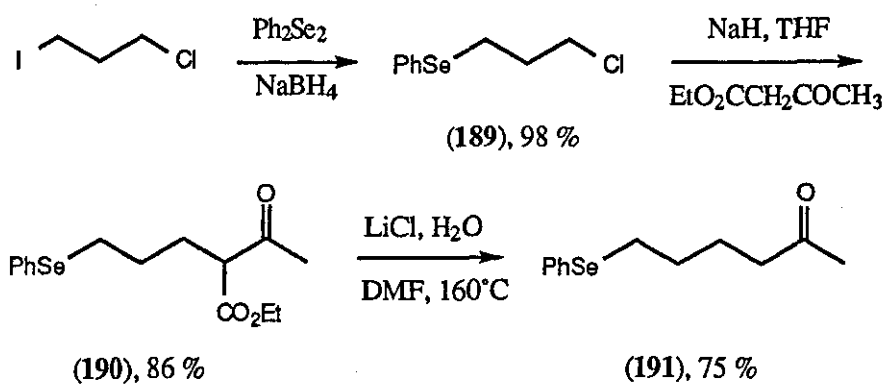
The monocyclisation of aliphatic imines was also investigated, to show whether aliphatic imines cyclise differently from aromatic imines. The precursors were the same as for the aromatic imines, but the imines themselves were prepared and reacted *in situ*. They were formed by azeotropic distillation in toluene, the advantage being that they could be formed and cyclised in the same reaction vessel. At this point in the work, the thermal stability of the benzeneselenyl functional group in refluxing toluene had been established. The formation of the imine was verified by infrared spectroscopy. The choice of aliphatic group was carefully made. A phenyl substituent two carbon atoms from the imine bond was used, thereby ensuring that the phenyl group was sufficiently remote form the imine, yet close enough so that the amine or aldehyde was readily available and to provide the cyclised products with sufficient molecular weight to prevent evaporating the products under vacuum. The range of cyclisations undertaken only covered 5-*exo* (6-*endo*) and 6-*exo* cyclisations as the shorter chain length was not thought to be synthetically worthwhile. In later studies, *N*-benzyl imines were synthesised for cyclisation. Initial fears that thermally induced conjugation of the imine bond with the aromatic ring were not realised.

4.6. Preparation of Ketimines.

Takano[94] had successfully added aryl radicals to ketimines and it was decided to synthesise aliphatic ketimines of both types and cyclise them. Type II imines were relatively easy to synthesise since they would require condensing suitable ketones with ω-benzeneselenyl amines which had already been synthesised. The two ketones chosen for the study were readily available 2-tetralone and 2-phenylcyclohexanone and these were condensed in turn with 4-benzeneselenylbutylamine, which on cyclisation would yield 5-*exo* or 6-*endo* addition.

Type I imines required the synthesis of a benzeneselenyl substituted ketone and a new synthetic sequence was developed as illustrated in Scheme 75. The first step involved displacement of iodide by benzeneselenide and the resulting 1-benzeneselenyl-3-chloropropane (**189**) was added to the sodium salt of ethyl 3-oxobutanoate to form the β-keto-ester (**190**). The following step, hydrolytic de-esterification using lithium chloride in a dipolar aprotic solvent, resulted in efficient cleavage of the ester group to yield the ketone (**191**). This reaction provided a test for the potentially labile benzeneselenyl group, as little was known about its thermal stability under such severe reaction conditions.

Scheme 75

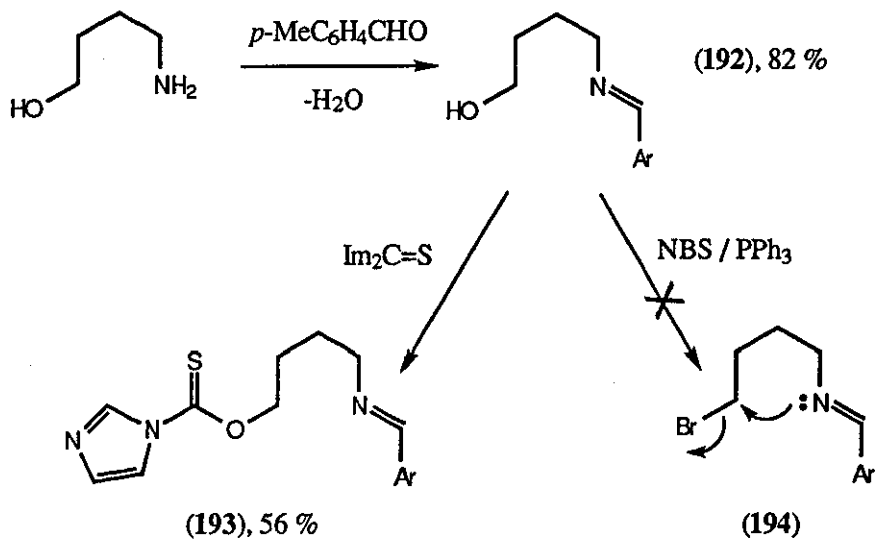


4.7. Exploration of Alternative Radical Leaving Groups

This work formed part of the studies since due to the toxicity and other problems associated with the benzeneselenyl group, the preparation of imines bearing other radical leaving groups was undertaken. One such leaving group, held in reserve during our initial assessment was the thiocarbamate derived from 1,1'-thiocarbonyldiimidazole. This reagent reacts with hydroxy compounds in hot toluene with acid catalysis to yield the thiocarbamate as a stable compound (Scheme 76). The hydroxy compound could be a ω-hydroxy-aldehyde formed from the DIBAL reduction of a lactone or a commercially available ω-hydroxy-amine. The latter was chosen and to protect the amine group from reacting with the imidazole, it was condensed with *p*-tolualdehyde to form the imine (**192**). Even though the reactivity of the imine nitrogen towards the imidazole carbamate was not known, reaction between the hydroxy -imine (**192**) and the imidazole took place to yield the thiocarbamate (**193**) in reasonable yield. However, the reaction produced many by-products and the thiocarbamate was hard to isolate. This reaction shows that the thiocarbamates form easily even with an imine group present in the molecule and could be a useful alternative radical leaving group.

Another radical leaving group that needed to be considered was the halogen leaving group (Scheme 76). The work of Warkentin, Takano and Frey all utilised imines bearing halogen groups,[93-97] but the bromides were either aromatic and hence inert or were

Scheme 76



postitioned in the molecule β to the imine nitrogen such that intramolecular S_N2 substitution could not occur. An attempt was made to prepare an imine where the bromine was positioned δ to the imine nitrogen, far enough away for S_N2 substitution to occur yet at the right distance for 5-*exo* radical cyclisation to occur if the former reaction failed to proceed. The imine (**192**) was stirred with *N*-bromosuccinimide and triphenylphosphine in an attempt to prepare imine (**194**). Unfortunately, only polymeric products were produced in this reaction.

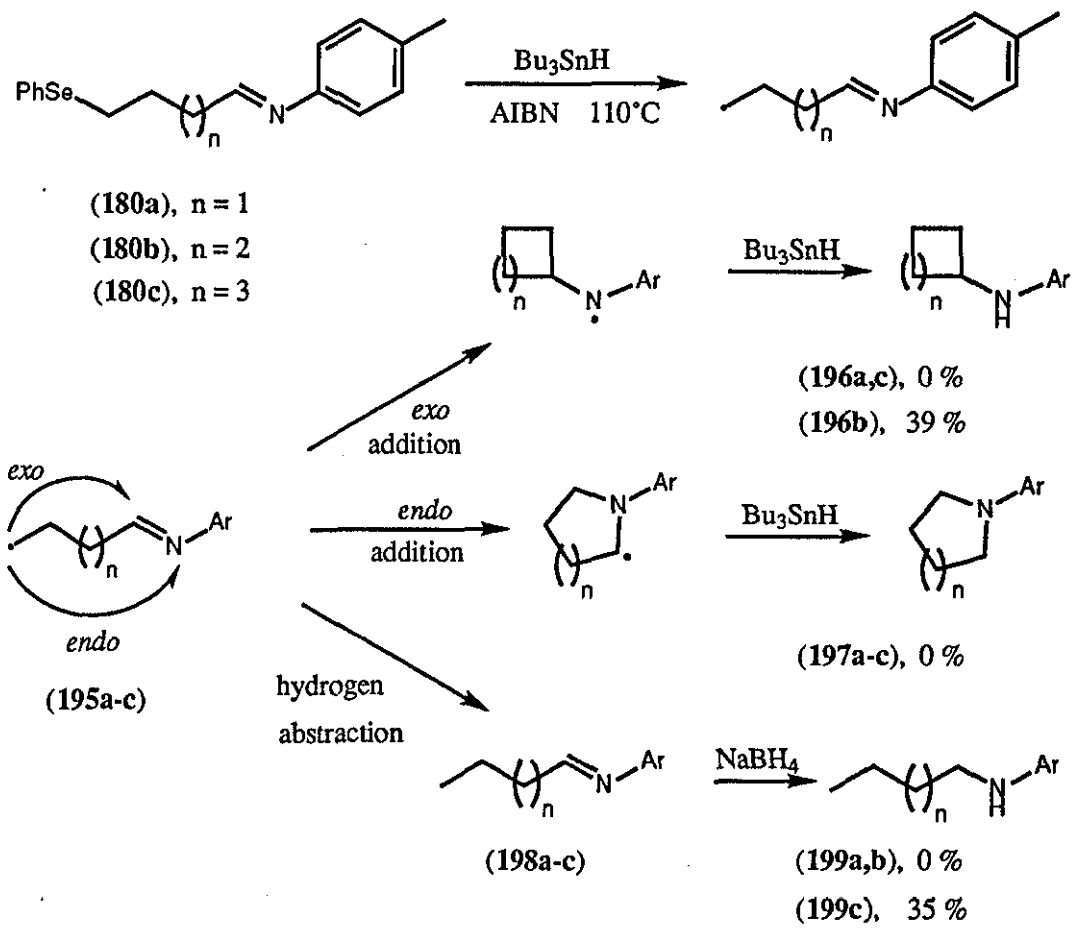
5. Cyclisation Reactions of Simple Imines.

5.1. Monocyclisation of Imines (Type I).

Free radical cyclisation reactions were undertaken according to the standard procedure (i.e. Bu_3SnH / AIBN in refluxing toluene). Toluene was used as solvent instead of the more traditional benzene which is carcinogenic and its use has been restricted under updated Health and Safety requirements. After the completion of the cyclisation an excess of solid sodium borohydride was added to reduce any uncyclised imine to the corresponding amine.

Scheme 77 shows the cyclisation reactions together with the theoretically possible products (*exo*, *endo* and acyclic).

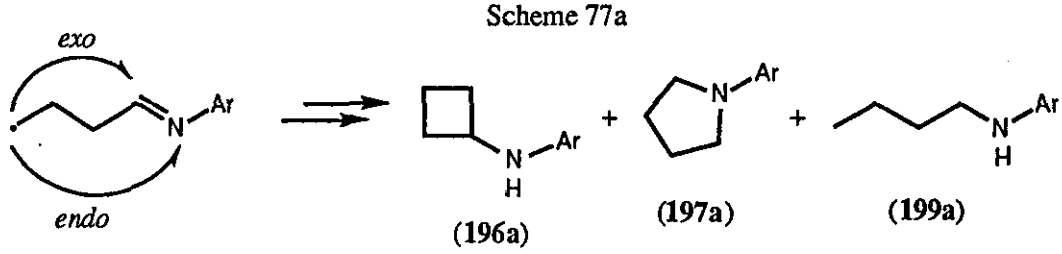
Scheme 77



The reaction conditions of the radical cyclisation reactions took time to master, especially the acid work-up. The main problems with the *N*-arylimine cyclisations were the poor yields of acid soluble products recovered from the reaction mixture. The yields of the crude amine products given in Scheme 77 were the best yields obtained in several attempts at cyclisation for each imine. Poor yields could result from the polymerisation of the anilines, once formed, under free radical conditions. The formation of red insoluble dyestuffs as by-products was evidence of substantial polymerisation. On

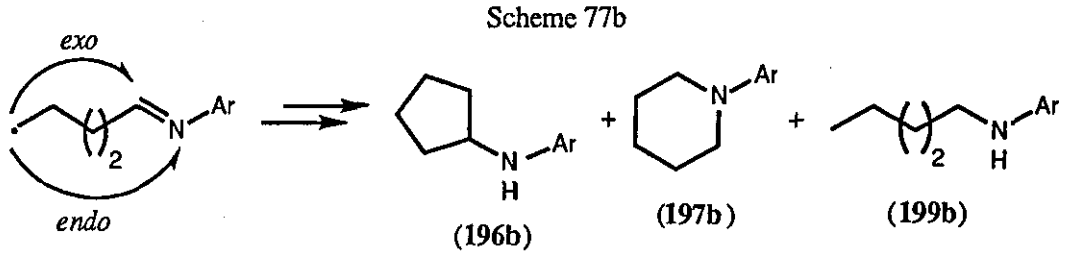
recovering the amines from the reaction mixture, a portion was set aside for GLC analysis, using authentic samples of cyclic and acyclic products as standards. The remainder was treated with acetic anhydride, and triethylamine to convert the secondary amines (**196b**) and (**199c**) to *N*-acetyl amides. The tertiary amines could then be isolated by acid extraction and the acetylated secondary amines isolated by TLC on alumina plates. Their formation was in each case confirmed by comparison of the spectroscopic data of the products with those of the authentic samples. The samples were prepared by three general methods as illustrated in Section *5.4*.

Scheme 77a



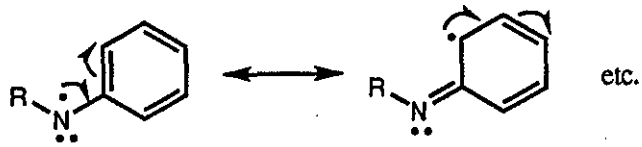
The possible products for the cyclisation of the imine (**180a**) (Scheme 77a) were the 4-*exo* product (**196a**), the 5-*endo* product (**197a**), or if cyclisation failed altogether, and after reduction of imine (**198a**), the acyclic amine (**199a**). The amine (**196a**) was not expected to be formed as it is known that the cyclobutylaminyl radical readily undergoes ring opening to yield the more stable radical (**195a**).[17a] If the amine (**196a**) were to form, it would only do so because the aryl group stabilises the cyclised radical. The likeliest reaction pathway was thought to be 5-*endo* addition forming the pyrrolidine (**197a**). Authentic samples of amines (**196a**) and (**197a**) were prepared, to verify by GLC, the absence of the 4-*exo* product and to determine the presence and yield of the 5-*endo* product. Unfortunately, analysis by GLC showed that neither of the cyclised amines were in the crude product, and ^{1}H NMR spectroscopic data showed no acyclic amine (**199a**). In fact no isolable product could be extracted from the reaction mixture and it is likely that an unknown side reaction occurred leading to a mixture of polymeric products.

Scheme 77b

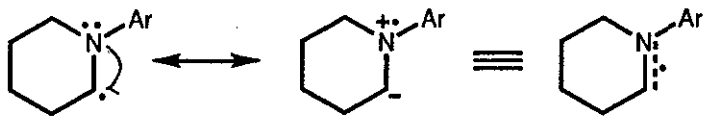


Cyclisation of imine (**180b**) (Scheme 77b) proved to be much more productive. The product expected to be formed in highest yield was the 5-*exo* adduct (**196b**), not just because of the favourable kinetics, but because the aminyl radical is stabilised by the aryl group. EPR spectroscopic studies show that in *N*-arylaminyl radicals, the unpaired

electron and not the lone pair is delocalised with the electrons of the aromatic ring and as a result, the lone pair is much more nucleophilic and the radicals more basic than the parent aniline.

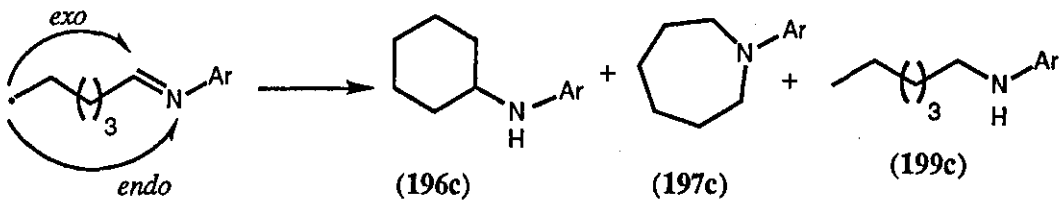


Other possible reaction pathways, expected to produce only minor products, were 6-*endo* attack onto the nitrogen and 1,5 hydrogen abstraction, favourable because of an unstrained 6-membered ring transition state. Samples of all three possible products were synthesised for GLC analysis, which when carried out on the crude product, verified that the *exo* product was indeed formed. This shows that 5-*exo* attack on the carbon of an imine proceeds in the same way as for other unsaturated systems. The 6-*endo* product (**197b**) was not present in the crude mixture despite the stabilisation of the radical so formed by the nitrogen.



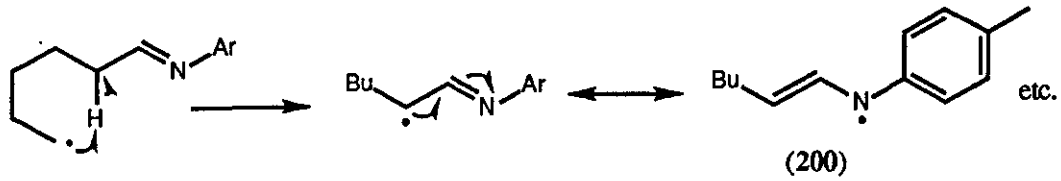
The absence of the amine (**197b**) from this reaction is probably because the nitrogen atom of this imine (**180b**) is too electron-rich for the nucleophilic carbon radical to attack, being part of a conjugated system. The strained transition state for 6-*endo* attack and the electronegativity of nitrogen are other factors that would discourage radical attack on the nitrogen of these imines. The acyclic product (**199b**) was also absent, which correlates with the 5-*exo* cyclisations onto other unsaturated systems where acyclic products are rarely formed.

Scheme 77c



The intramolecular addition to imine (**180c**) (Scheme 77c) was expected to follow a similar pattern to that of imine (**180b**). 6-*exo* Cyclisation is nearly as favourable as 5-*exo* in most unsaturated systems so the amine (**196c**) was likely to be the only product. The 7-*endo* product (**197c**) was not considered to be a possible product. Not only does entropy play a part in discouraging 7-*endo* attack, the radical would have to attack the

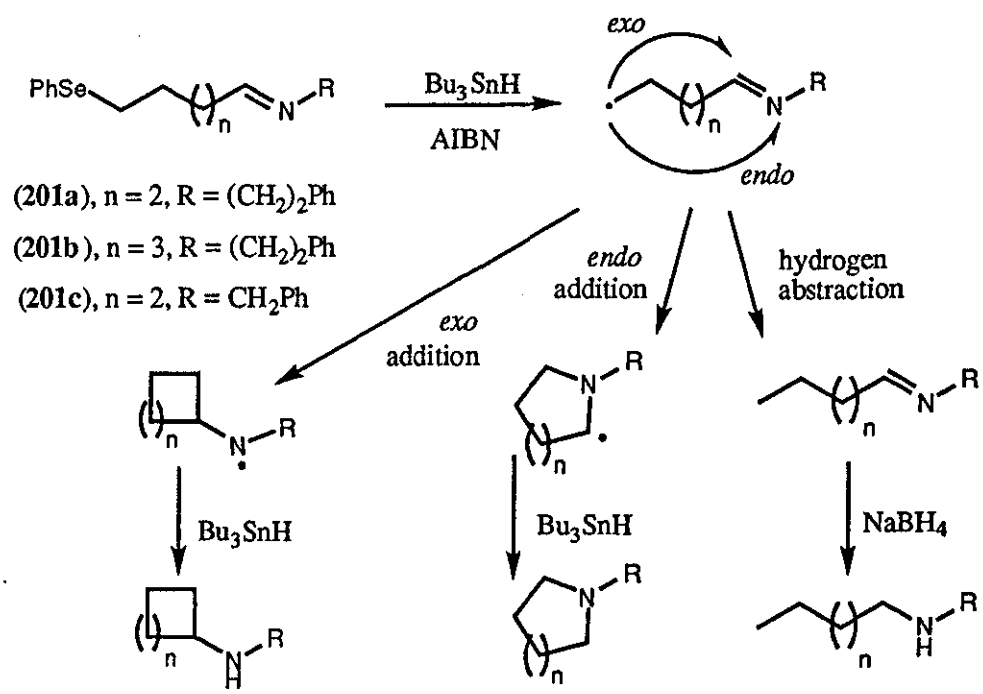
electron-rich nitrogen (which failed to occur in the much more favourable 6-*endo* situation). However abstraction of the hydrogen α to the imine group was thought to be a possible side reaction.



1,5-Hydrogen abstraction occurs via a six membered cyclic transition state and the radical (**200**) so formed is highly stabilised by delocalisation with the imine bond and with the aromatic ring. Such an abstraction would compete very favourably with cyclisation even though the latter also produces a stabilised radical. Amines (**196c**) and (**199c**) were prepared for analysis. Analysis by GLC and NMR spectroscopy both showed that the only isolable product was that arising from 1,5-hydrogen abstraction. This unusual result shows that the formation of a highly conjugated radical can override cyclisation.

Scheme 78 shows the cyclisation of aliphatic Type I imines (**201a-c**). In the cyclsation of imine (**201a**), the major product was the 5-*exo* product (**202a**) as was predicted. The 6-*endo* product (**203a**) was expected to be either absent or a minor product and its formation (5%, by GLC) was a surprise. *6-endo* Attack onto nitrogen

Scheme 78



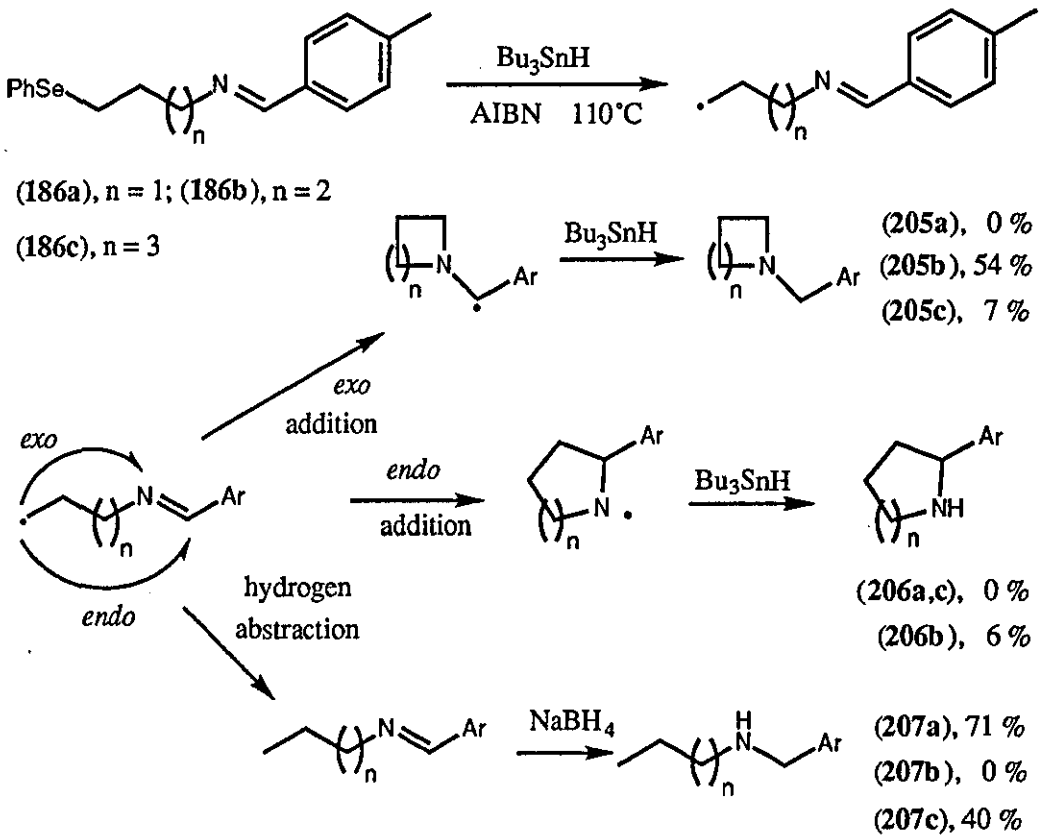
was unknown up until this experiment, even though the cyclised radical is stabilised by being α to the nitrogen. The absence of the uncyclised product (**204a**) was expected. The amines (**202a**) and (**203a**) were synthesised for analysis by GLC which confirmed the 5-*exo* adduct as the major product.

In the cyclisation of imine (**201b**), prediction of the result of the cyclisation could not be made. 1,5-Hydrogen abstraction was still a distinct possibility and the radical so formed would still be stabilised though, not to the same degree. 6-*exo* Cyclisation would produce an unstabilised aminyl radical. Both the 6-*exo* and acyclic products (**202b**) and (**204b**) were synthesised but the NMR spectroscopic data showed that the amine (**202b**) was the sole product, which was confirmed by GLC. Where there is no aromatic stabilisation for the radical formed by 1,5-hydrogen abstraction, 6-*exo* addition onto carbon is exclusively observed. The cyclisation of the *N*-benzyl imine (**201c**), carried out at a much later stage in the work, produced only the 5-*exo* product (**202c**) in one of the highest yields of cyclisation.

5.2. Cyclisation of Imines (Type II)

The cyclisation reactions of imines (**186a-c**), summarised in Scheme 79, were carried out under exactly the same conditions as for the *N*-aryl imines only this time there

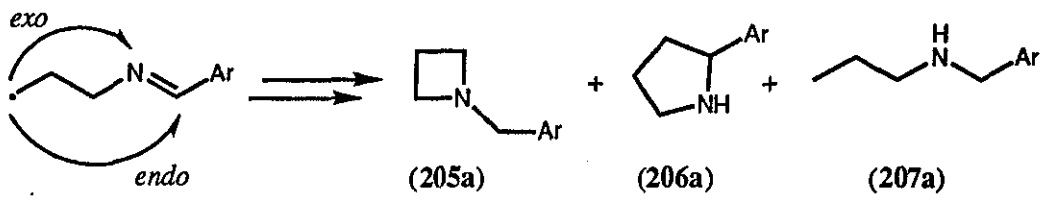
Scheme 79



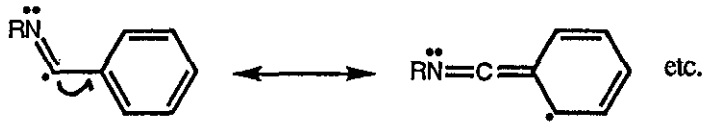
were no problems in the acid work-up. The same procedures for analysis of the crude products and the isolation of each amine (or a derivative of an amine) were the same as for the *N*-aryl imines. The yields were generally good, though each reaction was performed twice to verify unexpected results or to isolate minor products.

In the reactions of these imines *exo* addition involves the attack of a nucleophilic radical on an electron-rich nitrogen atom. For kinetic and stereochemical reasons, *exo* attack should take place. Because the imine bond is polar, attack on the imine carbon atom could be biased on electronic grounds, and thus *endo* attack could be more favoured. Warkentin[93] found that *endo* attack of aryl radicals on the carbon was favoured but for reasons much more widespread than just the polarisation of the imine bond. On the other hand *exo* attack onto an imine nitrogen, producing a stabilised benzylic radical, is the intermediate in the 1,2 shift of the imine group in Frey's work.[97] In these cyclisations the results would demonstrate to what degree *exo* attack is inhibited, *endo* attack is encouraged or whether neither is favoured.

Scheme 79a



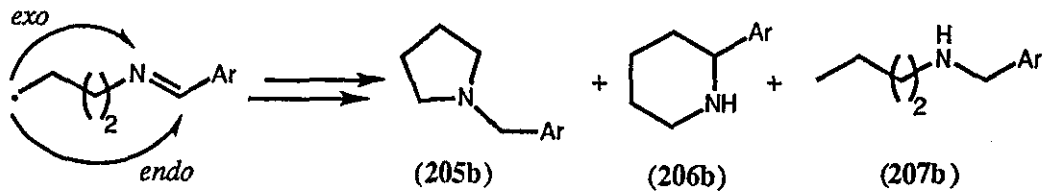
The cyclisation of imine (**186a**) (Scheme 79a) would have involved 4-*exo* attack onto the imine nitrogen. This would be very unfavourable under normal circumstances but in this example, the formation of a radical, highly stabilised by both the nitrogen atom and the benzene ring may result in the formation of the azetidine (**205a**). The formation of the 5-*endo* product (**206a**), formed by the attack onto the electrophilic carbon was considered more likely, though the addition involves a strained transition state. Though the cyclised radical is not particularly stabilised, the formation of the pyrrolidine (**206a**) could be predicted. The acyclic product (**207a**) however was the most likely product (after reduction by $NaBH_4$), formed by either intermolecular hydrogen abstraction from Bu_3SnH or intramolecular abstraction of the aldimine hydrogen, the resulting radical being stabilised by delocalisation.



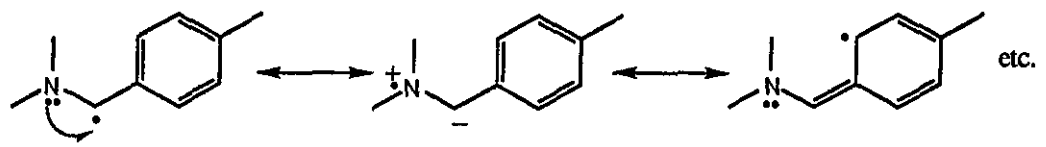
An attempt was made to synthesise amine (**206a**) for comparison purposes, but without success. The amine (**207a**) was not synthesised because an authentic sample was already available[17a] The crude ^1H NMR spectrum showed that the only product was the acyclic amine (**207a**) which was verified by GLC. The formation of the product does not

prove that it was formed by 1,5 abstraction of the aldimine hydrogen and the same product would result from 4-*exo* cyclisation followed by ring opening. The reaction does show that 5-*endo* cyclisation is not favoured despite the polarity of the imine bond.

Scheme 79b

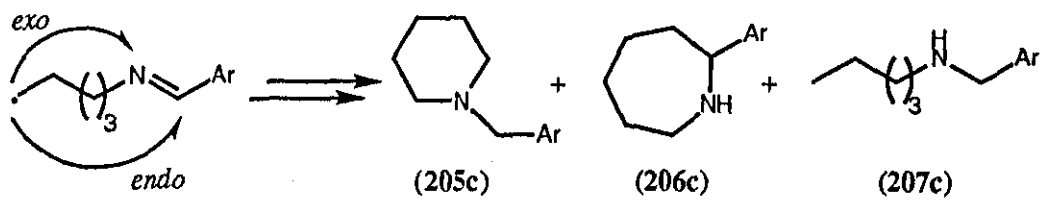


The cyclisation of imine (**186b**) (Scheme 79b) was expected to produce the 5-*exo* (**205b**), 6-*endo* (**206b**) or possibly the acyclic product (**207b**), the proportions of which were unknown before the work started. Because of the highly stabilised cyclised radical, there was a bias towards 5-*exo* cyclisation in this case:



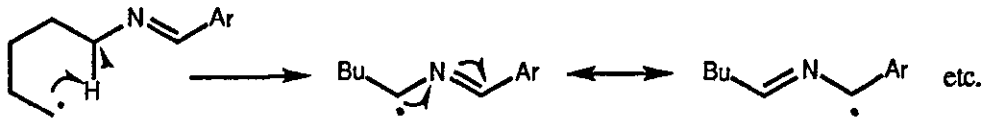
The amount of 6-*endo* adduct would show what contribution the polarisation of the imine bond plays in cyclisation. The presence of any uncyclised material would show whether both *exo* and *endo* attack were inhibited. Intramolecular hydrogen abstraction is a less favoured reaction pathway as 1,5-abstraction cannot occur. However 1,6-abstraction with the formation of a stabilised benzylic radical leading to the formation of (**207b**) was a possibility. The syntheses of amines (**205b-207b**) were undertaken for comparison purposes. Amines (**205b**) and (**207b**) were easy to prepare, whereas the synthesis of the piperidine (**206b**) was more difficult. Three different methods were tried, with success on the third attempt.[115] The cyclisation reaction yielded the 5-*exo* adduct (**205b**) as the main product, as expected. However most of the remainder was the 6-*endo* adduct (**206b**) which was isolated as its *N*-acetyl derivative in 6% yield. This result shows that 5-*exo* cyclisation onto nitrogen is favourable but it cannot be shown to what degree the formation of the stabilised radical contributes to the yield. The formation of an isolable amount of the 6-*endo* product (**206b**) shows that the polarisation of the imine bond contributed substantially to the reaction since the product

Scheme 79c



is formed despite the formation of an unstabilised radical. The absence of amine (**207b**) shows that unfavourable electronic and stereochemical conditions do not inhibit cyclisation in this case.

Cyclisation of imine (**186c**) (Scheme 79c) was thought to proceed similarly to imine (**186b**). But comparing imine (**186c**) with imine (**180c**), the radical formed by an analogous 1,5 hydrogen abstraction of imine (**186c**) is just as stabilised as that of imine (**180c**), so an acyclic product was likely to be formed:



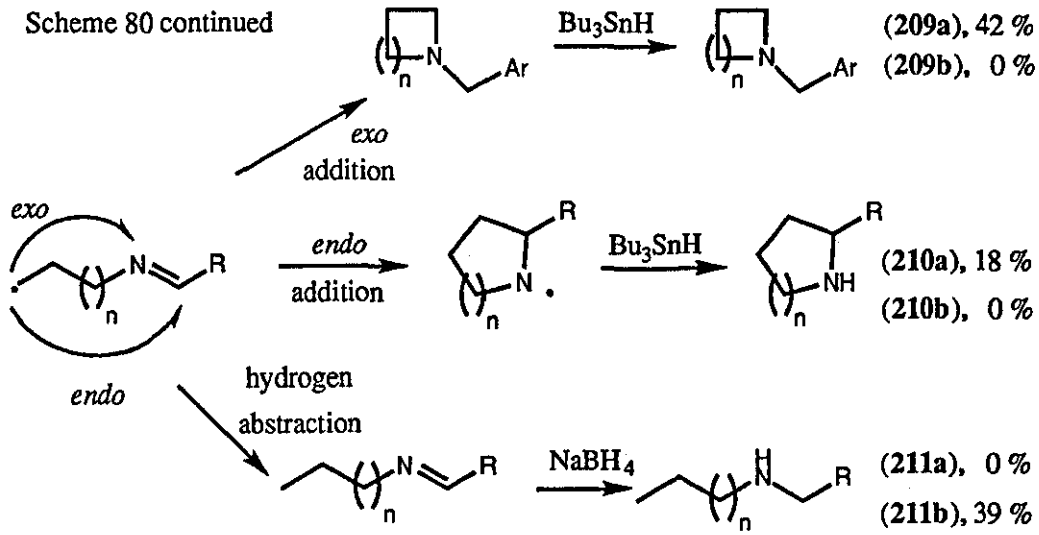
One factor in favour of 6-*exo* cyclisation is the same as for 5-*exo* cyclisation, i.e. the formation of a stabilised radical. Therefore 6-*exo* cyclisation was expected. However, the ratio of each product needed to be determined. The 7-*endo* product (**206c**) was not likely to be present in the products due to the unfavourable entropy of the transition state so no attempt was made to prepare an authentic sample for comparison. However, the amines (**205c**) and (**207c**) were prepared for the GLC analysis of the crude product. The results for this cyclisation were confusing to start with. The first reaction gave a 6-*exo* : acyclic product ratio of around 3 : 1. Repeating the cyclisation gave a ratio of around 5 : 1 in favour of the acyclic product. The third run gave the same result as the second. Owing to difficulties incurred in the work-up in the first run, the results of the latter two reactions showed the behaviour of the radicals in this cyclisation. 6-*exo* Cyclisation onto nitrogen is much more unfavourable than 5-*exo* cyclisation. Even with the formation of a stabilised radical, the 6-*exo* product was only isolated in 7% yield. As predicted, 7-*endo* cyclisation was not a viable reaction pathway. Intramolecular hydrogen abstraction is probably the major reaction pathway.

The second set of aliphatic imines are analogous to the *C*-aryl imines as 5-*exo* and 6-*exo* attack occur on the imine nitrogen (Scheme 80). Cyclisation of imine (**208a**) could have given any of the three products (**209a-211a**) and all three were prepared. 5-*exo* Addition would be favoured kinetically and stereochemically whereas 6-*endo* would be favoured electronically. In addition, 5-*exo* addition would form a stabilised radical. The uncyclised material would only form if both 5-*exo* and 6-*endo* attack were inhibited. Analysis of the crude showed that though the 5-*exo* adduct (**209a**) was the major product, it was not formed exclusively, and ca. 25% of the product was the 6-*endo* adduct (**210a**).

Scheme 80

(**208a**), n = 2; (**208b**), n = 3 R = $Ph(CH_2)_2$

Scheme 80 continued



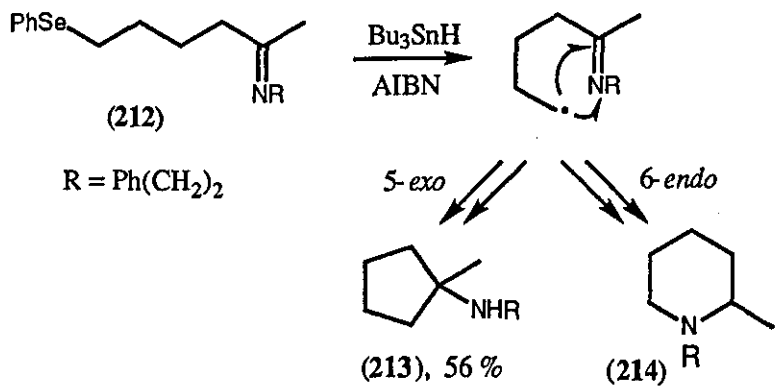
This shows that there is a substantial, though not overwhelming, contribution to the outcome of the cyclisation by the polarisation of the C=N bond.

In the cyclisation of imine (**208b**), 6-*exo* addition onto the imine nitrogen and intramolecular hydrogen abstraction both result in the formation of stabilised radicals and a mixture of reaction products were expected and both amines (**209b**) and (**211b**) were prepared for comparison purposes. However no evidence for the presence of 6-*exo* product (**209b**) was found by NMR spectroscopy or by GLC, the sole product being the acyclic amine (**211b**). This shows that 6-*exo* attack onto nitrogen is highly unfavoured and with 7-*endo* attack also unfavoured, the only reaction possible was abstraction.

5.3. Cyclisation of Ketimines.

The cyclisation reactions of aliphatic ketimines introduces another factor influencing the cyclisation reactions - steric hindrance. In the cyclisation of the ketimine (**212**), a Type I imine, formed by condensing ketone (**191**) with 2-phenylethylamine (Scheme 81), the 5-*exo* position is hindered from attack by the methyl group. (In analogous reactions of alkenes, 5-*exo* cyclisation is impeded and a larger proportion of 6-*endo* adducts are formed.) For this reaction a mixture of the 5-*exo* adduct (**213**) and the

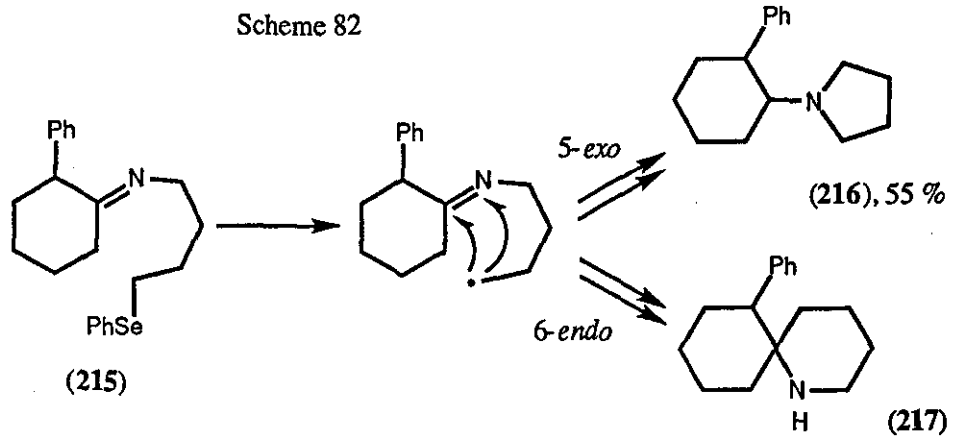
Scheme 81



6-*endo* adduct (**214**) was predicted. However only the amine (**213**) was isolated from the reaction mixture with only traces of the amine (**214**). Thus the imine carbon is thus sufficiently electropositive for the radical to add, despite the relatively unfavourable steric environment.

For the cyclisation of Type II ketimines (Schemes 82 and 83), 5-*exo* addition onto the imine nitrogen was predicted to be largely unaffected by steric hindrance around the imine carbon, but 6-*endo* addition would be reduced or eliminated. This was found to be

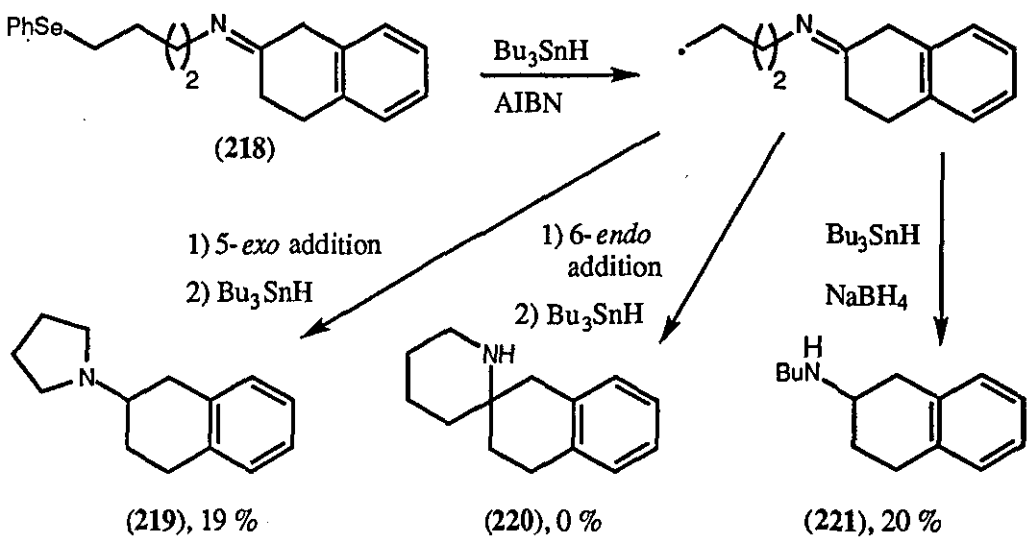
Scheme 82



the case for the cyclisation of the imine (**215**) (Scheme 82). The only product isolated from the cyclisation was the 5-*exo* product (**216**) and the spirocyclic amine (**217**) was not produced.

A different result was obtained for the cyclisation of the imine (**218**), where the 5-*exo* adduct (**219**) was isolated together with the uncyclised amine (**221**) in roughly equal proportions, and again the 6-*endo* adduct (**220**) was not formed.

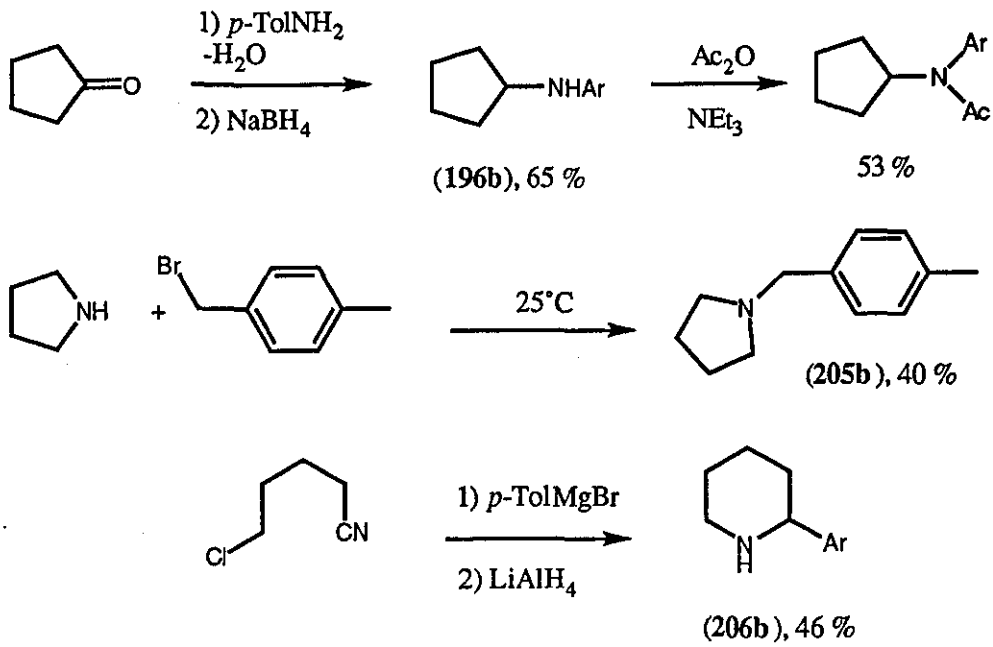
Scheme 83



5.4. Preparation of Authentic Products for Comparison Purposes.

The general procedure employed was the reaction between an amine and an appropriate halogen substituted compound. Some reactions proceeded well, e.g. the reaction between pyrrolidine and *p*-methylbenzyl bromide to form amine (**205b**) which occurred at room temperature. Other reactions required more rigorous conditions, e.g. *n*-pentyl bromide and *p*-toluidine required refluxing for 3 days in toluene and only 6% yield of the amine (**199b**) was obtained. The reaction between cyclopentyl bromide and *p*-toluidine failed altogether. A second method was adopted, that is to start with a carbonyl compound, form an imine either by molecular sieves or by using a Dean-Stark water separator, and reduce with sodium borohydride. This method was found to be suitable for the preparation of amines such as amine (**196b**). For amines such as the 2-arylpiperidine (**206b**), a completely different strategy was required. The addition of a Grignard reagent to an imine failed as did reduction of a pyridinium salt. The addition of a Grignard reagent to a ω-chloronitrile with reduction of the intermediate imine proved to be a success. Scheme 84 shows one example of each synthesis. Many of the secondary amines were acetylated to enable direct comparison with the acetylated products of the cyclisation reactions.

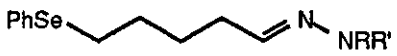
Scheme 84



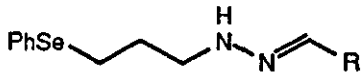
6. Additional Monocyclisation Reactions of Imines and Hydrazones

6.1. Cyclisation Reactions of Hydrazones.

Up until Fallis[92] published his studies on the cyclisation reactions of simple hydrazones in the spring of 1994 (see Section *3.3.2*), little information was available on this important class of compounds, which was surprising as the reactions of oxime ethers were becoming well known. In parallel with the early studies of imines, cyclisation reactions of a range of hydrazones were investigated.[108] As with the imines, two types of hydrazone were reacted. The Type I hydrazones were generated in good yield by condensing the ω-benzeneselenyl aldehydes (**179b,c**) with a variety of different hydrazines. One example of a Type II hydrazone was synthesised (see Scheme 88). The advantage of studying hydrazones over imines is that they are stable and can be isolated and purified before cyclisation. Though hydrazones are much less reactive than imines towards reduction or hydrolysis, the reactivity of the hydrazone bond towards radical attack was not known at the start of the studies.



Type I Hydrazone

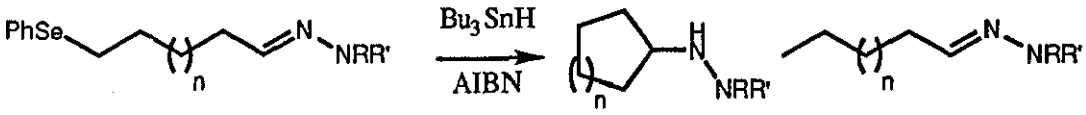


Type II Hydrazone

6.1.1. Reactions of Type I Hydrazones.

Scheme 85 shows the reactions of the hydrazones that were investigated. The most successful reactions were 5-*exo* cyclisations of the *N*-acyl hydrazones (**222c,d**). The reactions of the *N*-aryl hydrazones presented problems especially during work up. The reaction of the hydrazone (**222a**) required six attempts and 18% of the 5-*exo* product (**223a**) was the maximum yield obtained, the remainder being largely polymeric material. The yield of 32% for the cyclisation of the *N,N*-diphenyl-hydrazone (**222b**) demonstrated a significant improvement, but Fallis reported yields of over 75% for similar cyclisations.

Scheme 85



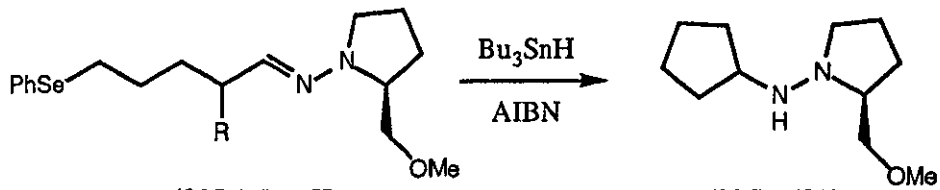
(**222a**) R = H, R' = Ph, n = 1	(**223a**), 18 %	(**224a-d**), 0 %
(**222b**) R = R' = Ph, n = 1	(**223b**), 32 %	(**224e**), 20 %
(**222c**) R = H, R' = COPh, n = 1	(**223c**), 50 %	(**224f**), 46 %
(**222d**) R = H, R' = $CONH_2$, n = 1	(**223d**), 60 %	
(**222e**) R = R' = Ph, n = 2	(**223e**), 0 %	
(**222f**) R = H, R' = COPh, n = 2	(**223f**), 0 %	

For the cyclisations of hydrazones (**222a-d**), no acyclic hydrazone products (**224a-d**) could be isolated. Attempts at 6-*exo* addition onto the hydrazone carbon failed to yield cyclised products, and instead low yields of acyclic hydrazones (**224e,f**) were produced. Fallis achieved yields of cyclised materials in yields comparable to the 5-*exo* reactions.

6.1.2. Attempts at Stereoselective Cyclisation.

In order to study the possible stereoselectivity of cyclisation of hydrazones, initial studies were carried out using a hydrazone synthesised from *S*-*N*-amino-2-(methoxymethyl)pyrrolidine (SAMP) and 5-benzeneselenylpentanal (**179b**) (Scheme 86). Cyclisation of the hydrazone (**225a**) gave a reasonable yield (42%) of the corresponding cyclised hydrazine (**226**)

Scheme 86



(**225a**), R = H

(**225b**), R = Me

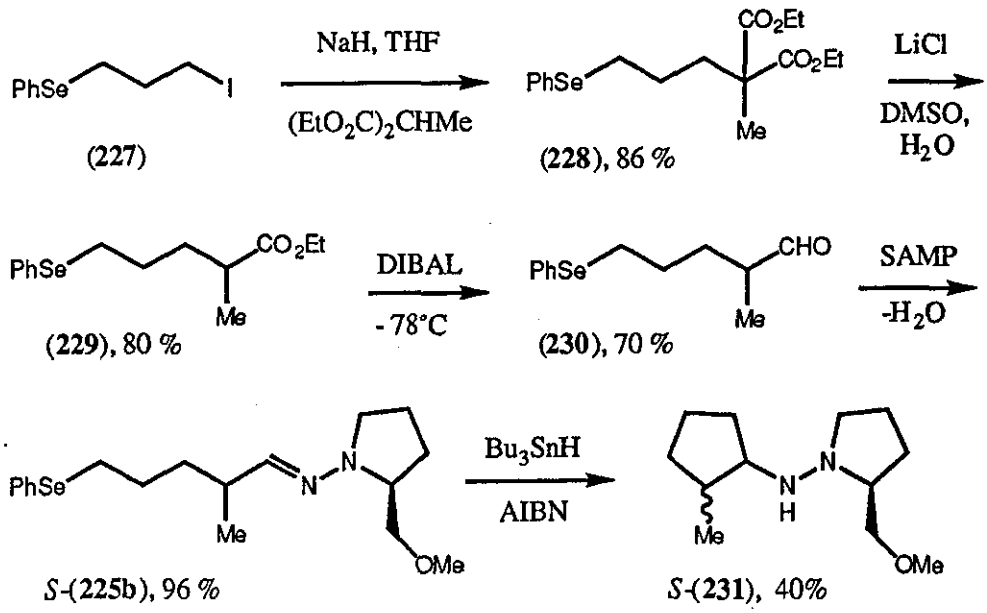
(**226**), 42%

The hydrazone (**225b**) was also prepared with a methyl substituent on the alkyl sidechain. With an extra asymmetric centre, the stereo-inductive effect of the enantiomerically pure chiral centre on the pyrrolidine ring could be determined.

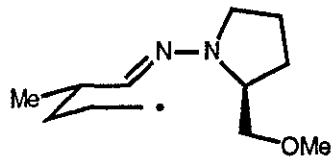
The synthetic sequence that was developed to prepare the hydrazone (**225b**) is shown in Scheme 87. This parallels the formation of the ketone (**191**) (Scheme 75), though conditions for some of the steps had to be changed accordingly. In the first step, the anion of diethyl methylmalonate could not be alkylated using 1-benzeneselenyl-3-chloropropane (**189**), but 1-benzeneselenyl-3-iodopropane (**227**), formed quantitatively from a Finklestein reaction, reacted efficiently yielding the diester (**228**). The second step required a change of solvent as hydrolytic decarboxylation was not achievable using DMF. The switch to DMSO presented a step into the unknown as the reactivity of the oxidatively sensitive PhSe group in DMSO at 170 °C was not known. The clean cleavage of one of the ester groups with the PhSe group intact was a pleasant surprise and enabled the synthetic sequence to continue as planned.

The reduction of the ester (**229**) with DIBAL and condensation of the aldehyde (**230**) with SAMP yielded the diastereomeric hydrazone (**225b**). The analogous *R*-hydrazone was also prepared by condensing the aldehyde (**230**) with *R*-*N*-amino-2-(methoxymethyl)pyrrolidine (RAMP). Both hydrazones were cyclised under standard conditions.

Scheme 87



Diastereoselective cyclisations were predicted to occur because of the arrangement of substituents on the carbon chain in the 5-*exo* transition state,[10b] i.e. substituents are arranged in the equatorial position:



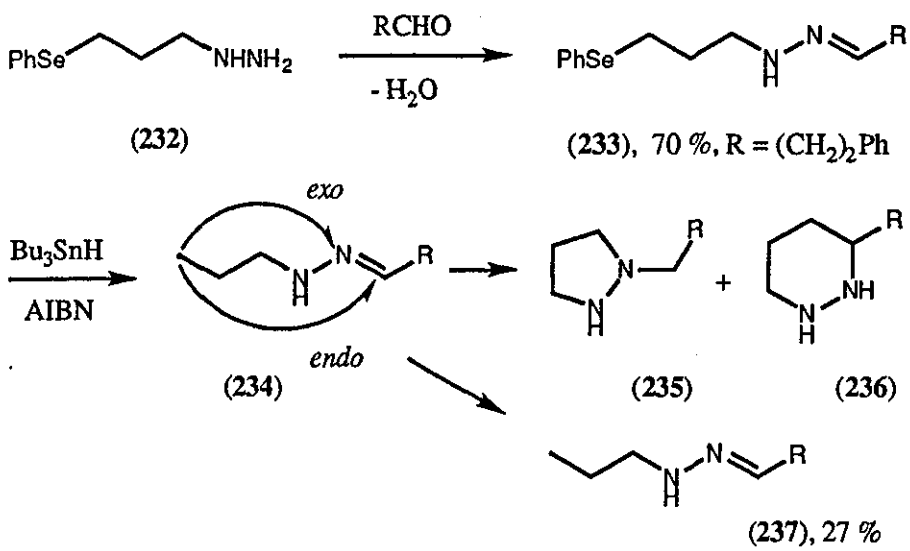
Though cyclisation of the hydrazones *S*-(**225b**) gave reasonable yields of 5-*exo* adduct *S*-(**231**), no diastereomeric excess in the product was observed by ^{1}H NMR spectroscopy. The reaction (**225b**) to (**231**) was carried out using the enantiomer of SAMP (RAMP), and a similar yield of the hydrazine *R*-(**231**) was achieved (39%), but no observed diastereomeric excess. The reason for this could be that the chiral centre is too far from the radical to influence attack on the hydrazone bond.

Attempts were made to deprotonate at the α position of both the hydrazone (**225a**), and the enantiomeric RAMP hydrazone using LDA and quenching with methyl iodide thus forming one pair of diastereomers of hydrazone (**225b**). The purpose of this work was to cyclise the hydrazones in the presence of a metal salt (e.g. a lithium halide) to bring about diastereoselective addition. Unfortunately, the alkylations failed, despite many attempts. At around the same time, Hatem's addition of alkenyl radicals to a SAMP hydrazone (see Scheme 54) was published, with a reported diastereomeric excess of 50%. At this stage attempts at diastereoselective cyclisation using SAMP and RAMP were discontinued.

6.1.2. Attempted Cyclisation of a Type II Hydrazone.

To complete the hydrazone work, attempts were made to cyclise radicals onto a Type II hydrazone (Scheme 88). Reactions of this type have not been reported among the radical cyclisations of the analogous oxime ethers. The aim was to test whether the philicity of the C=N bond would bias the reaction towards 6-*endo* attack, or whether stereoelectronic control would bring about attack on the imine nitrogen. The hydrazine (**232**), prepared from 1-benzeneselenyl-3-iodopropane (**226**) and an excess of hydrazine, was condensed with 3-phenylpropanal. The cyclisation of the hydrazone (**233**), was predicted to form the pyrazolidine (**235**) or the saturated pyridazine (**236**). Unfortunately the radical (**234**) failed to cyclised each of the three times, the reaction was attempted, the hydrazone (**237**) being the only isolable product. The reason for the failure to cyclise could be that the 6-*endo* attack is restricted by the rigidity of the C=N-N linkage of the hydrazone and 5-*exo* attack is limited by the high electron density around the imine nitrogen.

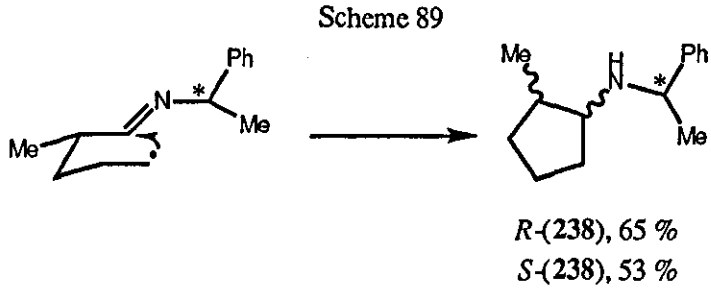
Scheme 88



6.2. Stereoselective Cyclisation of Imines.

Following the unsuccessful attempts at stereoselective cyclisaion of the SAMP and RAMP hydrazones (Scheme 87), attention was drawn to similar studies of imines bearing a homochiral group. The imines were prepared from the aldehyde (**229**) and both *R*- and *S*-α-methylbenzylamine. 5-*exo* Cyclisations were achieved giving high yields of 5-*exo*

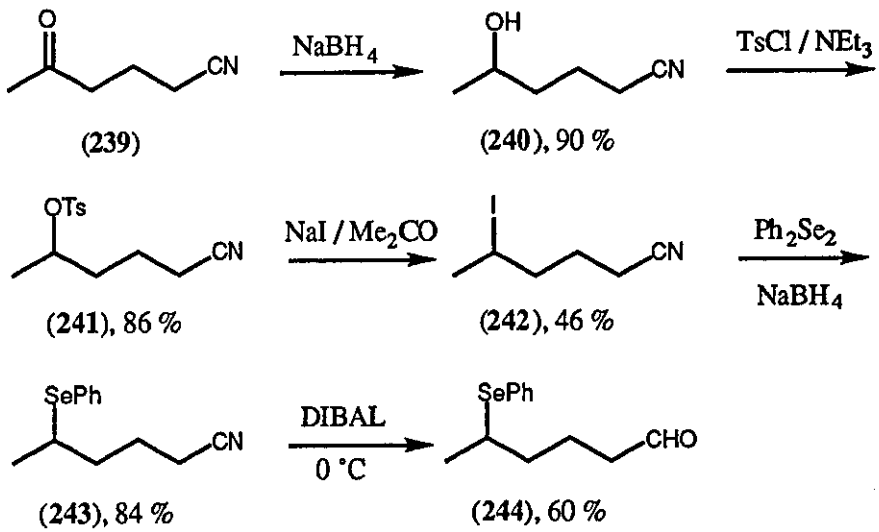
Scheme 89



products (238), but again no diastereoselectivity was observed by ^{1}H NMR spectroscopy (Scheme 89).

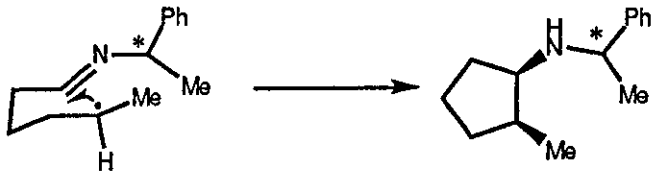
Though, the chiral centre is now much closer to the imine bond, the 2-methyl substituent does not sufficiently influence stereoselective addition of the radical. To overcome this, a bulky group could replace the methyl group in the alkyl chain or a more bulky chiral auxiliary could be used. Another alternative explored involved a cyclisation where a new asymmetric centre was formed at the point of the radical attack, i.e. a prochiral radical. Scheme 90 shows the steps required to form the aldehyde (244).

Scheme 90



The aldehyde (244) was condensed with *R*- and *S*-α-methylbenzylamine and the imines cyclised (Scheme 91). The secondary radical (245) adds to the imine with the stereochemistry shown,[10b] and from ^{1}H NMR spectroscopy, diastereomeric excesses of up to 44% were observed in the 5-*exo* products (246). These were predicted to be of 1,2-*cis* stereochemistry, but this could not be confirmed.

Scheme 91



(245)

R-(246), 51 %, 29 % d.e.

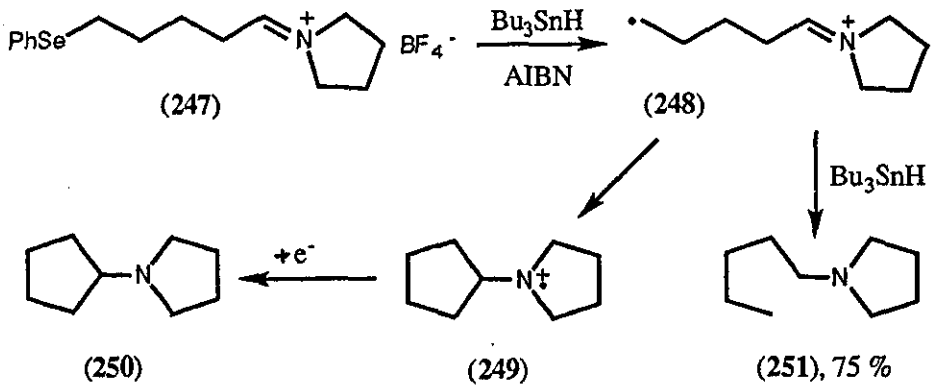
S-(246), 55 %, 44 % d.e.

Though the level of diastereoselectivity is relatively low, the use of other substituents or other chiral auxiliaries could improve the situation. Work is underway to cyclise imines of a range of α-aminoacids.

6.3. Reactions of Iminium Salts.

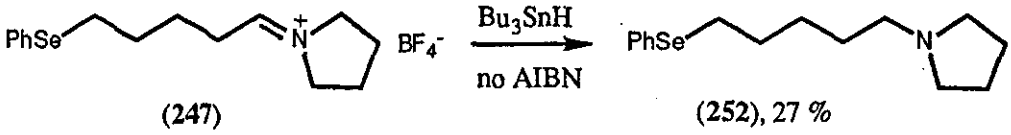
The original research plan involved the radical cyclisation onto both imines and iminium salts. This section deals with the few reactions carried out on the latter, which proved not to be a success. Scheme 92 illustrates a simple reaction where iminium salt (**247**) was subjected to standard radical reaction conditions. The salt was formed from 5-benzeneselenylpentanal (**179b**) and pyrrolidine in the presence of HBF_4, thus providing an inert counter-ion. The radical (**248**) was predicted to cyclise to form the bicyclic amine (**250**) after electron transfer of the intermediate radical cation (**249**). Instead *N*-pentylpyrrolidine (**251**) was formed (isolated as the hydrochloride salt) resulting from (i) the addition of a hydride ion to the highly electrophilic iminium carbon, and (ii) the normal free radical reaction of the benzeneselenyl group.

Scheme 92



In a control reaction in which AIBN was omitted, the ionic reaction was confirmed (Scheme 93), where amine (**252**) was isolated, together with a white precipitate of Bu_3SnF. Bu_3SnH is known to react as a weak hydride, as the Bu_3Sn^+ cation is relatively stabilised. The alternative radical reagent tris(trimethylsilyl)silane (TTSS) is not normally associated with the donation of H^- and a reaction of iminium salt (**248**) was carried out using TTSS. However the same salt (**251**) was isolated in almost the same yield (68%). This last result shows that the iminium ion is very reactive towards any reagent remotely capable of donating a hydride ion, or that another reaction pathway is involved in the formation of the observed product.

Scheme 93



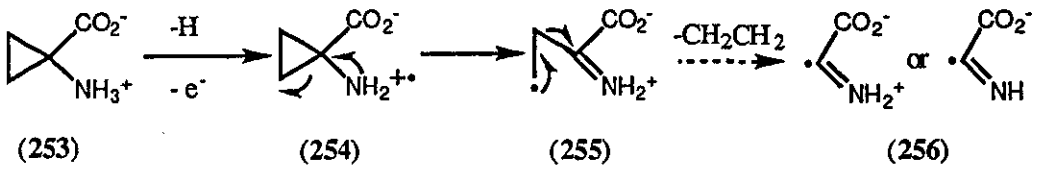
The initial studies of aliphatic iminium salts show that they are too reactive to be subject to standard free radical conditions and a decision was made to postpone these studies because the imine cyclisations were proceeding to plan. The reactions of the

iminium salts could be successful if another method of generating radicals without using Bu_3SnH were employed, e.g. transition metal salts.

6.4. Ethylene Biosynthesis Investigation.

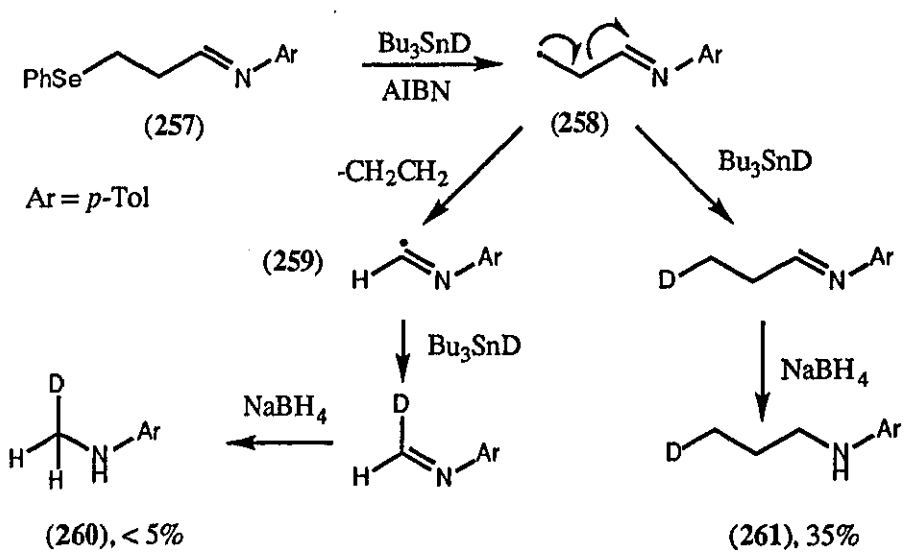
The biosynthesis of ethylene and the role of the gas in the ripening of fruit has been subject to much studies,[115] and 1-aminocyclopropane-1-carboxylic acid (**253**) has been identified as the ethylene precursor.[116] However the mechanism whereby amino acid (**253**) decomposes with the liberation of ethylene has been the subject of much study, and no satisfactory mechanism has yet been proposed. Pirrung and co-workers proposed the radical (**254**) as a species involved in the mechanism, with the facile opening of the three membered ring, yielding the acyclic iminium radical (**255**).[117] The mechanism by which the radical (**255**) decomposes to generate ethylene is not well understood, though it is possible that it involves simple β-elimination of ethylene from the radical (**255**). This reaction could occur because the resulting radical (**256**) is stabilised (see Scheme 94).

Scheme 94



In order to assess whether the radical (**255**) could decompose in this manner, a decision was made to synthesise imines, which on reaction with Bu_3SnH yield radicals analogous to (**255**), thus mimicking the postulated mechanism for the liberation of ethylene. A simple imine (**257**) was synthesised and reacted as illustrated in Scheme 95, first using Bu_3SnH an subsequently using Bu_3SnD. The radical (**258**) could abstract

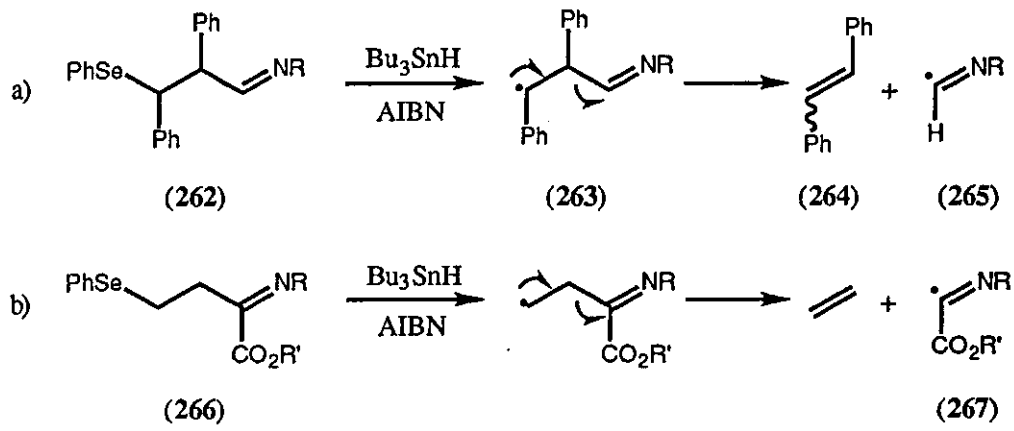
Scheme 95



hydrogen to yield the amine (**261**) after reduction of the intermediate imine with sodium borohydride and was predicted to be the major reaction pathway. The alternative minor pathway was to eliminate ethylene, the driving force being the formation of the stabilised radical (**259**). From the initial results, ^{1}H and ^{13}C NMR spectroscopic evidence indicated that the amine (**260**) was formed as a trace product (ca. 5% yield), by the singlets at δ 2.90 and 31.60 ppm respectively. As predicted, the amine (**261**) was isolated as the major product (35%). However the two products could not be separated and the formation of the minor product (**260**) could not be confirmed by GC-MS analysis. A total of six attempts were made to verify the formation of the amine (**260**). Another reaction was considered but not carried out - the cyclisation of the imine (**257**) in a closed system with any liberated ethylene detected by FT infra-red spectroscopy. At this point, the investigations into ethylene biosynthesis was postponed because of time pressures.

