Stereoselective synthesis using aminyl radicals derived from [alpha]-amino acids

Stereoselective Synthesis using Aminyl Radicals Derived from α-Amino Acids

by

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ABSTRACT

Chapter 1 is the introduction to the thesis. It contains an overview of amino acids and aminyl radicals. The amino acids section includes material on their synthesis through traditional methods and asymmetric syntheses, as well as the use of radical reactions in their formation. The aminyl radical section gives a description of the nature of the radical and then proceeds with general techniques for aminyl radical formation. A more detailed account of our own group's use of sulfenamides and imines in aminyl radical formation is covered and the chapter is ended with a look at the work of aminyl radicals in amino acid synthesis and my subsequent intentions in this area.

The preparation and cyclisation of sulfenamide precursors derived from α-amino acids is discussed in chapter 2. Both the cyclisations of aminyl and urethanyl (introduction of benzyloxycarbonyl and tosyl protecting groups onto amine) radicals onto suitably placed alkenyl substituents were investigated. 5-*Exo-trig* cyclisation reactions successfully afforded the cyclic products in moderate yield with reasonable diastereoselectivity. The effects of the α-CO_2R (where R = Me or ^tBu), the size of the amino acid side chain and placement of alkenyl substituent (*N*-substituted or side-chain containing alkene) are discussed.

The use of imines as aminyl radical precursors is explored in chapter 3. α-Amino acids and aldehydes were condensed and the cyclisation products isolated. The formation of aminyl radicals by 5-*exo-trig* cyclisation and subsequent H-atom abstraction gave moderate to good yields of *N*-cyclopentyl substituted α-amino acids. Preparation of the aldehydes is discussed.

Tandem cyclisations involving aspects of chapters 2 and 3 are looked at in chapter 4. The preparation of the unnatural α-amino acids required for tandem cyclisation and subsequent formation of the sulfenamide or imine is reported. 5-*Exo*, 6-*exo* cyclisation of the sulfenamide derivative gave the tandem product in low yield and with moderate diastereoselectivity. This was in contrast to the imine derived reaction which proved unsuccessful.

The remaining chapters incorporate the detailing of experimental relevant to the discussion and the presentation of references quoted throughout the thesis.

ACKNOWLEDGEMENTS

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CONTENTS

1.0 INTRODUCTION 1

1.1 Amino Acids 1
1.2 Standard Methods of Amino Acid Synthesis 1
1.3 Modern Stereoselective Synthesis of Amino Acids 2
1.3.1 Asymmetric Derivatization of Glycine 3
1.3.2 Homologation of the β-Carbon 5
1.3.3 Electrophilic Amination of Enolates 6
1.3.4 Nucleophilic Amination of α-Substituted Acids 6
1.3.5 Asymmetric Strecker Synthesis 6
1.3.6 Asymmetric Hydrogenation of α, β-Dehydroamino Acids 7
1.3.7 Enzymatic Syntheses of α-Amino Acids 8
1.4 Synthesis of Amino Acids using Radical Chemistry 8
1.4.1 α-Carbon Centred Radicals 8
1.4.2 Side Chain Manipulation 11
1.4.3 Miscellaneous Syntheses 13
1.5 Aminyl Radicals 16
1.5.1 General Methods of Aminyl Radical Generation 17
1.5.2 Sulfenamides as Aminyl Radical Precursors 29
1.5.3 Imines as Aminyl Radical Precursors 36
1.6 Synthesis of α-Amino Acids using Amino Acid Aminyl Radicals 39

2.0 THE PREPARATION AND CYCLISATION OF SULFENAMIDE DERIVATIVES OF α-AMINO ACIDS 42

2.1 Cyclisation onto Amino Acid Side Chains 42
2.1.1 Synthesis and Radical Reactions of Urethane Derived Sulfenamides 44
2.1.2 Synthesis and Radical Reactions of Urethane Derived α-Amino Ester Sulfenamides 47
2.1.3 Cyclisation of Urethanyl Radicals 51
2.1.4 Synthesis and Radical Reactions of *N*-(Benzenesulfenyl) -*L*-Phenylalanine Methyl Ester 53

2.1.5 Synthesis and Radical Reactions of *N*-Tosyl Derived Sulfenamides 54
2.1.6 Radical Reactions of α-Amino Ester Sulfenamides using Alkenyl Side Chains 56
2.2 Cyclisation onto *N*-Substituted Side Chains 58
2.2.1 Derivatisation of the α-Amino Acids 59
2.2.2 Cyclisation Reactions of the *N*-Alkylated Sulfenamide Precursors 69
2.3 Summary of the Results for the Sulfenamide Derivatives 75
2.3.1 Summary of the Amino Acid Side Chain Research 75
2.3.2 Summary of the *N*-Alkylated Amino Acid Research 76

3.0 THE PREPARATION AND GENERATION OF AMINYL RADICALS DERIVED FROM IMINE DERIVATIVES OF α-AMINO ACIDS 77

3.1 Preparation of ω-Benzeneselenyl Aldehydes 77
3.2 Synthesis and Cyclisation of the Imine Derivatives 78
3.3 Summary of the Results for the Imine Derivatives 85

4.0 TANDEM CYCLISATIONS UTILISING α-AMINO ACID DERIVATIVES 87

4.1 Tandem Cyclisations using Sulfenamide Derivatives 87
4.2 Tandem Cyclisations using Imine Derivatives 92
4.3 Summary of Results for Tandem Cyclisations 95

5.0 EXPERIMENTAL 96

5.1 General Information 96
5.2 Index of Experimental 97
5.3 Experimental for Chapter Two 102
5.4 Experimental for Chapter Three 152
5.5 Experimental for Chapter Four 162

6.0 REFERENCES 174

ABBREVIATIONS

abs.	=	absolute
Ac	=	acetyl
AIBN	=	azo*iso*butyronitrile
AMBN	=	azomethyl*iso*butyronitrile
BINAP	=	binapthol
Bn	=	benzyl
Boc	=	*tert*-butoxycarbonyl
bpy	=	bipyridyl
BTEAC	=	benzyltriethylammonium chloride
Bu	=	butyl
Cbz	=	benzyloxycarbonyl
CHIRAPHOS	=	bis(diphenylphosphino)butane
DCM	=	dichloromethane
d.e.	=	diastereomeric excess
DIBAL	=	di*iso*butylaluminium hydride
DKP	=	diketopiperazine
DMAD	=	dimethylazodicarboxylate
DMF	=	dimethylformamide
DNA	=	deoxyribose nucleic acid
e.e.	=	enantiomeric excess
Et	=	ethyl
GC	=	gas chromatography
GLC	=	gas liquid chromatography
HMPA	=	hexamethylphosphoramide
Me	=	methyl
MOM	=	methoxymethyl
MS	=	mass spectroscopy
NBS	=	*N*-bromosuccinimide
NCS	=	*N*-chlorosuccinimide
NMR	=	nuclear magnetic resonance
PCC	=	pyridinium chlorochromate
Ph	=	phenyl
Pr	=	propyl
PTOC	=	pyridinethioneoxycarbonyl
THF	=	tetrahydrofuran
TLC	=	thin layer chromatography

TMS	=	trimethylsilyl
Ts	=	*p*-tosyl
UV	=	ultraviolet

INTRODUCTION

Our initial plans for research were:

a) to develop the use of aminyl radicals derived from enantiomerically pure α-amino acids for stereoselective synthesis, and

b) to develop new synthetic methodologies using α-amino acid aminyl radicals.

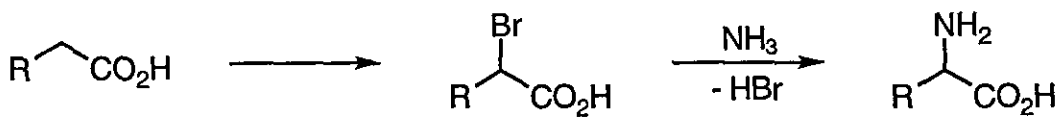
1.1 Amino Acids

α-Amino acids and monosaccharides are probably the most important chiral building blocks and chiral auxiliaries[1-3] available for the synthesis of chiral compounds. There are 20 naturally occurring proteinogenic (DNA encoded) α-amino acids (approaching 1000 non-proteinogenic) and these make up the peptides and proteins responsible for all biological processes. The interactions and inhibitions of the peptide chains of these amino acids have been thoroughly investigated. It follows that there are few aspects within the medical and agrochemical industries where the need for new amino acids is not of paramount importance.

1.2 Standard Methods of Amino Acid Synthesis[4,5]

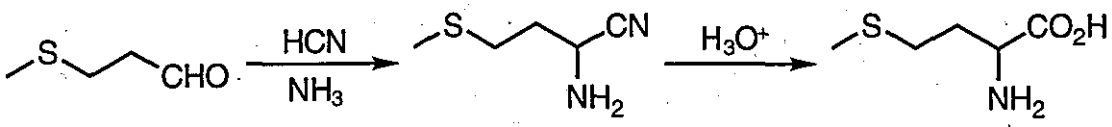
There are now over 500 synthetic amino acids and the synthesis of these has been carried out using several general methods such as:

i) Displacement reactions on α-halo acids. The simplest method involves conversion of a carboxylic acid into its α-bromo derivative (Hell-Volhard-Zelinsky procedure) and treatment with ammonia (Scheme 1). The conversion of α-bromo acid into α-amino acid gives better yields and purer compounds when employing the Gabriel procedure.



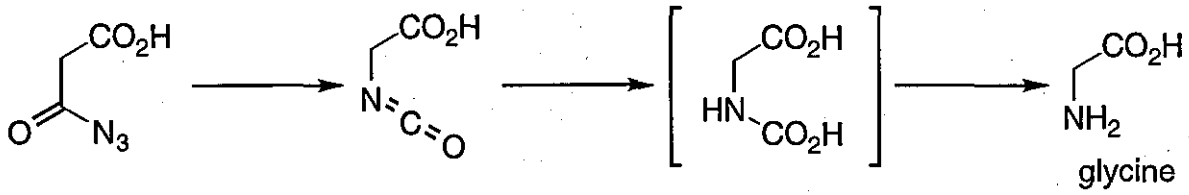
Scheme 1

ii) Strecker reaction. An intermediate α-aminonitrile, formed using a potassium cyanide/ammonium chloride mix, is hydrolysed with sulfuric acid, *e.g.* synthesis of methionine (Scheme 2),



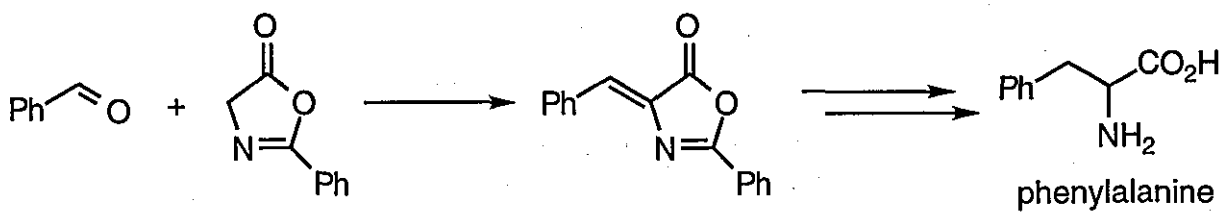
Scheme 2

iii) Curtius method. Acid azides obtained from malonic esters and derivatives of malonic esters undergo thermal rearrangement to isocyanates which, in the presence of water, react to form an amine *via* the unstable carbamic acid (Scheme 3).



Scheme 3

iv) Condensation methods. The aromatic-containing α-amino acids are usually prepared by Perkin-type reactions between aromatic aldehydes and the activated methylene groups of hydantoin and related cyclic compounds, *e.g.* the synthesis of phenylalanine (Scheme 4).



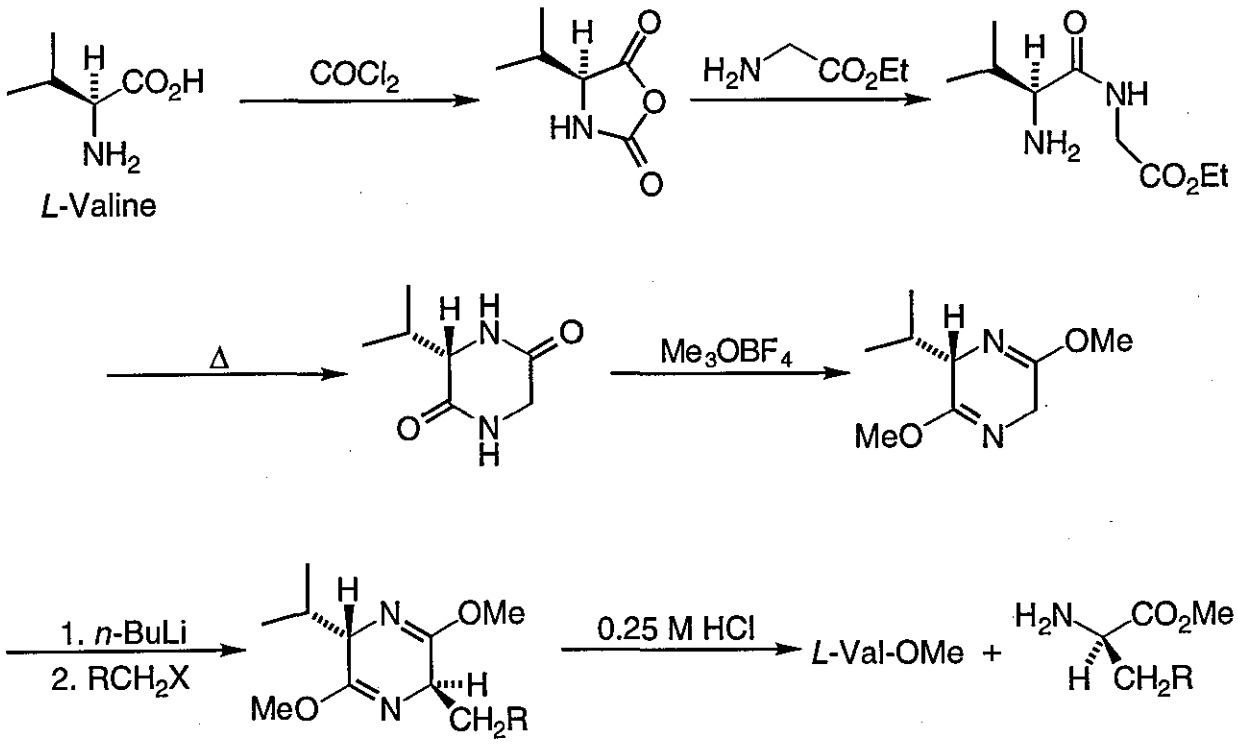
Scheme 4

With the importance of chirality within the amino acid and the need for new optically active amino acids of such high interest, chemists have applied themselves to finding further synthetic stereoselective methods.

1.3 Modern Stereoselective Synthesis of Amino Acids

The vast amount of literature available on this subject cannot be reviewed fully here.[2] As a consequence, a selection of methods have been categorised and described in brief detail.

1.3.1 Asymmetric Derivatization of Glycine

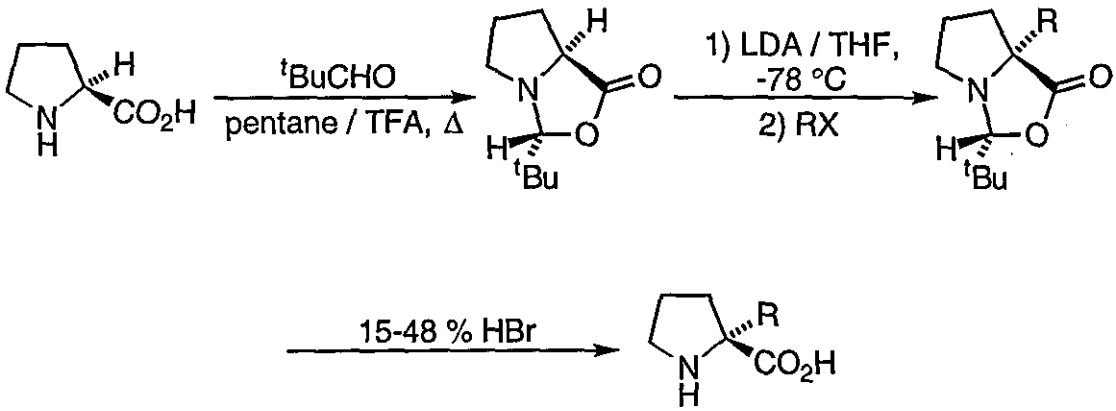


Scheme 5

Glycine derivatization offers, potentially, the greatest versatility for amino acid synthesis due to its simple structure and possible route to α, α-disubstituted amino acids. Schölkopf and workers[6] devised a very versatile method based on the metallation and subsequent alkylation of bis-lactim ethers. The general protocol involves diketopiperazide formation from two amino acids and subsequent bis-lactim production with trimethyloxonium tetrafluoroborate. The most popular bis-lactim ether is that derived from *L*-valine and glycine.[7] Metallation with *n*-butyllithium in THF at low temperature followed by alkylation with various electrophiles furnishes the *anti*-adducts with high *d.e.* (at least 80 %). The amino acid can then be obtained by hydrolytic cleavage of the heterocycle with dilute hydrochloric acid (Scheme 5).

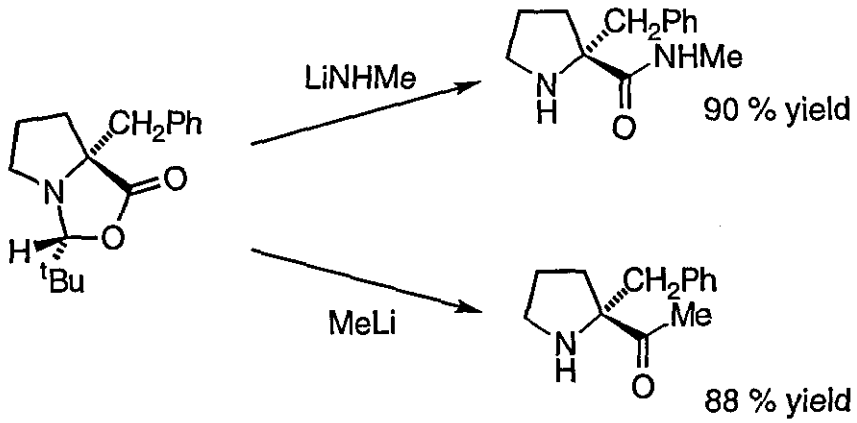
Various usage of chiral auxiliaries in the bis-lactims to increase asymmetric induction during alkylation found few advantages over the *L*-valine derivative. However, there were specific cases where alkylation or *d.e.* were so poor that a change in bis-lactim structure proved fruitful. For instance, with 3-bromopropyne, the *L*-valine/glycine derived bis-lactim gave a *d.e.* of 60-65 % compared with >95 % for the *L*-*tert*-leucine/glycine derivative (utilisation limited though by cost and availability of *L*-

tert-leucine).[8] Further examples for the use of bis-lactim ethers may be found in a review by Schölkopf[6].



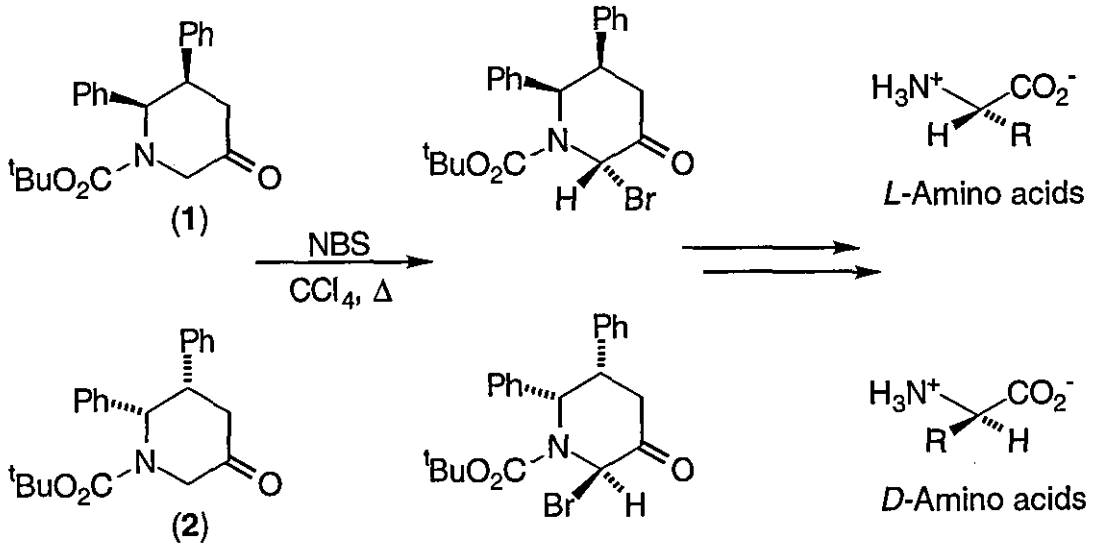
Scheme 6

Seebach and workers[9] have contributed to asymmetric amino acid synthesis with the formation of various cyclic aminals and subsequent enolate alkylation. The first reported system is shown in scheme 6.[10] By similarly functionalising imidazolidinones, oxazolidinones and oxazolines, a number of novel amino acids may be obtained. The major limitation to this method has been the difficulty in obtaining the free amino acids. Quite severe conditions are required (typically requiring 15-48 % HBr at ambient to reflux temperatures) and the bulkier the α-R residue, the harsher the acid conditions needed to cleave the aminal. Fortunately, the authors found that the aminal was opened by several richly nucleophilic reagents such as lithium amides or alkyl lithium reagents. The corresponding amides and ketones were formed (*e.g.* Scheme 7).



Scheme 7

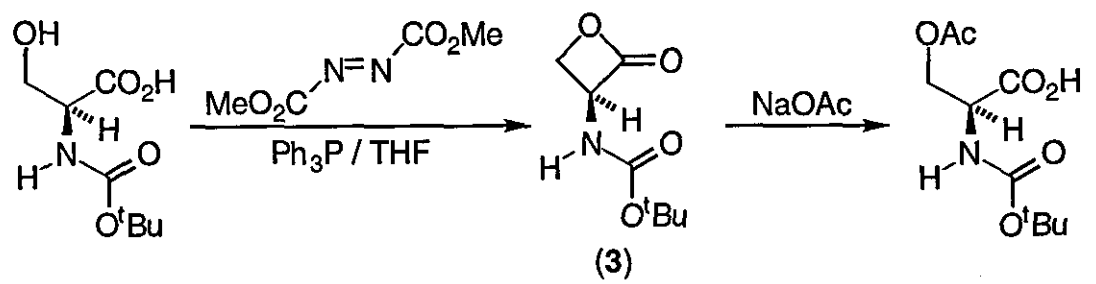
Alternatively, the use of an electrophilic glycine template has been investigated by R. M. Williams *et al.*[11] Prepared from benzoin and *L*-glutamic acid, the oxazinone templates formed **1** and **2** are brominated with NBS (anti stereochemistry, one diastereoisomer only) and reacted with various organometallics in the presence of zinc chloride. Deprotection gives access to either the *D*- or *L*-stereochemistry depending on the template originally used (Scheme 8).



Scheme 8

1.3.2 Homologation of the β-Carbon

Most approaches for homologation at the β-carbon use serine as a starting material but amino acids such as cysteine and aspartic acid may, in theory, also be used. Vederas and associates have investigated the preparation and ring-opening reactions of β-lactones derived from serine (Scheme 9).[12] It should be noted that the Ph_3P-DMAD complex was pre-formed to allow generation of the β-lactone in the absence of the free, nucleophilic Ph_3P.

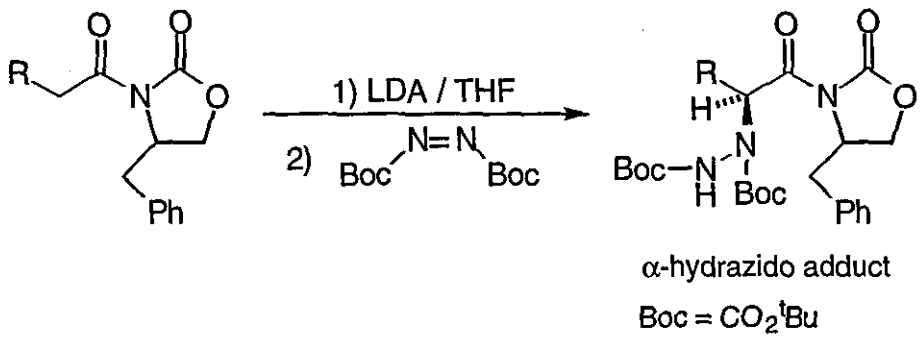


Scheme 9

A variation giving the free amino acids[13] directly involves removing the *tert*-butoxycarbonyl group from **3** with acid. The resultant salt readily adds very weak nucleophiles (such as trifluoroacetate), the yields are generally excellent (>80 %) and the diversity of nucleophiles is high (S, O, N, C and halogen included). The use of various organocuprates allows regiospecific addition at the β-methylene for C-C bond formation[14] but diprotection of the nitrogen, necessary for higher yields, causes a loss in optical purity for the product.

1.3.3 Electrophilic Amination of Enolates

Electrophilic amination of chiral enolates with azodicarboxylate esters (an electrophilic source of nitrogen) affords α-hydrazido adducts. These adducts can then be manipulated to give the desired amino acids. Evans and workers[15] applied this technique to chiral carboximide enolates (Scheme 10) to give the adducts in high yield (>90 %) and high *d.e.* (>90 %). The Boc groups are removed with trifluoroacetic acid and subsequent reduction with hydrogen on Raney-Nickel yields the α-amino acids.



α-hydrazido adduct

Boc = $CO_2{}^tBu$

Scheme 10

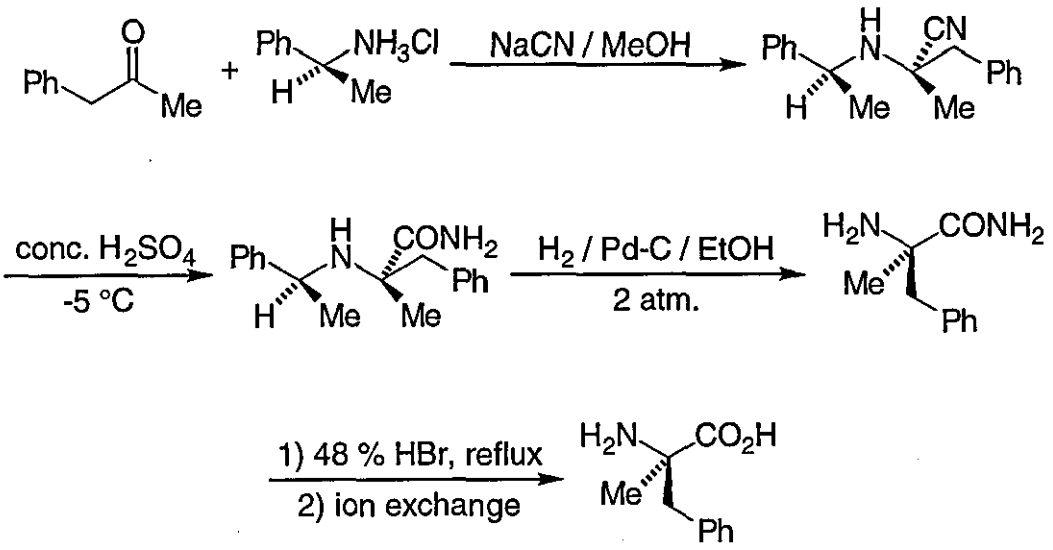
1.3.4 Nucleophilic Amination of α-Substituted Acids

In this case, the displacement of a leaving group α to a carboxylic acid results in the formation of the optically active amino acid or derivative. Once again, we can look to Evans and workers[16] where the formation of a chiral carboximide reacts with a boron triflate to give a di-*n*-butylboron enolate. Oxidation with NBS yielded the α-bromo derivative which could be displaced with azide before recovering the chiral auxiliary and producing the α-azido acid through hydrolysis. The α-amino acid can then be formed.