Scheme 96 shows two reaction pathways which were considered to shed more light on the undetermined last stage of the ethylene biosynthesis reaction. In the first, the radical (**263**) formed by the reaction of the imine (**262**) would fragment giving stilbene (**264**) and the stabilised radical (**265**), the reaction thus producing an easily isolable alkene by-product. The second reaction of the dehydroaminoacid ester (**266**) was considered to be a close mimic of the biological reaction and would liberate ethylene, producing the radical (**267**), which after hydrogen abstraction would be ultimately isolated as an amino-acid derivative.

Scheme 96



6.5. Summary of the Results of the Monocyclisation Reactions.

These studies have shown that imines undergo free radical cyclisation and a variety of monocyclic compounds including heterocycles have been synthesised by this method. The reactions are on the whole analogous to cyclisation onto other unsaturated bonds, though the polarisation of the C=N bond does contribute to the regiochemistry in some cases. The results of the cyclisations are summarised as follows:

i) 4-*exo* and 5-*endo* Cyclisation are both unfavoured whether attack is on the nitrogen or on the carbon.

ii) 5-*exo* Cyclisation onto both carbon and nitrogen is highly favoured for both imines and 5-*exo* cyclisation onto the carbon of hydrazones and proceed with some degree of diastereoselectively depending on the substituents around the imine bond.

iii) 6-*endo* Cyclisation onto carbon competes favourably with 5-*exo* cyclisation onto nitrogen and substantial amounts of 6-*endo* products are produced. 6-*endo* Cyclisation onto nitrogen has been shown to occur but only on relatively electron deficient imines.

iv) 6-*exo* Cyclisation onto carbon competes with 1,5-hydrogen abstraction, the latter prevailing if the uncyclised radical is highly stabilised - in the case of the *N*-aryl imines and hydrazones. 6-*exo* Cyclisation prevails in the absence of such stabilisation.

v) 6-*exo* Cyclisation onto nitrogen is unfavoured and the cyclised product only forms as a minor product if the cyclised radical is stabilised.

vi) Radical cyclisation of sterically hindered imines proceed well in the cases studied. 5-*exo* Cyclisation onto the carbon and nitrogen of ketimines yield good yields of cyclised products, though 6-*endo* cyclisation has not been shown to occur.

7. Tandem Cyclisation Reactions - 1.

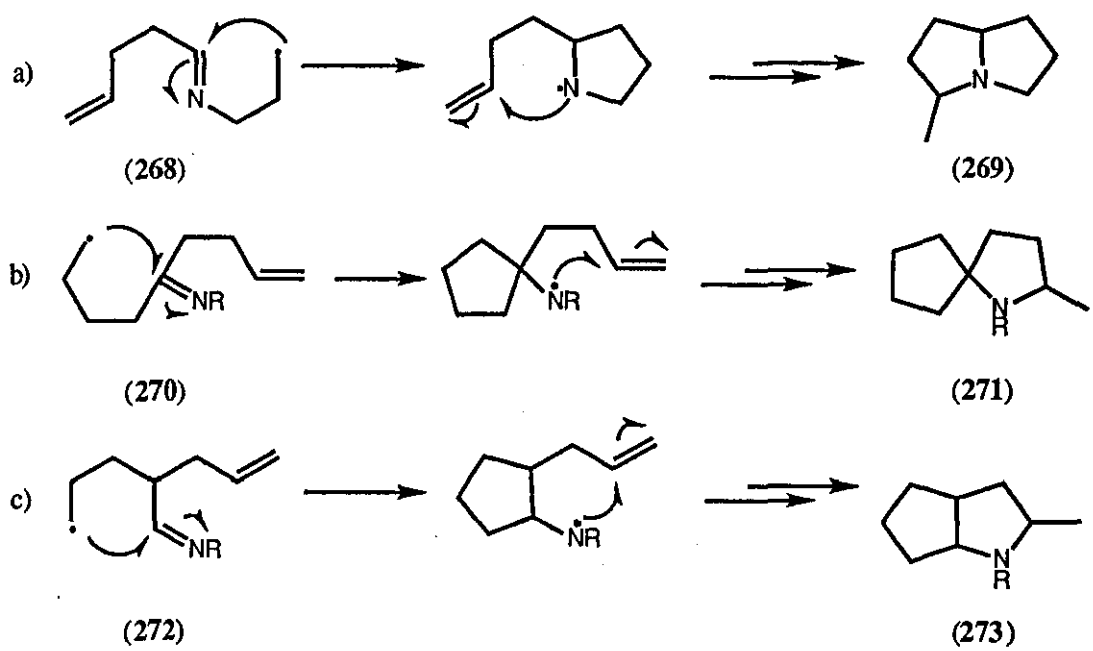
7.1. Introduction.

Following the successful reactions of simple imines,[108] the next stage of the research was to utilise the pattern of regioselectivity determined during the monocyclisation work to synthesise polycyclic heterocycles by tandem or cascade cyclisation.[119] In these tandem reactions, the intermediate aminyl radical, generated by the cyclisation of the carbon-centred radical onto the imine, is predicted to cyclise onto a suitably placed alkene. The cyclisation of aminyl radicals has been extensively studied in the group,[17] and also by Newcomb.[16]

There were several ring systems that were target molecules in tandem reactions as illustrated in scheme 97. The first example was the reaction of radicals analogous to (**268**) cyclising first by 5- (or 6-)*endo* addition onto C=N, followed by 5-*exo* addition onto the alkene, yielding the pyrrolizidine (or indolizidine) ring system (**269**). Cyclisations of this type are further discussed in Section *7.3*.

The second and third examples show different imine precursors, which on reaction with Bu_3SnH give radicals (**270**) and (**272**), cyclising by successive 5-*exo* addition yielding bicyclic heterocycles (**271**) and (**273**). The reactions leading to the formation of spirocyclic amines such as (**271**) are covered in Chapter 8. In Chapter 9, the reactions leading to bicyclic heterocycles such as (**273**) are discussed.

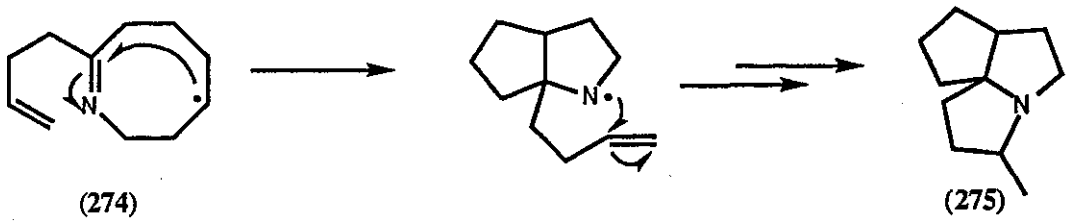
Scheme 97



The synthesis of other polycyclic systems were also briefly considered, for example the cyclisation of the cyclic imine (**274**) (Scheme 98) leading to the interesting angular

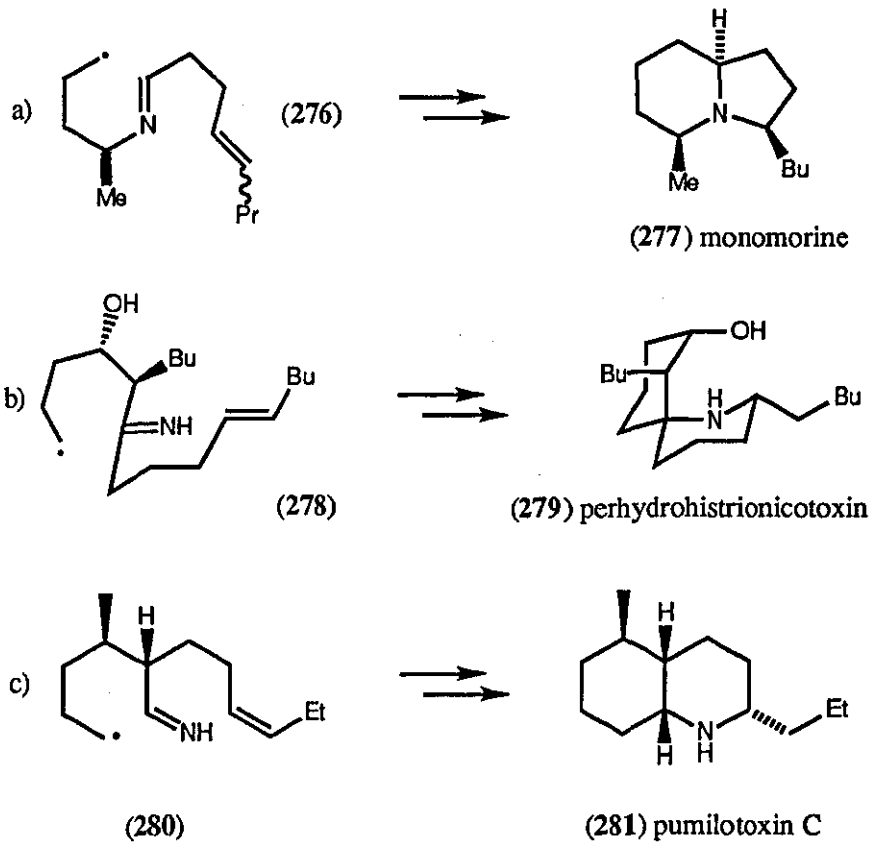
triquinane derivative (**275**), but as the work progressed, there was not enough time to explore all the possible structures that were considered to be potential synthetic targets.

Scheme 98



Many saturated heterocyclic systems are found in a variety of natural products notably alkaloids. The ultimate aim of the research was to develop strategies leading to the synthesis of some natural products. Scheme 99 shows some of the compounds that in theory are accessible via radical cyclisation onto imines. Syntheses of these natural products were planned as part of the work.

Scheme 99

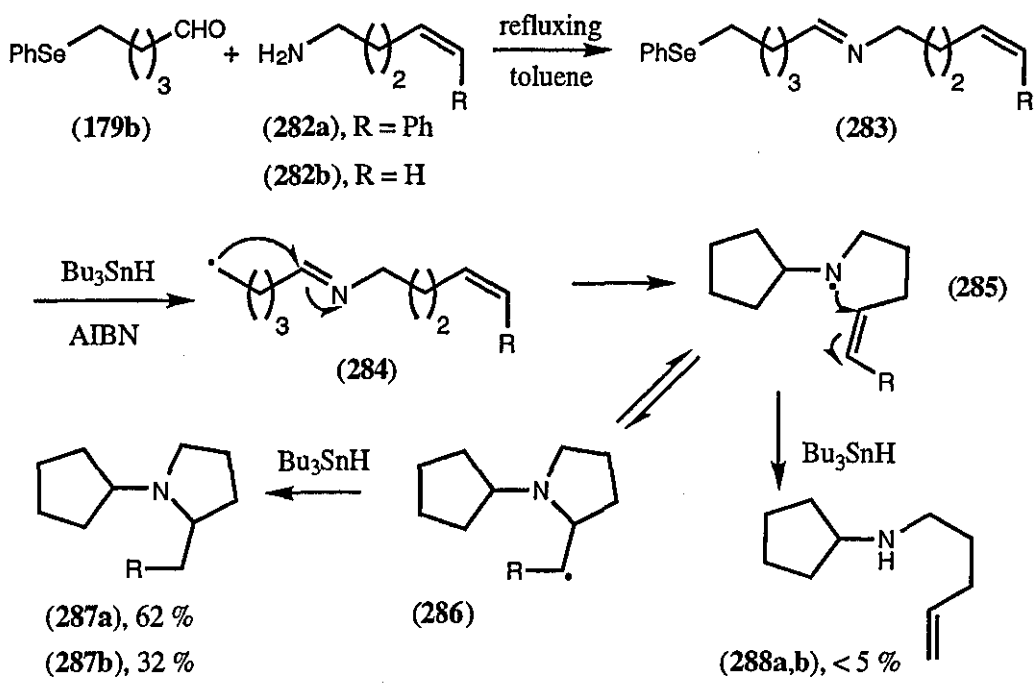


7.2. The Synthetic Potential of the Tandem Reaction.

To determine the potential utility of the tandem reactions, imines were synthesised and cyclised as shown in Scheme 100. These reactions provided a useful bridge between the monocyclisations already discussed and the more complex reactions illustrated in Scheme 97. The starting materials for the imines (**283a,b**), were readily obtained by

simple procedures. The aldehyde (**179b**) was condensed in turn with 5-phenyl-4-pentenylamine (**282a**) and 4-pentenylamine (**282b**). The former was prepared by the reduction of 5-phenyl-4-pentenonitrile[17] using lithium aluminium hydride. Two methods were explored to synthesise 4-pentenylamine (**282b**) and a yield of 39% of the amine hydrochloride was isolated from the reaction of hydrazine and *N*-(4-pentenyl)-phthalimide. The imines (**283a,b**) were generated and reacted in what was at this stage a standard 'one-pot' procedure. The radical (**284**) cyclised by 5-*exo* addition onto the imine, as predicted from the monocyclisation studies forming the aminyl radical (**285**) which cyclised again by 5-*exo* addition, producing the bicyclic amines (**287**) as the only isolable products, with only trace amounts of monocyclised products. For the reaction of the imine (**283a**), the latter step was predicted by studies carried out by other members of the research group.[17] The phenyl group on the alkene stabilises the radical (**286a**) formed by the addition of the radical (**285a**) to the alkene bond, and prevents the reverse reaction from taking place. As a result little monocyclic product (**288a**) was observed. For this cyclisation the yield of 62% for the formation of the bicyclic product was one of the highest yields achieved for a tandem reaction in these studies. This was the first tandem reaction carried out and demonstrated the potential of these cyclisations.

Scheme 100



For the cyclisation of the imine (**283b**) there is no stabilisation of the bicyclic radical (**286b**), and under such circumstances the second cyclisation [(**285b**) to (**286b**)] would be be predicted to reversible,[16,17] and the production of the monocyclic amine (**288b**) would be observed. However only trace amounts of amine (**288b**) were detected by ^{1}H NMR spectroscopy and the bicyclic amine (**287b**) was the only product isolated in 32% yield (as the hydrochloride salt). This surprising result does illustrate that the

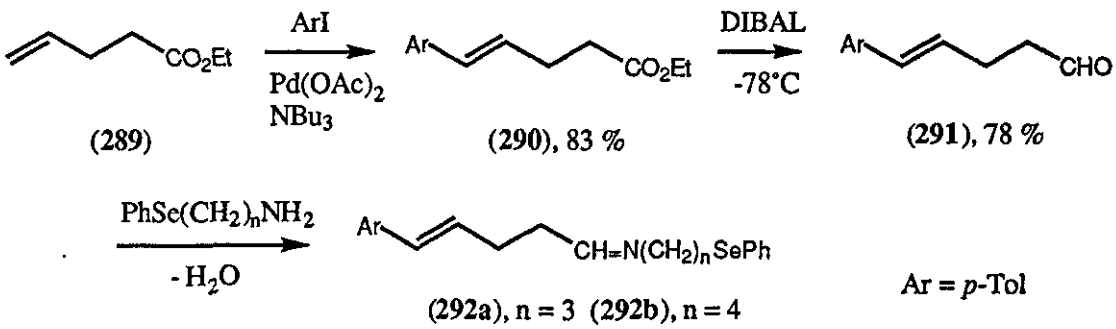
tandem cyclisation of an imine does occur even when the intermediate aminyl radical adds to an unsubstituted double bond. Because the structures of the amines (**287a,b**) are not found in any known natural product, these two reactions are not very useful synthetically. However these two results constitute major steps forward in the development of the synthetic strategies for other bicyclic systems, including the target natural products.

7.3. Synthesis of Pyrrolizidines and Indolizidines.

The tandem cyclisation illustrated in Scheme 97(a) was the first of such reactions to be studied in detail, with the aim of synthesising derivatives of the bicyclic amines, pyrrolizidines and indolizidines, which are found in many natural products. The reactions contained an element of risk as they depended on 5- and 6-*endo* addition as the first cyclisation in the series where for monocyclisation, yields of no more than 20% were obtained. But as the cyclisation of the imine (**283b**) in Section *7.2* showed, tandem reactions can produce yields of products which would not be predicted from the monocyclisation reaction alone.

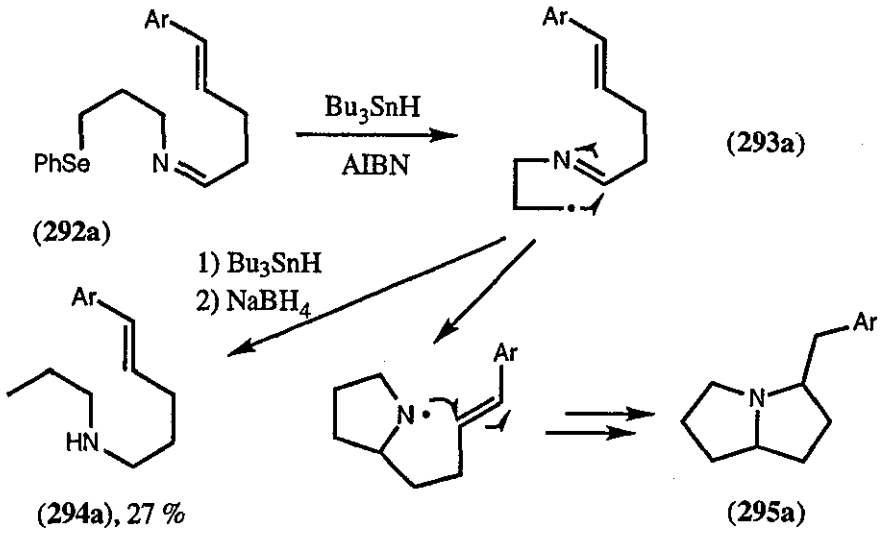
Scheme 101 shows the synthesis of the imines (**292**) which, upon cyclisation, would give the required bicyclic heterocycles. The aldehyde (**291**) was prepared in two steps from ethyl 4-pentenoate (**289**) and was condensed with ω-benzeneselenyl amines (**185a,b**), the formation of which were discussed in Section *4.4*.

Scheme 101



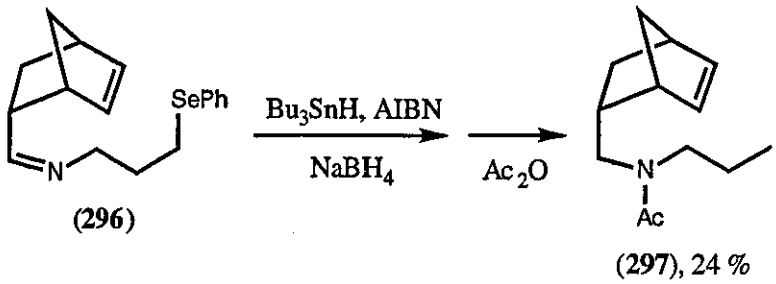
The target of the cyclisation of the imine (**292a**) was the pyrrolizidine (**295a**) (Scheme 102) which required initial 5-*endo* cyclisation onto the imine carbon. None of the attempts at monocyclisation have produced any 5-*endo* products and it was no surprise to find that the major product was the acyclic amine (**294a**) in 27% yield, formed by direct reduction of the radical (**293a**) with Bu_3SnH followed by reduction of the intermediate imine with $NaBH_4$ prior to work-up. However a tertiary amine which showed no alkene peaks in the ^1H NMR spectrum was isolated but owing to the small (< 2 mg) amount of pure amine, positive identification was not achieved. This reaction was repeated three times yielding the same result.

Scheme 102

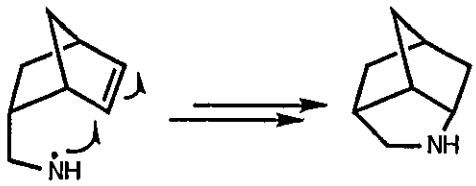


Another 5-*endo* cyclisation was attempted by cyclising the imine (**296**) formed by condensing 3-benzeneselenylpropylamine with bicyclo[2.2.1]hept-5-en-2-carboxaldehyde (Scheme 103a). If the initial cyclisation was an equilibrium, the strained alkene would behave as a radical trap and hence encourage a higher yield of polycyclic product. Studies in the group[17] have shown that the cyclisation of the bicyclo[2.2.1]hept-5-en-2-ylmethylaminyl radical is particularly favoured (Scheme 103b). However no heterocyclic product was obtained from this reaction which was carried out three times, the only isolable product (**297**) being derived from the direct reduction of the PhSe group with Bu_3SnH and which was isolated as the *N*-acetyl amide.

Scheme 103a



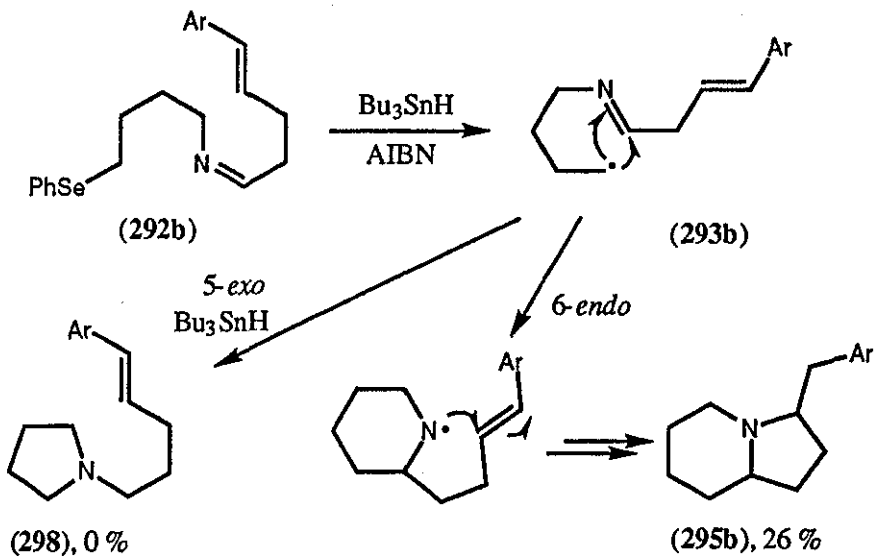
Scheme 103b



The next target was the formation of the indolizidine (**295b**) which would require 6-*endo* / 5-*exo* tandem cyclisation of the imine (**292b**) as shown in Scheme 104. However, as previous monocyclisation results have shown, 6-*endo* addition produced only minor products in cyclisation reactions but if the first cyclisation was to occur, the

second would be relatively facile. The other product, arising from 5-*exo* addition, was predicted to be the major product. Fortunately this reaction gave an interesting and useful result. The 5-*exo* adduct (**298**) was not isolated in any of the four occasions the reaction was carried out and the only isolable product was the indolizidine (**295b**), with a maximum yield of 26%. The remainder of the product was a red insoluble dye, from which it was hard to isolate the amine product. The formation of the dye was thought to arise from 5-*exo* addition followed by polymerisation under the reaction conditions.

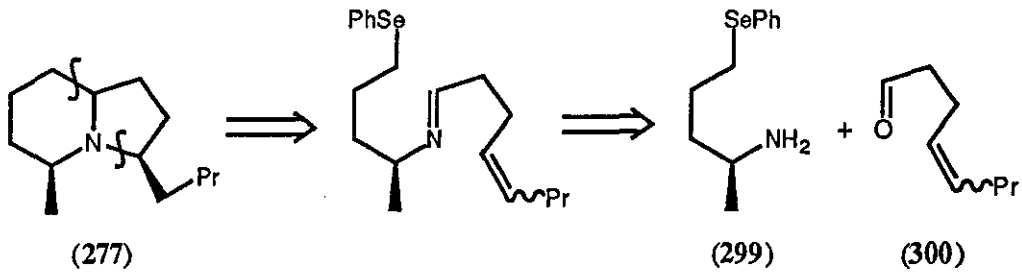
Scheme 104



7.4. Towards Monomorine.

The reaction illustrated in Scheme 104 presented a major breakthrough in the research, showing that the required heterocyclic skeleton for monomorine[120] (**277**) was able to be synthesised by the tandem reaction, though the yield was not great. The next stage required synthesising the imine with the required substitution pattern (Scheme 105), derived from the homochiral amine (**299**) and the aldehyde (**300**).

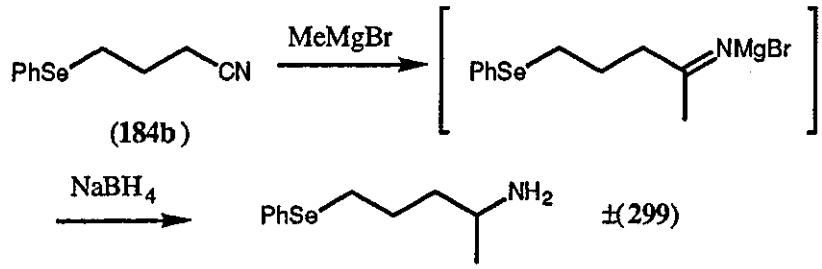
Scheme 105



A racemic sample of the amine (**299**) was synthesised relatively easy by a 'one-pot' synthesis from 4-benzeneselenylbutanonitrile (**184b**) involving (i) the addition of one equivalent MeMgBr to the nitrile and (ii) reducing the intermediate imine with sodium

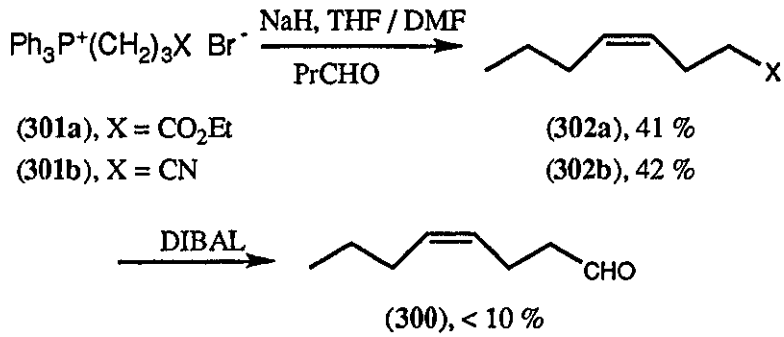
borohydride, though the amine was difficult to isolate from the by-products (Scheme 106).

Scheme 106



The aldehyde (**300**) was thought to be as simple to prepare as the amine (**299**), but that was not the case. The synthetic strategy was to form the alkene bond by a Wittig reaction and then to form the aldehyde by reduction (Scheme 107). The Wittig reaction proved to be a greater problem than was first anticipated and after much effort both the ester (**302a**) and the nitrile (**302b**) were formed from the corresponding phosphonium salts (**301a,b**), the formation of the nitrile being the most efficient. The reduction of both the ester and nitrile with DIBAL did not proceed according to plan, not that the reduction failed in either case, but the volatility of the aldehyde (**300**) meant that isolation and characterisation proved very hard to achieve, though it was detected in the infra-red spectrum of the solution prior to the evaporation of solvent. In fact, by the end of the research, not enough of the compound had been isolated to allow the formation of the imine and cyclisation.

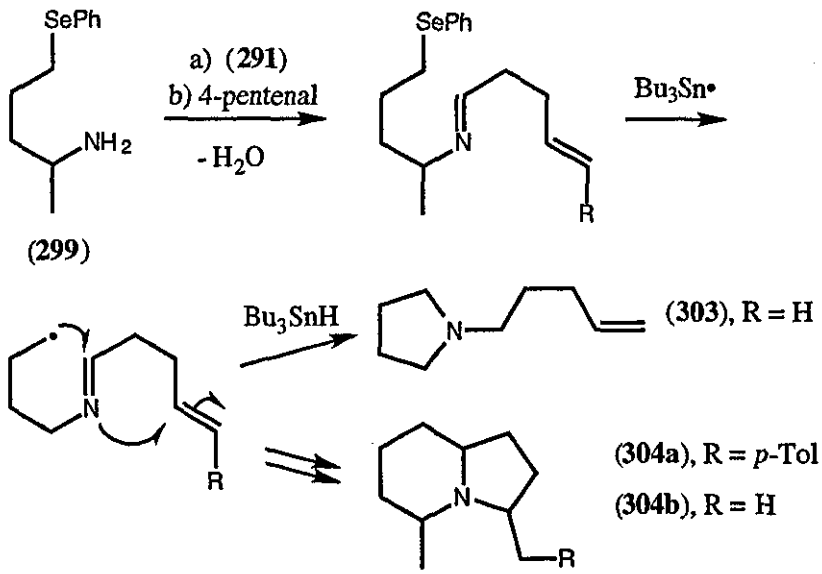
Scheme 107



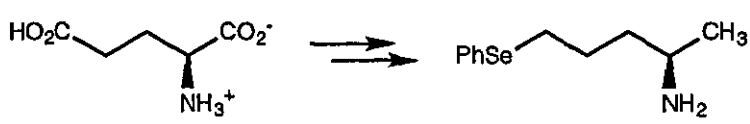
The amine (**299**) was condensed with 5-(4-methylphenyl)-4-pentenal (**291**) and cyclised, yielding indolizidine (**304a**) as the only isolable product (19%) (Scheme 108, R = *p*-Tol). In order to assess whether the indolizidine could be formed without the stabilising aryl group attached, commercially available 4-pentenal was condensed with the amine (**299**) and cyclised. A relatively high yield (63%) of two products were isolated as hydrochloride salts, and though they could not be separated, ^{1}H NMR spectroscopic evidence indicated that the amines (**303**) and (**304b**) were formed in a ratio

of around 1.6 to 1. This shows that indolizidine such as (**304b**) can be formed as a minor product even without an aromatic stabilising group, and indicates that monomorine (or one of its isomers) could have been formed by this reaction if the aldehyde (**300**) had been available to react. Interestingly when R ≠ aryl, the products from 5-*exo* cyclisation are obtained along with the product arising from 6-*endo* / 5-*exo* tandem cyclisation. This supports the proposal that the lack of 5-*exo* product when R = aryl is due to the polymerisation of the styrene moiety under the reaction conditions.

Scheme 108



The formation of the indolizidine (**304b**) was the last reaction completed at the end of the research and no time was available to synthesise any of the diastereomers of monomorine[120a] or any of its isomers (the 5-*epi* isomer[120b] also being a natural product). The strategy would have involved the synthesis of the amine (**299**) in enantiomerically pure form, possibly from an amino acid starting material.



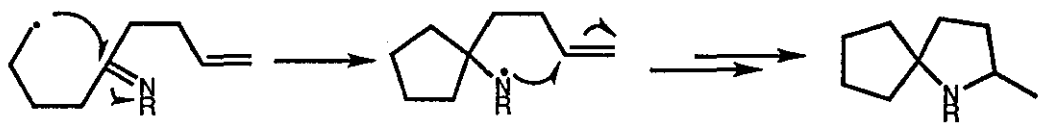
glutamic acid

(**299**)

8. Tandem Reactions - 2: The Synthesis of Spirocyclic Amines.

The second series of tandem reactions that were investigated is shown in Scheme 97b. The scheme illustrates a simple radical tandem reaction where the spirobicyclic amine (**271**) is formed by successive 5-*exo* additions from the radical (**270**). These tandem reactions were predicted to proceed as (i) the cyclisation of radicals onto the ketimine carbon has been shown to occur during the early phase of the studies (Section *5.3*) and (ii) the aminyl radicals produced by the addition to the imine carbon cyclise onto unsubstituted alkenes in reasonable yield (Sections *7.2* and *7.4*).

Scheme 97b

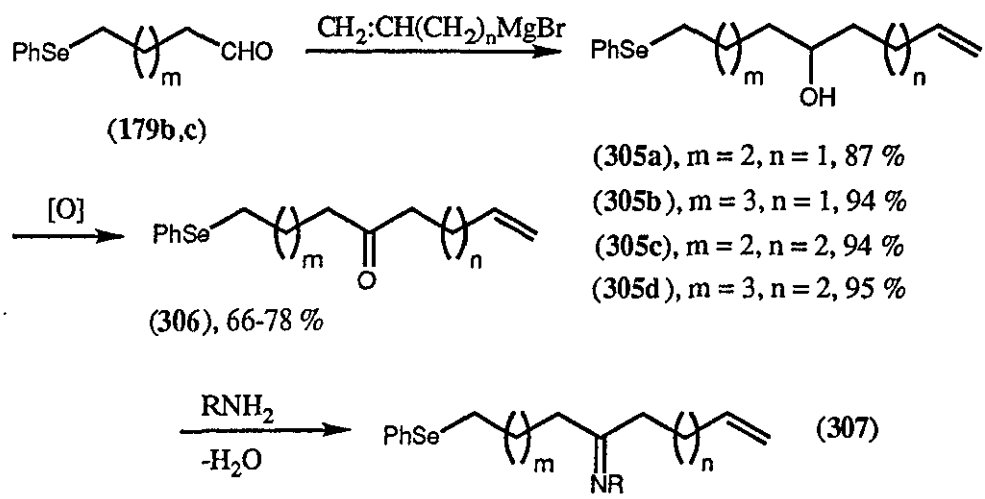


(**270**) (**271**)

8.1. The Preparation of the Starting Imines.

The syntheses of a range of suitable radical precursors are shown in Scheme 109. The target molecules at the start of the syntheses were the ketones (**306**), with varying chain lengths either side of the ketone group to enable the synthesis of a series of 5- and 6-membered spirocycles. It was envisaged that the ketones (**306**) could be prepared in two steps from the aldehydes (**179b,c**), first by the addition of Grignard reagents to form the secondary alcohols (**305**), followed by oxidation as illustrated in Scheme 109.

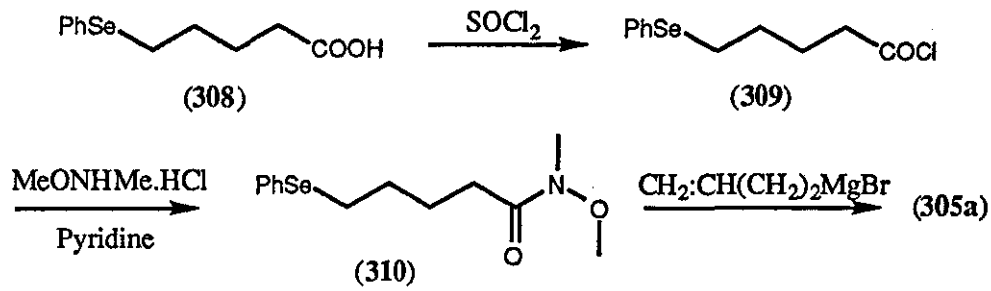
Scheme 109



The first stage was not predicted to present any particular problems, but the oxidation step required careful thought. The PhSe group is easily oxidised by oxidants such as hydrogen peroxide, MCPBA, PCC and other common oxidants, but is stable to

DDQ. The stability to Swern oxidation conditions was unknown at the start of the research and initial tests involving the oxidation of 4-benzeneselenylbutan-1-ol (**182**) (see Section *4.2*) proved inconclusive. A different method of synthesis was tried first as illustrated in Scheme 110. 5-Benzeneselenylpentanoic acid (**308**) was prepared from δ-valerolactone and converted to the acyl chloride (**309**). This was converted to the amide (**310**) using *N,O*-dimethylhydroxylamine in good yield. Reaction of the amide (**310**) with the Grignard reagent failed to react on four attempts and the pathway was eventually abandoned.

Scheme 110



At this stage, the alcohols (**305a-d**) had been prepared in good yield (87-95%) and oxidation was attempted. *N*-Chlorosuccinimide and dimethyl sulphide was initially used as oxidant, but the yields of the oxidised product were poor and the ketone was hard to separate from the by-products. A decision was then made to oxidise the alcohol (**305a**) by Swern oxidation which yielded the ketone (**306a**) in high yield and relatively pure. As it turned out, activated DMSO does not readily oxidise the benzeneselenyl group. Having successfully prepared ketone (**306a**)in 66% yield, the other three ketones (**306b-d**) in the series were prepared by the same route (67-78%).

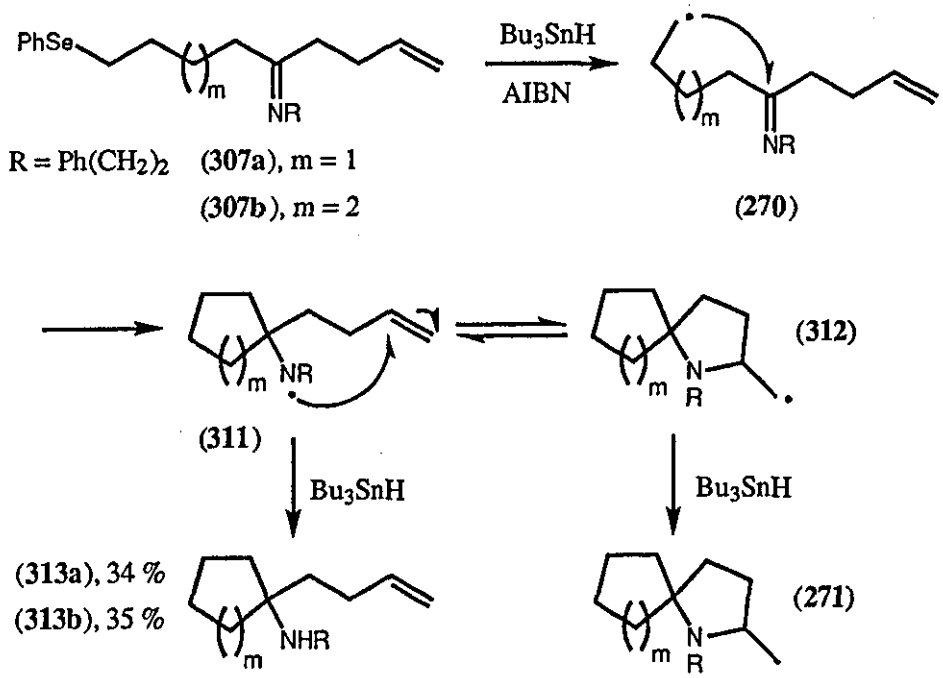
This reaction illustrates the surprising stability of the PhSe group in the reactions carried out during the research. The functional group has been shown to be stable to reduction by lithium aluminium hydride and DIBAL, Grignard additions, reactions and work up procedures involving both aqueous acid and base, and Swern oxidation conditions. The PhSe group is thermally stable in dipolar aprotic solvents including DMSO at temperatures above 160 °C, yet is cleaved efficiently under standard free radical conditions. Of all the cyclisations attempted, there were very few reactions where selenium containing starting materials were recovered. The $PhSeCH_2$ unit is easy to identify by ^1H NMR spectroscopy, with two aromatic multiplets at δ 7.45-7.49 and δ 7.22-7.27 with a ratio of 2 : 3 and a well defined triplet at around δ 2.90 (J = 7.0 Hz). In the infra-red spectrum, the PhSe group invariably absorbs at 1576-1578 cm^{-1}, with two other peaks at around 1477 and 1437 cm^{-1}.

8.2. Cyclisation Reactions.

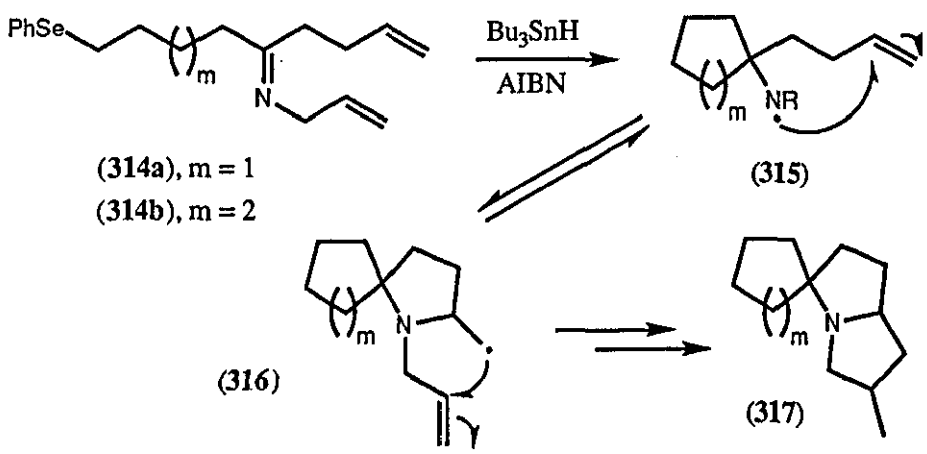
Scheme 111 illustrates the initial cyclisation reactions of the imines (**307a,b**)

derived from the ketones (**306a,b**), the formation of which needed more forcing conditions than normal owing to the greater steric hindrance around the imine bond. Due to the sterically crowded imine bond, the first cyclisation was predicted to be relatively slow, but unexpected results were obtained. The only products isolated from both reactions were the monocyclic amines (**313**) in reasonable yield (34-35%). The spiroamines (**271**) were only fromed in trace amounts which could not be isolated despite many attempts. For reasons that are not clear, the equilibrium between the radicals (**311**) and (**312**) lies in favour of the monocyclic radical and the formation of the radical (**312**) appears to be a very slow reaction. The spirocyclic substituent on the radical (**311**) may present unforeseen steric demands on the *5-exo* transition state resulting from the attack of the aminyl radical onto the alkene bond.

Scheme 111



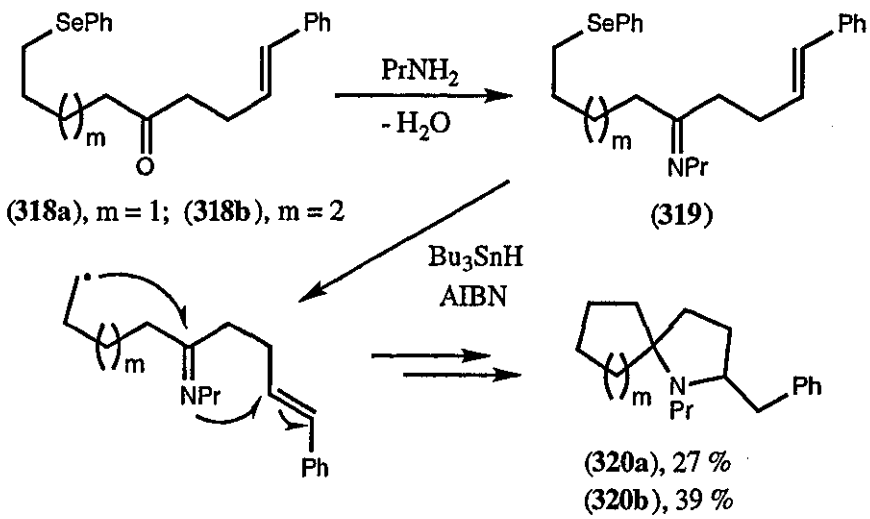
Scheme 112



In order to encourage cyclisation beyond the first stage, imines were prepared replacing 2-phenylethylamine with allylamine (Scheme 112). The equilibrium between the radicals (**315**) and (**316**) was predicted to be affected by the extra alkene group, which would trap the radical (**316**), by 5-*exo* addition. The cyclisation reactions gave disappointing results, with yields of cyclised products in the range 8-10%, the remainder being polymeric materials. Despite much effort, positive identification of the tricyclic amine products (**317**) could not be achieved.

A decision was made to explore other ways that would force the second cyclisation, to produce the required spirocyclic amines (**271**) in high yield. The first option was to synthesise ketones with a radical stabilising group on the alkene (Scheme 113), which has already been shown to facilitate tandem cyclisation. This was relatively easy to accomplish and the ketones (**318a,b**) were formed in good yields (71% and 85% respectively) from the ketones (**306a,b**) by the Heck reaction. The imines (**319a,b**) were formed by condensation of the ketones (**318**) with *n*-propylamine and cyclised. In these reactions, the bicyclic amines (**320**) were the only products isolated from the reaction, thus showing that the spirocyclic amines could be synthesised.

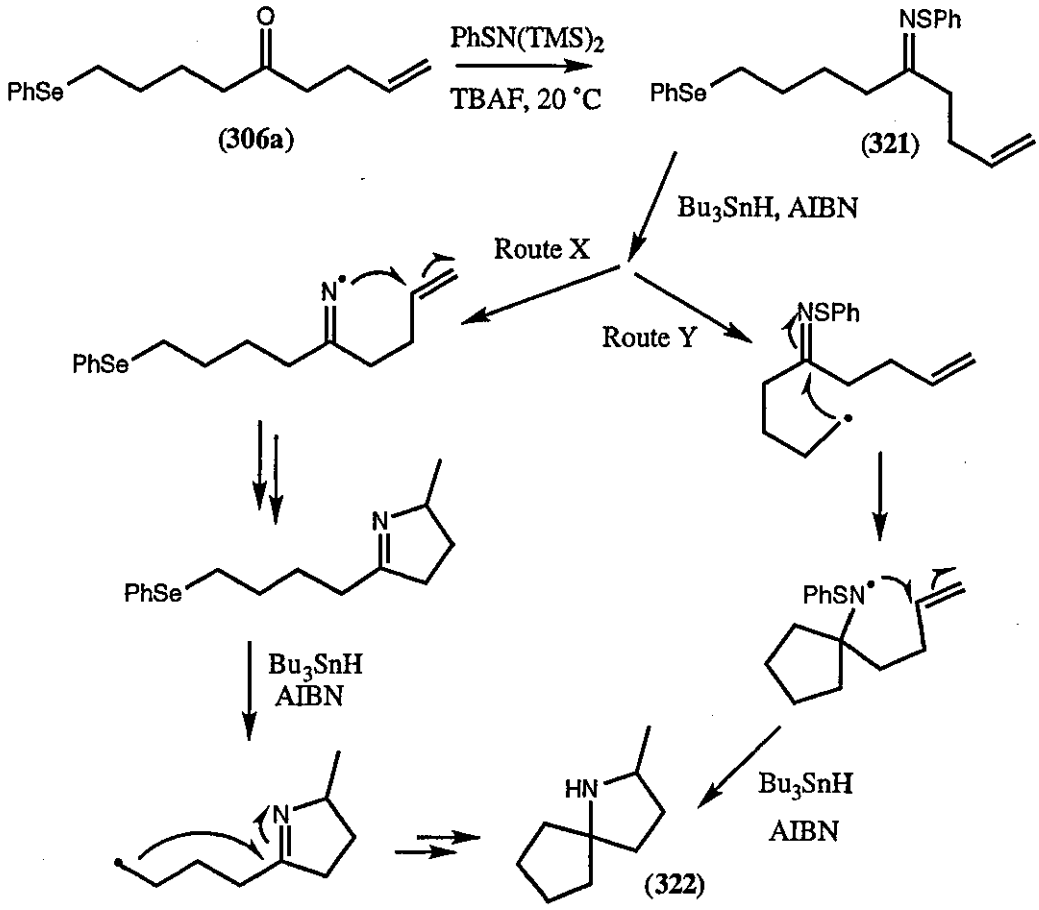
Scheme 113



In order to synthesise the spirocyclic amines without the phenyl substituent, another synthetic strategy was considered. Cyclisation of the imines (**307a,b**) could be facilitated in the presence of a Lewis acid, which by coordination to the imine nitrogen would render the imine more reactive to radical attack and subsequent cyclisation. The reactions of protonated[16,19] or Lewis acid complexed[19] aminyl radicals have been shown to cyclise irreversibly onto alkenes. The complexation of the imines would be predicted to increase the reactivity of the imine bond towards cyclisation, yet would not bring about such a level of reactivity that the complexed imine would react directly with Bu_3SnH with the addition of hydride to the electropositive imine carbon. In Section *8.3* the reactions carried out in the presence of magnesium bromide etherate are discussed.

A second alternative considered was to prepare and cyclise *N*-benzenesulfenyl-imines which Zard and co-workers showed to form iminyl radicals which add to unactivated double bonds.[18] Such compounds were predicted to be relatively easy to synthesise from the ketones (**306**). Scheme 114 illustrates the double cyclisation reactions envisaged, combining Zard's cyclisations with that of imines. These interesting reactions would provide a way of synthesising the secondary amines (**322**), which are analogous to perhydrohistrionicotoxin (**279**). Imines of the type $R_1R_2C{=}NH$ are unstable and readily hydrolyse or polymerise and were never considered as cyclisable imines. From the earliest stages of the work, groups were chosen as nitrogen substituents (e.g. 2-phenylethyl or benzyl) which could be easily removed after cyclisation (by base induced elimination of styrene and catalytic hydrogenation respectively). In these imines (**321**), the PhS group acts as a nitrogen protecting group removed during the cyclisation, thus eliminating the need to carry out an extra step.

Scheme 114



The reaction sequence also presented an interesting kinetic challenge, that is the relative rate at which $Bu_3Sn\bullet$ reacts with PhSe relative to PhS in these systems. A prediction of which of the two cyclisations would occur at the fastest rate could not be made, though both would be expected to be fast. For the reactions shown in Scheme 114, the same product would be produced regardless of whether the reaction proceeded

by Route X or Route Y. Competition studies were considered where one equivalent each of a benzeneselenyl derivative and an *N*-benzenesulfenyl imine were reduced with one equivalent of Bu_3SnH and all the products isolated and analysed. This would have provided an indication of the route of formation of the amines (**322**).

However the method that Zard utilised to form *N,N*-bis(trimethylsilyl)benzene-sulfenamide, the reagent used to form the imines (**321**), could not be repeated and the whole synthetic strategy was shelved, possibly for a future research project.

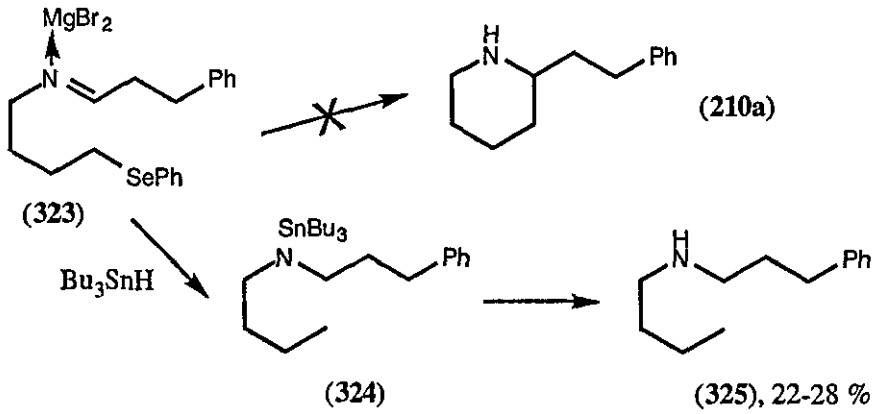
8.3. Lewis Acid Mediated Cyclisation Reactions.

The aim of this part of the research was to cyclise imine-Lewis acid complexes to form the spirocyclic amines (**271**). Magnesium dibromide was chosen as the Lewis acid, and was added to the toluene solution of the pre-formed imine in the form of the commercially available complex with diethyl ether. The reactivity of the complexes under free radical conditions was unknown at the start of the work and several reactions were carried out to test the suitability of the $MgBr_2$ complexes in radical reactions. Magnesium dibromide was the only Lewis acid used, and if more time had been available, others would have been investigated.

In the first test reaction, the imine formed by condensing 5-benzeneselenylpentanal (**179b**) with benzylamine was cyclised yielding *N*-cyclopentylbenzylamine (**202c**) in a yield similar to that obtained without the Lewis acid (62%). 5-*exo* Addition onto the imine carbon occurs in the presence of the Lewis acid.

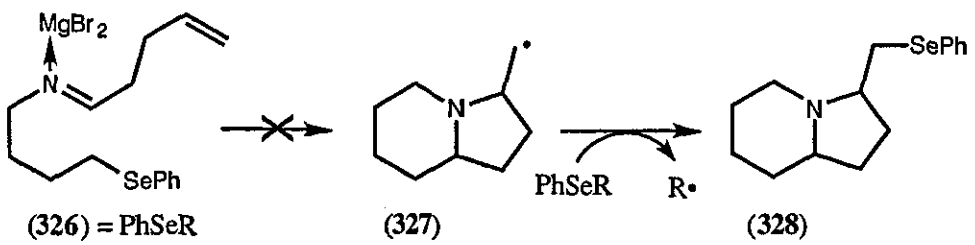
The next test was to determine whether 6-*endo* addition is enhanced by the complexation of the imine. In the first reaction (Scheme 115a), the imine-complex (**323**) was cyclised and the result showed that cyclisation was inhibited. 5-*exo* Addition onto the nitrogen failed presumably for steric and stereo-electronic reasons, and 6-*endo* cyclisation failed because of a slow reaction rate. The product isolated was the amine (**325**) formed by (i) the addition of hydride to the electropositive carbon and (ii) the free radical reduction of the PhSe group. In one reaction, the intermediate tributylstannyl-amine (**324**) was identified by ^1H NMR spectroscopy but hydrolysed during the attempted isolation.

Scheme 115a



Attempts were made to enhance the formation of the 6-*endo* product in the cyclisation of the imine complex (**326**) (Scheme 115b). The initial results seemed to indicate that the benzeneselenyl substituted indolizidine (**328**) was the product, formed by intramolecular abstraction of PhSe by the radical (**327**), the Bu_3SnH not participating in the reaction. The reaction was repeated with a non-stoichiometric amount of hexa-*n*-butylditin / AIBN, giving the same result. However, a closer examination of the spectroscopic evidence showed that the amine (**328**) could not have been the product. A control reaction was carried out in which the imine-complex (**326**) was refluxed in toluene without any radical generating reagent and the same product was produced, with the selenium functionality intact and with both the imine and alkene functionalities absent. The product could not be isolated and its identity could not be deduced but its formation could have been formed by a polar reaction brought about by the proximity of the alkene group to the electropositive carbon, a reaction which prevailed over the desired radical reaction.

Scheme 115b

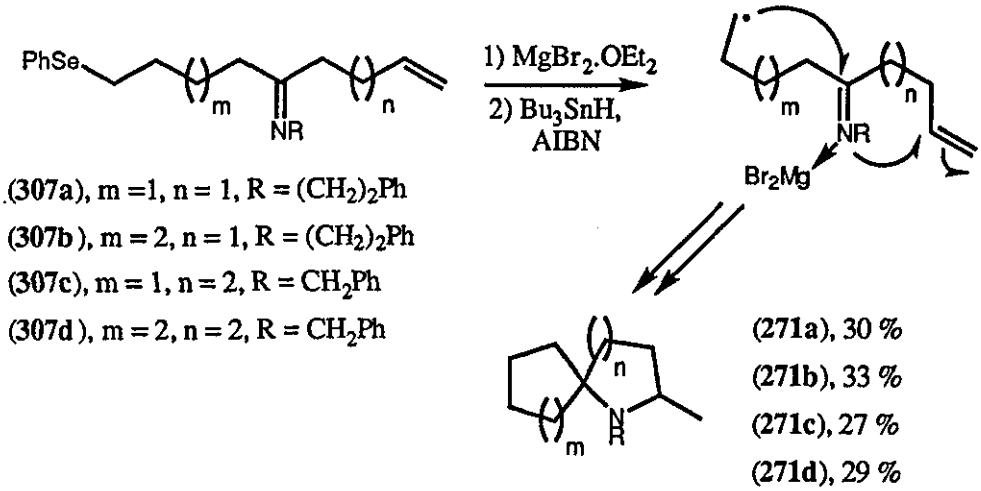


(**326**) = PhSeR (**327**) (**328**)

From these test reactions, 6-*endo* cyclisations do not compete with alternative reaction pathways. The complexes of imines with magnesium dibromide render the C=N bond reactive enough to bring about the addition of hydride ions if cyclisation reactions are slow or impeded. The evidence from the test reactions appear to show that fast cyclisations, e.g. 5-*exo* addition, compete favourably with the alternative polar pathways.

A decision was made to proceed with the 5- and 6-*exo* cyclisations to form a range of spirocyclic amines (Scheme 116). The imines (**307a-d**) were synthesised and cyclised in the presence of one equivalent of the Lewis acid. In all these reactions only trace amounts of the monocyclic amines (**313**) were detected by ^1H NMR spectroscopy. The only isolable products were the bicyclic amines (**271a-d**) formed in reasonable yield. A significant by-product in the reactions were insoluble polymers. Magnesium dibromide imparts significant reactivity to the imine bond and other polar reaction pathways appear to compete with tandem cyclisation. More research is required to optimise the tandem reaction and limit polymerisation, by using different Lewis acids, e.g. lithium salts or organoaluminium reagents.

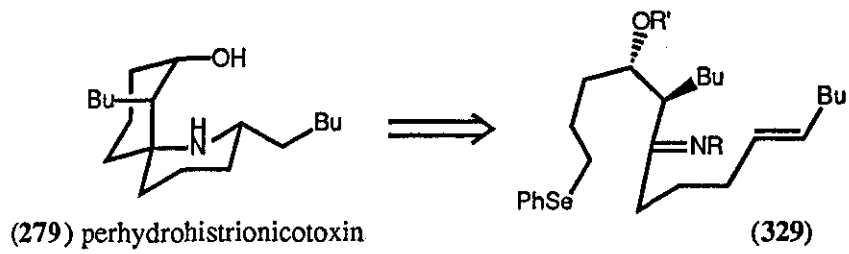
Scheme 116



8.4. The Synthesis of Perhydrohistrionicotoxin.

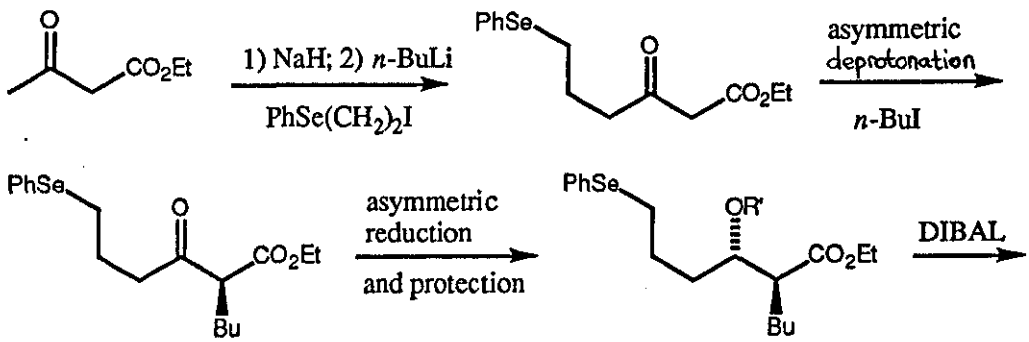
The use of magnesium bromide in the cyclisations of the imines (**307**) did overcome the problem associated with the unfavourable tandem cyclisations shown in Scheme 111. The last cyclisation stage of the synthetic route towards perhydrohistrionicotoxin[121] (**279**) is thus predicted to be a possibility (Scheme 117).

Scheme 117

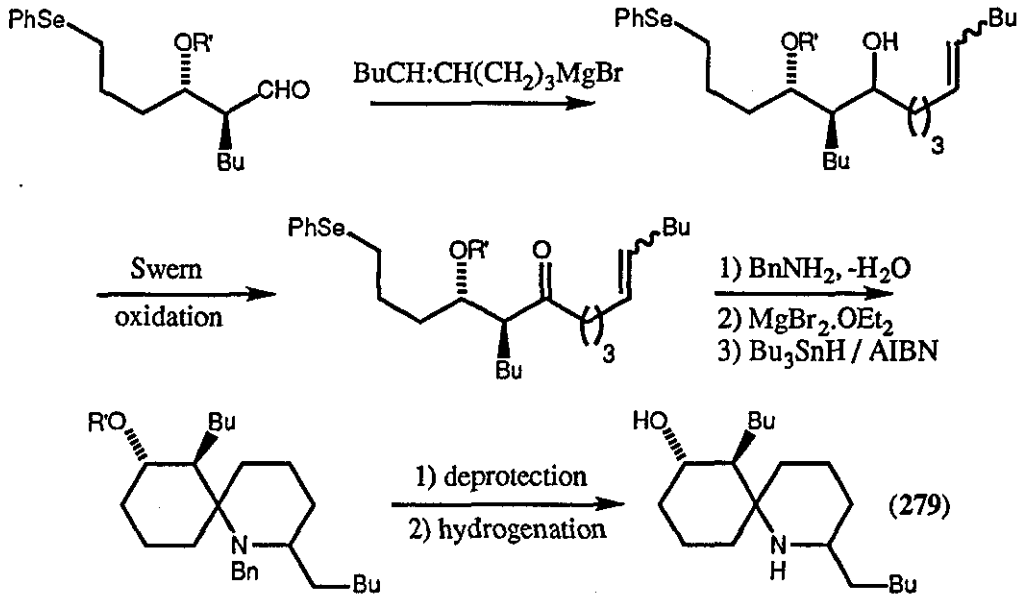


The ketimine (**329**) was the target for synthesis and cyclisation would have yielded the product (**279**) after removal of the protecting groups R and R'. However, the synthesis was not started because of time constraints, though a proposed nine-step synthetic strategy, illustrated in Scheme 118, would utilise many procedures developed

Scheme 118



Scheme 118 continued



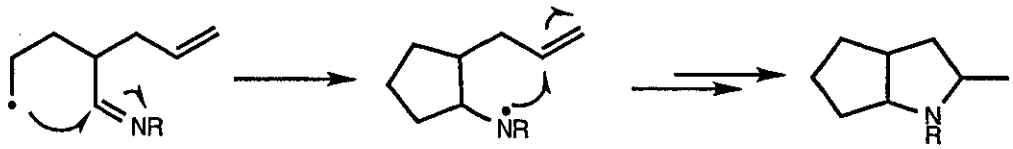
(279)

in other areas of the research. Only the asymmetric alkylation and reduction steps early in the synthesis would have required extra study, as such reactions have not been attempted at any time during the research.

9. Tandem Cyclisations - 3: The Synthesis of Perhydroindoline and Related Systems.

The third series of tandem reactions that were investigated is shown in Scheme 97c. The scheme illustrates a radical tandem reaction where the bicyclic amine (**273**) is formed by successive 5-*exo* additions from the radical (**272**). These reactions were predicted to proceed in good yield as they combined the same elements as the successful cyclisations of Section *7.2*, i.e. addition to the aldimine carbon followed by cyclisation of the aminyl radical onto the alkene. The main difference between these cyclisations and those already discussed, lies in the *cis / trans* stereochemistry at the ring junction of the bicyclic products. Though *cis* stereochemistry could be predicted for the 5-*exo*, 5-*exo* reaction product (**273**), the level of stereoselectivity could not be predicted for reactions involving 6-*exo* addition and so diastereomeric mixtures were expected for the reactions where 6-membered rings were formed.

Scheme 97c

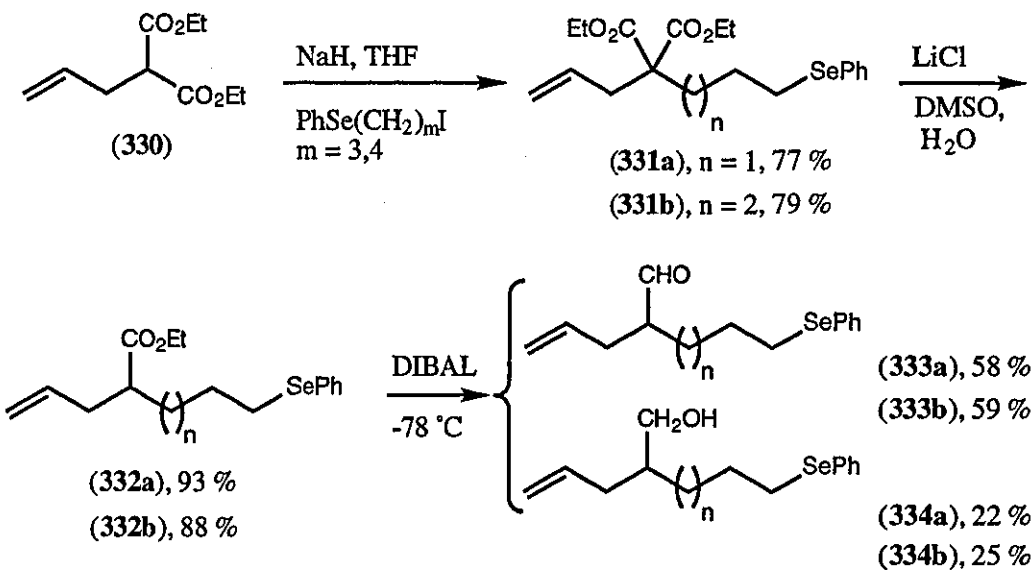


(**272**) (**273**)

9.1. The Preparation of the Starting Imines.

Scheme 119 shows the synthetic steps used to synthesise the aldehydes (**333**), the target compounds for the cyclisations, and parallels the synthesis of the aldehyde (**230**) in Scheme 87. The synthesis of the esters (**332a,b**) was achieved in good yield from diethyl allylmalonate (**330**) in two steps. The DIBAL reduction of the esters to the

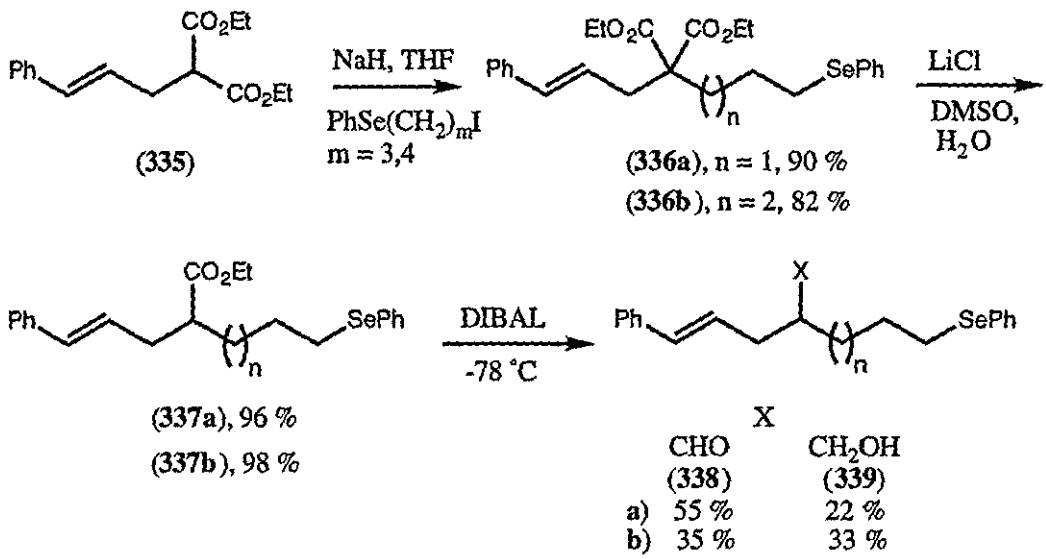
Scheme 119



aldehydes (**333a,b**) proved more difficult than had been anticipated and time was spent establishing the optimum conditions for their formation. The main problem was over-reduction of the esters by DIBAL, even at -78 °C, yielding the alcohols (**334a,b**). The problem was resolved by using only a slight excess of the reducing agent instead of the usual two or three-fold excess. The aldehydes (**333**) were eventually produced as the major products.

The corresponding aldehydes with a phenyl group on the alkene were also synthesised (Scheme 120). The starting material, diethyl 2-cinnamylmalonate (**335**), was formed from diethyl allylmalonate (**330**) by the Heck reaction. The reduction of the esters (**337a,b**) by DIBAL also proved difficult and for the aldehyde (**338b**), the maximum yield obtainable was only 35%, but enough was produced to allow further reaction.

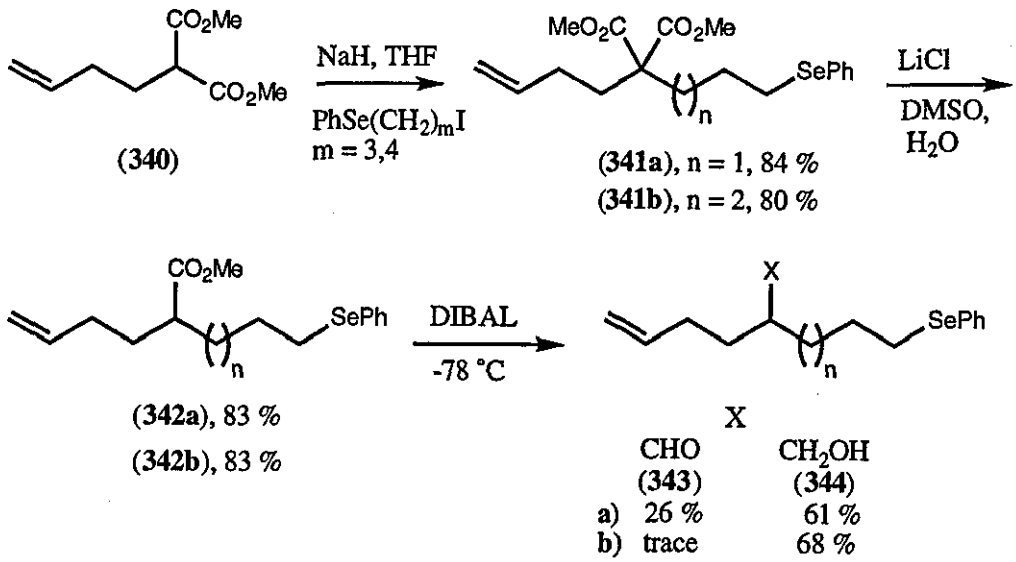
Scheme 120



The syntheses of a third series of aldehydes (**343**) were attempted, starting from dimethyl 3-butenylmalonate (**340**) (Scheme 121). Though the first two steps were carried out in good yield, the esters (**342**) could not be efficiently reduced to the aldehydes (**343**), no matter which DIBAL conditions were employed. In one reaction, using one equivalent of DIBAL, a 1 : 1 mixture of the ester (**342b**) and the alcohol (**344b**) resulted. The maximum yield achieved for the formation of the aldehyde (**343a**) was 26%, and not enough was isolated to enable further reaction, whereas the aldehyde (**343b**) could not be detected. For both reactions the alcohols (**344a,b**) were isolated in over 60% yield. Attempts were made to reoxidise the alcohols (**344**) by Swern oxidation but without success and in both cases unidentifiable products resulted.

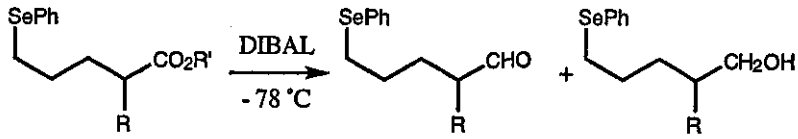
The reactions shown in Schemes 119-121 appear to show that reduction of esters to aldehydes by DIBAL is affected by the size of the substituents α to the ester group as Scheme 122 illustrates. For the simple aldehydes (**179**) (R = H) and the α-methyl

Scheme 121



aldehyde (**229**) (R = Me), the reaction proceeds without difficulty. Increasing the size of R to allyl or cinnamyl reduces the yield of the aldehyde to less than 60% and if the lengths of the alkyl chains are increased further by just one carbon, the yield of aldehyde is reduced dramatically. For the reduction of the ester (**345**) the only product isolated was the alcohol (**347**), with no trace observable of the aldehyde (**346**). The third series of aldehydes were not produced, but two series of imines were produced from the aldehydes (**333a,b**) and (**338a,b**) for cyclisation.