1.3.5 Asymmetric Strecker Synthesis

The basic concept involves the condensation of an optically active amine with an aldehyde forming a chiral Schiff base. Subsequent addition of HCN forms an optically

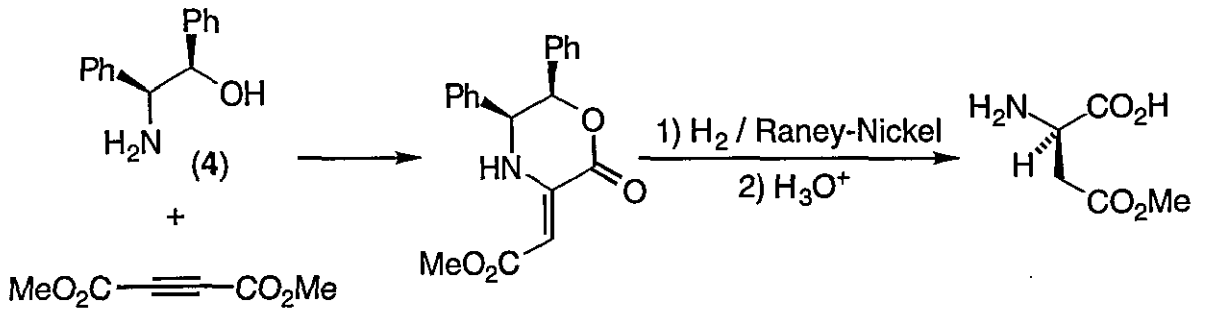
active α-amino nitrile which is then hydrolysed to the α-amino acid. The first asymmetric synthesis can be attributed to Harada[17] in 1963 (the formation of *L*-alanine in 17 % yield, 90 % optically pure) but the method has been vastly improved since then with much higher yields and *d.e.*'s. For instance, Subramanian and Woodward[18] used the method to synthesise optically pure α-methyl phenylalanine in 64 % overall yield and >98 % *e.e.* (Scheme 11).



Scheme 11

1.3.6 Asymmetric Hydrogenation of α, β-Dehydroamino Acids

There are two basic conceptual approaches here. The first is the heterogeneous hydrogenation of dehydroamino acids that contain an appended chiral auxiliary.[19] For instance, Kagan and workers[20] (Scheme 12) condensed the amino alcohol 4 with dimethylacetylene dicarboxylate. The resultant dehydro lactone was hydrogenated with Raney-Nickel and an acid work-up afforded *D*-β-methyl aspartate in high yield and *d.e.* (>98 %).



Scheme 12

The second approach involves the homogenous hydrogenation of achiral dehydroamino acids using optically active, soluble hydrogenation catalysts.[21] Modification of Wilkinson's olefin hydrogenation catalyst with optically active phosphine ligands (*e.g.* BINAP/CHIRAPHOS ligands) has been the main field of study.

1.3.7 Enzymatic Syntheses of α-Amino Acids

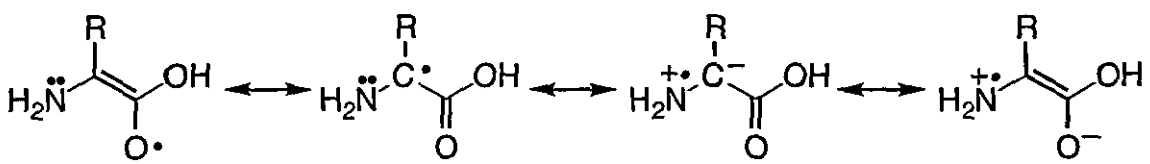
Syntheses of amino acids with purified, immobilized enzymes have become an important commercial method.[22] Enzymes can be used to resolve a racemic mixture (obtained from a cheap amino acid synthesis) or catalyze asymmetric bond-forming reactions on prochiral substrates. The two methods have been reviewed elsewhere.[23]

1.4 Synthesis of Amino Acids using Radical Chemistry

The application of radical reactions, especially those involving radical cyclisation of carbon-centred radicals, has also been at the forefront of the development of modern synthetic organic chemistry in recent years.[24,25] Radical cyclisation reactions and acyclic radical reactions can be carried out with full stereochemical control. The use of radicals in monosaccharide synthetic studies has been well developed by Giese[24] and others. Yet, there is little work on radicals in amino acid synthesis. It is therefore of no surprise that the combination of two important strands of modern synthesis, amino acids and radicals, is receiving increasing investigation.

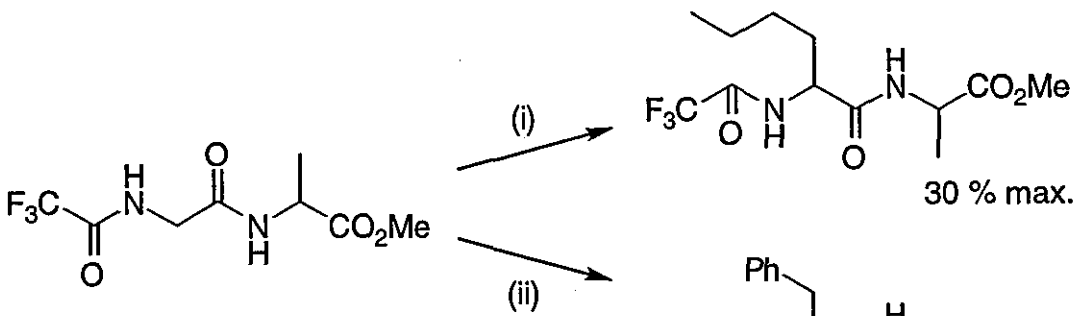
1.4.1 α-Carbon Centred Radicals

Much of the synthetic work investigated over past years has involved the utilisation of the stable α-carbon centred radical obtained from glycine derivatives. These radicals belong to the class of captodative radicals. Enhanced stability is achieved through the action of the electron-releasing amino substituent and the electron-withdrawing carboxy group (Scheme 13). A significant advantage of radical reactions is the possible high *d.e.*'s obtainable at a newly formed α-stereocentre.



Scheme 13

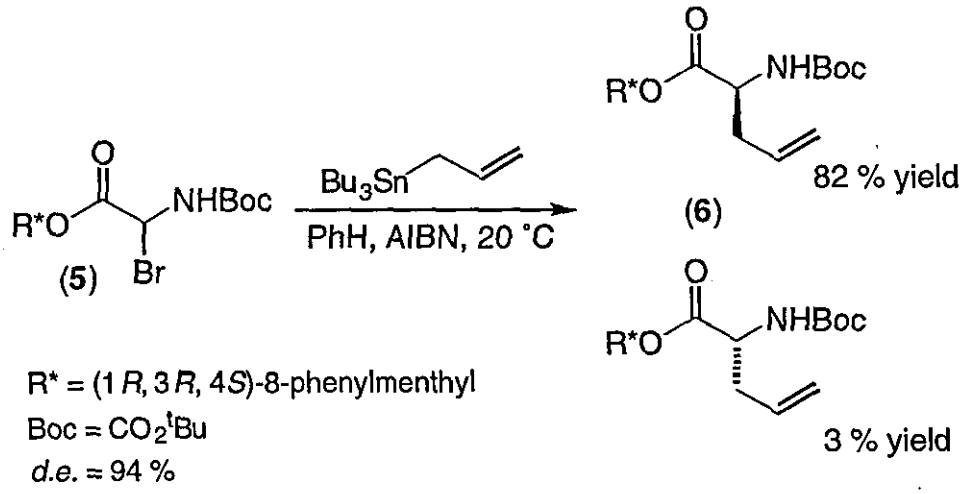
Elad and workers[26] pioneered the work of intermolecular hydrogen abstraction to give the α-carbon centred radical. Initially, the use of ultraviolet light to obtain the radical was able to be replaced with visible light which greatly increased the scope of the reaction. This was managed by using an α-diketone (such as camphorquinone) and di-*tert*-butyl peroxide. The diketone absorbed the light and induced photolysis of the peroxide. The resultant radical then abstracted the glycine α-hydrogen and allowed further reaction with an alkene or aralkyl radical to yield the α-amino acid (Scheme 14) albeit in low yield and with little diastereoselectivity.



i) visible light, α-diketone, peroxide, 1-butene.
ii) visible light, a-diketone, peroxide, toluene.

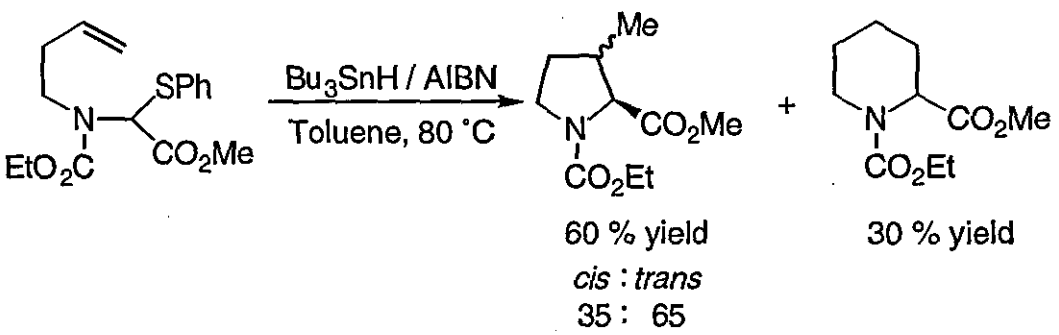
Scheme 14

The formation of α-carbon centred radicals is achieved *via* the synthesis of the α-haloglycine derivative. Free radical bromination with NBS gives the bromide which is, generally, unstable and not isolated, but is reacted further with various nucleophiles to give the derivatised amino acids in good yields. For instance, both Baldwin[27] and Easton[28] reported the synthesis of allyl transfer reactions using NBS with various substituted allyltributylstannanes in yields approaching 70 %. Hamon and workers[29] have introduced high diastereoselectivity into this reaction by incorporating the chiral auxiliary (1*R*, 3*R*, 4*S*)-8-phenylmenthyl group as a bulky ester moiety. The bromide **5** can be isolated in this case. With allyltri-*n*-butylstannane, a yield of 85 % of the 8-phenylmenthyl-*N*-Boc-allylglycinate **6** and *d.e.* (favouring the *S* configuration) of 94 were obtained (Scheme 15). Other tin substrates have been used with similar results. Easton has, also, investigated the use of chiral auxiliaries such as dipeptides, diketopiperazides (complementing Schölkopf's bis-lactim ether method, see Section 1.3.1) and *N*-phthaloyl-protected amino acids.[30] This research is currently ongoing and few results have been published to date.

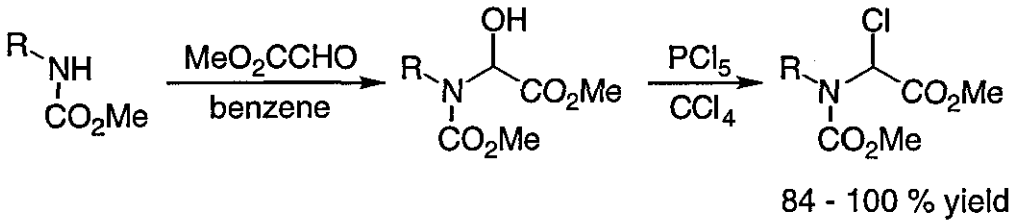


Scheme 15

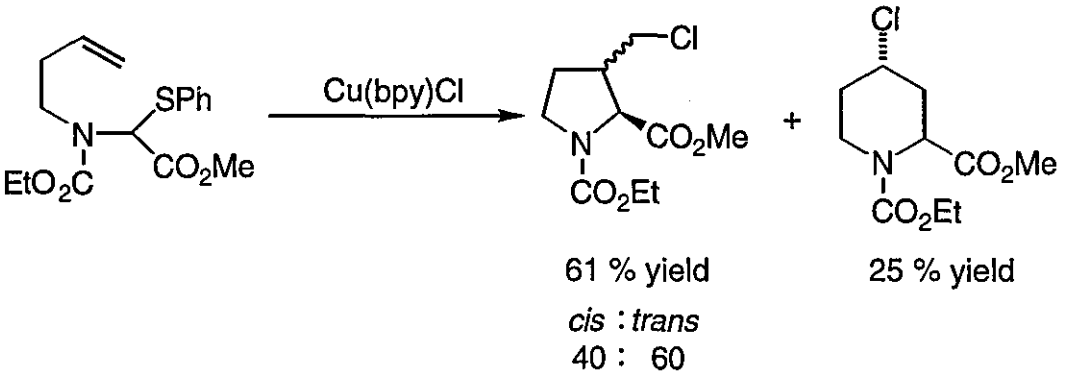
As a contrast, Hiemstra, Speckamp and workers investigated the formation of cyclic α-amino acids from carbon centred glycine radicals.[31] Initial work used α-(benzenesulfenyl)glycine derivatives as radical precursors and a tri-*n*-butyltin hydride/AIBN combination for radical formation. Typically, the reactions gave cyclisation yields of 90 % with both 5-*exo* and 6-*endo* cyclisation products isolated (*e.g.* Scheme 16). The *d.e.*'s varied from low to moderate and, surprisingly in several cases, the 6-*endo* cyclisation was the major product. It was stipulated that the carboxymethyl *N*-substitution was influencing the geometry of the molecule in such a way that the 6-*endo* pathway was becoming more competitive. Hiemstra and Speckamp followed up their early work by looking at transition metal-catalyzed chlorine transfer reactions.[32] α-Chloroglycine derivatives were synthesised using phosphorous pentachloride (Scheme 17) and refluxed in a 1, 2-dichloroethane solution of copper (I) chloride and bipyridine. The results obtained were very similar to those from their α-(benzenesulfenyl)glycine work although the cyclised products had an extra chlorine atom incorporated (Scheme 18).



Scheme 16

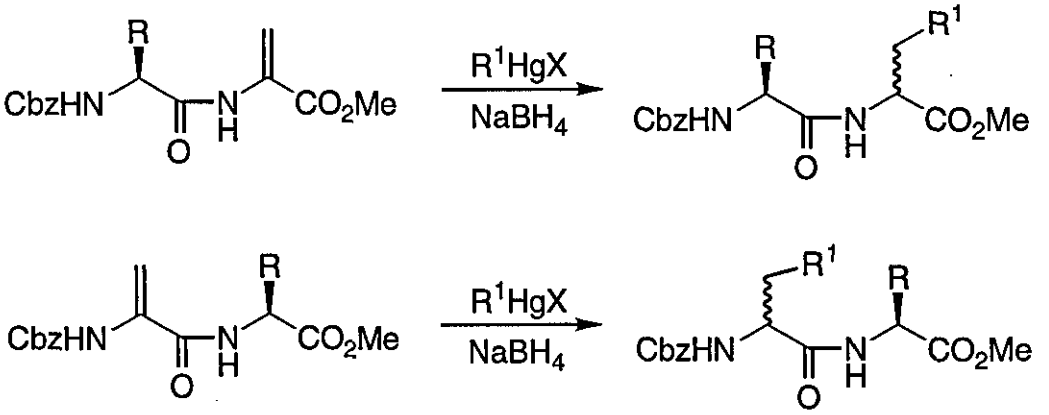


Scheme 17



Scheme 18

1.4.2 Side Chain Manipulation

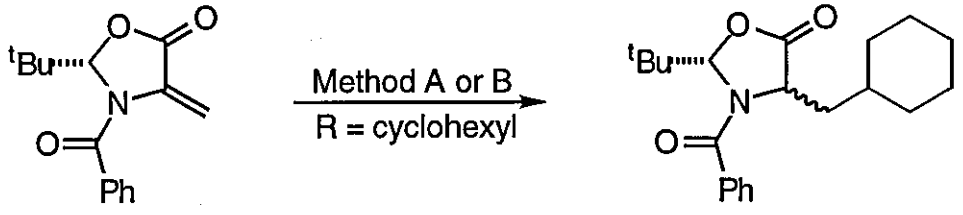


Scheme 19

Research into manipulating the side chain of an amino acid provides another option for novel compounds and may avoid possible racemisation of the α-chiral centre.

Crich and Davies[33] looked at the addition of free radicals to dehydroalanine residues contained within di- and tri-peptides (Scheme 19). Problems encountered with competing radical reactions were overcome by using the alkylmercury/sodium borohydride methodology developed by Giese.[34] The yields were good (typically 70-90 %) but the resultant chirality at the α-carbon was poor (0-28 % *d.e.*).

Beckwith and workers extended this work to cyclic derivatives of Crich's compounds, particularly the *N*-protected methylene oxazolidinones.[34] High *d.e.*'s and excellent yields from the use of alkylmercuric chlorides and sodium cyanoborohydride in THF was the result (*e.g.* Scheme 20). Even higher *d.e.*'s but lower yields were obtained when tributylstannane and AIBN were used. The degree and direction of diastereoselectivity (*cis* or *trans*) was determined by radical adduct and *N*-protecting group.

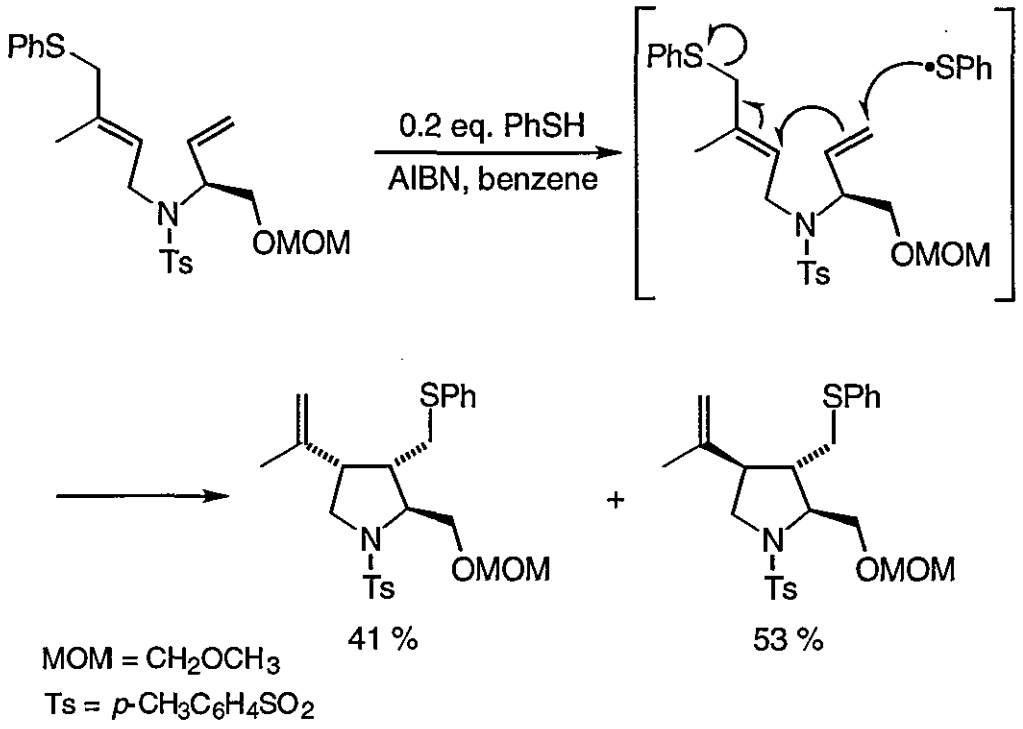


	trans : *cis*	yield
A = Bu_3SnH / AIBN / RI	91 : 9	52 %
B = RHgI, $NaCNBH_3$	84 : 16	89 %

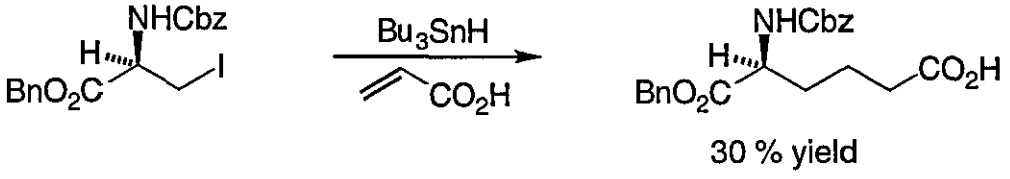
Scheme 20

Similarly, Broxterman and workers[35] carried out the addition of sulfur-based radicals to α-allylglycine. The protection at one, both or neither of the amino acid functions (NH_2 and/or CO_2H) was varied. Yields were generally good but they still found evidence of small amounts of racemisation, the amount depending on the thiol and type of protection used. A recent paper from Naito and workers[36] described the synthesis of (-)-α-kainic acid using a similar thiyl radical addition-cyclisation-elimination reaction. The radical step produces two isomers in 41 (desired isomer) and 53 % yield (Scheme 21), which are separated by chromatography before the six synthetic steps to the marine product. Overall yield (8 step synthesis) for the (-)-α-kainic acid is 9 %.

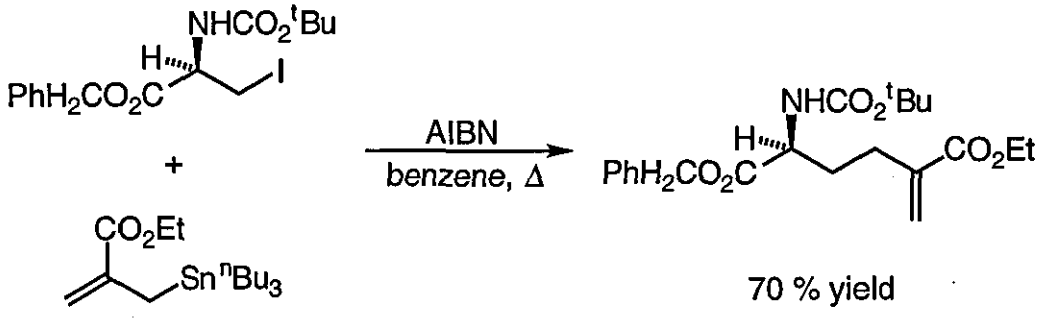
One final side-chain manipulation from Baldwin and Adlington involves using 3-iodo-*L*-alanine as a template for radical addition. Examples including addition to acrylic acid[37] to give optically active aminoadipic acid in 30 % yield (Scheme 22) and reaction with various methylacryl stannanes (*e.g.* Scheme 23).[38]



Scheme 21



Scheme 22

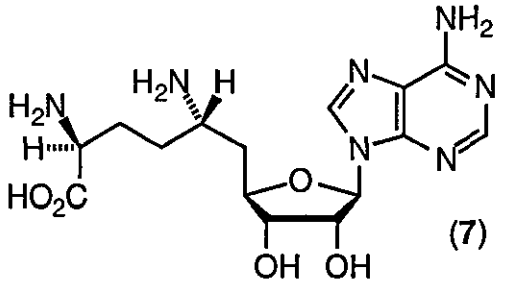


Scheme 23

1.4.3 Miscellaneous Syntheses

Barton, Crich and co-workers developed a method using *O*-esters of *N*-hydroxy-2-thiopyridone for the decarboxylative functionalisation of carboxylic acids (see section

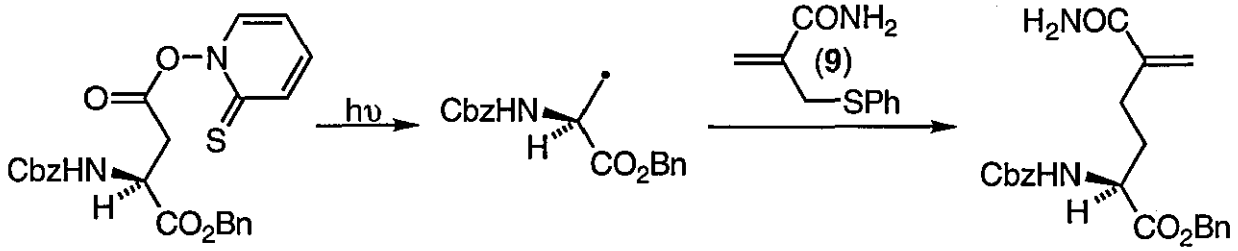
1.5.1 for mechanistic details).[39] Its use has been well documented (*e.g.* the synthesis of aminoadipic acids[40] and a "convenient synthesis of *L*-vinylglycine"[41]). The synthesis of natural (*S*)-sinefungin, a nucleosidic antibiotic 7 is described here.[42]



(7)

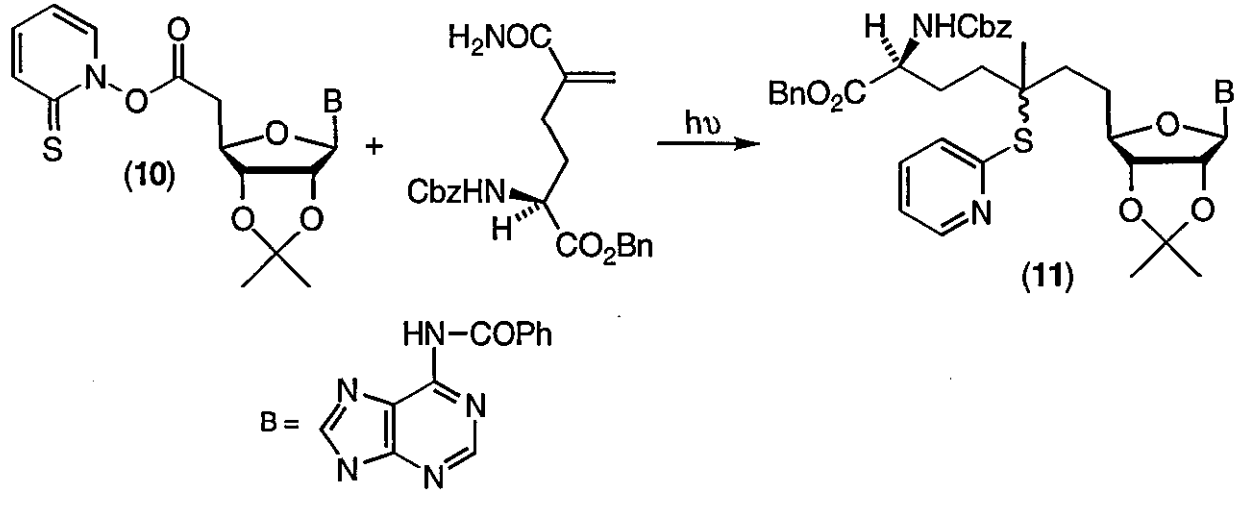
The relevant radical steps were:

i) The synthesis of the alkenyl amide 8. Photolysis of the *N-O* bond within the *L*-aspartic acid derivative (Scheme 24) leaves the radical which adds to the olefin **9** to give the desired alkenyl intermediate 8 in 62 % yield.