Scheme 122



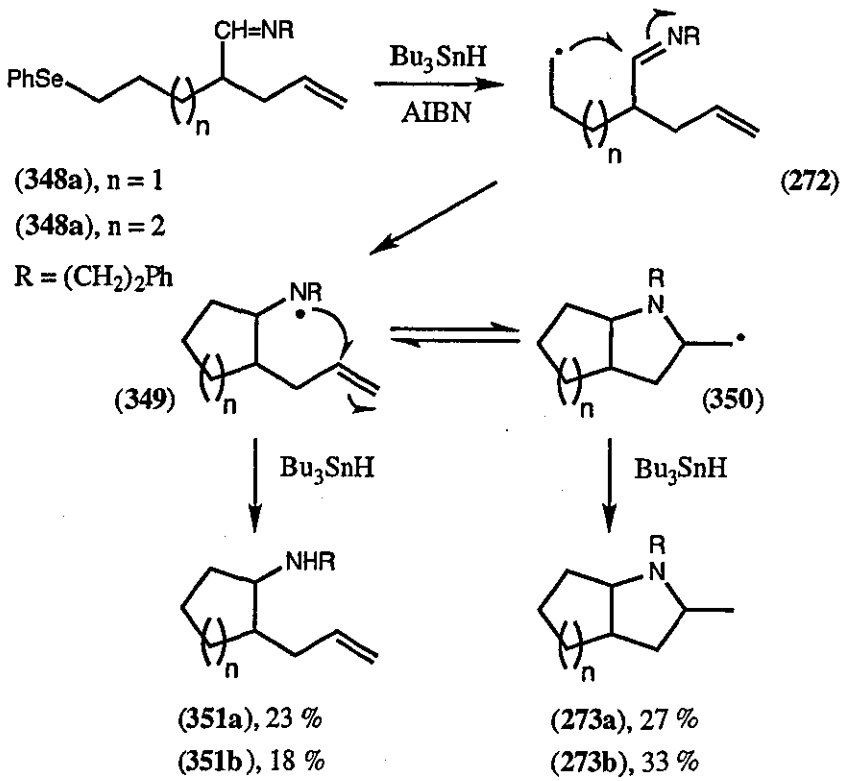
(**178**), R = H	(**179**), 93%	n.a.
(**229**), R = Me	(**230**), 70 %	n.a.
(**332**), R = allyl	(**333**), 58 %	(**334**), 22 %
(**337**), R = cinnamyl	(**338**), 55 %	(**339**), 22 %
(**342**), R = 3-butenyl	(**343**), 26 %	(**344**), 61 %
(**345**), R = PhCH:CH$(CH_2)_2$-	(**346**), 0 %	(**347**), 77 %

9.2. Cyclisation Reactions.

The imines (**348a,b**) were produced using much milder conditions than the precursors for the spirocyclic amines - stirring over 4 Å molecular sieves over three days and were cyclised as shown in Scheme 123. The reaction of these imines produced much more encouraging initial results than for the spirocyclic amines (Section *8.2*). With no aromatic stabilising group to encourage tandem cyclisation, the bicyclic amines (**273a,b**) were formed as the major product. The equilibrium between the radicals (**349**) and (**350**)

was more evenly balanced, especially in the case of the formation of the perhydro-indoline (**273b**). The monocyclic amines (**351a,b**) were isolated as the *N*-acetyl derivatives. From ^{1}H NMR spectroscopy, two stereoisomers of the bicyclic product (**273b**) were produced, and one of the amine (**273a**). Unfortunately no crystalline derivatives of either products could be obtained, by precipitation as hydrochloride or even perchlorate salts, despite much effort. This was probably due to the very small isolated yield (< 20 mg) of the pure amines. Therefore, no crystallographic data could be gathered, and hence the absolute stereochemistry of these products could not be determined. The two isomers of the amine (**273b**) were predicted to be those with *cis* and *trans* ring junctions. The single stereoisomer of the 5-*exo*, 5-*exo* tandem product (**273a**) was predicted to be that with the *cis* ring junction, being much more stable and easier to form than the strained *trans* isomer.

Scheme 123

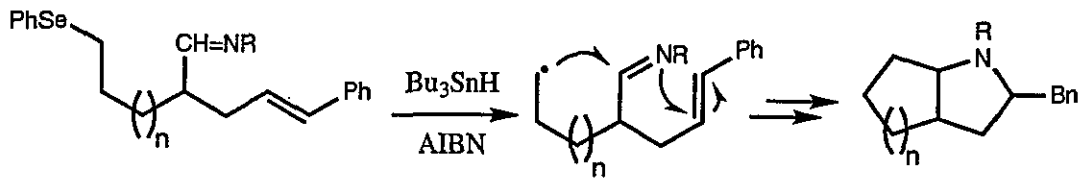


The cyclisation of the imine (**348a**) was repeated with the addition of magnesium dibromide etherate and following the pattern of the reactions of in Section *8.3*, the bicyclic amine (**273a**) was isolated as the sole product in increased yield (35%). This reaction was carried out towards the end of the studies and the yield was not optimised. The use of the Lewis acid in the cyclisation of the other precursors was not attempted. However this result provides further evidence that the yields of tandem cyclisations of imines are improved by complexation to Lewis acids.

With the additional phenyl group in the molecule, cyclisation of the imines (**352a,b**) yielded almost exclusively the tandem products (**353**), and only traces of

monocyclic products (Scheme 124). Again two isomers of the perhydroindoline product (**353b**) were produced (^{1}H NMR spectroscopy), and only one isomer of the amine (**353a**), though no crystalline derivatives of any of these compounds could be prepared.

Scheme 124

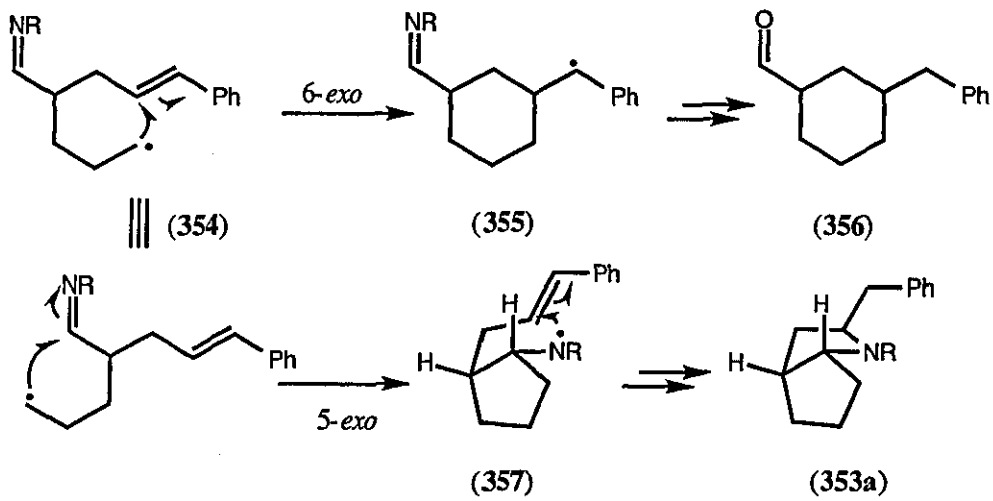


(**352a**), n = 1
(**352b**), n = 2
R = n-Pr

(**353a**), 40 %
(**353b**), 57 %

Though the yield of the 6-*exo*, 5-*exo* tandem product (**353b**) was one of the best yields obtained for a tandem reaction, the same was not the case for the 5-*exo*, 5-*exo* product (**353a**). Scheme 125 shows that a side reaction is also possible where the radical (**354**) can add directly to the alkene by 6-*exo* addition, producing the stabilised radical (**355**), leading to the aldehyde (**356**) as a by-product. This undesired side reaction was not predicted for the cyclisation of the imine (**348b**), because it would have involved the relatively unfavourable 7-*exo* addition. At first, no attempt was made to isolate the product (**356**), but a repeat cyclisation of the imine (**348a**) was considered in order to find the aldehyde (**356**), but was not carried out owing to the scarcity of the starting aldehyde (**343a**). Another factor, which may have contributed to the relatively low yield of the amine (**353a**) [and also amine (**273a**)], is the axial arrangement of the cyclopentyl ring of the aminyl radical (**357**) as it approaches the alkene bond.

Scheme 125

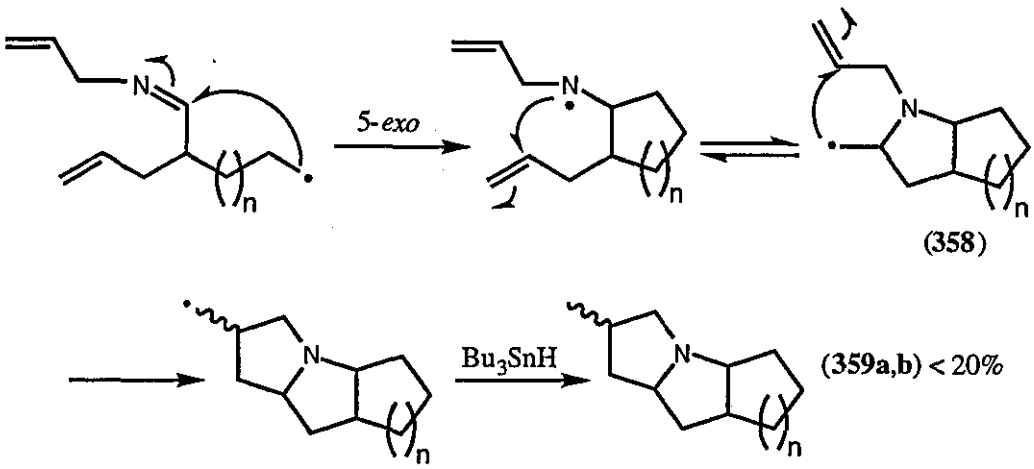


(**357**) (**353a**)

In an attempt to improve the yield of polycyclic products without the phenyl substituent, the aldehydes (**333a,b**) were condensed with allylamine and cyclised (Scheme 126). The formation of the tricyclic amines (**359**) was expected, arising from

the trapping of the radical (**358**) by the alkene bond prior to hydrogen abstraction. These reactions proceeded better than the parallel reactions illustrated in Scheme 112, and from ^{1}H NMR spectroscopic data, tricyclic products were produced. These could not be isolated despite many attempts and positive identification was not achieved.

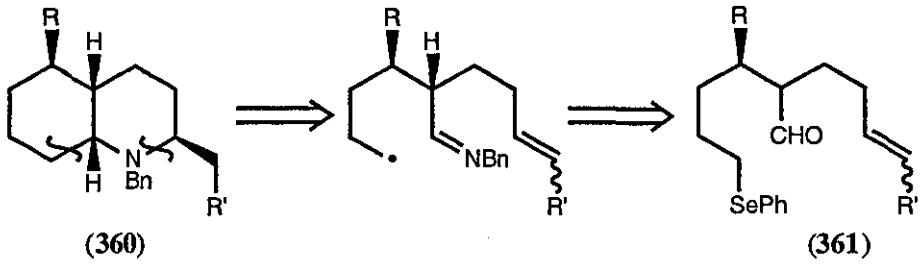
Scheme 126



9.3. The Synthesis of Pumilotoxin C - Route 1.

The dendrobate alkaloids, pumilotoxins (**360**) with various substitutents R and R', are potentially synthesisable by tandem cyclisation of imines. The alkaloid chosen as the synthetic target was the relatively simple derivative pumilotoxin C (**360**, R = Me, R' = Et). Scheme 127 shows one of two synthetic pathways that were investigated, the target aldehyde (**361**) being the key intermediate.

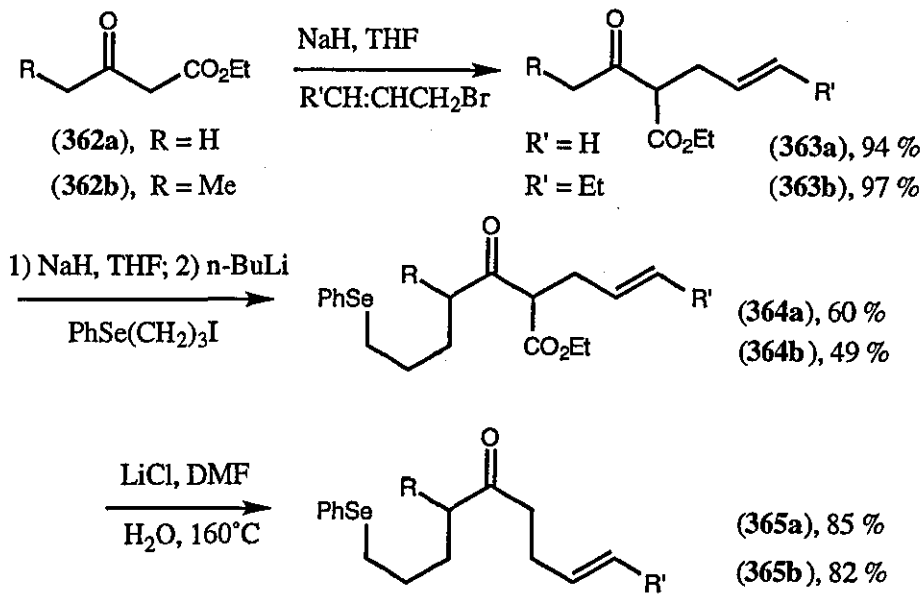
Scheme 127



*Unfortunately, the simple aldehyde (**361**, R = R' = H) could not be produced by* extending the methodology discussed in Section *9.2*. Despite many attempts, this aldehyde was the only one in the series to elude synthesis. A decision was made to investigate a synthesis that adapts many synthetic steps that have already been shown to be successful in other areas of the work (Scheme 128). Two synthetic series were carried out in parallel. The first (**362-365a**), with no substitution pattern, was carried out on a relatively large scale using cheap starting materials to test the viability of the method. The second series (**362-365b**) with the appropriate substituents was carried out on a smaller scale. The β-ketoesters (**362a,b**), were alkylated in the α position almost

quantitatively yielding the esters (**363**). The next step was to alkylate the γ position, by deprotonating the α position using sodium hydride, deprotonating a second time using *n*-BuLi and reacting the resulting dianion with 1-benzeneselenyl-3-iodopropane (**227**). This reaction took much effort to produce the esters (**364**) in the yields shown and the separation of the esters (**364**) from the starting materials was difficult. The conversion of the esters (**364**) to the ketones (**365**) using lithium chloride in DMF / water was relatively easy to accomplish. The ketones (**365**) were thus obtained in good yield. The simpler ketone (**365a**) was found to be identical to the ketone (**306a**), produced via Grignard addition, thus providing a successful second route to these compounds.

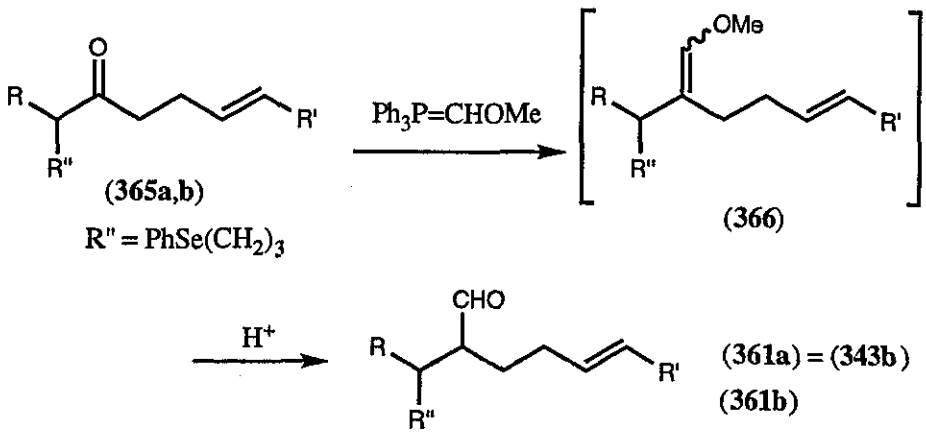
Scheme 128



A variation of the Wittig reaction was investigated as a 'one-pot' reaction to convert the ketones (**365**) to the aldehydes (**361**) (Scheme 129). This reaction presented many problems, which could not be adequately resolved in the time available. The main problem was finding the conditions where the methoxymethylene(triphenyl)phosphorane was able to form and react with the ketones. Various bases were tried (e.g. PhLi, *n*-BuLi) and solvents (THF, THF/DMF). At first, the problem seemed to be the insolubility of the starting phosphonium salt in THF, the addition of DMF resolving this. However *n*-BuLi reacted with DMF and could not be used and PhLi failed to react at all. In all these reactions the starting ketones were isolated from the reaction mixtures at a level of 80-90% recovery. KO^{t}Bu in refluxing dioxane was an alternative reagent system that was used. Under these conditions the ketones (**365**) reacted to yield a mixture of products, which were very hard to separate. It must be noted that no attempt was made to isolate the enol ethers (**366**) and the crude product mixture was treated with acid prior to work-up. Though one of the products stained yellow using 2,4-dinitrophenyl-hydrazine, and on analysis showed infra-red spectroscopic peaks characteristic of a the presence of an aldehyde, no more data could be obtained confirming this. In spite of

much effort, the aldehydes (**361a,b**) remained elusive, and were not isolated by the end of the laboratory time.

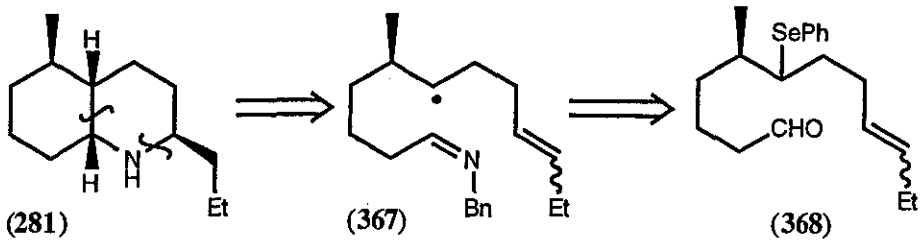
Scheme 129



9.4. The Synthesis of Pumiliotoxin C - Route 2.

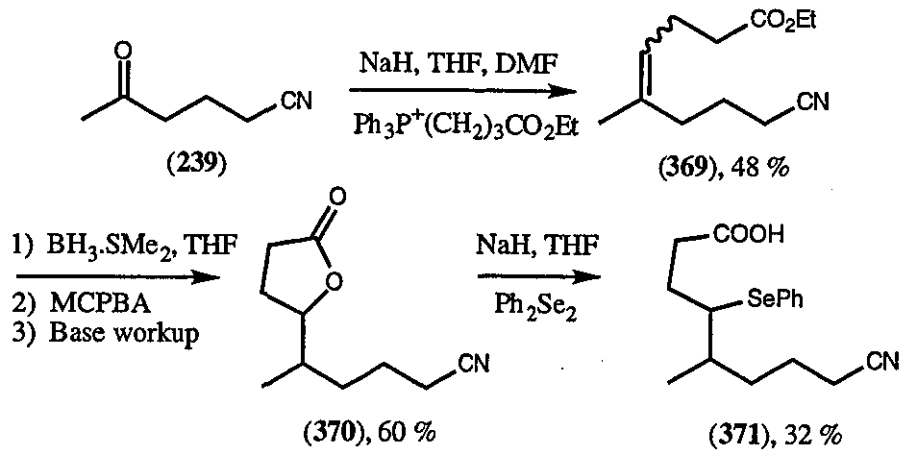
Scheme 130 shows an alternative tandem cyclisation pathway that would lead to pumilotoxin C (**281**). Cyclisations of this type, where the secondary radical (**367**) is an intermediate in the reaction, were not considered until the last stages of the research, and simple model reactions were not attempted to show the viability of these cyclisations.

Scheme 130



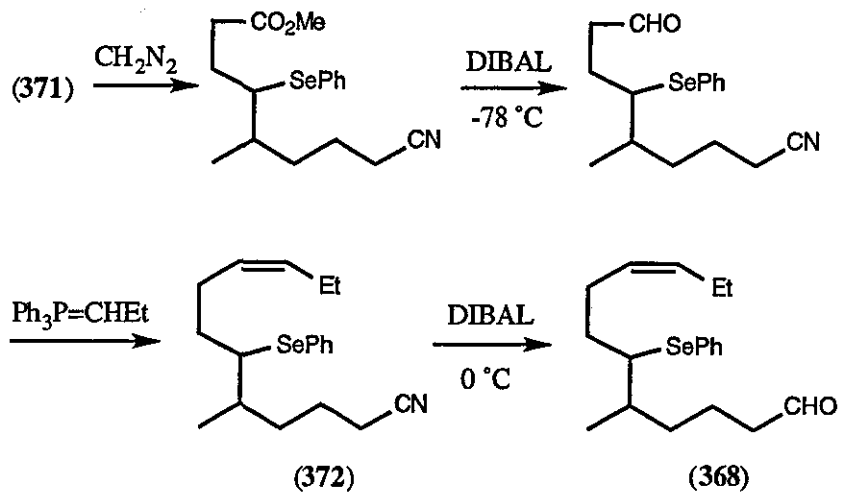
As this was the last major work project attempted in the research, the proposed synthesis of the aldehyde (**368**), was only partly completed. Scheme 131 shows a sequence of reactions achieved, leading to the carboxylic acid (**371**). Starting from 5-oxohexanonitrile (**239**), the Wittig reaction using (3-ethoxycarbonylpropyl)triphenyl-phosphonium bromide and sodium hydride in a 10:1 mixture of THF and DMF gave the poly-functional alkene (**369**) in reasonable yield though it did take some time for the reaction to work. The next stage was to incorporate the PhSe group into the correct position in the molecule. A number of methods of achieving this were considered but the best procedure involved hydroboration at low temperature, followed by oxidation by MCPBA, and a basic work-up to yield the lactone (**370**) in moderate yield. The PhSe group was introduced by opening the lactone using the benzeneselenide anion formed *in situ* from sodium hydride and diphenyl diselenide. After a difficult work-up procedure, the carboxylic acid (**371**) was isolated in an unoptimised 32%.

Scheme 131



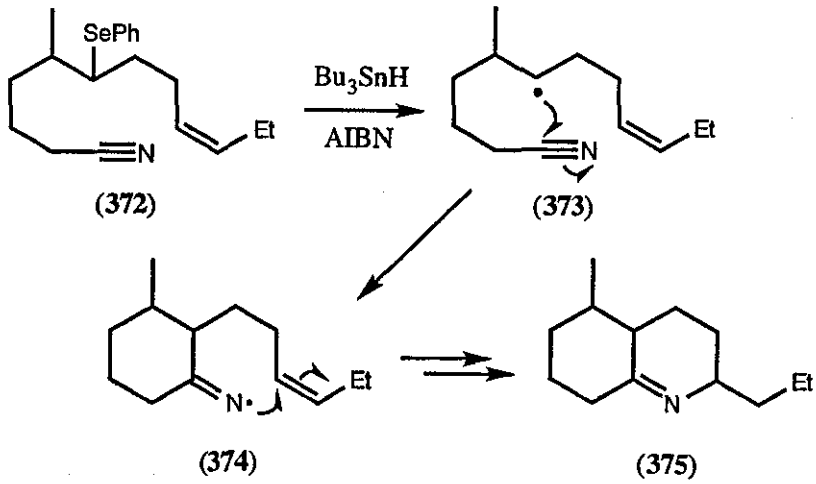
Scheme 132 shows the sequence of reactions which would have led to the aldehyde (**368**) if time had allowed. With the exception of the esterification using diazomethane, all the reaction steps had been successfully employed in other areas of the work. The reduction of the ester group using DIBAL would have been a risky step as the nitrile group can also reduce, and careful temperature control would have been essential.

Scheme 132



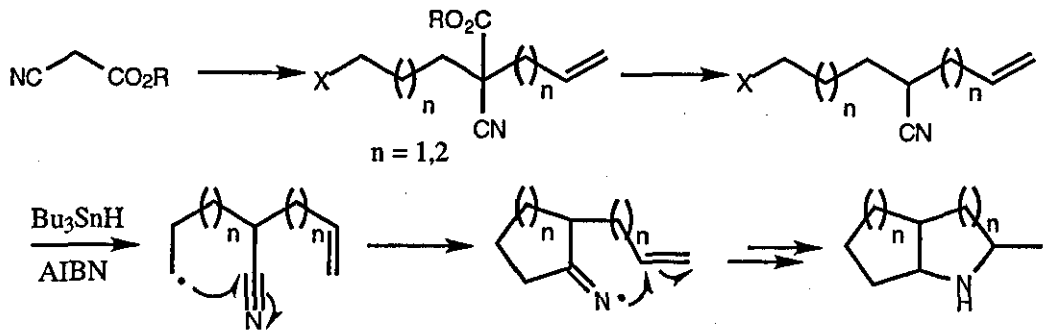
The nitrile (**372**) could be reduced to the aldehyde (**368**) using DIBAL as shown, which would be cyclised after condensation with an amine. Alternatively the nitrile (**372**) itself could be cyclised as illustrated in Scheme 133. This is an example of a tandem cyclisation which has no known literature precedent, though both cyclisations are known independently. The secondary alkyl radical (**373**) attacks the nitrile by 6-*exo* addition to form the iminyl radical (**374**), cyclising by further 6-*exo* addition to the alkene forming the imine (**375**). Reduction of the product under mild anhydrous conditions should yield pumiliotoxin C (**281**) or an isomer.

Scheme 133



This reaction has one problem associated with it, that is the slowness and unpredictability of 6-*exo* addition onto the nitrile group (see Section *3.1*). If this reaction had been attempted, a Lewis acid would have been added to the reaction mixture prior to cyclisation. This would have complexed to the nitrile group, thus rendering the CN moiety more reactive to radical attack. In any case, this reaction illustrated the potential synthetic utility of a tandem protocol that has so far received no known study. In Scheme 134, a sequence of reactions is shown that could result in the formation of a range of bicyclic heterocycles similar to those synthesised in the research but using nitrile intermediates instead of imines. There are several advantages of using nitriles. Halogen atoms can be used as radical leaving groups instead of the toxic PhSe group. The nitriles are stable intermediates and can be isolated and purified before cyclisation. The principal disadvantage of using nitriles is the generally slow rate of radical addition and there are distinct possibilities of other reactions competing with cyclisation.

Scheme 134



9.5. Summary of the Results of the Tandem Cyclisations.

1) All three of the principal tandem reactions investigated gave yields of bicyclic heterocycles. The syntheses of the three target natural products were not achieved during the research time, but the production of these product (or isomers) would be predicted based on the results of the work.

2) The cyclisation reactions producting indolizidines (Chapter 7) were as successful as expected and isolable yields of tandem products were observed in all the reactions attempted. However the yields of the tandem cyclisation products were not significantly improved when compared to those of the monocyclisation reactions. 6-*endo* Addition onto the imine carbon is a slow process and is largely unaffected by being part of a tandem reaction.

3) The formation of spirocyclic amines from ketimines (Chapter 8) was found to be a relatively inefficient process, but occurred in good yield by the complexation of the imine with a Lewis acid ($MgBr_2$) prior to cyclisation. This adaptation of the standard radical reaction resulted in a series of bicyclic amines being produced including the 6-*exo*, 6-*exo* tandem cyclisation product containing the ring system of perhydrohistrio-nicotoxin.

4) Reactions producing bicyclic amines analogous to pumilotoxin alkaloids (Chapter 9) yielded generally good yields of 5-*exo*, 5-*exo* and 6-*exo*, 5-*exo* tandem reaction products. However some of the reaction steps presented more problems than had been predicted for all three synthetic strategies attempted. As a result 6-*exo*, 6-*exo* and 5-*exo*, 6-*exo* cyclisations were not achieved.

10. Experimental Section.

10.1. Index of Compounds..

Chapter 4: Initial Studies - Preparation of Simple Imines for Cyclisation.

Chapter 7: Tandem Cyclisation Reactions - 1.

Chapter 8: Tandem Reactions 2 - The Synthesis of Spirocyclic Amines.

10.2. General Information.

All solvents were distilled before use: light petroleum (b.pt. 40-60°C), diethyl ether and ethyl acetate from calcium chloride; dichloromethane and toluene from phosphorus pentoxide; ethanol and methanol from magnesium, and THF from sodium benzophenone ketyl. DMF was distilled, under reduced pressure, from calcium hydride. Chemicals used in the work were ordered predominantly from Aldrich Chemical Co. Ltd. and Lancaster Synthesis Ltd. and were distilled or recrystallised as required. TLC silica was used in the purification of compounds by dry flash chromatography and the products of the cyclisation reactions were separated on alumina TLC plates.

The instruments and conditions for spectroscopic analyses were as follows except where indicated:

Infra-red spectra were recorded using neat films on a Nicolet 205 FT-IR Spectrometer.

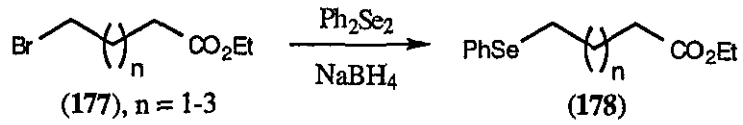
NMR spectroscopic analysis were carried out using deuterochloroform as solvent and tetramethylsilane as internal standard. 250 MHz ^{1}H NMR spectra and 62.9 MHz ^{13}C NMR spectra were run on a Brucker AC250 Spectrometer. ^{1}H NMR spectra were also run at 300 MHz on a Varian Unity 300 Spectrometer. ^{13}C NMR spectra were also run at 75 MHz on a Brucker AC300 Spectrometer. In later work, 400 MHz ^{1}H NMR spectra and 100 MHz ^{13}C NMR spectra were carried out on a Brucker DPX 400 Spectrometer. For the calculation of yields by ^{1}H NMR spectroscopy, *p*-dimethoxybenzene was used as an internal standard.

GLC analyses were undertaken using a Pye series 104 Chromatograph on a column of 15% diethylene glycol succinate (DEGS) on alumina at 150°C. *N*-Methylcyclohexylamine was the internal standard for aliphatic amines and *N*-methylaniline for aromatic amines.

Electron impact (E.I.) mass spectra were recorded on a Kratos MS80 Mass Spectrometer. GC-MS spectra and chemical ionisation (C.I.) spectra were provided by the EPSRC Mass Spectroscopy Service at University College, Swansea.

Elemental analyses were carried out on a Perkin Elmer 2400 CHN Elemental Analyser. Only data for solid compounds and some fluids have been included. Compounds containing selenium were not submitted for elemental analysis and the data obtained for oils were unsatisfactory. The spectroscopic data obtained from other techniques permitted characterisation of these compounds.

Ethyl 4-benzeneselenylbutyrate (178a, n = 1).



General procedure for the preparation of benzeneselenyl compounds. Diphenyl diselenide (476 mg, 1.5 mmol) was stirred in absolute ethanol (25 cm^3) at room temperature under nitrogen and sodium borohydride (152 mg, 4.5 mmol) was added. After 30 min, ethyl 4-bromobutyrate (**177a**) (632 mg, 3.3 mmol) dissolved in absolute ethanol (5 cm^3) was added and the mixture was stirred for 16 h. The reaction was quenched with hydrochloric acid (2 M, 10 cm^3) and the solution extracted with diethyl ether (8 x 20 cm^3). The combined extracts were washed with saturated sodium hydrogen carbonate (2 x 20 cm^3) and brine (10 cm^3) and dried with magnesium sulphate. The solution was evaporated to dryness and the residue was purified by dry flash chromatography using silica gel as absorbent and light petroleum / ethyl acetate mixtures as eluent. *Ethyl 4-benzeneselenyl-butyrate* (**178a**) was obtained as a yellow oil (782 mg, 89%); ν_{max} 3057, 2930, 1735 (ester), 1576 (phenyl), 1477, 1437, 1025, and 739 cm^{-1}.; δ_H 7.53 (2 H, m, phenyl ortho-H), 7.24 (3 H, m, phenyl H), 4.11 (2 H, q, J = 7.1 Hz, ethyl CH_2), 2.94 (2 H, t, J = 7.3 Hz, 4-H), 2.44 (2 H, t, J = 7.3 Hz, 2-H), 1.98 (2 H, t, J = 7.3 Hz, 3-H), and 1.24 (3 H, t, J = 7.1 Hz, Me); δ_C 172.8 (C=O), 132.57 (Ar-CH), 129.92 (Ar-C), 129.02 and 126.61 (Ar-CH), 60.29 (ethyl CH_2), 33.89 (2-C), 26.91 and 25.31 (3,4-C), and 14.19 (Me); *m/z* 272.0305 [M^+, (11%), $C_{12}H_{16}O_2Se$ requires 272.0315], 227 (M^+-EtO, 8), 157 ($PhSe^+$, 12), 115 (59), 87 (100), 77 (Ph^+, 15), 69 (8.7), 51 (11), and 43 (38).

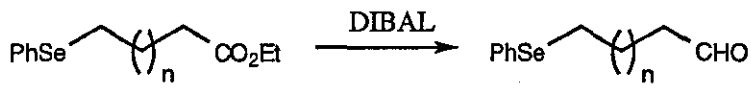
Ethyl 5-benzeneselenylpentanoate (178b, n = 2).

The general procedure for the introduction of the benzeneselenyl group was used. Diphenyl diselenide (475 mg, 1.5 mmol), sodium borohydride (150 mg, 4.4 mmol) and ethyl 5-bromo-pentanoate (**177b**) (676 mg, 3.2 mmol) gave *ethyl 5-benzeneselenyl-pentanoate* (**178b**) as an orange-yellow oil (824 mg, 90%); ν_{max} 3057, 2935, 1736 (C=O stretch), 1576 (phenyl), 1477, 1437, and 739 cm^{-1}; δ_H 7.47 (2 H, m, phenyl ortho-H), 7.24 (3 H, m, phenyl H), 4.10 (2 H, q, J = 7.1 Hz, ethyl CH_2), 2.90 (2 H, t, J = 7.0 Hz, 5-H), 2.29 (2 H, t, J = 7.1 Hz, 2-H), 1.70-1.76 (4 H, m, 3,4-H), and 1.23 (3 H, t, J = 7.1 Hz, Me); δ_C 173.15 (C=O), 132.46 (Ar-CH), 130.20 (Ar-C), 128.97 and 126.68 (Ar-CH), 60.19 (ethyl CH_2), 33.65 (2-C), 29.52, 27.21 and 25.03 (3,4,5-C), and 14.22 (Me); *m/z* 286.0460 [M^+, (9.4%), $C_{13}H_{18}O_2Se$ requires 286.0472], 157 ($PhSe^+$, 15), 129 (M^+-PhSe, 75), 101 (92), 83 (48), 77 (Ph^+, 27), and 55 (70).

Ethyl 6-benzeneselenylhexanoate (178c, n = 3).

The general procedure for the introduction of the benzeneselenyl group was used. Diphenyl diselenide (477 mg, 1.5 mmol), sodium borohydride (143 mg, 4.2 mmol) and ethyl 6-bromo-hexanoate (**177c**) (716 mg, 3.2 mmol) gave *ethyl 6-benzeneselenyl-hexanoate* (**178c**) as an orange-yellow oil (876 mg, 92%); ν_{max} 3055, 2937, 1733 (C=O stretch), 1577 (phenyl), 1480, 1437, and 739 cm^{-1}; δ_H 7.47 (2 H, m, phenyl ortho-H), 7.24 (3 H, m, phenyl H), 4.11 (2 H, q, J = 7.1 Hz, ethyl CH_2), 2.90 (2 H, t, J = 7.4 Hz, 6-H), 2.27 (2 H, t, J = 7.4 Hz, 2-H), 1.45-1.65 (6 H, m, 3,4,5-H), and 1.24 (3 H, t, J = 7.1 Hz, CH_3); δ_C 173.24 (C=O), 132.37 (Ar-CH), 130.25 (Ar-C), 128.95 and 126.61 (Ar-CH), 60.16 (ethyl CH_2), 34.07 (2-C), 29.71 (6-C), 29.18, 27.49, 24.35 (3,4,5-C), and 14.23 (Me); *m/z* 300.0620 [M^+, (12%), $C_{14}H_{20}O_2Se$ requires 300.0628], 158 ($PhSeH^+$, 12), 143 (M^+-PhSe, 28), 115 (23), 97 (63), 69 (100), 55 (25), and 41 (49).

4-Benzeneselenylbutanal (179a, n = 1).



(**178**), n = 1-3 (**179**)

General procedure for the reduction of an ester to an aldehyde. A stirred solution of diisobutylaluminium hydride (25% w/w in toluene, 12.0 cm^3, 2.390 g, 17.0 mmol) in in dry toluene (50 cm^3) was cooled to -78°C and ethyl 4-benzeneselenylbutyrate (**178a**) (1.058 g, 3.9 mmol) dissolved in dry toluene (10 cm^3) was added dropwise over 0.5 h. Stirring was continued at -78°C for 3 h after which acetic acid (5 cm^3 in 10 cm^3) of toluene was added dropwise over 1 h, keeping the temperature inside the reaction flask below -50°C. The solution was allowed to warm to 0°C before water (3 cm^3) was added. Solid sodium carbonate (10 g) was added in small portions and the solid residue extracted with ethyl acetate (7 x 20 cm^3). The combined extracts were evaporated to dryness. The crude product was purified by dry flash chromatography using silica gel as absorbent and light petroleum / ethyl acetate mixtures as eluent to yield *4-benzene-selenylbutanal* (**179a**) as a yellow oil (816 mg, 92%); ν_{max} 3057, 2925, 1720 (C=O stretch), 1577 (phenyl), 1479, and 1440 cm^{-1}; δ_H 9.72 (1 H, s, 1-H), 7.43 (2 H, m, phenyl ortho-H), 7.21 (3 H, m, phenyl H), 2.94 (2 H, t, J = 7.1 Hz, 4-H), 2.60 (2 H, t, J = 7.0 Hz, 2-H), and 2.05 (2H, m, J = 7.1 Hz, 3-H); δ_C 194.25 (C=O), 132.48 (Ar-CH), 130.05 (Ar-C), 129.10 and 127.02 (Ar-CH), 27.62 (2-C), 27.15 (4-C), and 25.27 (3-C); *m/z* 228.0052 [M^+, (13%), $C_{10}H_{12}OSe$ requires 228.0053], 158 (26, $PhSeH^+$), 108 (11), 91 (14), 78 (34), 71 (M^+-PhSe, 100), 51 (13), and 43 (37).

5-Benzeneselenylpentanal (179b, n = 2).

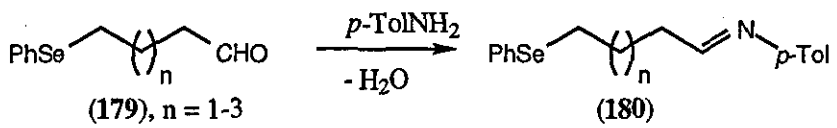
The general procedure for the synthesis of aldehydes was used. Ethyl 5-benzeneselenyl-pentanoate (**178b**) (920 mg, 3.2 mmol) and diisobutylaluminium hydride (2.990 g, 21.3

mmol) gave *5-benzeneselenylpentanal* (**179b**) as a yellow oil (727 mg, 93%); ν_{max} 3055, 2937, 1720 (C=O stretch), 1577 (phenyl), 1479, and 1439 cm^{-1}; δ_H 9.72 (1 H, s, 1-H), 7.48 (2 H, m, phenyl ortho-H), 7.25 (3 H, m, phenyl H), 2.89 (2 H, t, J = 7.6 Hz, 5-H), 2.42 (2 H, t, J = 6.9 Hz, 2-H), and 1.72 (4 H, m, 3,4-H); δ_C 202.03 (C=O), 132.58 (Ar-CH), 130.20 (Ar-C), 129.02 and 126.78 (Ar-CH), 43.15 (2-C), 29.46, 27.28, and 22.05 (3,4,5-C); *m/z* 242.0224 [M^+, (19%), $C_{11}H_{13}OSe$ requires 242.0210], 158 ($PhSeH^+$, 61), 108 (77), 91 (46), 85 (M^+-PhSe, 38), 79 (83), 69 (100), and 57 (46).

6-Benzeneselenylhexanal (**179c**, n = 3).

The general procedure for the synthesis of aldehydes was used. Ethyl 6-benzeneselenylhexanoate (**178c**) (939 mg, 3.1 mmol) and diisobutylaluminium hydride (1.992 g, 14.2 mmol) gave *6-benzeneselenylhexanal* (**179c**) as a yellow oil (656 mg, 82%); ν_{max} 3055, 2933, 1725 (C=O stretch), 1577 (phenyl), 1477, and 1437 cm^{-1}; δ_H 9.75 (1 H, s, 1-H), 7.47 (2 H, m, phenyl ortho-H), 7.24 (3 H, m, phenyl H), 2.90 (2 H, t, J = 7.3 Hz, 6-H), 2.40 (2 H, t, J = 7.0 Hz, 2-H), and 1.45-1.65 (6 H, m, 3,4,5-H); δ_C 202.32 (C=O), 132.42 (Ar-CH), 130.23 (Ar-C), 128.97 and 126.67 (Ar-CH), 43.60 (2-C), 29.77 (6-C), 29.13, 27.45, and 21.42 (3,4,5-C); *m/z* 256.0347 [*M*+, (23%), $C_{12}H_{16}OSe$ requires 256.0366], 158 ($PhSeH^+$, 46), 129 (75), 101 (92), 83 (48), 77 (Ph^+, 27), 55 (100), and 29 (88).

***N*-(4-Benzeneselenylbut-1-ylidene)-4-methylaniline** (**180a**, n = 1).



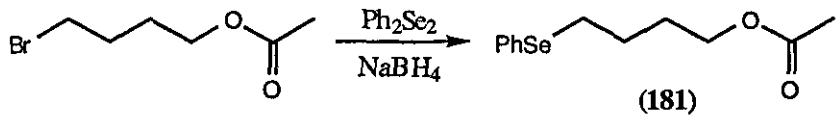
General procedure for the synthesis of imines using molecular sieves (method A). A solution of *p*-toluidine (127 mg 1.18 mmol) in of dry toluene (20 cm^3) was added a solution of 4-benzeneselenylbutanal (**179a**) (268 mg, 1.18 mmol) in dry toluene (20 cm^3) followed by type 4 Å molecular sieves (ca. 5 g). The mixture was stirred at room temperature for 24 h after which the sieves were removed by filtration and washed with dry toluene. The solution was evaporated to dryness to give the crude imine which was purified by flash sinter chromatography using silica gel as absorbent and light petroleum / ethyl acetate mixtures as eluent. The solution of the imine was evaporated to dryness to give *N-(4-benzeneselenylbut-1-ylidene)-4-methylaniline* (**180a**) as an orange-red oil (300 mg, 80%); ν_{max} 3051, 2921, 2853, 1660 (C=N), 1617, 1577 (phenyl), 1476, and 1437 cm^{-1}; δ_H 7.44 (2 H, m, PhSe ortho-H), 7.20-7.28 (3 H, m, aromatic H), 6.98 (1 H, m, imine H), 6.90 (2 H, m), 6.52 (2 H, m, *p*-tolyl H), 2.80-2.96 (2 H, m, 4-H), 2.28 (3 H, s, Me), and 1.46-1.77 (4 H, m, 2,3-H); δ_C 144.27 (Ar-C), 132.60 and 132.31 (Ar-CH), 130.03 (Ar-C), 129.07 and 126.61 (Ar-CH), 120.67 (C=N), 113.86 (Ar-CH), 112.66 (Ar-C), 54.19 (2-C), 32.56, 27.68 (3,4-C), and 20.53 (Me); *m/z* 317.0383 [M^+, (1.7%),

$C_{17}H_{19}NSe$ requires 317.0682], 314 (37), 235 (18), 157 ($PhSe^+$, 80), 77 (Ph^+, 100), and 55 (86).

***N*-(5-Benzeneselenylpent-1-ylidene)-4-methylaniline (180b**, n = 2).
The imine was synthesized according to the general procedure for imine formation (method A). 5-Benzeneselenylpentanal (**179b**) (345 mg, 1.4 mmol) and *p*-toluidine (153 mg, 1.4 mmol) gave *N-(5-benzeneselenylpent-1-ylidene)-4-methylaniline* (**180b**) as an orange-red oil (390 mg, 84%); ν_{max} 3024, 2931, 2858, 1663 (C=N), 1616, 1576 (phenyl), 1477, 1437, and 739 cm^{-1}; δ_H 7.47 (2 H, m, PhSe ortho-H), 7.20-7.28 (m, aromatic H), 6.98 (1 H, m, 1-H), 6.90 (2 H, m), 6.52 (2 H, m, *p*-tolyl H), 2.85 (2 H, m, 5-H), 2.25 (3 H, s, Me), and 1.61-1.72 (6 H, m, alkyl H); δ_C 145.42 (Ar-C), 132.65 (Ar-CH), 130.00 (Ar-C), 129.13, 126.73 and 125.42 (Ar-CH), 120.40 (C=N), 113.57 (Ar-CH), 112.65 (Ar-C), 54.21 (2-C), 30.26, 28.21, 28.05 (3,4,5-C), and 20.55 (Me); *m/z* 331.0359 [M^+, (0.3%), $C_{18}H_{21}NSe$ requires 331.0839], 314 (51), 234 (23), 157 ($PhSe^+$, 100), 106 (82), 77 (Ph^+, 82), and 69 (49).

***N*-(6-Benzeneselenylhex-1-ylidene)-4-methylaniline (180c**, n = 3).
The imine was synthesized according to the general procedure for imine formation (method A). 6-Benzeneselenylhexanal (**179c**) (285mg, 1.0 mmol) and *p*-toluidine (120 mg, 1.0 mmol) gave *N-(6-benzeneselenylhex-1-ylidene)-4-methylaniline* (**180c**) as an orange-red oil (346 mg, 90%); ν_{max} 3024, 2931, 2858, 1663 (C=N), 1616, 1576 (phenyl), 1483, 1437, and 733 cm^{-1}; δ_H 7.45 (2 H, m, PhSe ortho-H), 7.12-7.27 (m, aromatic H), 6.99 (1 H, m, 1-H), 6.89 (2 H, m), 6.57 (2 H, m, p-tolyl H), 2.85 (2 H, t, J = 7.5 Hz, 6-H), 2.32 (3 H, s, Me), 2.22 (2 H, m, 2-H), and 1.36-1.65 (6 H, m, alkyl H); δ_C 145.38 (Ar-C), 132.52 (Ar-CH), 130.62, (Ar-C), 129.08, 128.21 and 126.46 (Ar-CH), 120.35 (C=N), 113.60 (Ar-CH), 112.71 (Ar-C), 54.10 (2-C), 29.71 (6-C), 27.67, 27.53, 25.51 (3,4,5-C), and 21.42 (Me); *m/z* 345.0980 [M^+, (8%), $C_{19}H_{23}NSe$ requires 345.0995], 190 (23), 158 ($PhSeH^+$, 19), 120 (100), 106 (40), 91 (22), 78 (PhH^+, 36), and 55 (28).

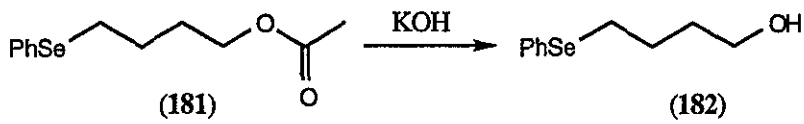
4-Benzeneselenylbutyl acetate (181).



The general procedure for the introduction of the benzeneselenyl group was used. Diphenyl diselenide (495 mg, 1.6 mmol), sodium borohydride (139 mg, 3.7 mmol) and 4-bromobutyl acetate (632 mg, 3.2 mmol) gave *4-benzeneselenylbutyl acetate* (**181**) as an orange oil (715 mg, 82%); ν_{max} 3055, 2937, 1738 (C=O stretch), 1578 (phenyl), 1477, 1438, 1365, and 1236 cm^{-1}; δ_H 7.49 (2 H, m, phenyl ortho-H), 7.25 (3 H, m, phenyl H),

4.06 (2H, q, J = 6.1 Hz, 1-H), 2.92 (2 H, t, J = 6.8 Hz, 4-H), 2.02 (3 H, s, Me), and 1.26 (4 H, m, 2,3-H); δ_C 171.25 (C=O), 132.64 (Ar-CH), 130.20 (Ar-C), 128.96 and 126.78 (Ar-CH), 63.69 (1-C), 28.60 (4-C), 27.25 and 26.50 (2,3-C), and 20.83 (Me); *m/z* 272.0315 [*M*+, (17%), $C_{12}H_{16}O_2Se$ requires 272.0315], 158 ($PhSeH^+$, 17), 115 (M^+-PhSe, 19), 91 (10), 73 (18), 55 (90), and 43 (100).

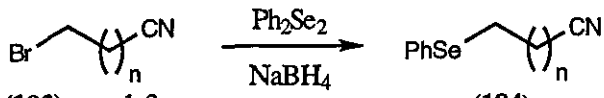
4-Benzeneselenylbutan-1-ol (182).



(181) (182)

4-Benzeneselenylbutyl acetate (**181**) (603 mg, 2.2 mmol) was dissolved in a solution of 0.2 M potassium hydroxide in 9:1 methanol / water (20 cm^3). The mixture was refluxed for 2 h and then the alcohol was extracted into diethyl ether (4 x 20 cm^3). The combined extracts were washed with hydrochloric acid (2 M) and dried ($MgSO_4$). The solution was evaporated to dryness to yield *4-benzeneselenylbutan-1-ol* (**182**) as an orange viscous oil (364 mg, 72%); ν_{max} 3500 (OH stretch), 3063, 2937, 1577 (phenyl), 1476, and 1436 cm^{-1}; δ_H 7.48 (2 H, m, phenyl ortho-H), 7.24 (3 H, m, phenyl H), 3.65 (2 H, t, J = 6.1 Hz, 1-H), 2.94 (2 H, t, J = 7.1 Hz, 4-H), and 1.70-1.80 (4 H, m, 2,3-H); δ_C 132.49 (Ar-CH), 130.29 (Ar-C), 128.96 and 126.69 (Ar-CH), 62.16 m(1-C), 32.63 (4-C), 27.58, and 26.41 (2,3-C); *m/z* 230.0217 [M^+, (0.2%), $C_{10}H_{14}OSe$ requires 230.0210], 196 (100), 151 (29), 132 ($C_4H_4Se^+$, 45), 122 (19), 105 (37), and 79 (13).

3-Benzeneselenylpropanonitrile (184a, n = 1).



(183), n = 1-3 (184)

The general procedure for the introduction of the benzeneselenyl group was used. Diphenyl diselenide (479 mg, 1.5 mmol), sodium borohydride (146 mg, 4.3 mmol) and 3-bromo-propanonitrile (**183a**) (437 mg, 3.3 mmol) gave *3-benzeneselenylpropanonitrile* (**184a**) as an orange oil (603 mg, 88%); ν_{max} 3057, 2944, 2247 (CN stretch), 1576 (phenyl), 1477, 1437, and 739 cm^{-1}; δ_H 7.54 (2 H, m, phenyl ortho-H), 7.27 (3 H, m, phenyl H), 3.02 (2 H, t, J = 7.6 Hz, 3-H), and 2.66 (2 H, t, J = 7.6 Hz, 2-H); δ_C 133.96 (Ar-CH), 129.39 (Ar-C), 128.04 and 127.58 (Ar-CH), 118.64 (CN), 21.70 (3-C), and 18.88 (2-C); *m/z* 210.9910 [M^+, (100%), C_9H_9NSe requires 210.9900], 171 ($PhSeCH_2^+$, 83), 157 ($PhSe^+$, 85), 115 (7), 91 (61), 77 (44), and 39 (8).

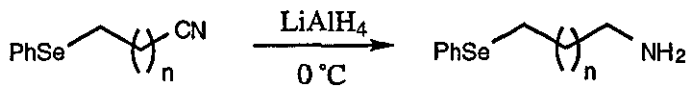
4-Benzeneselenylbutanonitrile (184b, n = 2).

The general procedure for the introduction of the benzeneselenyl group was used. Diphenyl diselenide (473 mg, 1.5 mmol), sodium borohydride (150 mg, 4.4 mmol) and 4-bromobutanonitrile (**183b**) (475 mg, 3.2 mmol) gave *4-benzeneselenylbutanonitrile* (**184b**) as a yellow oil (578 mg, 81%); ν_{max} 3057, 2931, 2247 (CN stretch), 1576 (phenyl), 1477, 1437, and 739 cm^{-1}; δ_H 7.48 (2 H, m, phenyl ortho-H), 7.28 (3 H, m, phenyl H), 2.98 (2 H, t, J = 7.0 Hz, 4-H), 2.49 (2 H, t, J = 7.4 Hz, 2-H), and 2.00 (2 H, q, J = 7.0 Hz, 3-H); δ_C 132.99 (Ar-CH), 129.22 (Ar-C), 128.75 and 127.34 (Ar-CH), 119.02 (CN), 25.92 (4-C), 25.61 (2-C), and 16.90 (3-C); *m/z* 225.0062 [M^+, (83%), $C_{10}H_{11}NSe$ requires 225.0056], 158 ($PhSeH^+$, 77), 91 (38), 78 (100), 68 (M^+-PhSe, 35), 39 (50), and 27 (30).

5-Benzeneselenylpentanonitrile (184c, n = 3).

The general procedure for the introduction of the benzeneselenyl group was used. Diphenyl diselenide (476 mg, 1.5 mmol), sodium borohydride (142 mg, 4.2 mmol) and 5-bromo-pentanonitrile (**183c**) (514 mg, 3.2 mmol) gave *5-benzeneselenylpentanonitrile* (**184c**) as a yellow oil (673 mg, 88%); ν_{max} 3057, 2938, 2247 (CN stretch), 1576 (phenyl), 1477, 1437, and 739 cm^{-1}; δ_H 7.46 (2 H, m, phenyl ortho-H), 7.25 (3 H, m, phenyl H), 2.89 (2 H, t, J = 7.0 Hz, 5-H), 2.29 (2 H, t, J = 7.0 Hz, 2-H), and 1.72-1.82 (4 H, m, 3,4-H); δ_C 132.70 (Ar-CH), 129.75 (Ar-C), 129.15 and 127.0 (Ar-CH), 119.47 (CN), 28.88 (5-C), 26.59 (2-C), 25.19, and 16.64 (3,4-C); *m/z* 239.0206 [M^+, (93%), $C_{11}H_{13}NSe$ requires 239.0213], 158 ($PhSeH^+$, 100), 91 (24), 82 (M^+-PhSe, 54), 78 (91), 55 (60), and 41 (35).

3-Benzeneselenyl-1-propylamine (185a, n = 1).



(**184**, n = 1-3) (**185**)

Dry diethyl ether (40 cm^3) was added to lithium aluminium hydride (140 mg, 4.8 mmol, 0.75 equiv) and the reaction mixture was cooled to 0°C. 3-Benzeneselenylpropanonitrile (**184a**) dissolved in dry diethyl ether (10 cm^3) was added dropwise and the mixture was stirred for 2 h. Sodium hydroxide solution (0.1 M, 20 cm^3) was added dropwise and the amine was extracted into the ether layer. The amine was purified by extracting into hydrochloric acid (2 M, 3 x 20 cm^3). The combined extracts were washed with diethyl ether (2 x 10 cm^3) and neutralised with solid sodium carbonate. Once all effervescing had ceased the solution was made strongly basic by sodium hydroxide and the amine extracted into ethyl acetate (4 x 20 cm^3), The combined extracts were dried ($MgSO_4$) and the solution evaporated to dryness. *3-Benzeneselenyl-1-propylamine* (**185a**) was obtained as an orange-red viscous oil (708 mg, 60%); ν_{max} 3367, 3293, (NH stretch),

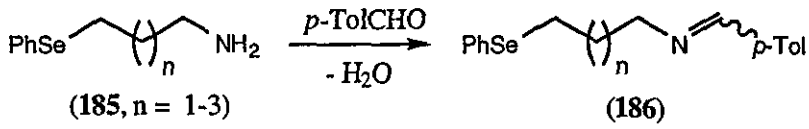
3056, 2933, 1635 (NH bend), 1574 (phenyl), 1479, and 1439 cm^{-1}; δ_H 7.48 (2 H, m, phenyl ortho-H), 7.24 (3 H, m, phenyl H), 2.94 (2 H, t, J = 7.4 Hz, 3-H), 2.73 (2 H, t, J = 5.8 Hz, 1-H), 1.85 (2 H, m, 2-H), and 1.73 (2 H, broad s, NH); δ_C 132.40 (Ar-CH), 130.16 (Ar-C), 129.20 and 126.76 (Ar-CH), 41.61 (1-C), 29.66 (3-C), and 24.95 (2-C); *m/z* 215 (M^+, 18%), 157 ($PhSe^+$, 15), 117 (3.5), 106 (14), 91 (4.7), 77 (16), and 30 ($CH_2{=}NH_2^+$, 100).

Alternative preparation of 3-benzeneselenylpropylamine (185a).
The general procedure for the introduction of the benzeneselenyl group was used. Diphenyl diselenide (959 mg, 3.1 mmol), sodium borohydride (76 mg, 2 mmol) and 3-bromopropylamine hydrobromide (1.40 g, 6.4 mmol) gave 3-benzeneselenylpropylamine (**185a**) as a colourless pungent oil (1.12 g, 82%) which was found to be identical to samples prepared by the first method.

4-Benzeneselenyl-1-butylamine (185b, n = 2).
The procedure used was the same as the preparation of 3-benzeneselenyl-1-propylamine (**185a**). Lithium aluminium hydride (129 mg, 3.8 mmol, 0.75 equiv) and 4-benzeneselenylbutanonitrile (**184b**) (1.135 g, 5.0 mmol) gave *4-benzeneselenyl-1-butylamine* (**185b**) as a yellow viscous oil (932 mg, 91%); ν_{max} 3390, 3293, (NH stretch), 3057, 2931, 1660 (NH bend), 1576 (phenyl), 1477, and 1437 cm^{-1}; δ_H 7.47 (2 H, m, phenyl ortho-H), 7.25 (3 H, m, phenyl H), 2.91 (2 H, t, J = 7.0 Hz, 4-H), 2.69 (2 H, t, J = 7.0 Hz, 1-H), 1.52-1.58 (4 H, m, 2,3-H), and 1.40 (2 H, broad s, NH); δ_C 132.38 (Ar-CH), 130.75 (Ar-C), 128.94 and 126.61 (Ar-CH), 50.66 (1-C), 41.35 (4-C), 28.11 (2-C), and 27.52 (3-C); *m/z* 229 (M^+, 4%), 157 ($PhSe^+$, 15), 117 (4), 106 (14), 91 (5), 77 (Ph^+, 16), 57 (26), and 30 ($CH_2{=}NH_2^+$, 100).

5-Benzeneselenyl-1-pentylamine (185c, n = 3).
The procedure used was the same as the preparation of 3-benzeneselenyl-1-propylamine (**185a**). Lithium aluminium hydride (94 mg, 2.8 mmol, 0.75 equiv) and 5-benzeneselenylpentanonitrile (**184c**) (875 mg, 3.6 mmol) gave *5-benzeneselenyl-1-pentylamine* (**185c**) as a yellow viscous oil (820 mg, 92%); ν_{max} 3363, 3293, (NH stretch), 3057, 2931, 1650 (NH bend), 1576 (phenyl), 1477, and 1437 cm^{-1}; δ_H 7.46 (2 H, m, phenyl ortho-H), 7.25 (3 H, m, phenyl H), 2.89 (2 H, t, J = 7.0 Hz, 5-H), 2.63 (2 H, t, J = 7.0 Hz, 1-H), 1.67 (2 H, m, J = 7.0 Hz, 2-H), 1.56 (2 H, broad s, NH), and 1.38-1.48 (4 H, m, 3,4-H); δ_C 132.40 (Ar-CH), 131.01 (Ar-C), 128.96 and 126.61 (Ar-CH), 41.93 (1-C), 33.09 (5-C), 29.88 (2-C), 27.78, and 27.00 (3,4-C); *m/z* 243 (M^+, 2%), 158 ($PhSeH^+$, 13), 112 (6), 91 (8), 77 (Ph^+, 15), 69 (23), and 30 ($CH_2{=}NH_2^+$, 100).

3-Benzeneselenyl-*N*-(4-methylbenzylidene)-1-propylamine (186a, n = 1).



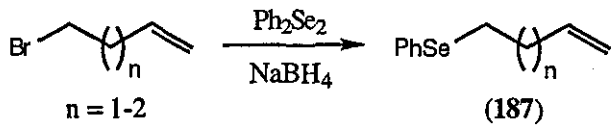
The imine was synthesized according to the general method for imine formation (method A). 3-Benzeneselenyl-1-propylamine (**185a**) (300mg, 1.4 mmol) and *p*-tolualdehyde (168 mg, 1.4 mmol) gave *3-benzeneselenyl-N-(4-methylbenzylidene)-1-propylamine* (**186a**) as an orange oil (330 mg, 75%); ν_{max} 3057, 2931, 2858, 1649 (C=N), 1603, 1576 (phenyl), 1477, 1437, and 739 cm^{-1}; δ_H 8.21 (1 H, s, CH=N), 7.60 (2 H, m), 7.43-7.47 (2 H, m, PhSe ortho-H), 7.18-7.25 (5 H, m, aromatic H), 3.68 (2 H, t, J = 6.5 Hz, propyl 1-H), 2.98 (2 H, t, J = 7.0 Hz, 3-H), 2.37 (3 H, s, Me), and 2.04-2.17 (2 H, m, 2-H); δ_C 161.50 (C=N), 140.85 (Ar-C), 133.53 and 132.43 (Ar-CH), 131.46 (Ar-C), 129.29 (Ar-CH), 128.20 (Ar-C), 126.69 and 126.15 (Ar-CH), 60.70 (1-C), 31.17 (3-C), 25.40 (2-C), and 21.48 (Me); *m/z* 317.0432 [M^+, (7.7%), $C_{17}H_{19}NSe$ requires 317.0682], 240 (M^+-Ph, 4.5), 159 (M^+-PhSeH, 30), 157 ($PhSe^+$, 31), 133 (100), 117 (65), 105 (42), 91 (24), and 77 (Ph^+, 50).

4-Benzeneselenyl-*N*-(4-methylbenzylidene)-1-butylamine (186b, n = 2).
General procedure for imine synthesis (method B). 4-Benzeneselenyl-1-butylamine (**185b**) (206 mg, 0.9 mmol) and *p*-tolualdehyde (108 mg, 0.9 mmol) were dissolved in dry dichloromethane and anhydrous sodium sulphate (ca. 3 g) was added. The reaction mixture was stirred for 3 days. The solution was filtered and the residue washed with dry dichloromethane. The solution was evaporated to dryness and *4-benzeneselenyl-N-(4-methylbenzylidene)-1-butylamine* (**186b**) was obtained as an orange oil (310 mg, 90%); ν_{max} 3059, 3026, 2933, 2840, 1645 (C=N), 1607, 1579 (phenyl), 1476, and 1438 cm^{-1}; δ_H 8.17 (1 H, s, CH=N), 7.58 (2 H, m), 7.45-7.49 (2 H, m, PhSe ortho-H), 7.16-7.22 (5 H, m, aromatic H), 3.58 (2 H, t, J = 6.8 Hz, butyl 1-H), 2.92 (2 H, t, J = 7.0 Hz, 4-H), 2.34 (3 H, s, Me), and 1.76-1.83 (4 H, m, 2,3-H); δ_C 160.93 (C=N), 140.74 (Ar-C), 133.61 and 132.44 (Ar-CH), 129.68 (Ar-C), 129.28 (Ar-CH), 128.02 (Ar-C), 126.62 and 125.29 (Ar-CH), 60.91 (1-C), 31.01(4-C), 27.92 (2-C), 27.63 (3-C), and 21.47 (Me); *m/z* 331.0384 [M^+, (0.7%), $C_{18}H_{21}NSe$ requires 331.0839], 314 (48), 234 (20), 174 (M^+-PhSe, 23), 157 ($PhSe^+$, 100), 132 (5), 119 (27), 91 ($C_7H_7^+$, 32), and 77 (Ph^+, 85).

5-Benzeneselenyl-*N*-(4-methylbenzylidene)-1-pentylamine (186c, n = 3).
The imine was prepared by general method B. 5-Benzeneselenyl-1-pentylamine (**185c**) (291 mg, 1.2 mmol) and *p*-tolualdehyde (144 mg, 1.2 mmol) gave *5-benzeneselenyl-N-(4-methylbenzylidene)-1-pentylamine* (**186c**) as an orange oil (376 mg, 91%); ν_{max} 3057, 2918, 2851, 1649 (C=N), 1609, 1576 (phenyl), 1477, 1437, and 733 cm^{-1}; δ_H 8.20 (1 H,

s, CH=N), 7.58 (2 H, d, J = 7.6 Hz, *p*-tolyl H), 7.42-7.45 (2 H, m, PhSe ortho-H), 7.14-7.23 (5 H, m, Ar-H), 3.52 (2 H, t, J = 6.8 Hz, 1-H), 2.85 (2 H, t, J = 7.5 Hz, 5-H), 2.25 (3 H, s, Me), and 1.45-1.64 (6 H, m, 2,3,4-H); δ_C 160.85 (C=N), 140.62 (Ar-C), 133.45 and 132.28 (Ar-CH), 129.21 (Ar-C), 128.89 and 127.96 (Ar-CH), 127.23 (Ar-C), 61.29 (1-C), 30.28 (5-C), 29.66 (2-C), 27.59 and 27.44 (3,4-C), and 21.41 (Me); *m/z* 345.0975 [M^+, (6%), $C_{19}H_{23}NSe$ requires 345.0995], 314 (2.8), 188 (M^+-PhSe 100), 157 ($PhSe^+$, 20), 146 (25), 119 (45), 105 (51), 91 (75), 77 (Ph^+, 44), 51 (32), and 41 (44).

4-Benzeneselenyl-1-butene (187a, n = 1).

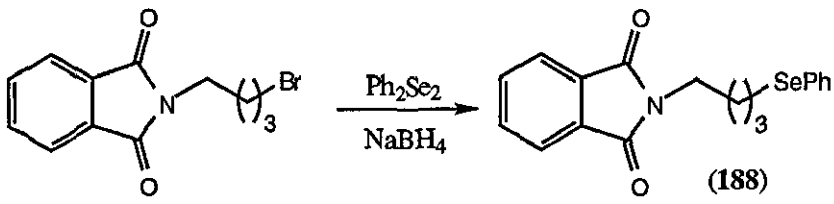


The general procedure for the introduction of the benzeneselenyl group was used. Diphenyl diselenide (481 mg, 1.5 mmol), sodium borohydride (141 mg, 4.1 mmol) and 4-bromo-1-butene (**O1s**) (432 mg, 3.2 mmol) gave alkene (**187a**) as a yellow oil (479 mg, 71%); ν_{max} 3074, 2977, 2931, 1640, 1577, 1479, and 1439 cm^{-1}; δ_H 7.49 (2 H, m), 7.24 (3 H, m, aromatic H), 5.83 (1 H, m, 2-H), 5.09 (1 H, m, *trans* 1-H), 5.04 (1 H, m, *cis* 1-H), 2.94 (2 H, t, J = 7.6 Hz, 4-H), and 2.45 (2 H, m, 3-H).

5-Benzeneselenyl -1-pentene (187b, n = 2).

The general procedure for the introduction of the benzeneselenyl group was used. Diphenyl diselenide (485 mg, 1.5 mmol), sodium borohydride (145 mg, 4.2 mmol) and 5-bromo-1-pentene (**O2s**) (477 mg, 3.2 mmol) gave alkene (**187b**) as a yellow oil (469 mg, 65%); ν_{max} 3072, 2974, 2933, 2851, 1638, 1579, 1475, and 1434 cm^{-1}; δ_H 7.48 (2 H, m), 7.23 (3 H, m, aromatic H), 5.76 (1 H, m, 2-H), 5.04 (1 H, m, *trans* 1-H), 4.97 (1 H, m, *cis* 1-H), 2.90 (2 H, t, J = 7.4 Hz, 5-H), 2.15 (2 H, m, 3-H), and 1.79 (2 H, m, 4-H).

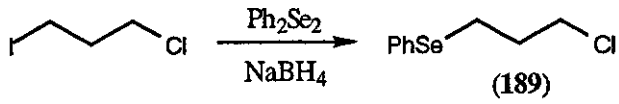
***N*-(4-Benzeneselenylbutyl)phthalimide (188).**



The general procedure for the introduction of the benzeneselenyl group was used. Diphenyl diselenide (0.487 g, 1.5 mmol), sodium borohydride (0.150 g, 4.4 mmol) and *N*-(4-bromobutyl)phthalimide (0.912 g, 3.2 mmol) gave *N-(4-benzeneselenylbutyl)-phthalimide* (**188**) as a yellow viscous oil (1.143 g, 90%); ν_{max} 3055, 2937, 1770, 1709, (C=O stretch) 1615, 1579 (phenyl), 1478, 1465, 1436, 1392, 1038, 738, 719, and 692

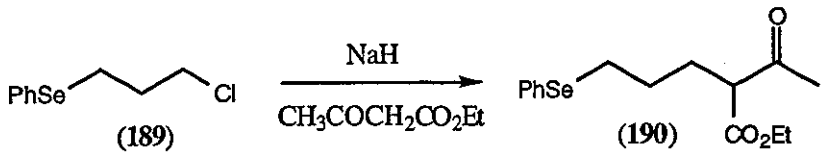
cm^{-1}; δ_H 7.82, (2 H, m) 7.69 (2 H, m), 7.46 (2 H,m), 7.20 (3 H, m, aromatic), 3.70 (2 H, t, J = 6.9 Hz, 1-H), 2.92 (2 H, t, J = 7.0 Hz, 4-H), and 1.76-1.84 (4 H, m, 2,3-H); δ_C 133.92, 133.84 (Ar-C), 132.67 (Ar-CH), 131.99 (Ar-C), 128.93, 126.73, 123.18 and 123.12 (Ar-CH), 37.23 (1-C), 32.74 (4-C), 28.52, and 27.08 (2,3-C).

1-Benzeneselenyl-3-chloropropane (189).



The general procedure for the introduction of the benzeneselenyl group was used. Diphenyl diselenide (1.96g, 6.3 mmol), sodium borohydride (600 mg, 15.8 mmol) and 1-chloro-3-iodopropane (2.62 g, 12.8 mmol) gave 1-benzeneselenyl-3-chloro-propane (**189**) as a yellow-orange oil (2.94 g, 98%); ν_{max} 3072, 2956, 2940, 1579 (phenyl), 1478, 1438, 1304, 1233, 1072, and 739 cm^{-1}; δ_H 7.44-7.49 (2 H, m, ortho-H), 7.25-7.30 (3 H, m, phenyl H), 3.62 (2H, t, J = 6.3 Hz, 3-H), 3.03 (2 H, t, J = 7.0 Hz, 1-H), and 2.10-2.15 (2 H, m, 2-H); δ_C 132.82 and 132.68 (Ar-CH), 129.23 (Ar-C), 127.25 (Ar-CH), 44.20 (3-C), 32.46, and 25.05; *m/z* 233.9710 [M^+, (100%), $C_9H_{11}ClSe$ requires 233.9714], 171 ($PhSeCH_2^+$, 15), 158 ($PhSeH^+$, 75), 117 (11), 91 (31), 78 (81), 51 (30), and 41 (56).

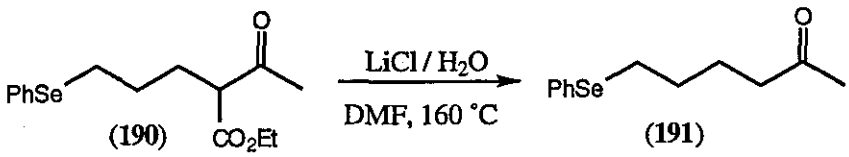
Ethyl 2-acetyl-5-benzeneselenylpentanoate (190).



General procedure for the 2-alkylation of 3-oxoalkanoate esters. Sodium hydride (160 mg of 60% suspension in mineral oil) was placed in a dried flask and was washed, under nitrogen, by dry light petroleum (2 x 10 cm^3). Freshly dried and distilled THF (20 cm^3) was added and to the suspension was added solution of ethyl 3-oxobutanoate (403 mg, 3.1 mmol) in THF (10 cm^3). After stirring at room temperature for 30 min, the solution was cooled to 0°C and 1-benzeneselenyl-3-chloropropane (**189**) (724 mg, 3.1 mmol) in THF (10 cm^3) was added dropwise over 10 min. The mixture was stirred at room temperature for 2 h after which the solvent was removed. To the residue, water (10 cm^3) was added and the organic products extracted into diethyl ether (5 x 10 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated to dryness. The crude product was purified by dry flash chromatography using silica gel as absorbent and light petroleum / ethyl acetate mixtures as eluent. *Ethyl 2-acetyl-5-benzeneselenylpentanoate* (**190**) was isolated as a light yellow oil (878 mg, 86%); ν_{max} 3072, 2957, 2939, 1741

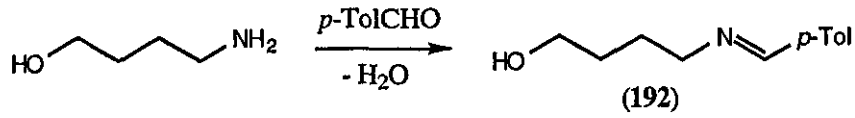
(ester), 1718 (C=O), 1579 (Ph), 1478, 1438, 1304, 1234, 1023, 735, and 691 cm^{-1}; δ_H 7.44-7.48 (2 H, m, phenyl ortho-H), 7.21-7.23 (3 H, m, phenyl H), 4.15 (2 H, q, J = 7.2 Hz, ethyl CH_2), 3.39 (1 H, t, J = 7.3 Hz, 2-H), 2.88 (2 H, t, J = 7.3 Hz, 5-H), 2.18 (3 H, s, acetyl CH_3), 1.91-1.99 (2 H, m), 1.60-1.67 (2 H, m), and 1.25 (3 H, t, J = 7.3 Hz, ethyl CH_3); δ_C 202.63 (ketone-CO), 169.49 (ester-CO), 132.62 (Ar-CH), 129.99 (Ar-C), 129.05 and 126.86 (Ar-CH), 61.35 (ethyl CH_2), 59.17 (2-C), 28.72 (acetyl CH_3), 28.02, 27.62, 26.63, and 14.06 (ethyl CH_3); *m/z* 328.0543 [M^+, (3.5%), $C_{15}H_{20}O_3Se$ requires 328.0577], 253 (8), 234 (66), 169 (M^+-PhSeH-H, 30), 158 ($PhSeH^+$, 62), 105 (23), 91 (51), 78 (86), and 41 (100).

6-Benzeneselenyl-2-hexanone (191).



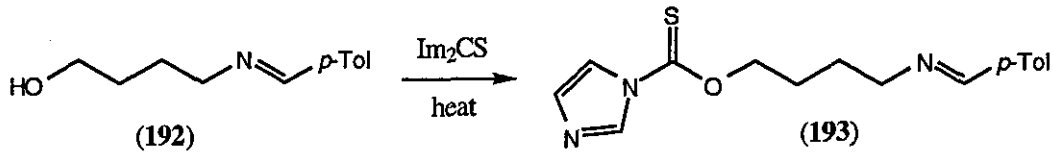
General procedure for hydrolytic decarboxylation using lithium chloride in DMF. Ethyl 2-acetyl-5-benzeneselenylpentanoate (**190**) (362 mg, 1.1 mmol) dissolved in freshly dried and distilled DMF (2 cm^3) was added to a solution of lithium chloride (46 mg, 1.1 mmol) in DMF (10 cm^3) containing water (40 mg, 2.2 mmol). The mixture was heated at 170°C for 18 h, cooled to room temperature and water (10 cm^3) was added followed by dilute hydrochloric acid (2 cm^3). The product was extracted into diethyl ether (3 x 10 cm^3) and the combined extracts were washed with water (7 x 10 cm^3), dried ($MgSO_4$), and evaporated to dryness. The product was purified by dry flash chromatography using silica gel as absorbent and light petroleum / ethyl acetate mixtures as eluent. *6-Benzeneselenyl-2-hexanone* (**191**) was isolated as a light yellow oil (213 mg, 75%); ν_{max} 3056, 2933, 2862, 1719 (C=O stretch), 1579 (phenyl), 1478, 1438, 1369, 1232, 1073, 1023, and 737 cm^{-1}; δ_H 7.44-7.48 (2 H, m, phenyl ortho-H), 7.20-7.25 (3 H, m, phenyl H), 2.87 (2 H, t, J = 8.0 Hz, 6-H), 2.39 (2 H, t, J = 7.8 Hz, 3-H), 2.09 (3 H, s, Me), and 1.64-1.69 (4 H, m, 4,5-H); δ_C 208.72 (C=O), 132.42 (Ar-CH), 131.40 (Ar-C), 128.97 and 126.69 (Ar-CH), 42.90 (CH_2), 29.77 (1-C), 29.51, 27.36 (CH_2), and 23.76 (6-C); *m/z* 256.0370 [M^+, (4.1%), $C_{12}H_{16}OSe$ requires 256.0366], 157 ($PhSe^+$, 9.1), 141 (3.2), 113 (3.2), 99 (M^+-PhSe, 28), 78 (12), and 43 (CH_3CO^+, 100).

4-Hydroxy-*N*-(4-methylbenzylidene)-1-butylamine (192).



4-Amino-1-butanol (2.23 g, 25 mmol) and *p*-tolualdehyde (3.00 g, 25 mmol) dissolved in toluene (100 cm^3) were refluxed for 2 h, and the water removed using a Dean-Stark water separator. The solution was evaporated to dryness to yield *4-hydroxy-N-(4-methyl-benzylidene)-1-butylamine* (**192**) as an orange oil (3.93 g, 82%); ν_{max} 3286 (OH stretch), 3027, 2933, 2860, 1648, (C=N stretch) 1610 (phenyl), 1513, 1447, 1380, 1308, 1046, and 814 cm^{-1}; δ_H 8.24, (1 H, s, CH=N), 7.59 (2 H, d, J = 8.0 Hz), 7.29 (2 H, d, J = 8.0 Hz), 3.68 (2 H, t, J = 5.8 Hz, 4-H), 3.63 (2 H, t, J = 5.8 Hz, 1-H), 2.37 (3 H, s, Me), and 1.72-1.80 (4 H, m, 2,3-H); δ_C 161.25 (C=N), 141.26 (Ar-C), 133.4 (Ar-CH), 129.46 (Ar-C), 128.22 (Ar-CH), 62.74 (4-C), 61.16 (1-C), 31.81 (2-C), 29.16 (3-C), and 21.52 (Me).

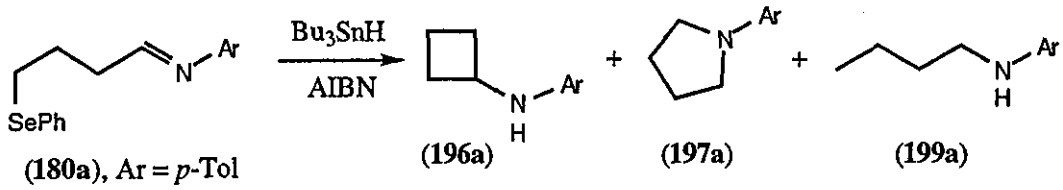
4-(1-Imidazolylthiocarbonyloxy)-*N*-(4-methylbenzylidene)-1-butylamine (193).



4-Hydroxy-*N*-(4-methylbenzylidene)-1-butylamine (**192**) (1.787 g, 9 mmol) and 1,1'-thiocarbonyldiimidazole (1.066 g, 6 mmol) were dissolved in dry toluene (100 cm^3) and the solution was refluxed for 6 h. The solution was evaporated to dryness and the crude product passed through a silica column using ethyl acetate / light petroleum mixtures as eluent. *4-(1-Imidazolylthiocarbonyloxy)-N-(4-methylbenzylidene)-1-butylamine* (**193**) was isolated as a red oil (1.003 g, 56%); ν_{max} 3118, 3026, 2924, 2861, 1648, (C=N stretch) 1609 (phenyl), 1496, 1449, 1064, 814, and 732 cm^{-1}; δ_H 7.87, (1 H, s, CH=N), 6.80-7.76 (7 H, m, Ph and imidazole), 4.17 (2 H, t, J = 5.8 Hz, 4-H), 2.80 (2 H, t, J = 5.8 Hz, 1-H), 2.37 (3 H, s, Me), and 1.77-1.94 (4 H, m, 2,3-H); δ_C 192.40 (C=S), 168.93 (C=N), 143.15 (Ar-C), 138.41 and 129.88 (Ar-CH), 129.73 (Ar-C), 129.45, 128.84, 127.22 (Ar-CH), 61.48 (1-C), 46.23 (4-C), 29.72 (2-C), 28.08 (3-C), and 21.35 (Me).

10.3. Experimental for Chapter 5.

Attempted cyclisation of *N*-(4-Benzeneselenylbut-1-ylidene)-4-methylaniline (180a).



(180a), Ar = *p*-Tol (196a) (197a) (199a)

General procedure for free radical cyclisation reactions. The imine (**180a**) (240 mg, 0.76 mmol) was dissolved in dry toluene (100 cm^3) and nitrogen was bubbled through the solution for 30 min and the brought to a steady reflux. Bu_3SnH (0.35 cm^3, 1.3 mmol, 1.7 equiv.) and AIBN (42 mg, 0.26 mmol, 0.34 equiv.) were dissolved in dry toluene (25 cm^3) and nitrogen was bubbled through for 30 min. The solution of Bu_3SnH / AIBN was transferred under nitrogen to a 50 cm^3 syringe and was added to the refluxing imine solution at a rate of 5.0 cm^3 / h using a syringe pump. After the addition of the tin hydride was completed, the reaction mixture was refluxed for a further 30 min before cooling to room temperature. An excess of sodium borohydride dissolved in methanol (5 cm^3) was added and the mixture stirred for 18 h. The mixture was extracted with hydrochloric acid (2 M, 5 x 25 cm^3) and the combined extracts were washed with light petroleum (3 x 15 cm^3). Solid sodium carbonate was added to neutralise the acid and once all effervescing had ceased the solution was made strongly basic by sodium hydroxide solution and the products extracted into diethyl ether (4 x 20 cm^3), The combined extracts were dried ($MgSO_4$) and the solution evaporated to dryness. The crude yield of recovered material was 65 mg (49%) (based on the calculated maximum yield taking into account the loss of phenylselenide and the abstraction of hydrogen). A sample of the crude product was analysed by GLC using samples of each of the most probable reaction products as standards The remainder of the crude product was dissolved in diethyl ether and acetic anhydride (0.2 cm^3) and triethylamine (0.2 cm^3) were added. The mixture was stirred at room temperature for 24 h. The tertiary amines were extracted into hydrochloric acid, neutralised with sodium carbonate, made strongly basic with sodium hydroxide and re-extracted into diethyl ether. The extracts were dried ($MgSO_4$) and the solution evaporated to dryness to yield the tertiary amine product. The residual diethyl ether solution was dried ($MgSO_4$) and the solution evaporated to dryness. The acetylated secondary amines were isolated by TLC using an alumina plate or purified by flash sinter chromatography using silica gel as absorbent and light petroleum / ethyl acetate mixtures as eluent.

In the cyclisation of the above imine, GLC analysis showed that no cyclised product was obtained neither was the acyclic product formed. The mixture was treated with acetic anhydride / triethylamine and an attempt was made to separate the products

by acid extraction and TLC but no identifiable products were found. Repetition of the cyclisation gave the same result.

***N*-Cyclobutyl-4-methylaniline (196a).**

General procedure for the synthesis of amines (method A). The primary amine and the aldehyde or ketone were dissolved in dry diethyl ether (10 cm^3). Type 4 Å molecular sieves (ca. 2 g) were added and the mixture was stirred at room temperature for 2 days. The solution was filtered and the molecular sieves washed with diethyl ether. The filtrate was evaporated to yield the crude imine as a red oil. The formation of the imine was confirmed by infra-red spectroscopy. The imine was redissolved in dry diethyl ether (25 cm^3) and an excess of sodium borohydride (300 mg) was added. The mixture was stirred for a further 2 h. The excess reducing agent was decomposed with water and the amines extracted into hydrochloric acid (2 M). Sodium carbonate was used to neutralise the acid and the amines were extracted into diethyl ether (5 x 10 cm^3). The combined extracts were washed with water and dried ($MgSO_4$). The above compound was purified by dry flash chromatography using silica gel as absorbent and light petroleum / ethyl acetate mixtures as eluent. For elemental analysis, the amine was further purified by isolation as the hydrochloride salt.

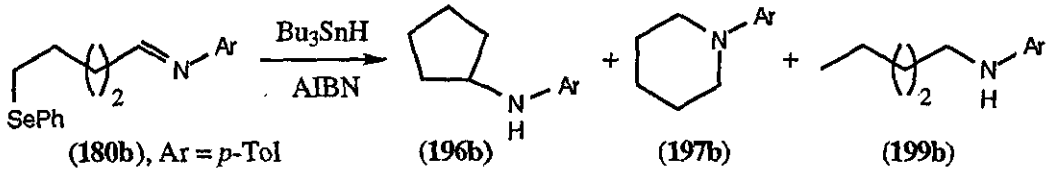
Cyclobutanone (487 mg, 6.95 mmol) and *p*-toluidine (744 mg, 6.95 mmol) gave *N*-cyclobutyl-4-methylaniline (**196a**), a dark red oil (866 mg, 77%); ν_{max} (imine) 2945, 2866, 1708 (C=N), 1617 (phenyl), 1545, 1452, and 814 cm^{-1}; ν_{max} (amine) 3355 (NH stretch), 3019, 2931, 2863, 1668, 1619 (phenyl), 1518, 1455, 1303, and 813 cm^{-1}; δ_H 6.95 (2 H, d, J = 8.0 Hz), 6.56 (2 H, d, J = 8.0 Hz, aromatic H), 3.58 (1 H, m, NH), 2.78 (1 H, m, CH-N), 2.22 (3 H, s, Me), and 1.40-1.80 (6 H, m, alkyl H); δ_C 143.49 (Ar-C), 129.34 and 115.56 (Ar-CH), 113.21 (Ar-C), 49.85 (1-C), 33.73, 28.94 [2(4),3-C], and 20.39 (Me).

***N*-*p*-Tolylpyrrolidine (197a).**

p-Toluidine (3.45 g, 32 mmol) was dissolved in light petroleum (100 cm^3) and 1,4-diiodobutane (2.00 g, 6.5 mmol) dissolved in light petroleum (10 cm^3) was added. The mixture was stirred at room temperature for 3 days. The resulting dark red solution was treated with acetic anhydride and triethylamine (both 5 equivs. relative to *p*-toluidine) and stirred for a further 24 h. The precipitate of *N*-acetyl-*p*-toluidine was filtered off and the solution extracted with hydrochloric acid (2 M, 4 x 20 cm^3). The combined extracts were washed with light petroleum and neutralised with sodium carbonate. The product was extracted into diethyl ether, washed with water and dried ($MgSO_4$). The solution was evaporated to dryness to yield *N*-*p*-tolylpyrrolidine (**197a**) as a deep red oily solid (550 mg, 53%); ν_{max} 3047, 2974, 2837, 1678, 1624 (Ph), 1525, 1442, 1188, and 1158 cm^{-1}; δ_H 7.05 (2 H, d, J = 8.5 Hz), 6.58 (2 H, d, J = 8.5 Hz, aromatic H), 3.27 (4 H, t, J = 6.8 Hz, 2,5-H), 2.25 (3 H, s, Me), and 2.00 (4 H, t, J = 6.8 Hz, 3,4-H); δ_C 146.25 (Ar-C),

129.62 and 113.01 (Ar-CH), 111.79 (Ar-C), 47.84 (2,5-C), 25.39 (3,4-C), and 20.27 (Me).

Cyclisation of*N*-(5-Benzeneselenylpent-1-ylidene)-4-methylaniline (180b).



The general procedure for cyclisation was used. The imine (**180b**) (390 mg, 1.18 mmol) was refluxed in toluene (100 cm^3). Injection of Bu_3SnH (0.42 cm^3, 1.6 mmol, 1.33 equiv.) and AIBN (66 mg, 0.4 mmol, 0.34 equiv.) in toluene using a syringe pump gave 97 mg of recovered material (47%). GLC analysis showed that the 5-*exo* cyclisation product (**196b**) as the only major product (yield using ^1H NMR spectroscopy = 39%). This was found to be identical with an authentic sample of the amine. Repeated cyclisations gave crude product yields of 35-42%.

***N*-Cyclopentyl-4-methylaniline (196b).**

The amine was prepared by the general method A. Cyclopentanone (1.683 g, 20 mmol) and *p*-toluidine (2.144 g, 20 mmol) gave the imine as a red oil (2.380 g, 69%) which on reduction gave *N-cyclopentyl-4-methylaniline* (**196b**) as an orange-red oil which gradually darkened (2.268 g, 65%); (Found: C, 67.25; H, 8.86; N, 6.73. $C_{12}H_{17}N.HCl$ requires C, 68.09; H, 8.51; N, 6.62%); ν_{max} (imine) 3031, 2957, 2871, 1669 (C=N), 1616 (phenyl), 1503, 1450, 1417, and 813 cm^{-1}; ν_{max} (amine) 3355 (NH stretch), 2921, 2866, 1671, 1621 (phenyl), 1548, 1274, and 814 cm^{-1}; δ_H 7.10 (2 H, d, J = 8.0 Hz), 6.64 (2 H, d, J = 8.0 Hz, aromatic H), 3.87 (1 H, m, CH-N), 3.52 (1 H, m, NH), 2.15 (3 H, s, Me), and 1.56 -2.10 (8 H, m, cyclopentyl); δ_C 145.92 (Ar-C), 129.69 and 115.24 (Ar-CH), 113.41 (Ar-C), 54.91 (1-C), 33.52 (2,5-C), 23.18 (3,4-C), and 20.35 (Me); *m/z* 175.1348 [M^+, (62%), $C_{12}H_{17}N$ requires 175.1361], 146 (M^+-C_2H_5, 100), 133 (37), 118 (M^+-C_4H_9, 15), 106 (M^+-cyclopentyl, 17), and 91 ($C_7H_7^+$, 19).

***N*-Acetyl-*N*-cyclopentyl-4-methylaniline.**

General method for the acetylation of amines. *N*-Cyclopentyl-4-methyl aniline (**196b**) (300 mg, 1.7 mmol) was dissolved in diethyl ether (20 cm^3) and an excess of acetic anhydride (0.2 cm^3) and triethylamine (0.2 cm^3) were added, the mixture was stirred at room temperature for 24 h. Aqueous sodium hydroxide (1 M, 5 cm^3) was added and the mixture stirred for a further 24 h to hydrolyse the excess anhydride. The ether layer was separated and the triethylamine and unreacted amine extracted with hydrochloric acid (2 M, 2 x 10 cm^3). The ether layer was washed with water, dried, and evaporated to dryness yielding *N-acetyl-N-cyclopentyl-4-methylaniline* as a yellow oil

(197 mg, 53%); ν_{max} 3032, 2959, 2928, 2873, 1655 (C=O), 1608 (phenyl), 1513, 1453, 1398, 1311, 1261, 910, and 738 cm^{-1}; δ_H 7.20 (2 H, d, J = 8.0 Hz), 6.98 (2 H, d, J = 8.0 Hz, aromatic H), 4.93 (1 H, m, 1-H), 2.39 (3 H, s, Me), 1.83-1.88 (2 H, m), 1.74 (3 H, s, MeCO), and 1.47-1.54 (6 H, m); δ_C 171.15 (C=O), 138.35 and 137.78 (Ar-C), 129.93 and 129.88 (Ar-CH), 56.32 (1-C), 29.52 (2,5-C), 23.59 (MeCO), 22.67 (3,4-C), and 20.35 (Me); *m/z* 217.1467 [M^+, (16%), $C_{14}H_{19}NO$ requires 217.1472], 174 (M^+-C_3H_7, 11), 149 (MH^+-cyclopentyl, 75), 107 (100), 91 ($C_7H_7^+$, 56), and 65 (24).

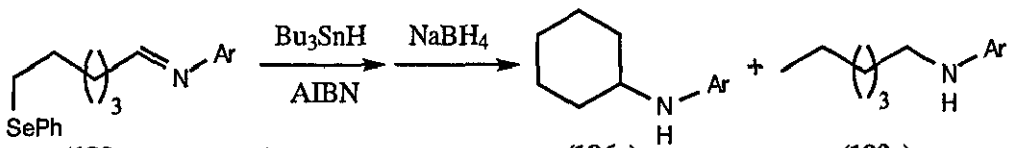
***N-p*-Tolylpiperidine (197b).**

The procedure was as for *N-p*-tolylpyrrolidine. *p*-Toluidine (2.679 g, 25 mmol) and 1,5-dibromopentane (1.153 g, 5 mmol) gave *N-p*-tolylpiperidine (**197b**) as an oily red-black solid (275 mg, 31%); ν_{max} 3054, 2985, 2939, 1678, 1608 (phenyl), 1514, 1453, and 815 cm^{-1}; δ_H 7.04 (2 H, d, J = 8.5 Hz), 6.84 (2 H, d, J = 8.5 Hz, aromatic H), 3.06 (4 H, t, J = 5.5 Hz, 2,6-H), 2.24 (3 H, s, Me), 1.69 (4 H, m, 3,5-H), and 1.52 (2 H, m, 4-H); δ_C 135.61 (Ar-C), 129.55 and 120.19 (Ar-CH) 117.04 (Ar-C), 51.43 (2,6-C), 25.86 (3,5-C), 24.23 (4-C), and 20.41 (Me).

4-Methyl-*N*-pentylaniline (199b).

1-Bromopentane (1.511g, 10 mmol), dissolved in toluene was added to *p*-toluidine (3.02g, 28 mmol) and the mixture was refluxed for 24 h. The resulting red solution was evaporated and the products separated by flash chromatography using silica gel as absorbent and light petroleum / ethyl acetate mixtures as eluent. 4-Methyl-*N*-pentyl-aniline (**199b**) was isolated as an orange-red oil (105 mg, 6%); ν_{max} 3410 (NH stretch), 3054, 2927, 2839, 1654, 1617 (phenyl), 1521, 1457, and 807 cm^{-1}; δ_H 6.96 (2 H, d, J = 8.0 Hz), 6.52 (2 H, d, J = 8.0 Hz, aromatic H), 3.07 (2 H, m, 1-H), 2.23 (3 H, s, Me), 2.15 (1 H, s, NH), 1.59 (2 H, m, 2-H), 1.36 (4 H, m, 3,4-H), and 0.95 (3 H, t, 7.5 Hz, 5-H); δ_C 130.17 (Ar-C), 129.76 and 124.43 (Ar-CH), 113.89 (Ar-C), 45.19 (1-C), 29.72, 28.95 and 22.5 (2,3,4-C), 20.43 (Me), and 14.02 (5-C).

Cyclisation of *N*-(6-Benzeneselenylhex-1-ylidene)-4-methylaniline (180c).



(**180c**), Ar = *p*-Tol (**196c**) (**199c**)

The general procedure for cyclisation was used. The imine (**180c**) (247 mg, 0.72 mmol) was refluxed in toluene (100 cm^3). Injection of Bu_3SnH (0.28 cm^3, 1.1 mmol, 1.33 equiv.) and AIBN (44 mg, 0.24 mmol, 0.34 equiv.) in toluene using a syringe pump gave 80 mg of recovered material (59%). GLC analysis showed that the acyclic product (**F2**) as the only major product (yield using ^1H NMR spectroscopy = 35%) which was found

to be identical with an authentic sample. Repeated cyclisations gave crude yields in the range 40-42%.

***N*-Cyclohexyl-4-methylaniline (196c).**

The amine was prepared by the general method A. Cyclohexanone (988 mg, 10 mmol) and *p*-toluidine (1.072 g, 10 mmol) gave the imine as an orange oil (1.782 g, 95%) which on reduction gave *N-cyclohexyl-4-methylaniline* (**196c**) as an orange-red oil which gradually darkened (1.155 g, 66%); ν_{max} (imine) 2927, 2858, 1658 (C=N), 1613 (phenyl), 1504, 1448, 1234, and 836 cm^{-1}; ν_{max} (amine) 3374 (NH stretch), 3015, 2928, 1671, 1620 (phenyl), 1528, 1450, and 809 cm^{-1}; δ_H 6.96 (2 H, d, J = 8.6 Hz), 6.50 (2 H, d, J = 8.6 Hz, aromatic H), 3.83 (1 H, m, NH), 3.20 (1 H, m, CH-N), 2.22 (3 H, s, Me), 1.73-2.04 (4 H, m, 2,6-H), and 1.13-1.38 (6 H, m, 3,4,5-H); δ_C 144.33 (Ar-C), 129.74 and 115.27 (Ar-CH), 113.6 (Ar-C), 52.66 (1-C), 33.28 (2,6-C), 25.95 (3,5-C), 25.06 (4-C), and 20.43 (Me); *m/z* 189.1513 [M^+, (46%), $C_{13}H_{19}N$ requires 189.1517], 146 (M^+-C_3H_7, 100), 134 (M^+-C_4H_7, 30), 120 (M^+-C_5H_9, 10), 106 (M^+-cyclohexyl, 17), and 91 ($C_7H_7^+$, 15).

***N*-Hexyl-4-methylaniline (199c).**

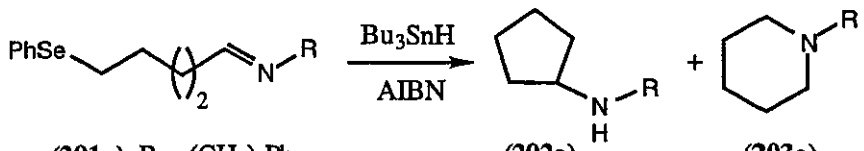
The amine was prepared by the general method A. Hexanal (1.002 g, 10 mmol) and *p*-toluidine (1.071 g, 10 mmol) gave the crude imine which on reduction gave *N-hexyl-4-methylaniline* (**199c**) as a viscous red oil which gradually darkened (211 mg, 11%); ν_{max} 3355 (NH stretch), 3048, 2927, 2860, 1672, 1621 (phenyl), 1515, 1466, and 813 cm^{-1}; δ_H 6.96 (2 H, d, J = 8.0 Hz), 6.54 (2 H, d, J = 8.0 Hz, aromatic H), 3.51 (1 H, s, NH), 2.22 (3 H, s, Me), 2.18 (2 H, t, J = 7.5 Hz, 1-H), 1.32-1.48 (8 H, m, 2,3,4,5-H), and 0.90 (3 H, t, J = 7.6 Hz, 6-H); δ_C 145.62 (Ar-C), 129.72 and 115.25 (Ar-CH), 112.74 (Ar-C), 50.00 (1-C), 39.01 (2-C), 36.38 (3-C), 26.13 (4-C), 25.72 (5-C), 20.44 (Me), and 14.09 (6-C); *m/z* 191.1673 [M^+, (26%), $C_{13}H_{21}N$ requires 191.1674], 149 (M^+-C_3H_6, 12), 134 (M^+-C_4H_9, 26), 120 (M^+-C_5H_{11}, 70), 106 (M^+-hexyl, 100), 91 ($C_7H_7^+$, 99), and 77 (Ph^+, 14).

***N*-Acetyl-*N*-hexyl-4-methylaniline.**

N-Hexyl-4-methylaniline (**199c**) (100mg, 5.2 mmol) was acetylated using the general procedure yielding *N-acetyl-N-hexyl-4-methylaniline* as an orange oil (61 mg, 50%); ν_{max} 3057, 2931, 2857, 1652 (C=O) 1609 (phenyl), 1558, 1540, 1515, 1457, 1118, 733, and 666 cm^{-1}; δ_H 7.09 (2 H, m), 6.98 (2 H, m, aromatic H), 2.35 (2 H, m, 1-H), 2.24 (3 H, s, MeAr), 2.16 (3 H, s, MeCO), 1.20-1.45 (8 H, m, 2,3,4,5-H), and 0.90 (3 H, t, J = 6.5 Hz, 6-H); δ_C 166.58 (C=O), 135.30 (Ar-C), 129.87 and 129.36 (Ar-CH), 128.32 (Ar-C), 37.34 (2-C), 31.58 (3-C), 29.00 (4-C), 24.47 (MeCO), 22.50 (5-C), 20.99 (MeAr), and 14.04 (6-C); *m/z* 233.1775 [M^+, (1.7%), $C_{15}H_{23}NO$ requires 233.1780], 176 (15),

149 (MH^+-hexyl, 42), 134 (15), 120 (26), 107 (100), 91 ($C_7H_7^+$, 49), 77 (23), and 43 (95).

Formation and cyclisation of *N*-(5-Benzeneselenyl-1-pentylidene)-2-phenylethylamine (201a).



(201a), R = $(CH_2)_2Ph$ **(202a)** **(203a)**

5-Benzeneselenylpentanal (**179b**) (404 mg, 1.68 mmol) and 2-phenylethylamine (203 mg, 1.68 mmol) were dissolved in toluene (120 cm^3) and refluxed for 3 h, and the water removed using a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure. Injection of Bu_3SnH (0.6 cm^3, 2.23 mmol) and AIBN (94 mg, 0.57 mmol) in toluene using a syringe pump gave 173 mg of recovered material (54%). Analysis of the crude product by GLC showed that the major product was the 5-*exo* adduct (**202a**) and the 6-*endo* adduct (**203a**) was a minor product. The yields (GLC) of each product were 150 mg, 47% (5-*exo*) and 17 mg, 5% (6-*endo*). Both the products were found to be identical with authentic samples.

***N*-Cyclopentyl-2-phenylethylamine (202a).**

General procedure for the synthesis of amines (method B). Cyclopentanone (1.26 g, 15 mmol) and 2-phenylethylamine (2.03 g, 15 mmol) dissolved in toluene were refluxed for 3 h, and the water removed using a Dean-Stark water separator. The crude imine, an orange oil (2.53 g), was reduced by stirring for 24 h with sodium borohydride. The crude product was extraction into dilute hydrochloric acid. The aqueous solution was washed with diethyl ether and neutralised with sodium carbonate and sodium hydroxide. The amine was re-extracted into diethyl ether and the combined extracts were washed with water, dried and the solution evaporated to dryness. For elemental analysis, the amine were further purified by isolation as the hydrochloride salt. *N-Cyclopentyl-2-phenylethylamine* (**202a**) was isolated as a yellow oil (1.36 g, 48%); (Found: C, 69.04; H, 9.29; N, 6.12. $C_{13}H_{19}N.HCl$ requires C, 69.20; H, 8.93; N, 6.20%); ν_{max} (imine) 3026, 2958, 1678 (C=N), 1604 (phenyl), 1496, 1454, 750, and 700 cm^{-1}; ν_{max} (amine) 3296 (NH stretch), 3027, 2953, 2866, 1678, 1604 (phenyl), 1496, 1454, 750, and 700 cm^{-1}; δ_H 7.17-7.34 (5 H, m, Ph), 3.45 (1 H, m, cyclopentyl 1-H), 3.06 (1 H, s NH), 2.77-2.88 (4 H, m, propyl 2,3-H), and 1.64-1.81 (8 H, m, cyclopentyl); δ_C 140.18 (Ar-CH), 128.69 (Ar-C), 128.28 and 126.11 (Ar-CH), 59.78 (CHN), 49.99 (CH_2N), 36.39 (CH_2Ar), 33.12, and 23.23 (cyclopentyl-C); *m/z* 189.1516 [M^+, (1.5%), $C_{13}H_{19}N$ requires 189.1517], 190 (MH^+, 7), 105 ($MeC_7H_6^+$, 14), 98 (MH^+-C_7H_8, 100), 91 ($C_7H_7^+$, 30), 69 (15) 41 (16), and 30 ($CH_2=NH_2^+$, 47).

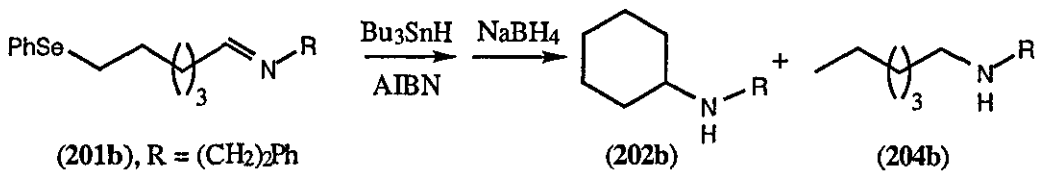
N-Acetyl-N-cyclopentyl-2-phenylethylamine.

N-Cyclopentyl-2-phenylethylamine (**202a**) (500 mg, 2.6 mmol) was acetylated according to the general procedure yielding *N-acetyl-N-cyclopentyl-2-phenylethylamine* as a yellow oil (331 mg 55%); ν_{max} 3027, 2954, 2870, 1655 (C=O), 1605 (phenyl), 1585, 1454, 1421, 1368, 1229, 748, and 701 cm^{-1}; δ_H (2 stereoisomers) 7.13-7.35 (5 H, m, Ph), 4.64 and 4.07 (1H, 2 x m, cyclopentyl 1-H), 3.32-3.40 (2 H, t, J = 8.0 Hz, ethyl 1-H), 2.81-2.91 (2 H, t, J = 8.0 Hz, ethyl 2-H), 2.15 and 2.08 (3 H, 2 x s, MeCO), and 1.50-1.81 (8 H, m, cyclopentyl); δ_C (2 stereoisomers) 171.22 and 170.75 (C=O), 128.82 (Ar-CH), 128.44 (Ar-C), 126.76 and 126.22 (Ar-CH), 59.70 and 56.30 (cyclopentyl 1-C), 47.30 and 43.95 (ethyl 1-C), 37.37 and 35.49 (ethyl 2-C), 29.77 and 29.22 (2,5-C), 23.47 (3,4-C), and 22.27 (MeCO); *m/z* 231.1629 [M^+, (4.8%), $C_{15}H_{21}NO$ requires 231.1623] 146 (6.0), 140 (MH^+-C_7H_8, 37), 98 (100), 91 ($C_7H_7^+$, 25), 72 (11), and 43 (34).

N-(2-Phenylethyl)piperidine (203a).

General method to prepare amines using alkyl bromides (method C). 1-Bromo-2-phenylethane (2.04 g, 10 mmol) was dissolved in dry diethyl ether (30 cm^3) and piperidine (0.85 g, 10 mmol) dissolved in diethyl ether (10 cm^3) was added. The mixture was stirred at room temperature for 18 h. The amine was extracted into hydrochloric acid (2 M), washed with diethyl ether and neutralised with sodium carbonate. The product was re-extracted into diethyl ether (3 x 20 cm^3) and the combined extracts were washed with water (4 x 10 cm^3) and dried ($MgSO_4$). The solution was evaporated to dryness to yield crude N-(2-phenylethyl)piperidine (**203a**) which was purified by short path distillation. The pure amine was isolated as a colourless oil (667 mg, 36%); ν_{max} 2934, 2855, 1603, 1497, 1470, 1468, 1453, 1374, 1352, 1115, 746, and 699 cm^{-1}; δ_H 7.18-7.30 (5 H, m, Ph), 2.81 (2H, t, J = 8.5 Hz, ethyl 1-H), 2.56 (2 H, t, J = 8.5 Hz, CH_2Ph), 2.46 (4 H, m, piperidine 2,6-H), 1.60-1.66 (4 H, m, 3,5-H), and 1.45 (2 H, m, 4-H); δ_C 140.81 (Ar-C), 128.72, 128.36 and 125.95 (Ar-CH), 61.43 and 54.56 (CH_2N), 33.64 (2,6-C), 25.97 (3,5-C), and 24.43 (4-C); *m/z* 189.1505 [M^+, (0.74%), $C_{13}H_{19}N$ requires 189.1517] 105 ($MeC_7H_6^+$, 7), 98 (MH^+-C_7H_8, 100), 91 ($C_7H_7^+$, 10), 77 (Ph^+, 6), 69 (6), and 42 (22).

Formation and cyclisation of N-(6-Benzeneselenyl-1-hexylidene)-2-phenylethylamine (201b).



(201b), R = $(CH_2)_2Ph$ (202b) (204b)

6-Benzeneselenylhexanal (**179c**) (180 mg, 0.71 mmol) and 2-phenylethylamine (85 mg, 0.71 mmol) were dissolved in toluene (120 cm^3) and refluxed for 3 h, and the water removed using a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure. Injection of Bu_3SnH (0.25 cm^3, 0.94 mmol) and AIBN (40 mg, 0.24 mmol) in toluene using a syringe pump gave 71 mg of recovered material (50%). Analysis of the crude product by GLC showed that the 6-*exo* adduct (**202b**) was the only product (yield using ^1H NMR spectroscopy = 61 mg, 43%) and was found to be identical with an authentic sample.

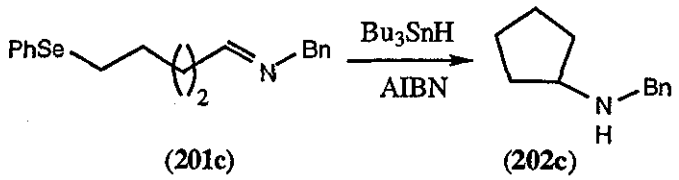
***N*-Cyclohexyl-2-phenylethylamine (202b).**

The amine was prepared by general method B. Cyclohexanone (1.568 g, 16 mmol) and 2-phenylethylamine (1.936 g, 16 mmol) gave the imine as an orange oil (2.250 g, 70%) which on reduction gave *N-cyclohexyl-2-phenylethylamine* (**202b**) as a yellow oil (1.501 g, 46%); (Found: C, 67.90; H, 8.70; N, 5.80. $C_{14}H_{21}N.HCl.\ 0.5H_2O$ requires C, 67.60; H, 8.91; N, 5.63%); ν_{max} (imine) 3026, 2934, 1660 (C=N), 1604 (phenyl), 1496, 1453, 1313, 749, and 700 cm^{-1}; ν_{max} (amine) 3288 (NH stretch), 3027, 2928, 2857, 1660, 1604 (phenyl), 1584, 1496, 1453, and 1346 cm^{-1}; δ_H 7.17-7.32 (5 H, m, Ph), 3.59 (1 H, m, NH), 2.81-2.87 (4 H, m, ethyl 1,2-H), 2.42 (1 H, m, cyclohexyl 1-H), 1.71-1.88 (4 H, m, 2,6-H), and 1.18-1.28 (6 H, m, 3,4,5-H); δ_C 140.05 (Ar-C), 128.76, 128.33 and 126.03 (Ar-CH), 56.63 (CHN), 48.07 (CH_2N), 35.51(CH_2Ar), 26.05 (2,6-C), 24.98 (3,5-C), and 24.10 (4-C); *m/z* 203.1664 [M^+, (0.7%), $C_{14}H_{21}N$ requires 203.1674], 190 (MH^+, 6), 112 (M^+-Ph, 99), 105 ($MeC_7H_6^+$, 17), 91 ($C_7H_7^+$, 25), 82 (12), 72 (89), 41 (21), and 30 ($CH_2{=}NH_2^+$, 100).

***N*-Hexyl-2-phenylethylamine (204b).**

The amine was prepared by general method A. Hexanal (750 mg, 7.5 mmol) and 2-phenylethylamine (910 mg, 7.5 mmol) gave the imine as a yellow oil (1.023 g, 67%) which on reduction gave *N*-hexyl-2-phenylethylamine (**204b**) as a yellow oil (315 mg, 20%); ν_{max} 3363 (NH stretch), 3028, 2956, 2871, 1664, 1604 (phenyl), 1497, 1455, 1378, 748, and 699 cm^{-1}; δ_H 7.16-7.32 (5 H, m, Ph), 3.63 (1 H, m, NH), 2.78-2.91 (4 H, m, ethyl 1,2-H), 2.62 (2 H, t, J = 7.5 Hz, hexyl 1-H), 1.89 (2 H, m, 2-H), 1.47 (2 H, m, 3-H), 1.23-1.28 (4 H, m, 4,5-H), and 0.87 (3 H, t, J = 6.9 Hz, 6-H); δ_C 139.96 (Ar-C), 128.77, 128.39 and 126.08 (Ar-CH), 51.06 and 49.76 (CH_2N), 36.13 (2-C), 31.66 (3-C), 29.77 and 22.52 (4,5-C), and 13.96 (6-C).

Formation and cyclisation of *N*-(5-Benzeneselenyl-1-pentylidene)benzylamine (201c).

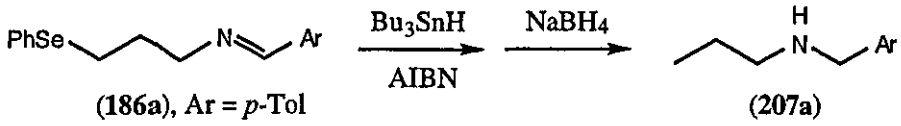


A solution of 5-benzeneselenylpentanal (**179b**) (363 mg, 1.51 mmol) and benzylamine (161 mg, 1.51 mmol) in toluene was refluxed for 3 h, and the water removed using a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure. Injection of Bu_3SnH (0.55 cm^3, 2.0 mmol) and AIBN (84 mg, 0.51 mmol) in toluene using a syringe pump yielded 205 mg of recovered material which, on purification gave the 5-*exo* adduct (**202c**) as the only reaction product (72%) which was found to be identical with an authentic sample.

***N*-Benzylcyclopentylamine (202c).**

The amine was prepared by general procedure B. Cyclopentylamine (967 mg, 11 mmol) and benzyl chloride (1.26 g, 10 mmol) dissolved in diethyl ether were stirred at room temperature for 24 h. The crude product was dissolved in water and washed with diethyl ether (2 x 10 cm^3) and the aqueous layer was neutralised (NaOH) and the product extracted into diethyl ether (2 x 20 cm^3). The combined extracts were washed with water, dried (Na_2SO_4) and the solution evaporated to dryness. *N-Benzylcyclopentyl-amine* (**202c**) was isolated as a yellow oil (490 mg, 30%) (Found: C, 68.04; H, 8.57; N, 6.30. $C_{12}H_{17}N.HCl$ requires C, 68.10; H, 8.57; N, 6.62%); ν_{max} 3296 (NH stretch), 3027, 2953, 2866, 1678, 1604 (phenyl), 1496, 1454, 750, and 700 cm^{-1}; δ_H 7.23-7.32 (5 H, m, Ph), 3.77 (2 H, s, benzyl CH_2), 3.59 (1 H, m, NH), 3.11 (1 H, s, cyclopentyl 1-H), 1.64-1.86 (4 H, m), and 1.24-1.38 (4 H, m, cyclopentyl); δ_C 140.63 (Ar-CH), 128.25 (Ar-C), 128.06 and 126.70 (Ar-CH), 59.04 (CHN), 52.64 (CH_2N), 33.06 (2,5-C), and 23.99 (3,4-C).

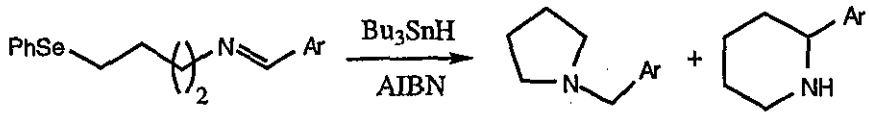
Attempted cyclisation of 3-Benzeneselenyl-*N*-(4-methylbenzylidene)-1-propyl-amine (186a).



The general procedure for free radical cyclisation was used. The imine (**186a**) (263 mg, 0.84 mmol) was refluxed in toluene (100 cm^3). Injection of Bu_3SnH (0.30 cm^3, 1.1 mmol, 1.33 equiv.) and AIBN (46 mg, 0.28 mmol, 0.34 equiv.) in toluene using a

syringe pump gave 97 mg of recovered material (71%). Analysis by GLC showed that the acyclic product 4-methyl-*N*-propylbenzylamine (**207a**) was the only product (yield using ^{1}H NMR spectroscopy = 63%). A repeated cyclisation gave the same result; ν_{max} 3308 (NH stretch), 3025, 2960, 2829, 1645, 1614 (phenyl), 1515, 1457, 1379, 806, and 753 cm^{-1}; δ_H 7.22 (2 H, d, J = 8.0 Hz), 7.10 (2 H, d, J = 8.0 Hz), 3.74 (2 H, s, $ArCH_2N$), 2.58 (2 H, t, J = 7.3 Hz, RCH_2N), 2.36 (1 H, s, NH), 2.31 (3 H, s, Me), 1.56 (2 H, m, J = 7.3 Hz, 2-H), and 0.93 (3 H, t, J = 7.3 Hz, 3-H); δ_C 136.46 (Ar-C), 129.18, 128.14 and 126.87 (Ar-CH), 53.62 and 51.18 (CH_2N), 24.10 (2-C), 21.06 (3-C), and 11.76 (Me).

Cyclisation of 4-Benzeneselenyl-*N*-(4-methylbenzylidene)-1-butylamine (186b).



(**186b**), Ar = *p*-Tol (**205b**) (**206b**)

The general procedure for free radical cyclisation was used. The imine (**186b**) (300 mg, 0.91 mmol) was refluxed in toluene (100 cm^3). Injection of Bu_3SnH (0.33 cm^3, 1.2 mmol, 1.33 equiv.) and AIBN (51 mg, 0.31 mmol, 0.34 equiv.) in toluene using a syringe pump gave 123 mg of recovered material (77%). Analysis by GLC showed that the 5-*exo* adduct as the major product (yield using ^{1}H NMR spectroscopy = 54%) and the 6-*endo* adduct as the minor product (yield using ^{1}H NMR spectroscopy = 6%). A repeated cyclisation gave the crude yield of 71% and the same ratio of products. The 5-*exo* product (**205b**) was found to be identical with an authentic sample. The crude product was acetylated and the 6-*endo* product was isolated by preparation TLC on alumina and was found to be identical with an authentic sample.

***N*-(4-Methylbenzyl)pyrrolidine (205b).**

The amine was prepared by general method C. 4-Methylbenzyl bromide (1.85 g, 10 mmol) and pyrrolidine (0.71 g , 10 mmol) gave *N-(4-methylbenzyl)pyrrolidine* (**206b**) as a colourless oil (708 mg, 40%, b.pt. 207°C at 10 mmHg); (Found: C, 68.04; H, 8.79; N, 6.69. $C_{12}H_{17}N.HCl$ requires C, 68.09; H, 8.51; N, 6.62%); ν_{max} 3025, 2925, 2780, 1616 (phenyl), 1515, 1459, 1445, 1374, 881, and 807 cm^{-1}; δ_H 7.19 (2 H, d, J = 8.0 Hz), 7.09 (2 H, d, J = 8.0 Hz, aromatic H), 3.55 (2 H, s, $ArCH_2N$), 2.47 (4 H, t, J = 6.8 Hz, RCH_2N), 2.31 (3 H, s, Me), and 1.73 (4 H, m, 3,4-H pyrrolidine); δ_C 136.26 and 136.22 (Ar-C), 128.83 and 128.80 (Ar-CH), 60.39 and 54.06 (CH_2N), 23.37 (pyrrolidine 3,4-C), and 21.07 (Me); *m/z* 175.1349 [M^+, (16%), $C_{12}H_{17}N$ requires 175.1361], 174 (M^+-H, 28), 146 (M^+-C_2H_5, 48), 136 (26), 119 (M^+-C_4H_8, 38), 105 ($MeC_7H_6^+$, 100), and 91 ($C_7H_7^+$, 54).

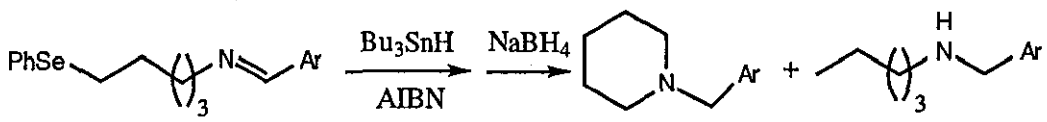
2-*p*-Tolylpiperidine (206b).

Freshly distilled *p*-bromotoluene (1.17 g, 8.5 mmol) and magnesium (1.43 g, 60 mmol, 7 equiv.) were stirred in dry diethyl ether (25 cm^3) at 34°C for 2 h until the Grignard reagent formed. The solution was cooled down to 0°C and 5-chloropentanonitrile (1.00g, 8.5 mmol) dissolved in diethyl ether (5 cm^3) were added dropwise. The solution was stirred at room temperature for 18 h. An excess of solid lithium aluminium hydride (289 mg, 8.5 mmol) was added to the reaction mixture which was stirred for a further 3 h. The reaction was quenched by the dropwise addition of aqueous sodium hydroxide (1 M) and the ether layer separated, filtered and extracted with dilute hydrochloric acid (3 x 25 cm^3). The acid solution was neutralised with sodium carbonate and the amines extracted into dichloro-methane. The combined organic extracts were dried ($MgSO_4$) and evaporated to dryness. 2-*p*-Tolylpiperidine (**206b**) was isolated as an orange oil (680 mg, 46%); ν_{max} 3329 (NH stretch), 3027, 2936, 2860, 1670, 1604, 1496, 1458, 1446, 1380, 1117, 730, and 695 cm^{-1}; δ_H 7.23 (2 H, d, J = 7.8 Hz), 7.15 (2 H, d, J = 7.8 Hz, aromatic H), 3.54 (1 H, m, 2-H), 3.50 (1 H, s, NH), 2.90 and 3.12 (2 H, 2 x m, 6-H), 2.33 (3 H, s, ArMe), and 1.40-1.81 (6 H, m, 3,4,5-H) ; δ_C 137.81 (Ar-C), 129.02 (Ar-CH), 128.21 (Ar-C), 125.29 (Ar-CH), 65.60 (2-C), 45.02 (6-C), 31.96 (5-C), 27.38 (3-C), 24.03 (4-C), and 21.44 (Me); *m/z* 175.1365 [M^+, (0.75%), $C_{12}H_{17}N$ requires 175.1361], 105 ($MeC_7H_6^+$, 5.6), 98 (MH^+-C_7H_8, 100), 91 ($C_7H_7^+$, 6), 83 (7), 55 (13), and 41 (15).

***N*-Acetyl-2-*p*-tolylpiperidine.**

2-*p*-Tolylpiperidine (**206b**) (300 mg, 1.7 mmol) was acetylated according to the general procedure yielding *N-acetyl-2-p-tolylpiperidine* as an orange oil (100 mg 24%); ν_{max} 2937, 2864, 1640 (C=O), 1609 (phenyl), 1450, 1428, 1312, 1222, 1119, and 649 cm^{-1}; δ_H 7.21-7.24 (4 H, m, aromatic H), 3.59 (1 H, t, J = 6.1 Hz, 2-H), 2.87 (2 H, t, J = 7.8 Hz, 6-H), 2.34 (3 H, s, MeAr), 2.24 (3 H, s, MeCO), 2.15-2.19 (2 H, m, 3-H), and 1.44-1.74 (4 H, m, 4,5-H); *m/z* 217.1458 [M^+ (1.6%), $C_{14}H_{19}NO$ requires 217.1467], 146 (6), 98 (11), 91 (17), 72 (20), 55 (18), and 30 (100).

Cyclisation of 5-Benzeneselenyl-*N*-(4-methylbenzylidene)-1-pentylamine (186c).



(**186c**), Ar = *p*-Tol (**205c**) (**207c**)

The general procedure for free radical cyclisation was used. The imine (**186c**) (342 mg, 1.00 mmol) was refluxed in toluene (100 cm^3). Injection of Bu_3SnH (0.35 cm^3, 1.33 mmol, 1.33 equiv.) and AIBN (56 mg, 0.34 mmol, 0.34 equiv.) in toluene using a syringe pump gave 100 mg of recovered material (53%). Analysis by GLC showed that the acyclic product (**207c**) as the major product (yield using ^1H NMR spectroscopy = 40%)

and the 6-*exo* adduct (**205c**) was the minor product (yield using ^{1}H NMR spectroscopy = 7%). Repeated cyclisations gave crude yields of 30% and 52%. The products were found to be identical with authentic samples.

***N*-(4-methylbenzyl)piperidine (205c).**

The amine was prepared by general method C. 4-Methylbenzyl bromide (1.86 g, 10 mmol) and piperidine (0.85 g, 10 mmol) gave *N-(4-methylbenzyl)piperidine* (**205c**) as a colourless oil (815 mg, 43%); (Found: C, 69.05; H, 9.15; N, 6.32. $C_{13}H_{19}N.HCl$ requires C, 69.18; H, 8.87; N, 6.21%); ν_{max} 3024, 2924, 2858, 1616, 1516, 1470, 1443, 1370, 1352, 806, and 779 cm^{-1}; δ_H 7.19 (2 H, d, J = 8.0 Hz), 7.09 (2 H, d, J = 8.0 Hz, aromatic H), 3.38 (2H, s, $ArCH_2N$), 2.34 (4 H, t, J = 7.4 Hz, RCH_2N), 2.31 (3 H, s, Me), 1.55(4 H, m, 3,5-H piperidine), and 1.41 (2 H, m, 4-H piperidine); δ_C 136.32 and 135.47 (Ar-C), 129.17 and 128.75 (Ar-CH), 63.61 and 54.42 (CH_2N), 25.99 (3,5-C), 24.43 (4-C), and 21.07 (Me); *m/z* 189.1513 [M^+, (56%), $C_{13}H_{19}N$ requires 189.1517], 188 (M^+-H, 54), 146 (M^+-C_3H_7, 5), 105 ($MeC_7H_6^+$, 100), 98 (MH^+-C_7H_8, 69), and 77 (Ph^+, 14).

4-Methyl-*N*-pentylbenzylamine (207c).

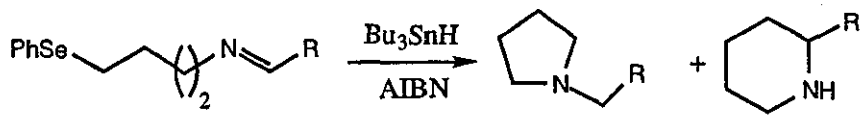
The amine was prepared by general method C. 4-Methylbenzyl bromide (1.53 g, 8.3 mmol) and *n*-pentylamine (722 mg, 8.3 mmol) gave *4-methyl-N-pentylbenzylamine* (**207c**) as a colourless oil (680 mg, 43%); ν_{max} 3308, 2926, 2859, 1665, 1604, 1547, 1515, 1377, 1114, 805, and 731 cm^{-1}; δ_H 7.21 (2 H, d, J = 7.0 Hz), 7.12 (2 H, d, J = 7.0 Hz, aromatic) H, 3.75 (2H, s, $ArCH_2N$), 2.80 (1 H, s, NH), 2.61 (2 H, t, J = 7.0 Hz, RCH_2N), 2.31 (3 H, s, ArMe), 1.48-1.54 (2 H, m, 2-H), 1.22-1.32 (4 H, m, 3,4-H), and 0.88 (3 H, t, J = 7.0 Hz, 5-H); δ_C 136.99 (Ar-C), 136.08 (Ar-CH), 128.77 (Ar-CH), 128.20 (Ar-CH), 57.80 and 49.26 (CH_2N), 32.35 (2-C), 26.69 (3-C), 22.63 (4-C), 21.10 (Me), and 14.16 (5-C); *m/z* 191.1674 [M^+, (3.6%), $C_{13}H_{21}N$ requires 191.1674] 146 (7), 134 (30), 105 ($MeC_7H_6^+$, 100), 91 ($C_7H_7^+$, 25), 72 (11), and 30 ($CH_2{=}NH_2^+$, 72).

***N*-Acetyl-4-methyl-*N*-pentylbenzylamine.**

4-Methyl-*N*-pentylbenzylamine (**207c**) (200 mg, 1.1 mmol) was acetylated according to the general procedure yielding *N-acetyl-4-methyl-N-pentylbenzylamine* as a yellow oil (110 mg 45%); ν_{max} 2958, 2858, 1650 (C=O), 1604 (phenyl), 1516, 1456, 1377, 924, and 731 cm^{-1}; δ_H (2 stereoisomers) 7.26 (2 H, d, J = 7.1 Hz), 7.14 (2 H, d, J = 7.1 Hz, aromatic H), 4.56 and 4.49 (2H, 2 x s, $ArCH_2N$), 3.34 and 3.17 (2 H, 2 x t, J = 7.5 Hz, 1-H), 2.34 and 2.32 (3 H, 2 x s, ArMe), 2.17 and 2.13 (3 H, 2 x s, MeCO), 1.52-1.56 (2 H, m, J = 7.5 Hz, 2-H), 1.20-1.25 (4 H, m, J = 7.5 Hz, 3,4-H), and 0.88 (3 H, t, J = 6.9 Hz, 5-H); δ_C (2 stereoisomers) 171.09 and 170.66 (C=O), 134.45, 133.57, 132.21 and 129.93 (Ar-C), 129.49, 129.14, 127.99 and 125.42 (Ar-CH), 56.24, 51.69, 47.76 and 46.05 (CH_2N), 28.88 (2-C), 27.90 (3-C), 22.28 (4-C), 21.98 and 21.66 (MeCO), 21.30 and 21.20 (MeAr), and 13.87 (5-C); *m/z* 233.1783 [M^+, (18%), $C_{15}H_{23}NO$ requires

233.1780], 162 (M^+-pentyl, 8.6), 134 (17), 120 (33), 105 ($MeC_7H_6^+$, 100), 72 (10), and 43 (23).

Formation and cyclisation of 4-Benzeneselenyl-*N*-(3-phenylpropylidene)-1-butylamine (208a).



(208a), R = $(CH_2)_2Ph$ **(209a)** **(210a)**

A solution of 4-benzeneselenylbutylamine (**185b**) (285 mg, 1.25 mmol) and 3-phenylpropionaldehyde (167 mg, 1.25 mmol) in toluene was refluxed for 3 h, and the water removed using a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure. Injection of Bu_3SnH (0.45 cm^3, 1.7 mmol) and AIBN (70 mg, 0.43 mmol) in toluene using a syringe pump gave 172 mg of recovered material (73%). Analysis of the crude product by GLC showed that the main product is the 5-*exo* adduct (**209a**) [yield (GLC) = 99 mg, 42%] which on isolation was found to be identical to an authentic sample. The second product was the 6-*endo* adduct (**210a**) [yield (GLC) = 42 mg, 18%], which was isolated as the *N*-acetyl derivative which was found to be identical to an authentic sample.

***N*-(3-Phenylpropyl)pyrrolidine (209a).**

The amine was prepared by general method C. 1-Bromo-3-phenylpropane (1.25 g, 6.3 mmol) and pyrrolidine (446 mg, 6.3 mmol) gave *N-(3-phenylpropyl)pyrrolidine* (**209a**) as a colourless oil (662 mg, 56%); (Found: C, 67.22; H, 9.07; N, 5.89. $C_{13}H_{19}N.HCl.H_2O$ requires C, 66.50; H, 9.01; N, 5.97%); ν_{max} 3026, 2938, 2875, 1603, 1497, 1454, 1351, 1146, 1123, 745, and 699 cm^{-1}; δ_H 7.15-7.32 (5 H, m, Ph), 2.65 (2H, t, J = 7.0 Hz, propyl 1-H), 2.48 (6 H, m, pyrrolidine 2,5-H and propyl 3-H), and 1.74-1.87 (6 H, m, propyl 2-H and pyrrolidine 3,4-H); δ_C 142.20 (Ar-C), 128.30, 128.21 and 125.63 (Ar-CH), 56.02 and 54.11 (CH_2N), 33.87 (propyl 3-C), 30.63 (propyl 2-C), and 23.35 (pyrrolidine 3,4-C); *m/z* 189.1519 [M^+, (6.4%), $C_{13}H_{19}N$ requires 189.1517], 91 ($C_7H_7^+$, 9), 84 (100), and 42 ($MeCH{=}NH_2^+$, 9).

2-(2-Phenylethyl)piperidine (210a).

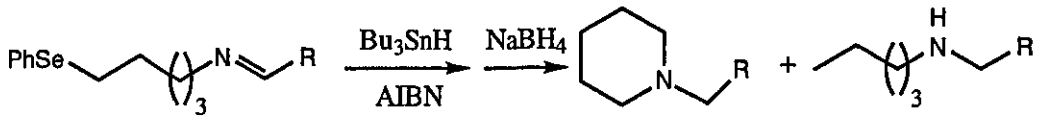
The Grignard reagent prepared from 1-bromo-2-phenylethane (1.57 g, 8.5 mmol) and magnesium (1.43 g, 60 mmol, 7 equiv.) was reacted with 5-chloropentanonitrile (1.00 g, 8.5 mmol) according to the same method as 2-*p*-tolylpiperidine. Reduction of the crude reaction mixture with an excess of lithium aluminium hydride yielded 2-(2-phenylethyl)-piperidine (**210a**) as a red oil (302 mg, 19%); ν_{max} 3369 (NH stretch), 2937, 2864, 1655 (C=O), 1604, 1497, 1454, 1311, 1117, 911, 731, and 701 cm^{-1}; δ_H 7.18-7.27 (5 H, m,

Ph), 4.98 (1 H, s, NH), 3.48-3.54 (3 H, m, 2,6-H), 2.89 (2 H, m, ethyl 2-H), 2.73 (2 H, m, ethyl 1-H), and 1.71-1.96 (6 H, 3,4,5-H); δ_C 140.29 (Ar-C), 128.32, 128.26 and 126.25 (Ar-CH), 56.72 (CHN), 44.62 (6-C), 41.99 (ethyl 1-C), 34.78 (ethyl 2-C), 31.28, 22.44, and 22.15 (piperidine 3,4,5-C)

***N*-Acetyl-2-(2-phenylethyl)piperidine.**

2-(2-phenylethyl)piperidine (**210a**) (202 mg, 1.1 mmol) was acetylated according to the general procedure yielding *N-acetyl-2-(2-phenylethyl)piperidine* as a red oil (87 mg 34%); ν_{max} 2936, 2862, 1634 (C=O), 1604, 1548, 1496, 1423, 1371, 1241, 751, and 701 cm^{-1}; δ_H (2 stereoisomers) 7.20-7.34 (5 H, m, Ph), 3.30 (1 H, m, piperidine 2-H), 3.18 and 2.89 (2 H, 2 x m, 6-H), 2.54-2.65 (2 H, m, ethyl 2-H), 2.07 and 2.03 (3 H, 2 x s, MeCO), 1.93-2.00 (2 H, m, ethyl 1-H), and 1.58-1.66 (6 H, m, 3,4,5-H); δ_C (2 stereo-isomers) 165.82 (C=O), 132.82 and 132.55 (Ar-C), 128.27, 128.22, 128.56, 128.31, 125.86 and 125.76 (Ar-CH), 53.12 and 48.88 (CHN), 41.83 and 36.38 (CH_2N), 32.73 and 31.71 (ethyl 2-C), 28.27 (5-C), 26.25 (3-C), 21.99 and 21.51 (MeCO), and 19.05 (4-C); *m/z* 231.1623 [M^+, (7.4%), $C_{15}H_{21}NO$ requires 213.1623] 133 (15), 126 (38), 105 (30), 91 (48), 84 (100), 77 (11), and 55 (29).

Formation and cyclisation of 5-Benzeneselenyl-*N*-(3-phenylpropylidene)-1-pentyl-amine (208b).



(**208b**), R = $(CH_2)_2Ph$ (**209b**) (**211b**)

A solution of 5-benzeneselenylpentylamine (**185c**) (202 mg, 0.83 mmol) and 3-phenyl-propionaldehyde (112 mg, 0.83 mmol) in toluene was refluxed for 3 h, and the water removed using a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure. Injection of Bu_3SnH (0.30 cm^3, 1.7 mmol) and AIBN (46 mg, 0.44 mmol) in toluene using a syringe pump gave 94 mg of recovered material (56%). Analysis of the crude material by GLC showed that the only product was the uncyclised amine (**211b**) (yield using ^1H NMR spectroscopy = 39%) which was found to be identical with an authentic sample.

***N*-(3-Phenylpropyl)piperidine (209b).**

The amine was prepared by general method C. 1-Bromo-3-phenylpropane (1.26 g, 6.3 mmol) and piperidine (540 mg, 6.3 mmol) gave *N-(3-phenylpropyl)piperidine* (**209b**) as a colourless oil (616 mg, 46%); (Found: C, 70.16; H, 9.63; N, 5.70. $C_{14}H_{21}N.HCl$ required C, 70.10; H, 9.25; N, 5.84%); ν_{max} 3026, 2935 2854, 1605, 1496, 1445, 1351, 1267, 1123, 747, and 700 cm^{-1}; δ_H 7.12-7.27 (5 H, m, Ph), 2.60 (2 H, t, J = 7.7 Hz,

propyl 1-H), 2.35 (4 H, m, piperidine 2,6-H), 1.83 (2 H, m, propyl 3-H), 1.52-1.62 (6 H, m, piperidine 3,5-H and propyl 2-H), and 1.42 (2 H, m, piperidine 4-H); δ_C 142.20 (Ar-C), 128.27, 128.15 and 125.57 (Ar-CH), 58.79 and 54.49 (CH_2N), 33.81 (propyl 3-C), 28.51 (propyl 2-C), 25.89 (3,5-C), and 24.40 (4-C); *m/z* 203.1692 [M^+, (4.2%), $C_{14}H_{21}N$ requires 203.1674], 127 (MH^+-Ph, 14), 98 (100), 91 ($C_7H_7^+$, 10), 84 (28), and 70 (16).

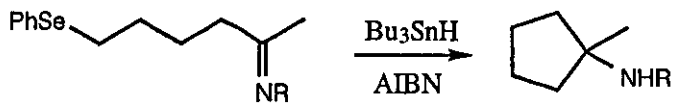
N-Pentyl-3-phenylpropylamine (211b).

The amine was prepared by general method C. 1-Bromo-3-phenylpropane (1.081 g, 5.4 mmol) and pentylamine (520 mg, 6.0 mmol) gave *N*-pentyl-3-phenylpropylamine (**211b**) as a colourless oil (523 mg, 47%); ν_{max} 3312, 2955, 2858, 1665, 1604, 1496, 1465, 1454, 1372, 1242, 1128, 746, and 699 cm^{-1}; δ_H 7.12-7.28 (5 H, m, Ph), 2.62 (2 H, t, J = 7.0 Hz, propyl 1-H), 2.57 (2 H, t, J = 7.3 Hz, pentyl 1-H), 1.78-1.84 (2 H, m, propyl 3-H), 1.44-1.47 (2 H, m, propyl 2-H), 1.20-1.30 (6 H, m, 2,3,4-H), and 0.89 (3 H, t, J = 6.8 Hz, 5-H); δ_C 142.15 (Ar-C), 128.35, 125.78 and 125.68 (Ar-CH), 49.99 and 49.52 (CH_2N), 33.76 (propyl 3-C), 31.68 (propyl 2-C), 29.75 (2-C), 29.62 (3-C), 22.72 (4-C), and 14.09 (5-C); *m/z* 205.1832 [M^+, (9.7%), $C_{14}H_{23}N$ requires 205.1830], 148 (M^+-butyl, 22), 118 (M^+-$C_5H_{11}NH_2$, 4.4), 100 (M^+-$Ph(CH_2)_2$, 48), 91 ($C_7H_7^+$, 32), 44 ($MeCH{=}NH_2^+$, 100), and 30 (38).

N-Acetyl-N-pentyl-3-phenylpropylamine.

N-Pentyl-3-phenylethylamine (**211b**) (400 mg, 2.0 mmol) was acetylated according to the general procedure yielding *N-acetyl-N-pentyl-3-phenylpropylamine* as a yellow oil (250 mg 52%); ν_{max} 2931, 2860, 1646 (C=O), 1604 (phenyl), 1496, 1454, 1422, 1368, 749, and 700 cm^{-1}; δ_H (2 stereoisomers) 7.17-7.33 (5 H, m, Ph), 3.15-3.36 (4 H, m, CH_2NCH_2), 2.62 (2 H, t, J = 8.0 Hz, propyl 3-H), 2.09 and 2.01 (3 H, 2 x s, MeCO), 1.83-1.87 (2 H, m, propyl 2-H), 1.50-1.52 (2 H, m, pentyl 2-H), 1.20-1.25 (4 H, m, 3,4-H), and 0.87 (3 H, t, J = 7.0 Hz, 5-H); δ_C 170.53, 170.45 (C=O), 141.62 (Ar-C), 128.58, 126.76 and 126.26 (Ar-CH), 48.96 and 45.64 (CH_2N), 33.30 (propyl 3-C) 30.23 (propyl 2-C), 29.22 (2-C), 28.56 (3-C), 22.45 (4-C), 21.33 (MeCO), and 13.99 (5-C); *m/z* 247.1940 [M^+, (18%), $C_{16}H_{25}NO$ requires 247.1936], 190 (M^+-butyl, 13), 148 (11), 128 (M^+-$Ph(CH_2)_3$, 34), 118 (16), 100 (47), 91 ($C_7H_7^+$, 39), 73 (16), 44 (100), and 43 (58).

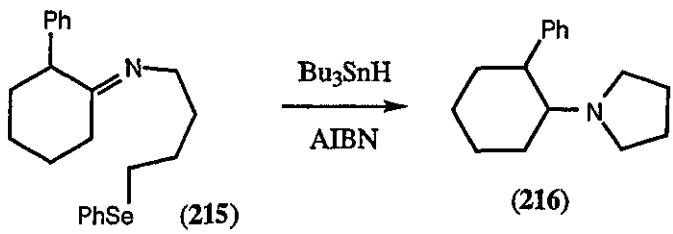
Formation and cyclisation of *N*-(6-Benzeneselenylhex-2-ylidene)-2-phenylethylamine (212).