(8)

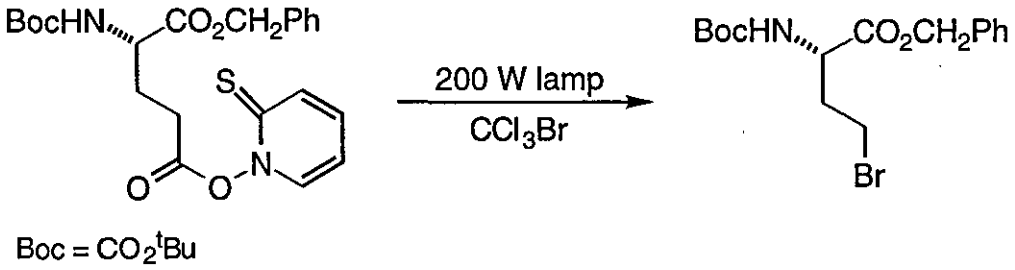
Scheme 24



Scheme 25

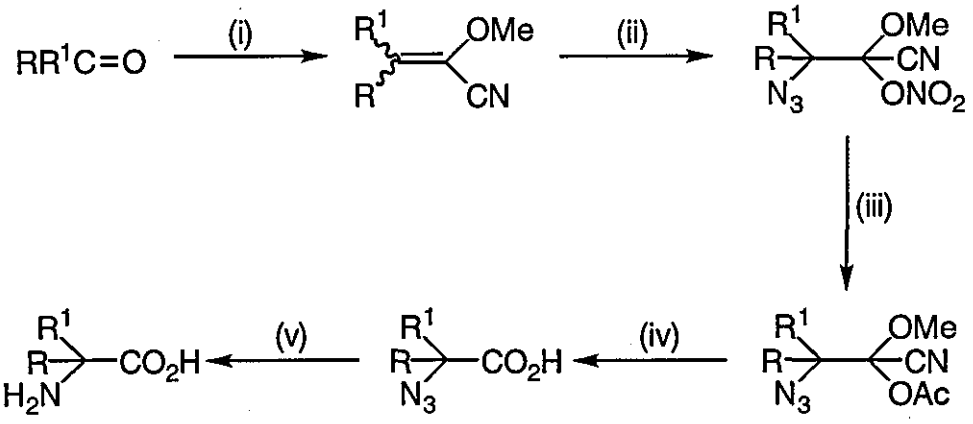
ii) in a similar fashion (Scheme 25), the acid derivative **10** is photolyzed and reacted with the alkene **8** to give the coupled derivative **11** in 45 % yield. Further derivatisation affords the (*S*)-sinefungin.

More recently, Taddei and workers[43] have employed the Barton-Crich protocol to give bromo derivatives derived from glutamic acid (Scheme 26). These compounds undergo nucleophilic substitution with nucleobases such as adenine, thymine, cytosine or guanine to give the optically active building blocks for the synthesis of chiral peptidic nucleic acids.



Boc = $CO_2{}^tBu$

Scheme 26



(i) $Ph_3P{=}C(OMe)CN$ or $(EtO)_2P(O)CH(OMe)CN$ / NaH,

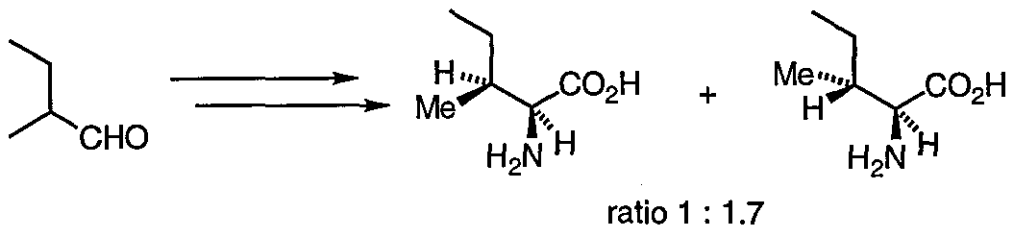
(ii) NaN_3 / $Ce(NH_4)_2(NO_3)_6$, (iii) AcOH / AcONa,

(iv) K_2CO_3 / MeOH / H_20 then HCl, (v) H_2 / Pd-C.

Scheme 27

This section is ended with a "complete" synthesis of α-amino acids. Clive and Etkin[44] made α-methoxyacrylonitriles, available from aldehydes and ketones, and reacted them with sodium azide in the presence of ceric ammonium nitrate (suspected formation of azido radicals). These compounds are reacted further to give the amino acid (Scheme 27) in moderate to good yields. Only benzaldehyde failed for azide addition (the only conjugated carbonyl group that they tried) and the synthesis of

isoleucine/alloisoleucine (Scheme 28) showed a diastereomeric ratio of 1:1.7 hence some selectivity within the method does exist.



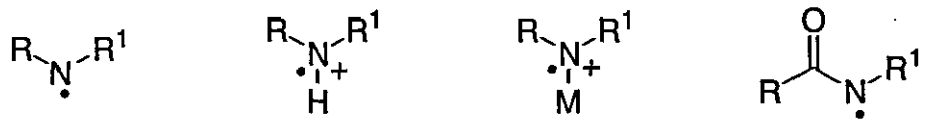
Scheme 28

A recent review by C. J. Easton[45] gives a comprehensive account of the use of free radicals in α-amino acid synthesis and is recommended for further reading.

The following section goes on to deal with the formation of the aminyl radicals needed for amino acid synthesis.

1.5 Aminyl Radicals

The chemistry of nitrogen centred radicals has received considerably less attention than the corresponding carbon centred species, although their generation and reactions have been reviewed briefly by Esker and Newcomb.[46] Also, Fallis and Brinza[47] have now completed a comprehensive review on free radical cyclisations involving nitrogen, the latter encompassing more recent research activity. Interest has increased as the cyclisation of nitrogen-containing systems leads to the possible synthesis of pyrrolidines, alkaloids and other related structures, particularly those with medicinal potential. Neutral aminyl radicals **12** are nucleophilic in nature. This contrasts with aminium cation radicals **13**, metal/Lewis acid complexed aminyl radicals **14** and amidyl radicals **15** which are electrophilic. Often, better yields may be obtained by using these electrophilic derivatives hence control of the reaction conditions is critical to ensure that the correct species is performing the radical reaction.



(12) **(13)** **(14)** **(15)**

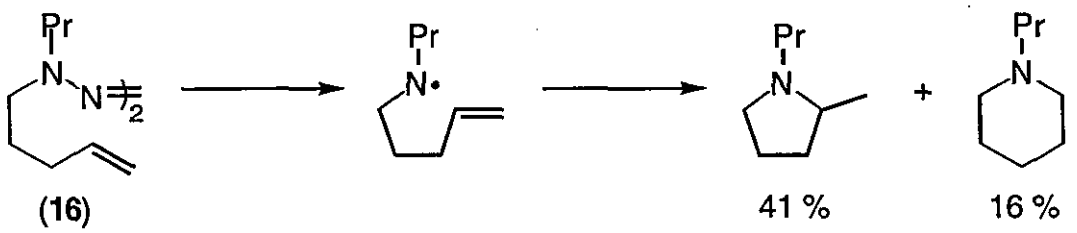
R, R^1 = alkyl, alkenyl, aryl

This chapter concentrates on the generation and use of the aminyl radicals **12** although radical types **13** and **14** will also be commented on. The first section will cover

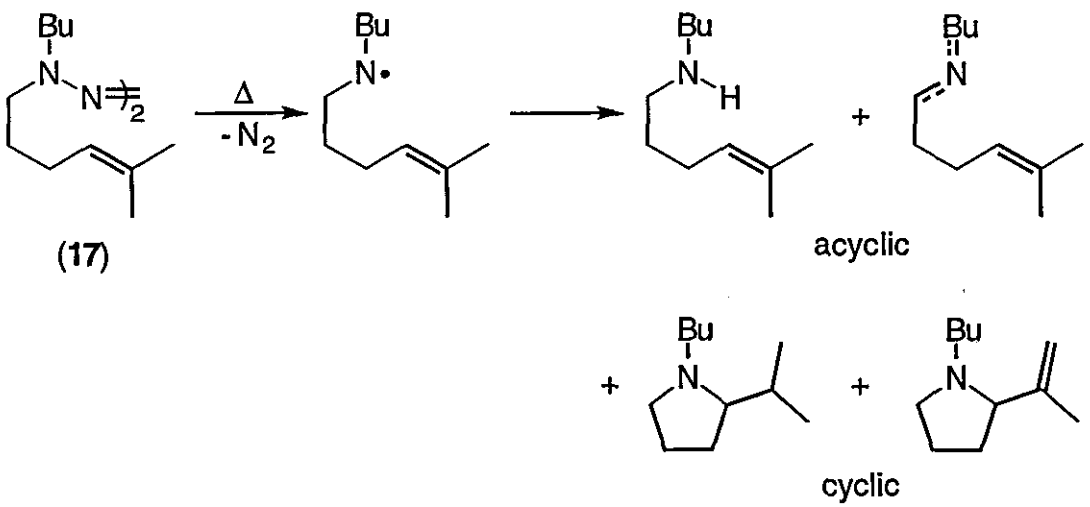
some general techniques for aminyl radical formation and, in the process, discuss the nature of the aminyl radical. The remaining sections will concentrate on substrates relevant to this thesis: sulfenamides and imines.

1.5.1 General Methods of Aminyl Radical Generation

Early investigations of aminyl radicals utilised photolysis or thermolysis of a tetrazene for generating the radicals. Michjeda[48] reported that the aminyl radicals generated from tetrazene **16** cyclised predominantly in a 5-*exo* manner to give the pyrrolidine in 41 % yield, accompanied by the piperidine (6-*endo* cyclisation) in 16 % yield (Scheme 29). The thermal decomposition of tetrazene **17** and subsequent cyclisation was studied by Newcomb[49] (Scheme 30). A 1:1 ratio of cyclic:acyclic products was found with a highly regioselective 5-*exo* cyclisation favoured (no 6-*endo* product observed). The tetrazenes are not favoured as aminyl radical precursors. They are difficult to prepare, potentially explosive and the high concentrations of radicals produced on thermolysis led to unwanted side reactions and subsequent impurity problems.



Scheme 29

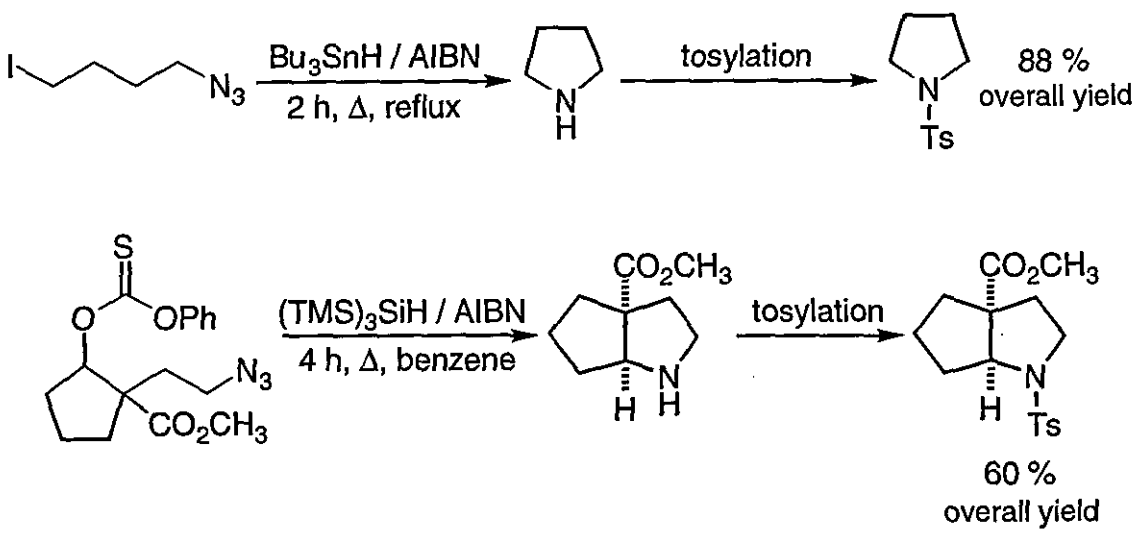


Scheme 30

Related options involving the evolution of nitrogen in aminyl radical generation have been developed by Kim and co-workers.[50,51] One approach involved the intramolecular addition of an alkyl radical to an azido group, followed by the loss of nitrogen to give the aminyl radical (Scheme 31).

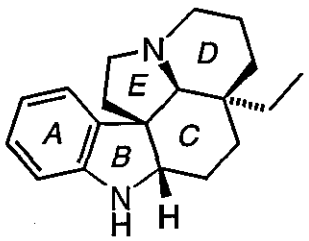
Scheme 31

The use of Bu_3SnH/AIBN in refluxing benzene for radical formation limited the alkyl radical precursor to iodo compounds (for other derivatives, the tin radical attacked the azide in preference). Fortunately, the method's usefulness was increased by replacing the tin hydride with *tris*(trimethylsilyl)silane. This also allowed the use of bromo and thionocarbonate groups as possible precursors. Yields for cyclisation using this method are generally good (50-90 %, *e.g.* Scheme 32).

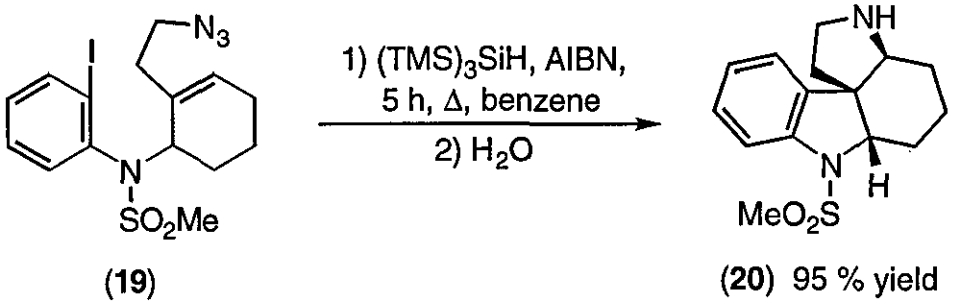


Scheme 32

Indeed, Murphy and Kizil[52] have investigated the use of Kim's method in the preparation of the *ABCE* tetracycle of aspidospermidine **18**, specifically an efficient route for the introduction of the *B/E* spirocyclic junction. Cyclisation of the azide **19** with *tris*(trimethylsilyl)silane followed by acid hydrolysis successfully gave the cyclised amine **20** in 95 % yield (Scheme 33).



(18)

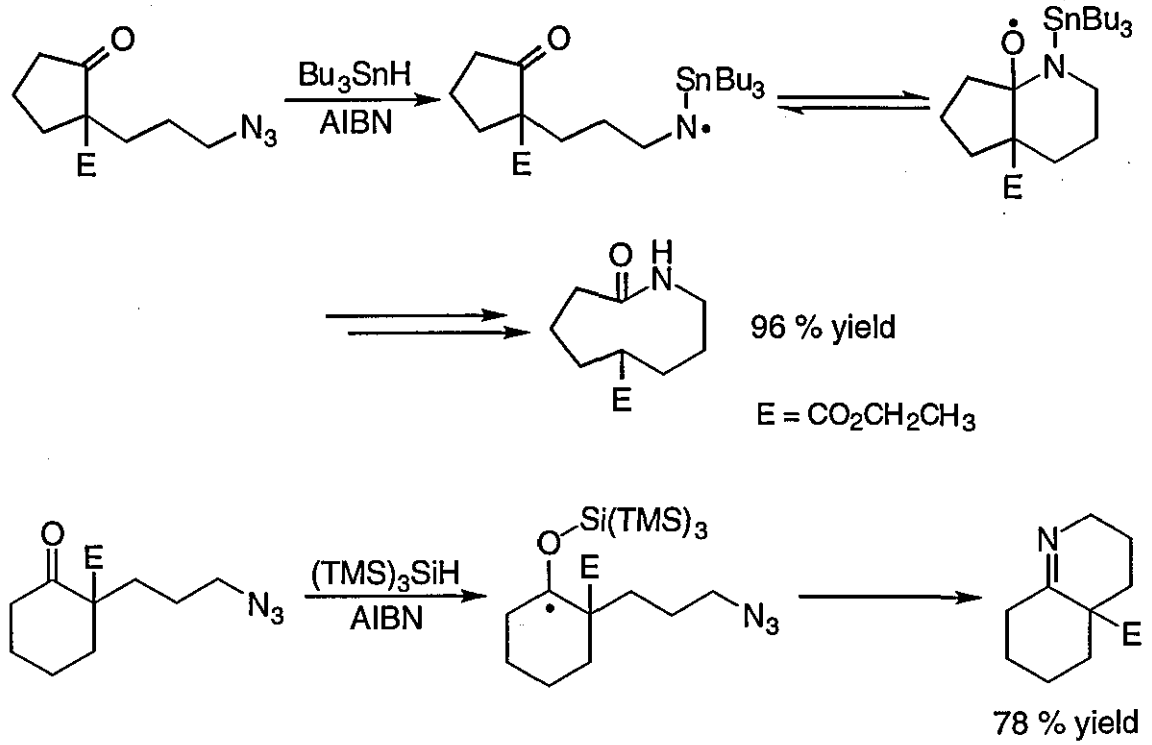


(19) (20) 95 % yield

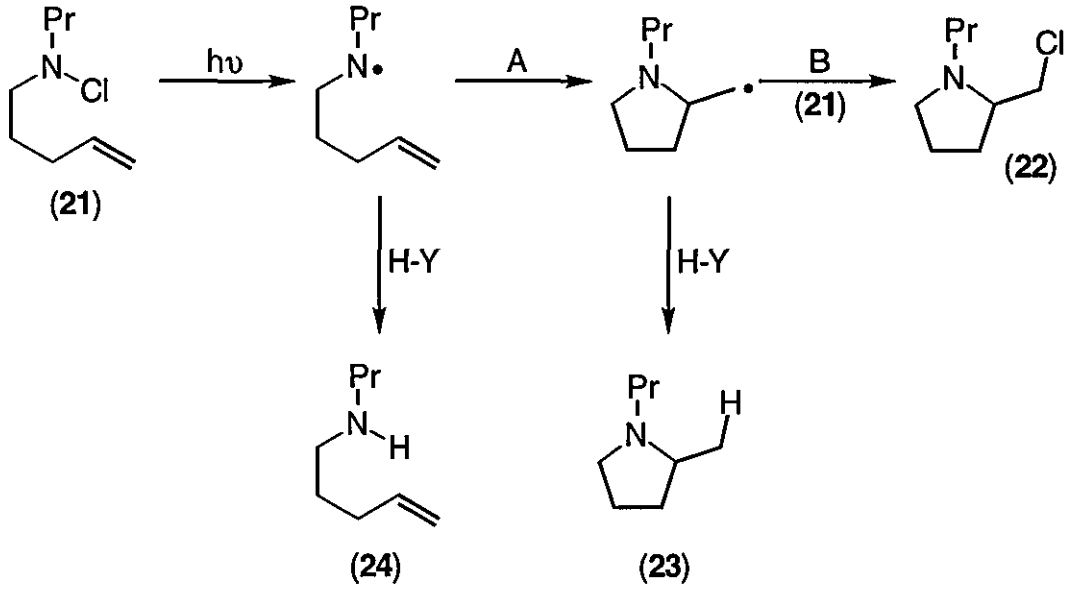
Scheme 33

Interestingly, Kim noted a variation in reaction with keto azides depending on the radical reagent used. With Bu_3SnH/AIBN, the expected intramolecular addition of the aminyl radical to keto group occurred. In contrast, with *tris*(trimethylsilyl)silane/ AIBN, the keto group became the radical precursor and the azido group a radical acceptor (Scheme 34).

N-Chloramines can be synthesised by the action of *N*-chlorosuccinimide on primary or secondary amines.[53] Photolysis (UV) in neutral media generated the aminyl radical. A possible reaction scheme (Scheme 35) is shown but steps A and/or B are slow hence other reaction pathways (*e.g.* disproportionation/solvent H-abstraction) compete. Surzur's study of the reaction of the *N*-chloramine **21** in scheme 35 used methanol or *iso*-propanol (hydrogen atom sources) as solvent and achieved acceptable ratios of cyclic, **22** and **23**, to acyclic products **24**.[54] When the reactions were carried out in acetic acid/water mixtures, only cyclised materials of type **22** were obtained. The high yields obtained from cyclisation were possible as the reacting species was, in fact, the aminium cation radical. Surzur and Stella have investigated the cyclisation of *N*-chloroalkenyl-amines under acidic (conditions as mild as aqueous acetic acid[54] or as harsh as 4M sulfuric acid in acetic acid[55] can be used!) or Lewis acidic conditions (metal salt in aqueous acetic acid is more efficient). The Lewis acidic reducing metal salt of choice was titanium trichloride, although a redox couple using catalytic copper (I) chloride with copper (II) chloride gave high yields and excellent stereoselectivity for the *trans* addition products (Scheme 36).[56] A review of these reactions has been published.[57]



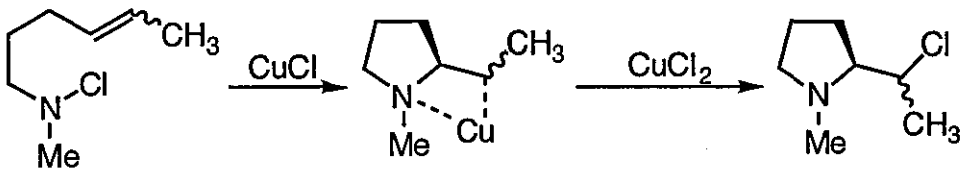
Scheme 34



Scheme 35

The copper complexed aminyl radical cyclisation has been used as a key step in a short total synthesis of gephyrotoxin 223AB (**26**) by Broka.[58] The alkenyl substituted *N*-chloropiperidine **25** was stereoselectively cyclised then dehalogenated to give the

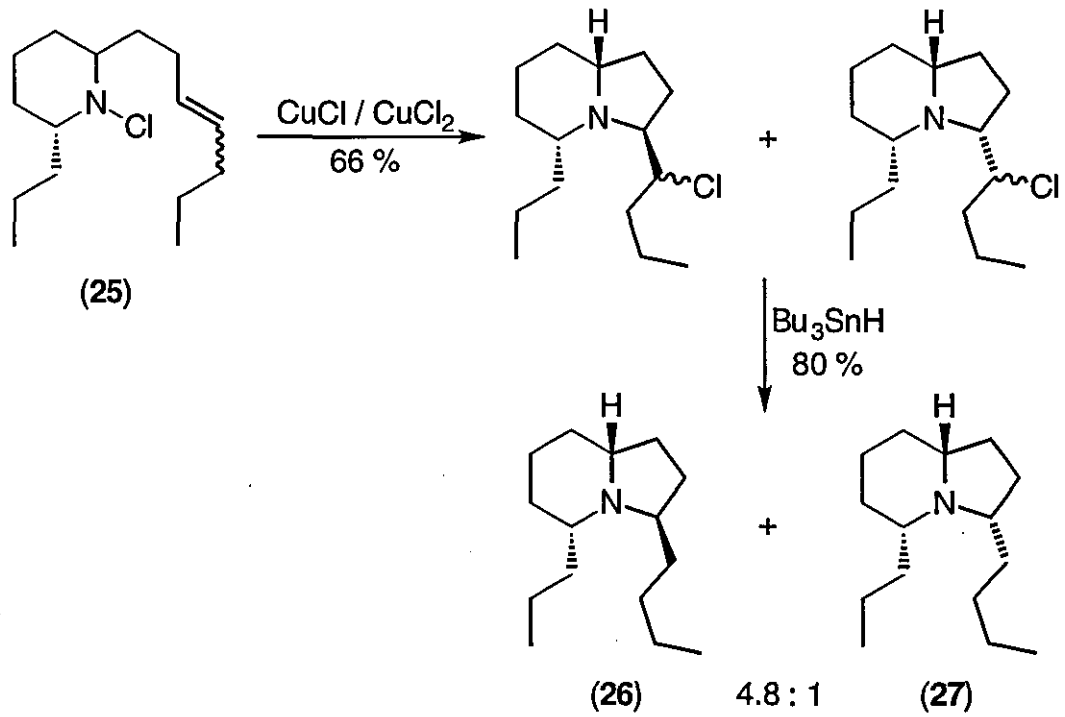
gephyrotoxin **26** in a 4.8:1 ratio with **27** (Scheme 37). The neutral aminyl radical obtained from *N*-chloramines in conjunction with the Lewis acid, silver (I) oxide, was used by Honda *et al.* in the synthesis of Aphanorphine **28**.[59] The compound **29** formed the *N*-chloro derivative **30** by reaction with *N*-chlorosuccinimide in dichloromethane. Refluxing in THF/water with silver oxide produced the cyclised material **31** in 83 % yield as a single isomer (Scheme 38).



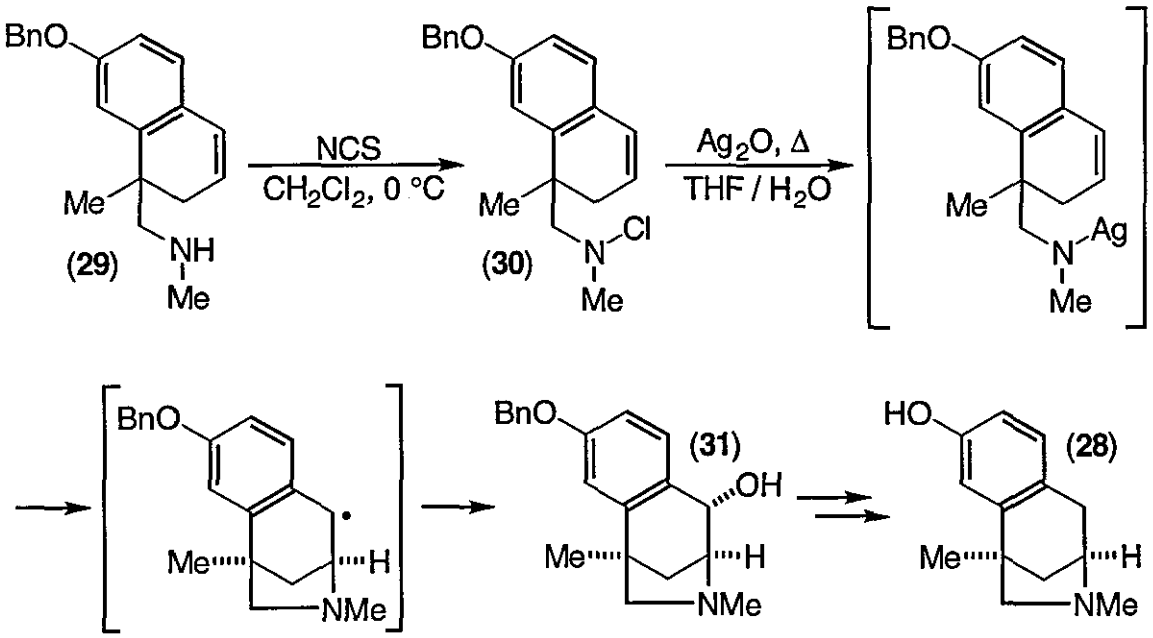
(bracketed values are results using $TiCl_3$)	threo	erythro	yield, %
cis	0 (42)	100 (58)	96 (95)
trans	91 (58)	9 (42)	93 (82)

Scheme 36

Further synthetic use for the *N*-chloramines has been limited as the cyclised pyrrolidines have been prone to rearrangements via aziridinium salts.