(212), R = $(CH_2)_2Ph$ **(213)**

A solution of 6-benzeneselenyl-2-hexanone (**191**) (197 mg, 0.77 mmol) and 2-phenylethylamine (93 mg, 0.77 mmol) in toluene was refluxed for 3 h, and the water removed using a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure. Injection of Bu_3SnH (0.28 cm^3, 1.01 mmol) and AIBN (43 mg, 0.26 mmol) in toluene over 5.5 h using a syringe pump yielded 95 mg of recovered material. This crude product was purified by flash chromatography, using alumina as absorbent and light petroleum / ethyl acetate mixtures as eluent gave *N-(1-methylcyclopentyl)-2-phenylethylamine* (**213**) as the only product, a yellow-brown oil (yield by ^1H NMR = 56%); ν_{max} 3027, 2956, 1668, 1603 (Ph), 1496, 1454, 1082, and 749 cm^{-1}; δ_H 7.20-7.34 (5 H, m, phenyl-H), 2.71-2.84 (4-H, m, CH_2CH_2Ph), 2.12-2.21 (2 H, m), 1.47-1.58 (4 H, m), 1.29-1.36 (2 H, m), and 1.21 (3 H, s, Me); δ_C 129.50 (Ar-C) 128.63, 128.00 and 126.10 (Ar-CH), 62.02 (cyclopentyl 1-C), 44.89, 39.00, 37.04 (CH_2), 25.57 (Me), and 23.85 (CH_2); *m/z* 203.1658 [M^+, (1.2%), $C_{14}H_{21}N$ requires 203.1674], 204 (MH^+, 4.1), 158 (34), 112 (MH^+-C_7H_8, 69), 104 ($PhCH{=}CH_2$, 28), 91 ($C_7H_7^+$, 37), 83 (20), 78 (44), 41 (48), and 30 ($CH_2{=}NH_2^+$, 100).

Formation and cyclisation of 4-Benzeneselenyl-*N*-(2-phenylcyclohexylidene)-1-butylamine (215).



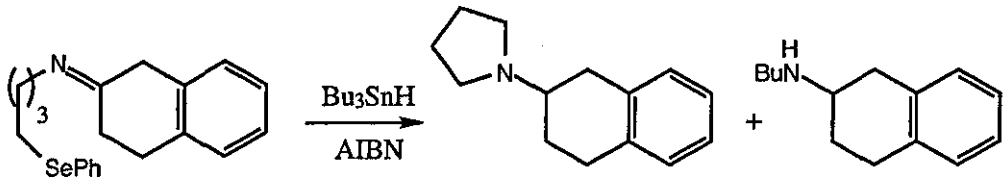
A solution of 4-benzeneselenylbutylamine (**185b**) (274 mg, 1.2 mmol) and 2-phenylcyclohexanone (209 mg, 1.2 mmol) in toluene was refluxed for 4 h, and the water removed using a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure. Injection of Bu_3SnH (0.42 cm^3, 1.6 mmol) and AIBN (67 mg, 0.41 mmol) in toluene over 5.5 h, gave on work-up, 165 mg of recovered material. This crude product was purified by flash chromatography, using alumina as absorbent and light petroleum / ethyl acetate mixtures as eluent yielding *N*-(2-phenylcyclohexyl)pyrrolidine (**216**) as the only product, (yield by ^1H NMR = 55%). This was found to be identical to an authentic sample.

N-(2-Phenylcyclohexyl)pyrrolidine (216).

2-Phenylcyclohexanone (871 mg, 5 mmol) and pyrrolidine (355 mg, 5 mmol) were dissolved in toluene (100 cm^3) and the mixture refluxed for 3 h, and the water removed using a Dean-Stark water separator. The resulting enamine was not isolated but was protonated by reaction with *p*-toluenesulphonic acid (859 mg, 5 mmol) under the same conditions to yield the iminium salt in solution. This was reduced by stirring the solution

with an excess of sodium borohydride (200 mg, 5.3 mmol) at room temperature for 18 h. The product was isolated from the reaction mixture by extraction into hydrochloric acid (2 M), neutralising with Na_2CO_3, and re-extraction into diethyl ether. The combined extracts were dried ($MgSO_4$) and evaporated to dryness to give the crude product, which was purified by flash chromatography, using alumina as absorbent and light petroleum / ethyl acetate mixtures as eluent. Evaporation of the solvent yielded *N-(2-phenylcyclohexyl)pyrrolidine* (**216**) as a yellow viscous oil (284 mg, 19%); ν_{max} 3025, 2926, 2763, 1634, 1601 (phenyl), 1496, 1454, 1224, 1172, 1121, 1033, and 731 cm^{-1}; δ_H 7.28-7.34 (5 H, m, aromatic H), 3.40-3.48 (2 H, m, cyclohexyl 1-H and 2-H), 2.87-2.91 and 3.22-3.26 (4-H, 2 x m, pyrrolidine 2,5-H), 2.15-2.25, 1.92-2.10, and 1.60-1.76 (12H, 3 x m); δ_C 144.88 (Ar-C), 128.62, 127.69 and 125.36 (Ar-CH), 67.09 (CHN), 52.63 (pyrrolidine 2,5-C), 45.11, (cyclohexyl 2-C), 30.11, 29.05, 24.31, 23.45, and 23.17; *m/z* 229.1817 [M^+, (27%), $C_{16}H_{23}N$ requires 229.1830], 130 (13), 117 (10), 110 (100), 91 ($C_7H_7^+$, 22), 84 (26), 70 ($C_4H_8N^+$, 25), and 43 (44).

Formation and cyclisation of 4-Benzeneselenyl-*N*-(1,2,3,4-tetrahydronaphth-2-ylidene)-1-butylamine (218).



(218) (219) (221)

A solution of 4-benzeneselenylbutylamine (**185b**) (428 mg, 1.88 mmol) and 2-tetralone (274 mg, 1.88 mmol) in toluene was refluxed for 3 h, and the water removed using a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure. Injection of Bu_3SnH (0.67 cm^3, 2.5 mmol) and AIBN (105 mg, 0.64 mmol) in toluene over 5.3 h using a syringe pump gave 379 mg of recovered material. Analysis of the crude product by GLC showed that the *exo* adduct (**219**) (yield by ^1H NMR spectroscopy = 19%) and acyclic amine (**221**) (yield by ^1H NMR spectroscopy = 20%) were the only products, which were found to be identical to authentic samples.

2-(1-Pyrrolidinyl)-1,2,3,4-tetrahydronaphthalene (219).

2-Tetralone (219 mg, 15 mmol) and pyrrolidine (107 mg, 15 mmol) were dissolved in toluene and refluxed for 3 h, the water being removed using a Dean-Stark water separator. The solution was evaporated to dryness and 2-(1-pyrrolidinyl)-3,4-dihydronaphthalene was obtained as a black solid (2.98 g, 100%, m.pt. 82-85°C); ν_{max} 3056, 3010, 2968, 1663 (C=C), 1603 (aromatic), 1561, 1481, 1453, 1411, 1368, 1216, and 1179 cm^{-1}; δ_H 7.00 (2 H, m, aromatic H), 6.81 (2 H, m, aromatic H), 5.12 (1 H, s, 1-H), 3.25 (4 H, t, J = 6.6 Hz, pyrrolidine 2,5-H), 2.81 (2 H, t, J = 7.5 Hz, 3-H), 2.47 (2 H, t, J

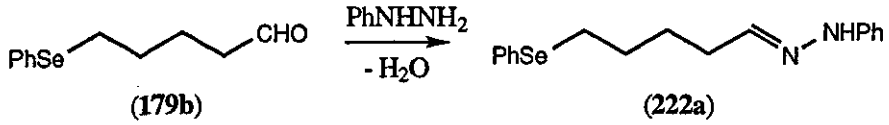
= 7.5 Hz, 4-H), and 1.81 (4 H, t, J = 6.6 Hz, pyrrolidine 3,4-H); δ_C 147.48 and 130.08 (Ar-C), 127.58, 122.76, 121.63 and 115.68 (Ar-CH), 104.75 (alkene CN), 93.19 (alkene CH), 47.32, (pyrrolidine 2,5-C), 28.62, 26.28, and 25.13 (3,4-C and pyrrolidine 3,4-C).

2-(1-Pyrrolidinyl)-3,4-dihydronaphthalene (200 mg, 1.0 mmol) was dissolved in diethyl ether (20 cm^3) and *p*-toluenesulphonic acid (190 mg, 1.0 mmol) dissolved in ethanol (1 cm^3) was added and the mixture stirred at room temperature. An excess of solid sodium borohydride (40 mg) was added and the mixture stirred for 48 h. The excess sodium borohydride was decomposed by the addition of water (5 cm^3) and the products extracted into hydrochloric acid (2 M, 2 x 10 cm^3). The extracts were washed with diethyl ether (3 x 10 cm^3) and the acid layer neutralised with sodium carbonate. Extraction of the liberated amine with ether and the combined ether extracts were washed with water and dried ($MgSO_4$). The solution was evaporated to dryness to yield the crude amine which was purified by flash chromatography, using alumina as absorbent and light petroleum / ethyl acetate mixtures as eluent. Evaporation of the solvent yielded the amine (**219**) as an orange oil (56 mg, 28%); ν_{max} 2972, 1606, 1562, 1482, 1455, 1412, 1365, 1214, 908, 733, and 651 cm^{-1}; δ_H 7.03 (2 H, m), 6.77 (2 H, m, aromatic H), 3.39 (1 H, s, 2-H), 3.25 (4 H, t, J = 6.8 Hz, pyrrolidine 2,5-H), 2.81 (2 H, t, J = 7.5 Hz, 3-H), 2.68 (2 H, m, 1-H), 2.45 (2 H, t, J = 7.5 Hz, 4-H), and 1.90 (4 H, t, J = 6.8 Hz, pyrrolidine 3,4-H); δ_C 130.05 (Ar-C), 126.51, 125.73, 125.64 and 122.73 (Ar-CH), 121.59 (Ar-C), 60.95 (2-C), 51.72, (pyrrolidine 2,5-C), 47.30 (1-C), 26.25, 25.12, and 23.24 (CH_2); *m/z* 201.1518 [*M*+, (78%), $C_{14}H_{19}N$ requires 201.1518], 199 (M^+-H_2, 55), 141 (16), 128 (39), 115 (31), 97 (34), 96 (100), 91 (26) and 84 (17).

***N*-Butyl-1,2,3,4-tetrahydro-2-naphthylamine (221).**

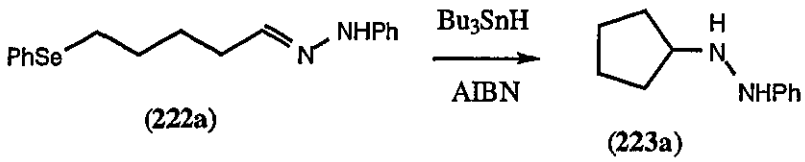
The amine was prepared by general method A. 2-Tetralone (1.168 g, 8 mmol) and *n*-butylamine (730 mg, 10 mmol) gave the imine as a red oil which after reduction gave *N*-butyl-1,2,3,4-tetrahydro-2-naphthylamine (**221**) as an oily red solid (642 mg, 40%); ν_{max} (imine) 3048, 3011, 2929, 2868, 1628 (C=N), 1598 (aromatic), 1567, 1482, 1340, 1196, 787, and 745 cm^{-1}; ν_{max} (amine) 3408 (NH stretch), 3048, 2923, 2868, 1628, 1598 (phenyl), 1567, 1482, 1340, 1196, 787, and 649 cm^{-1}; δ_H 7.01-7.12 (4 H, m, aromatic), 3.75 (1 H, s, NH), 3.03 (1 H, m, NH), 3.46 (1 H, m, 2-H) 3.04-3.07 (2 H, m, 1-H), 2.73-2.87 (4 H, m, ethyl 3,4-H), 1.56-1.65 (2 H, m, butyl 1-H), 1.32-1.38 (4 H, m, butyl 2,3-H), and 0.95 (3 H, t, J = 7.5 Hz, butyl 4-H); δ_C 136.25 (Ar-C), 134.52, 129.32, 128.65 and 125.98 (Ar-CH), 125.60 (Ar-C), 53.85 (CHN), 46.22 (CH_2N), 35.40, 31.22, 28.58, 28.01 and 20.49 (tetralin 1,3,4-C and butyl 2,3-C), and 13.91 (4-C); *m/z* 203.1635 [M^+, (47%), $C_{14}H_{21}N$ requires 203.1674], 160 (M^+-C_3H_7, 97), 131 (M^+-C_4H_9NH, 100), 115 (34), 104 (25), 91 (33), and 57 (47).

1-(5-Benzeneselenylpentylidene)-2-phenylhydrazine (222a).



Phenylhydrazine (179 mg, 1.66 mmol) and 5-benzeneselenylpentanal (**179b**) (400 mg, 1.66 mmol) were dissolved in dry toluene (50 cm^3). The solution was refluxed for 3 h, and the water removed using a Dean-Stark water separator. The solvent was removed by distillation and the hydrazone purified by flash sinter chromatography using silica gel as absorbent and light petroleum / ethyl acetate mixtures as eluent. *1-(5-Benzeneselenyl-pentylidene)-2-phenylhydrazine* (**222a**) was isolated as a viscous orange-red oil (495 mg, 90%); ν_{max} 3343 (NH), 3027, 2921, 1688 (C=N), 1604 (phenyl), 1579 (PhSe), 1478, 1438, 1380, 1081, 1023, and 729 cm^{-1}; δ_H 7.43-7.49 (2 H, m, PhSe ortho-H), 7.18-7.26 (9 H, m, aromatic H, CH=N), 4.29 (1 H, broad s, NH), 2.89 (2 H, t, 5-H), 2.38 (2 H, t, J = 7.0, 2-H), and 1.70-1.76 (4 H, m, 3,4-H); δ_C 136.05, 132.62, 129.29, 128.20, 127.30, 126.95, 122.71, 121.09 (aromatic-C), 113.51 (C=N), 43.23, 29.52, 27.27, and 25.47 (CH_2); *m/z* 332.0781 [M^+, (0.2%), $C_{17}H_{20}N_2Se$ requires 332.0791], 157 ($PhSe^+$, 38), 108 ($PhN_2H_3^+$, 30), 91 (PhN^+, 45), 77 (Ph^+, 100), 65 (40), 51 (60), and 39 (53).

Cyclisation of 1-(5-Benzeneselenylpentylidene)-2-phenylhydrazine (222a).



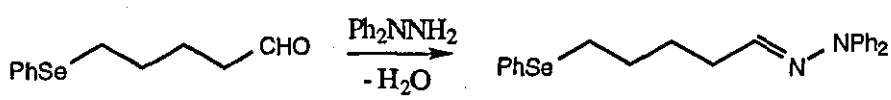
The hydrazone (**222a**) (203 mg, 0.84 mmol) was dissolved in toluene (100 cm^3) and was cyclised using the general procedure. Injection of Bu_3SnH (0.27 cm^3, 1.12 mmol) and AIBN (42 mg, 0.28 mmol) in toluene over 5 h using a syringe pump yielded 40 mg of recovered material, which on purification yielded the 5-*exo* adduct (**223a**) (26mg, 18%), which was found to be identical to an authentic sample. Repeated cyclisation attempts gave yields of cyclised products in the range 6-18%.

1-Cyclopentyl-2-phenylhydrazine (223a).

Cyclopentanone (185 mg, 2.2 mmol) and phenylhydrazine (238 mg, 2.2 mmol) were dissolved in toluene (50 cm^3). The solution was refluxed for 3 h, and the water removed using a Dean-Stark water separator. The solvent was removed by distillation to yield the crude hydrazone, which was not purified, but was dissolved in diethyl ether and added to

lithium aluminium hydride (42 mg, 1.1 mmol) suspended in dry ether (5 cm^3) at 0 °C. The mixture was stirred for 2 h at room temperature and sodium hydroxide (2 M) was added dropwise until all the effervescing had ceased. Dilute hydrochloric acid (5 cm^3) was added and the aqueous solution washed with diethyl ether (4 x 10 cm^3). The acid layer was neutralised with sodium carbonate and made strongly basic with sodium hydroxide. The hydrazine was extracted into ethyl acetate (4 x 10 cm^3) and the combined extracts washed with water (2 x 10 cm^3), dried ($MgSO_4$) and evaporated to dryness. The crude product was purified by flash chromatography using silica gel as absorbent and light petroleum / ethyl acetate mixtures as eluent, yielding 1-cyclopentyl-2-phenylhydrazine (**223a**) as a dark red viscous oil (89mg, 23%); hydrazone: ν_{max} 3334, 2961, 1728 (C=N), 1603 (phenyl), 1504, 1062, and 750 cm^{-1}; δ_H 6.99-7.24 (5 H, m, phenyl), 7.69 (1 H, s, NH), 2.42-2.49 (2 H, m), 2.20-2.26 (2 H, m), and 1.71-1.94 (4 H, m); hydrazine: ν_{max} 3054, 2929, 2855, 1617 (phenyl), 1517, 1422, 896, and 738 cm^{-1}; δ_H 7.47 (1 H, m, NH), 7.17-7.23 (3 H, m, Ph), 6.99-7.03 (2 H, m, o-Ph), 6.80 (1 H, m, 1-H), 6.67 (1 H, s, NH), 2.42-4.48 [2 H, m, 2(5)-H], 2.19-2.24 [2 H, m, 5(2)-H], and 1.68-1.84 (4 H, m, 3,4-H); δ_C 129.45 (ArCH), 128.31 (ArC), 119.46, 112.96 (ArCH), 112.82 (1-C), 33.10, 26.45, and 24.95 (CH_2); *m/z* 176.1323 [M^+, (1.7%), $C_{11}H_{16}N_2$ requires 176.1313], 146 (100), 132 (50), 106 (M^+-C_5H_9, 44), 94 ($PhNH_3^+$, 26), 91 (51), 82 ($C_5H_8N^+$, 27), 77 (Ph^+, 45), 65 ($C_5H_9^+$, 42), and 41 (90).

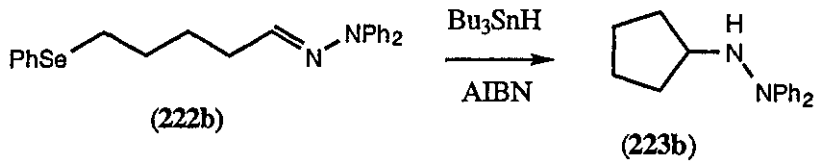
1-(5-Benzeneselenylpentylidene)-2,2-diphenylhydrazine (222b).



(179b) (222b)

Sodium acetate (86 mg, 1.04 mmol) and 1,1-diphenylhydrazine hydrochloride (230 mg, 1.04 mmol) were added to a solution of 5-benzeneselenylpentanal (**179b**) (250 mg, 1.04 mmol) in dry toluene (50 cm^3). The solution was refluxed for 3 h, and the water removed using a Dean-Stark water separator. The solvent was removed by distillation and the hydrazone purified by flash sinter chromatography using silica gel as absorbent and light petroleum / ethyl acetate mixtures as eluent. *1-(5-Benzeneselenylpentylidene)-2,2-diphenylhydrazine* (**222b**) was isolated as a viscous dark purple oil (394 mg, 93%); ν_{max} 3058, 2930, 2855, 1596 (phenyl), 1578 (PhSe), 1495, 1479, 1438, 1300, 1211, 1072, 748, and 638 cm^{-1}; δ_H 7.43-7.47 (2 H, m, PhSe ortho-H), 7.30-7.36 (4 H, m, phenyl orth-H), 7.19-7.23 (3 H, m, PhSe), 7.03-7.10 (6 H, m, phenyl), 6.47 (1 H, t, J = 4.3 Hz, CH=N), 2.90 (2 H, t, J = 8.0 Hz, 5-H), 2.25 (2 H, m, 2-C), 1.65-1.71 (2 H, m), and 1.56-1.61 (2 H, m); δ_C 144.20 (C=N), 139.12, 132.34 and 129.64 (Ar-CH), 129.28 (Ar-C), 128.97 (Ar-CH), 126.62 (Ar-C), 123.85 and 122.29 (Ar-CH), 32.03, 29.01, 27.48, and 27.05 (CH_2); *m/z* 408.1107 [M^+, (12%), $C_{23}H_{24}N_2Se$ requires 408.1104], 183 (Ph_2NNH^+, 39), 168 (Ph_2N^+, 100), 91 (PhN^+, 9), 77 (Ph^+, 46), and 51 (35).

Cyclisation of 1-(5-Benzeneselenylpentylidene)-2,2-diphenylhydrazine (222b).

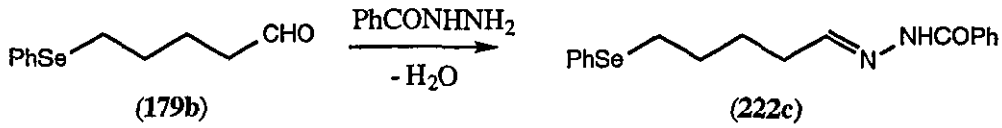


The hydrazone (**222b**) (407 mg, 1.0 mmol) was dissolved in toluene (100 cm^3) and was cyclised using the general procedure. Injection of Bu_3SnH (0.35 cm^3, 1.33 mmol) and AIBN (56 mg, 0.34 mmol) in toluene over 5 h using a syringe pump yielded 120 mg of recovered material, which on purification yielded the 5-*exo* adduct (**223b**) (70mg, 32%), which was found to be identical to an authentic sample.

1-Cyclopentyl-2,2-diphenylhydrazine (223b).

Sodium acetate (410 mg, 5 mmol) and 1,1-diphenylhydrazine hydrochloride (1.104 g, 5 mmol) were added to a solution of cyclopentanone (420 mg, 5 mmol) in toluene (50 cm^3). The solution was refluxed for 3 h, and the water removed using a Dean-Stark water separator. The solvent was removed by distillation to yield the crude hydrazone, which was not purified, but dissolved in diethyl ether and added to lithium aluminium hydride (95 mg, 2.5 mmol) suspended in dry ether (5 cm^3) at 0 °C. The mixture was stirred for 2 h at room temperature and sodium hydroxide (2 M) was added dropwise until all the effervescing had ceased. Dilute hydrochloric acid (5 cm^3) was added and the aqueous solution washed with ether (4 x 10 cm^3). The acid layer was neutralised with sodium carbonate and made strongly basic with sodium hydroxide. The hydrazine was extracted into ethyl acetate (4 x 10 cm^3) and the combined extracts washed with water (2 x 10 cm^3), dried ($MgSO_4$) and evaporated to dryness,. The crude product was purified by flash chromatography using silica gel as absorbent and light petroleum / ethyl acetate mixtures as eluent, yielding 1-cyclopentyl-2,2-diphenylhydrazine (**223b**) as a dark purple viscous oil (157 mg, 16%); hydrazone: ν_{max} 3035, 2961, 1591 (phenyl), 1457, 1312, 1174, and 748 cm^{-1}; δ_H 7.14-7.26 (10 H, m, phenyl), 2.57, [2 H, t, J = 7.5 Hz 2(5)-H], 1.97 [2 H, t, J = 7.5 Hz, 5(2)-H], and 1.61-1.70 (4 H, m, 3,4-H); hydrazine: ν_{max} 3305 (NH), 3060, 2954, 1588 (phenyl), 1498, 1360, 1212, 1090, 1028, 749, and 692 cm^{-1}; δ_H 7.21-7.34 and 7.02-7.14 (10 H, 2 x m, aromatic H), 3.25 (1 H, m, cyclopentyl 1- H, 2.90-3.00 (1 H, s, NH), 2.02-2.10 (2 H, m), 1.78-1.87 (2 H, m), and 1.40-1.61 (4 H, m, cyclopentyl); δ_C 129.16 (Ar-CH), 129.65 (Ar-C), 122.47 and 120.46 (Ar-CH), 65.58 (1-C), 33.70, and 28.83 (CH_2); *m/z* 252.1612 [M^+, (7.5%), $C_{17}H_{20}N_2$ requires 252.1626], 183 (Ph_2NNH^+, 75), 168 (Ph_2N^+, 100), 77 (Ph^+, 46), 66 ($C_5H_6^+$, 12), and 51 (35).

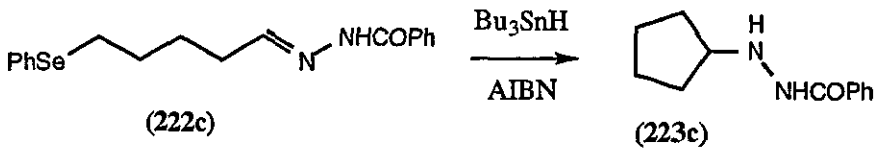
1-(5-Benzeneselenylpentylidene)-2-benzoylhydrazine (222c).



(179b) (222c)

Benzoyl hydrazine (204 mg, 1.5 mmol) and 5-benzeneselenylpentanal (**179b**) (362 mg, 1.5 mmol) were dissolved in dry toluene (50 cm^3). The solution was refluxed for 3 h, and the water removed using a Dean-Stark water separator. The solvent was removed by distillation and the hydrazone purified by flash sinter chromatography using silica gel as absorbent and light petroleum / ethyl acetate mixtures as eluent.. *1-(5-Benzeneselenyl-pentylidene)-2-benzoylhydrazine* (**222c**) was isolated as a yellow oil (510 mg, 95%); ν_{max} 3307 (NH), 3058, 2933, 1656 (C=N), 1603 (Ph), 1578 (PhSe), 1478, 1437, 1288, 1073, 1023, 737, and 692 cm^{-1}; δ_H 7.72-7.85 (3 H, m, benzoyl ortho-H, imine H), 7.47-7.53 (2 H, m, PhSe ortho-H), 7.34-7.41 (3 H, m, benzoyl-H), 7.20-7.28 (3 H, m, PhSe), 3.45 (1 H, m, NH), 2.90 (2 H, t, J = 7.4 Hz, 5-H), 2.35 (2 H, m, 2-H), and 1.49-1.75 (4 H, m, 3,4-H); δ_C 168.56 (C=O), 152.20 (C=N), 132.43, 132.16, 128.98 and 128.93 (Ar-CH), 128.62 and 126.83 (Ar-C), 126.70 and 126.61 (Ar-CH), 32.06, 28.97, 27.30, and 25.81 (CH_2); *m/z* (C.I.) 361.0819 [MH^+ (11%), $C_{18}H_{21}N_2OSe$ requires 361.0819], 239 (M^+-$PhCONH_2$, 100), 225 (25), 205 (22), 139 (42), 122 ($PhCONH_3^+$, 52), and 105 ($PhCO^+$, 14).

Cyclisation of 1-(5-Benzeneselenylpentylidene)-2-benzoylhydrazine (222c).



(222c) (223c)

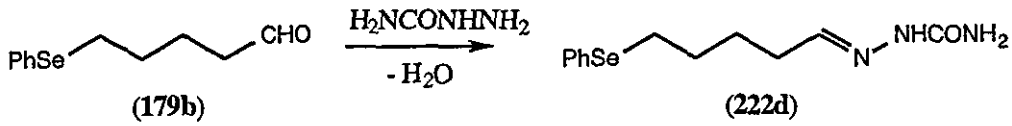
The hydrazone (**222c**) (480 mg, 0.98 mmol) was dissolved in toluene (100 cm^3) and was cyclised using the general procedure. Injection of Bu_3SnH (0.47 cm^3, 1.78 mmol) and AIBN (75 mg, 0.45 mmol) in toluene over 5 h using a syringe pump yielded 229 mg of recovered material, which on purification yielded the 5-*exo* adduct (**223c**) (136mg, 50%), which was found to be identical to an authentic sample.

1-Benzoyl-2-cyclopentylhydrazine (223c).

Benzoylhydrazine (204 mg, 1.5 mmol) and cyclopentanone (126 mg, 1.5 mmol) were dissolved in toluene (50 cm^3). The solution was refluxed for 3 h, and the water removed using a Dean-Stark water separator. The solvent was removed by distillation to yield the crude hydrazone, which was not purified, but dissolved in ethanol and added to a flask containing sodium borohydride (29 mg, 0.75 mmol). The mixture was stirred for 18 h at room temperature and water was added until all the effervescing had ceased. Dilute

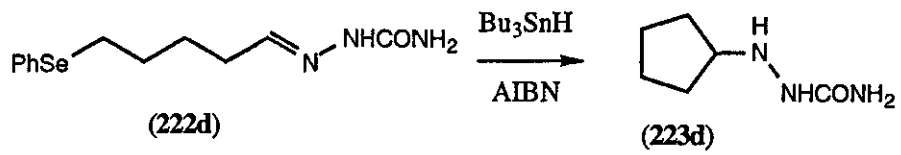
hydrochloric acid (5 cm^3) was added and the aqueous solution washed with ether (4 x 10 cm^3). The acid layer was neutralised with sodium carbonate and made strongly basic with sodium hydroxide. The hydrazine was extracted into ethyl acetate (4 x 10 cm^3) and the combined extracts washed with water (2 x 10 cm^3), dried ($MgSO_4$) and evaporated to dryness, yielding *1-benzoyl-2-cyclopentylhydrazine* (**223c**) as a yellow oil (42 mg, 14%); hydrazone: (Found: C, 71.28; H, 6.78; N, 13.56. $C_{12}H_{14}N_2O$ requires C, 71.29; H, 6.93; N, 14.86%); ν_{max} 3218, 2933, 1664 (C=N), 1603 (phenyl), 1537, 1413, 1378, 1210, 1076, and 874 cm^{-1}; δ_H 8.57 (1 H, s, NH), 7.77-7.80 (2 H, m, ortho-H), 7.40-7.50 (3 H, m, Ar-H), 2.53-2.58 (2 H, m), 2.31-2.37 (2 H, m), and 1.74-1.96 (4 H, m); hydrazine: ν_{max} 3360 (NH), 2927, 1649 (C=N), 1630, 1578, 1458, and 1438 cm^{-1}; δ_H 7.75-7.78 (2 H, m, ortho-H), 7.40-7.48 (3 H, m, Ar-H), 3.63 (1 H, t, J = 6.5 Hz, cyclopentyl 1-H), 3.40-3.50 (2 H, broad s, NH), 1.72-1.74 (4 H, m), and 1.30-1.52 (4 H, m); δ_C 167.80 (C=O), 131.74 and 128.59 (Ar-CH), 127.50 (Ar-C), 126.89 (Ar-CH), 61.75 (cyclopentyl 1-C), 30.96, and 24.04 (CH_2); *m/z* 204.1261 [M^+, (6.8%), $C_{12}H_{16}N_2O$ requires 204.1263], 169 (9.7), 122 ($PhCONH_3^+$, 42), 105 ($PhCO^+$, 100), 84 (48), 77 (Ph^+, 49), 69 ($C_5H_9^+$, 25), and 41 (36).

1-(5-Benzeneselenylpentylidene)semicarbazide (222d).



Semicarbazide hydrochloride (112 mg, 1.0 mmol) and sodium acetate (82 mg, 1.0 mmol) were dissolved in water (5 cm^3) and the solution was added to 5-benzene-selenylpentanal (**179b**) (241 mg, 1.0 mmol) in ethanol (5 cm^3). The solution was stirred at room temperature for 24 h and the resulting precipitate was extracted into ethyl acetate (4 x 10 cm^3). The combined extracts were dried ($MgSO_4$), evaporated to dryness and purified by flash sinter chromatography using silica gel as absorbent and light petroleum / ethyl acetate mixtures as eluent. *1-(5-Benzeneselenylpentylidene)semicarbazide* (**222d**) was isolated as a yellow oil (320 mg, 70%); ν_{max} 3461 (NH), 3070, 2930, 2835, 1702 (C=O), 1684 (C=N), 1634, 1576 (PhSe), 1479, 1436, 1134, 731, and 690 cm^{-1}; δ_H (d^6-acetone) 7.41-7.46 (2 H, m, PhSe ortho-H), 7.18-7.24 (3 H, m, aromatic H), 7.15 (1 H, t, J = 5.5 Hz, 1-H), 6.11 (1 H, s, NH), 3.41 (2 H, s, NH_2), 2.94 (2 H, m, 5-H), 2.14 (2 H, m, 2-H), 1.63-1.69 (2 H, m), and 1.38-1.43 (2 H, m); δ_C 161.96 (C=O), 148.14 (C=N), 136.47 (Ar-CH), 135.33 (Ar-C), 134.21 and 131.44 (Ar-CH), 35.06, 34.25, 31.41, and 31.15 (CH_2); *m/z* (C.I.) 300.0615 [MH^+ (37%), $C_{12}H_{19}N_3O$ requires 300.0615], 277 (18), 224 (76), 157 ($PhSe^+$, 62), 142 (MH^+-PhSeH), 125 (100), 78 (83), 67 (87), 55 (93), and 41 (88).

Cyclisation of 1-(5-Benzeneselenylpentylidene)semicarbazide (222d).

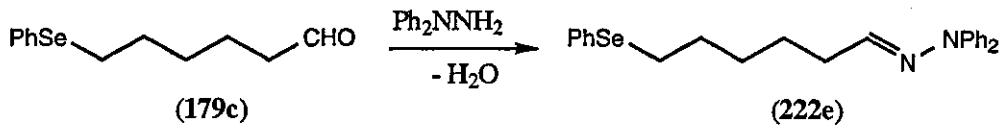


The hydrazone (**222d**) (160 mg, 0.54 mmol) was dissolved in toluene (100 cm^3) and was cyclised using the general procedure. Injection of Bu_3SnH (0.2 cm^3, 0.71 mmol) and AIBN (30 mg, 0.18 mmol) in toluene over 4.5 h using a syringe pump yielded 58 mg of recovered material, which on purification yielded the 5-*exo* adduct (**223d**) (46mg, 60%), which was found to be identical to an authentic sample.

1-Cyclopentylsemicarbazide (223d).

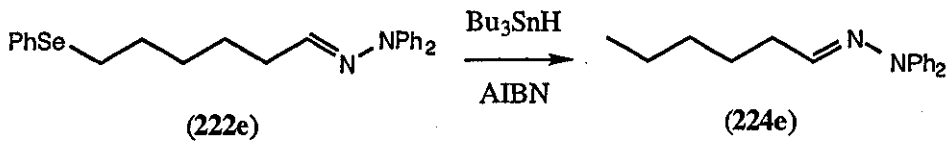
Semicarbazide hydrochloride (112 mg, 1.0 mmol) and sodium acetate (82 mg, 1.0 mmol) were dissolved in water (5 cm^3) and the solution was added to cyclopentanone (241 mg, 1.0 mmol) in ethanol (5 cm^3). The solution was stirred at room temperature for 24 h and the resulting precipitate was extracted into ethyl acetate (4 x 10 cm^3). The combined extracts were dried ($MgSO_4$) and evaporated to dryness to yield the crude hydrazone, a white solid, purified by recrystallisation from ethyl acetate. A sample of the hydrazone (250 mg, 2.0 mmol), dissolved in ethanol was added to sodium borohydride (29 mg, 0.75 mmol). The solution was refluxed stirred for 18 h at room temperature and water was added until all the effervescing had ceased. Dilute hydrochloric acid (5 cm^3) was added and the aqueous solution washed with ether (4 x 10 cm^3). The acid layer was neutralised with sodium carbonate and made strongly basic with sodium hydroxide. The hydrazine was extracted into ethyl acetate (4 x 20 cm^3) and the combined extracts dried ($MgSO_4$) and evaporated to dryness, yielding *1-cyclopentylsemicarbazide* (**223d**) as a white solid. This was purified by recrystallisation from ethyl acetate / diethyl ether mixture, yielding the pure hydrazine (42 mg, 14%, m.pt. 149-151 °C); hydrazone: (Found: C, 50.58; H, 7.83; N, 29.76. $C_6H_{11}N_3O$ requires C, 51.06; H, 7.80; N, 29.79%); ν_{max} (Nujol), 3453 (NH), 1669 (C=N), 1409, 1239, 1163, and 722 cm^{-1}; δ_H (d^6-DMSO) 7.56 (1 H, s NH), 5.31 (2 H, s, NH_2), 2.38 (2 H, t, J = 7.5 Hz, 2(5)-H), 2.21 (2 H, t, J = 7.5 Hz, 5(2)-H), and 1.69-1.88 (4 H, m, 3,4-H); hydrazine: (Found: C, 50.40; H, 9.43; N, 29.10. $C_6H_{13}N_3O$ requires C, 50.35; H, 9.09; N, 29.37%); ν_{max} (Nujol) 3430 (NH), 3290, 1691, 1584, and 722 cm^{-1}; δ_H 6.69 (1 H, s, NH), 5.63 (1 H, s, NH), 3.29-3.36 (1 H, m, cyclopentyl 1-H), 2.90-3.60 (2 H, broad s, NH_2), 1.33-1.71 (8 H, m, 2,3,4,5-C); δ_C 161.75 (C=O), 62.26 (CH), 30.63, and 23.94 (CH_2); *m/z* 143.1052 [M^+, (7.7%), $C_6H_{13}N_3O$ requires 143.1057], 144 (MH^+, 81), 97 (17), 84 ($C_5H_9NH^+$, 100), 71 (30), 61 ($H_2NCONH_3^+$, 42), and 41 (63).

1-(6-Benzeneselenylhexylidene)-2,2-diphenylhydrazine (222e).



Sodium acetate (100 mg, 1.2 mmol) and 1,1-diphenylhydrazine hydrochloride (244 mg, 1.11 mmol) were added to a solution of 6-benzeneselenylhexanal (**179c**) (282 mg, 1.11 mmol) in dry toluene (50 cm^3). The solution was refluxed for 3 h, and the water removed using a Dean-Stark water separator. The solvent was removed by distillation and the hydrazone purified by flash sinter chromatography using silica gel as absorbent and light petroleum / ethyl acetate mixtures as eluent. *1-(6-Benzeneselenylhexylidene)-2,2-diphenylhydrazine* (**222e**) was isolated as a viscous dark purple oil (455 mg, 97%); ν_{max} 3058, 2930, 1596 (phenyl), 1578 (PhSe), 1495, 1479, 1438, 1211, 1072, 748, and 638 cm^{-1}; δ_H 7.46-7.49 (2 H, m, PhSe ortho-H), 7.10-7.27 (13 H, m, aromatic H), 6.47 (1 H, t, J = 6.0 Hz, 1-H), 2.91 (2 H, t, J = 7.0 Hz, 6-H), 2.15-2.20 (2 H, m, 2-H), and 1.35-1.65 (6 H, m, 3,4,5-H); δ_C 144.31 (Ar-C), 139.65 (C=N), 132.34, (Ar-CH), 130.15 (Ar-C), 129.65, 129.16, 128.21, 128.82, and 122.34 (Ar-CH), 32.51, 29.85, 29.29, 27.75, and 27.43 (CH_2); *m/z* 422.1261 [M^+, (13%), $C_{24}H_{26}N_2Se$ requires 422.1261], 206 (6), 183 ($Ph_2N_2H^+$, 20), 168 (Ph_2N^+, 100), 155 (8), 140 (4), 115 (7), 91 (8), and 77 (Ph^+, 22).

Attempted cyclisation of 1-(6-Benzeneselenylhexylidene)-2,2-diphenylhydrazine (222e).



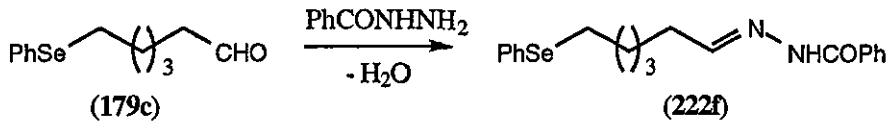
The hydrazone (**222e**) (358 mg, 0.85 mmol) was dissolved in toluene (100 cm^3) and was cyclised using the general procedure. Injection of Bu_3SnH (0.4 cm^3, 1.51 mmol) and AIBN (64 mg, 0.39 mmol) in toluene over 5.5 h using a syringe pump yielded 56 mg of recovered material, which on purification yielded the acyclic compound (**224e**) (46mg, 20%) as the only isolable product. This was found to be identical to an authentic sample.

1-Hexylidene-2,2-diphenylhydrazine (224e).

Sodium acetate (410 mg, 5 mmol) and 1,1-diphenylhydrazine hydrochloride (1.103 g, 5 mmol) were added to a solution of hexanal (500 mg, 5 mmol) in dry toluene (50 cm^3). The solution was refluxed for 3 h, and the water removed using a Dean-Stark water separator. The solvent was removed by distillation and the hydrazone purified by flash sinter chromatography using silica gel as absorbent and light petroleum / ethyl acetate mixtures as eluent. *1-Hexylidene-2,2-diphenylhydrazine* (**224e**) was isolated as a dark

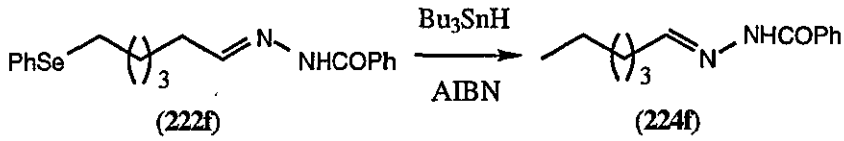
purple viscous oil (532 mg, 40%); ν_{max} 3061, 1687 (C=N), 1596, 1496, 1456, 1300, 1211, 1091, 748, and 701 cm^{-1}; δ_H 7.31-7.38 and 7.05-7.12 (10 H, m, aromatic H), 6.53 (1 H, t, J = 5.5 Hz, 1-H), 2.20-2.30 (2 H, m, 2-H), 1.41-1.52 (2 H, m), 1.28-1.33 (4 H, m), and 0.90 (3 H, t, J = 7.2 Hz, 6-H); δ_C 144.27 (Ar-C), 140.32 (C=N), 129.57, 123.71 and 122.30 (Ar-CH), 32.64, 31.37, 26.67, 22.40 (CH_2), and 13.94 (Me); *m/z* 266.1802 [M^+, (29%), $C_{18}H_{22}N_2$ requires 266.1783], 168 (Ph_2N^+, 100), 155 (15), 124 (8.7), 113 (15), 77 (Ph^+, 28), 51 (33), and 41 (28).

1-(6-Benzeneselenylhexylidene)-2-benzoylhydrazine (222f).



Benzoyl hydrazine (96 mg, 0.71 mmol) and 6-benzeneselenylhexanal (**179c**) (180 mg, 0.71 mmol) were dissolved in dry toluene (50 cm^3). The solution was refluxed for 3 h, and the water removed using a Dean-Stark water separator. The solvent was removed by distillation and the hydrazone purified by flash sinter chromatography using silica gel as absorbent and light petroleum / ethyl acetate mixtures as eluent. *1-(6-Benzeneselenyl-hexylidene)-2-benzoylhydrazine* (**222f**) was isolated as a yellow oil (265 mg, 80%); ν_{max} 3236 (NH), 3063, 2935, 1656 (C=N), 1604 (PhCO), 1580 (PhSe), 1478, 1438, 1366, 1286, 1023, and 732 cm^{-1}; δ_H 9.20 (1 H, s, NH), 7.77-7.82 (3 H, m, benzoyl ortho-H, imine H), 7.41-7.50 and 7.20-7.26 (8 H, m, aromatic H), 2.89 (2 H, t, J = 7.0 Hz, 6-H), 2.35-2.42 (2 H, m, 2-H), and 1.45-1.55 (6 H, m, 3,4,5-H); δ_C 168.56 (C=O), 155.60 (C=N), 132.53 and 131.77 (Ar-CH), 130.15 (Ar-C), 128.98, 128.49, 127.20 and 126.67 (Ar-CH), 30.01, 29.45, 27.54, 25.94, and 25.15 (CH_2); *m/z* (C.I.) 375.0976 [MH^+ (100%), $C_{17}H_{19}NSe$ requires 375.0976], 256 (MH^+-PhCON, 11), 219 (31), 139 (34), 122 ($PhCONH_3^+$, 34), and 105 ($PhCO^+$ 15).

Attempted cyclisation of 1-(6-Benzeneselenylhexylidene)-2-benzoylhydrazine (222f).

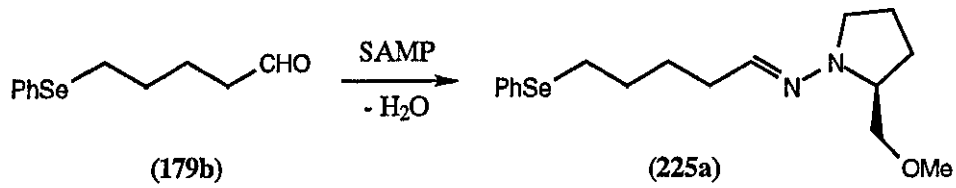


The hydrazone (**222f**) (261 mg, 0.70 mmol) was dissolved in toluene (100 cm^3) and was cyclised using the general procedure. Injection of Bu_3SnH (0.25cm^3, 0.94 mmol) and AIBN (40 mg, 0.25 mmol) in toluene over 5.3 h using a syringe pump yielded 100 mg of recovered material, which on purification yielded the acyclic compound (**224f**) (64mg, 42%) as the major product. This was found to be identical to an authentic sample.

1-Benzoyl-2-hexylidenehydrazine (224f).

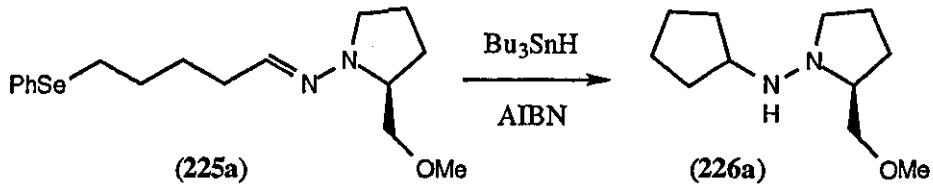
Benzoylhydrazine (680 mg, 5 mmol) and hexanal (500 mg, 5 mmol) were dissolved in toluene (50 cm^3). The solution was refluxed for 3 h, and the water removed using a Dean-Stark water separator. The solvent was removed by distillation to yield the crude hydrazone which was purified by recrystallisation from ethyl acetate / diethyl ether mixture. *1-Benzoyl-2-hexylidenehydrazine* (**224f**) was isolated as a white solid (752 mg, 69%, m.pt. 177-179 °C); (Found: C, 71.86; H, 8.38; N, 12.68. $C_{13}H_{18}N_2O$ requires C, 71.52; H, 8.31; N, 12.83%); ν_{max} 3300 (NH), 3050, 2952, 2884, 1747 (C=O), 1643 (C=N), 1604 (Ph), 1534, 1450, and 1290 cm^{-1}; δ_H 7.82-7.85 (2 H, m, until ortho-H), 7.75 (1 H, t, J = 4.8 Hz, 1-H), 7.28-7.43 (3 H, m, aromatic H), 2.20-2.31 (2 H, m, 2-H), 1.58-1.62 (2 H, m), 1.25-1.44 (4 H, m), and 0.88 (3 H, t, J = 6.4 Hz, 6-H); δ_C 164.51 (C=O), 153.56 (C=N), 132.60, 131.56 (Ar-CH), 130.03 and 129.88 (Ar-C), 129.07, 128.28, 127.49, 126.61 (Ar-CH), 32.44, 31.33, 26.21, 22.30 (CH_2), and 13.82 (6-C); *m/z* 218.1407 [M^+, (3.3%), $C_{13}H_{18}N_2O$ requires 218.1419], 217 (M^+-H, 30), 186 (M^+-Et, 29), 163 (M^+-C_4H_7, 23), 155 (56), 132 (38), 124 (33), 113 (50), 70 ($C_5H_{12}^+$, 30), 51 (100), and 28 (89).

1-[(5-Benzeneselenylpentylidene)amino]-2*S*-(methoxymethyl)pyrrolidine (225a).



S-1-Amino-2-methoxymethylpyrrolidine (210 mg, 1.54 mmol) and 5-benzeneselenyl-pentanal (**179b**) (370 mg, 1.54 mmol) were dissolved in dry toluene (50 cm^3). The solution was refluxed for 3 h, and the water removed using a Dean-Stark water separator. The solvent was removed by distillation and the hydrazone purified by flash sinter chromatography using silica gel as absorbent and light petroleum / ethyl acetate mixtures as eluent. *1-[(5-Benzeneselenyl-pentylidene)amino]-2S-(methoxymethyl)pyrrolidine* (**225a**) was isolated as an orange oil (480 mg, 88%); ν_{max} 3058, 3025, 2920, 1579 (PhSe), 1478, 1438, 1379, 1310, 1197, 1023, 731, and 694 cm^{-1}; δ_H 7.44-7.48 (2 H, m, PhSe ortho-H), 7.20-7.26 (3 H, m, aromatic H), 3.55-3.58 (1 H, m, pyrrolidine 2-H), 3.27-3.43 (3 H, m), 3.35 (3 H, s, MeO), 2.90 (2 H, t, J = 7.2 Hz, CH_2Se), 2.66-2.70 (1 H, m), 2.15-2.22 (2 H, m, 2-H), 1.68-1.92 (6 H, m), and 1.54-1.60 (2 H, m); δ_C 138.18 (C=N), 132.40 (Ar-CH), 130.80 (Ar-C), 128.99 and 128.71 (Ar-CH), 74.82 (CH_2O), 63.41 (CH_3O), 59.15 (CHN), 50.36 (CH_2N), 32.43, 29.58, 27.86, 27.58, 26.55, and 22.12 (CH_2); *m/z* 354.1210 [M^+, (4.8%), $C_{17}H_{26}N_2OSe$ requires 354.1210], 325 (36), 281 (14), 211 (30), 181 (21), 157 ($PhSe^+$, 100), 114 (38), 91 (54), 77 (Ph^+, 78), and 70 (76); $[\alpha]_D^{20}(CH_2Cl_2)$ -37.5

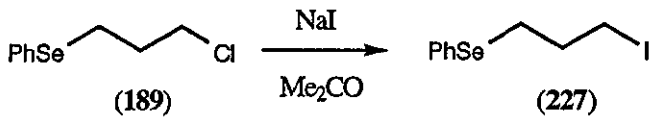
Cyclisation of 1-[(5-Benzeneselenylpentylidene)amino]-2*S*-(methoxymethyl)-pyrrolidine (225a).



(225a) (226a)

The hydrazone (**225a**) (353 mg, 1.0 mmol) was dissolved in toluene (100 cm^3) and was cyclised using the general procedure. Injection of Bu_3SnH (0.35 cm^3, 1.33 mmol) and AIBN (56 mg, 0.34 mmol) in toluene over 5 h using a syringe pump yielded 104 mg of recovered material, which on purification yielded the 5-*exo* adduct, *1-cyclopentylamino-2S-(methoxymethyl)pyrrolidine* (**226a**) (84 mg, 42%); ν_{max} 3425 (NH), 2951, 1469, 1356, 1197, 1123, and 920 cm^{-1}; δ_H 3.67-3.71 (1 H, m, cyclopentyl CHN), 3,44-3.53 (3 H, m) 3.23-3.32 (2 H, m), 3.28 (3 H, s, MeO), 2.07-2.11 (1 H, m), and 1.59-1.86 (11 H, m); δ_C 74.90 (CH_2O), 60.65 (CH_3O), 59.15 (pyrrolidine 2-C), 56.11 (cyclo-pentyl 1-C), 50.36 (CH_2N), 33.44, 30.47, 23.99, and 20.80 (CH_2); *m/z* 198.1703 [M^+, (3.3%), $C_{11}H_{22}N_2O$ requires 198.1732], 197 (M^+-H, 15), 169 (M^+-MeO, 29), 130 (MH^+-C_5H_9, 22), 94 (30), 84 ($C_5H_9NH^+$, 86), 69 ($C_5H_9^+$, 37), 55 (31), 45 (88), and 41 ($C_3H_5^+$, 100); $[\alpha]_D^{20}$(CH_2Cl_2) -46.7.

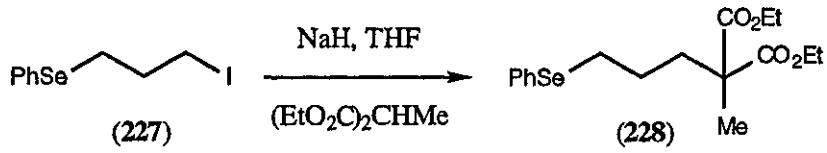
1-Benzeneselenyl-3-iodopropane (227).



(189) (227)

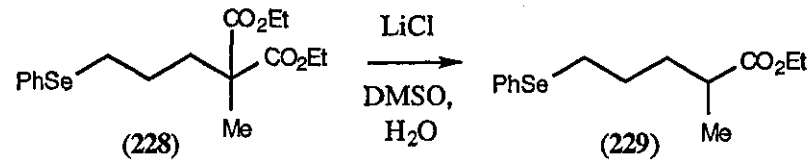
Sodium iodide (6.37 g, 42 mmol), dissolved in dried acetone (10 cm^3) was added to a solution of 1-benzeneselenyl-3-chloropropane (**189**) (2.48 g, 10.6 mmol) in acetone (40 cm^3) and the mixture refluxed for 4 h. The precipitated sodium chloride was removed by filtration and the filtrate evaporated to dryness. The solid residue was triturated with ether and the solution filtered a second time. The ether solution was evaporated to dryness yielding the product which was purified by quick filtration through silica gel. *1-Benzeneselenyl-3-iodopropane* (**227**) was isolated as a clear light yellow oil which gradually darkens to orange-red (3.45 g, 99%); ν_{max} 3058, 2931, 1579 (Ph), 1477, 1436, 1417, 1282, 1072, 1022, and 734 cm^{-1}; δ_H 7.42-7.50 (2 H, m, phenyl ortho-H), 7.21-7.26 (3 H, m, phenyl H), 3.24 (2H, t, J = 6.5 Hz, 3-H), 2.97 (2 H, t, J = 6.1 Hz, 1-H), and 2.05-2.16 (2 H, m, 2-H); δ_C 132.87 (Ar-CH), 129.15 (Ar-C), 129.10 and 127.16 (Ar-CH), 33.20 (1-C), 28.28 (2-C), and 6.14 (3-C); *m/z* 325.9071 [M^+, (60%), $C_9H_{11}ISe$ requires 325.9030], 199 (MH^+-I, 100), 169 (MH^+-PhSe, 34), 157 ($PhSe^+$, 58), 117 (12), 91 (46), 77 (39), and 41 (58).

Diethyl (3-Benzeneselenylpropyl)(methyl)propanedioate (228).



General procedure for the 2-alkylatiion of propanedioate (malonate) esters. Sodium hydride (100 mg of 60% suspension in mineral oil) was placed in a dried flask and was washed, under nitrogen, by dry light petroleum (2 x 10 cm^3). Freshly dried and distilled DMF (20 cm^3) was added and to the suspension was added solution of diethyl methyl-propanedioate (348 mg, 2 mmol) in DMF (5 cm^3) After stirring at 50 °C for 30 min, 1-benzeneselenyl-3-iodopropane (**227**) (633 mg, 2 mmol) in DMF (5 cm^3) was added dropwise over 10 min. The mixture was stirred at 50 °C for 8 h, and on cooling water (20 cm^3) and 2 M hydrochloric acid (10 cm^3) was added and the organic products extracted into diethyl ether (5 x 20 cm^3). The combined extracts were washed with water (6 x 10 cm^3), dried ($MgSO_4$) and evaporated to dryness. The crude product was purified by flash sinter chromatography using silica gel as absorbent and light petroleum / ethyl acetate mixtures as eluent. *Diethyl (3-benzeneselenylpropyl)(methyl)propanedioate* (**228**) was isolated as a yellow-orange oil (640 mg, 86%); ν_{max} 3057, 2938, 1737 (ester), 1580 (PhSe), 1479, 1439, 1379, 1251, 1175, 1023, 737, and 691 cm^{-1}; δ_H 7.45-7.48 (2 H, m, phenyl ortho-H), 7.21-7.26 (3 H, m, phenyl H), 4.13 (4 H, q, J = 7.2 Hz, ethyl CH_2), 2.88 (2 H, t, J = 7.2 Hz, CH_2Se), 1.94-2.01 (2 H, m), 1.61-1.67 (2 H, m), 1.36 (3 H, s, 2-Me), and 1.21 (6 H, t, J = 7.2 Hz, ethyl CH_3); δ_C 172.15 (C=O), 132.60 (Ar-CH), 130.15 (Ar-C), 129.01 and 126.81 (Ar-CH), 61.19 (ethyl CH_2), 53.37 (2-C), 33.70, 27.77 and 25.06 (3,4,5-C), 19.93 (2-Me) and 14.02 (ethyl-CH_3); *m/z* 372.0852 [M^+, (14%), $C_{17}H_{24}O_4Se$ requires 372.0840], 215 (M^+-PhSe, 100), 187 (26), 157 ($PhSe^+$, 40), 141 (70), 123 (31), 113 (36), 85 (45), 69 (69), and 29 (Et^+, 88).

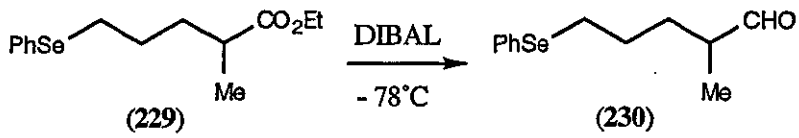
Ethyl 5-Benzeneselenyl-2-methylpentanoate (229).



General procedure for hydrolytic decarboxylation using lithium chloride in DMSO. Diethyl (3-benzeneselenylpropyl)(methyl)propanedioate (**228**) (325 mg, 0.87 mmol) dissolved in freshly dried and distilled DMSO (1 cm^3) was added to a solution of lithium chloride (100 mg, 1.31 mmol) in DMSO (2 cm^3) containing water (100 mg, 1.75 mmol). The mixture was heated at 170°C for 24 h, cooled to room temperature and water (20

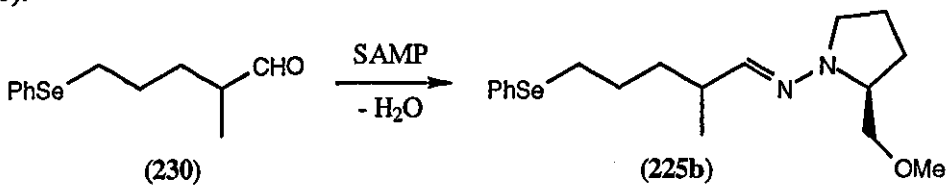
cm^3) was added followed by dilute hydrochloric acid (5 cm^3). The product was extracted into diethyl ether (5 x 10 cm^3) and the combined extracts were washed with water (6 x 10 cm^3), dried ($MgSO_4$), and evaporated to dryness. The product was purified by flash sinter chromatography using silica gel as absorbent and light petroleum / ethyl acetate mixtures as eluent. *Ethyl 5-benzeneselenyl-2-methylpentanoate* (**229**) was isolated as a light yellow oil (208 mg, 80%); ν_{max} 3057, 2933, 1731 (ester), 1579 (PhSe), 1477, 1438, 1378, 1242, 1182, 1022, 735, and 690 cm^{-1}; δ_H 7.44-7.50 (2 H, m, phenyl ortho-H), 7.22-7.28 (3 H, m, phenyl H), 4.12 (2 H, q, J = 7.0 Hz, ethyl CH_2), 2.90 (2 H, t, J = 7.2 Hz, 5-H), 2.35-2.43 (1 H, m, 2-H), 1.52-1.78 (4 H, m, 3,4-H) 1.22 (3 H, d, J = 7.0 Hz, 2-Me), and 1.13 (3 H, t, J = 7.2 Hz, ethyl CH_3); δ_C 171.15 (C=O), 131.53 (Ar-CH), 129.90 (Ar-C), 129.18 and 127.72 (Ar-CH), 60.45 (ethyl CH_2), 39.11 (2-C), 33.61, 27.81, 27.57 (3,4,5-C), 17.10 (2-Me), and 14.23 (ethyl CH_3); *m/z* 300.0638 [M^+, (16%), $C_{14}H_{20}O_2Se$ requires 300.0628], 157 ($PhSe^+$, 50), 143 (M^+-PhSe, 100), 115 [M^+-$PhSe(CH_2)_2$, 86], 97 (13), 91 (17), 77 (51), 69 (85), and 41 (49).

5-Benzeneselenyl-2-methylpentanal (230).



The general procedure for the synthesis of aldehydes was used, except that a reaction time of 2.5 h was employed. Ethyl 5-benzeneselenyl-2-methylpentanoate (**229**) (323 mg, 1.08 mmol) and diisobutylaluminium hydride (25% w/w in toluene, 3.8 cm^3, 757 mg, 5.38 mmol) in toluene (50 cm^3) gave *5-benzeneselenyl-2-methylpentanal* (**230**) as a yellow oil (167 mg, 70%); ν_{max} 3071, 2928, 2854, 1723 (C=O), 1579 (PhSe), 1478, 1437, 1073, 1022, 735, and 691 cm^{-1}; δ_H 9.57 (1 H, s, 1-H), 7.45-7.50 (2 H, m, phenyl ortho-H), 7.21-7.27 (3 H, m, phenyl H), 2.90 (2 H, t, J = 7.1 Hz, 5-H), 2.31-2.35 (2 H, m, 2-H), 1.68-1.77 (4 H, m, 3,4-H), and 1.06 (3 H, d, J = 6.9 Hz, 2-Me); δ_C 204.56 (C=O), 132.65 (Ar-CH), 130.15 (Ar-C), 129.03 and 126.86 (Ar-CH), 45.76 (2-C), 30.36, 27.58, 27.40 (3,4,5-C), and 16.48 (2-Me); *m/z* 256.0349 [M^+, (30%), $C_{12}H_{16}OSe$ requires 256.0366], 158 ($PhSeH^+$, 98), 124 (21), 113 (33), 99 (M^+-PhSe, 66), 83 (51), 77 (Ph^+, 100), 51 (66), and 41 (72).

1-[(5-Benzeneselenyl-2-methylpentylidene)amino]-2*S*-(methoxymethyl)pyrrolidine *S*-(225b).

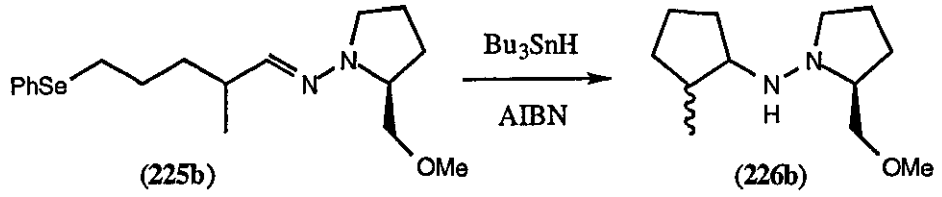


S-1-Amino-2-(methoxymethyl)pyrrolidine (102 mg, 0.78 mmol) and 5-benzeneselenyl-2-methylpentanal (**230**) (200 mg, 0.78 mmol) were dissolved in dry toluene (50 cm^3). The solution was refluxed for 3 h, and the water removed using a Dean-Stark water separator. The solvent was removed by distillation and the hydrazone purified by flash sinter chromatography using silica gel as absorbent and light petroleum / ethyl acetate mixtures as eluent. *1-[(5-Benzeneselenyl-2-methylpentylidene)amino]-2S-(methoxymethyl)-pyrrolidine S-*(**225b**) was isolated as an orange oil (274 mg, 96%); ν_{max} 2926, 2855, 1579 (PhSe), 1478, 1438, 1379, 1196, 1099, 1073, 1023, 736, and 691 cm^{-1}; δ_H 7.43-7.51 and 7.21-7.27 (6 H, m, aromatic-H, imine-H), 3.29-3.42 (6 H, m), 2.95-3.02 (2 H, m, CH_2Se), 2.89-2.93 (1 H, m), 2.15-2.34 (2 H, m), 1.96-2.08 and 1.82-1.88 (8 H, m), and 1.02 and 0.88 (3 H, 2 x d, J = 7.0 Hz, 2-Me); δ_C 143.52 (C=N), 132.47 (Ar-CH), 130.05 (Ar-C), 129.15 and 126.79 (Ar-CH), 67.90 (CH_2O), 63.48 (CH_3O), 59.16 (CHN), 50.43 (CH_2N), 36.60 (sidechain 2-C), 35.54, 32.74, 30.19, 27.67, 22.06 (CH_2), and 19.60 (Me); *m/z* 368.1367 [M^+, (24%), $C_{18}H_{28}N_2OSe$ requires 368.1367], 323 (81 M^+-$MeOCH_2$), 176 (19), 157 ($PhSe^+$, 22), 91 (28), 77 (Ph^+, 32), and 70 (100); $[\alpha]_D^{20}(CH_2Cl_2)$ -32.6.

1-[(5-Benzeneselenyl-2-methylpentylidene)amino]-2*R*-(methoxymethyl)pyrrolidine *R*-(225b).

R-1-Amino-2-(methoxymethyl)pyrrolidine (111 mg, 0.85 mmol) and 5-benzeneselenyl-2-methylpentanal (**230**) (217 mg, 0.85 mmol) were dissolved in dry toluene (50 cm^3). The solution was refluxed for 3 h, and the water removed using a Dean-Stark water separator. The solvent was removed by distillation and the hydrazone purified by flash sinter chromatography using silica gel as absorbent and light petroleum / ethyl acetate mixtures as eluent. *1-[(5-Benzeneselenyl-2-methylpentylidene)amino]-2R-(methoxy-methyl)pyrrolidine R-*(**225b**) was isolated as an orange oil (305 mg, 98%) which was found to be spectro-scopically identical to the *S* diastereomer; $[\alpha]_D^{20}(CH_2Cl_2)$ +32.6.

Cyclisation of 1-[(5-Benzeneselenyl-2-methylpentylidene)amino]-2*S*-(methoxy-methyl)pyrrolidine *S*-(225b).



(**225b**) (**226b**)

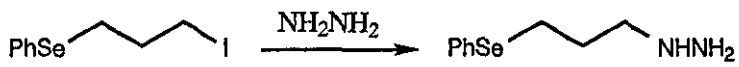
The hydrazone *S*-(**225b**) (199 mg, 0.54 mmol) was dissolved in toluene (100 cm^3) and was cyclised using the general procedure. Injection of Bu_3SnH (0.19 cm^3, 0.72 mmol) and AIBN (30 mg, 0.18 mmol) in toluene over 5.3 h using a syring pump yielded 60 mg

of recovered material, which on purification yielded the 5-*exo* adduct, *1-(2-methylcyclopentyl)amino-2S-(methoxymethyl)pyrrolidine S-*(**226b**) (46 mg, 40%); ν_{max} 320 (NH), 2953, 2870, 1455, 1374, 1197, 1095, and 921 cm^{-1}; δ_H (2 stereoisomers) 4.10 (1 H, s, NH), 3.68-3.72 (1 H, m, cyclopentyl CHN), 3.52-3.60 (1 H, m), 3.43-3.47 (2 H, m), 3.33 and 3.35 (3 H, 2 x s, MeO), 3.21-3.24 (2 H, m), 2.43-2.47 (1 H, m, cyclopentyl 2-H), 2.14-2.21 (2 H, m), 1.71-2.02 (8 H, m), and 1.10 and 1.07 (3 H, 2 x d, J = 8.0 Hz, 2-Me); δ_C (2 stereoisomers) 75.64 and 74.70 (CH_2O), 66.22 (MeO), 80.95 and 63.30 (cyclopentyl 1-C), 59.04 (pyrrolidine 2-C), 53.95 and 53.48 (pyrrolidine 5-C), 39.16 and 39.98 (cyclopentyl 2-C), 33.17, 30.20. 26.60, 22.18, 22.03 (CH_2), and 19.13 and 17.36 (2-Me); *m/z* 212.1879 [M^+, (14%), $C_{12}H_{24}N_2O$ requires 212.1889], 155 (M^+-C_4H_9, 32), 149 (22), 132 (15), 124 (20), 113 (M^+-$C_6H_{11}NH_2$, 32), 83 (2-$MeC_5H_8^+$, 18), 69 (31), 57 (46), 51 (100), 41 (54), and 31 (82); $[\alpha]_D^{20}(CH_2Cl_2)$ -30.0.

Cyclisation of 1-[(5-Benzeneselenyl-2-methylpentylidene)amino]-2*R*-(methoxymethyl)pyrrolidine *R*-(225b).

The hydrazone *R*-(**225b**) (190 mg, 0.52 mmol) was dissolved in toluene (100 cm^3) and was cyclised using the general procedure. Injection of Bu_3SnH (0.2 cm^3, 0.69 mmol) and AIBN (29 mg, 0.18 mmol) in toluene over 5 h using a syring pump yielded 50 mg of recovered material, which on purification yielded the 5-*exo* adduct, *1-(2-methylcyclopentyl)amino-2R-(methoxymethyl)pyrrolidine R-*(**226b**) (43 mg, 39%) which was found to be spectroscopically identical to the *S* diastereomer; $[\alpha]_D^{20}(CH_2Cl_2)$ +29.1.

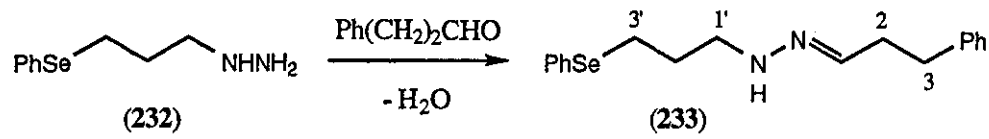
(3-Benzeneselenylpropyl)hydrazine (232).



(227) (232)

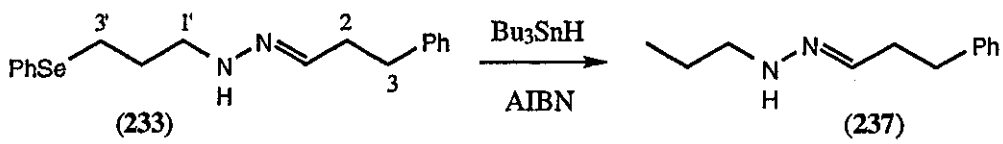
1-Benzeneselenyl-3-iodopropane (**227**) (650 mg, 2 mmol) and hydrazine hydrate (500 mg, 10 mmol) were dissolved in ethanol (10 cm^3) and stirred at room temperature for 72 h. Water (30 cm^3) was added and the crude product extracted into CH_2Cl_2 (3 x 30 cm^3). The hydrazine was isolated by extraction into 2 M hydrocloric acid (2 x 20 cm^3), neutralised (Na_2CO_3, NaOH) and re-extracted into CH_2Cl_2 (3 x 20 cm^3). The combined organic layers were dried (Na_2SO_4) and evaporated to dryness to yield *(3-benzeneselenylpropyl)hydrazine* (**232**) as a yellow oil (344 mg, 75%); ν_{max} 3337 (NH), 3055, 2931, 1667, 1579 (Ph), 1476, 1437, 1073, 1023, 735, and 691 cm^{-1}; δ_H 7.42-7.51 (2 H, m, phenyl ortho-H), 7.20-7.26 (3 H, m, phenyl H), 4.13 (3 H, broad s, NH, NH_2), 2.88-3.01 (4 H, m, 1,3-H), 1.89-1.94 (2 H, m, 2-H); δ_C 132.54 (Ar-CH), 130.20 (Ar-C), 129.02 and 126.84 (Ar-CH), 60.88 (1-C), 28.50 (3-C), and 24.14 (2-C); *m/z* 199 (M^+-$NHNH_2$, 22), 157 ($PhSe^+$, 79), 91 (48), 77 (Ph^+, 100), 51 (83), 41 (71), and 31 (88).

1-(3-Benzeneselenylpropyl)-2-(3'-phenylpropylidene)hydrazine (233).



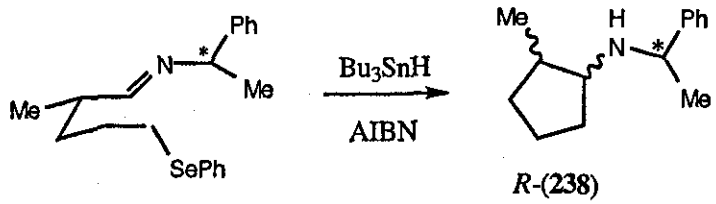
(3-Benzeneselenylpropyl)hydrazine (**232**) (243 mg, 1.06 mmol) and 3-phenylpropanal (143 mg, 1.06 mmol) were dissolved in dry toluene (50 cm^3). The solution was refluxed for 3 h, and the water removed using a Dean-Stark water separator. The solvent was removed by distillation and the hydrazone purified by flash sinter chromatography using silica gel as absorbent and light petroleum / ethyl acetate mixtures as eluent. *1-(3-Benzene-elenylpropyl)-2-(3'-phenylpropylidene)hydrazine* (**233**) was isolated as a yellow oil (172 mg, 47%); ν_{max} 3420 (NH), 3027, 2927, 1653 (C=N), 1603 (Ph), 1579 (PhSe), 1496, 1477, 1454, 1437, 1217, 1023, and 736 cm^{-1}; δ_H 7.43-7.49 (2 H, m, PhSe ortho-H), 7.19-7.28 (9 H, m, aromatic H, imine H), 2.97 (2 H, t, J = 7.2 Hz, 1-H), 2.88 (2 H, t, J = 7.3 Hz, 3-H), 2.62-2.69 (4 H, m, 2'-3'-H), and 2.01-2.05 (2 H, m, 2-H); δ_C 164.22 (C=N), 132.7 (Ar-CH), 131.46 and 129.86 (Ar-C), 129.04, 128.50, 128.36, 126.88 and 126.17 (Ar-CH) 34.27, 32.65, 30.16, 27.41, and 24.15 (CH_2).

Attempted cyclisation of 1-(3-Benzeneselenylpropyl)-2-(3'-phenylpropylidene)-hydrazine (233).



The hydrazone (**233**) (212 mg, 0.62 mmol) was dissolved in toluene (100 cm^3) and was cyclised using the general procedure. Injection of Bu_3SnH (0.22 cm^3, 0.82 mmol) and AIBN (34 mg, 0.21 mmol) in toluene over 5 h using a syring pump yielded 35 mg of recovered material, which on purification yielded the acyclic hydrazone, 1-(3'-phenyl-propylidene)-2-propylhydrazine (**237**) as the only product (30 mg, 26%); ν_{max} 2926, 2850, 1685 (C=N), 1604 (phenyl), 1496, 1453, 1074, 1023, 739, and 699 cm^{-1}; δ_H 7.18-7.25, (6 H, m, phenyl, imine-H), 2.64-2.72 (2 H, m, 1-H), 1.57-1.67 (2 H, m, 3'-H), 1.25-1.37 (4 H, m, 2,2'-H), and 0.92 (3 H, t, J = 7.3 Hz, 3-H); δ_C 154.75 (C=N), 132.54 (Ar-C), 128.37, 128.27 and 126.01 (Ar-CH), 34.34, 29.57, 27.78, 26.78 (CH_2), and 13.54 (Me); *m/z* 190 (M^+, 7.8%), 131 (17, M^+-$PrNH_2$), 117 (38), 105 (34, $MeC_7H_6^+$), 91 (100, $C_7H_7^+$), and 77 (15, Ph^+).

Cyclisation of the Imine formed from 5-Benzeneselenyl-2-methylpentanal and *R*-α-Methylbenzylamine.



5-Benzeneselenyl-2-methylpentanal (**230**) (63 mg, 0.25 mmol) and *R*-α-methylbenzylamine (30 mg, 0.27 mmol) in toluene were refluxed for 4 h, the water condensing in a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure. Injection of Bu_3SnH (0.12 cm^3, 0.33 mmol) and AIBN (14 mg, 0.09 mmol) in toluene yielded *N-(2-methylcyclopentyl)-1R-phenylethylamine R-*(**238**) as a yellow oil (33 mg, (65%, d.e. < 5%), which was found to be identical with a racemic authentic sample.

***N*-(2-Methylcyclopentyl)-1*R*-phenylethylamine *R*-(238).**

The amine was prepared by general method A. 2-Methylcyclopentanone (980 mg, 10 mmol) and *R*-α-methylbenzylamine (1.21 g, 10 mmol) gave *N-(2-methylcyclopentyl)-1R-phenylethylamine R-*(**238**) as a light yellow oil (1.08 g, 53%); ν_{max} 3304, 3026, 2931, 1664, 1603, 1496, 1454, 1377, 1128, 737, and 691 cm^{-1}; δ_H (2 stereoisomers) 7.22-7.34 (5 H, m, Ar-H), 4.42-4.47 (1 H, m, NH), 3.79-3.85 (1 H, m, PhCH), 2.80-2.85 (1 H, m, cyclopentyl 1-H), 2.00-2.09 (1 H, m, cyclo-pentyl 2-H), 1.33-1.74 (6 H, m), 1.18 (3 H, 2 x d, J = 6.8 Hz, α-Me), and 0.89 and 0.99 (3 H, 2 x d, J = 7.0 Hz, 2-Me); δ_C (2 stereo-isomers) 146.27 (Ar-C), 128.40, 126.72, 126.73 (Ar-CH), 64.72, 59.51, 57.03, 56.28 (CHN), 41.29, 40.89 (cyclopentyl 2-C), 33.67, 32.75, 28.80, 28.60, 22.57, 22.40 (CH_2), 25.62, 25.24 (α-Me), and 17.60 (2-Me); *m/z* 203.1677 [M^+, (4.7%), $C_{14}H_{21}N$ requires 203.1674], 188 (M^+-Me, 41), 160 (16), 120 (MH^+-MeC_5H_8, 7), 106 (75), 105 ($MeC_7H_6^+$, 100), 91 ($C_7H_7^+$, 28), 79 (29), 77 (8), and 70 (27); $[\alpha]_D^{20}(CH_2Cl_2) = -18.2$.

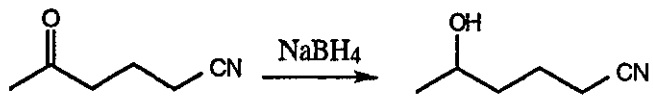
Cyclisation of the Imine formed from 5-Benzeneselenyl-2-methylpentanal and *S*-α-Methylbenzylamine.

5-Benzeneselenyl-2-methylpentanal (**230**) (65 mg, 0.25 mmol) and *S*-α-methylbenzylamine (30 mg, 0.25 mmol) in toluene were refluxed for 4 h, the water condensing in a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure. Injection of Bu_3SnH (0.12 cm^3, 0.33 mmol) and AIBN (14 mg, 0.09 mmol) in toluene yielded *N-(2-methylcyclopentyl)-1S-phenylethylamine S-*(**238**) as a yellow oil (32 mg, 53%, d.e. < 5%), which was found to be identical with a racemic authentic sample.

***N*-(2-Methylcyclopentyl)-1*S*-phenylethylamine *S*-(238).**

The amine was prepared by general method A. 2-Methylcyclopentanone (980 mg, 10 mmol) and *S*-α-methylbenzylamine (1.21 g, 10 mmol) gave *N-(2-methylcyclopentyl)-1S-phenylethylamine S-*(**238**) as a light yellow oil (1.12 g, 55%) which was found to be spectroscopically identical to the *R* diastereomer; $[\alpha]_D^{20}(CH_2Cl_2) = +18.4$.

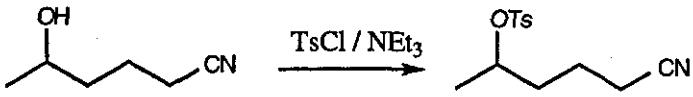
5-Hydroxyhexanonitrile (*240*).



(239) (240)

Sodium borohydride (2.28g, 0.33 equiv.) in absolute ethanol (10 cm^3) was added to 5-oxohexanonitrile (**239**) (20 g, 180 mmol) in diethyl ether (30 cm^3), and the mixture stirred at room temperature for 18 h. Water (20 cm^3) was added followed by slow addition of dilute hydrochloric acid (10 cm^3) and the product was extracted into diethyl ether. The organic extracts were dried ($MgSO_4$) and evaporated to dryness. The alcohol was purified by flash sinter chromatography using silica as absorbent and light petroleum / ethyl acetate mixtures as eluent. *5-Hydroxyhexanonitrile* (**240**) was isolated as a colourless liquid (18.3 g, 90%); ν_{max} 3520 (OH), 2969, 2875, 2247 (CN), 1459, 1426, 1377, 1331, 1132, 1090, and 976 cm^{-1}; δ_H 6.30 (1 H, br s, OH), 3.76-3.83 (1 H, m, 5-H), 2.35 (2 H, t, J = 7.0 Hz, 2-H), 1.61-1.74 (2 H, m), 1,50-1.60 (2 H, m), and 1.16 (3 H, d, J = 6.2 Hz); δ_C 119.69 (CN), 66.96 (5-C), 37.41 (2-C), 23.24 (6-C), 21.62, and 16.99 (3,4-C); *m/z* 113.0845 [M^+, (3.0%), $C_6H_{11}NO$ requires 113.0841], 112 (M^+-H, 1), 96 (M^+-OH, 40), 85 (4), 69 (23), 55 ($MeC_3H_4^+$, 23), 45 ($MeCHOH^+$, 98), and 41 ($C_3H_5^+$, 100).

5-(4-Methylbenzenesulfonyloxy)hexanonitrile (241).



(240) (241)

5-Hydroxyhexanonitrile (**240**) (4.0 g, 36 mmol) was dissolved in dichloromethane (10 cm^3) and *p*-toluenesulfonyl chloride (6.87 g, 36 mmol) and triethylamine (3.6 g, 100 mmol) in dichloromethane (40 cm^3) were added and the mixture stirred at room temperature for 10 h. The precipitated salts were filtered and the filtrate washed with saturated sodium bicarbonate solution, dried (Na_2SO_4) and evaporated to dryness. The product was purified by dry flash chromatography using silica as absorbent and light petroleum / ethyl acetate mixtures as eluent. *5-(4-Methylbenzenesulfonyloxy)hexanonitrile* (**241**) was isolated as a colourless glassy solid (8.3 g, 86%); ν_{max} 2907, 2876,

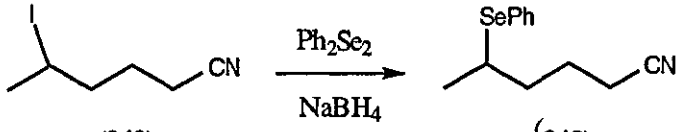
2705, 2246 (CN), 1596 (Ar), 1375, 1176, 1033, 1010, 900, 817, and 683 cm^{-1}; δ_H 7.53, 7.50, 7.35 and 7.17 (4 H, 4 x d, J = 8.0 Hz, Ar-H), 4.58-4.65 (1 H, m, 5-H), 3.17-3.25 (2 H, m, 2-H), 2.44 (3 H, s, MeAr), 2.04-2.28 (2 H, m, 4-H), 1.54-1.73 (2 H, m, 3-H), and 1.20 (3 H, d, J = 6.2 Hz, 6-H); δ_C 129.77, 128.69, (ArCH), 127.80 (Ar-C), 127.41, 125.50 (Ar-CH), 118.32 (Ar-C), 119.70 (CN), 78.90 (5-C), 46.18 (2-C), 34.97 (4-C), 16.34 (3-C), 21.29 and 20.44 (MeAr), and 8.28 (6-C); *m/z* 266.9998 [M^+, (2.0%), $C_{13}H_{17}NO_3S$ requires 267.1216], 172 ($TsOH^+$, 17), 155 (Ts^+, 21), 107 (10), 96 (M^+-Ts, 19), 91 ($C_7H_7^+$, 50), 86 (44), 70 (37), 55 ($MeC_3H_4^+$, 46), 45 (73), and 41 ($C_3H_5^+$, 100).

5-Iodohexanonitrile (242).

(241) (242)

5-(4-Methylbenzenesulfonyloxy)hexanonitrile (**241**) (8.0 g, 30 mmol) was dissolved in distilled acetone (100 cm^3) and an excess of sodium iodide (6 g) was added. The mixture was refluxed for 10 h and precipitated salts filtered. The acetone was removed by evaporation and the residue dissolved in water. The product was extracted into diethyl ether and the combined extracts dried ($MgSO_4$) and evaporated to dryness. The product was purified by flash sinter chromatography using silica as absorbent and light petroleum / ethyl acetate mixtures as eluent. *5-Iodohexanonitrile* (**242**) was isolated as an orange light-sensitive oil (3.06 g, 46%); ν_{max} 2925, 2871, 2246 (CN), 1491, 1453, 1323, 1193, 1017, 812, and 655 cm^{-1}; δ_H 4.10-4.14 (1 H, m, 5-H), 2.35-2.44 (2 H, m, 2-H), 1.93 (3 H, d, J = 6.6 Hz, 6-H), and 1.50-1.88 (4 H, m, 3,4-H); δ_C 41.09 (2-C), 28.82 (6-C), 27.50 (5-C), 25.69, and 16.31 (3,4-C); *m/z* 222.9856 [M^+, (0.1%), $C_6H_{10}IN$ requires 222.9860], 224 (MH^+, 1), 155 ($CH_2CH_2I^+$, 2), 127 (I^+, 8), 96 (M^+-I, 100), 69 (MH^+-I-CH_2=CH_2, 30), 55 ($MeC_3H_4^+$, 72), and 41 ($C_3H_5^+$, 48).

5-Benzeneselenylhexanonitrile (243).

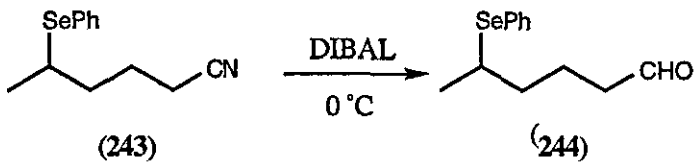


(242) (243)

The general procedure for the introduction of the benzeneselenyl group was used. Diphenyl diselenide (975 mg, 3.1 mmol), sodium borohydride (80 mg, 2.1 mmol) and 5-iodohexanonitrile (**242**) (1.43 g, 6.4 mmol) gave *5-benzeneselenylhexanonitrile* (**243**) as an orange oil (1.36 g, 84%); ν_{max} 3056, 2924, 2868, 2246 (CN), 1578 (PhSe), 1476, 1437, 1377, 1151, 1021, 739, and 693 cm^{-1}; δ_H 7.54-7.59 (2 H, m, ortho-H), 7.25-7.31

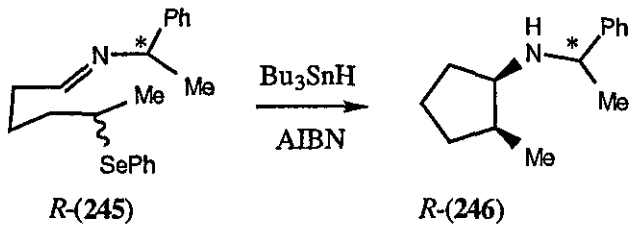
(3 H, m, Ar-H), 3.21-3.47 (1 H, m, 5-H), 2.31-2.36 (2 H, m, 2-H), 1.71-1.88 (4 H, m, 3,2-H), and 1.44 (3 H, d, J = 7.0 Hz, 6-H); δ_C 135.15 (Ar-CH), 130.05 (Ar-C), 128.96, 127.51 (Ar-CH), 119.40 (CN), 38.50 (5-C), 36.31, 23.64 (CH_2), 22.54 (6-C), and 16.86 (CH_2); *m/z* 253.0349 [M^+, (8.1%), $C_{12}H_{15}NSe$ requires 253.0369], 158 ($PhSeH^+$, 44), 124 (13), 96 (M^+-PhSe, 56), 77 (Ph^+, 41), 55 ($MeC_3H_4^+$, 100), and 41 ($C_3H_5^+$, 81).

5-Benzeneselenylhexanal (244).



An adaptation to the general procedure for the synthesis of aldehydes was employed. 5-Benzeneselenylhexanonitrile (**243**) (364 mg, 1.4 mmol) and diisobutylaluminium hydride (217 mg, 1.54 mmol) were reacted at 0°C for 3 h and after the addition of acetic acid (300 mg, 6 mmol) and water (0.5 cm^3), the mixture was stirred at room temperature for 24 h, which on work up gave *5-benzeneselenylhexanal* (**244**) as a yellow oil (215 mg, 60%); ν_{max} 3059, 2925, 2865, 2725, 1723 (C=O), 1578 (PhSe), 1476, 1437, 1374, 1156, 1073, 1022, 733, and 694 cm^{-1}; δ_H 9.75 (1 H, t, J = 1.5 Hz, 1-H), 7.56-7.60 (2 H, m, ortho-H), 7.21-7.31 (3 H, m, Ar-H), 3.27-3.32 (1 H, m, 5-H), 2.36-2.44 (2 H, m, 2-H), 1.63-1.84 (4 H, m, 3,2-H), and 1.54 (3 H, d, J = 6.5 Hz, 6-H); δ_C 202.02 (C=O), 134.99 (Ar-CH), 130.15 (Ar-C), 128.58, 127.67 (Ar-CH), 43.43 (2-C), 39.33 (5-C), 35.33, 22.04 (6-C), and 20.32 (CH_2); *m/z* 256.0354 [M^+, (5.0%), $C_{12}H_{16}OSe$ requires 256.0366], 158 ($PhSeH^+$, 53), 99 (M^+-PhSe, 35), 91 (36), 81 (60), 77 (Ph^+, 48), and 55 (100).

Cyclisation of Imine *R*-(245).

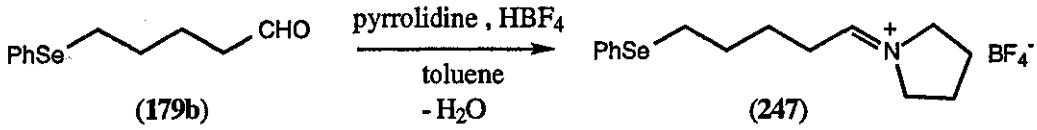


5-Benzeneselenylhexanal (**244**) (68 mg, 0.27 mmol) and *R*-α-methylbenzylamine (32 mg, 0.27 mmol) in toluene were refluxed for 4 h, the water condensing in a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure. Injection of Bu_3SnH (0.137 cm^3, 0.36 mmol) and AIBN (15 mg, 0.09 mmol) in toluene yielded *N-(2-methylcyclopentyl)-1R-phenylethylamine R*-(**246**) as a yellow oil (28 mg, (51%, d.e. = 29%), which was found to be identical with a racemic authentic sample.

Cyclisation of Imine *S*-(245).

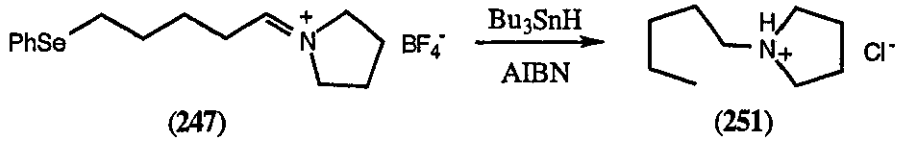
5-Benzeneselenylhexanal (**244**) (68 mg, 0.27 mmol) and *S*-α-methylbenzylamine (32 mg, 0.27 mmol) in toluene were refluxed for 4 h, the water condensing in a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure. Injection of Bu_3SnH (0.137 cm^3, 0.36 mmol) and AIBN (15 mg, 0.09 mmol) in toluene yielded *N-(2-methylcyclopentyl)-1S-phenylethylamine S*-(**246**) as a yellow oil (30 mg, 55%, d.e. = 44%), which was found to be identical with a racemic authentic sample.

***N*-(5-Benzeneselenylpent-1-ylidene)pyrrolidinium tetrafluoroborate (247).**



The iminium salt was prepared by general procedure C. 5-Benzeneselenylpentanal (**179b**) (781 mg, 3.24 mmol), pyrrolidine (250 mg, 3.52 mmol) and tetrafluoroboric acid (500 mg of 54 % solution in Et_2O, 3.20 mmol) were dissolved in toluene (120 cm^3) and refluxed for 3 h, the water removed using a Dean-Stark water separator. The solution was evaporated to dryness to yield the iminium salt (**247**) as an orange-brown low melting solid (1.22 g, 98%) which did not require further purification; ν_{max} 2932, 2861, 1733, 1579 (PhSe), 1478, 1457, 1438, 1374, 1196, 1018, 736, and 691 cm^{-1}; δ_H 7.56-7.58 (2 H, m, o-Ph), 7.20-7.26 (3 H, m, PhSe), 7.16 (1 H, t, J = 6.5 Hz, 1-H), 3.35-3.49 (4 H, m, pyrrolidine 2,5-H), 2.92 (2 H, t, J = 7.3 H, 5-H), 1.98-2.12 (6 H, m), and 1.70-1.79 (4 H, m); δ_C 132.30 (ArCH), 130.15 (ArC), 128.95, 126.71 and 125.20 (ArC and 1-C), 46.62 (pyrrolidine 2,5-C), 29.73, 29.12, 27.45, 24.31, and 23.79 (CH_2).

Attempted cyclisation of *N*-(5-Benzeneselenylpent-1-ylidene)pyrrolidinium tetrafluoroborate (247) using tri-*n*-butyltin hydride.



A refluxing solution of iminium salt (**247**) (407 mg, 1.1 mmol) was cyclised using the general procedure. Injection of Bu_3SnH (0.4 cm^3, 1.46 mmol) and AIBN (61 mg, 0.37 mmol) in toluene using a syringe pump yielded 146 mg of the product, isolated as the hydrochloride salt (75%), which was found to be the acyclic product *N*-pentyl-pyrrolidinium hydrochloride (**251**). This was found to be identical with an authentic sample.

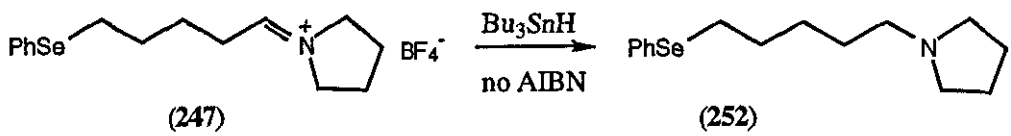
Attempted cyclisation of *N*-(5-Benzeneselenylpent-1-ylidene)pyrrolidinium tetrafluoroborate (247) using tris(trimethylsilyl)silane.

A refluxing solution of the iminium salt (**247**) (531 mg, 1.39 mmol) in toluene was cyclised using the general procedure. Injection of $(Me_3Si)_3SiH$ (460 mg, 1.85 mmol) and AIBN (78 mg, 0.4 mmol) in toluene using a syringe pump gave 167 mg of the product, isolated as the hydrochloride salt (68%), which was found to be the acyclic product *N*-pentylpyrrolidinium hydrochloride (**251**). This was found to be identical with an authentic sample.

***N*-Pentylpyrrolidinium hydrochloride (251).**

1-Bromopentane (250 mg, 3.5 mmol) and pyrrolidine (529 mg, 3.5 mmol) were stirred at 60°C in ethyl acetate for 3 h. Acetyl chloride (157 mg, 2 mmol) was added and the mixture stirred for a further 0.5 h to react with excess pyrrolidine. The tertiary amine was extracted into 2 M HCl, washed with water, neutralised (NaOH) and extracted into diethyl ether (5 x 10 cm^3). The combined extracts were washed with water (5 x 10 cm^3) and dried (Na_2SO_4). The amine was precipitated out of the ether solution by dry HCl and the soluent evaporated. The salt, a white solid, was recrystallised from ethyl acetate / ethanol mixture (112 mg, 18%, m.pt. 145-146 °C) (Found: C, 60.91; H, 11.08; N, 7.72. $C_9H_{19}N$ HCl requires C, 60.80; H, 11.30; N, 7.88 %); ν_{max} 3443 (NH), 2959, 2873, 2689, 2346, 1459, 1275, 11047, 733, and 699 cm^{-1}; δ_H 9.50 (1 H, broad s, NH^+), 7.62 and 7.45 (1 H, 2 x m), 4.15 (1 H, m, pentyl 1-H), 3.23-3.27 (4 H, m, pyrrolidine 2,5-H), 1.92-1.96 (4 H, m, pyrrolidine 3,4-H), 1.20-1.30, (6 H, m, pentyl, 2,3,4-H), and 0.86 (3 H, t, J = 7.3 Hz, pentyl 5-H); δ_C 130.77 and 128.63 (pentyl 1-C), 67.98 (pyrrolidine 2,5-C), 39.54, 30.18, 28.75, 23.56, 22.82 (CH_2), and 13.91 (Me).

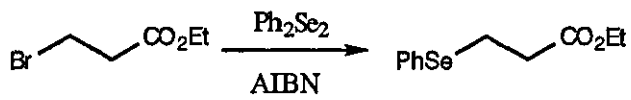
***N*-(5-Benzeneselenylpent-1-yl)pyrrolidine (252).**



The iminium salt (**247**) (391 mg, 1.02 mmol) was dissolved in toluene (50 cm^3) and Bu_3SnH (0.6 cm^3, 2.23 mmol) was added. The solution was stirred under nitrogen at 100°C for 3 h. The white precipitate (Bu_3SnF) was filtered and the filtrate extracted with 2 M HCl (3 x 20 cm^3), neutralised (NaOH) and the amine extracted into ethyl acetate. The combined extracts were dried (Na_2SO_4) and evaporated to dryness. The residue was purified by chromatography using alumina as absorbent and CH_2Cl_2 as eluent. The amine (**252**) was isolated as a yellow oil (82 mg, 27%); ν_{max} 2955, 2859, 1578 (PhSe), 1477, 1453, 1438, 1376, 1290, 1073, 1023, 733, and 691 cm^{-1}; δ_H 7.46-7.50 (2 H, m, o-Ph), 7.23-7.27 (3 H, Ph), 2.88-2.94 (2 H, t, J = 7.5 Hz, 5-H), 2.54-2.58 (2 H, m, 1-H), 2.12-2.20 (4 H, m, pyrrolidine 2,5-H), 1.70-1.80 (4 H, m), and 1.44-1.60 (6 H, m); δ_C

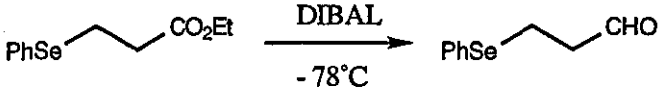
132.38 (ArCH), 130.55 (ArC), 128.94, 126.62 (ArCH), 54.39, 53.59 (CH_2N), 30.38, 29.66, 27.99, 27.52, 23.70, and 23.54 (CH_2).

Ethyl 3-Benzeneselenylpropanoate.



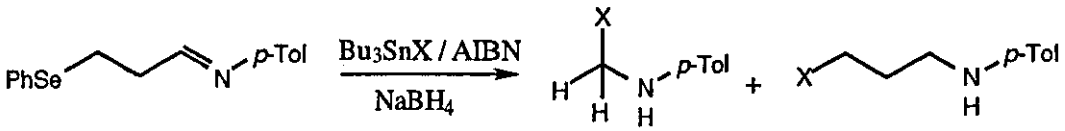
The general procedure for the introduction of the benzeneselenyl group was used. Diphenyl diselenide (1.95 g, 6.3 mmol), sodium borohydride (76 mg, 2 mmol) and ethyl 3-bromo-propanoate (2.32 g, 12.8 mmol) gave *ethyl 3-benzeneselenylpropanoate* as a yellow pungent oil (2.813 g, 86%); ν_{max} 3057, 2981, 1733 (C=O), 1577 (PhSe), 1476, 1438, 1371, 1221, 1021, and 736 cm^{-1}; δ_H 7.51-7.55 (2 H, ortho-H), 7.21-7.26 (3 H, Ar-H), 4.12 (2 H, q, J = 7.2 Hz, CH_2O), 3.09 (2 H, t, J = 7.4 Hz, 3-H), 2.70 (2 H, t, J = 7.4 Hz, 2-H), and 1.26 (3 H, t, J = 7.2 Hz, Me); δ_C 172.10 (C=O), 133.21 (Ar-CH), 131.15 (Ar-C), 129.09, 127.34 (Ar-CH), 60.68 (CH_2O), 35.35, 21.78 (2,3-C), and 14.18 (Me); *m/z* 258.0159 [M^+, (44%), $C_{11}H_{14}O_2Se$ requires 258.0159], 185 [$PhSe(CH_2)_2^+$, 14], 157 ($PhSe^+$, 35), 101 (M^+-PhSe, 59), 77 (Ph^+, 44), and 73 ($EtOCO^+$, 100).

3-Benzeneselenylpropanal.



The general procedure for the synthesis of aldehydes was used. Ethyl 3-benzeneselenyl-propanoate (718 mg, 2.8 mmol) and diisobutylaluminium hydride (1.594 g, 11.2 mmol) gave *3-benzeneselenylpropanal* as a yellow oil (437 mg, 72%); ν_{max} 3058, 3026, 2921, 2825, 2726, 1724 (C=O), 1579 (PhSe), 1478, 1438, 1383, 1256, 1074, 1023, 732, and 694 cm^{-1}; δ_H 9.73 (1 H, s, CHO), 7.48-7.51 (2 H, ortho-H), 7.24-7.28 (3 H, Ar-H), 3.08 (2 H, t, J = 7.0 Hz, 3-H), and 2.86 (2 H, t, J = 7.0 Hz, 2-H); δ_C 200.66 (C=O), 133.31 (Ar-CH), 132.56 (Ar-C), 129.23, 127.41 (Ar-CH), 44.18, and 18.92 (aliphatic C); *m/z* 213.9910 [M^+, (48%), $C_9H_{10}OSe$ requires 213.9897], 158 ($PhSeH^+$, 95), 91 ($C_7H_7^+$, 16), 78 (PhH^+, 100), 57 (11), and 51 (36).

Radical reaction of Imine (257).



(257) X = H, D (260) (261)

3-Benzeneselenylpropanal (130 mg, 0.61 mmol) and *p*-toluidine (65 mg, 0.61 mmol) were dissolved in toluene (120 cm^3) and refluxed for 3 h, and the water removed using a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure. Injection of Bu_3SnH (0.5 cm^3, 1.4 mmol) and AIBN (80 mg, 0.49 mmol) in toluene gave 50 mg of recovered material (55%), after *in situ* reduction of the intermediate imines with lithium aluminium hydride. ^1H and ^{13}C NMR spectroscopic data indicated that the main product was the reduced compound 4-methyl-N-propyl-aniline (**261**), which was found to be identical to an authentic sample. A second product (< 5%) was also present with ^1H and ^{13}C NMR peaks at δ 2.90 and δ 31.60 ppm respectively, indicative of the NMe group of amine (**260**). However attempted separation of the compounds by GC-MS was unsuccessful and positive evidence of the formation of amine (**260**) was not obtained.

Radical reaction of Imine (257) using tri-*n*-butyltin deuteride.

Exactly the same procedure was carried out as for the normal Bu_3SnH reaction. Imine (**257**) (152 mg, 0.5 mmol) in refluxing toluene was treated with a solution of Bu_3SnD (0.23 cm^3, 0.66 mmol) and AIBN (30 mg, 0.18 mmol) injected over 5 h. *4-Methyl-N-(3d-propyl)aniline* (**261**) was isolated as a red oil (40 mg, 54%) which was found to be identical to the authentic sample of the non-deuterated amine, except for the reduced size of the methyl triplet at δ 0.94 ppm. Again a second trace product was formed, but GC-MS data could not be obtained to give positive identification of deuterated amine (**261**).

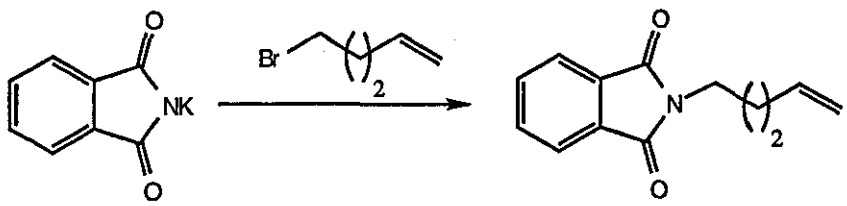
4-Methyl-*N*-propylaniline (261).

This amine was prepared by general method A. Propanal (174 mg, 3 mmol) and *p*-toluidine (268 mg, 2.5 mmol) gave *4-methyl-N-propylaniline* (**261**) as a red oil (89 mg, 20%); ν_{max} 3440 (NH), 2968, 2937, 2869, 2726, 1653, 1617 (Ph), 1524, 1154, and 959 cm^{-1}; δ_H 6.96 and 6.56 (2 H and 2 H, 2 x d, J = 8.5 Hz, Ar-H), 3.60 (1 H, br s, N-H), 3.04 (2 H, t, J = 7.2 Hz, CH_2N), 2.23 (3 H, s, MeAr), 1.44-1.48 (2 H, m, 2-H), and 0.94 (3 H, t, J = 7.2 Hz, 3-H); δ_C 129.66 (Ar-CH), 126.05 (Ar-C), 115.27 (Ar-CH), 113.16 (Ar-C), 46.16 (CH_2N), 27.87 (2-C), 20.29 (MeAr), and 13.78 (3-C); *m/z* 149.1178 [M^+, (8.7%), $C_{10}H_{15}N$ requires 149.1204], 148 (M^+-H, 58), 120 (M^+-Et, 100), 107 (MH^+-C_3H_7, 34), 91 ($C_7H_7^+$, 30), 77 (13), 65 (13), and 41 (21).

5-Phenyl-4-penten-1-ylamine (282a).

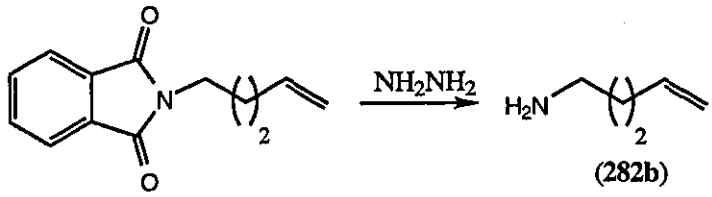
The reaction of 5-phenyl-4-pentenonitrile[17] (1.003 g, 6.4 mmol) and lithium aluminium hydride (146 mg, 3.6 mmol) yielded 680 mg (66%) of the amine (**282a**).

***N*-(4-Pentenyl)phthalimide.**



Potassium phthalimide (1.852 g, 10 mmol) and 5-bromo-1-pentene (1.49 g, 10 mmol) were stirred in DMF (20 cm^3) for 3 h at 100°C. The crude mixture was diluted with water (20 cm^3) and the product extracted into diethyl ether (4 x 20 cm^3). The combined extracts were washed with water (7 x 10 cm^3), dried ($MgSO_4$) and evaporated to dryness. *N-(4-Pentenyl)phthalimide* was isolated as a light yellow viscous oil which was not further purified (1.964 g, 91%); ν_{max} 3078, 2938, 1774 and 1713 (C=O), 1641 (C=C), 1616 (Ph), 1467, 1438, 1397, 1188, 1073, 994, 885, and 720 cm^{-1}; δ_H 7.79-7.85 (2 H m), 7.67-7.73 (2 H, m, Ar-H), 5.74-5.86 (1 H, m, 4-H), 4.95-5.09 (2 H, m, 5-H), 3.70 (2 H, t, J = 7.1 Hz, 1-H), 1.82-1.88 (2 H, m), and 1.41-1.52 (2 H, m); δ_C 168.25 (C=O), 137.20 (4-C), 133.73 (Ar-CH), 132.10 (Ar-C), 123.04 (Ar-CH), 115.17 (5-C), 37.47, 30.87, and 27.55 (1,2,3-C); *m/z* 215.0948 [M^+, (9.0%), $C_{13}H_{13}NO_2$ requires 215.0946], 173 (M^+-H-C_3H_5, 15), 160 (M^+-MeC_3H_4, 100), 148 (27), 130 (16), 104 (17), and 76 ($C_6H_4^+$, 24).

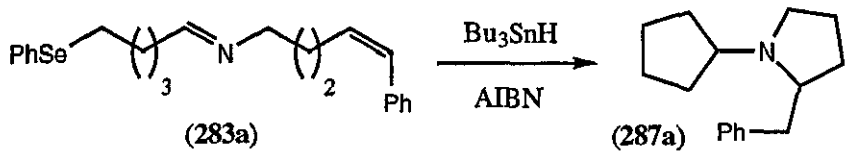
4-Penten-1-ylamine hydrochloride (282b).



A solution of hydrazine hydrate (400 mg, 8 mmol) and *N*-(4-pentenyl)phthalimide (860 mg, 4 mmol) in ethanol (20 cm^3) was refluxed for 10 h. The white precipitate of

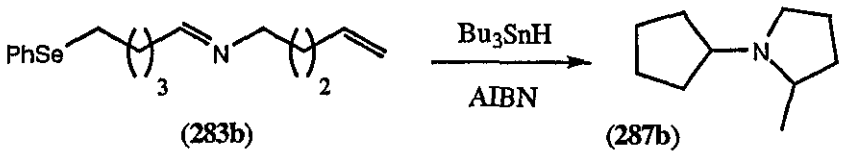
phthalimide was filtered and dry HCl bubbled through the filtrate. The hydrochloride salt of the amine (**282b**) was precipitated as a colourless oil which was dried in a vacuum desiccator for 48 h (376 mg, 39%); δ_H 7.87 (3 H, br s, NH_3), 5.40-5.52 (1 H, m, 4-H), 4.68-4.76 (2 H, m, 5-H), 2.56-2.60 (2 H, m), 1.82-1.88 (2 H, m), and 1.41-1.52 (2 H, m); δ_C 136.38 (4-C), 115.92 (5-C), 39.88, 26.33, and 21.91 (1,2,3-C).

Cyclisation of Imine (283a).



A solution of 5-benzeneselenylpentanal (**179b**) (188 mg, 0.78 mmol) and 5-phenyl-4-penten-1-ylamine (**282a**) (126 mg, 0.78 mmol) in toluene was refluxed for 4 h, and the water removed using a Dean-Stark water separator. The imine was not isolated but was cyclised using the general procedure. Injection of Bu_3SnH (0.3 cm^3, 0.86 mmol) and AIBN (48 mg, 0.29 mmol) in toluene using a syringe pump yielded *2-benzyl-N-cyclopentylpyrrolidine* (**287a**) as a yellow-orange oil (111 mg, 62%); ν_{max} 3025, 2930, 2858, 1656, and 1444 cm^{-1}; δ_H 7.16-7.32 (5 H, m, Ph), 3.28-3.46 (4 H, m, cyclopentyl 1-H, pyrrolidine 2,5-H), 2.87-2.95 (2 H, m, benzylic-H), and 1.56-1.81, (12 H, m); δ_C 129.09 (Ar-CH), 128.95 (Ar-C), 128.17, 125.79 (Ar-CH), 64.62 and 64.05 (CHN), 51.50 (CH_2N), 40.85 (CH_2Ph), 32.14, 28.94, 23.67, and 22.68 (4 x CH_2); *m/z* (C.I.) 230.1909 [MH^+, (49%), $C_{16}H_{24}N$ requires 230.1909], 225 (M^+-4 H, 13), 180 (8), and 138 (MH^+-C_7H_8), 100).

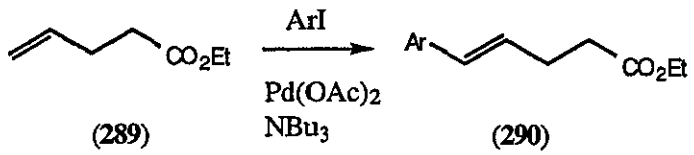
Cyclisation of Imine (283b).



A solution of 5-benzeneselenylpentanal (**179b**) (323 mg, 1.34 mmol) and 4-penten-1-ylamine hydrochloride (**282b**) (360 mg, 2.96 mmol) in toluene was refluxed for 4 h with sodium acetate (240 mg, 3 mmol). The water was removed using a Dean-Stark water separator. The imine was not isolated but was cyclised using the general procedure. A solution of Bu_3SnH (0.56 cm^3, 1.6 mmol) and AIBN (75 mg, 0.5 mmol) were added using a syringe pump. Careful work-up using diethyl ether as solvent which was distilled at atmospheric pressure yielded a crude product 90 mg. ^1H NMR spectroscopy indicated that the residue was the bicyclic product which was further purified by precipitation as the hydrochloride salt. *N-Cyclopentyl-2-methylpyrrolidine hydrochloride* (**287b**) was

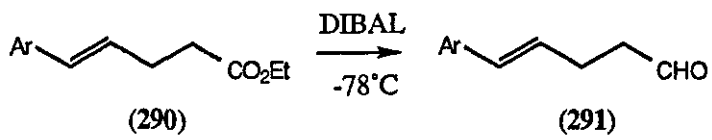
isolated as a yellow-orange oil which gradually darkened (81 mg, 32%); ν_{max} (amine) 3054, 2960, 2871, 1671 1641, 1434, 896, 739 and 704 cm^{-1}; δ_H (2 stereoisomeric salts) 5.90 (1 H, t, J = 3.1 Hz, NH), 3.98-4.04 (1 H, m), 3.45-3.51 (1 H, m), 2.47-2.49 (1 H, m) and 2.39-2.41 (1 H, m, CHN), 2.12-2.19 (4 H, m), 1.80-1.98 (4 H, m), and 1.40-1.75 (4 H, m); δ_C 50.90 and 48.72 (CNH), 38.19 (CH_2N), 32.75, 24.01, 23.37 and 23.09 (CH_2), and 19.66 (Me); *m/z* 154.1596 [MH^+, (100%), $C_{10}H_{20}N$ requires 154.1596], 150 (MH^+-4 H, 22), and 128 (25).

Ethyl 5-(4-Methylphenyl)-4-pentenoate (290).



General procedure for the Heck reaction. Ethyl 4-pentenoate (**289**) (2.56 g, 20 mmol), 4-iodo-toluene (4.36 g, 20 mmol) and tri-*n*-butylamine (4.54 g, 25 mmol) were dissolved in acetonitrile (10 cm^3). (Alternatively triethylamine was used as base.) To the solution was added palladium acetate (77 mg, 0.36 mmol) and the mixture refluxed for 3 h. (For some reactions 5 mol% of tri-*o*-tolylphosphine was also added.) The solvent was removed by evaporation and the brown residue treated with hydrochloric acid (1 M, 20 cm^3). The product was extracted into diethyl ether (5 x 20 cm^3) and the combined extracts washed with water (5 x 10 cm^3), dried ($MgSO_4$) and evaporated to dryness. The product was purified by flash chromatography using silica as absorbent and light petroleum / ethyl acetate mixtures as eluent. *Ethyl 5-(4-methylphenyl)-4-pentenoate* (**290**) was isolated as a colourless oil (3.635 g, 83%); (Found: C, 77.0; H, 8.16. $C_{14}H_{18}O_2$ requires C, 77.0; H, 8.31%); ν_{max} 2962, 2936, 2875, 1735 (C=O), 1654 (alkene), 1603 (Ar), 1514, 1464, 1371, 1252, 1181, 1037, 969, and 803 cm^{-1}; δ_H 7.23 and 7.09 (4 H, 2 x d, J = 8.0 Hz, Ar-H), 6.39 (1 H, d, J = 16 Hz, 5-H), 6.14 (1 H, dt, J = 16, 6.5 Hz, 4-H), 4.13 (2 H, q, J = 7.0 Hz, CH_2O), 2.46-2.53 (4 H, m, 2,3-H), 2.31 (3 H, s, MeAr), and 1.25 (3 H, t, J = 7.0 Hz, Me); δ_C 177.96 (C=O), 138.13 and 136.77 (Ar-C), 130.71, 129.11, 127.36 and 125.88 (alkene and Ar-CH), 60.29 (CH_2O), 34.08 and 28.25 (2,3-C), 21.05 (MeAr), and 14.19 (Me).

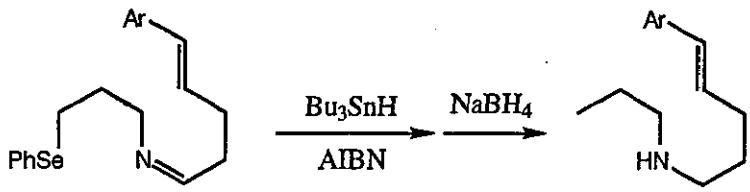
5-(4-Methylphenyl)-4-pentenal (291).



The general procedure for the synthesis of aldehydes was used. Ethyl 5-(4-methyl-

phenyl)-4-pentenoate (**290**) (1.53 g, 7 mmol) and diisobutylaluminium hydride (3.98 g, 28 mmol) gave *5-(4-methylphenyl)-4-pentenal* (**291**) as a yellow oil (947 mg, 78%); ν_{max} 3023, 2922, 2861, 2714, 1724 (C=O), 1675 (alkene), 1605 (phenyl), 1514, 1446, 1118, 1042, 814, and 698 cm^{-1}; δ_H 9.78 (1 H, s, 1-H), 7.20 and 7.09 (4 H, 2 x d, J = 8.0 Hz, Ar-H), 6.38 (1 H, d, J = 16 Hz, 5-H), 6.12 (1 H, dt, J = 16, 6.5 Hz, 4-H), 2.60 (2 H, m, 3-H), 2.52 (2 H, t, J = 6.8 Hz, 2-H), and 2.30 (3 H, s, MeAr); δ_C 201.86 (C=O), 130.92 and 130.12 (Ar-C), 129.50, 129.18, 127.03 and 125.90 (alkene and Ar-CH), 43.31, 25.47 (2,3-C), and 21.08 (MeAr); *m/z* 174.1033 [M^+, (35%), $C_{12}H_{14}O$ requires 174.1045], 158 (11), 143 (14), 131 (39), 118 (62), 105 (100), and 91 ($C_7H_7^+$, 35).

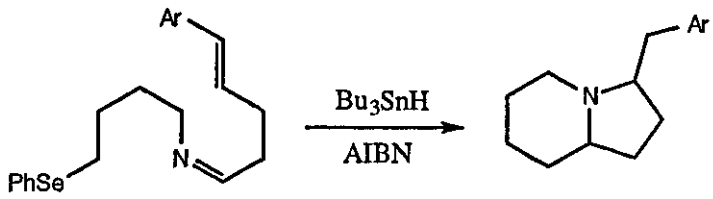
Attempted cyclisation of Imine (292a).



(292a) **(294a)**

A solution of the aldehyde (**291**) (261 mg, 1.5 mmol) and 3-benzeneselenyl-1-propylamine (**185a**) (321 mg, 1.5 mmol) in toluene was refluxed for 4 h, and the water removed using a Dean-Stark water separator. The imine was not isolated but was cyclised using the general procedure. Injection of Bu_3SnH (0.7 cm^3, 2.0 mmol) and AIBN (82 mg, 0.5 mmol) in toluene using a syringe pump yielded *5-(4-methylphenyl)-N-propyl-4-penten-1-ylamine* (**294a**) as the only isolable product, a yellow oil (88 mg, 27%); ν_{max} 3380, 2955, 2925, 2854, 1656 (alkene), 1605 (Ph), 1465, 1136, and 739 cm^{-1}; δ_H 7.22 (2 H, d, J = 8.1 Hz), 7.07 (2 H, d, J = 8.1 Hz, Ar-H), 6.35 (1 H, d, J = 16 Hz, 5-H), 6.15 (1 H, dt, J = 16, 6.8 Hz, 4-H), 2.55-2.66 (4 H, m, 2 x CH_2N), 2.31 (3 H, s, MeAr), 2.24-2.29 (2 H, m, 3-H), 1.47-1.68 (4 H, m), and 0.91 (3 H, t, J = 7.5 Hz, propyl 3-H); δ_C 136.57, 134.96 (Ar-C), 130.00, 129.17, 128.27, 125.84, (alkene and aromatic Ar-CH), 51.82, 49.39 (CH_2N), 30.83, 29.62, 23.04 (CH_2), 21.12 (MeAr), and 11.78 (propyl 3-C); *m/z* 217.1830 [M^+, (15%), $C_{15}H_{23}N$ requires 217.1830], 188 (M^+-Et, 10), 129 (11), 115 (9), 105 (25), 98 (36), 91 ($C_7H_7^+$, 17), and 72 ($PrNH{=}CH_2^+$, 100).

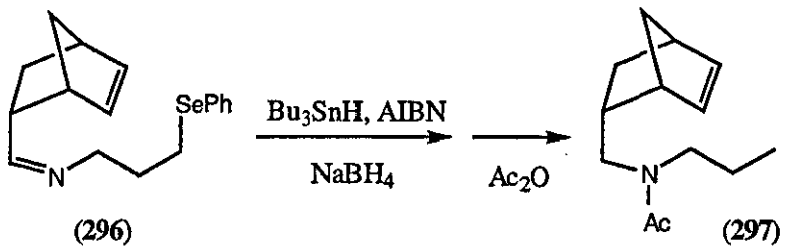
Cyclisation of Imine (292b).



(292b) **(295b)**

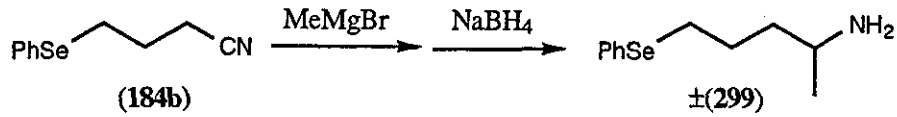
A solution of the aldehyde (**291**) (160 mg, 0.92 mmol) and 4-benzeneselenyl-1-butylamine (**185b**) (210 mg, 0.92 mmol) in toluene was refluxed for 4 h, and the water removed using a Dean-Stark water separator. The imine was not isolated but was cyclised using the general procedure. Injection of Bu_3SnH (0.43 cm^3, 1.2 mmol) and AIBN (51 mg, 0.31 mmol) in toluene using a syringe pump yielded *3-(4-methylbenzyl)indolizidine* (**264**) as the only isolable product, a yellow oil which gradually darkened (55 mg, 26%); ν_{max} 3052, 2934, 2859, 1667, 1615 (Ph), 1445, 1115, 740 and 704 cm^{-1}; δ_H (300 MHz) (2 stereoisomers) 7.07-7.11 (4 H, m, phenyl H), 3.59-3.63 and 2.21-2.29 (2 H, 2 x m, CH_2Ph), 3.22-3.26 (1 H, m, 8a-H), 3.01-3.05 and 2.71-2.74 (2 H, 2 x m, 5-H), 2.88-2.90 (1 H, m, 3-H), 2.33 (3 H, m, MeAr), 2.10-2.11 (2 H, m), and 1.30-1.89 (8 H, m); δ_C (100 MHz), 132.40, 132.25 (Ar-C), 128.94, 128.13 (Ar-CH), 46.35 (8a-C), 40.65 (CH_2Ph), 35.64 (5-C), 39.46 (3-C), 30.52, 29.71, 27.96, 27.14, 23.36 (CH_2), and 21.02 (Me); *m/z* 229.1825 [M^+, (3.4%), $C_{16}H_{23}N$ requires 229.1830], 228 (M^+-H, 4), 124 (69), 104 (42), 91 ($C_7H_7^+$, 18), 72 (21), and 30 ($CH_2{=}NH_2^+$, 100).

Attempted cyclisation of Imine (296).



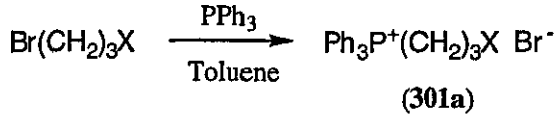
A solution of bicyclo[2.2.1]hept-5-en-2-carboxaldehyde (648 mg, 3 mmol) and 3-benzeneselenyl-1-propylamine (**185a**) (367 mg, 3 mmol) in toluene was refluxed for 8 h, and the water removed using a Dean-Stark water separator. The imine was not isolated but was cyclised using the general procedure. Injection of Bu_3SnH (1.08 cm^3, 4 mmol) and AIBN (223 mg, 1.4 mmol) in toluene using a syringe pump yielded 180 mg of crude material which was treated with acetic anhydride and triethylamine, from which *N-acetyl-N-propylbicyclo[2.2.1]hept-5-ene-2-ylmethylamine* (**297**) was the only isolable product, a yellow-orange oil (159 mg, 24%); ν_{max} 2965, 2873, 1648 (C=O), 1648 (alkene), 1424, 1340, 1252, and 715 cm^{-1}; δ_H (4 stereoisomers) 5.96-6.24 (2 H, m, alkene H), 3.39-3.42 (1 H, m), 3.20-3.43 (2 H, m, propyl 1-H), 2.98-3.05 (1 H, m), 2.79-2.83 (1 H, m), 2.30-2.40 (1 H, m), 2.06-2.11 (3 H, 4 x s, Ac), 1.75-1.85 (1 H, m), 1.48-1.61 (2 H, m), 1.20-1.46 (3 H, m), 0.88 (3 H, t, J = 7.1 Hz, propyl 3-H), and 0.50-0.59 (1 H, m); *m/z* 207.1624 [M^+, (1.0%), $C_{13}H_{21}NO$ requires 207.1623], 208 (MH^+, 100), 178 (M^+-Et, 11), 142 (37), 126 (27), 98 (24), 91 ($C_7H_7^+$, 16), 72 (49), and 43 (Ac^+, 45).

5-Benzeneselenyl-2-pentylamine (299).



4-Benzeneselenylbutanonitrile (**184b**) (896 mg, 4.0 mmol) was dissolved in anhydrous diethyl ether (30 cm^3) and a solution of methylmagnesium bromide in diethyl ether (1.3 cm^3 of 3 M solution) was added dropwise over 10 min. The mixture was stirred at room temperature for 4 h. The intermediate imine was not isolated but was treated with sodium borohydride (60 mg, 1.6 mmol) in dry methanol (5 cm^3) and stirred for 18 h. Water (10 cm^3) was added to the mixture followed by careful addition of HCl (1 M, 20 cm^3) until the aqueous layer was pH 1. The ether layer was separated and the acidic layers washed with dichloromethane before being basified (Na_2CO_3 followed by NaOH). The aqueous layer was stirred with dichloromethane for 1 h before extraction. The organic phase was dried ($MgSO_4$) and evaporated to dryness yielding the amine (**299**) as a light orange oil which was not purified further (436 mg, 45%); ν_{max} 3053, 2958, 2927, 2865, 1650, 1577 (PhSe), 1475, 1436, 1375, 737, and 691 cm^{-1}; δ_H 7.46-7.50 (2 H, m, o-H), 7.23-7.25 (3 H, m, Ar-H), 2.91 (2 H, t, J = 7.3 Hz, 5-H), 2.84-2.87 (1 H, m, 2-H), 1.66-1.78 (2 H, m, 3-H), 1.63 (2 H, br s, NH_2), 1.40-1.48 (2 H, m, 4-H), and 1.04 (3 H, d, J = 7.5 Hz, 1-H); *m/z* 243.0526 [M^+, (1.1%), $C_{11}H_{17}NSe$ requires 243.0526], 157 ($PhSe^+$, 5), 86 (M^+-PhSe, 59), 77 (Ph^+, 11), 69 (25), and 44 ($MeCH{=}NH_2^+$, 100).

(3-Ethoxycarbonylpropyl)triphenylphosphonium bromide (301a), X = CO_2Et



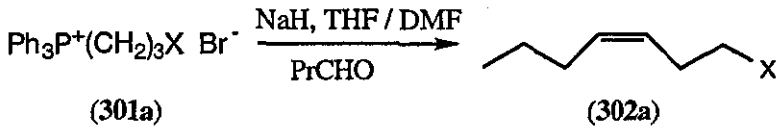
Triphenylphosphine (26.2 g, 100 mmol) and ethyl 4-bromobutanoate (8.36 g, 40 mmol) were dissolved in dry toluene (150 cm^3) and refluxed for 72 h. The precipitated salts were filtered and washed with diethyl ether (5 x 50 cm^3) and recrystallised from ethanol to yield the pure salt as a white powder (9.70 g, 53%, m.pt. 165 °C); (Found: C, 61.9; H, 5.69. $C_{24}H_{26}BrO_2P$ requires C, 63.0; H, 5.73%); ν_{max} (Nujol) 1720 (C=O), 1682, 1593 (Ph), and 1402 cm^{-1}; δ_H 7.66-7.90 (15 H, m, Ph), 4.10 (2 H, q, J = 7.0 Hz, CH_2O), 4.09-4.12 (2 H, m, CH_2P), 2.89 (2 H, t, J = 6.1 Hz, CH_2CO), 1.89-1.93 (2 H, m), and 1.23 (3 H, t, J = 7.0 Hz, Me); δ_C 1.72 (C=O), 135.15, 133.60, 130.54 (Ar-CH), 118.67 (Ar-C), 60.62 (CH_2O), 33.46 (CH_2CO), 22.17, 18.06, and 14.17 (Me).

(3-Cyanopropyl)triphenylphosphonium bromide (301b), X = CN

Triphenylphosphine (26.2 g, 100 mmol) and ethyl 4-bromobutanoate (5.92 g, 40 mmol) were dissolved in dry toluene (150 cm^3) and refluxed for 72 h. The precipitated salts

were filtered and washed with diethyl ether (5 x 50 cm^3) and recrystallised from ethanol to yield the pure salt as a white powder (10.8 g, 66%, m.pt. 215 °C); (Found: C, 64.0; H, 5.11; N, 3.45. $C_{22}H_{21}BrNP$ requires C, 64.4; H, 5.16; N, 3.41%); ν_{max} (Nujol) 2252 (CN), and 1587 (Ph) cm^{-1}; δ_H 7.69-7.90 (15 H, m, Ph), 4.05-4.17 (2 H, m, CH_2P), 3.11 (2 H, t, J = 6.8 Hz, CH_2CN), and 2.00-2.09 (2 H, m); δ_C 1.72 (C=O), 135.28, 133.67, 130.67 (Ar-CH), 119.06 (Ar-C), 116.71 (CN), 22.16, 19.65, and 17.94 (CH_2).

Ethyl Z-4-octenoate (302a), X = CO_2Et.



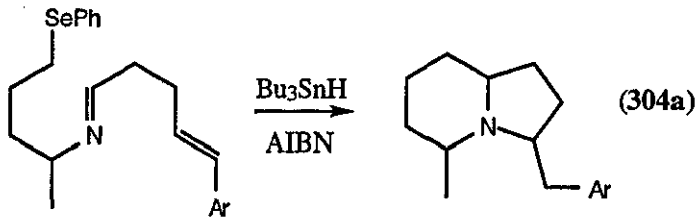
General procedure for the Wittig reaction. (3-Ethoxycarbonylpropyl)triphenylphosphonium bromide (**301a**) (4.57 g, 10 mmol) and sodium hydride (400 mg, 10 mmol) were stirred in freshly distilled THF (50 cm^3) for 16 h at room temperature before butanal (720 mg, 10 mmol) in THF (20 cm^3) was added. In later experiments DMF (5 cm^3) was added to increase the solubility of the salts. The mixture was heated for 48 h at 55 °C after which the solvent was removed by evaporation. The residue was triturated with dry diethyl ether (5 x 25 cm^3) and the insoluble salts filtered. (For experiments where DMF was used the filtrate was washed with water (6 x 20 cm^3) before drying with $MgSO_4$). The ether solution was evaporated to dryness and the product purified by flash sinter chromato-graphy using silica as absorbent and light petroleum / ethyl acetate mixtures as eluent. *Ethyl Z-4-octenoate* (**302a**) was isolated as a pale yellow oil (697 mg, 41%); ν_{max} 2961, 2874, 1727 (C=O), 1649, 1439, 1268, 1196, 1119, 722, and 696 cm^{-1}; δ_H 5.29-5.39 (2 H, m, 4,5-H), 4.12 (2 H, q, J = 7.3 Hz, CH_2O), 2.33-2.38 (2 H, t, J = 5.9 Hz, 2-H), 2.01-2.05 (2 H, m, 3-H), 1.31-1.41 (4 H, m, 6,7-H), 1.25 (3 H, t, J = 7.3 Hz, Me), and 0.91 (3 H, t, J = 7.2 Hz, 8-H); δ_C 133.79, 133.48 (4,5-C), 60.19 (CH_2O),34.35, 29.61, 29.14, 22.75 (2,3,6,7-C), 14.15, and 13.66 (2 x Me); *m/z* 170.1095 [M^+, (5.4%), $C_{10}H_{18}O_2$ requires 170.1307], 171 (MH^+, 3), 124 (M^+-EtO-H, 24), 107 (30), 96 (M^+-EtOCO-H, 18), 88 (45), 82 (M^+-$EtOCOCH_3$, 52), 67 (48), 55 ($MeC_3H_4^+$, 100), and 41 ($C_3H_5^+$, 74).

Z-4-Octenonitrile (302b), X = CN.

The general procedure for the Wittig reaction was used. Phosphonium salt (**301b**) (4.92 g, 12 mmol), sodium hydride (480 mg, 12 mmol) and butanal (864 mg, 12 mmol) yielded *Z-4-octenonitrile* (**302b**) as a colourless oil (620 mg, 42%); ν_{max} 2925, 2858, 2246 (CN), 1668 (C=C), 1459, and 1156 cm^{-1}; δ_H 5.52-5.62 (1 H, m) and 5.36-5.45 (1 H, m, 4,5-H), 2.34-2.45 (2 H, m, 2-H), 2.02-2.09 (2 H, m, 3-H), 1.29-1.45 (4 H, m, 6,7-H), and 0.92 (3 H, t, J = 7.0 Hz, 8-H); δ_C 133.80, 133.38 (4,5-C), 116.80 (CN), 29.24, 23.18, 22.54 and 17.50 (2,3,6,7-C), and 13.65 (8-C); *m/z* 123.1053 [M^+, (12%), $C_8H_{13}N$

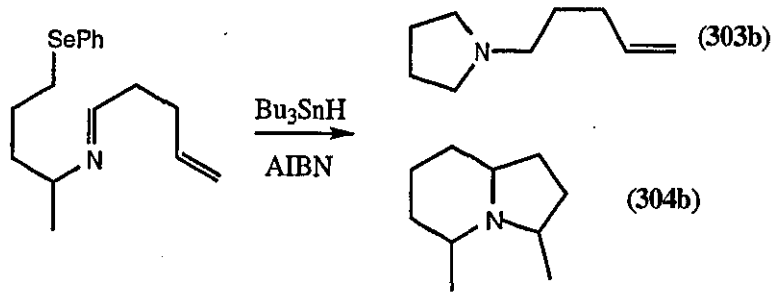
requires 123.1048], 107 (48), 95 (MH^+-CH_2=CH_2, 42), 89 (54), 79 (M^+-Pr-H, 52), 71 (98), 55 ($MeC_3H_4^+$, 88), 43 (Pr^+, 90), and 41 ($C_3H_5^+$, 100).

Cyclisation of the Imine formed from 5-Benzeneselenyl-2-pentylamine (299) and 5-*p*-Tolyl-4-pentenal (291).



A solution of the aldehyde (**291**) (226 mg, 1.3 mmol) and 5-benzeneselenyl-2-pentyl-amine (**299**) (315 mg, 1.3 mmol) in toluene was refluxed for 8 h, and the water removed using a Dean-Stark water separator. The imine was not isolated but was cyclised using the general procedure. Injection of Bu_3SnH (0.60 cm^3, 1.7 mmol) and AIBN (71 mg, 0.43 mmol) in toluene using a syringe pump yielded *5-methyl-3-(4-methylbenzyl)-indolizidine* (**304a**) as the only isolable product, a red oil (60 mg, 19%); ν_{max} 2924, 1669, 1609 (Ar), 1515, 1438, 1038, 812, and 737 cm^{-1}; δ_H 6.98-7.05 (4 H, m, Ar-H), 3.64-3.67 and 2.33-2.38 (2 H, 2 x m, CH_2Ph), 3.43-3.46 (1 H, m, 8a-H), 2.77-2.83 (1 H, m, 5-H), 2.59-2.66 (1 H, m, 3-H), 2.34 (3 H, s, MeAr), 1.95-2.08 (2 H, m), 1.45-1.76 (8 H, m), and 0.95 (3 H, d, J = 6.8 Hz, 5-Me); δ_C (100 MHz) 132.36, 132.15 (Ar-C), 128.94, 127.99 (Ar-CH), 49.62 (5-C), 47.73 (8a-C), 39.46 (3-C), 35.11, 34.06, 32.37, 31.91, 29.71, 29.32 (CH_2), 21.15, and 21.02 (Me); *m/z* 243.1978 [M^+, (0.2%), $C_{17}H_{25}N$ requires 243.1987], 195 (6), 143 (11), 128 (8), 119 (13), 105 ($MeC_7H_6^+$, 100), 91 ($C_7H_7^+$, 24), and 77 (19).

Cyclisation of the Imine formed from 5-Benzeneselenyl-2-pentylamine (299) and 4-Pentenal.



A solution of 4-pentenal (210 mg, 2.5 mmol) and 5-benzeneselenyl-2-pentyl-amine (**299**) (124 mg, 0.51 mmol) in toluene was refluxed for 8 h, and the water removed using a Dean-Stark water separator. The imine was not isolated but was cyclised using the general procedure. Injection of Bu_3SnH (0.24 cm^3, 0.68 mmol) and AIBN (28 mg, 0.17

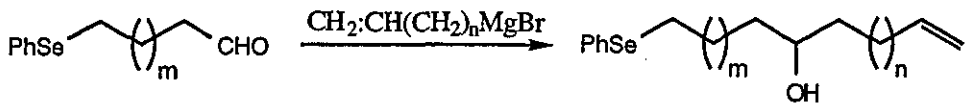
mmol) over 5 h using a syringe pump gave a yellow solution from which the amine products were precipitated as a colourless oil by bubbling dry HCl through the solution. The amount of salts produced was 94 mg (63%), after drying under vacuum. ^{1}H NMR and COSY spectroscopic data indicated that there were two main products, the monocyclic amine (**303b**) and the bicyclic product (**304b**) in the ratio of 1.60 : 1. Separation of the two compounds could not be not achieved; ν_{max} 2960, 1671 1641, 1434, and 896 cm^{-1}; δ_C (100 MHz), 136.75, 114.37 (alkene-C), 76.12, 62.99, 55.54, 54.02 (4 x CH), 38.46, 32.74, 31.99, 31.01, 29.49, 28.78, 28.49, 25.92, 25.55, 22.12, 21.77 (11 x CH_2), 16.20, 13.19, and 12.39 (3 x CH_3); *m/z* 154.1531 [*MH*$^+$, (4.0%), $C_{10}H_{20}N$ requires 154.1598], 131 (19), 98 (MH^+-C_4H_8, 45), 91 (38), 79 (33), 69 (95), 55 (73), and 41 ($C_3H_5^+$, 100).

2-Methyl-N-(4-pentenyl)pyrrolidine hydrochloride (**303b**); δ_H (400 MHz) 5.60-5.67 (1 H, m, 4'-H), 4.88-4.98 (5'-H), 3.35-3.44 and 3.16-3.19 (2 H, 2 x m, 5-H), 3.00-3.09 (2 H, m, 1'-H), 2.10-2.35 (8 H, m, 3,4-H, 2'-3'-H), and 1.25 (3 H, d, J = 6.5 Hz, Me).

3,5-Dimethylindolizidine hydrochloride (**304b**); δ_H (400 MHz) 4.28-4.32 (1 H, m, 8a-H), 4.02-4.08 and 3.89-3.95 (2 H, 2 x m, 3,5-H), 1.66-1.92 (8 H, m, 1,2,6,7-H) and 1.53 (3 H, d, J = 6.5 Hz), and 1.30 (6 H, d, 3,5-Me).

10.7. Experimental for Chapter 8.

9-Benzeneselenylnon-1-en-5-ol (305a), m = 2, n = 1.



(179) (305)

General procedure for Grignard reactions. Magnesium turnings (300 mg, 12.5 mmol) and 4-bromo-1-butene (1.35 g, 10 mmol), in a flame-dried 3-necked flask, were reacted in anhydrous diethyl ether (20 cm^3) under nitrogen until the Grignard reagent formed. A solution of 5-benzeneselenylpentanal (**179b**) (1.184 g, 4.6 mmol) in ether (20 cm^3) was added dropwise at 0°C over 30 min. The mixture was stirred for 24 h, after which water (5 cm^3) was added followed by hydrochloric acid (1.0 M, 10 cm^3). The products were extracted into ether and washed with water, dried ($MgSO_4$) and the solution evaporated to dryness. The product was purified by flash chromatography using silica as absorbent and light petroleum / ethyl acetate mixtures as eluent. *9-Benzeneselenylnon-1-en-5-ol* (**305a**) was isolated as a pale yellow oil (1.197 g, 87%); ν_{max} 3442 (OH), 3075, 2977, 2931, 2838, 1641 (alkene), 1578 (PhSe), 1478, 1438, 1390, 1151, 1119, 1092, 1042, 999, 737, and 692 cm^{-1}; δ_H 7.46-7.49 (2 H, m, ortho-H), 7.22-7.25 (3 H, m, Ar-H), 5.74-5.88 (1 H, m, 2-H), 4.99-5.05 (2 H, m, 1-H), 3.60-3.66 (1 H, m, 5-H), 2.91 (2 H, t, J = 7.0 Hz, 9-H), 2.16-2.24 (2 H, m, 3-H), 1.88 (1 H, s, OH), 1.68-1.73 (2 H, m), and 1.46-1.55 (6 H, m); δ_C 138.46 (2-C), 132.40 (Ar-CH), 130.80 (Ar-C), 128.93, 126.62 (Ar-CH), 114.75 (1-C), 71.16 (5-C), 36.73, 36.37, 30.07, 29.83, 27.72, and 25.74 (CH_2); *m/z* 298.0883 [M^+, (7.1%), $C_{15}H_{22}OSe$ requires 298.0836], 227 (21), 158 ($PhSeH^+$, 29), 139 (52), 84 (32), 78 (PhH^+, 45), 69 (72), 61 (88), 55 ($MeC_3H_4^+$, 85), 41 ($C_3H_5^+$, 100).

10-Benzeneselenyldec-1-en-5-ol (305b), m = 3, n = 1.