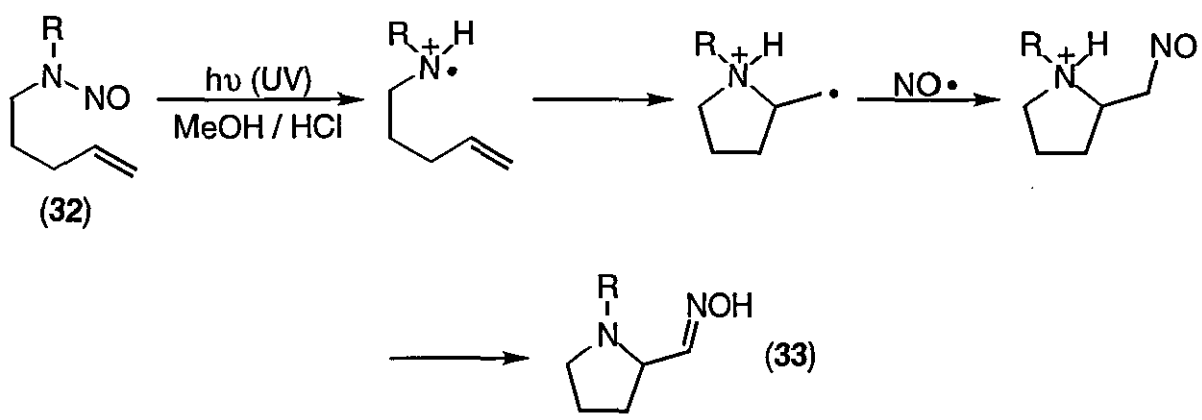


Scheme 37

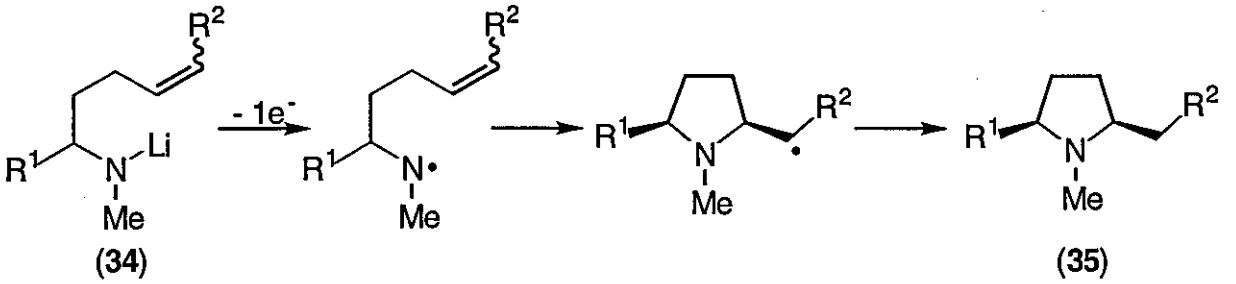


Scheme 38

N-Nitrosamines do not undergo cyclisations or other radical reactions upon photolysis in neutral conditions.[60] The two radicals formed, aminyl and nitrosyl, are presumed to recombine faster than is possible for cyclisation/further radical reactions to occur. Toxic, carcinogenic and generally unstable to purification, the *N*-nitrosamines have limited synthetic use. However, aminium cation radical cyclisations under mildly acidic conditions (pH>1) have been carried out.[61] Ultraviolet photolysis of nitrosamine **32** in acidic methanol resulted in a radical reaction that led to nitroso group transfer and, finally, oxime products **33** (Scheme 39).

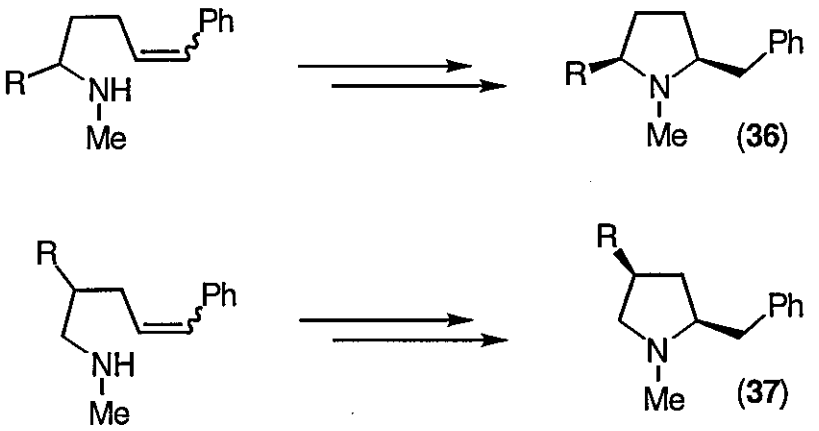


Scheme 39



R^1= alkyl, aryl
R^2 = H, aryl

Scheme 40

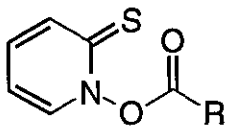


R = H, alkyl, aryl
yields 57-85 %

Scheme 41

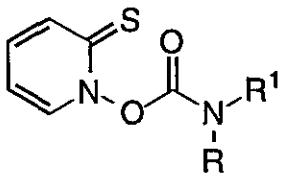
Electrochemical oxidation of amide bases, particularly lithium salts, provided an alternative preparation of aminyl radicals. Their generation is believed to operate by single electron transfer. Indeed, Newcomb[62] has used this method, along with other generation methods, to investigate the rate of cyclisation of a model aminyl radical. Suginome has used this method as a route to *cis*-1-methyl-2, 5-disubstituted pyrrolidines (Scheme 40).[63] The required lithium dialkylamide **34**, generated from the alkenylamine and *n*-butyllithium at -78 °C, was electrolysed in a mixture of THF/HMPA (30:1) and lithium perchlorate with a platinum electrode at -10 °C. Yields of cyclised material were moderate (30-52 %). Reducing the electrolyte temperature had the unexpected effect of lowering these yields further. Of interest was the high regio- and stereoselective nature of the reaction in forming exclusively the *cis*-products **35**. This was in contradiction to the rules that governed the less selective 5-hexenyl

radical[64] and the explanation provided by Suginome[65] indicated that steric constraints for the reaction on the surface of the electrode were responsible. The position of the alkene for cyclisation was crucial. No *endo* products were observed, substrates for 6-*exo* cyclisations gave only a trace of compound and for 4-*exo* cyclisations, only acyclic amine and β-scission products were formed. Yields of up to 80 % could be obtained for the 5-*exo* cyclisations by using a phenyl-substituted double bond. Suginome[66] obtained good yields of 5-unsubstituted, 5-alkyl and 5-aryl-2-benzylpyrrolidines **36**, and moderate yields of 4-substituted-2-benzylpyrrolidines **37** (Scheme 41).



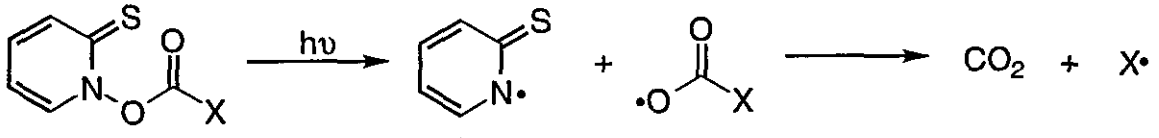
(38)

R, R^1 = alkyl, aryl



(39)

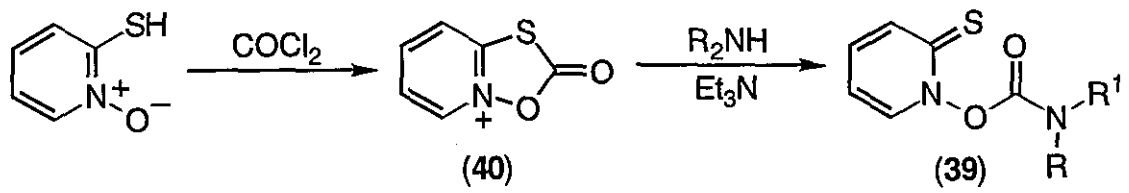
The *N*-hydroxypyridine-2(1H)thione acyl derivatives **38** developed by Barton *et al.*[39] (termed PTOC esters and briefly mentioned in Section 1.4.3) have been widely used for the generation of carbon radicals. Newcomb and co-workers extended this methodology to produce aminyl radicals by forming the carbamate derivatives of *N*-hydroxypyridine-2(1H)thione **39** (PTOC carbamates).[67] The mechanism for radical generation in both cases was very similar. Photolysis using tungsten filament lamps cleaved the weak *N-O* bond (other methods for cleavage are possible) to give a carbamoyloxy radical that rapidly decarboxylated to give the appropriate radical (Scheme 42).



X = R, NRR^1

Scheme 42

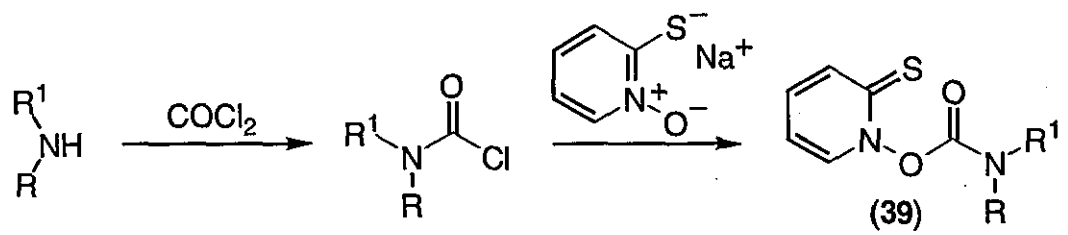
There are two general methods for the preparation of PTOC carbamates. The first involves the reaction of 2-mercaptopyridine-*N*-oxide or its sodium salt with phosgene to generate the adduct pyridinium salt **40** (stable for up to a year if protected from light and moisture). Treatment of the salt with a nucleophilic secondary amine produced the PTOC carbamate **39** (Scheme 43).



(40) (39)

Scheme 43

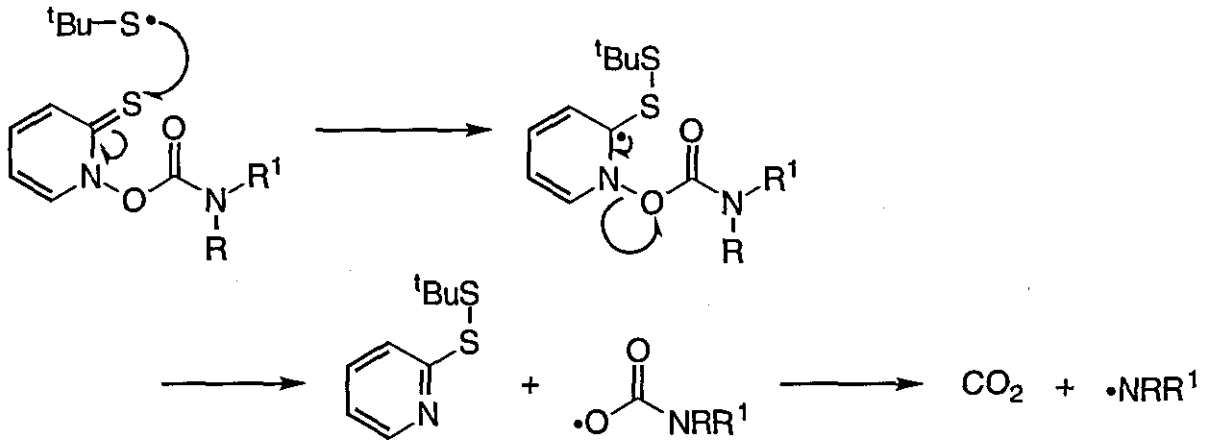
The second method, for hindered amines, involved reaction of the amine with phosgene to give a carbamoyl chloride. Subsequent treatment with the sodium salt of 2-mercaptopyridine-*N*-oxide gave **39** (Scheme 44).



(39)

Scheme 44

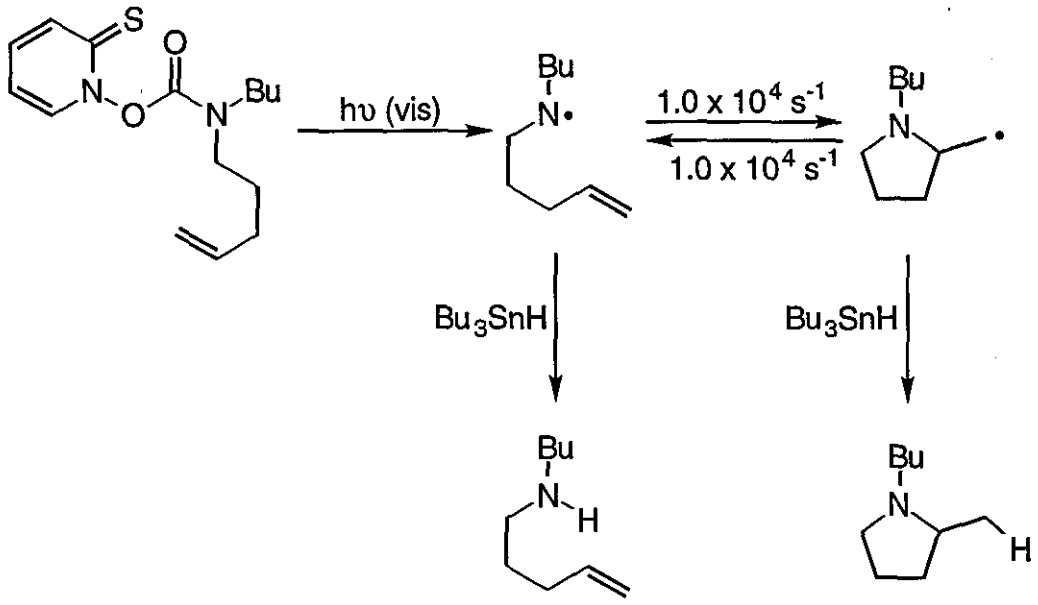
The PTOC carbamates are yellow, photo-sensitive compounds. They can be isolated in subdued light, purified by chromatography on silica gel and stored for months. Once initiated, propagation of the radical chain reactions could be achieved through the addition of a hydrogen atom donor *e.g. tert*-butylthiol (Scheme 45).



Scheme 45

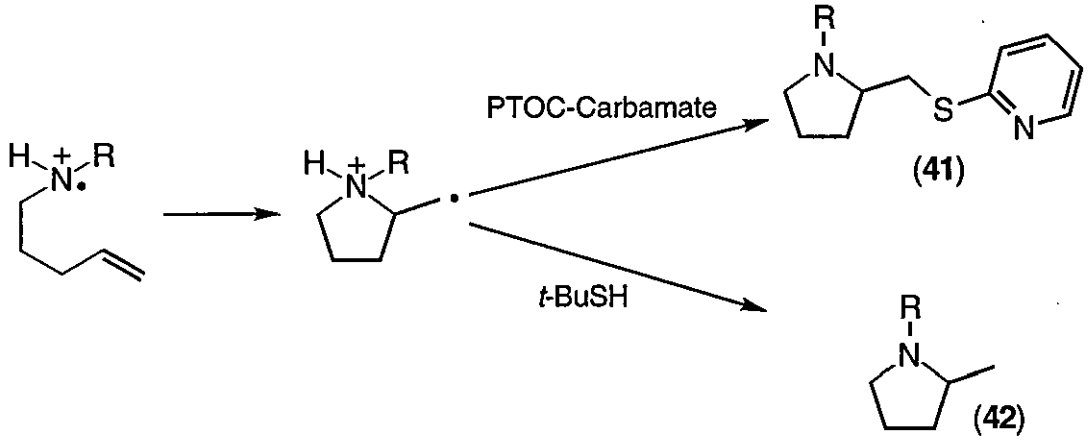
Newcomb wanted to study the competition between 5-*exo* cyclisation and H-atom trapping.[68] Initially, the *tert*-butylthiol (electrophilic H-atom donor) gave only

acyclic amine but with tri-*n*-butyltin hydride (a nucleophilic H-atom donor), competition studies were possible (Scheme 46). They showed that the cyclisation reaction for an aminyl radical was reversible.

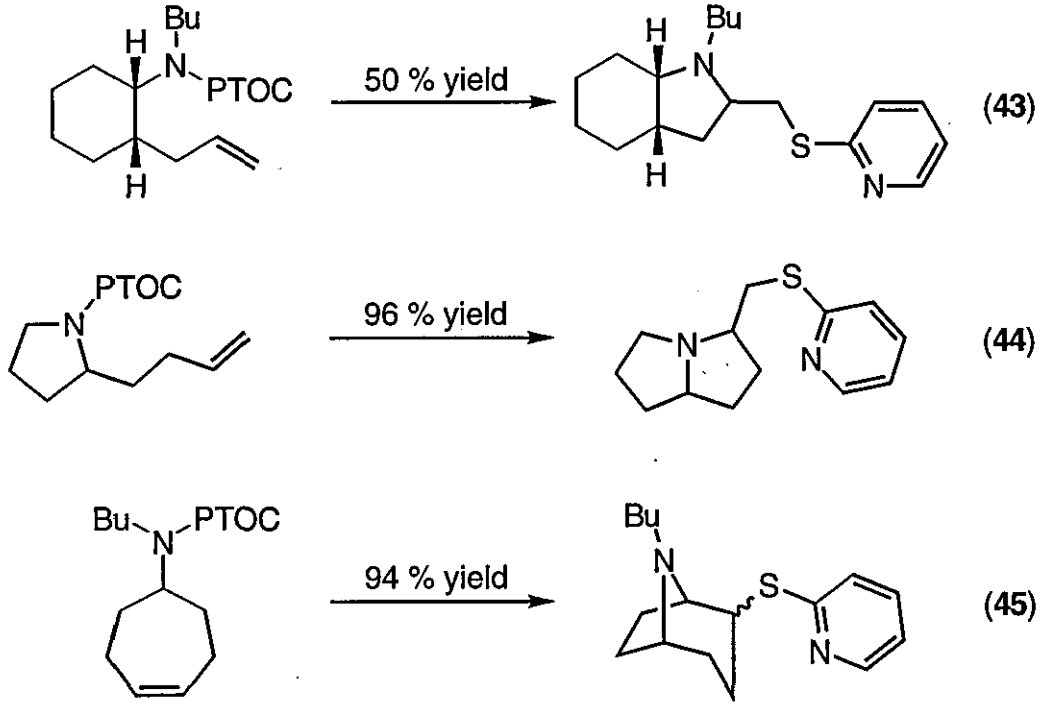


Scheme 46

As a consequence, the method was adapted to form the aminium cation radical for cyclisation. The ideal conditions for protonation of the aminyl radical were found to be malonic acid in acetonitrile.[68,69] Malonic acid was used for its ease of handling and its reluctance to protonate the PTOC precursor (once protonated, the precursor was unable to form the aminyl radical). Acetonitrile had a high enough dielectric constant to enable efficient protonation of the radical and consequently higher yields of cyclisation. *tert*-Butylthiol was the H-atom donor for this type of reaction as increased cyclisation was observed with its use. With the aminyl radicals, self-condensation was not observed as a termination step in the presence of a good H-atom donor. With the aminium species, this occurred to give two cyclic products **41** and **42** in excellent combined yield (Scheme 47, mechanism similar to propagation in scheme 45 with thiyl radical). Without the H-atom donor, the self-condensed product **41** was the only cyclised material formed. A variety of alkaloid skeletons from 5-*exo* cyclisations such as perhydroindoles **43**, substituted pyrrolizidines **44** and tropanes **45** have all been prepared in 50-96 % yield (Scheme 48).[70] The PTOC system may be compared in some reactions to *N*-chloramines and *N*-nitrosamines. In all cases, results were equal or better in yield for construction of the ring system.

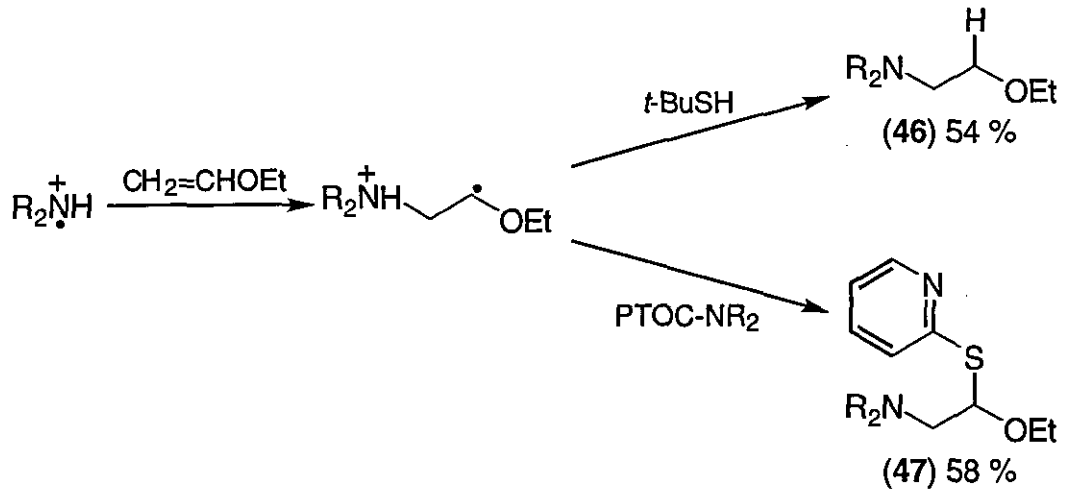


Scheme 47

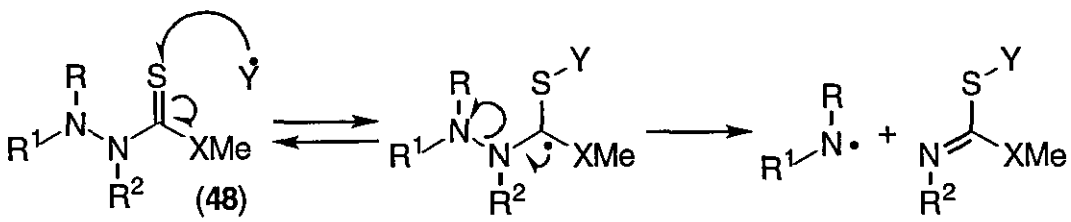


Scheme 48

Other reactions with aminium cation radicals derived from PTOC carbamates included intermolecular addition and addition-cyclisation reactions (*e.g.* addition to ethyl vinyl ether gave products containing the *N-C-C-O* moiety of β-amino ethers **46** or the equivalent of β-amino aldehydes **47** (Scheme 49)) and the use of Lewis acids where milder reaction conditions were required.[71]

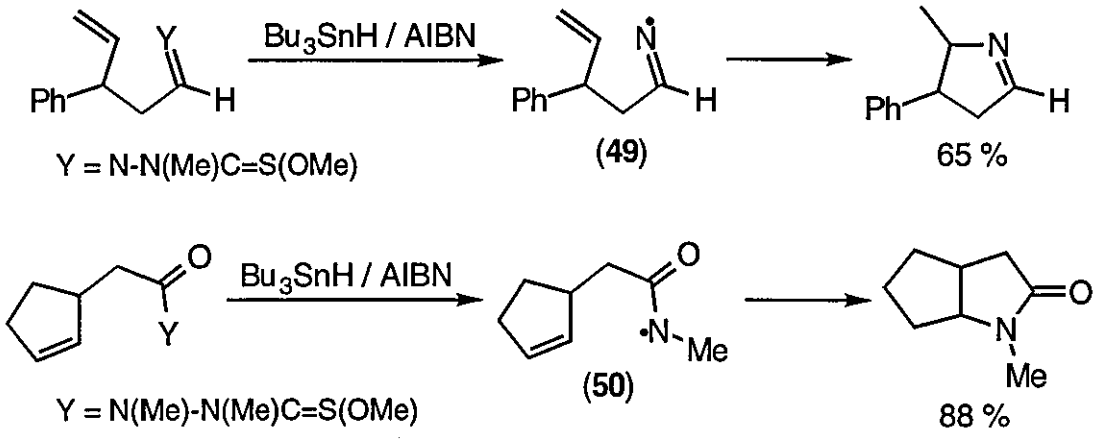


Scheme 49

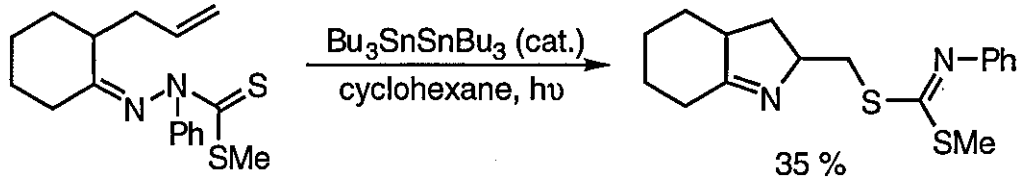


Scheme 50

A further method for generating radicals on nitrogen was developed by Zard and co-workers.[72] They exploited the relative weakness of the nitrogen-nitrogen bond to obtain the radical *via* the reaction of thiocarbazone derivatives **48** with tri-*n*-butyltin hydride and AIBN (Scheme 50). Zard, himself, has applied this relatively new reaction in the use of iminyl radicals **49** and amidyl radicals **50** (Scheme 51). Also, he has investigated the possibility that a reactive thiocarbonyl group, when irradiated, could form a carbon radical and subsequently propagate the chain reaction by addition to the sulfur of a second thiocarbonyl. The feasibility of this statement was demonstrated by the reaction in scheme 52. Although further optimisation was needed, the reaction could eventually avoid the use of tri-*n*-butyltin hydride.



Scheme 51



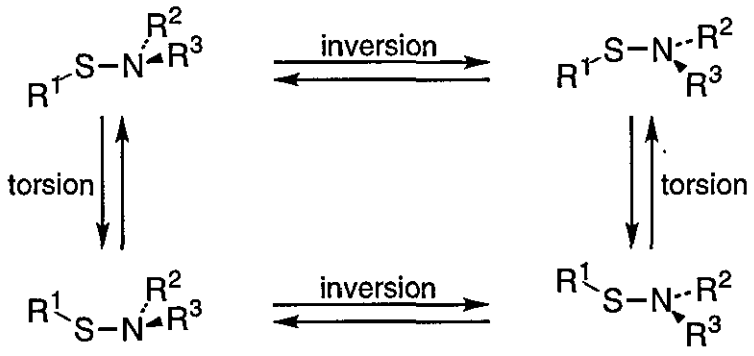
Scheme 52

1.5.2 Sulfenamides as Aminyl Radical Precursors

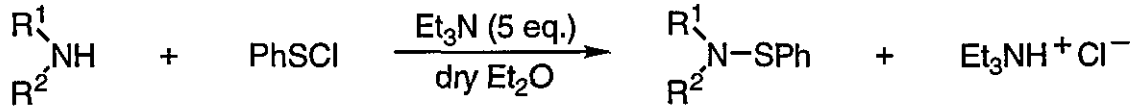
Sulfenamides[73,74,75] can be defined as compounds containing trivalent nitrogen attached to divalent sulfur. They are the amide derivatives of sulfenic acids (RSOH) as are sulfonamides and sulfinamides derived from sulfonic and sulfinic acids respectively. Their use as herbicides in the agrochemical industries[76] and as accelerators for the vulcanisation of rubber[77] has been documented in the literature. There have also been references for their use in the treatment of after-effects from radiation sickness,[78] as polymerisation initiators[79] and even in rocket technology as spontaneously igniting fuels.[80]

Their chemistry is very much defined by the nature of the *N-S* bond. Nucleophiles readily attack at the sulfur atom whilst electrophiles target the nitrogen atom. Oxidation at either nitrogen or sulfur is possible as is reductive cleavage of the sulfenamide and hydrolysis by aqueous acids. They are relatively stable in cold aqueous and basic aqueous media. The sulfenamides have the unusual characteristic of a "chiral nitrogen". The interconversion of one enantiomer into the other one requires the intervention of two different processes: rotation around the *N-S* bond and pyramidal inversion at nitrogen (Scheme 53). One of these processes must have been slow enough to produce enantiomers and studies were carried out to determine which one.[81] Structural variations affected the two processes in different ways. Inversion

barriers were increased by going from acyclic to cyclic sulfenamides and from large to small and strained rings. In contrast, the torsional barriers were increased by bulky substituents at the nitrogen atom and by strong electronegative groups at the sulfenyl sulfur.[82] The sulfenamide torsional barrier was the determining effect with several other contributions, *e.g.* overlap repulsion between non-bonding electrons on sulfur and nitrogen, increasing its energy value (typically, torsional barrier ranges from 12-20 kcal mol^{-1}). Since there is a significant barrier to torsion around the N-S bond, it would be correct to say that the bond was an axis of chirality, such as that found in allenes.