The general procedure for Grignard reactions was used. 6-Benzeneselenylhexanal (**179c**), (1.12 g, 4.4 mmol) was added to the Grignard reagent formed from magnesium turnings (200 mg, 8 mmol) and 4-bromo-1-butene (810 mg, 6 mmol) and yielded *10-benzeneselenyldec-1-en-5-ol* (**305b**) as a pale yellow oil (1.294g, 94%); ν_{max} 3545 (OH), 3072, 2931, 2857, 1639 (alkene), 1579 (PhSe), 1478, 1438, 1374, 1292, 1243, 1073, 1023, 736, and 691 cm^{-1}; δ_H 7.44-7.48 (2 H, m, ortho-H), 7.20-7.26 (3 H, m, Ar-H), 6.70 (1 H, br s, OH), 5.71-5.79 (1 H, m, 2-H), 4.96-5.04 (2 H, m, 1-H), 3.58-3.62 (1 H, m, 5-H), 2.88 (2 H, t, J = 7.1 Hz, 10-H), 2.10-2.29 (2 H, m, 3-H), 1.64-1.73 (4 H, m), 1.50-1.59 (2 H, m), and 1.33-1.47 (4 H, m); δ_C 138.58 (2-C), 132.41 (Ar-CH), 130.50 (Ar-C), 128.99, 126.64 (Ar-CH), 114.79 (1-C), 71.35 (5-C), 37.27, 36.47, 32.57, 30.07, 29.77, 27.81, and 25.05 (CH_2); *m/z* (C.I.) 330.1336 [MH^+, (100%), $C_{16}H_{25}OSe$ requires 330.1336].

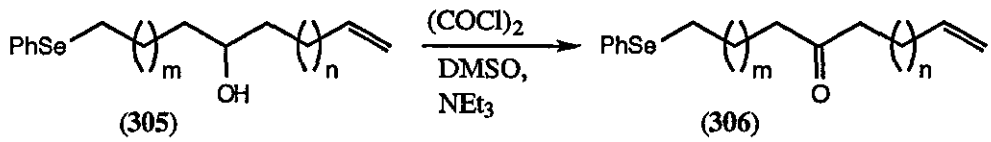
10-Benzeneselenyldec-1-en-6-ol (305c), m = 2, n = 2.

The general procedure for Grignard reactions was used. 5-Benzeneselenylpentanal (**179b**), (402 mg, 1.7 mmol) was added to the Grignard reagent formed from magnesium turnings (130 mg, 5.5 mmol) and 5-bromo-1-pentene (742 mg, 5.5 mmol) and yielded *10-benzeneselenyldec-1-en-6-ol* (**305c**) as a pale yellow oil (486 mg, 94%); ν_{max} 3344 (OH), 3074, 2931, 2857, 1640 (alkene), 1579 (PhSe), 1478, 1438, 1374, 1292, 1243, 1073, 1023, 912, 736, and 691 cm^{-1}; δ_H 7.44-7.49 (2 H, m, ortho-H), 7.20-7.27 (3 H, m, Ar-H), 5.75-5.84 (1 H, m, 2-H), 4.94-5.08 (2 H, m, 1-H), 3.58-3.64 (1 H, m, 6-H), 2.90 (2 H, t, J = 7.1 Hz, 10-H), 2.02-2.14 (2 H, m, 3-H), 1.90 (1 H, s, OH), 1.62-1.72 (4 H, m), 1.40-1.53 (6 H, m); δ_C 138.18 (2-C), 132.38 (Ar-CH), 130.30 (Ar-C), 128.93, 126.61 (Ar-CH), 114.81 (1-C), 71.47 (6-C), 36.76, 33.62, 29.83, 28.78, 27.72, 25.89, and 24.81 (CH_2); *m/z* (C.I.) 330.1336 [MH^+, (100%), $C_{16}H_{25}OSe$ requires 330.1336].

11-Benzeneselenylundec-1-en-6-ol (305d), m = 3, n = 2.

The general procedure for Grignard reactions was used. 6-Benzeneselenylhexanal (**179c**), (730 mg, 2.9 mmol) was added to the Grignard reagent formed from magnesium turnings (240 mg, 10 mmol) and 5-bromo-1-pentene (1.31 g, 9.7 mmol) and yielded *11-benzeneselenylundec-1-en-6-ol* (**305d**)as a pale yellow oil (895 mg, 95%); ν_{max} 3361 (OH), 3072, 2930, 2855, 1640 (alkene), 1579 (PhSe), 1478, 1438, 1292, 1073, 1023, 911, 735, and 691 cm^{-1}; δ_H 7.46-7.49 (2 H, m, ortho-H), 7.21-7.25 (3 H, m, Ar-H), 5.71-5.79 (1 H, m, 2-H), 4.95-5.05 (2 H, m, 1-H), 3.57-3.67 (1 H, m, 6-H), 2.91 (2 H, t, J = 7.1 Hz, 11-H), 2.04-2.12 (2 H, m, 3-H), 1.90 (1 H, s, OH), 1.63-1.71 (4 H, m), 1.37-1.46 (8 H, m); δ_C 138.58 (2-C), 132.43 (Ar-CH), 130.25 (Ar-C), 128.86, 126.54 (Ar-CH), 114.47 (1-C), 71.58 (6-C), 37.22, 36.83, 33.59, 30.00, 29.69, 27.77, 24.97, and 24.82 (CH_2); *m/z* (C.I.) 344.1493 [MH^+, (100%), $C_{17}H_{27}OSe$ requires 344.1492].

9-Benzeneselenylnon-1-en-5-one (306a), m = 2, n = 1.



General procedure for Swern oxidation. DMSO (200 mg, 2.5 mmol) in CH_2Cl_2 (10 cm^3) was added dropwise over 5 min to a solution of oxalyl chloride (291 mg, 2.3 mmol) in CH_2Cl_2 (10 cm^3) at -78 °C. The mixture was stirred for 10 min before a solution of the alcohol (**305a**) (618 mg, 2.1 mmol) in CH_2Cl_2 (10 cm^3) was added dropwise over 5 min. The mixture was stirred for a further 10 min and triethylamine (500 mg, 5 mmol) was added. After stirring for 15 min, the mixture was warmed to 0°C and water and dilute hydrochloric acid were added. The product was extracted into the CH_2Cl_2 layer which was washed with water, dried (MgSO4) and the solution evaporated to dryness.

The product was purified by flash chromatography using silica as absorbent and light petroleum / ethyl acetate mixtures as eluent. *9-Benzeneselenylnon-1-en-5-one* (**306a**) was isolated as a pale orange oil (405 mg, 66%); ν_{max} 3078, 2929, 2858, 1708 (C=O), 1641 (alkene), 1579 (PhSe), 1478, 1438, 1381, 1326, 1162, 1073, 1022, 1000, 914, 734, and 691 cm^{-1}; δ_H 7.46-7.49 (2 H, m, ortho-H), 7.22-7.26 (3 H, m, Ar-H), 5.74-5.84 (1 H, m, 2-H), 4.94-5.10 (2 H, m, 1-H), 2.91 (2 H, t, J = 7.0 Hz, 9-H), 2.28-2.36 (2 H, m, 3-H), 2.05-2.12 (2 H, m, 4-H), and 1.44-1.72 (6 H, m); δ_C 210.30 (C=O), 137.07 (2-C), 132.40 (Ar-CH), 129.30 (Ar-C), 129.01, 126.61 (Ar-CH), 115.23 (1-C), 33.70, 32.10, 29.97, 29.57, 27.44, and 26.50 (CH_2); *m/z* 296.0650 [M^+, (0.9%), $C_{15}H_{20}OSe$ requires 296.0679], 234 (9), 158 ($PhSeH^+$, 16), 91 ($C_7H_7^+$, 31), 77 (Ph^+, 32), 55 ($MeC_3H_4^+$, 100), 51 (34), and 41 ($C_3H_5^+$, 92).

10-Benzeneselenyldec-1-en-5-one (306b), m = 3, n = 1.

The general procedure for Swern oxidations was used. The alcohol (**305b**) (1.28 g, 4.1 mmol), was added to the oxidising mixture formed from DMSO (618 mg, 8 mmol) and oxalyl chloride (1.01 g, 8 mmol) and yielded *10-benzeneselenyldec-1-en-5-one* (**306b**) as a pale orange oil (892 mg, 71%); ν_{max} 3072, 2931, 2856, 1714 (C=O), 1641 (alkene), 1579 (PhSe), 1478, 1438, 1366, 1246, 1190, 1073, 1023, 914, 737, and 692 cm^{-1}; δ_H 7.45-7.49 (2 H, m, ortho-H), 7.22-7.26 (3 H, m, Ar-H), 5.71-5.79 (1 H, m, 2-H), 4.97-5.09 (2 H, m, 1-H), 2.89 (2 H, t, J = 7.1 Hz, 10-H), 2.31-2.44 (4 H, m, 3,4-H), 1.67-1.70 (2 H, m), 1.57-1.60 (2 H, m), and 1.33-1.44 (4 H, m); δ_C 210.20 (C=O), 137.14 (2-C), 132.50 (Ar-CH), 129.20 (Ar-C), 129.00, 128.70 (Ar-CH), 115.21 (1-C), 42.59, 41.81, 29.90, 29.30, 28.11, 27.63, and 23.13 (CH_2); *m/z* (C.I.) 328.1180 [MNH_4^+, (0.3%), $C_{16}H_{22}OSe$ requires 328.1179], 157 ($PhSe^+$, 3), 139 (6), 91 ($C_7H_7^+$, 6), 83 (42), 67 (12), 55 ($MeC_3H_4^+$, 100), and 41 ($C_3H_5^+$, 23).

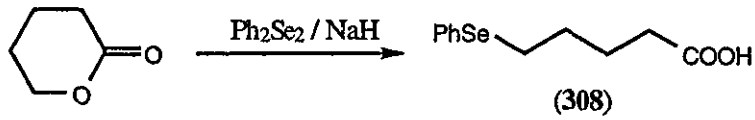
10-Benzeneselenyldec-1-en-6-one (306c), m = 2, n = 2.

The general procedure for Swern oxidations was used. The alcohol (**305c**) (366 g, 1.2 mmol), was added to the oxidising mixture formed from DMSO (184 mg, 2 mmol) and oxalyl chloride (299 mg, 2 mmol) and yielded *10-benzeneselenyldec-1-en-6-one* (**306c**) as a pale orange oil (244 mg, 67%); ν_{max} 3073, 2932, 2860, 1714 (C=O), 1640 (alkene), 1579 (PhSe), 1478, 1438, 1181, 1073, 1023, 913, 737, and 692 cm^{-1}; δ_H (300 MHz) 7.51-7.55 (2 H, m, ortho-H), 7.25-7.30 (3 H, m, Ar-H), 5.77-5.82 (1 H, m, 2-H), 4.98-5.02 (2 H, m, 1-H), 2.93 (2 H, t, J = 6.8 Hz, 10-H), 2.41-2.47 (4 H, m, 5,7-H), 2.16-2.21 (4 H, m), and 1.67-1.74 (4 H, m); δ_C (100 MHz) 192.02 (C=O), 132.95 (2-C), 132.13 (Ar-CH), 130.15 (Ar-C), 129.15, 128.87 (Ar-CH), 113.17 (1-C), 37.04, 36.80, 32.66, 29.53, 27.63, 25.80, and 22.61 (CH_2); *m/z* 310.0830 [M^+, (0.7%), $C_{16}H_{22}OSe$ requires 310.0836], 241 (M^+-C_5H_9, 9), 157 ($PhSe^+$, 19), 125 (32), 91 (40), 81 (57), and 55 ($MeC_3H_4^+$, 100).

11-Benzeneselenylundec-1-en-6-one (306d), m = 3, n = 2.

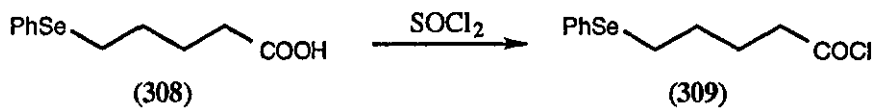
The general procedure for Swern oxidations was used. The alcohol (**305d**) (951 mg, 2.9 mmol) was added to the oxidising mixture formed from DMSO (502 mg, 4.7 mmol) and oxalyl chloride (818 mg, 4.7 mmol) and yielded *11-benzeneselenylundec-1-en-6-one* (**306d**) as a pale orange oil (735 mg, 78%); ν_{max} 3073, 2935, 2860, 1717 (C=O), 1643 (alkene), 1579 (PhSe), 1478, 1438, 1372, 1073, 1023, 737, and 692 cm^{-1}; δ_H (300 MHz) 7.53-7.57 (2 H, m, ortho-H), 7.26-7.29 (3 H, m, Ar-H), 5.79-5.85 (1 H, m, 2-H), 4.99-5.02 (2 H, m, 1-H), 2.93 (2 H, t, J = 6.8 Hz, 11-H), 2.40-2.46 (4 H, m, 5,7-H), 2.09-2.14 (4 H, m), and 1.50-1.74 (6 H, m); δ_C (100 MHz) 192.26 (C=O), 133.05 (2-C), 132.37 (Ar-CH), 130.15 (Ar-C), 129.22, 127.45 (Ar-CH), 112.95 (1-C), 37.01, 36.80, 33.54, 32.39, 31.37, 26.75, 24.78, and 22.75 (CH_2); *m/z* 324.0995 [M^+, (4%), $C_{17}H_{24}OSe$ requires 324.0992], 242 (9), 189 (22), 171 ($PhSeCH_2^+$, 31), 157 ($PhSe^+$, 22), 135 (27), 81 (38), 69 ($C_5H_9^+$, 79), 55 ($MeC_3H_4^+$, 65), and 41 ($C_3H_5^+$, 100).

5-Benzeneselenylpentanoic acid (308).



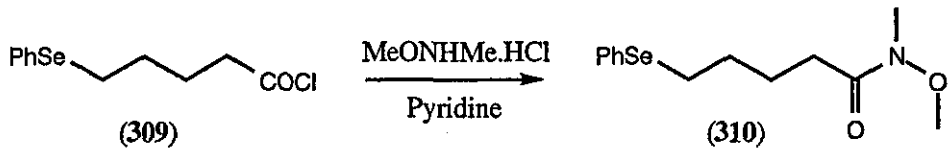
δ-Valerolactone (228 mg, 2 mmol) was dissolved in THF and added dropwise to a cooled (-78°C) suspension of sodium benzeneselenide in THF, formed from sodium hydride (120 mg, 3 mmol) and diphenyl diselenide (468 mg, 1.5 mmol). The mixture was stirred for 4 h at room temperature and refluxed for 1 h. The solvent was removed by evaporation and the residues dissolved in sodium hydroxide (1 M, 20 cm^3). The basic solution was washed with dichloromethane (5 x 10 cm^3), before being acidified with dilute hydrochloric acid, extracted into ethyl acetate, dried ($MgSO_4$) and evaporated to dryness. *5-Benzeneselenylpentanoic acid* (**308**) was isolated as an orange pungent oil (308 mg, 57%); ν_{max} 3057, 2981, 1733 (C=O), 1577 (PhSe), 1476, 1438, 1371, 1221, 1021, and 736 cm^{-1}; δ_H 10.21 (1 H, br s, COOH), 7.46-7.50 (2 H, ortho-H), 7.21-7.26 (3 H, Ar-H), 2.95 (2 H, t, J = 7.1 Hz, 5-H), 2.34 (2 H, t, J = 7.1 Hz, 2-H), and 1.71-1.77 (4 H, m, 3,4-H); δ_C 179.21 (C=O), 132.54 (Ar-CH), 130.20 (Ar-C), 129.00, 126.77 (Ar-CH), 33.42, 27.22, 24.71, and 21.92 (CH_2); *m/z* 258 (M^+, 1.7%), 158 ($PhSeH^+$, 21), 128 (59), 100 (M^+-PhSeH, 58), 83 (25), 78 (20), 73 (39), 60 (80), 55 (88), and 41 (100).

5-Benzeneselenylpentanoyl chloride (309).



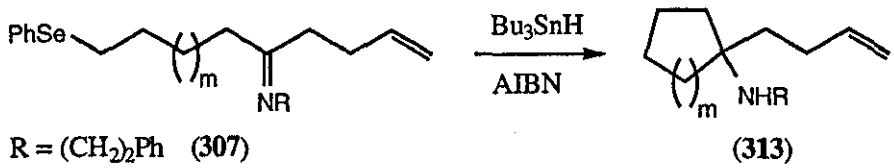
5-Benzeneselenylpentanoic acid (**308**) (521 mg, 1.18 mmol) was dissolved in dichloromethane (25 cm^3) and cooled to 0°C. Thionyl chloride (362 mg, 3 mmol) was added dropwise and the mixture stirred for 0.5 h. (Alternatively oxalyl chloride was used.) The solution was evaporated to dryness yielding *5-benzeneselenylpentanoyl chloride* (**309**) as a dark brown viscous oil (325 mg, 100%) which was not purified further; ν_{max} 3057, 2959, 2871, 1798 (C=O), 1575 (PhSe), 1475, 1438, 1021, 737, and 628 cm^{-1}; δ_H 7.56-7.61 (2 H, ortho-H), 7.24-7.34 (3 H, m, Ar-H), 3.55 (2 H, t, J = 6.0 Hz, 2-H), 2.94 (2 H, t, J = 6.9 Hz, 5-H), and 1.82-1.88 (4 H, m, 3,4-H); δ_C 173.75 (C=O), 131.05 (Ar-C), 129.79, 129.18, 127.72 (Ar-CH), 47.84, 46.19, 32.16, and 22.40 (CH_2).

***N*-Methyl-*N*-methoxy-5-benzeneselenylpentanamide (310).**



5-Benzeneselenylpentanoyl chloride (**309**) (578 mg, 2.1 mmol) (582 mg, 92%) and *N,O*-dimethylhydroxylamine hydrochloride (207 mg, 2.1 mmol) were dissolved in distilled chloroform (20 cm^3) and the solution was cooled to 0°C. Pyridine (363 mg, 4.6 mmol) in chloroform (20 cm^3) was added and the solution was stirred at room temperature for 1 h and the solvent was removed by evaporation. To the residue was added brine (10 cm^3) and 1:1 diethyl ether / dichloromethane mixture (20 cm^3) and the amide product was extracted into the organic layer which was dried ($MgSO_4$) and evaporated to dryness. The product was purified by flash sinter chromatography using silica as absorbent and light petroleum / ethyl acetate mixtures as eluent. *N-Methyl-N-methoxy-5-benzene-selenylpentanamide* (**310**) was isolated as a pale orange oil (582 mg, 92%); ν_{max} 3056, 2936, 2869, 1736 (C=O), 1662, 1578 (PhSe), 1476, 1438, 1385, 1250, 1178, 1072, 998, 737, and 690 cm^{-1}; δ_H (2 stereoisomers) 7.44-7.48 (2 H, ortho-H), 7.21-7.25 (3 H, Ar-H), 3.65 and 3.73 (3 H, 2 x s, OMe), 3.16 and 3.23 (3 H, 2 x s, NMe), 2.92 (2 H, t, J = 7.1 Hz, 5-H), 2.42 (2 H, t, J = 7.1 Hz, 2-H), and 1.71-1.79 (4 H, m, 3,4-H); δ_C 177.35 (C=O), 131.43 (Ar-CH), 130.82 (Ar-C), 129.12, 126.66 (Ar-CH), 61.21 (OMe), 35.73 (NMe), 31.30, 29.90, 27.48, and 24.78 (CH_2); *m/z* 301.0566 [M^+, (3.3%), $C_{13}H_{19}NO_2Se$ requires 301.0581], 213 (10), 157 ($PhSe^+$, 26), 144 (MH^+-PhSe, 100), 91 (13), 77 (37), 55 (70), and 41 (28).

Cyclisation of Imine (307a), m = 1.

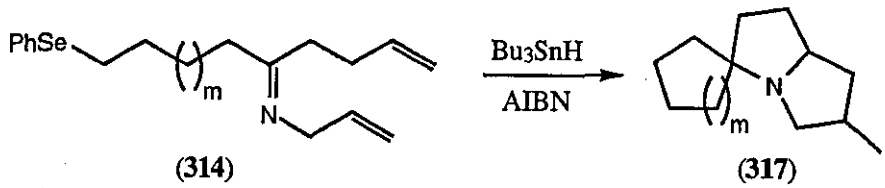


A solution of the ketone (**306a**) (225 mg, 0.76 mmol) and 2-phenylethylamine (92 mg, 0.76 mmol) in toluene was refluxed for 8 h, and the water removed using a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure. Injection of Bu_3SnH (0.35 cm^3, 1.0 mmol) and AIBN (42 mg, 0.26 mmol) in toluene using a syringe pump yielded *1-(3-buten-1-yl)-N-(2-phenylethyl)cyclopentylamine* (**313a**) as the only isolable product, a yellow oil (138 mg, 34%); ν_{max} 3054, 2959, 2869, 1668, 1603 (Ph), 1497, 1455, and 1031 cm^{-1}; δ_H 7.25-7.32 (5 H, m, phenyl H), 5.78-5.84 (1 H, m, butenyl 3-H), 5.00-5.04 (2 H, m, butenyl 4-H), 3.50 (1 H, br s, NH), 2.98 (2 H, t, J = 6.3 Hz, CH_2N), 2.77 (2 H, t, J = 6.3 Hz, CH_2Ph), 2.52-2.54 (2 H, m, butenyl 2-H), 2.31-2.34 (2 H, m, butenyl 1-H), 2.11-2.21 (2 H, m), and 1.52-1.75 (6 H, m, cyclopentyl H); δ_C (75 MHz) 139.88 (Ar-C), 137.09 (alkene CH), 128.77, 128.38, 126.09 (Ar-CH), 115.16 (alkene CH_2), 65.90 (cyclopentyl 1-C), 43.49, 41.77, 40.01, 36.74, 30.45, and 27.64 (CH_2); *m/z* 243.1987 [M^+, (1.0%), $C_{17}H_{25}N$ requires 243.1987], 182 (34), 149 (17), 105 ($MeC_7H_6^+$, 100), 91 ($C_7H_7^+$, 35), and 77 (Ph^+, 79).

Cyclisation of Imine (307b), m = 2.

A solution of the ketone (**306b**) (153 mg, 0.5 mmol) and 2-phenylethylamine (60 mg, 0.5 mmol) in toluene was refluxed for 8 h, and the water removed using a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure. Injection of Bu_3SnH (0.24 cm^3, 0.68 mmol) and AIBN (28 mg, 0.17 mmol) in toluene using a syringe pump yielded 70 mg of crude products which were treated with acetyl chloride and triethylamine. The only isolable product from the reaction was *N-acetyl-1-(3-buten-1-yl)-N-(2-phenylethyl)cyclohexylamine* (**313b**), an orange oil (52 mg, 35%); ν_{max} 3055, 2931, 2859, 1671 (C=O), 1638 (alkene), 1604 (Ph), 1455, 1084, 1031, and 896 cm^{-1}; δ_H (300 MHz) 7.20-7.25 (5 H, m, phenyl H), 5.79-5.83 (1 H, m, butenyl 3-H), 4.97-5.02 (2 H, m, butenyl 4-H), 3.56-3.60 (2 H, m, CH_2N), 2.84-2.87 (4 H, m), 2.31-2.47 (2 H, m, butenyl 1-H), 2.11 (3 H, s, Ac), and 1.25-1.69 (10 H, m, cyclohexyl H); δ_C (75 MHz), 176.62 (C=O), 140.20 (Ar-C), 137.11 (alkene CH), 128.74, 128.36, 126.06 (Ar-CH), 112.87 (alkene CH_2), 60.93 (cyclopentyl 1-C), 43.47, 41.68, 42.02, 40.00, 32.85, 32.52, 27.44 (CH_2), and 23.34 (MeCO); *m/z* 299.2237 [M^+, (0.4%), $C_{20}H_{29}NO$ requires 299.2249], 225 (15), 165 (9), 149 (27), 105 ($MeC_7H_6^+$, 100), 104 (95), 91 ($C_7H_7^+$, 60), 77 (Ph^+, 68), 55 ($MeC_3H_4^+$, 37), and 41 ($C_3H_5^+$, 49).

Attempted cyclisation of Imine (314a), m = 1.

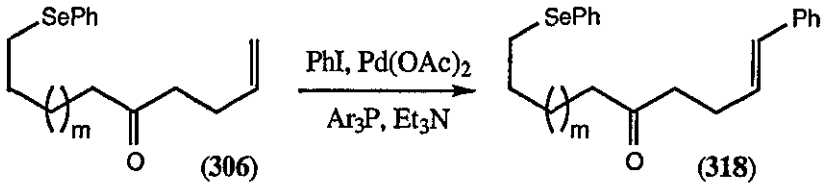


A solution of the ketone (**306a**) (225 mg, 0.76 mmol) and 2-propen-1-ylamine (57 mg, 1.0 mmol) in toluene was refluxed for 8 h, and the water removed using a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure. Injection of Bu_3SnH (0.4 cm^3, 1.14 mmol) and AIBN (42 mg, 0.26 mmol) in toluene using a syringe pump yielded 31 mg recovered material. Though ^1H NMR and mass spectral evidence indicated the possible formation of saturated polycyclic amine (**317a**), no positive identification could be made; δ_H 3.63-3.69 (m), 3.42-3.47 (m), 3.08-3.47 (m), 2.79-2.85 (m), 2.01-2.21 (m), 1.19-1.61 (m), and 0.84 and 0.82 (2 x d, J = 7.3 Hz, Me); *m/z* 179.1692 [M^+, (1.5%), $C_{12}H_{21}N$ requires 179.1674], 149 (33), 111 (MH^+-C_5H_9, 16), 97 (29), 83 (33), 71 (56), 69 ($C_5H_9^+$, 48), 57 (100), 55 (66), and 41 ($C_3H_5^+$, 64).

Attempted cyclisation of Imine (314b), m = 2.

A solution of the ketone (**306b**) (267 mg, 0.86 mmol) and 2-propen-1-ylamine (57 mg, 1.0 mmol) in toluene was refluxed for 8 h, and the water removed using a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure. Injection of Bu_3SnH (0.4 cm^3, 1.14 mmol) and AIBN (48 mg, 0.29 mmol) in toluene using a syringe pump yielded 22 mg recovered material. Though ^1H NMR and mass spectral evidence indicated the possible formation of saturated polycyclic amine (**317b**), no positive identification could be made; δ_H (300 MHz) 3.22-3.50 (2 x m), 2.98-3.02 (m), 1.30-1.92 (m), and 1.15 (d, J = 6.5 Hz, Me); *m/z* (C.I.) 194 (MH^+, 100).

9-Benzeneselenyl-1-phenylnon-1-en-5-one (318a), m = 1.



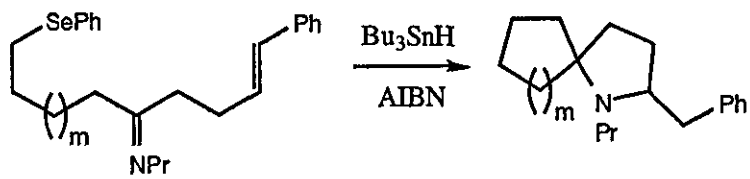
The general procedure for Heck reactions was used. The ketone (**306a**) (204 mg, 0.69 mmol), iodobenzene (141 mg, 0.69 mmol) and triethylamine (100 mg, 1 mmol) in the presence of palladium acetate (5 mg, 0.02 mmol) yielded *9-benzeneselenyl-1-phenylnon-1-en-5-one* (**318a**) as a red oil (182 mg, 71%); ν_{max} 3057, 2929, 2856, 1717 (C=O), 1671 (alkene), 1598 (Ph), 1579 (PhSe), 1478, 1438, 1120, 1073, 1023, 737, and 693

cm^{-1}; δ_H 7.44-7.48 (2 H, m, ortho-H), 7.26-7.29 (8 H, m, Ar-H), 6.42 (1 H, d, J = 15.8 Hz, 1-H), 6.22 (1 H, dt, J = 15.8, 7.7 Hz, 2-H), 2.90 (2 H, t, J = 7.2 Hz, 9-H), 2.41-2.54 (4 H, m), 2.05-2.08 (2 H, m), and 1.62-1.75 (4 H, m); δ_C 209.11 (C=O), 132.42, 132.34, 130.68, 129.26, 128.94, 127.03, 126.67, 125.70 (alkene and Ar-CH), 131.40, 130.15 (Ar-C), 32.04, 29.81, 29.64, 27.54, 25.42, and 23.09 (CH_2); *m/z* 372.0983 [M^+, (0.3%), $C_{21}H_{24}OSe$ requires 372.0992], 264 (5), 158 ($PhSeH^+$, 12), 133 (28), 117 (30), 91 (46), 69 (81), 55 (83), and 41 (100).

10-Benzeneselenyl-1-phenyldec-1-en-5-one (318b), m = 2.

The general procedure for Heck reactions was used. The ketone (**306b**) (220 mg, 0.57 mmol), iodobenzene (116 mg, 0.57 mmol) and triethylamine (60 mg, 0.6 mmol) in the presence of palladium acetate (5 mg, 0.02 mmol) yielded *10-benzeneselenyl-1-phenyl-dec-1-en-5-one* (**318b**) as a red oil (187 mg, 85%); ν_{max} 3056, 2931, 2859, 1714 (C=O), 1655 (alkene), 1603 (Ph), 1579 (PhSe), 1478, 1438, 1072, 1023, 966, 737, and 692 cm^{-1}; δ_H 7.46-7.49 (2 H, m, ortho-H), 7.22-7.31 (8 H, m, Ar-H), 6.41 (1 H, d, J = 15.7 Hz, 1-H), 6.20 (1 H, dt, J = 15.7, 7.8 Hz, 2-H), 2.90 (2 H, t, J = 7.5 Hz, 10-H), 2.39-2.50 (4 H, m), 2.03-2.07 (2 H, m), and 1.45-1.73 (6 H, m); δ_C 209.00 (C=O), 133.03, 132.96, 129.30, 128.99, 128.72, 128.46, 127.12, 126.13 (alkene and Ar-CH), 131.40, 130.08 (Ar-C), 32.10, 30.42, 29.64, 27.53, 27.22, 26.58, and 24.09 (CH_2); *m/z* 386.1129 [M^+, (0.3%), $C_{22}H_{26}OSe$ requires 386.1149], 242 (13), 182 (18), 157 ($PhSe^+$, 17), 154 (37), 117 (39), 105 (48), 91 (63), 77 (Ph^+, 77), and 71 (100).

Cyclisation of Imine (319a), m = 1.



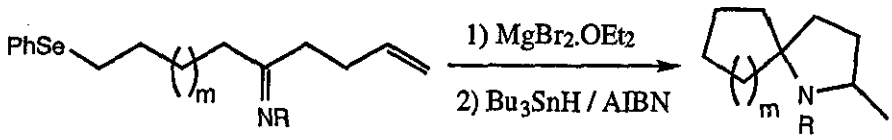
(319) (320b)

A solution of the ketone (**318a**) (171 mg, 0.46 mmol) and *n*-propylamine (136 mg, 2.3 mmol) in toluene was refluxed for 8 h, and the water removed using a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure. Injection of Bu_3SnH (0.23 cm^3, 0.66 mmol) and AIBN (27 mg, 0.16 mmol) in toluene using a syringe pump yielded *2-benzyl-1-propyl-1-azaspiro[4.4]nonane* (**320a**) as a yellow oil (32 mg, 27%); ν_{max} 3055, 2930, 2858, 1658, 1604 (Ph), 1438, 1185, 1120, and 896 cm^{-1}; δ_H 7.22-7.34 (5 H, m, phenyl H), 3.51-3.54 (1 H, m, CHN), 3.16-3.20 (1 H, m, PhCH), 2.80-2.84 (1 H, m, PhCH), 2.43-2.57 (2 H, m, CH_2N), 2.10-2.16 (2 H, m), 1.26-1.66 (12 H, m), and 0.91 (3 H, t, J = 7.5 Hz, Me); *m/z* 257.2131 [M^+, (1.9%), $C_{17}H_{25}N$ requires 257.2143], 201 (9), 155 (17), 91 ($C_7H_7^+$, 19), and 77 (Ph^+, 33), 69 ($C_5H_9^+$, 39), 55 (64), and 41 ($C_3H_5^+$, 100).

Cyclisation of Imine (319b), m = 2.

A solution of the ketone (**318b**) (177 mg, 0.42 mmol) and *n*-propylamine (124 mg, 2.1 mmol) in toluene was refluxed for 8 h, and the water removed using a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure. Injection of Bu_3SnH (0.2 cm^3, 0.6 mmol) and AIBN (23 mg, 0.14 mmol) in toluene using a syringe pump yielded *2-benzyl-1-propyl-1-azaspiro[4.5]decane* (**320b**) as a yellow oil (44 mg, 39%); ν_{max} 3057, 2932, 2859, 1658, 1604 (Ph), 1455, 1073, 1023, and 737 cm^{-1}; δ_H 7.26-7.30 (5 H, m, phenyl H), 3.61-3.68 (1 H, m, CHN), 2.99 (2 H, m, $PhCH_2$), 2.47-2.50 (2 H, m, CH_2N), 2.24-2.30 (1 H, m), 2.00-2.07 (1 H, m), 1.45-1.90(16 H, m), and 0.89 (3 H, t, J = 6.8 Hz, Me).

Cyclisation of Imine (307a) in the presence of magnesium dibromide, m = 1.



R = $(CH_2)_2Ph$ (**307**) (**271**)

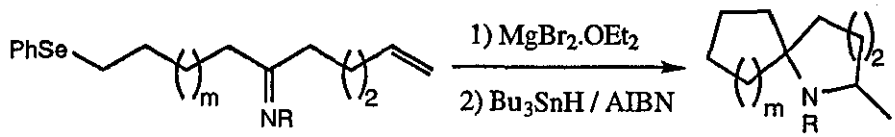
The procedure for the cyclisation of imine (**307a**) (274 mg, 0.69 mmol) was repeated with the addition of $MgBr_2.OEt_2$ (206 mg, 0.8 mmol) prior to the addition of Bu_3SnH. Injection of Bu_3SnH (0.32 cm^3, 0.9 mmol) and AIBN (38 mg, 0.23 mmol) using a syringe pump yielded *2-methyl-1-(2-phenylethyl)-1-azaspiro[4.4]nonane* (**271a**) as a pale yellow oil (50 mg, 30%); ν_{max} 3029, 2930, 2858, 1658, 1604 (Ph), 1496, 1455, 1367, 1082, and 1031 cm^{-1}; δ_H 7.25-7.32 (5 H, m, phenyl H), 3.49-3.56 (2 H, m, CH_2N), 3.35-3.30 (1 H, m, 2-H), 2.83 (2 H, t, J = 7.0 Hz, CH_2Ph), 2.06-2.15 (2 H, m), 1.39-1.80 (10 H, m), and 0.89 (3 H, d, J = 6.3 Hz, Me); δ_C (100 MHz) 138.89 (Ar-C), 128.84, 128.47, 126.32 (Ar-CH), 57.80 (5-C), 52.12 (2-C), 40.65 (CH_2N), 35.65, 35.12, 30.93, 29.71, 23.35 (CH_2), and 14.02 (Me); *m/z* 243.1986 [M^+, (0.4%), $C_{17}H_{25}N$ requires 243.1987], 212 (13), 188 (9), 167 (MH^+-Ph, 100), 152 (M^+-$PhCH_2$, 15), 105 ($MeC_7H_6^+$, 25), 91 ($C_7H_7^+$, 23), and 77 (Ph^+, 12).

Cyclisation of Imine (307b) in the presence of magnesium dibromide, m = 2.

The procedure for the cyclisation of imine (**307a**) (307 mg, 0.74 mmol) was repeated with the addition of $MgBr_2.OEt_2$ (210 mg, 0.8 mmol) prior to the addition of Bu_3SnH. Injection of Bu_3SnH (0.34 cm^3, 1.0 mmol) and AIBN (41 mg, 0.25 mmol) using a syringe pump yielded *2-methyl-1-(2-phenylethyl)-1-azaspiro[4.5]decane* (**271b**) as a pale yellow oil (63 mg, 33%); ν_{max} 3027, 2926, 2856, 1654, 1603 (Ph), 1497, 1453, 1364, and 1126 cm^{-1}; δ_H 7.22-7.32 (5 H, m, phenyl H), 3.47-3.55 (2 H, m, CH_2N), 3.27-3.33 (1 H, m, 2-C), 2.83 (2 H, t, J = 7.0 Hz, CH_2Ph), 2.05-2.12 (2 H, m), 1.28-1.80 (10 H, m), and 0.88 (3 H, d, J = 6.0 Hz, Me); δ_C (100 MHz) 137.60 (Ar-C), 128.73, 128.57, 126.44

(Ar-CH), 57.75 (5-C), 51.88 (2-C), 40.57 (CH_2N), 35.56, 35.04, 32.85, 30.72, 30.31, 27.76 (CH_2), and 19.71 (Me); *m/z* 257.2157 [M^+, (0.2%), $C_{18}H_{27}N$ requires 257.2143], 212 (13), 188 (9), 167 (MH^+-Ph, 100), 152 (M^+-$PhCH_2$, 15), 105 ($MeC_7H_6^+$, 25), 91 ($C_7H_7^+$, 23), and 77 (Ph^+, 12).

Cyclisation of Imine (307c), m = 1.



R = CH_2Ph (307) (271)

A solution of the ketone (**306c**) (154 mg, 0.5 mmol) and benzylamine (53 mg, 0.5 mmol) in toluene was refluxed for 6 h, and the water removed using a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure, with the addition of $MgBr_2.OEt_2$ (258 mg, 1 mmol) prior to the addition of Bu_3SnH. Injection of Bu_3SnH (0.23 cm^3, 0.66 mmol) and AIBN (27 mg, 0.16 mmol) in toluene using a syringe pump yielded *6-benzyl-7-methyl-6-azaspiro[4.5]decane* (**271c**) as a pale yellow oil (32 mg, 27%); ν_{max} 3030, 2925, 2854, 1655, 1603 (Ph), 1459, 1376, 1155, 1074, and 1029 cm^{-1}; δ_H 7.27-7.35 (5 H, m, phenyl H), 3.83 (2 H, s, CH_2Ph), 3.71-3.75 (1 H, m, 7-H), 1.95-2.09 (2 H, m), 1.20-1.72 (12 H, m), and 0.88 (3 H, d, J = 6.5 Hz, Me); *m/z* 243.1996 [M^+, (0.3%), $C_{17}H_{25}N$ requires 243.1987], 149 (7), 97 (13), 91 ($C_7H_7^+$, 100), 83 (17), 71 (26), 57 (52), and 43 (59).

Cyclisation of Imine (307d), m = 2.

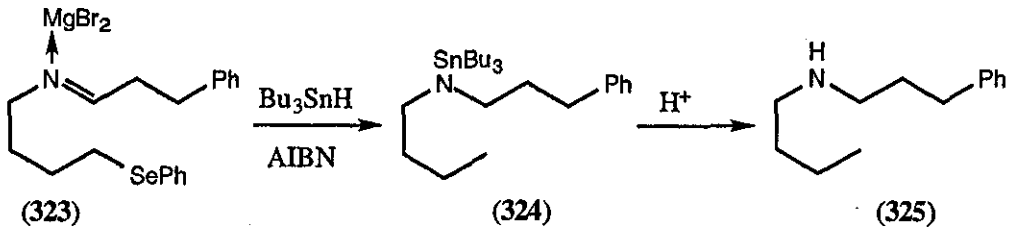
A solution of the ketone (**306d**) (244 mg, 0.8 mmol) and benzylamine (81 mg, 0.8 mmol) in toluene was refluxed for 8 h, and the water removed using a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure, but with the addition of $MgBr_2.OEt_2$ (258 mg, 1 mmol) prior to the addition of Bu_3SnH. Injection of Bu_3SnH (0.37 cm^3, 1.06 mmol) and AIBN (44 mg, 0.27 mmol) in toluene using a syringe pump yielded *1-benzyl-2-methyl-1-azaspiro[5.5]undecane* (**271d**) as a pale yellow oil (60 mg, 29%); ν_{max} 3059, 2930, 2855, 1668, 1603 (Ph), 1496, 1454, 1076, and 1029 cm^{-1}; δ_H 7.27-7.35 (5 H, m, phenyl H), 3.82 (2 H, 3, CH_2Ph), 3.59-3.63 (1 H, m, 2-H), 1.38-1.80 (16 H, m), and 0.87 (3 H, d, J = 6.5 Hz, Me); δ_C (100 MHz) 140.67 (Ar-C), 128.93, 128.53, 127.32 (Ar-CH), 60.02 (6-C), 53.54 (CH_2Ph), 48.22 (3-C), 30.53, 30.06, 28.23, 29.90, 27.27, 25.97 (CH_2), and 18.22 (Me); *m/z* 257.2134 [M^+, (0.3%), $C_{18}H_{27}N$ requires 257.2143], 188 (5), 149 (5), 134 (6), 106 ($PhCH{=}NH_2^+$, 29), 91 ($C_7H_7^+$, 100), 77 (Ph^+, 9), and 65 (14).

Formation and cyclisation of imine (201c) in the presence of magnesium dibromide.

5-Benzeneselenylpentanal (**179b**) (100 mg, 0.41 mmol) and benzylamine (44 mg, 0.41

mmol) were dissolved in toluene (70 cm^3) and refluxed for 3 h, and the water removed using a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure, with the addition of $MgBr_2.OEt_2$ (107 mg, 0.41 mmol) prior to the addition of Bu_3SnH. Injection of Bu_3SnH (0.15 cm^3, 0.55 mmol) and AIBN (23 mg, 0.14 mmol) in toluene gave 60 mg of recovered material which, on purification gave the 5-*exo* adduct (**202c**) as the only reaction product (44 mg, 62%) which was found to be identical with an authentic sample.

Formation and attempted cyclisation of Imine-Lewis acid complex (323).

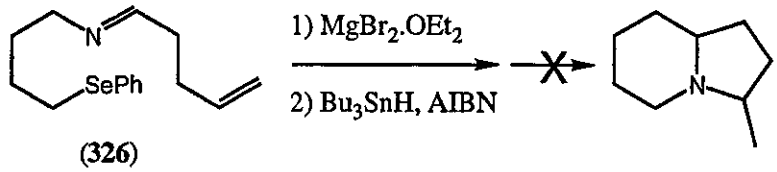


4-Benzeneselenylbutylamine (**185b**) (228 mg, 1 mmol) and 3-phenylpropionaldehyde (134 mg, 1 mmol) were dissolved in toluene (80 cm^3) and refluxed for 3 h, and the water removed using a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure, with the addition of $MgBr_2.OEt_2$ (258 mg, 1 mmol) prior to the addition of Bu_3SnH. Injection of Bu_3SnH (0.47 cm^3, 1.3 mmol) and AIBN (56 mg, 0.34 mmol) yielded amine (**325**) (76 mg, 40%) as the only isolable product resulting from (i) the addition of hydride from Bu_3SnH across the activated imine bond, and (ii) reduction of the benzeneselenyl group. The amine (**325**) was found to be identical to an authentic sample. The experiment was repeated three times with yields in the range 22-28%. One experiment appeared to yield (from ^1H NMR spectroscopic data) the *N*-tri-*n*-butylstannylamine (**324**) (16%) which could not be sufficiently purified for full characterisation; δ_H 7.07-7.24 (5 H, m, Ph), 2.40-2.57 (6 H, m, CH_2N, CH_2Ph), 1.68-1.85 (m), 1.47-1.62 (m), 1.20-1.35 (m), and 0.83 and 0.85 (2 x t, J = 7.0 Hz, Me).

***N*-Butyl-3-phenyl-1-propylamine (325).**

The amine was prepared by general method C. 1-Bromo-3-phenylpropane (997 mg, 5 mmol) and 1-butylamine (730 mg, 10 mmol) gave *N*-butyl-3-phenyl-1-propylamine (**325**) as a colourless oil (219 mg, 23%); ν_{max} 3304, 3026, 2931, 1664, 1604, 1496, 1454, 1377, 1128, 745, and 699 cm^{-1}; δ_H 7.17-7.32 (5 H, m, Ph), 5.29 (1 H, s, NH), 2.05-2.08 (2 H, m, propyl 2-H), 1.63-1.76 (2 H, m, butyl 2-H), 1.29-1.38 (2 H, m, butyl 3-H), and 0.90 (3 H, t, J = 7.6 Hz, 4-H); δ_C 142.20 (Ar-C), 128.48, 126.09 and 125.73 (Ar-CH), 53.50 and 46.68 (CH_2N), 32.26, 29.87, 28.58, 20.29, and 13.73 (4-C); *m/z* 191.1671 [M^+, (6.7%), $C_{13}H_{21}N$ requires 191.1674], 148 (M^+-Pr, 19), 117 (51), 104 (3), 91 ($C_7H_7^+$, 38), 86 (64), and 44 (100).

Formation and attempted cyclisation of Imine-Lewis acid complex (326).

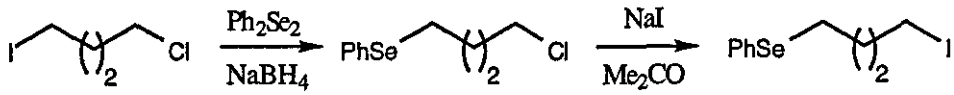


(326)

A solution of 4-pentenal (252 mg, 3 mmol) and 4-benzeneselenyl-1-butylamine (**185b**) (173 mg, 0.76 mmol) in toluene was refluxed for 8 h, and the water removed using a Dean-Stark water separator. The imine was not isolated and was cyclised using the general procedure, with the addition of $MgBr_2.OEt_2$ (200 mg, 0.76 mmol) prior to the addition of Bu_3SnH. Injection of Bu_3SnH (0.27 cm^3, 1.01 mmol) and AIBN (41 mg, 0.25 mmol) gave a yellow solution from which the amine products were precipitated, as a colourless oil, by bubbling dry HCl through the solution. The amount of salts produced was 74 mg (29%). Analysis of the product showed that the cyclised amine was not present in the product, neither was any other recognisable compound. The presence of the PhSe group suggests that the radical reaction failed altogether, yet the absence of alkene peaks and a complex ^1H NMR spectrum in the δ 3-4 ppm region points to an unknown reaction pathway. Control experiments using i) hexa-*n*-butylditin / AIBN and ii) refluxing toluene with no tin reagents gave similar complex spectra, but in any case no products were isolable.

10.8. Experimental for Chapter 9.

1-Benzeneselenyl-4-chlorobutane.

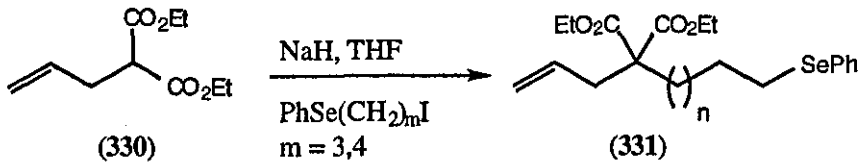


The general procedure for the introduction of the benzeneselenyl group was used. Diphenyl diselenide (1.96g, 6.3 mmol), sodium borohydride (600 mg, 15.8 mmol) and 1-chloro-4-iodobutane (2.80 g, 12.8 mmol) gave *1-benzeneselenyl-4-chlorobutane* as a yellow-orange oil (3.04 g, 96%); ν_{max} 3072, 2938, 2866, 1579 (phenyl), 1478, 1437, 1073, 1022, 734, and 691 cm^{-1}; δ_H 7.44-7.49 (2 H, m, o-H), 7.20-7.26 (3 H, m, Ar-H), 3.49 (2 H, t, J = 6.2 Hz, 4-H), 2.89 (2 H, t, J = 6.8 Hz, 1-H), and 2.76-1.90 (4 H, m, 2,3-H); δ_C 132.62 and 129.01 (Ar-CH), 128.19 (Ar-C), 126.86 (Ar-CH), 44.30 (4-C), 32.37, 27.29, and 26.95 (CH_2); *m/z* 247.9871 [M^+, (9.7%), $C_{10}H_{13}ClSe$ requires 247.9871], 234 (6), 213 (47), 157 ($PhSe^+$, 39), 91 (65), 78 (62), and 55 (100).

1-Benzeneselenyl-4-iodobutane.

Sodium iodide (6.0 g, 40 mmol), dissolved in dry acetone (10 cm^3) was added to a solution of 1-benzeneselenyl-4-chlorobutane (2.50 g, 10.1 mmol) in acetone (40 cm^3) and the mixture refluxed for 4 h. The precipitated sodium chloride was removed by filtration and the filtrate evaporated to dryness. The solid residue was triturated with diethyl ether and the solution filtered a second time. The ether solution was evaporated to dryness yielding the product which was purified by quick filtration through silica gel. *1-Benzeneselenyl-4-iodobutane* was isolated as a viscous orange oil which gradually darkened (3.39 g, 99%); ν_{max} 3071, 2934, 1579 (PhSe), 1478, 1437, 1299, 1073, 1023, 735, 691, and 670 cm^{-1}; δ_H 7.46-7.50 (2 H, m, o-H), 7.23-7.27 (3 H, m, Ar-H), 3.15 (2H, t, J = 6.8 Hz, 4-H), 2.91 (2 H, t, J = 6.8 Hz, 1-H), and 1.80-1.91 (4 H, m, 2,3-H); δ_C 132.67 (Ar-CH), 130.05 (Ar-C), 129.07, 126.88 (Ar-CH), 33.23, 30.79, 28.28 (1,2,3-C), and 5.80 (4-C); *m/z* 339.9227 [M^+, (5.6%), $C_{10}H_{13}ISe$ requires 339.9227], 213 (MH^+-I, 26), 158 ($PhSeH^+$, 28), 91 (100), 78 (39), and 55 (99).

Diethyl (3-benzeneselenylpropyl)(2-propen-1-yl)propanedioate (331a), n = 1.

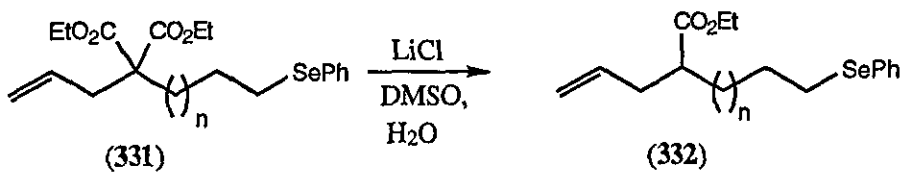


The general procedure for the 2-alkylation of propanedioate esters was used. Diethyl (2-propen-1-yl)propanedioate (**330**) (605 mg, 3 mmol), sodium hydride (160 mg, 4 mmol)

and 1-benzeneselenyl-3-iodopropane (975 mg, 3 mmol) yielded *diethyl (3-benzeneselenylpropyl)(2-propen-1-yl)propanedioate* (**331a**) as an orange oil (952 mg, 77%); ν_{max} 3075, 2979, 2935, 2871, 1731 (ester), 1642 (alkene), 1580 (PhSe), 1478, 1438, 1299, 1229, 1154, 1023, 921, 736, and 691 cm^{-1}; δ_H 7.44-7.48 (2 H, m, ortho-H), 7.22-7.26 (3 H, m, Ar-H), 5.55-5.69 (1 H, m, allyl 2-H), 5.00-5.08 (2 H, m, allyl 3-H), 4.13 (4 H, q, J = 7.0 Hz, CH_2O), 2.87 (2 H, t, J = 7.1 Hz, CH_2Se), 2.59 (2 H, d, J = 7.5 Hz, allyl 1-H), 1.94-2.01 (2 H, m), 1.56-1.63 (2 H, m), and 1.20 (6 H, t, J = 7.0 Hz, Me); δ_C 171.03 (C=O), 132.57, 132.32, 129.02, 126.81 (alkene and Ar-CH), 130.10 (Ar-C), 119.02 (alkene CH_2), 61.25 (CH_2O), 57.10 (quaternary C), 37.01, 32.45, 27.68, 24.70 (CH_2), and 14.09 (Me); *m/z* 398.0998 [M^+, (14%), $C_{19}H_{26}O_4Se$ requires 398.0996], 322 (13), 241 (M^+-PhSe, 100), 157 ($PhSe^+$, 40), 93 (46), 78 (61), and 41 ($C_3H_5^+$, 77).

Diethyl (4-benzeneselenylbutyl)(2-propen-1-yl)propanedioate (331b), n = 2.
The general procedure for the 2-alkylation of propanedioate esters was used. Diethyl (2-propen-1-yl)propanedioate (605 mg, 3 mmol), sodium hydride (160 mg, 4 mmol) and 1-benzeneselenyl-4-iodobutane (1.071 g, 3 mmol) yielded *diethyl (4-benzeneselenylbutyl)(2-propen-1-yl)propanedioate* (**217**) as an orange oil (1.01 g, 79%); ν_{max} 3074, 2934, 2866, 1729 (ester), 1642 (alkene), 1579 (PhSe), 1478, 1438, 1367, 1221, 1096, 1023, 922, 736, and 692 cm^{-1}; δ_H 7.45-7.48 (2 H, m, ortho-H), 7.22-7.26 (3 H, m, Ar-H), 5.50-5.67 (1 H, m, allyl 2-H), 5.05-5.12 (2 H, m, allyl 3-H), 4.17 (4 H, q, J = 7.0 Hz, CH_2O), 2.89 (2 H, t, J = 6.8 Hz, CH_2Se), 2.64 (2 H, d, J = 7.5 Hz, allyl 1-H), 1.82-1.89 (2 H, m), 1.69 (2 H, t, J = 7.5 Hz, $Se(CH_2)_3CH_2$), 1.31-1.34 (2 H, m), and 1.23 (6 H, t, J = 7.0 Hz, Me); δ_C 171.10 (C=O), 132.56, 132.40, 128.91, 126.67 (alkene and Ar-CH), 130.15 (Ar-C), 118.82 (alkene CH_2), 61.09 (CH_2O), 57.19 (quaternary C), 36.80, 31.48, 30.07, 27.37, 23.69 (CH_2), and 14.04 (Me); *m/z* 412.1152 [M^+, (5.3%), $C_{20}H_{28}O_4Se$ requires 412.1152], 242 (15), 157 ($PhSe^+$, 40), 139 (100), 91 (28), 81 (52), and 55 (87).

Ethyl 5-benzeneselenyl-2-(2-propen-1-yl)pentanoate (332a), n = 1.



(331) (332)

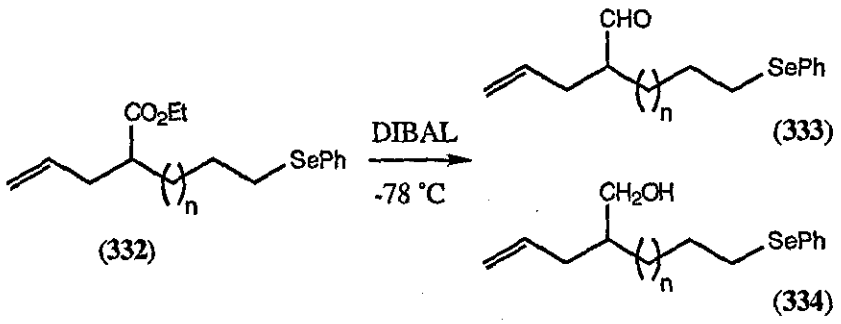
The general procedure for hydrolytic decarboxylation using lithium chloride in DMSO was used. The diester (**331a**) (717 mg, 1.7 mmol), lithium chloride (2 equiv.) and water (1.2 equiv.) in refluxing DMSO yielded *ethyl 5-benzeneselenyl-2-(2-propen-1-yl)-pentanoate* (**332a**) as a red oil (534 mg, 93%); ν_{max} 2983, 2931, 1737 (ester), 1655 (alkene), 1578 (PhSe), 1478, 1438, 1299, 1232, 1158, 1023, 909, 733, and 691 cm^{-1}; δ_H 7.44-7.49 (2 H, m, ortho-H), 7.22-7.26 (3 H, m, Ar-H), 5.60-5.76 (1 H, m, allyl 2-H), 4.98-5.06 (2 H, m, allyl 3-H), 4.09 (2 H, q, J = 7.0 Hz, CH_2O), 2.87 (2 H, t, J = 6.8 Hz,

CH_2Se), 2.30-2.39 (2 H, m), 2.16-2.21 (1 H, m, 2-H), 1.60-1.74 (4 H, m), and 1.20 (3 H, t, J = 7.0 Hz, Me); δ_C 175.18 (C=O), 135.18 (alkene CH), 132.54 (Ar-CH), 130.31 (Ar-C), 128.94, 126.71 (Ar-CH), 116.78 (alkene CH_2), 60.18 (CH_2O), 44.70 (CH), 36.35, 31.70, 27.75, 27.41 (CH_2), and 14.23 (Me); *m/z* 326.0787 [M^+, (7.7%), $C_{16}H_{22}O_2Se$ requires 326.0785], 258 (6), 169 (M^+-PhSe, 57), 157 ($PhSe^+$, 25), 109 (77), 77 (Ph^+, 52), 67 (74), 55 ($MeC_3H_4^+$, 97), and 41 ($C_3H_5^+$, 100).

Ethyl 6-benzeneselenyl-2-(2-propen-1-yl)hexanoate (332b), n = 2.

The general procedure for hydrolytic decarboxylation using lithium chloride in DMSO was used. The diester (**331b**) (742 mg, 1.7 mmol), lithium chloride (2 equiv.) and water (1.2 equiv.) in refluxing DMSO yielded *ethyl 6-benzeneselenyl-2-(2-propen-1-yl)-hexanoate* (**332b**) as a red oil (543 mg, 88%); ν_{max} 3071, 2936, 2834, 1731 (ester), 1641 (alkene), 1579 (PhSe), 1478, 1438, 1367, 1299, 1222, 1154, 1023, 922, 737, and 692 cm^{-1}; δ_H 7.44-7.50 (2 H, m, ortho-H), 7.21-7.26 (3 H, m, Ar-H), 5.66-5.76 (1 H, m, allyl 2-H), 4.98-5.07 (2 H, m, allyl 3-H), 4.12 (2 H, q, J = 7.1 Hz, CH_2O), 2.88 (2 H, t, J = 7.2 Hz, CH_2Se), 2.31-2.39 (2 H, m), 2.18-2.26 (1 H, m, 2-H), 1.61-1.73 (4 H, m), 1.39-1.48 (2 H, m), and 1.23 (3 H, t, J = 7.1 Hz, Me); δ_C 175.43 (C=O), 135.34 (alkene CH), 132.43 (Ar-CH), 130.15 (Ar-C), 128.93, 126.82 (Ar-CH), 116.66 (alkene CH_2), 60.13 (CH_2O), 45.08 (CH), 36.38, 31.10, 29.91, 27.53, 27.28 (CH_2), and 14.28 (Me); *m/z* 340.0941 [M^+, (0.5%), $C_{17}H_{24}O_2Se$ requires 340.0941], 296 (MH^+-EtO, 5), 157 ($PhSe^+$, 13), 139 (15), 115 (11), 83 (29), and 55 ($MeC_3H_4^+$, 100).

Reduction of Ester (332a).



The general procedure for the synthesis of aldehydes was used. The ester (**332a**) (321 mg, 1.0 mmol) and diisobutylaluminium hydride (498 mg, 3.5 mmol) were reacted over 2 h yielding **5-***benzeneselenyl-2-(2-propen-1-yl)pentanal* (**333a**) as a colourless oil (163 mg, 58%) and *5-benzeneselenyl-2-(2-propen-1-yl)pentan-1-ol* (**334a**) as a yellow oil (62 mg, 22%).

Aldehyde (**333a**): ν_{max} 3073, 2925, 2854, 2721, 1725 (C=O), 1640 (alkene), 1579 (PhSe), 1478, 1438, 1232, 1073, 1023, 736, and 691 cm^{-1}; δ_H (300 MHz) 9.59 (1 H, s, CHO), 7.46-7.49 (2 H, m, ortho-H), 7.26-7.29 (3 H, m, Ar-H), 5.72-5.76 (1 H, m, allyl 2-H), 5.01-5.05 (2 H, m, allyl 3-H), 2.91 (2 H, t, J = 7.0 Hz, CH_2Se), 2.21-2.37 (2 H, m,

allylic H), 2.08-2.12 (1 H, m, 2-H), and 1.52-1.80 (4 H, m); δ_C (75 MHz) 204.19 (C=O), 134.50 (alkene CH), 132.59 (Ar-CH), 130.15 (Ar-C), 128.99, 126.83 (Ar-CH), 113.23 (alkene CH_2), 50.60 (2-C), 32.88, 28.10, 27.51, and 27.31 (CH_2); *m/z* 282.0509 [M^+, (7.9%), $C_{14}H_{18}OSe$ requires 282.0523], 198 (13), 157 ($PhSe^+$, 34), 117 (16), 91 (32), 77 (Ph^+, 55), 55 (75), and 41 ($C_3H_5^+$, 100).

Alcohol (**334a**): ν_{max} 3365 (OH), 3073, 2925, 2875, 1640 (alkene), 1579 (PhSe), 1478, 1438, 1246, 1073, 1023, 915, 736, and 691 cm^{-1}; δ_H (300 MHz) 7.46-7.49 (2 H, m, ortho-H), 7.24-7.27 (3 H, m, Ar-H), 5.74-5.78 (1 H, m, allyl 2-H), 5.00-5.04 (2 H, m, allyl 3-H), 3.52 (2 H, d, J = 4.9 Hz, CH_2O), 2.91 (2 H, t, J = 7.2 Hz, CH_2Se), 2.06-2.10 (2 H, m, allylic H), 1.70-1.73 (2 H, m), 1.58-1.61 (2 H, m), and 1.41-1.45 (2 H, m); δ_C (75 MHz) 136.62 (alkene CH), 132.41 (Ar-CH), 130.15 (Ar-C), 128.93, 126.64 (Ar-CH), 116.36 (alkene CH_2), 65.15 (CH_2O), 39.83 (2-C), 35.53, 30.65, 27.99, and 27.37 (CH_2); *m/z* 284.0679 [M^+, (12%), $C_{14}H_{20}OSe$ requires 284.0679], 184 (38), 157 ($PhSe^+$, 39), 109 (94), 91 (40), 77 (Ph^+, 41), and 67 ($C_4H_3O^+$, 100).

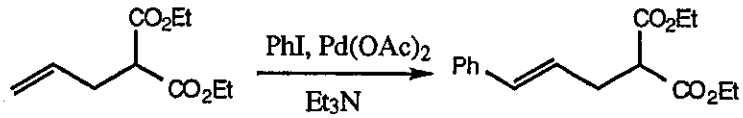
Reduction of Ester (332b).

The general procedure for the synthesis of aldehydes was used. The ester (**332b**) (513 mg, 1.5 mmol) and diisobutylaluminium hydride (896 mg, 6.3 mmol) were reacted over 2 h yielding *6-benzeneselenyl-2-(2-propen-1-yl)hexanal* (**333b**) as a colourless oil (261 mg, 59%) and *6-benzeneselenyl-2-(2-propen-1-yl)hexan-1-ol* (**334b**) as a yellow oil (111 mg, 25%).

Aldehyde (**333b**): ν_{max} 3073, 2928, 2858, 2712, 1725 (C=O), 1638 (alkene), 1579 (PhSe), 1477, 1438, 1265, 1073, 1023, 738, and 691 cm^{-1}; δ_H (300 MHz) 9.59 (1 H, s, CHO), 7.46-7.49 (2 H, m, ortho-H), 7.25-7.27 (3 H, m, Ar-H), 5.72-5.76 (1 H, m, allyl 2-H), 5.03-5.07 (2 H, m, allyl 3-H), 2.91 (2 H, t, J = 7.0 Hz, CH_2Se), 2.32-2.40 (2 H, m, allylic H), 2.09-2.13 (1 H, m, 2-H), and 1.42-1.86 (6 H, m); δ_C (75 MHz) 204.42 (C=O), 134.73 (alkene CH), 132.56 (Ar-CH), 130.15 (Ar-C), 128.97, 126.74 (Ar-CH), 113.24 (alkene CH_2), 51.00 (2-C), 35.64, 32.94, 30.05, 27.45, and 27.11 (CH_2); *m/z* 296.0697 [M^+, (9.4%), $C_{15}H_{20}OSe$ requires 296.0679], 212 (21), 171 ($PhSeCH_2^+$, 15), 158 ($PhSeH^+$, 47), 91 (40), 78 (52), and 55 (100).

Alcohol (**334b**): ν_{max} 3380 (OH), 3073, 2929, 2857, 1640 (alkene), 1579 (PhSe), 1478, 1438, 1365, 1241, 1074, 1023, 914, 737, and 691 cm^{-1}; δ_H (300 MHz) 7.46-7.49 (2 H, m, ortho-H), 7.24-7.27 (3 H, m, Ar-H), 5.73-5.79 (1 H, m, allyl 2-H), 5.01-5.06 (2 H, m, allyl 3-H), 3.56 (2 H, d, J = 5.4 Hz, CH_2O), 2.92 (2 H, t, J = 7.2 Hz, CH_2Se), 2.06-2.14 (2 H, m, allylic H), 1.84 (1 H, s, OH), 1.70-1.76 (3 H, m), 1.43-1.49 (2 H, m), and 1.32-1.37 (2 H, m); δ_C (75 MHz) 135.86 (alkene CH), 132.36 (Ar-CH), 130.15 (Ar-C), 128.92, 126.59 (Ar-CH), 117.28 (alkene CH_2), 66.57 (CH_2O), 40.05 (2-C), 35.43, 30.17, 29.87, 27.63, and 26.77 (CH_2); *m/z* 298.0836 [M^+, (4.6%), $C_{15}H_{22}OSe$ requires 298.0836], 213 (28), 171 ($PhSeCH_2^+$, 13), 157 ($PhSe^+$, 28), 123 (30), 107 (24), 91 (37), 81 ($C_5H_5O^+$, 100), 77 (Ph^+, 39), 67 (50), and 43 ($C_3H_5^+$, 94).

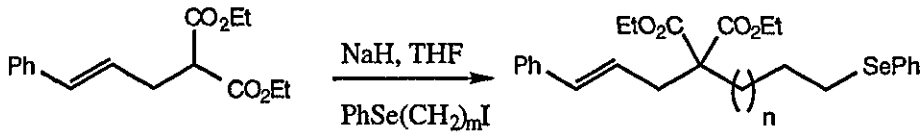
Diethyl (3-phenyl-2-propen-1-yl)propanedioate (335).



(330) (335)

The general procedure for the Heck reaction was used. Diethyl (2-propen-1-yl)propanedioate (4.0 g, 20 mmol), iodobenzene (4.08 g, 20 mmol) and tri-*n*-butylamine (3.7 g, 20 mmol) in the presence of palladium acetate (77 mg, 0.35 mmol) yielded *diethyl (3-phenyl-2-propen-1-yl)propanedioate* (**335**) as a yellow viscous oil (4.96 g, 90%); (Found: C, 69.1; H, 7.39. $C_{16}H_{26}O_4$ requires C, 69.5; H, 7.30%); ν_{max} 2983, 1737 (ester), 1655 (alkene), 1599 (Ph), 1448, 1370, 1227, 1153, 1096, 1033, 747, and 695 cm^{-1}; δ_H (300 MHz) 7.30-7.34 (5 H, m, Ph), 6.50 (1 H, d, J = 15.6 Hz, 3-H), 6.18 (1 H, dt, J = 15.6, 7.8 Hz, cinnamyl 2-H), 4.25 (4 H, q, J = 7.4 Hz, CH_2O), 3.54 (1 H, t, J = 7.8 Hz, malonate 2-H), 2.85 (2 H, dd, J = 7.8, 7.8 Hz, 1-H), and 1.32 (6 H, t, J = 7.4 Hz, Me); δ_C (75 MHz) 168.80 (C=O), 132.69, 128.40, 127.28, 126.08, 125.49 (alkene and Ar-CH), 131.41 (Ar-C), 61.36 (CH_2O), 51.91 (malonate 2-C), 32.13 (sidechain 1-C), and 14.01 (Me); *m/z* (C.I.) 277.1440 [MH^+, (100%), $C_{16}H_{21}O_4$ requires 277.1440], 202 (M^+-H-EtOCO, 6), and 178 (7).

Diethyl (3-benzeneselenylpropyl)(3-phenyl-2-propen-1-yl)propanedioate (336a), n = 1.



(335) (336)

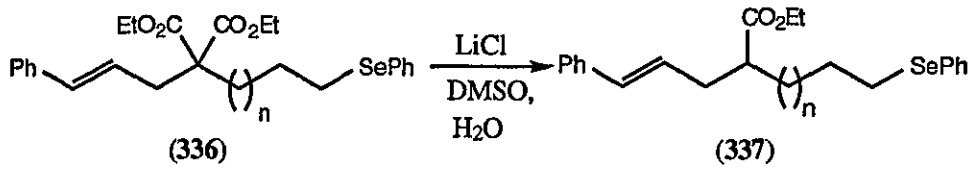
The general procedure for the 2-alkylation of propanedioate esters was used. Diethyl (3-phenyl-2-propen-1-yl)propanedioate (**335**) (825 mg, 3 mmol), sodium hydride (160 mg, 4 mmol) and 1-benzeneselenyl-3-iodopropane (962 g, 3 mmol) yielded *diethyl (3-benzeneselenylpropyl)(3-phenyl-2-propen-1-yl)propanedioate* (**336a**) as a red oil (1.276 g, 90%); ν_{max} 3075, 2934, 1737 (ester), 1655 (alkene), 1603 (Ph), 1579 (PhSe), 1478, 1438, 1158, 1095, 1023, 968, 737, and 692 cm^{-1}; δ_H (300 MHz) 7.44-7.52 (2 H, m, ortho-H), 7.25-7.32 (8 H, m, Ar-H), 6.44 (1 H, d, J = 15.6 Hz, cinnamyl 3-H), 6.07 (1 H, dt, J = 15.6, 7.8 Hz, cinnamyl 2-H), 4.21 (4 H, q, J = 7.2 Hz, CH_2O), 2.93 (2 H, t, J = 7.3 Hz, CH_2Se), 2.80 (2 H, d, J = 7.8 Hz, 1-H), 2.05-2.09 (2 H, m), 1.70-1.74 (2 H, m), and 1.25 (6 H, t, J = 7.2 Hz, Me); δ_C (75 MHz) 171.59 (C=O), 133.75, 132.45, 128.95, 128.40, 127.32, 126.73, 126.14, 123.82 (alkene and Ar-CH), 131.41, 130.15 (Ar-C),

61.25 (CH_2O), 57.63 (quaternary C), 36.28, 32.66, 27.58, 24.75 (CH_2), and 14.04 (Me); *m/z* 474.1307 [M^+, (3.4%), $C_{25}H_{30}O_4Se$ requires 474.1309], 404 (MH^+-EtOCO, 2), 317 (M^+-PhSe, 13), 245 (MH^+-PhSe-EtOCO, 11), 169 (12), 157 ($PhSe^+$, 17), 129 (38), 117 ($PhC_3H_4^+$, 100), and 77 (Ph^+, 22).

Diethyl (4-benzeneselenylbutyl)(3-phenyl-2-propen-1-yl)propanedioate (336b), n = 2.

The general procedure for the 2-alkylation of propanedioate esters was used. Diethyl (3-phenyl-2-propen-1-yl)propanedioate (**335**) (825 mg, 3 mmol), sodium hydride (160 mg, 4 mmol) and 1-benzeneselenyl-4-iodobutane (1.02 g, 3 mmol) yielded *diethyl (4-benzeneselenylbutyl)(3-phenyl-2-propen-1-yl)propanedioate* (**336b**) as a red viscous oil (1.195 g, 82%); ν_{max} 3072, 2935, 2862, 1737 (ester), 1651 (alkene), 1603 (Ph), 1579 (PhSe), 1478, 1438, 1156, 1095, 1023, 968, 738, and 692 cm^{-1}; δ_H (300 MHz) 7.46-7.52 (2 H, m, ortho-H), 7.25-7.31 (8 H, m, Ar-H), 6.43 (1 H, d, J = 15.6 Hz, cinnamyl 3-H), 6.04 (1 H, dt, J = 15.6, 7.8 Hz, cinnamyl 2-H), 4.18 (4 H, q, J = 7.2 Hz, CH_2O), 2.93 (2 H, t, J = 7.3 Hz, CH_2Se), 2.81 (2 H, d, J = 7.8 Hz, 1-H), 1.89-1.93 (2 H, m), 1.71-1.75 (2 H, m), 1.41-1.45 (2 H, m), and 1.26 (6 H, t, J = 7.2 Hz, Me); δ_C (75 MHz) 171.32 (C=O), 133.70, 132.55, 128.95, 128.42, 127.30, 126.69, 126.13, 124.13 (alkene and Ar-CH), 131.41, 130.15 (Ar-C), 61.19 (CH_2O), 57.74 (quaternary C), 36.16, 31.78, 29.96, 27.39, 23.99 (CH_2), and 14.08 (Me); *m/z* 488.1466 [M^+, (6.7%), $C_{26}H_{32}O_4Se$ requires 488.1465], 416 (MH^+-EtOCO, 3), 213 (26), 183 (19), 158 ($PhSeH^+$, 25), 129 (26), 117 ($PhC_3H_4^+$, 100), and 91 (84) $MeC_3H_4^+$,

Ethyl 5-benzeneselenyl-2-(3-phenyl-2-propen-1-yl)pentanoate (337a), n = 1.



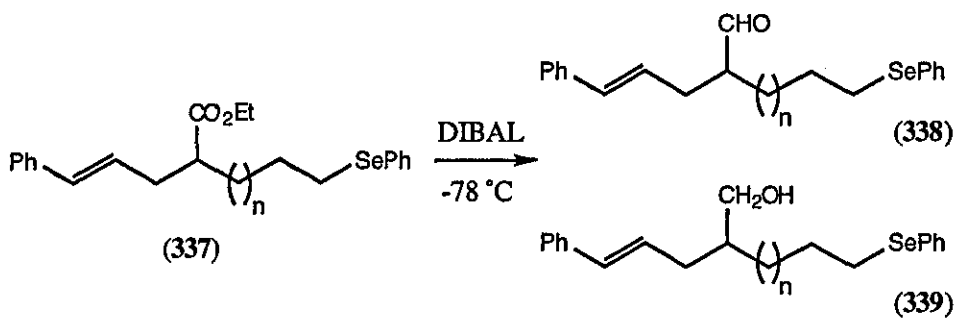
(336) (337)

The general procedure for hydrolytic decarboxylation using lithium chloride in DMSO was used. The diester (**336a**) (1.02 g, 2.2 mmol), lithium chloride (2 equiv.) and water (1.2 equiv.) in refluxing DMSO yielded *ethyl 5-benzeneselenyl-2-(3-phenyl-2-propen-1-yl)pentanoate* (**337a**) as a red oil (834 mg, 96%); ν_{max} 3070, 2932, 1731 (ester), 1652 (alkene), 1603 (Ph), 1579 (PhSe), 1478, 1438, 1160, 1073, 1023, 966, 739, and 692 cm^{-1}; δ_H (300 MHz) 7.46-7.50 (2 H, m, ortho-H), 7.23-7.30 (8 H, m, Ar-H), 6.42 (1 H, d, J = 14.6 Hz, alkene H), 6.07 (1 H, dt, J = 14.6, 7.3 Hz, alkene H), 4.16 (2 H, q, J = 7.2 Hz, CH_2O), 2.92 (2 H, t, J = 7.2 Hz, CH_2Se), 2.52 (2 H, dd, J = 7.3,7.2 Hz, allylic H), 1.98-2.05 (1 H, m, 2-H), 1.61-1.82 (4 H, m), and 1.23 (3 H, t, J = 7.2 Hz, Me); δ_C (75 MHz) 175.20 (C=O), 132.53, 132.00, 128.96, 128.42, 127.11, 126.86, 126.73, 126.02 (alkene and Ar-CH), 131.41, 130.15 (Ar-C), 60.27 (CH_2O), 44.08 (CH), 35.64, 31.77, 27.80,

27.39 (CH_2), and 14.26 (Me); *m/z* 402.1097 [M^+, (4.0%), $C_{22}H_{26}O_2Se$ requires 402.1098], 157 ($PhSe^+$, 28), 129 (33), 127 (80), 91 (83), 77 (Ph^+, 47), and 51 (100).

Ethyl 6-benzeneselenyl-2-(3-phenyl-2-propen-1-yl)hexanoate (337b), n = 2.
The general procedure for hydrolytic decarboxylation using lithium chloride in DMSO was used. The diester (**336b**) (1.08 g, 2.2 mmol), lithium chloride (2 equiv.) and water (1.2 equiv.) in refluxing DMSO yielded *ethyl 6-benzeneselenyl-2-(3-phenyl-2-propen-1-yl)hexanoate* (**337b**) as a red oil (895 mg, 98%); ν_{max} 3057, 2933, 2860, 1737 (ester), 1652 (alkene), 1599 (Ph), 1579 (PhSe), 1478, 1438, 1177, 1073, 1023, 967, 737, and 692 cm^{-1}; δ_H (300 MHz) 7.48-7.52 (2 H, m, ortho-H), 7.26-7.32 (8 H, m, Ar-H), 6.43 (1 H, d, J = 14.6 Hz, alkene H), 6.15 (1 H, dt, J = 14.6, 7.3 Hz, alkene H), 4.16 (2 H, q, J = 7.2 Hz, CH_2O), 2.92 (2 H, t, J = 7.2 Hz, CH_2Se), 2.45-2.49 (2 H, m, allylic H), 1.84-1.86 (1 H, m, 2-H), 1.67-1.73 (2 H, m), 1.44-1.56 (4 H, m), and 1.25 (6 H, t, J = 7.2 Hz, Me); δ_C (75 MHz) 175.51 (C=O), 132.40, 131.96, 128.93, 128.41, 127.06, 126.62, 126.12, 125.99 (alkene and Ar-CH), 131.41, 130.15 (Ar-C), 60.20 (CH_2O), 45.66 (CH), 35.64, 31.17, 29.89, 27.52, 27.39 (CH_2), and 14.29 (Me); *m/z* 416.1347 [M^+, (4.0%), $C_{23}H_{28}O_2Se$ requires 416.1254], 204 (17), 157 ($PhSe^+$, 26), 130 (53), 117 ($PhC_3H_4^+$, 97), 91 ($C_7H_7^+$, 100), 83 (64), and 77 (62).

Reduction of Ester (337a).



The general procedure for the synthesis of aldehydes was used. The ester (**337a**) (300 mg, 0.75 mmol) and diisobutylaluminium hydride (398 mg, 2.8 mmol) were reacted over 1.25 h yielding *5-benzeneselenyl-2-(3-phenyl-2-propen-1-yl)pentanal* (**338a**) as an orange oil (147 mg, 55%) and *5-benzeneselenyl-2-(3-phenyl-2-propen-1-yl)pentan-1-ol* (**339a**) as a yellow oil (59 mg, 22%).
Aldehyde (**338a**): ν_{max} 3070, 2928, 2856, 2725, 1723 (C=O), 1640 (alkene), 1579 (PhSe), 1478, 1438, 1073, 1023, 968, 737, and 692 cm^{-1}; δ_H (300 MHz) 9.68 (1 H, s, CHO), 7.48-7.52 (2 H, m, ortho-H), 7.26-7.32 (8 H, m, Ar-H), 6.45 (1 H, d, J = 15.6 Hz, cinnamyl 3-H), 6.16 (1 H, dt, J = 15.6, 7.8 Hz, cinnamyl 2-H), 2.94 (2 H, t, J = 7.4 Hz, CH_2Se), 2.44-2.54 (2 H, m, allylic H), 2.25-2.29 (1 H, m, 2-H), and 1.50-1.90 (4 H, m); δ_C (75 MHz) 203.26 (C=O), 132.62, 132.40, 128.96, 128.45, 128.15, 126.84, 126.04, 125.22 (alkene and Ar-CH), 131.41, 130.20 (Ar-C), 51.26 (2-C), 32.11, 28.18, 27.50, and

27.29 (CH_2); *m/z* 358.0826 [M^+, (2.3%), $C_{20}H_{22}OSe$ requires 358.0836], 199 (M^+-H-PhSeH, 19), 171 ($PhSeCH_2^+$, 14), 157 ($PhSe^+$, 38), 129 (13), 117 ($PhC_3H_4^+$, 55), 91 ($C_7H_7^+$, 100), and 77 (63).

Alcohol (**339a**): ν_{max} 3380 (OH), 3071, 2928, 2860, 1640 (alkene), 1603, 1579 (PhSe), 1478, 1438, 1236, 1073, 1023, 967, 737, and 692 cm^{-1}; δ_H (300 MHz) 7.48-7.52 (2 H, m, ortho-H), 7.26-7.32 (8 H, m, Ar-H), 6.45 (1 H, d, J = 15.6 Hz, cinnamyl 3-H), 6.16 (1 H, dt, J = 15.6, 7.8 Hz, cinnamyl 2-H), 3.59 (2 H, d, J = 4.9 Hz, CH_2O), 2.94 (2 H, t, J = 7.4 Hz, CH_2Se), 2.26-2.29 (2 H, m, allylic H), 2.17 (1 H, s, OH), 1.95-2.07 (1 H, m, 2-H), 1.66-1.85 (2 H, m), and 1.44-1.53 (2 H, m); δ_C (75 MHz) 132.44, 131.57, 128.95, 128.43, 128.14, 126.96, 126.66, 125.90 (alkene and Ar-CH), 131.30, 130.20 (Ar-C), 65.12 (CH_2O), 40.38 (2-C), 34.59, 30.72, 28.00, and 27.46 (CH_2); *m/z* 360.1010 [M^+, (3.5%), $C_{20}H_{24}OSe$ requires 360.1010], 342 (M^+-H_2O, 9), 184 (22), 169 (19), 157 ($PhSe^+$, 23), 143 (31), 129 (27), 117 ($PhC_3H_4^+$, 87), 91 ($C_7H_7^+$, 100), and 77 (23).

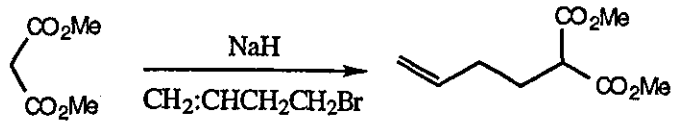
Reduction of Ester (337b).

The general procedure for the synthesis of aldehydes was used. The ester (**337b**) (300 mg, 0.72 mmol) and diisobutylaluminium hydride (398 mg, 2.8 mmol) were reacted over 1.25 h yielding *6-benzeneselenyl-2-(3-phenyl-2-propen-1-yl)hexanal* (**338b**) as an orange oil (93 mg, 35%) and *6-benzeneselenyl-2-(3-phenyl-2-propen-1-yl)hexan-1-ol* (**339b**) as a yellow oil (87 mg, 33%).

Aldehyde (**338b**): ν_{max} 3057, 2929, 2857, 2721, 1723 (C=O), 1640 (alkene), 1578 (PhSe), 1478, 1438, 1073, 1023, 967, 737, and 692 cm^{-1}; δ_H (300 MHz) 9.68 (1 H, s, CHO), 7.47-7.51 (2 H, m, ortho-H), 7.26-7.32 (8 H, m, Ar-H), 6.45 (1 H, d, J = 15.4 Hz, (cinnamayl 3-H), 6.18 (1 H, dt, J = 15.4, 7.7 Hz, cinnamyl 2-H), 2.91 (2 H, t, J = 7.3 Hz, CH_2Se), 2.36-2.47 (2 H, m, allylic H), 2.01-2.05 (1 H, m, 2-H), and 1.33-1.82 (6 H, m); δ_C (75 MHz) 204.19 (C=O), 132.22, 131.47, 128.94, 128.44, 128.15, 126.70, 126.01, 125.89 (alkene and Ar-CH), 131.23, 130.10 (Ar-C), 51.35 (2-C), 34.63, 32.14, 29.97, 27.73, and 26.96 (CH_2); *m/z* 372.0985 [M^+, (3.0%), $C_{21}H_{24}OSe$ requires 372.0992], 213 (M^+-PhSeH-H, 3), 157 ($PhSe^+$, 21), 129 (17), 117 ($PhC_3H_4^+$, 90), 91 ($C_7H_7^+$, 100), and 77 (44).

Alcohol (**339b**): ν_{max} 3380 (OH), 2928, 2860, 1640 (alkene), 1603, 1578 (PhSe), 1477, 1437, 1236, 1073, 1023, 968, 737, and 692 cm^{-1}; δ_H 7.47-7.50 (2 H, m, ortho-H), 7.25-7.30 (8 H, m, Ar-H), 6.42 (1 H, d, J = 16 Hz, cinnamyl 3-H), 6.26 (1 H, dt, J = 16, 7.0 Hz, cinnamyl 2-H), 3.59 (2 H, d, J = 4.9 Hz, CH_2O), 2.93 (2 H, t, J = 7.1 Hz, CH_2Se), 2.24-2.30 (2 H, m, allylic H), 2.06 (1 H, s, OH), 1.65-1.85 (3 H, m), and 1.31-1.52 (4 H, m); δ_C (100 MHz) 132.91, 131.97, 129.55, 129.01, 128.86, 127.39, 127.06, 126.37, (alkene and Ar-CH), 131.30, 130.40 (Ar-C), 65.75 (CH_2O), 41.19 (2-C), 35.14, 30.70, 30.50, 28.23, and 27.45 (CH_2); *m/z* 374.1160 [M^+, (2.0%), $C_{21}H_{26}OSe$ requires 374.1160], 356 (M^+-H_2O, 4), 199 (4), 183 (5), 157 ($PhSe^+$, 20), 143 (21), 117 ($PhC_3H_4^+$, 100), 91 ($C_7H_7^+$, 73), and 77 (20).

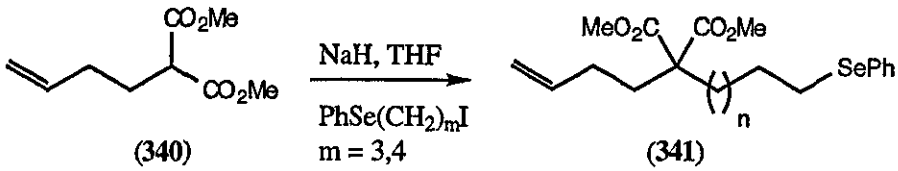
Dimethyl (3-buten-1-yl)propanedioate (340).



(340)

The general procedure for the 2-alkylation of propanedioate esters was used. Dimethyl propanedioate (4.752 g, 36 mmol), sodium hydride (960 mg, 36 mmol) and 4-bromo-1-butene 4.32 g, 32 mmol) yielded *dimethyl 2-(3-buten-1-yl)propanedioate* (**340**) as a colourless oil (5.135g, 77%); (Found: C, 56.5; H, 7.51. $C_9H_{14}O_4$ requires C, 58.1; H, 7.58%); ν_{max} 2979, 2957, 1736 (ester), 1643 (alkene),1438, 1374, 1283, 1156, 1026, and 918 cm^{-1}; δ_H (300 MHz) 5.74-5.78 (1 H, 3-H), 5.00-5.03 (2 H, m, 4-H), 3.74 (6 H, s, Me), 3.40 (1 H, t, J = 8.0 Hz, malonate 2-H), and 1.99-2.12 (4 H, m, 1,2-H); δ_C (75 MHz) 171.12 (C=O), 136.62 (3-C), 115.94 (4-C), 52.39 (MeO), 50.72 (malonate 2-C), 31.17, and 27.78 (butenyl 1,2-C); *m/z* 187.0970 [M^+, (49%), $C_9H_{14}O_4$ requires 187.0970], 161 (12), 150 (23), 94 (14), 86 (13), 74 (37), 58 (31), and 52 (100).

Dimethyl (3-benzeneselenylpropyl)(3-buten-1-yl)propanedioate (341a), n = 1.



(340) (341)

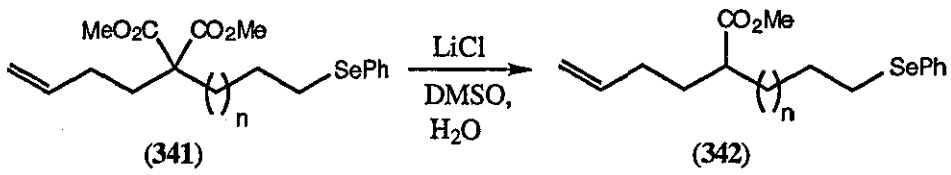
The general procedure for the 2-alkylation of propanedioate esters was used. Dimethyl (3-buten-1-yl)propanedioate (**340**) (1.12 g, 6 mmol), sodium hydride (240 mg, 6 mmol) and 1-benzeneselenyl-3-iodopropane (1.96 g, 6 mmol) yielded *dimethyl (3-benzene-selenylpropyl)(3-buten-1-yl)propanedioate* (**341a**) as an orange oil (1.937 g, 84%); ν_{max} 3073, 2952, 1735 (ester), 1641 (alkene), 1579 (PhSe), 1479, 1438, 1247, 1156, 1023, 738, and 692 cm^{-1}; δ_H (300 MHz) 7.47-7.49 (2 H, m, ortho-H), 7.23-7.26 (3 H, m, Ar-H), 5.70-5.76 (1 H, m, butenyl 3-H), 4.97-5.01 (2 H, m, butenyl 4-H), 3.69 (6 H, s, Me), 2.90 (2 H, t, J = 6.9 Hz, CH_2Se), 1.92-2.09 (6 H, m), and 1.54-1.61 (2 H, m); δ_C (75 MHz) 172.02 (C=O), 137.24 (alkene CH), 132.60 (Ar-CH), 130.15 (Ar-C), 128.96, 126.80 (Ar-CH), 115.06 (alkene CH_2), 57.19 (quaternary C), 52.32 (MeO), 32.53, 31.68, 28.27, 27.61, and 24.52 (CH_2); *m/z* 384.0840 [M^+, (17%), $C_{18}H_{24}O_4Se$ requires 384.0839], 227 (M^+-PhSe, 100), 195 (16), 173 (19), 157 ($PhSe^+$, 115), and 107 (44).

Dimethyl (4-benzeneselenylbutyl)(3-buten-1-yl)propanedioate (341b), n = 2.

The general procedure for the 2-alkylation of propanedioate esters was used. Dimethyl

(3-buten-1-yl)propanedioate (**340**) (1.12 g, 6 mmol), sodium hydride (160 mg, 4 mmol) and 1-benzeneselenyl-4-iodobutane (2.04 g, 6 mmol) yielded *dimethyl (4-benzeneselenyl-butyl)(3-buten-1-yl)propanedioate* (**341b**) as an orange oil (1.907 g, 80%); ν_{max} 3073, 2952, 2861, 1736 (ester), 1642 (alkene), 1579 (PhSe), 1479, 1437, 1265, 1156, 1023, 737, and 691 cm^{-1}; δ_H (300 MHz) 7.45-7.48 (2 H, m, ortho-H), 7.21-7.25 (3 H, m, Ar-H), 5.73-5.78 (1 H, m, butenyl 3-H), 4.97-5.00 (2 H, m, butenyl 4-H), 3.72 (6 H, s, Me), 2.90 (2 H, t, J = 7.0 Hz, CH_2Se), 1.85-2.00 (6 H, m), 1.66-1.75 (2 H, m), and 1.25-1.33 (2 H, m); δ_C (75 MHz) 171.92 (C=O), 137.34 (alkene CH), 132.61 (Ar-CH), 130.15 (Ar-C), 128.93, 126.72 (Ar-CH), 115.03 (alkene CH_2), 57.15 (quaternary C), 52.30 (MeO), 31.86, 31.58, 30.01, 28.32, 27.30, and 24.07 (CH_2); *m/z* 398.0996 [M^+, (12%), $C_{19}H_{26}O_4Se$ requires 398.0996], 344 (11), 284 (9), 227 (23), 213 (30), 157 ($PhSe^+$, 65), 123 (63), 77 (86), and 55 ($MeC_3H_4^+$, 100).

Methyl 5-benzeneselenyl-2-(3-buten-1-yl)pentanoate (342a), n = 1.



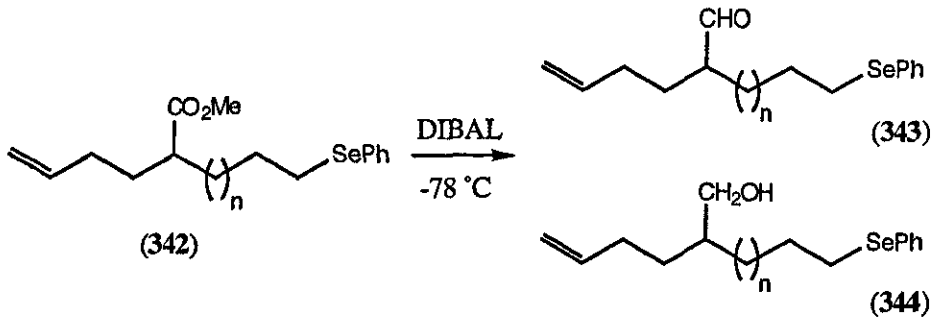
The general procedure for hydrolytic decarboxylation using lithium chloride in DMSO was used. The diester (**341a**) (1.75 g, 4.6 mmol), lithium chloride (2 equiv.) and water (1.2 equiv.) in refluxing DMSO yielded *methyl 5-benzeneselenyl-2-(3-buten-1-yl)-pentanoate* (**342a**) as a red viscous oil (1.24 g, 83%); ν_{max} 3074, 2931, 2857, 1739 (ester), 1640 (alkene), 1579 (PhSe), 1478, 1437, 1243, 1162, 1073, 1023, 735, and 691 cm^{-1}; δ_H (300 MHz) 7.48-7.50 (2 H, m, ortho-H), 7.24-7.27 (3 H, m, Ar-H), 5.73-5.76 (1 H, m, butenyl 3-H), 4.97-5.00 (2 H, m, butenyl 4-H), 3.67 (3 H, s, Me), 2.91 (2 H, t, J = 7.0 Hz, CH_2Se), 2.33-2.39 (1 H, m, 2-H), 2.01-2.06 (2 H, m), and 1.55-1.77 (6 H, m); δ_C (75 MHz) 176.43 (C=O), 137.71 (alkene CH), 132.54 (Ar-CH), 130.15 (Ar-C), 128.94, 126.72 (Ar-CH), 115.09 (alkene CH_2), 51.36 (MeO), 44.31 (CH), 32.20, 31.40, 27.74, 27.65, and 27.41 (CH_2); *m/z* 326.0785 [M^+, (13%), $C_{16}H_{22}O_2Se$ requires 326.0785], 169 (M^+-PhSe, 100), 157 ($PhSe^+$, 50), 109 (82), 91 (35), 77 (Ph^+, 48), 67 (74), 55 ($MeC_3H_4^+$, 70), and 41 (74).

Methyl 6-benzeneselenyl-2-(3-buten-1-yl)hexanoate (342b), n = 2.

The general procedure for hydrolytic decarboxylation using lithium chloride in DMSO was used. The diester (**341b**) (1.53 g, 3.9 mmol), lithium chloride (2 equiv.) and water (1.2 equiv.) in refluxing DMSO yielded *methyl 6-benzeneselenyl-2-(3-buten-1-yl)-hexanoate* (**342b**) as a red oil (1.09 g, 83%); ν_{max} 3073, 2933, 2857, 1735 (ester), 1639 (alkene), 1579 (PhSe), 1478, 1438, 1166, 1073, 1023, 737, and 691 cm^{-1}; δ_H (300 MHz) 7.46-7.49 (2 H, m, ortho-H), 7.24-7.27 (3 H, m, Ar-H), 5.74-5.79 (1 H, m, butenyl 3-H),

4.97-5.01 (2 H, m, butenyl 4-H), 3.68 (6 H, s, Me), 2.91 (2 H, t, J = 7.0 Hz, CH_2Se), 2.33-2.37 (1 H, m, 2-H), 2.03-2.06 (2 H, m), and 1.38-1.78 (8 H, m); δ_C (75 MHz) 176.59 (C=O), 137.70 (alkene CH), 132.40 (Ar-CH), 130.15 (Ar-C), 128.92, 126.62 (Ar-CH), 115.03 (alkene CH_2), 51.35 (MeO), 44.72 (CH), 31.69, 31.59, 31.40, 29.91, 27.49, and 24.40 (CH_2); *m/z* 340.0944 [M^+, (8.7%), $C_{17}H_{24}O_2Se$ requires 340.0941], 213 (19), 157 ($PhSe^+$, 34), 123 (43), 91 (38), 69 (42), and 55 ($MeC_3H_4^+$, 100).

Reduction of Ester (342a).



The general procedure for the synthesis of aldehydes was used. The ester (**342a**) (300 mg, 0.9 mmol) and diisobutylaluminium hydride (498 mg, 3.5 mmol) were reacted over 2 h yielding *5-benzeneselenyl-2-(3-buten-1-yl)pentan-1-ol* (**344a**) (168 mg, 61%) and *5-benzeneselenyl-2-(3-buten-1-yl)pentanal* (**343a**) (71 mg, 26%), both colourless oils. Unsuccessful attempts were made to increase to yield of aldehyde (**343a**) by using smaller amounts of reducing agent.

Aldehyde (**343a**): ν_{max} 2929, 2857, 2725, 1716 (C=O), 1643 (alkene), 1579 (PhSe), 1478, 1437, 1239, 1091, 1073, 1023, 737, and 691 cm^{-1}; δ_H 9.57 (1 H, s, CHO), 7.44-7.50 (2 H, m, ortho-H), 7.24-7.29 (3 H, m, Ar-H), 5.72-5.77 (1 H, m, butenyl 3-H), 4.94-5.04 (2 H, m, butenyl 4-H), 2.93 (2 H, t, J = 7.0 Hz, CH_2Se), 2.18-2.21 (1 H, m, 2-H), 2.01-2.07 (2 H, m), 1.65-1.73 (4 H, m), and 1.40-1.57 (2 H, m); δ_C (100 MHz) 205.02 (C=O), 137.92 (alkene CH), 133.04 (Ar-CH), 130.25 (Ar-C), 129.47, 127.20 (Ar-CH), 115.95 (alkene CH_2), 51.03 (2-C), 32.68, 31.43, 30.42, 27.91, and 27.72 (CH_2); *m/z* 296.0676 [M^+, (9.4%), $C_{15}H_{20}OSe$ requires 296.0679], 199 (15), 185 (10), 171 ($PhSeCH_2^+$, 14), 157 ($PhSe^+$, 57), 109 (23), 91 (48), 77 (Ph^+, 61), 67 (62), and 41 ($C_3H_5^+$, 100).

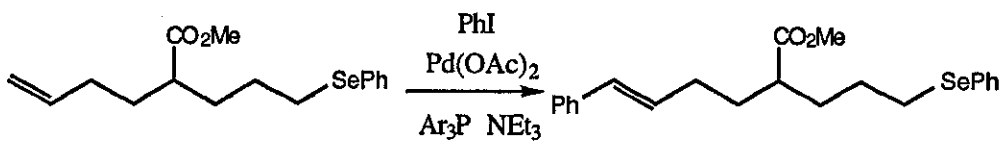
Alcohol (**344a**): ν_{max} 3370 (OH), 3078, 2929, 2857, 1639 (alkene), 1579 (PhSe), 1478, 1438, 1073, 1023, 999, 910, 737, and 691 cm^{-1}; δ_H (300 MHz) 7.46-7.49 (2 H, m, ortho-H), 7.22-7.27 (3 H, m, Ar-H), 5.75-5.79 (1 H, m, butenyl 3-H), 4.97-5.01 (2 H, m, butenyl 4-H), 3.54 (2 H, d, J = 6.5 Hz, CH_2O), 2.92 (2 H, t, J = 6.9 Hz, CH_2Se), 2.03-2.06 (2 H, m, allylic H), 1.71-1.75 (2 H, m, 2-H, OH), 1.35-1.57 (6 H, m); δ_C (75 MHz) 138.70 (alkene CH), 132.43 (Ar-CH), 130.15 (Ar-C), 128.95, 126.66 (Ar-CH), 114.50 (alkene CH_2), 65.07 (CH_2O), 39.40 (2-C), 30.96, 30.82, 29.91, 28.12, and 27.22 (CH_2);

m/z 298.0839 [M^+, (7.4%), $C_{15}H_{22}OSe$ requires 298.0836], 184 (9), 158 ($PhSe^+$, 29), 123 (17), 91 (26), 81 ($C_5H_5O^+$, 77), 67 (54), and 41 ($C_3H_5^+$, 100).

Reduction of Ester (342b).

The general procedure for the reduction of the ester group using DIBAL-H was used. The ester (**342b**) (600 mg, 1.76 mmol) and diisobutylaluminium hydride (996 mg, 7.0 mmol) were reacted over 2 h yielding *6-benzeneselenyl-2-(3-buten-1-yl)hexan-1-ol* (**344b**) as a colourless oil (372 mg, 68%). Unsuccessful attempts were made to synthesise aldehyde (**343b**) by using smaller amounts of reducing agent; ν_{max} 3380 (OH), 2928, 2856, 1640 (alkene), 1579 (PhSe), 1477, 1438, 1073, 1023, 735, and 691 cm^{-1}; δ_H (300 MHz) 7.47-7.50 (2 H, m, ortho-H), 7.22-7.26 (3 H, m, Ar-H), 5.77-5.82 (1 H, m, butenyl 3-H), 4.97-5.00 (2 H, m, butenyl 4-H), 3.56 (2 H, d, J = 6.5 Hz, CH_2O), 2.93 (2 H, t, J = 7.0 Hz, CH_2Se), 2.07-2.11 (2 H, m, allylic H), 1.85 (1 H, br s, OH), 1.71-1.74 (1 H, m, 2-H), 1.29-1.65 (8 H, m); δ_C (75 MHz) 138.45 (alkene CH), 132.38 (Ar-CH), 130.10 (Ar-C), 128.96, 126.60 (Ar-CH), 113.16 (alkene CH_2), 65.14 (CH_2O), 39.70 (2-C), 31.02, 30.33, 30.15, 29.96, 27.75, and 26.86 (CH_2); *m/z* 312.0999 [M^+, (1.7%), $C_{16}H_{24}OSe$ requires 312.0992], 172 (18), 158 ($PhSeH^+$, 34), 91 (34), 77 (Ph^+, 50), 67 (38), and 55 ($MeC_3H_4^+$, 100).

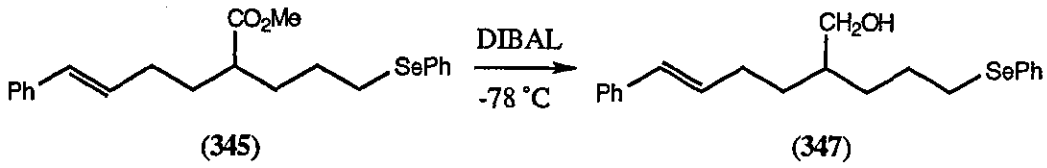
Methyl 5-benzeneselenyl-2-(4-phenyl-3-buten-1-yl)pentanoate (345).



(342) (345)

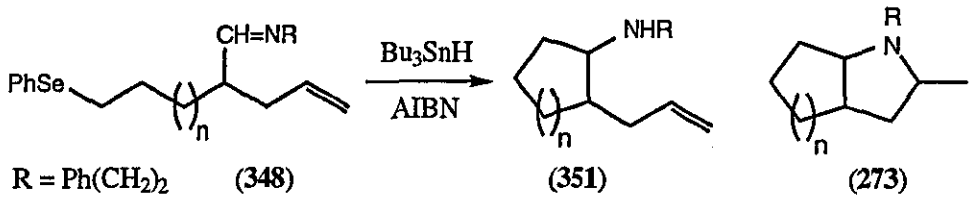
The general procedure for Heck reactions was used. The ester (**342a**) (247 mg, 0.73 mmol), iodobenzene (149 mg, 0.73 mmol) and triethylamine (200 mg, 2 mmol) in the presence of palladium acetate (7 mg, 0.03 mmol) and tri-*o*-tolylphosphine (16 mg, 0.06 mmol) yielded *methyl 5-benzeneselenyl-2-(4-phenyl-3-buten-1-yl)pentanoate* (**345**) as a red oil (263 mg, 87%); ν_{max} 3057, 2934, 2858, 1723 (ester), 1655 (alkene), 1599 (Ph), 1579 (PhSe), 1478, 1438, 1159, 1073, 1023, 967, 738, and 693 cm^{-1}; δ_H 7.46-7.49 (2 H, m, ortho-H), 7.24-7.32 (8 H, m, Ar-H), 6.38 (1 H, d, J = 15.6 Hz, alkene H), 6.19 (1 H, dt, J = 15.6, 7.8 Hz, alkene H), 3.66 (3 H, s, Me), 2.91 (2 H, t, J = 7.7 Hz, CH_2Se), 2.15-2.40 (3 H, m), 1.62-1.80 (4 H, m), and 1.33-1.43 (4 H, m); δ_C 175.01 (C=O), 132.46, 132.13, 128.94, 128.60, 128.41, 128.10, 126.89, 125.90 (alkene and Ar-CH), 131.41, 130.40 (Ar-C), 62.38 (MeO), 44.94 (CH), 32.62, 31.85, 30.83, 29.94, 27.53, and 27.22 (CH_2); *m/z* 416.1254 [M^+, (0.6%), $C_{23}H_{28}O_2Se$ requires 416.1254], 234 (32), 157 ($PhSe^+$, 34), 154 (100), 115 (28), 91 (52), 77 (76), and 55 (96).

Reduction of Ester (345).



The general procedure for the synthesis of aldehydes was used. The ester (**345**) (219 mg, 0.53 mmol) and diisobutylaluminium hydride (299 mg, 2.1 mmol) were reacted over 1.25 h yielding *5-benzeneselenyl-2-(4-phenyl-3-buten-1-yl)pentan-1-ol* (**347**) as a pale yellow oil (158 mg, 77%); ν_{max} 3530, 3058, 2929, 2857, 1655 (alkene), 1603 (Ph), 1579 (PhSe), 1478, 1437, 1073, 1023, 966, 737, and 692 cm^{-1}; δ_H 7.46-7.49 (2 H, m, ortho-H), 7.24-7.32 (8 H, m, Ar-H), 6.38 (1 H, d, J = 15.6 Hz, alkene H), 6.19 (1 H, dt, J = 15.6, 7.8 Hz, alkene H), 3.66 (3 H, s, Me), 2.91 (2 H, t, J = 7.7 Hz, CH_2Se), 2.15-2.40 (3 H, m), 1.62-1.80 (4 H, m), and 1.33-1.43 (4 H, m); δ_C 175.01 (C=O), 132.46, 132.13, 128.94, 128.60, 128.41, 128.10, 126.89, 125.90 (alkene and Ar-CH), 131.41, 130.40 (Ar-C), 62.38 (MeO), 44.94 (CH), 32.62, 31.85, 30.83, 29.94, 27.53, and 27.22 (CH_2); *m/z* 388.1293 [M^+, (3.4%), $C_{22}H_{28}OSe$ requires 388.1305], 213 (77), 158 ($PhSeH^+$, 15), 154 (22), 131 (30), 117 ($PhC_3H_4^+$, 48), 91 ($C_7H_7^+$, 100), 77 (37), and 55 (46).

Cyclisation of Imine (348a), n = 1.



The aldehyde (**333a**) (189 mg, 0.67 mmol) and 2-phenylethylamine (81 mg, 0.67 mmol) were dissolved in toluene (20 cm^3) and stirred at room temperature over 4 Å molecular sieves for 24 h. The imine was not isolated and was cyclised using the general procedure. Injection by syringe pump of Bu_3SnH (0.3 cm^3, 0.9 mmol) and AIBN (56 mg, 0.34 mmol) in toluene to the refluxing solution of the imine in toluene (100 cm^3) gave 130 mg of the crude amine products, which were dissolved in diethyl ether (10 cm^3) and treated with acetyl chloride and triethylamine. The acylated product (**351a**) was separated from bicyclic amine (**273a**) by acid extraction. Both compounds were purified by column chromatography using TLC alumina as absorbent and light petroleum / ethyl acetate mixtures as eluent. *N-Acetyl-N-(2-phenylethyl)-2-(2-propen-1-yl)cyclopentyl-amine* (**351a**) was isolated as a light yellow oil (42 mg, 23%). *3-Methyl-2-(2-phenyl-ethyl)-2-azabicyclo[3.3.0]octane* (**273a**) was isolated as an orange oil which slowly darkened (41 mg, 27%).

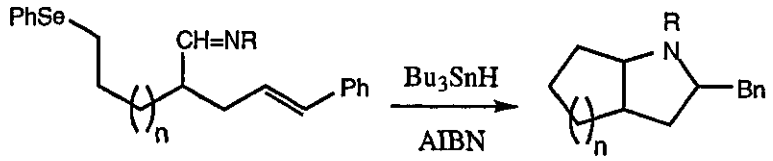
Amide (**351a**): ν_{max} 3054, 2958, 2873, 1637 (alkene), 1668, 1603 (Ph), 1453, 1422, and 916 cm^{-1}; δ_H (300 MHz) 7.18-7.32 (5 H, m, phenyl H), 5.74-5.78 (1 H, m, allyl 2-H), 5.02-5.06 (2 H, m, allyl 3-H), 3.71-3.73 (1 H, m, CHN), 3.41-3.44 (2 H, m, CH_2N), 2.90 (2 H, t, J = 7.5 Hz, CH_2Ph), 2.36-2.40 (1 H, m, cyclopentyl 2-H), 2.27-2.31 (2 H, m, allylic H), 2.09 (3 H, s, Ac), and 1.33-1.96 (6 H, m); δ_C (75 MHz) 176.85 (C=O), 138.80 (Ar-C), 135.85 (alkene CH), 128.66, 128.52, 126.45 (Ar-CH), 116.46 (alkene CH_2), 65.08 (cyclopentyl 1-C), 44.50 (CH_2N), 41.95 (CH), 37.29, 34.64, 29.37, 29.13, 21.56 (CH_2), and 21.30 and 20.71 (MeCO); *m/z* 271.1938 [M^+, (2.7%), $C_{18}H_{25}NO$ requires 271.1936], 180 (M^+-,C_7H_7, 46), 138 (MH^+-C_7H_7-Ac, 100), 105 ($MeC_7H_6^+$, 21), 77 (10), 67 (29), and 43 (31, $MeCO^+$).
Amine (**273a**): ν_{max} 2936, 1670, 1603 (Ph), 1455, 1373, 749, and 699 cm^{-1}; δ_H (300 MHz) 7.17-7.32 (5 H, m, phenyl H), 3.49-3.52 (1 H, m, 1-H), 2.81-2.85 (2 H, m, CH_2N), 2.60-2.64 (2 H, m, CH_2Ph), 2.39-2.46 (1 H, m, 5-H), 1.41-1.77 (8 H, m, 4,6,7,8-H), and 1.01 (3 H, d, J = 6.8 Hz, Me); δ_C (75 MHz) 140.80 (Ar-C), 128.56, 128.23, 125.87 (Ar-CH), 66.64 (1-C), 56.31 (3-C), 51.22 (CH_2N), 40.45 (CH_2Ph), 39.77 (5-C), 35.57, 33.52, 29.01, 25.21 (CH_2), and 15.47 (Me); *m/z* (C.I.) 230.1909 [MH^+, (11%), $C_{16}H_{24}N$ requires 230.1910], 164 (12), 138 (M^+-C_7H_7, 11), 122 (19), 108 (18), 98 (29), 78 (PhH^+, 35), 58 (77), and 44 ($MeCH{=}NH_2^+$, 100).

Cyclisation of imine (348a) in the presence of magnesium dibromide.
The procedure for the cyclisation of imine (**348a**) (174 mg, 0.45 mmol) was repeated with the addition of $MgBr_2.OEt_2$ (129 mg, 0.5 mmol) prior to the addition of Bu_3SnH. Injection of Bu_3SnH (0.16 cm^3, 0.6 mmol) and AIBN (25 mg, 0.15 mmol) yielded amine (**273a**) (36 mg, 35%) as an orange oil which was found to be identical to the amine produced above.

Cyclisation of Imine (348b), n = 2.
Exactly the same procedure was used as for imine (**348a**). The imine, formed by condensing aldehyde (**333b**) (197, 0.67 mmol) and 2-phenylethylamine (81 mg, 0.67 mmol), was cyclised using the standard procedure. Injection of Bu_3SnH (0.3 cm^3, 0.9 mmol) and AIBN (56 mg, 0.34 mmol) in toluene using a syringe pump yielded 136 mg of crude product mixture. *N-Acetyl-N-(2-phenylethyl)-2-(2-propen-1-yl)cyclohexylamine* (**351b**) was isolated as a yellow oil (34 mg, 18%). *2-Methyl-1-(2-phenylethyl)perhydro-indoline* (**273b**) was isolated as an orange oil which slowly darkened (54 mg, 33%).
Amide (**351b**): ν_{max} 3054, 2932, 2860, 1663, 1639 (alkene), 1605 (Ph), 1455, 1429, 1125, 1028, and 803 cm^{-1}; δ_H (300 MHz) 7.18-7.28 (5 H, m, phenyl H), 5.70-5.74 (1 H, m, allyl 2-H), 5.00-5.05 (2 H, m, allyl 3-H), 3.54 (2 H, m, CH_2N), 3.18-3.23 (1 H, m, CHN), 2.84 (2 H, t, J = 7.5 Hz, CH_2Ph), 2.38-2.42 (1 H, m, cyclohexyl 2-H), 2.30-2.36 (2 H, m, allylic H), 2.11 (3 H, s, Ac), and 1.29-1.70 (8 H, m); δ_C (75 MHz) 176.93 (C=O), 137.54 (Ar-C), 133.23 (alkene CH), 128.64, 127.43, 126.50 (Ar-CH), 113.09

(alkene CH_2), 51.03 (cyclopentyl 1-C), 40.94 (CH_2N), 32.63 (CH), 35.22, 34.14, 33.24, 27.91, 26.75, 26.55 (CH_2), and 22.65 and 20.75 (MeCO); *m/z* 285.2072 [M^+, (1.2%), $C_{19}H_{27}NO$ requires 285.2072], 245 (13), 197 (39), 152 (MH^+-C_7H_7-Ac, 36), 135 (74), 105 ($MeC_7H_6^+$, 62), 97 (52), 81 (48), 55 (60), and 43 (Ac^+, 100).
Amine (**273b**): ν_{max} 2928, 2857, 1653, 1605 (Ph), 1542, 1456, 749, and 699 cm^{-1}; δ_H (300 MHz) (2 stereoisomers) 7.18-7.32 (5 H, m, phenyl H), 3.66.3.70 (1 H, m, 7a-H), 3.26-3.30 (1 H, m, 2-H), 2.85-2.88 (2 H, m, CH_2N), 2.70-2.74 (2 H, m, CH_2Ph), 2.45-2.48 (1 H, m, 3a-H), 2.27-2.30 (2 H, m), 1.45-1.75 (8 H, m), and 1.01 and 1.06 (3 H, 2 x d, J = 6.8 Hz, Me); δ_C (75 MHz) 140.46 (Ar-C), 128.57, 128.44, 128.32 (Ar-CH), 66.46 (7a-C), 59.96 (2-C), 50.01 (CH_2N), 38.74 (CH_2Ph), 35.28 (3a-C), 34.54, 28.82, 26.25, 24.73, 21.02 (CH_2), and 18.13 (Me); *m/z* 243.1981 [M^+, (0.5%), $C_{17}H_{25}N$ requires 243.1987], 242 (M^+-H, 1), 152 (M^+-C_7H_7, 100), 105 ($MeC_7H_6^+$, 15), 91 ($C_7H_7^+$, 21), 77 (Ph^+, 13), and 41 ($C_3H_5^+$, 46).

Cyclisation of Imine (352a), n = 1.



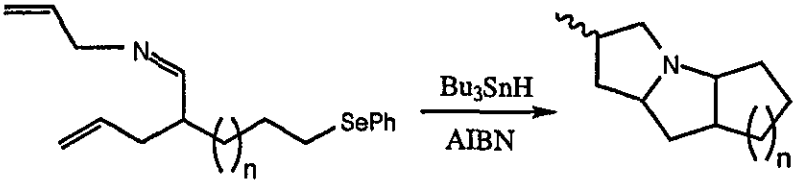
R = n-Pr (352) (353)

The aldehyde (**338a**) (246 mg, 0.69 mmol) and *n*-propylamine (80 mg, 1.35 mmol) were dissolved in toluene (20 cm^3) and stirred at room temperature over 4 Å molecular sieves for 24 h. The imine was not isolated and was cyclised using the general procedure. Injection of Bu_3SnH (0.32 cm^3, 0.92 mmol) and AIBN (39 mg, 0.23 mmol) in toluene using a syringe pump yielded *3-benzyl-2-propyl-2-azabicyclo[3.3.0]octane* (**353a**) as a yellow oil (67 mg, 40%); ν_{max} 2957, 2930, 2872, 1639, 1603 (Ph), 1453, 1125, 1074, 1023, 747, and 700 cm^{-1}; δ_H (300 MHz) 7.22-7.32 (5 H, m, phenyl H), 2.96-3.04 (1 H, m, 1-H), 2.73-2.77 (1 H, m, 3-H), 2.55-2.60 (2 H, m, CH_2N), 2.33-2.43 (2 H, m, CH_2Ph), 1.34-1.99 (11 H, m), 0.91 (3 H, t, J = 7.6 Hz, Me); δ_C (75 MHz) 137.76 (Ar-C), 129.05, 128.39, 125.84 (Ar-CH), 64.35 (1-C), 50.44 (CH_2N), 46.02 (3-C), 38.02 (CH_2), 32.37 (5-C), 30.76, 29.46, 25.45, 23.01, 22.78 (CH_2), and 11.73 (Me); *m/z* 243.1987 [M^+, (3.1%), $C_{16}H_{23}N$ requires 243.1987], 242 (M^+-H, 3), 229 (24), 214 (M^+-Et, 36), 152 (M^+-C_7H_7, 88), 105 ($MeC_7H_6^+$, 26), 91 ($C_7H_7^+$, 51), and 41 ($C_3H_5^+$, 100).

Cyclisation of Imine (352b).
The aldehyde (**338b**) (130 mg, 0.35 mmol) and *n*-propylamine (50 mg, 0.85 mmol) were dissolved in toluene (20 cm^3) and stirred at room temperature over 4 Å molecular sieves for 24 h. The imine was not isolated and was cyclised using the general procedure. Injection of Bu_3SnH (0.13 cm^3, 0.47 mmol) and AIBN (20 mg, 0.12 mmol) in toluene

using a syringe pump yielded *2-benzyl-1-propylperhydroindoline* (**353b**) as a yellow oil (52 mg, 57%); ν_{max} 2954, 2925, 2857, 1644, 1603 (Ph), 1455, 1065, 1031, 740, and 700 cm^{-1}; δ_H (300 MHz) (2 stereoisomers) 7.21-7.29 (5 H, m, phenyl H), 3.01-3.11 and 3.41-3.45 (1 H, 2 x m, 7a-H), 2.92-2.97 (1 H, m, 2-H), 2.56-2.67 (2 H, m, CH_2Ph), 2.29-2.33 (1 H, m, 3a-H), 1.45-1.75 (12 H, m), and 0.92 (3 H, t, J = 7.6 Hz, Me); δ_C (75 MHz) 140.46 (Ar-C), 128.57, 128.44, 128.32 (Ar-CH), 66.46 (7a-C), 59.96 (2-C), 50.01 (CH_2N), 38.74 (CH_2Ph), 35.28 (3a-C), 34.54, 28.82, 26.25, 24.73, 21.02 (CH_2), and 18.13 (Me); *m/z* 257.2131 [M^+, (1.7%), $C_{17}H_{25}N$ requires 257.2143], 256 (M^+-H, 1), 228 (M^+-Et, 8), 214 (M^+-Pr, 7), 166 (M^+-C_7H_7, 100), 122 (5), 91 ($C_7H_7^+$, 21), and 43 ($C_3H_7^+$, 20).

Attempted cyclisation of the Imine formed from the Aldehyde (333a) and allylamine, (n = 1).



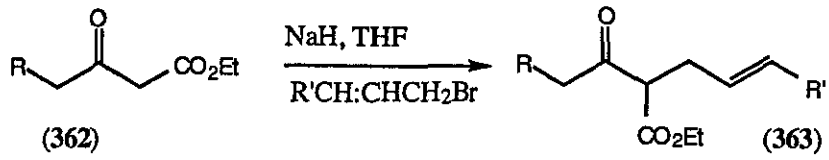
(359)

The aldehyde (**333a**) (195 mg, 0.7 mmol) and 2-propen-1-ylamine (57 mg, 1.0 mmol) were dissolved in toluene (20 cm^3) and stirred at room temperature over 4 Å molecular sieves for 24 h. The imine was not isolated but was cyclised using the general procedure. Injection of Bu_3SnH (0.33 cm^3, 0.93 mmol) and AIBN (38 mg, 0.23 mmol) in toluene yielded 53 mg recovered material. Though ^1H NMR and mass spectrum evidence indicate the possible formation of saturated polycyclic amine (**359a**), no positive identification could be made; δ_H (300 MHz) 4.11-4.16 (m), 3.69-3.75 (m), 2.88-2.92 (m), 2.75-2.79 (m), 2.31-2.40 (m), 1.33-1.81 (m), 1.06 and 1.02 (2 x d, J = 7.0 Hz, Me); *m/z* 165.1056 [M^+, (5.0%), $C_{17}H_{25}N$ requires 165.1517], 151 (MH^+-Me, 19), 136 (M^+-Et, 15), 113 (24), 95 (22), 91 (30), 81 (27), 67 (34), 57 (46), and 41 ($C_3H_5^+$, 100).

Attempted cyclisation the Imine formed from the Aldehyde (333b) and allylamine, (n = 2).

The aldehyde (**333b**) (175 mg, 0.6 mmol) and 2-propen-1-ylamine (57 mg, 1.0 mmol) were dissolved in toluene (20 cm^3) and stirred at room temperature over 4 Å molecular sieves for 24 h. The imine was not isolated but was cyclised using the general procedure. Injection of Bu_3SnH (0.28 cm^3, 0.8 mmol) and AIBN (33 mg, 0.2 mmol) in toluene yielded 42 mg recovered material. Though ^1H NMR and mass spectrum evidence indicate the possible formation of saturated polycyclic amine (**359b**), no positive identification could be made; δ_H (300 MHz) 3.18-3.40 (2 x m), 2.95-3.01 (m), 1.95-2.20, 1.62-1.82, and 1.30-1.47 (m), and 1.08 and 1.15 (2 x d, J = 6.5 Hz, Me); *m/z* (C.I.) 180 (MH^+, 100%).

Ethyl 2-acetyl-4-pentenoate (363a), R = R' = H.



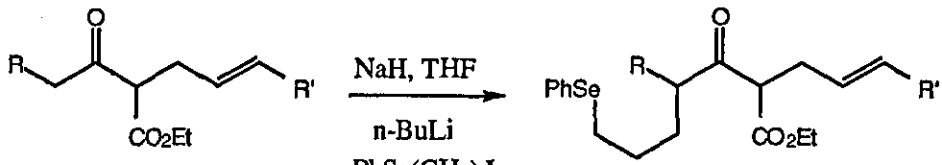
(362) (363)

The general procedure for the 2-alkylation of 3-oxoalkanoate esters was used. Ethyl 3-oxobutanoate (**362a**) (7.8 g, 60 mmol), sodium hydride (2.0 g, 50 mmol) and 3-bromopropene (4.8 g, 40 mmol) in THF (20 cm^3), gave, after purification by short path distillation, *ethyl 2-acetyl-4-pentenoate* (**363a**) as a colourless oil (6.4 g, 94%); ν_{max} 3070, 2984, 2935, 1741 (ester CO), 1717 (ketone CO), 1643 (C=C), 1439, 1360, 1158, 1025, 999, and 922 cm^{-1}; δ_H 5.68-5.75 (1 H, m, 4-H), 5.02-5.13 (2 H, m, 5-H), 4.19 (2 H, q, J = 7.7 Hz, CH_2O), 3.51 (1 H, t, J = 7.4 Hz, 2-H), 2.59 (2 H, dd, J = 7.3, 7.4 Hz, 3-H), 2.22 (3 H, s, MeCO), and 1.26 (3 H, t, J = 7.7 Hz, Me); δ_C 205.30 (ketone CO), 169.40 (ester CO), 134.12 (4-C), 117.33 (5-C), 61.31 (CH_2O), 59.13 (2-C), 32.06 (3-C), 28.99 (MeCO), and 13.99 (Me); *m/z* 170.0942 [M^+, (3.3%), $C_9H_{14}O_3$ requires 170.0943], 171 (MH^+, 59), 127 (M^+-Ac, 52), 97 (M^+-EtOCO, 28), 83 (34), 69 (23), 55 (38), and 43 (Ac^+, 100).

Ethyl 2-propanoyl-4-heptenoate (363b), R = Me, R' = Et.

The general procedure for the 2-alkylation of 3-oxoalkanoate esters was used. Ethyl 3-oxopentanoate (**362b**) (1.15 g, 8 mmol), sodium hydride (320 mg, 8 mmol) and 1-bromo-2-pentene (1.0 g, 6.7 mmol) in THF (10 cm^3), gave, after purification by short path distillation, *ethyl 2-propanoyl-4-heptenoate* (**363b**) as a colourless oil (1.38 g, 97%); ν_{max} 2968, 2923, 1745 (ester CO), 1720 (ketone CO), 1655 (C=C), 1462, 1369, 1178, 1032, and 970 cm^{-1}; δ_H 5.40-5.49 and 5.20-5.29 (2 H, 2 x m, 4,5-H), 4.09 (2 H, q, J = 7.6 Hz, CH_2O), 3.39 (1 H, t, J = 7.3 Hz, 2-H), 2.42-2.49 (4 H, m, 3,6-H), 1.86-1.90 (2 H, m, CH_2CO), 1.15 (3 H, t, J = 7.6 Hz, CH_3CH_2O), 0.97 (3 H, t, J = 7.0 Hz, CH_3CH_2CO), and 0.85 (3 H, t, J = 7.7 Hz, 7-H); δ_C 205.33 (ketone CO), 169.34 (ester CO), 135.10, 124.40 (4,5-C), 61.10 (CH_2O), 58.71 (2-C), 35.40 (3-C), 31.15, 25.25 (CH_2), 13.93, 13.57, and 7.34 (Me); *m/z* 212.1413 [M^+, (4.0%), $C_{12}H_{20}O_3$ requires 212.1412], 213 (MH^+, 36), 167 (M^+-EtO, 11), 155 (M^+-Ac, 52), 139 (M^+-EtOCO, 24), 127 (36), 109 (69), 57 ($EtCO^+$, 100), and 29 (Et^+, 97).

Ethyl 6-benzeneselenyl-3-oxo-2-(2-propen-1-yl)hexanoate (364a), R = H, R' = H.



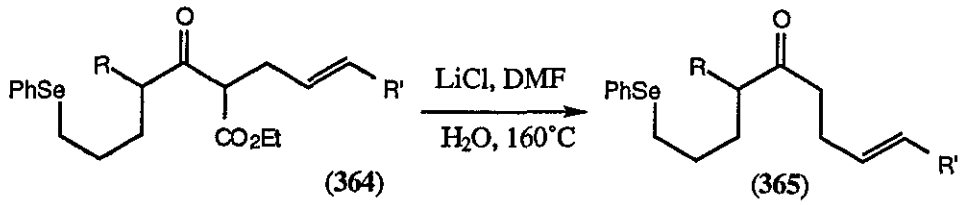
(363) (364)

The ester (**363a**) (850 mg, 5 mmol) in THF (5 cm^3) was added slowly to sodium hydride (200 mg, 5 mmol) at 0°C. When the evolution of hydrogen had stopped, the solution was cooled to -78°C and *n*-butyllithium (4 cm^3 of 1.3 M solution in hexanes) was added dropwise over 5 min. The solution was stirred at -78°C for 30 min before 1-benzene-selenyl-3-iodopropane (**227**) (1.625 g, 5 mmol) in THF (5 cm^3) was added slowly. The reaction was stirred at -78°C for 1 h and then at room temperature for 2 h. Ethanol (1 cm^3) was slowly added and the solvent remove by evaporation. The residue was treated with dilute hydrochloric acid (5 cm^3) and the products extracted into diethyl ether (5 x 10 cm^3), dried ($MgSO_4$) and evaporated to dryness. The unreacted starting materials were removed by short path distillation and the crude alkylated product purified by flash chromatography using silica as absorbent and light petroleum / ethyl acetate mixtures as eluent. *Ethyl 6-benzeneselenyl-3-oxo-2-(2-propen-1-yl)hexanoate* (**364a**) was isolated as a yellow oil (1.10 g, 60%); ν_{max} 2938, 1745 (ester CO), 1715 (ketone CO), 1641 (C=C), 1579 (PhSe), 1478, 1438, 1178, 1073, 1023, 737, and 692 cm^{-1}; δ_H 7.44-7.49 (2 H, m, o-H), 7.22-7.30 (3 H, m, Ar-H), 5.67-5.77 (1 H, m, allyl 2-H), 5.01-5.11 (2 H, m, allyl 3-H), 4.16 (2 H, q, J = 7.0 Hz, CH_2O), 3.51 (1 H, t, J = 7.5 Hz, 2-H), 2.99 (2 H, t, J = 7.7 Hz, 6-H), 2.86-2.92 (2 H, m, 5-H), 2.54-2.62 (2 H, dd, J = 7.2, 7.2 Hz, allylic H), 1.68-1.76 (2 H, m, 5-H), and 1.25 (3 H, t, J = 7.0 Hz, Me); δ_C 204.90 (ketone CO), 169.65 (ester CO), 134.21 (4-C), 132.21 (Ar-CH), 130.20 (Ar-C), 128.97, 126.71 (Ar-CH), 117.42 (5-C), 61.35 (CH_2O), 58.39 (2-C), 41.42, 31.12, 29.39, 27.32, 23.40 (CH_2), and 14.06 (Me); *m/z* 368.0884 [M^+, (6.5%), $C_{18}H_{24}O_3Se$ requires 368.0890], 317 (4), 211 (M^+-PhSe, 19), 157 ($PhSe^+$, 38), 137 (46), 83 (59), and 55 (100).

Ethyl 7-benzeneselenyl-4-methyl-3-oxo-2-(pent-2*E*-en-1-yl)heptanoate (**364b**), R = Me, R' = Et.

The same procedure was employed as used for ester (**364a**). The ester (**363b**) (636 mg, 3 mmol) and sodium hydride (120 mg) *n*-butyllithium (2.3 cm^3) and 1-benzeneselenyl-3-iodopropane (**227**) (975 mg, 3 mmol) yielded the ester (**364b**) as an orange oil (603 mg, 49%); ν_{max} 2933, 2872, 1745 (ester CO), 1715 (ketone CO), 1641 (C=C), 1579 (PhSe), 1478, 1438, 1369, 1178, 1074, 1023, 970, 735, and 691 cm^{-1}; δ_H 7.44-7.52 (2 H, m, ortho-H), 7.22-7.27 (3 H, m, Ar-H), 5.47-5.51 and 5.29-5.33 (2 H, 2 x m, pentenyl 2,3-H), 4.19 (2 H, q, J = 7.2 Hz, CH_2O), 3.49 (1 H, t, J = 6.8 Hz, 2-H), 3.25-3.29 (1 H, m, 4-H), 2.97 (2 H, t, J = 7.0 Hz, 7-H), 2.49-2.57 (4 H, m), 1.95-2.05 (4 H, m), 1.25 (3 H, t, J = 7.0 Hz, CH_3CH_2O), 1.07 (3 H, d, J = 7.2 Hz, 4-Me), and 0.95 (3 H, t, J = 7.2 Hz, Me); δ_C 204.30 (ketone CO), 169.60 (ester CO), 136.61 (alkene CH), 132.64 (Ar-CH), 130.05 (Ar-C), 128.97, 126.81 (Ar-CH), 124.45 (alkene CH), 61.13 (CH_2O), 58.83 (2-C), 48.92 (4-C), 35.39, 31.20, 30.12, 25.42, 24.38 (CH_2), 14.04, 13.59, and 7.49 (Me); *m/z* 410.0341 [M^+, (0.3%), $C_{21}H_{30}O_3Se$ requires 410.1360], 213 (2), 199 (4), 185 (2), 157 ($PhSe^+$, 4), 155 (42), 139 (14), 127 (19), 57 (100), and 41 (52).

9-Benzeneselenylnon-1-en-5-one (365a), R = R' = H.



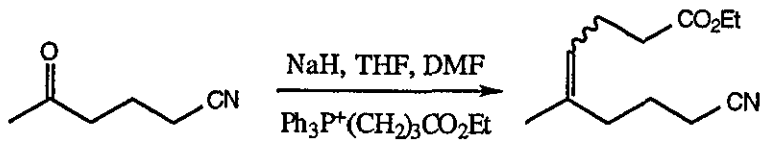
(364) (365)

The general procedure for hydrolytic decarboxylation using lithium chloride in DMF was used. The ester (**364a**) was refluxed in DMF for 24 h and yielded 9-benzeneselenylnon-1-en-5-one (**306a**) as an orange-red oil (654 mg, 85%) which was identical with that formed by the Swern oxidation of the alcohol (**305a**).

1-Benzeneselenyl-4-methylundec-8-en-5-one (365b), R = Me, R' = Et.

The general procedure for hydrolytic decarboxylation using lithium chloride in DMF was used. The ester (**364b**) was refluxed in DMF for 24 h and yielded *1-benzeneselenyl-4-methylundec-8-en-5-one* (**365b**) as a red oil (748 mg, 82%); ν_{max} 2933, 2872, 1715 (ketone CO), 1641 (C=C), 1579 (PhSe), 1478, 1438, 1369, 1073, 1023, 735, and 691 cm^{-1}; δ_H 7.45-7.48 (2 H, m, ortho-H), 7.23-7.27 (3 H, m, Ar-H), 5.40-5.46 (2 H, m, 8,9-H), 2.99 (2 H, t, J = 7.2 Hz, 11-H), 2.88-2.92 (1 H, m, 4-H), 2.25-2.40 (4 H, m), 1.97-2.08 (4 H, m), 1.62-1.72 (2 H, m), 1.05 (3 H, d, J = 7.2 Hz, 4-Me), and 0.95 (3 H, t, J = 7.0 Hz, 1-H); δ_C 203.60 (ketone CO), 136.49 (alkene CH), 132.65 (Ar-CH), 129.90 (Ar-C), 128.97, 126.75 (Ar-CH), 122.09 (alkene CH), 51.69 (4-C), 42.17, 35.88, 27.36, 26.80, 25.42 (CH_2), 13.71, and 7.69 (Me); *m/z* 338.1139 [M^+, (5.3%), $C_{18}H_{26}OSe$ requires 338.1149], 199 (15), 171 (10), 157 ($PhSe^+$, 30), 137 (M^+-PhSe-EtOCOH, 46), 113 (52), 91 (36), 77 (Ph^+, 45), 57 (100), and 41 ($C_3H_5^+$, 2).

Ethyl 8-cyano-5-methyloct-4-enoate (*E* and *Z*), (**369**).

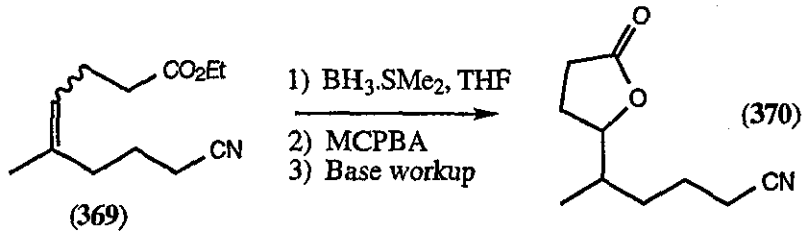


(239) (369)

The general procedure for the Wittig reaction was used. Phosphonium salt (**301a**) (8.0 g, 17.5 mmol), sodium hydride (800 mg, 20 mmol) and 5-oxohexanenitrile (**239**) in THF (50 cm^3) and DMF (5 cm^3) yielded *ethyl 8-cyano-5-methyloct-4-enoate* (**369**) as a pale yellow oil (1.76 g, 48%, 2 isomers: ratio 4 : 1); ν_{max} 2962, 2936, 2860, 2246 (CN), 1743 (C=O), 1686 (alkene), 1438, 1375, 1241, 1047, and 753 cm^{-1}; δ_H (2 stereoisomers) 5.38-5.45 (1 H, m) and 5.16-5.19 (1 H, m, 4-H), 4.12 (2 H, q, J = 7.0 Hz, CH_2O), 2.34 (3 H, s,

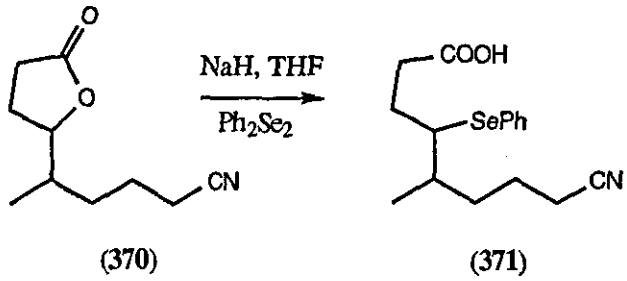
5-Me), 2.30-2.33 (2 H, t, J = 5.9 Hz, 2-H), 2.10-2.28 (4 H, m), 1.61-1.81 (4 H, m), and 1.24 (3 H, t, J = 7.0 Hz, Me); δ_C (2 stereoisomers) 173.60 (C=O), 134.04 (5-C), 125.21 and 124.56 (4-C), 119.80 (CN), 60.24 (CH_2O), 38.04, 34.35, 34.20, 30.38, 23.56, 23.24, 16.58, 16.14 (CH_2), 22.94 and 15.53 (5-Me), and 14.16 (Me); *m/z* 209.1409 [M^+, (19%), $C_{12}H_{19}NO_2$ requires 209.1416], 164 (M^+-EtO, 34), 135 (M^+-EtOCO-H, 86), 122 (M^+-$EtOCOCH_2$, 55), 95 (97), 88 (36), 81 (100), 67 (56), 55 (53), and 41 ($C_3H_5^+$, 97).

4-(5-Cyanopent-2-yl)butyrolactone (370).



The alkene (**369**) (1.0 g, 4.8 mmol) was dissolved in THF (50 cm^3) and was cooled to -78°C. Borane-dimethyl sulphide complex in THF (2.4 cm^3 of 1.0 M solution, 0.5 equiv.) was added dropwise and the mixture stirred for 1 h. On warming to 0°C, *m*-chloroper-benzoic acid (2 equiv.) was added in small portions, keeping a limit on the temperature rise and the mixture was stirred at room temperature for 16 h. Dilute sodium hydroxide was added and the products extracted into diethyl ether (5 x 20 cm^3). The combined ether extracts were washed with water (5 x 10 cm^3) and saturated salt solution (10 cm^3), dried ($MgSO_4$) and evaporated to dryness. The crude product was purified by flash sinter chromatography using silica as absorbent and light petroleum / ethyl acetate mixtures as eluent. *4-(5-Cyanopent-2-yl)butyrolactone* (**370**) was isolated as a colourless oil (504 mg, 58%); ν_{max} 3480, 2933, 2875, 2246 (CN), 1713 (C=O), 1436, 1376, 1303, 1145, and 944 cm^{-1}; δ_H 3.67-3.74 (1 H, m, C*H*O), 2.53 (2 H, t, J = 7.0 Hz, CH_2CN), 2.26-2.34 (4 H, m, 2,3-H), 1.65-1.79 (1 H, m, 2'-H), 1.57-1.62 (2 H, m), 1.42-1.47 (2 H, m), and 1.09 (3 H, d, J = 6.5 Hz, Me); δ_C 207.10 (C=O), 66.92 (CHO), 41.27, 37.72 (CH_2), 30.05 (CH), 23.60 (Me), 21.88, 19.33, and 17.11 (CH_2); *m/z* 181.1081 [M^+, (0.3%), $C_{10}H_{15}NO_2$ requires 181.1103], 180 (M^+-H, 0.3), 139 (7), 112 (9), 96 (M^+-$C_4H_5O_2$, 14), 69 (17), 55 (15), and 43 (100).

4-Benzeneselenyl-8-cyano-5-methyloctanoic acid (371).



The lactone (**370**) (450 mg, 2.49 mmol) was dissolved in THF and added dropwise to a cooled (-78°C) suspension of sodium benzeneselenide in THF, formed from sodium hydride (160 mg, 4 mmol) and diphenyl diselenide (780 mg, 2.5 mmol). The mixture was stirred for 4 h at room temperature and refluxed for 1 h. Methyl iodide (750 mg, 5 mmol) was added to the solution when cooled to room temperature and the mixture stirred overnight. The solvent was removed by evaporation and the residues dissolved in sodium hydroxide (1 M, 20 cm^3). The basic solution was washed with CH_2Cl_2 (5 x 10 cm^3), the organic layer dried and evaporated to dryness. The aqueous layer was acidified with dilute hydrochloric acid, extracted into ethyl acetate, dried ($MgSO_4$) and evaporated to dryness. Both compounds were purified by flash chromatography using silica as absorbent and light petroleum / ethyl acetate mixtures as eluent. Analysis of the first extract showed that none of the methyl ester was produced, the only isolable compound being methaneselenylbenzene (PhSeMe). Analysis of the second extract showed that *4-benzeneselenyl-8-cyano-5-methyloctanoic acid* (**371**) was produced and was isolated as a red oil (269 mg, 32%); ν_{max} 3420 (OH), 3056, 2948, 2872, 2247 (CN), 1728 (C=O), 1578 (PhSe), 1475, 1338, 1301, 1067, 1032, 739, and 690 cm^{-1}; δ_H 7.56-7.62 (2 H, m, o-H), 7.25-7.32 (3 H, m, Ar-H), 3.79-3.85 (1 H, m, 4-H), 3.56-3.61 (1 H, m, 5-H), 2.20-2.35 (4 H, m), 1.69-1.81 (4 H, m), 1.16-1.28 (2 H, m), and 0.66 and 0.76 (3 H, 2 x d, J = 6.5 Hz, Me); δ_C 175.37 (C=O), 134.59 (Ar-CH), 130.14 (Ar-C), 129.06, 128.06 (Ar-CH), 39.76 (5-C), 39.49, 35.34, 30.94 (CH_2), 23.90 (4-C), 17.42 (CH_2), and 14.14 (Me); *m/z* 353.0910 [M^+ (3.3%), $C_{17}H_{23}NO_2Se$ requires 353.0894], 233 (7), 215 (9), 196 (M^+-PhSe, 17), 185 (20), 157 ($PhSe^+$, 66), 113 (26), 91 (26), and 77 (Ph^+, 100).

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