Scheme 53



R^1 = *p*-methylbenzyl, R^2 = cyclopropyl, 96 % yield

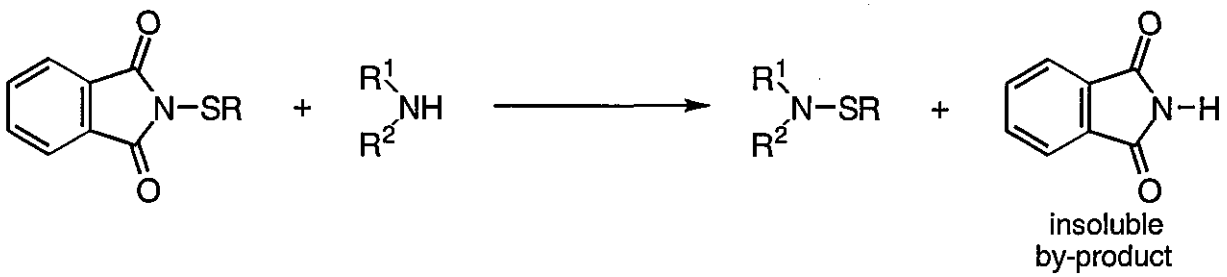
R^1 = butyl, R^2 = 4-pentenyl, 95 % yield

Scheme 54

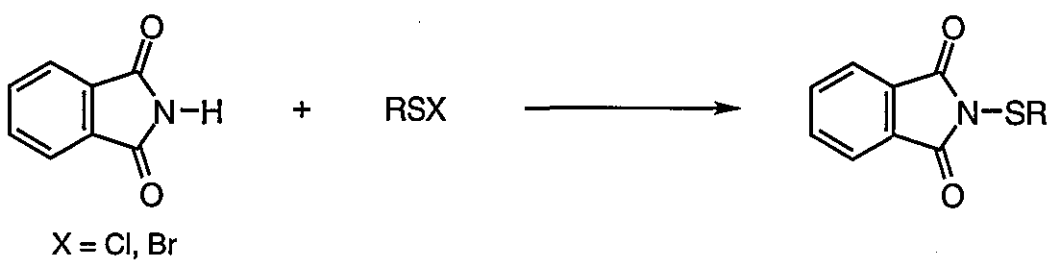
Preparation of sulfenamides can be achieved through a variety of methods. The best known method involved the reaction of primary or secondary amines with a sulfenyl halide.[83,84,85] Excess amine or a base, such as triethylamine, was required to react with any acid generated during the reaction (Scheme 54) and therefore avoid decomposition of the acid sensitive sulfenamide. Purification of the resulting sulfenamide was then achieved through distillation, crystallisation or alumina chromatography. Alkylsulfenyl chlorides often gave complex mixtures of products.[86] In contrast, the arenesulfenyl chlorides led to high yields of sulfenamides. However, the sulfenyl halides were quite capable of reacting with other species present in the reaction such as hydroxyls, active methylene compounds or alkenes,[87] yet sulfenamides containing active double bonds have been prepared by this method.[88,89] Predominantly, the sulfenyl halide of choice was the chloride. There are no examples of

sulfenyl fluoride or iodide of use in this reaction. It could be assumed that the fluoride was too stable to react with amines whereas the iodide far too unstable. Sulfenyl bromides have been reacted with secondary amines in the formation of organophosphorous sulfenamides (Scheme 55).[90]

Scheme 55

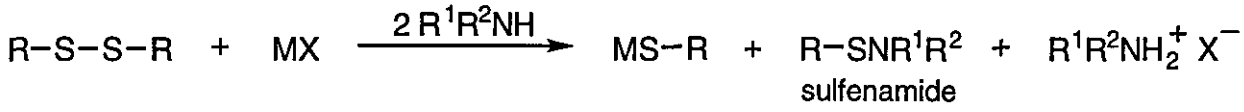


Scheme 56



Scheme 57

A second method used the displacement of phthalimide from *N*-sulfenyl substituted phthalimide by amines (Scheme 56).[88] The *N*-sulfenyl substituted phthalimide was prepared from the reaction of sulfenyl halide with phthalimide (Scheme 57). The reaction has the advantage of mild conditions (an equivalent of amine stirred with the phthalimide derivative in a non-polar solvent, either at room temperature or under reflux conditions) and the phthalimide by-product can be filtered off to leave the sulfenamide in good yield. Unfortunately, the reaction with sterically hindered amines was slow, even in refluxing toluene, and the method did not work for the substituted phthalimides where bulky alkyl groups, such as isopropyl or cyclohexyl, were employed.



R = alkyl, 30-50 % yields

R = aryl, 60-90 % yields

MX = $AgNO_3$, AgOAc, $HgCl_2$

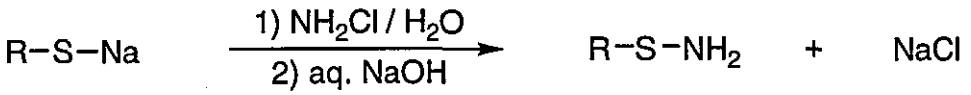
Scheme 58

Disulfides have been utilised in a number of syntheses of sulfenamides. Davis and co-workers[91] developed the reaction of alkyl or aryl disulfides in the presence of silver or mercuric salts (Scheme 58). Complexation of the metal ion with one sulfur atom in the disulfide enabled nucleophilic attack on the second sulfur from the amine. Reasonable yields were obtained under mild conditions, and the method allowed the use of amines containing functional groups such as hydroxyl and carbon-carbon double bonds. However, the method required at least two equivalents of amine hence it would be unsuitable for reactions where amine was not readily available. In a variant of this reaction, lithium salts of primary or secondary amines were reacted with alkyldisulfides to give the corresponding sulfenamides in excellent yield (Scheme 59).[92]

R = propyl, R^1 = ethyl, propyl, *iso*-butyl

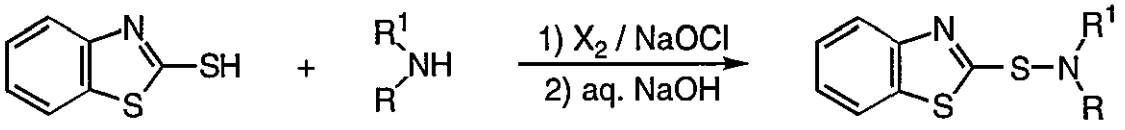
Scheme 59

Thiols have also been used as precursors. Sulfenamides with a free amino group can be obtained in yields of up to 50 % when mercaptides are reacted with chloramines (Scheme 60).[93] Other methods involved the reaction of aromatic mercaptans with ammonia, or with primary or secondary amines in the presence of an oxidising agent, such as hypochlorites, halogens or potassium ferricyanide in aqueous solution (Scheme 61).[94] This method is similar to the chloramine route since mercaptans react with chlorine or hypochlorite with formation of sulfenyl chlorides and chloramines, following which the former would interact with the amines and the latter with the mercaptans. The main disadvantage of the method was the formation of the disulfide via oxidation of the thiol. In extreme cases, the disulfide was the only isolated product. There are further reactions involving the synthesis of sulfenamides not discussed here.[73,74]



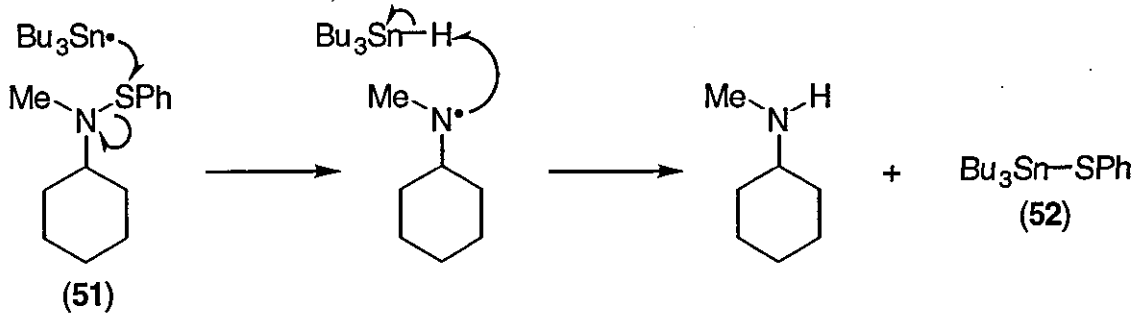
R = pyridyl, pyrimidyl, 1,2-$Cl_2C_6H_3$, 4-NO_2-C_6H_4

Scheme 60



R^1 = H, ethyl
R = H, cyclopentyl
X = Cl, Br, I

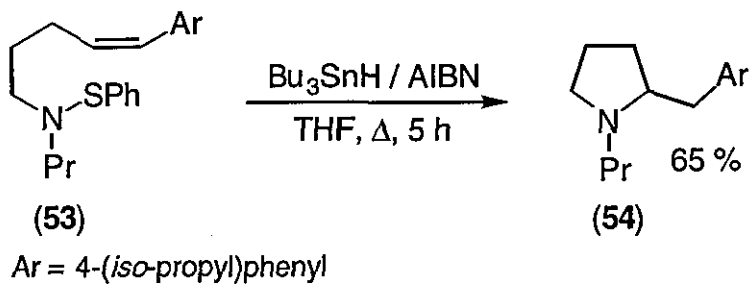
Scheme 61



Scheme 62

The generation of aminyl radicals from sulfenamides has been extensively studied by Bowman and co-workers.[73,88,89] Initial studies, determining the suitability of the sulfenamide precursors, involved the use of *N*-(benzenesulfenyl)-*N*-methyl-cyclohexylamine **51**. Abstraction of the benzenesulfenyl group by the tributyltin radical to produce the aminyl radical was achieved in an S_H2 mechanism (Scheme 62). Subsequent H-abstraction gave the *N*-methylcyclohexylamine in 93 % yield (GLC). The by-product, tributyltin phenyl sulfide **52** was also isolated. When the reaction was carried out under an atmosphere of oxygen, no initiator (AIBN) and in the dark, unreacted sulfenamide was recovered in quantitative yield. Thus indicating that a radical process was responsible. This was confirmed by a series of reactions *e.g.* the cyclisation of a simple precursor **53** (Scheme 63). Syringe pump addition of Bu_3SnH and

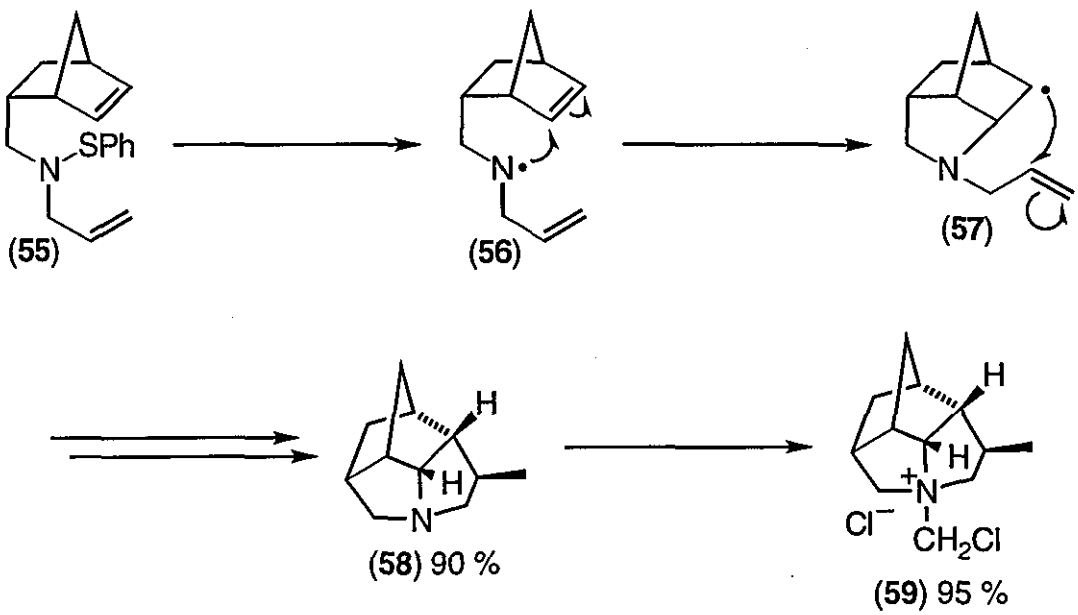
AIBN to a refluxing solution of **53** in THF over 5 h gave the pure cyclised product **54** in 65 % yield.



(53) **(54)**

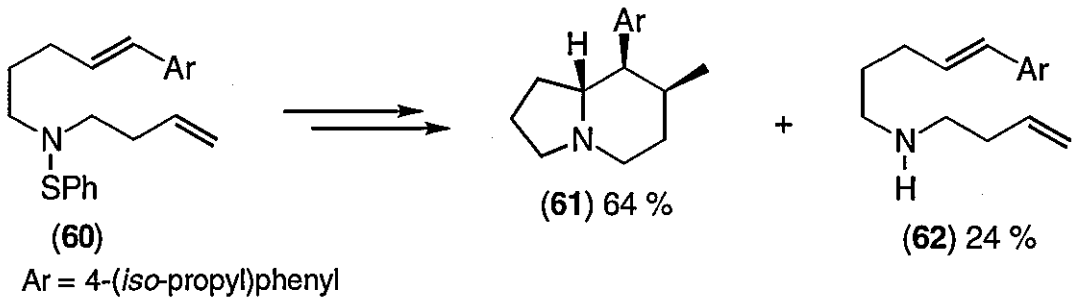
Ar = 4-(*iso*-propyl)phenyl

Scheme 63



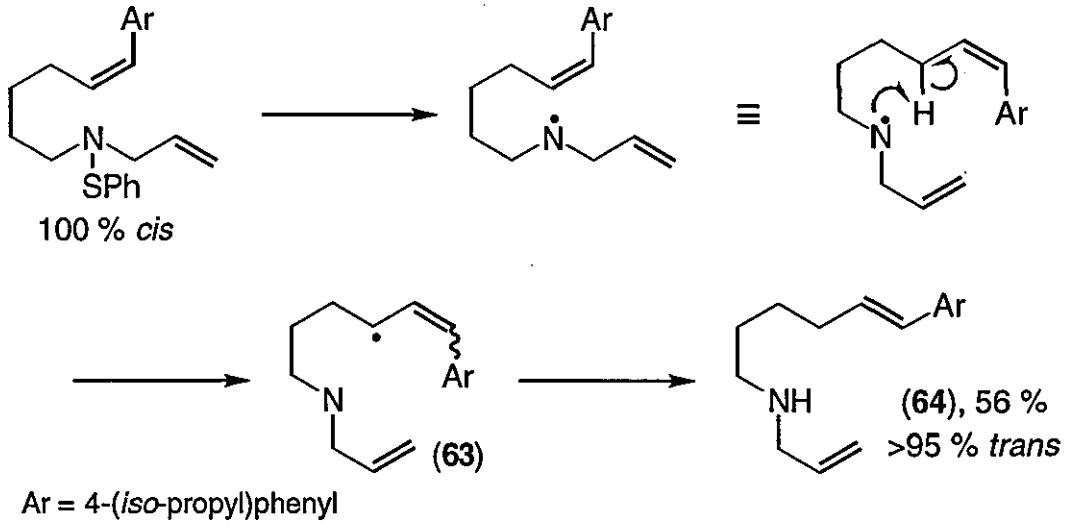
Scheme 64

Further investigation of the sulfenamide precursors took the route of trapping the aminyl radical through tandem cyclisations. The precursors were designed in such a way that cyclisation was the most favourable reaction pathway and some excellent results were obtained. *N*-(Benzenesulfenyl)-*N*-allyl-(bicyclo[2.2.1]hept-5-en-2-yl)methylamine **55** was cyclised under standard Bu_3SnH conditions to give the tetracyclic pyrrolizidine product **58** in 90 % yield (Scheme 64). The high yield was obtainable as the initial cyclisation of the intermediate aminyl radical **56** was fast. A strained alkene, buttressing effects and the close orientation of the aminyl radical to the alkene were all contributors to the cyclisation step **56** to **57**. It should be noted that the high nucleophilicity of the product **58** led to an S_N2 type substitution reaction with dichloromethane on work-up and the corresponding chloride salt **59** was isolated.



Scheme 65

Only partial success was obtained in the synthesis of indolizidines. The 5-*exo*, 6-*exo* cyclisation strategy gave positive results. The reaction between sulfenamide **60** and Bu_3SnH gave 7-methyl-8-(4-isopropylphenyl)indolizidine **61** in 64 % yield (Scheme 65) as a pair of invertomers (55:45 ratio). 24 % of uncyclised amine **62** was also isolated. However, when the strategy was reversed (6-*exo*, 5-*exo* cyclisation), the cyclisation failed and the aminyl radical generated underwent intramolecular H-abstraction to yield the uncyclised amine **64**. Proof for the H-abstraction was provided by the loss of alkene geometry, presumably *via* styrryl radical **63**, to yield the more stable *trans* diastereomer. This abstraction would not occur if the 6-*exo* cyclisation had been attempted on a non-conjugated alkene. Aminyl radicals are not good H-abstractors but the formation of the stable styryl radical **63** allowed the H-abstraction to proceed (Scheme 66).

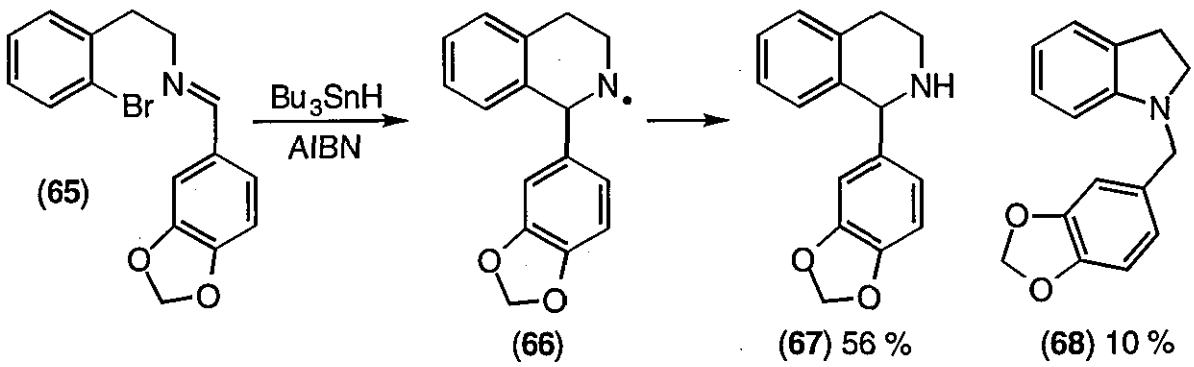


Scheme 66

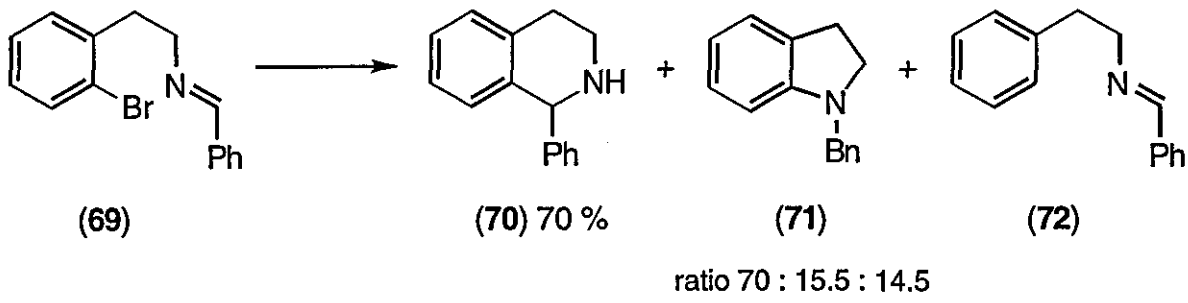
In conclusion, sulfenamides make excellent precursors for aminyl radicals. They can be synthesised in good to excellent yields and stored for several months under the right conditions.

1.5.3 Imines as Aminyl Radical Precursors

The investigation into the use of imines within radical chemistry has been receiving increasing interest in the last three years. An early example was reported by Takano and co-workers[95] in 1990. In their synthesis of Cryptostyline alkaloids, the key step used an intramolecular radical addition onto an imine bond. Cyclisation of the aryl bromide **65** gave, as the major product, the isoquinoline skeleton **67** from a 6-*endo* addition onto the carbon of the imine bond (Scheme 67).



Scheme 67

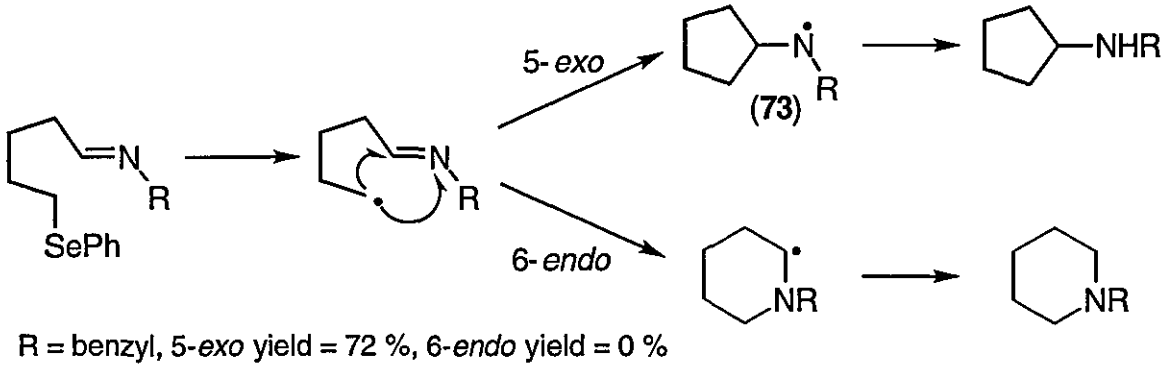


Scheme 68

An alternative pathway, *via* 5-*exo* addition onto the nitrogen, produced the dihydroindole **68** in 10 % yield. Studies by Warkentin,[96] involving the addition of an aryl radical onto an aldimine acceptor, also reported a large 6-*endo* preference. A typical example involved the cyclisation of bromide **69**. The 6-*endo* product **70** was produced in 70 % yield accompanied by lesser amounts of the 5-*exo* product **71** and reduced starting material **72** in an approximate ratio of 70:15.5:14.5 (Scheme 68). The selectivity could be explained by the aryl radical reacting with the electrophilic imine carbon in the

formation of a *C-C* bond rather than a *C-N* bond. The transition state for the 6-*endo* approach was sterically favoured (less strained) and the less strained cyclic product was formed by the 6-*endo* addition. Kinetic studies also indicated that the 5-*exo* cyclisation was around four to five times slower than the 6-*endo*. In both of the reaction sequences described though, the intermediate formed during the highly favoured 6-*endo* cyclisations was the aminyl radical (*e.g.* **66** in Scheme 67).

Bowman and co-workers[97] investigated the use of imines as precursors solely for the formation of the aminyl radical. The imines were formed in quantitative yield by the condensation of an amine with a ω-benzeneselenyl-substituted aldehyde. For the substrates used, the anilyl imines could be purified prior to radical reaction whereas the aliphatic imines were formed and reacted *in situ*. The reaction conditions for radical formation utilised the syringe pump addition of a Bu_3SnH/AIBN toluene solution over 5 h. An example of aminyl radical formation is shown in Scheme 69. The aminyl radical **73** is formed *via* 5-*exo* cyclisation and then quenched by H-atom abstraction. However, unlike the aryl radical previously mentioned, the 6-*endo* formation of the aminyl radical was not favoured by either the aromatic or aliphatic imines tested. Further studies indicated that neither 6-*exo* nor 7-*endo* cyclisations could be used to form the aminyl radical as only acyclic products were formed in useful yield.

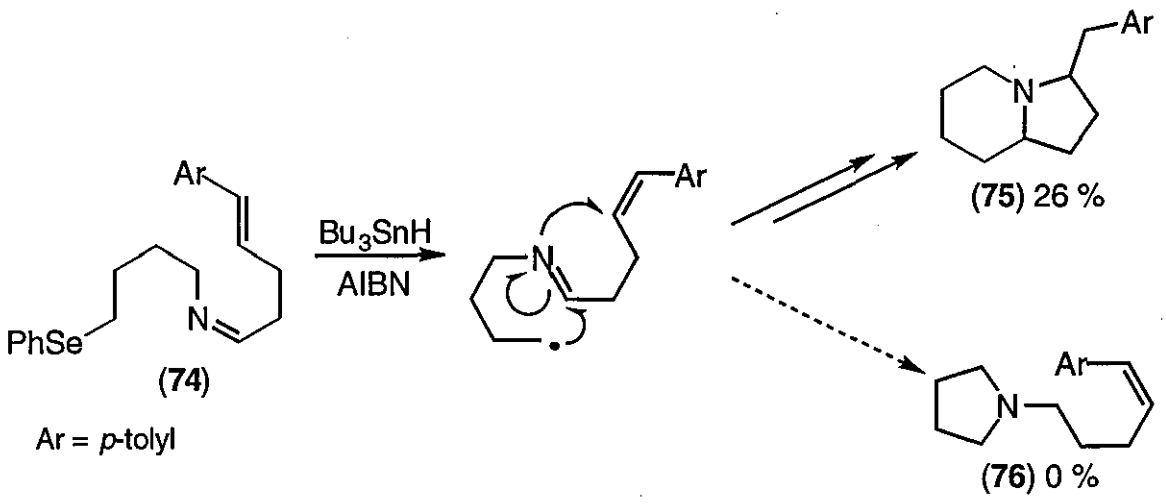


R = benzyl, 5-*exo* yield = 72 %, 6-*endo* yield = 0 %

Scheme 69

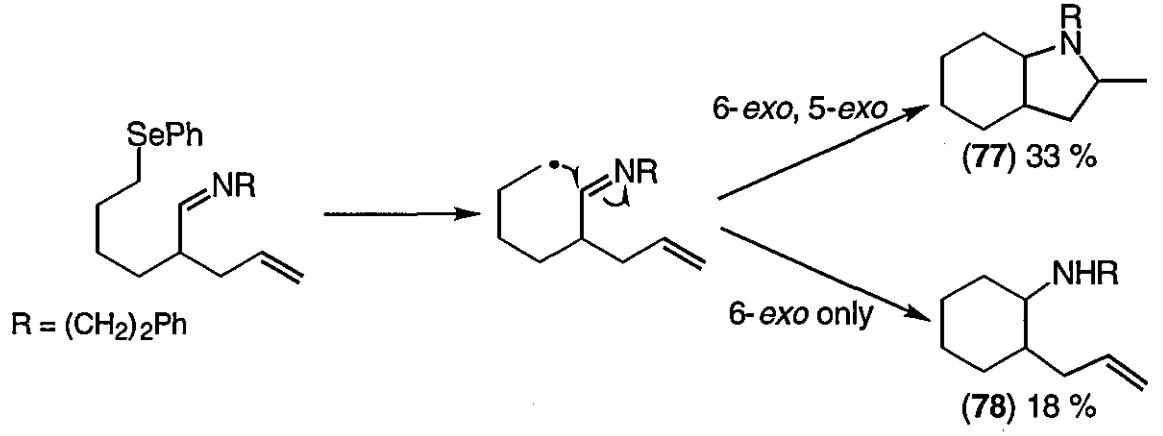
Research into the use of the aminyl radical intermediates as part of tandem cyclisations has not been extensively studied. However, Bowman and co-workers[98] have reported that such syntheses were possible. They targeted several ring systems, of which the two bicyclic heterocycles, indolizidines and perhydroindolines (Schemes 70 and 71) and spirocyclic amines (Scheme 72 and 73) received initial interest. The cyclisation reactions involving the production of indolizidines were successful although yields were typically only 20-30 %. For instance, the radical precursor **74** cyclised in a 6-*endo* then 5-*exo* fashion to give the indolizidine **75** in 26 % yield. Curiously, none of the

expected product **76**, produced from a very favoured 5-*exo* cyclisation then H-atom abstraction, was isolated (Scheme 70).



Scheme 70

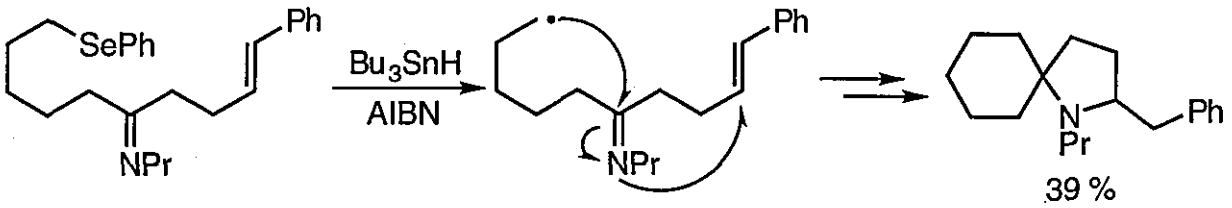
The perhydroindoline **77** was synthesised through a tandem 6-*exo*,5-*exo* cyclisation in 33 % yield as a pair of stereoisomers. In this case, though, the competing H-atom abstraction (not seen in the formation of the indolizidine derivative **75**) was apparent with a yield of 18 % of the monocyclised product **78** obtained.



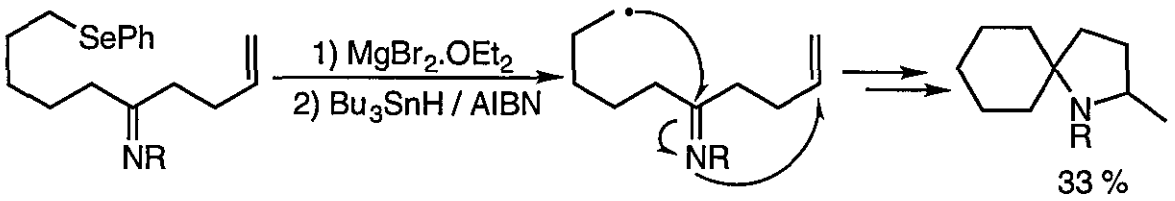
Scheme 71

The application of the protocol to the formation of spirocyclic derivatives proved troublesome. Tandem cyclisation was only achieved when the aminyl radical intermediate was able to add to an alkene with a radical stabilising substituent (Scheme 72). In order to synthesise the spirocyclic amine without the phenyl substituent, another strategy was employed. The use of magnesium dibromide etherate as a Lewis acid,

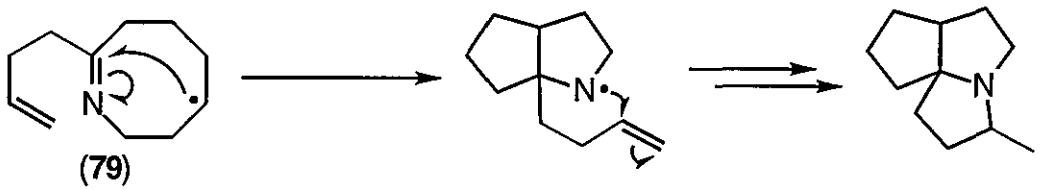
complexed with the aminyl radical intermediate, increasing its electrophilicity and subsequently cyclising to form the spirocyclic products in moderate yields (typically 30 %, *e.g.* Scheme 73).



Scheme 72

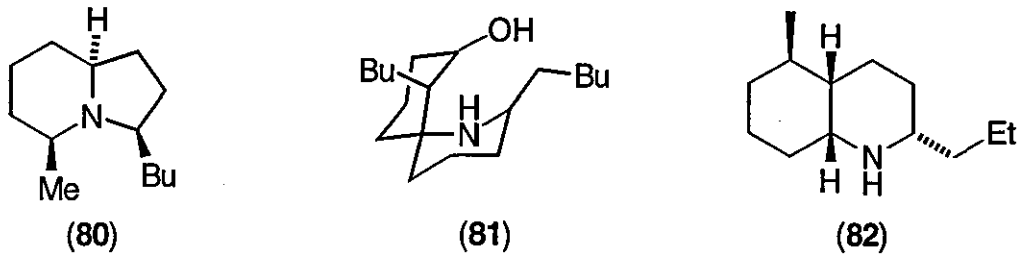


Scheme 73



Scheme 74

The synthesis of polycyclic systems, such as cyclisation of the cyclic imine **79** (Scheme 74), was also used for studies towards the synthesis of the natural products, monomorine **80**, perhydrohistrionicotoxin **81** and pumilotoxin C **82**.



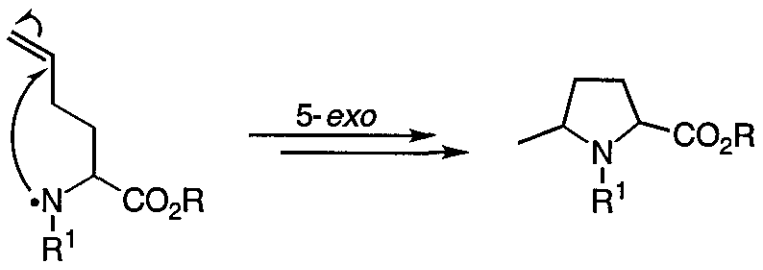
1.6 Synthesis of α-Amino Acids using Amino Acid Aminyl Radicals

There has been no reported research into the use of α-amino acids as precursors for aminyl radicals. This is somewhat surprising because the presence of the chiral

centre adjacent to the site of formation for the aminyl radical would be expected to confer diastereoselectivity upon the cyclised product. We envisaged the synthesis of α-amino acids *via* amino acid aminyl radical cyclisation by three methods:

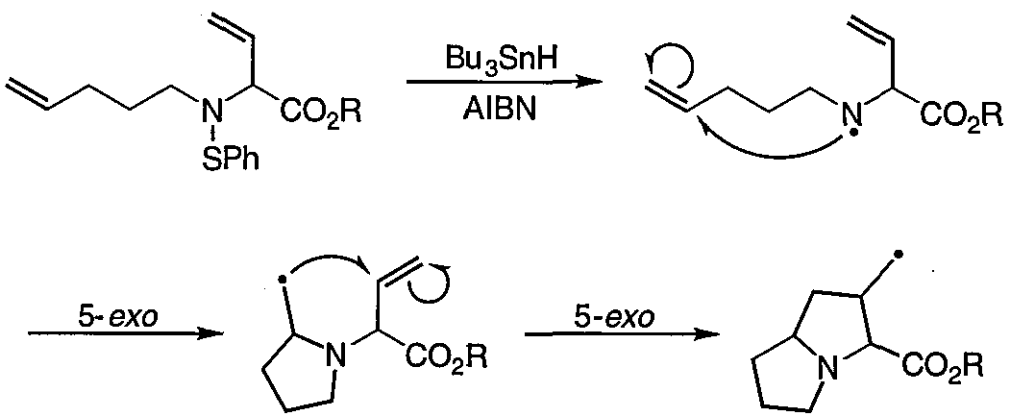
i) Cyclisation onto *C*-substituted side-chains

Natural amino acids containing unsaturation suitably positioned for cyclisation include the aromatic substrates, phenylalanine and tyrosine. For further reactions, unnatural derivatives would have to be synthesised and these could possibly include side chain alkenes or side chain cycloalkenes (*e.g.* Scheme 75). Formation of the sulfenamide from these derivatives would provide the precursor for cyclisation.



Scheme 75

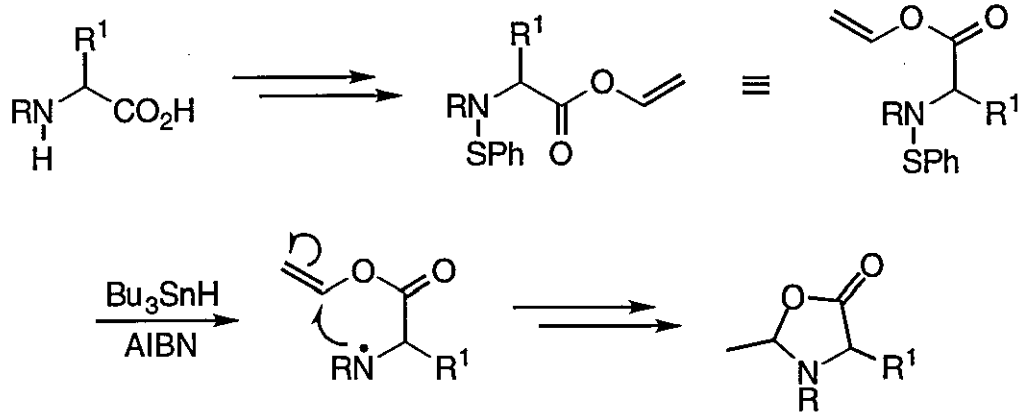
ii) Cyclisation onto *N*-substituted side-chains,



Scheme 76

N-alkylation of an amino acid substrate (in theory, the majority of amino acids could be used as starting material) followed by sulfenamide formation would provide the cyclisation precursor. Using the unnatural amino acids containing side chain alkenes, it should also be possible to attempt various tandem cyclisations (Scheme 76).

iii) Cyclisation onto *O*-substituted side chains,



Scheme 77

Once again, a range of amino acids could be used as starting materials. Ester formation using suitable alkenyl substituents would provide the side chain for cyclisation (Scheme 77).

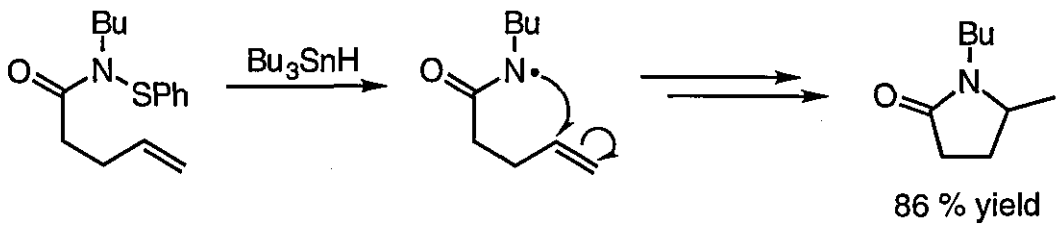
This thesis will include the research obtained from investigation into elements contained within sections (i) and (ii).

THE PREPARATION AND CYCLISATION OF SULFENAMIDE DERIVATIVES OF α-AMINO ACIDS

2.1 Cyclisation onto Amino Acid Side Chains

Prolines are highly desirable targets for testing for biological activity and cyclisation onto side chain alkenes would provide a new route for the production of novel compounds. It would also provide an initial test of stereoselectivity for the radical reaction. Since the routes of addition for electrophilic radicals to arenes and alkenes are similar, the obvious option of research was to use existing amino acids with an aromatic side chain (*e.g.* phenylalanine).

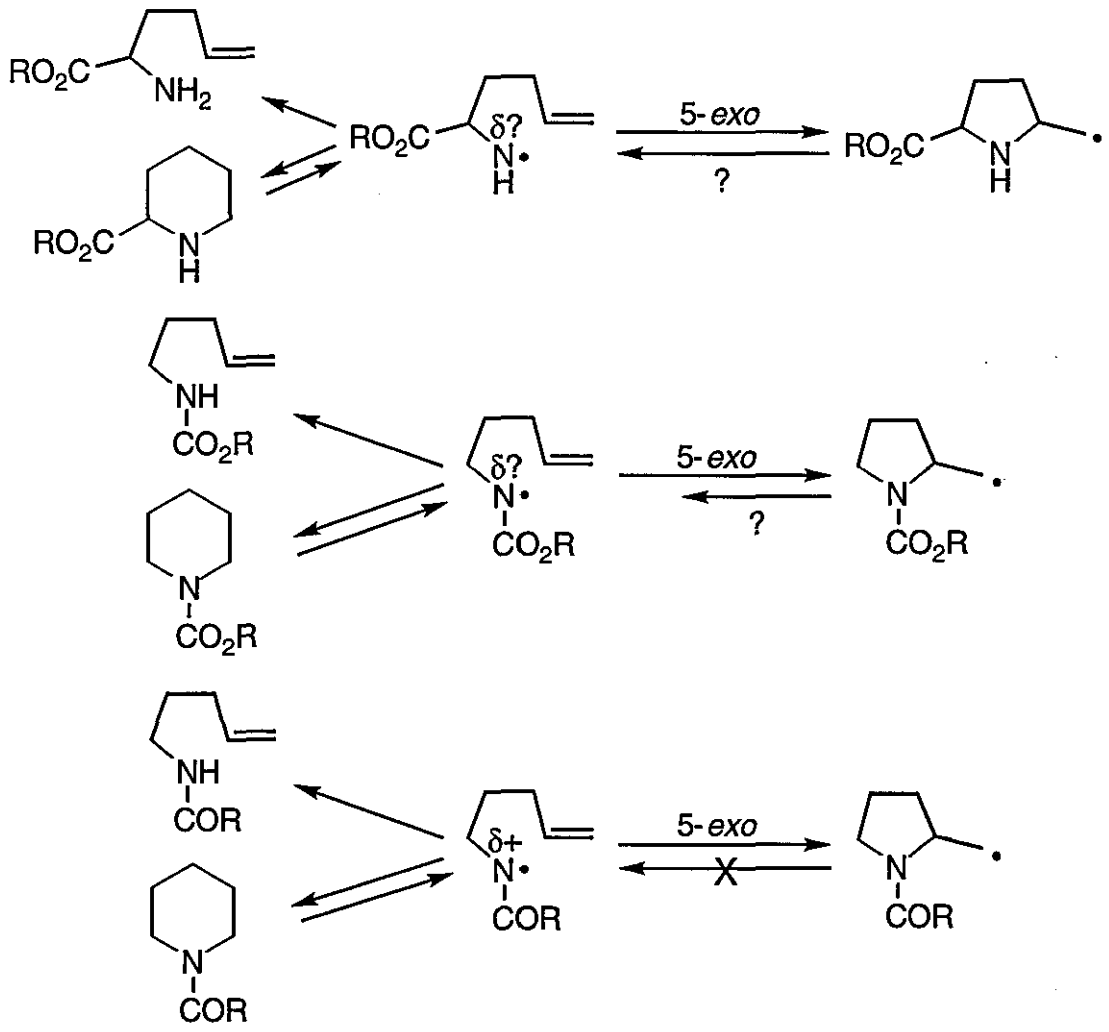
Previous studies within the group[73,88,89] (see section 1.5.2) and by other groups[46,47] have shown that "ordinary" aminyl radicals do not give high yields of cyclisation because of their nucleophilic behaviour. The presence of the α-carboxy methyl group may have a large enough electron-withdrawing effect to make the nitrogen radical electrophilic. An α-ester lowers the pK_{BH^+} of primary amines by *ca.* 3 pH units. For instance, the pK_{BH^+} of glycine ($H_2NCH_2CO_2^-$) and ethylamine ($H_2NCH_2CH_3$) at 25 °C are 9.78 and 10.81 respectively compared with only 7.59 for glycine methyl ester ($H_2NCH_2CO_2Me$) at the same temperature.[99] Our question for this project is whether it is possible that the α-ester would have a similar effect on the aminyl radical as there was no literature to support this. We decided to investigate whether the α-ester would impart sufficient electrophilicity onto the aminyl radical to facilitate cyclisation. Methods for synthesising precursors for aminyl radicals of amino acids were considered. Section 1.5.2 in the introduction describes a number of possible different precursors. As the use of sulfenamides as precursors of aminyl radicals had been developed within the group, these appeared an obvious choice for our studies.



Scheme 78

Amidyl radicals[46] were known to be electrophilic and sulfenamides had been shown to act as precursors for cyclisation (*e.g.* Scheme 78).[100] As a consequence, sulfenamide derivatives of amides of these amino acids could be synthesised and cyclisation attempted. Unfortunately, the removal of the amide to obtain any novel

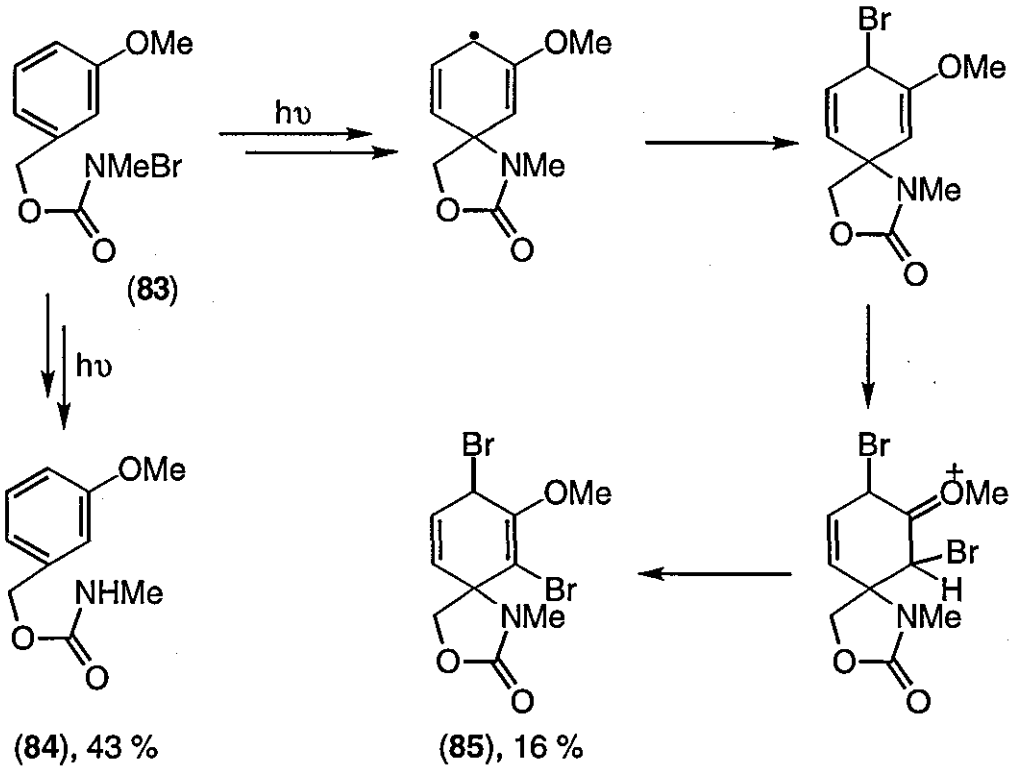
cyclised amino acid would probably be problematic with over vigorous conditions required. This disadvantage meant that we required a replacement electron-withdrawing group on the amine which could be easily removed under mild conditions. Our answer was to investigate the use of urethanes as radical precursors. Urethanes are common protective groups in amino acid chemistry and well established methods for their introduction exist. Also, they are easier to remove than other protective groups.[101] Unfortunately, the sulfenamides of urethanes had not been previously made and would therefore be novel compounds. The urethanyl radical formed would not be as electrophilic as the amidyl radical but should be more electrophilic than the amino acid aminyl radical (Scheme 79) therefore, our initial studies were centred on urethanyl radicals (Scheme 79 also shows the competing formation of 6-*endo* and uncyclised products).



Scheme 79

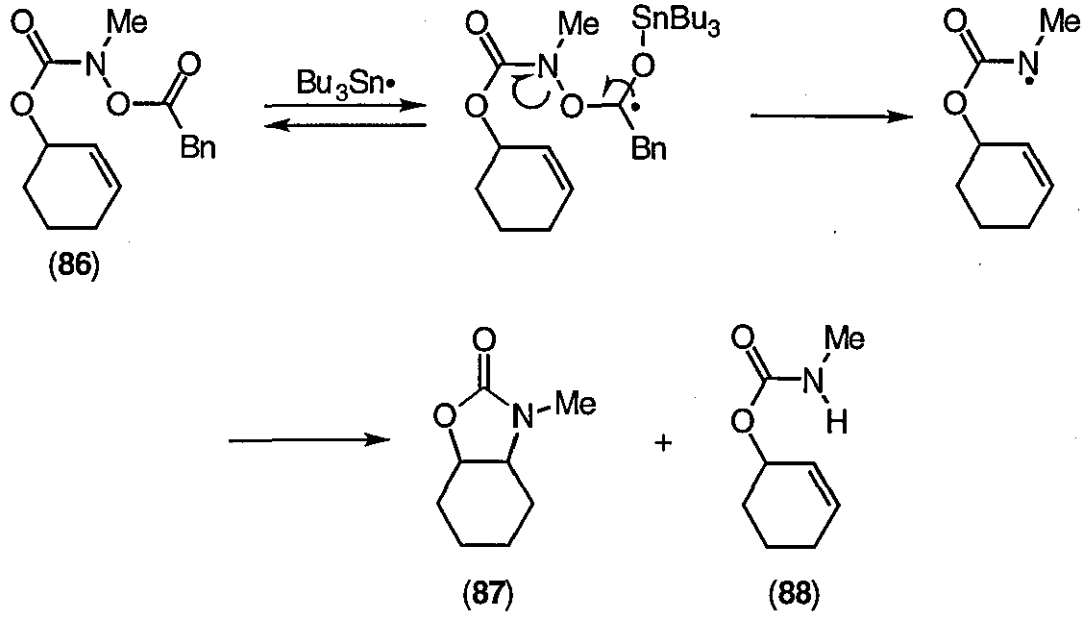
2.1.1 Synthesis and Radical Reactions of Urethane Derived Sulfenamides

There is little known about the preparation and reactivity of urethanyl (carbamyl) radicals, especially their propensity to undergo 5-*exo* cyclisations. Dicks and co-workers studied hydrogen abstraction reactions of the radical using the irradiation of *N*-bromo derivatives[102] and discovered that intramolecular aromatic additions could be achieved by the influence of an aryl methoxy group.[103] The compound *m*-methoxybenzyl *N*-bromo-*N*-methylurethane **83** was irradiated in the presence of 3,3-dimethylbut-1-ene. The reaction afforded mainly the parent urethane **84** (43 % yield) but the cyclisation product 2,4-dibromo-3-methoxy-*N'*-methylcyclohexa-2,5-dienespiro-4'-1',3'-oxazolidin-2-one **85** was also obtained in 16 % yield (Scheme 80).

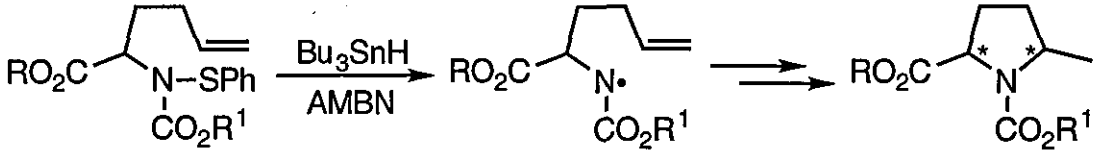


Scheme 80

The intramolecular cyclisation of urethanyl radicals has been further investigated by Zard *et al.* (Scheme 81).[104] To a refluxing solution of the radical precursor **86** in cyclohexane was added a tri-*n*-butyltin hydride/AIBN solution over 4 h to yield the desired cyclic urethane **87**, along with uncyclised material **88** in a ratio of 40:60 (the isolated yield of **87** was only 20 % however). Our intention was to extend the use of urethanyl radicals by attempting 5-*exo-trig* cyclisations onto alkenes in the synthesis of various prolines as shown in Scheme 82.

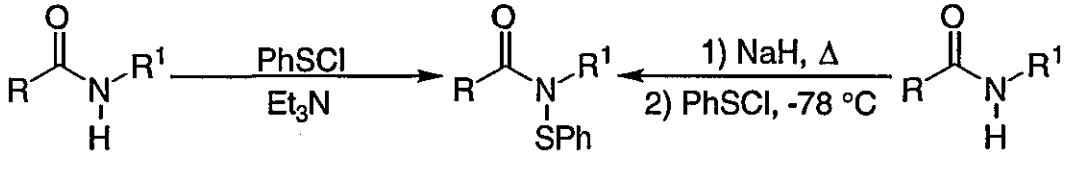


Scheme 81



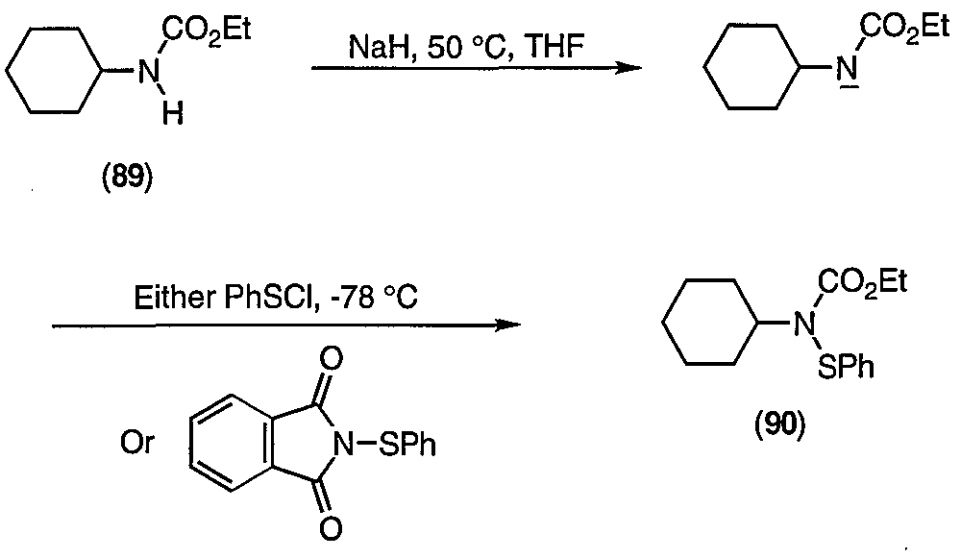
Scheme 82

To discover whether urethanyl radicals could be produced by the reaction between tri-*n*-butyltin hydride and sulfenamides of urethanes, the simple urethane *N*-ethoxycarbonylcyclohexylamine **89** was used as a model. There were no reports in the literature for the formation of sulfenamides of urethanes. However, Newcomb and Esker have reported methods for the synthesis of *N*-(benzenesulfenyl) derivatives of amides (Scheme 83).[100]



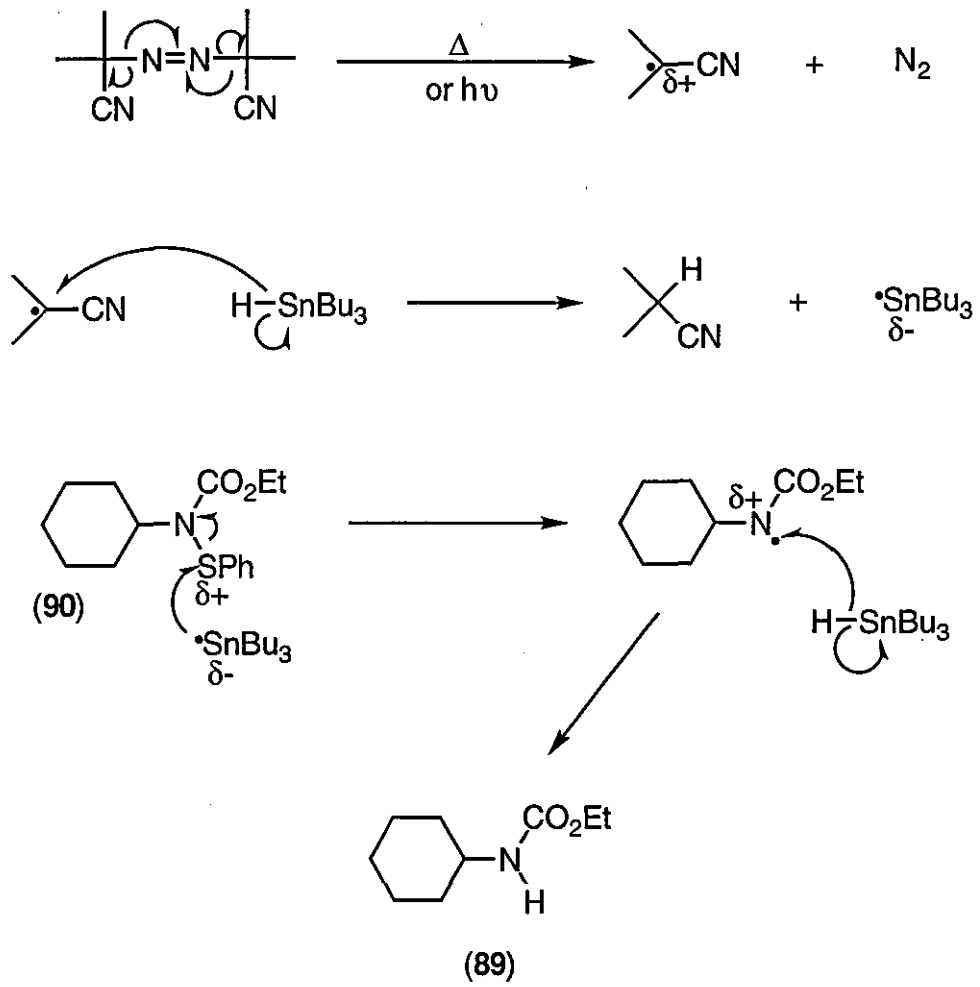
Scheme 83

N-Ethoxycarbonylcyclohexylamine **89** was stirred at 50 °C in THF with sodium hydride for 2 h and benzenesulfenyl chloride added to yield *N*-(benzenesulfenyl)-*N*-ethoxycarbonylcyclohexylamine **90** in 20 % yield (Scheme 84). Unfortunately, purification of the sulfenamide was hampered by impurities of similar polarity whilst utilising flash column chromatography owing to the side reactions of the benzenesulfenyl chloride (*e.g.* formation of diphenyl disulfide). In order to attempt to avoid these impurities, the less reactive *N*-(benzenesulfenyl)phthalimide was used as an alternative to the benzenesulfenyl chloride (Scheme 84). The *N*-(benzenesulfenyl)-*N*-ethoxycarbonylcyclohexylamine **90** produced was indeed cleaner with only two main impurities which could both be separated but the yield of 26 % was still disappointing. Although the yield was low, our results showed that the synthesis of sulfenamide derivatives of urethanes was possible.



Scheme 84

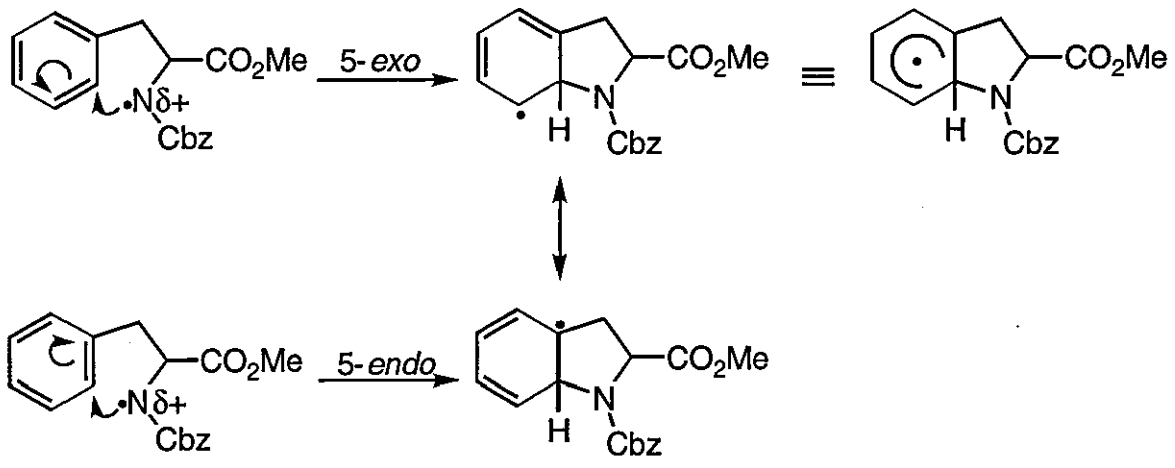
Of course, no cyclisation was possible with sulfenamide **90** but its reaction with tri-*n*-butyltin hydride was carried out to determine whether the tri-*n*-butyltin radical would abstract the benzenesulfenyl group to yield intermediate urethanyl radicals. The reaction with tri-*n*-butyltin hydride proved successful and the *N*-ethoxycarbonylcyclohexylamine **89** was obtained in quantitative yield. The reaction and proposed mechanism are shown in scheme 85. The reaction does not absolutely prove that urethanyl radicals were intermediates and inhibition studies would be required. However, the result was promising, so we proceeded to study α-amino esters.



Scheme 85

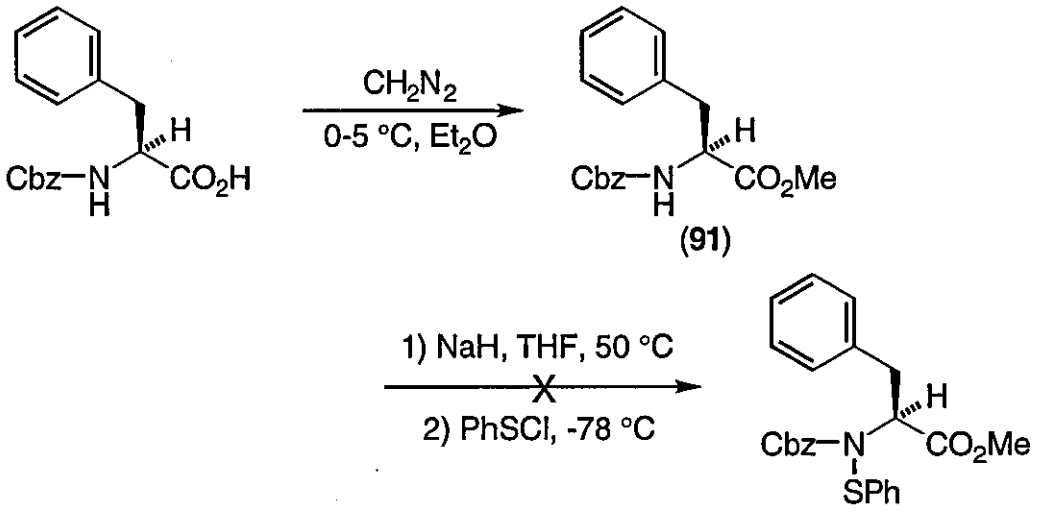
2.1.2 Synthesis and Radical Reactions of Urethane Derived α-Amino Ester Sulfenamides

Ideally, we wished to study the cyclisation onto side-chain alkenes to yield prolines. However, a number of natural amino acids have unsaturation in the δ-position in the form of aromatic rings, *e.g.* phenylalanine, tyrosine, histidine and tryptophan. Phenylalanine was chosen as the "model" amino acid because it was the cheapest, had the simplest structure for the reaction and was more easily protected than the others. However, cyclisation onto the arene of phenylalanine was unknown and could be considered as either 5-*endo* (unfavoured) or 5-*exo* (favoured). To our knowledge, this dichotomy of mechanism has not been commented on in the literature. Both types of mechanism lead to the same π-radical (Scheme 86). We decided to investigate because the target precursor was envisaged to be simple to synthesise.



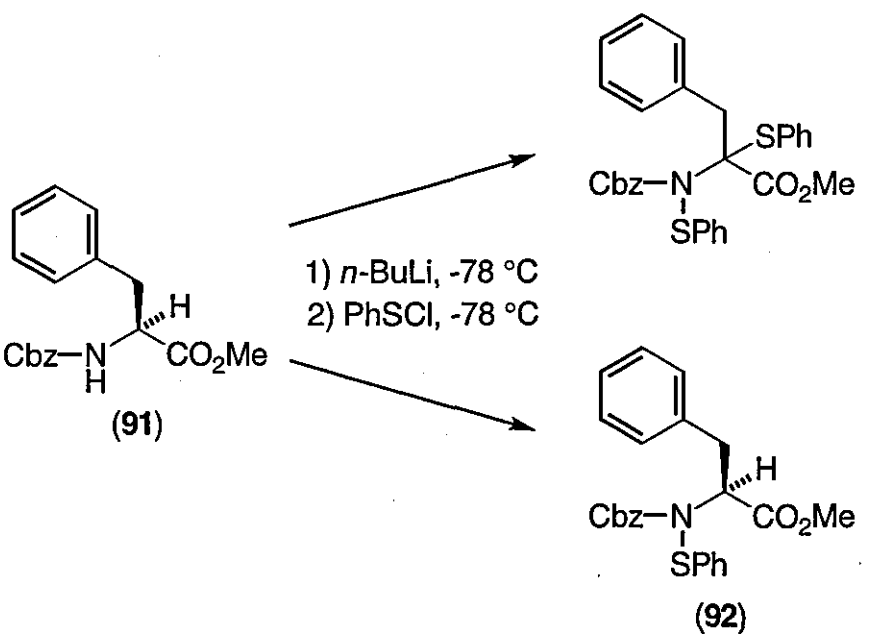
Scheme 86

As it turned out, the synthesis of the sulfenamides of the amino acids proved more troublesome. *N*-(Benzyloxycarbonyl)-*L*-phenylalanine was reacted with diazomethane to give *N*-(benzyloxycarbonyl)-*L*-phenylalanine methyl ester **91** and then reacted using Newcomb's method (Scheme 87) to form the sulfenamide but neither starting material nor recognisable product was obtained. A possible cause was identified in the work-up where an "evaporation to dryness" step was exposing the reaction mixture to highly concentrated alkaline conditions. This was avoided with an aqueous work-up using phosphate buffer solution (pH = 7.0) but the sulfenamide was still only produced in low yield. Studies indicated that the sodium hydride in tetrahydrofuran method was not completely forming the required anion. Also, at the reaction temperature employed, any anion that was formed was reacting with itself or further protected amino acid to give diketopiperazide and polymeric material.



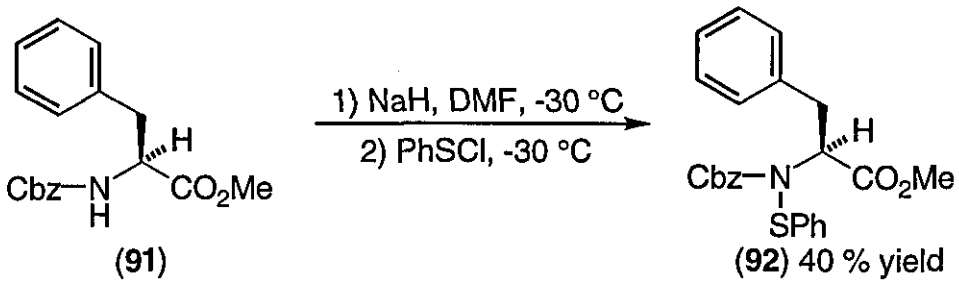
Scheme 87

The stronger base *n*-butyllithium was certain to fully deprotonate the nitrogen rapidly and at lower temperature. However, the use of *n*-butyllithium also had the possibility of deprotonation at the α-carbon and, consequently, formation of the *C, N*-disulfenamide (Scheme 88). This did occur and the reproducibility of the reaction was poor with variable results. For instance, *N*-(benzenesulfenyl)-*N*-(benzyloxycarbonyl)-*L*-phenylalanine methyl ester **92** was obtained in 40 % yield but, when disulfenamide was produced, separation of the two derivatives was impossible. One infuriating aspect of the reaction was the ability for disulfenamide and starting material to co-exist. Hence, even calculated addition of base produced a mix of sulfenamides. *N*-(Benzenesulfenyl)-*L*-phenylalanine methyl ester had also been made (see section 2.1.2) but an attempt to introduce the *N*-benzyloxycarbonyl group as the second step proved unsuccessful.



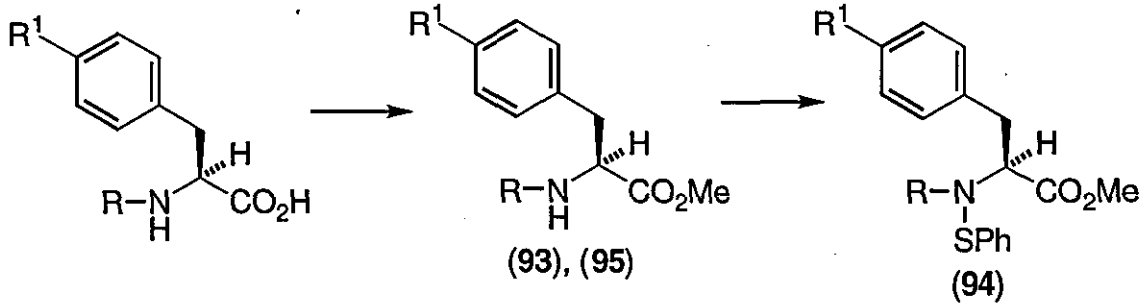
Scheme 88

Fortunately, replacing tetrahydrofuran with the dipolar aprotic solvent, dimethylformamide, as reaction solvent and returning to sodium hydride as base produced *N*-(benzenesulfenyl)-*N*-(benzyloxycarbonyl)-*L*-phenylalanine methyl ester **92** in 40 % yield, even after the lengthy work-up of removing the dimethylformamide (Scheme 89). A possible reason for the average yields may have been the presence of hydrogen chloride in the benzenesulfenyl chloride. It was hoped that this "general method" would be applicable to a variety of urethanes.



Scheme 89

With the success of the synthesis of the sulfenamide of phenylalanine, tyrosine was chosen to be studied next. To this end, *N*-(benzyloxycarbonyl)-*L*-tyrosine was reacted with diazomethane to give the diprotected *N*-(benzyloxycarbonyl)-*O*-methyl-*L*-tyrosine methyl ester **93** in excellent yield (Scheme 90). The reaction to protect the phenol was very slow with excess diazomethane and a long reaction time required to ensure diprotection. However, when attempts were made to produce *N*-(benzenesulfenyl)-*N*-(benzyloxycarbonyl)-*O*-methyl-*L*-tyrosine methyl ester **94** using the "general method", several unidentifiable products and only trace amounts of the desired sulfenamide were formed. The amide derivative *N*-acetyl-*L*-phenylalanine methyl ester **95** was produced from diazomethane and *N*-acetyl-*L*-phenylalanine (Scheme 90). When this too was exposed to the benzenesulfenylation "general method", there was no trace of any phenylalanine derivative on analysis. It was evident that further investigation into derivatising sulfenamides of alkene/arene-containing natural α-amino acids was required and, although the intention was to return to the topic and pursue the possible use of *L*-tryptophan, no further research was carried out.



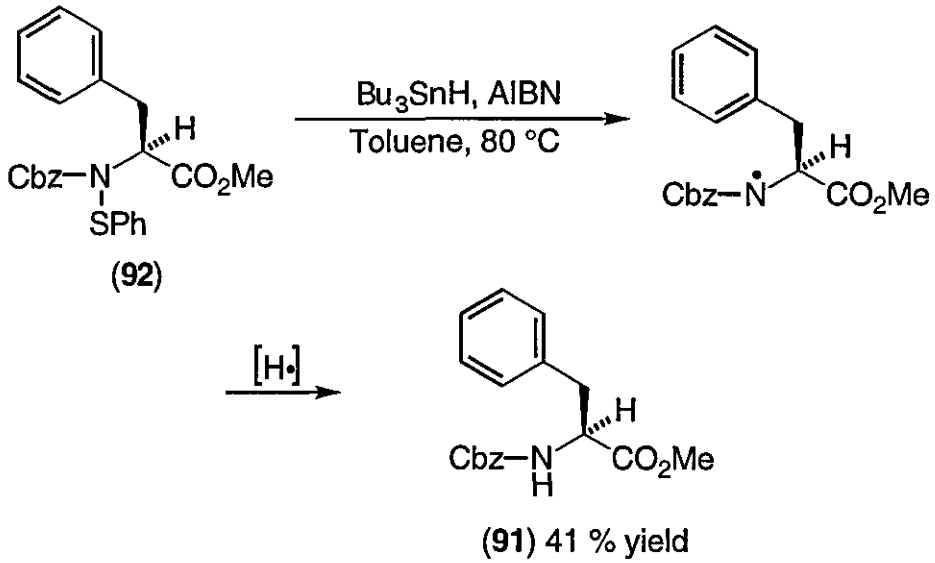
(93), R = Cbz, R^1 = OMe, 95 % yield

(94), R = Cbz, R^1 = OMe, trace amounts

(95), R = Ac, R^1 = H, 97 % yield

Scheme 90

The sulfenamide *N*-(benzenesulfenyl)-*N*-ethoxycarbonylcyclohexylamine **90** was reacted with tri-*n*-butyltin hydride in refluxing toluene (110 °C) and degradation of the urethane to the acid was observed. The thermal degradation of urethanes, especially those of an aryl nature, has been documented.[105] As a consequence, subsequent radical reactions were carried out at 80 °C in order to avoid this thermal degradation. A blank reaction using *N*-(benzenesulfenyl)-*N*-(benzyloxycarbonyl)-*L*-phenylalanine methyl ester **92** showed no degradation of compound and, therefore, that the reduction of the urethane **90** was due to a radical reaction and not from an ionic/thermal source. Phenylalanine had been initially chosen for its simplicity but it also meant that it was the least reactive and therefore the least likely to cyclise. It was no surprise then that the reaction of the sulfenamide **92** with tri-*n*-butyltin hydride produced *N*-(benzyloxy-carbonyl)-*L*-phenylalanine methyl ester **91** as the sole product in 41 % yield (Scheme 91). The tri-*n*-butyltin hydride and AIBN were added using a syringe pump to keep the concentration of hydride low and therefore encourage cyclisation but no such cyclisation product was observed. The lack of cyclisation may be due to problems of stereoelectronic effects in the transition state which could be regarded as a 5-*endo* cyclisation which is unfavoured (see Scheme 86).

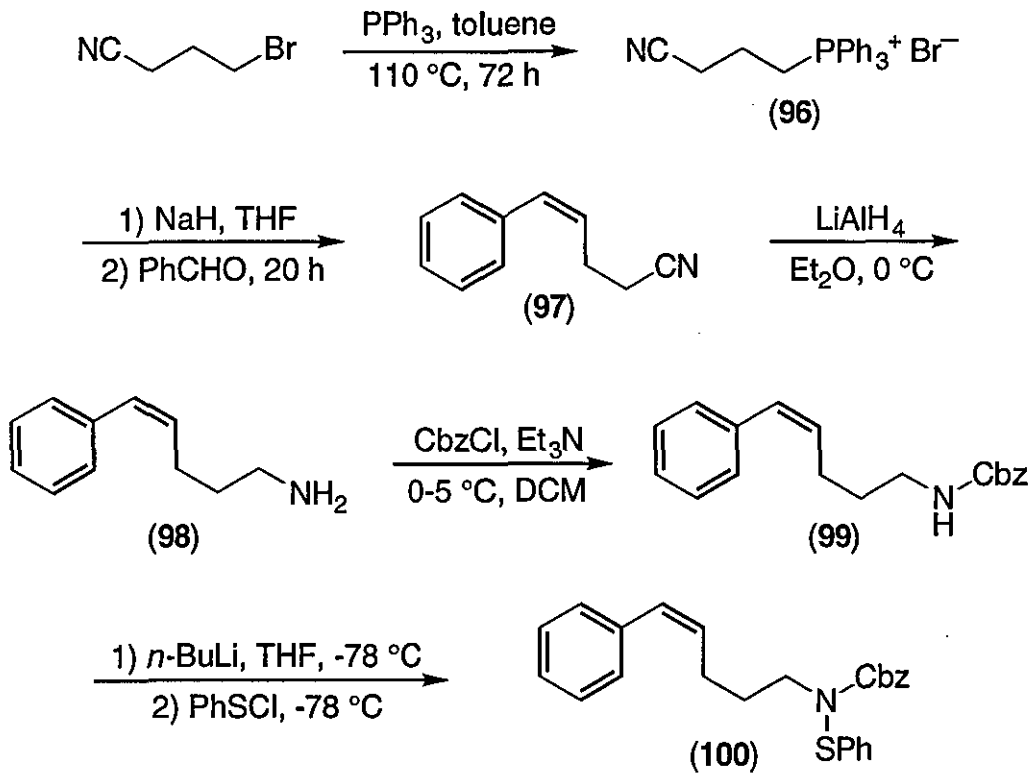


Scheme 91

2.1.3 Cyclisation of Urethanyl Radicals

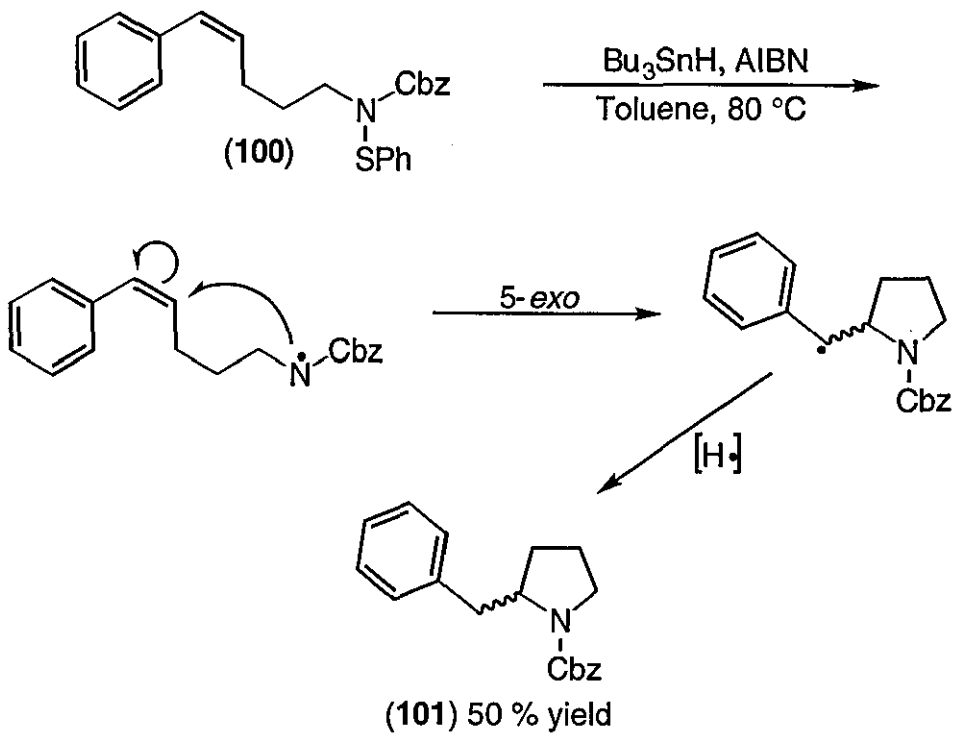
In order to prove further the existence of urethanyl radicals and to examine their cyclisation potential, we decided to study a simple δ-alkenyl urethane. To this end, the radical precursor *N*-(benzenesulfenyl)-*N*-(benzyloxycarbonyl)-(Z)-5-amino-1-phenylpent-1-ene **100** was synthesised (Scheme 92). The phosphonium salt **96** was reacted with benzaldehyde in a Wittig reaction to give the nitrile **97** and then reduced

with lithium aluminium hydride to produce the amine **98**. Protection of the amine **98** gave *N*-(benzyloxycarbonyl)-(*Z*)-5-amino-1-phenylpent-1-ene **99** in good overall yield. However, when the sodium hydride/dimethylformamide method was used in the benzenesulfenylation, a complex mixture of product and impurity was obtained. Unlike the amino acids though, there would be no problem with deprotonation at the α-carbon. Hence, deprotonation of the urethane **99** using *n*-butyllithium in dimethylformamide at -78 °C and subsequent reaction with benzenesulfenyl chloride gave *N*-(benzenesulfenyl)-*N*-(benzyloxycarbonyl)-(*Z*)-5-amino-1-phenylpent-1-ene **100** in 60-70 % yield.



Scheme 92

Reaction between the sulfenamide **100** and tri-*n*-butyltin hydride produced a 5-*exo-trig* cyclisation to give benzyl 2-benzyl-1-pyrrolidinecarboxylate **101** in 50 % yield as a pair of rotamers (1:1 ratio, Scheme 93). It should be noted that, similarly to amides, the urethane *NHCO* bond shows considerable double bond character hence the consequent restricted rotation resulted in rotamers. It was shown therefore that cyclisation using urethanyl radicals was a viable route for addition to double bonds. Further investigation into the addition of urethanyl radicals onto alkene containing side chains of amino acids has been carried out within the group and the results produced have yet to be published.

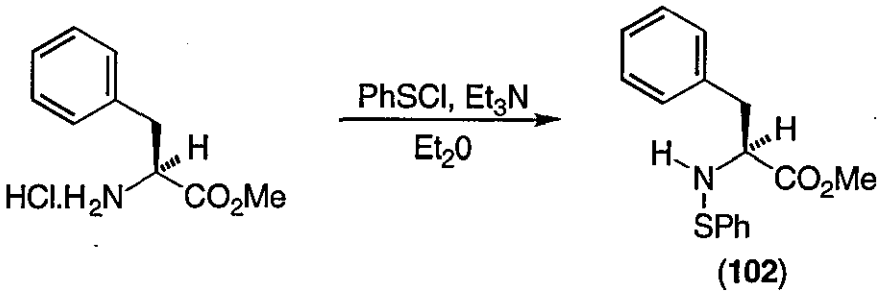


Scheme 93

2.1.4 Synthesis and Radical Reactions of *N*-(Benzenesulfenyl)-*L*-Phenylalanine Methyl Ester

We then turned our attention to non-protected amino acids to determine whether the α-ester would make the aminyl radical electrophilic enough for cyclisation. Again, phenylalanine was chosen as a model for developing the synthetic method. However, with the failure of the phenylalanine urethanyl radical to cyclise, we were not too hopeful that the non-protected amino acid would cyclise. Phenylalanine methyl ester hydrochloride was reacted with triethylamine (>20 equivalents) in diethyl ether to liberate the free amine before cooling to 0-5 °C in an ice bath. The dropwise addition of benzenesulfenyl chloride over a 30 minute period gave *N*-(benzenesulfenyl)-*L*-phenylalanine methyl ester **102** in a crude mixture (Scheme 94, for a detailed mechanism of the reaction of amines with benzenesulfenyl chloride, see section 2.2.1 (iii)).[73,88,89] Apart from the expected impurities resulting from benzenesulfenyl chloride, two products were observed by both ^{1}H NMR spectroscopy and thin layer chromatography. These turned out to be diastereomers of *N*-(benzenesulfenyl)-*L*-phenylalanine methyl ester **102** in the ratio 4:1. The diastereomers arise as the N-S bond is, in fact, a chiral axis as a result of the high torsional energy of the N-S bond. A detailed description of this property can be found in section 1.5.2. Purification using either silica or alumina columns resulted in degradation of the compound and an

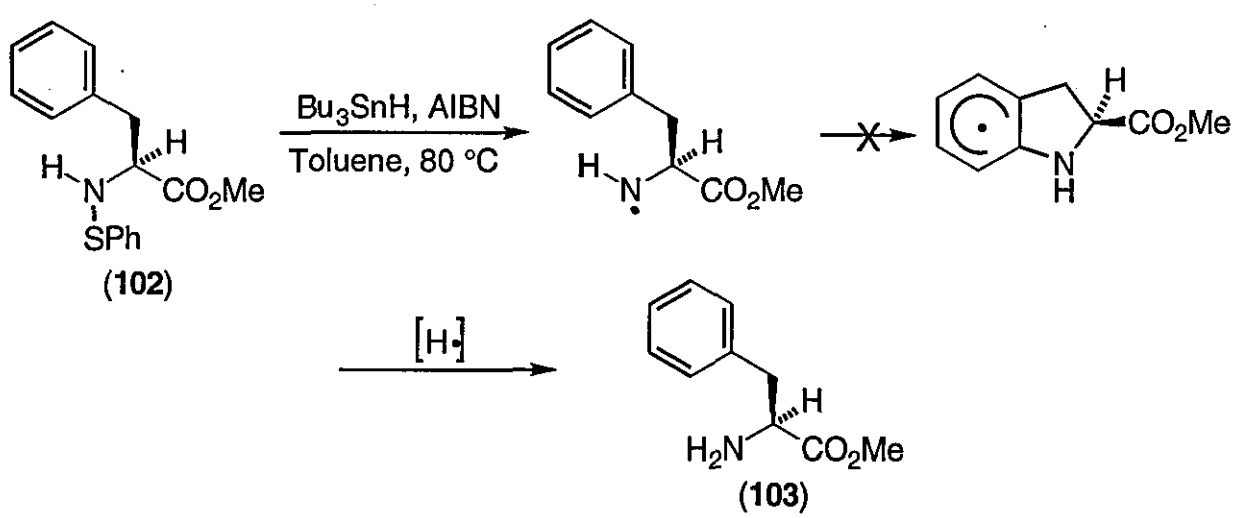
apparent reduction in diastereoselectivity between the two diastereomers (a ratio of approximately 3:2 by ^1H NMR spectroscopy). It is not known whether the loss in diastereoselectivity was due to inter-conversion of the diastereomers or the quicker degradation of one over the other.



(102)

Scheme 94

Benzenesulfenyl chloride is obviously a strong enough electrophile to react with the weakly nucleophilic α-aminoester group. Replacing the benzenesulfenyl chloride with the pure *N*-(benzenesulfenyl)phthalimide meant refluxing the dichloromethane solution for 4 days in order to obtain the sulfenamide **102** but no gain in purity of the product was observed. Consequently, the crude mixture had to be used for the radical reaction. Not unexpectedly, no cyclisation was observed and *L*-phenylalanine methyl ester **103** was the only identifiable amine product (Scheme 95).



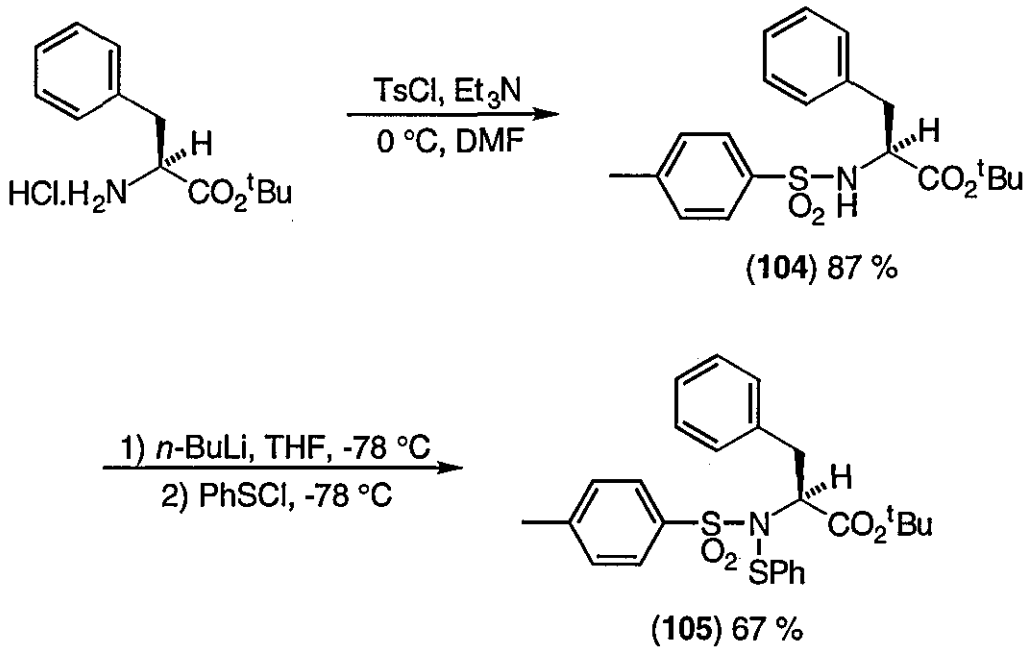
(102) **(103)**

Scheme 95

2.1.5 Synthesis and Radical Reactions of *N*-Tosyl Derived Sulfenamides

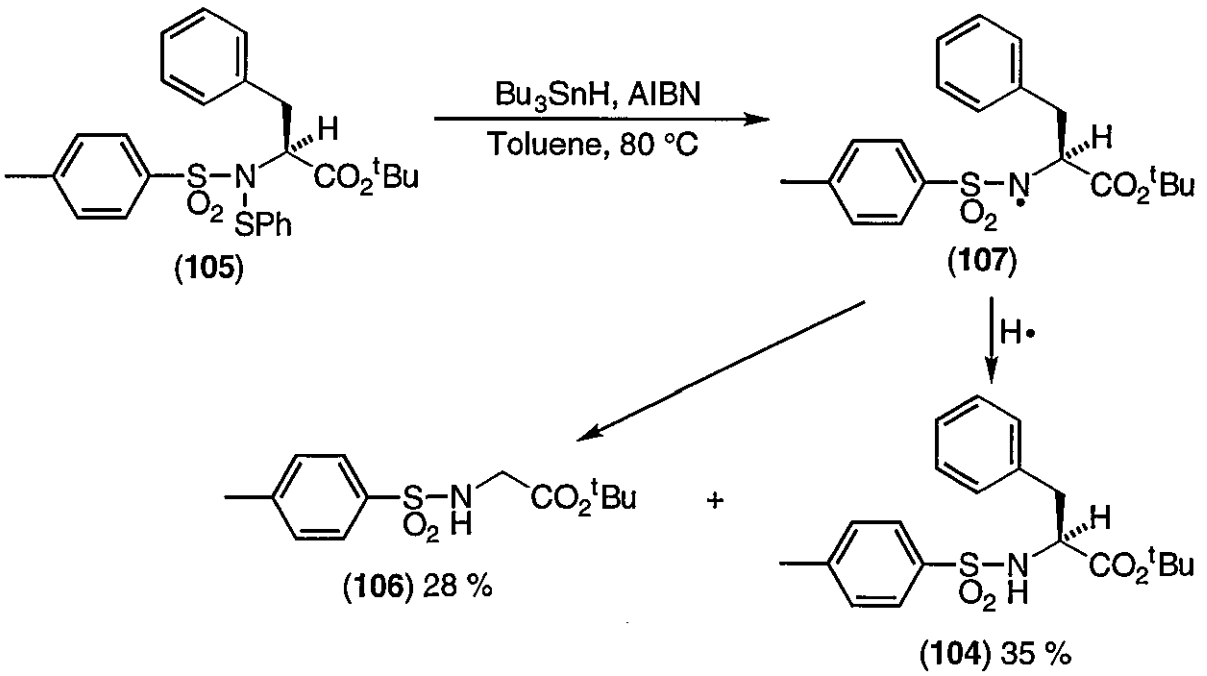
With the problems and lack of cyclisation involved with the previous derivatives, would the use of another *N*-protecting group facilitate the required

addition onto an aromatic ring? Tosyl groups are stronger electron-withdrawing groups than amides or urethanes and could be expected to make the aminyl radical more electrophilic, possibly enhancing the ability to cyclise. To this end, *L*-phenylalanine *tert*-butyl ester hydrochloride salt (the synthesis of amino acid *tert*-butyl esters is discussed in section 2.2.1) was reacted with tosyl chloride to give *N*-tosyl-*L*-phenylalanine *tert*-butyl ester **104**. The tosylate **104** was reacted using the "general method" (sodium hydride/dimethylformamide/benzenesulfenyl chloride) described in section 2.1.1 to yield *N*-(benzenesulfenyl)-*N*-tosyl-*L*-phenylalanine *tert*-butyl ester **105** in 67 % yield (scheme 96).

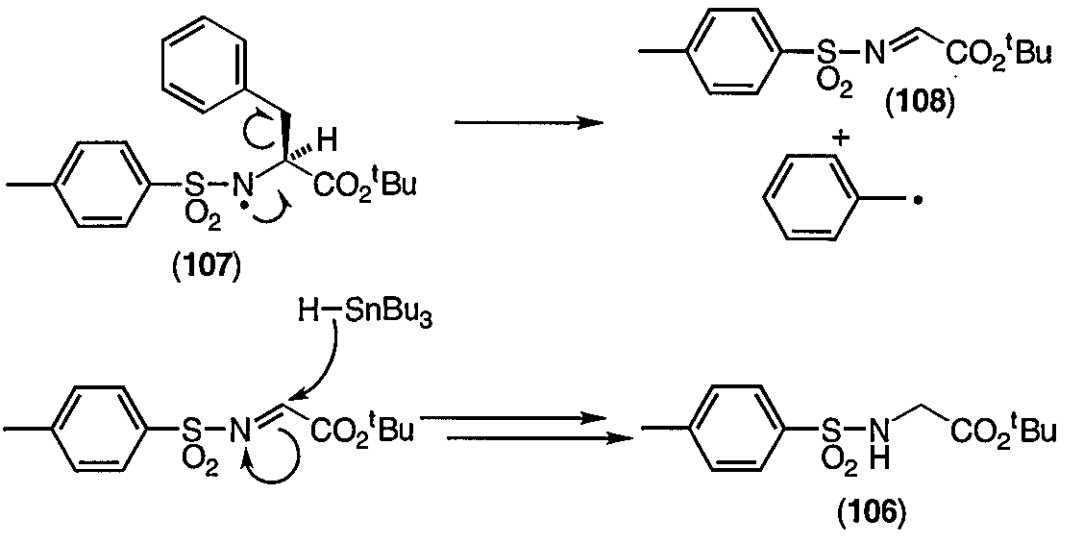


Scheme 96

The reaction between the tosyl sulfenamide **105** and tri-*n*-butyltin hydride and AIBN proved interesting. No cyclic product was observed and the reduced tosylate **104** was obtained in 35 % yield. Of interest was the cleavage of the amino acid side chain, the benzyl group, to give *N*-tosylglycine *tert*-butyl ester **106** in 28 % yield (Scheme 97). Repeating the reaction without the tin reagent resulted in quantitative recovery of the sulfenamide hence the method of cleavage must have been radical. It is possible that the aminyl radical **107** underwent β-scission (Scheme 98) to give the imine **108** and the stable benzyl radical. The imine was very electrophilic, facilitated by the α-ester and *N*-tosyl group, and could easily be reduced by the tri-*n*-butyltin hydride, acting as a hydride reductant, to give the tosylglycine derivative **106**. No further work was carried out on tosyl derivatives for cyclisation.



Scheme 97

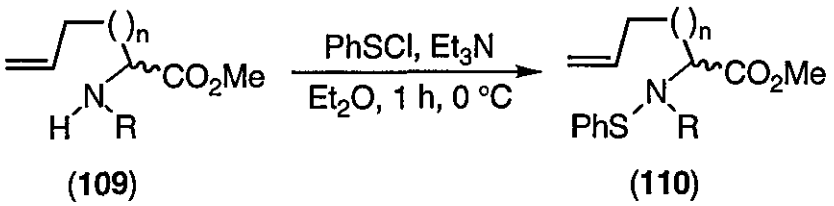


Scheme 98

2.1.6 Radical Reactions of α-Amino Ester Sulfenamides using Alkenyl Side Chains

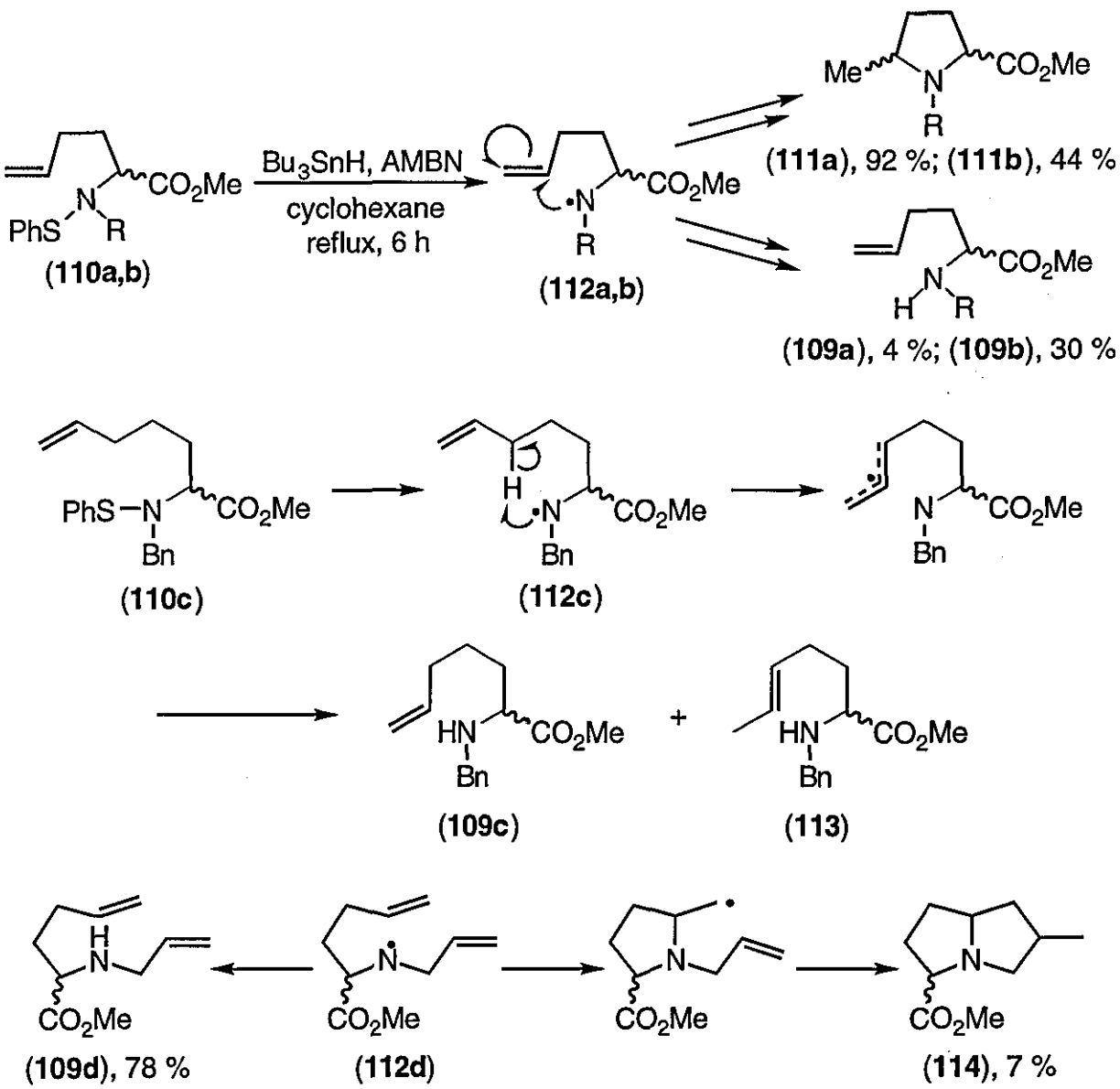
At this point, whilst I turned my attention towards cyclisations involving *N*-substituted side chains (section 2.2), Dr D. R. Coghlan continued to complete the topic by investigating the addition of aminyl radicals onto alkenyl (not arenyl) side chains and this work is briefly summarised. For initial convenience, the racemic α-alkenyl amino acids **109a-d** used in the study were synthesised by alkylation of the benzal imine of methyl glycine (see section 4.1 for details of the method). The sulfenamide

precursors **110a-d** were synthesised by the same procedure as described in section 2.2.1 (iii), although lower yields were obtained than for their *N*-substituted counterparts due to poor stability on a silica column (Scheme 99).



a, n = 1, R = H; 24 %
b, n = 1, R = Bn; 74 %
c, n = 2, R = Bn; 76 %
d, n = 1, R = allyl; 94 %

Scheme 99

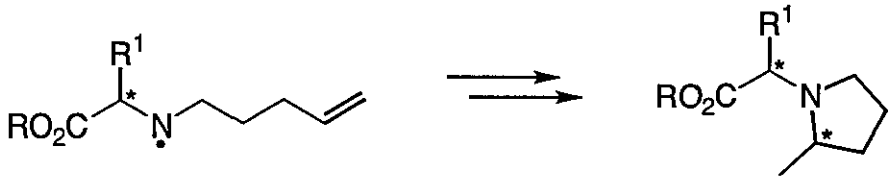


Scheme 100

As in the case of the urethanes, a lower temperature for the cyclisation was required. To this end, cyclohexane was used as solvent in place of toluene and AMBN (trade name for 2-[(*E*)-2-(1-cyano-1-methylpropyl)-1-diazenyl]-2-methylbutanonitrile) as initiator in place of AIBN (due to its greater solubility in cyclohexane). Cyclisation of **110a** gave two diastereomers of the proline derivative **111a** in 92 % yield with a *d.e.* of 57 %. The secondary aminyl radical **112b** was less electrophilic than the primary radical **112a** and only cyclised in 44 % yield with an increase in uncyclised product **109b**. The 6-*exo* cyclisation of **110c** was unsuccessful and 1,5-hydrogen abstraction occurred faster than the cyclisation to give a 1:1 ratio of the alkenes **109c** and **113** (Scheme 100). The analogous aminyl radicals lacking the α-ester undergo 6-*exo* cyclisation and not 1,5-hydrogen abstraction indicating that the electrophilicity imparted by the α-ester causes the H-abstraction for the intermediate aminyl radical **112c**. The tandem cyclisation of **110d** was also not very successful and gave a 7 % yield of diastereomers (3:1 ratio) of the pyrrolizidine **114**. This low yield could be explained by poor electrophilicity of the dialkyl aminyl radical intermediate **112d** (as was proposed for **112b**). These results have been published in preliminary form.[106]

2.2 Cyclisation onto *N*-Substituted Side Chains

Although the cyclisation onto arenes had proved unsuccessful, it was hoped that the 5-*exo-trig* cyclisation of an aminyl radical onto a *N*-substituted alkenyl component would readily occur. Various areas of investigation were targeted as we sought to answer several questions (Scheme 101). For instance, would the α-carbon stereocentre impart diastereoselectivity to any cyclised material? Would the size of the amino acid side-chain or the size of the ester moiety have any influence on the *d.e.* ? To this end, the *L*-amino acids alanine, valine, phenylalanine and *tert*-leucine were chosen to be derivatised. Methyl, benzyl and the more bulky *tert*-butyl esters were also selected to test the effect on stereoselectivity.



R = Me or ^{t}Bu

R^1 = Me, *iso*-Pr, Bn or ^{t}Bu

* = chiral centre

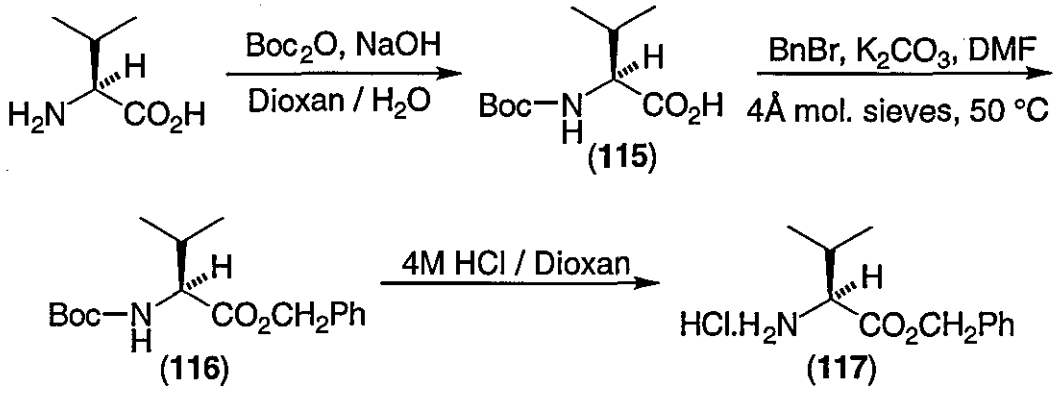
Scheme 101

2.2.1 Derivatisation of the α-Amino Acids

(i) Synthesis of α-Amino Acid Esters

The methyl esters of many amino acids can readily be bought or synthesised. As a consequence, there is little discussion here. The two methods used during my research involved methylation using diazomethane of *N*-benzyloxycarbonyl protected amino acids (section 2.1) and the use of acid chloride (thionyl or oxalyl) in methanol for amino acids and their hydrochloride salts (section 4.1). Of more interest is the formation of the benzyl and *tert*-butyl esters and these are described.

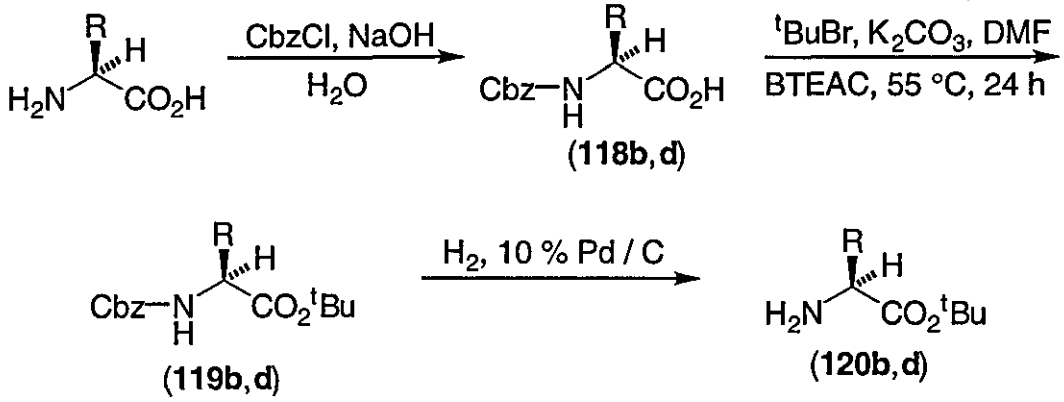
Only one method was used for benzyl esterification (Scheme 102). *N*-butoxy-carbonyl-*L*-valine **115** was formed in excellent yield from the reaction of *L*-valine with sodium hydroxide and di-*tert*-butyl dicarbonate. Stirring **115** for 4 h at 50 °C with benzyl bromide and potassium carbonate in dimethylformamide gave *N*-butoxy-carbonyl-*L*-valine benzyl ester **116**. Deprotection in 4 M HCl/dioxan solution afforded the desired *L*-valine benzyl ester hydrochloride **117**. The method was clean, easy and the overall yield for the 3 steps was 86 %. The benzyl esters for further amino acid substrates were never required.



Scheme 102

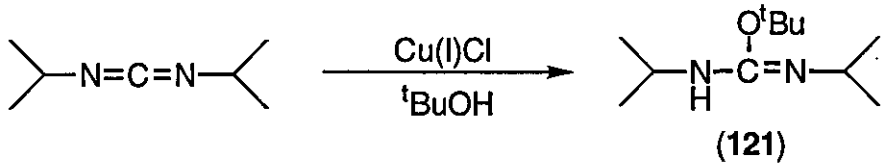
Two methods were eventually used for the preparation of *tert*-butyl esters. The first was a variation on the benzyl ester formation (Scheme 102).[107] For example, *N*-(benzyloxycarbonyl)-*L*-valine **118b**, produced from the reaction between *L*-valine, sodium hydroxide and benzyl chloroformate, was stirred for 24 h at 55 °C with *tert*-butyl bromide, potassium carbonate and benzyltriethylammonium chloride in dimethylformamide to give *N*-(benzyloxycarbonyl)-*L*-valine *tert*-butyl ester **119b** in 84 % yield. Deprotection of the urethane **119b** to give *L*-valine *tert*-butyl ester **120b** was achieved by hydrogenation. Similarly, *L-tert*-leucine *tert*-butyl ester **120d** was synthesised in 50 % overall yield (only 64 % yield was obtained for **118d** to **119d**). This method was probably more suitable for use in laboratories within industry as there

were several disadvantages for a smaller research laboratory. For instance, esterification of the benzyloxycarbonyl derivatives required several equivalents of reactants. Also, an efficient, and probably expensive, overhead stirrer was required whose performance was unaffected by the condensing fumes of *tert*-butyl bromide and the large amounts of inorganic solid present during the reaction. These disadvantages would not be a problem within industry where funds are more forthcoming.



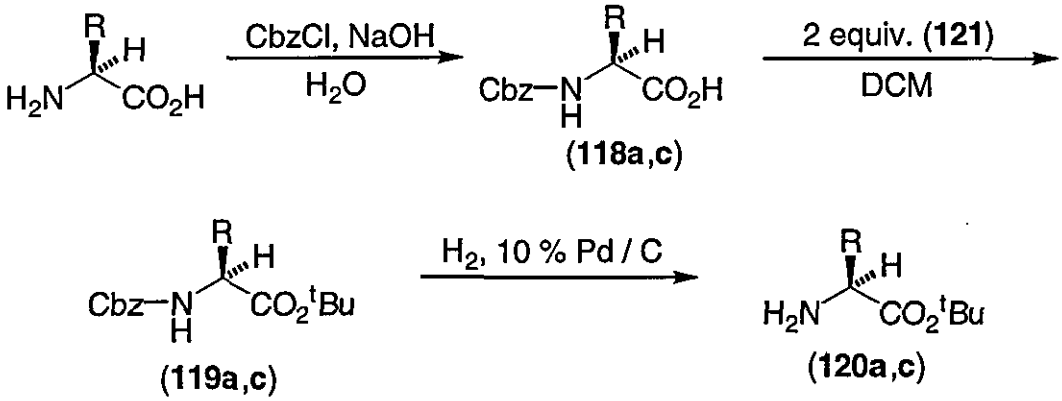
b, R = *iso*-Pr, 84 % overall yield
d, R = ^{t}Bu, 50 % overall yield

Scheme 103



Scheme 104

The second method was much more suitable for small scale synthesis within the postgraduate laboratory.[108] Protection and deprotection of the amino acids was identical to the first method but the esterification step required stirring the *N*-benzyloxycarbonyl derivative with 2 equivalents of the reagent *tert*-butyl *N-iso*propyl-(*iso*propylamino)methanimidate **121** in dichloromethane. This was prepared by the reaction of *N,N*-di*iso*propylcarbodiimide with *tert*-butanol in the presence of copper (I) chloride (Scheme 104). Although we used the crude mix for esterifications, purification of the imidate **121** could be achieved by distillation and higher ester yields subsequently achieved. Increasing the amount of imidate **121** used also increased the yields of ester. *L*-alanine *tert*-butyl ester **120a** and *L*-phenylalanine *tert*-butyl ester **120c** were prepared using this technique (Scheme 105).

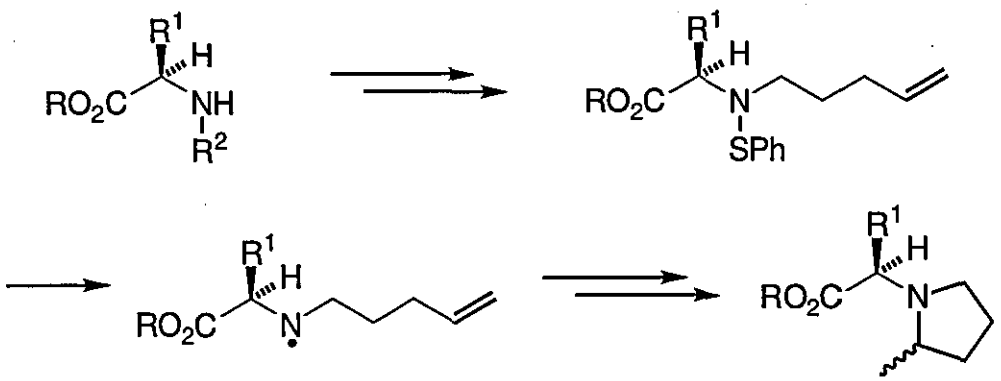


a, R = Me, 45 % overall yield
c, R = Bn, 59 % overall yield

Scheme 105

(ii) N-*Alkylation of α-Amino Acid Derivatives*

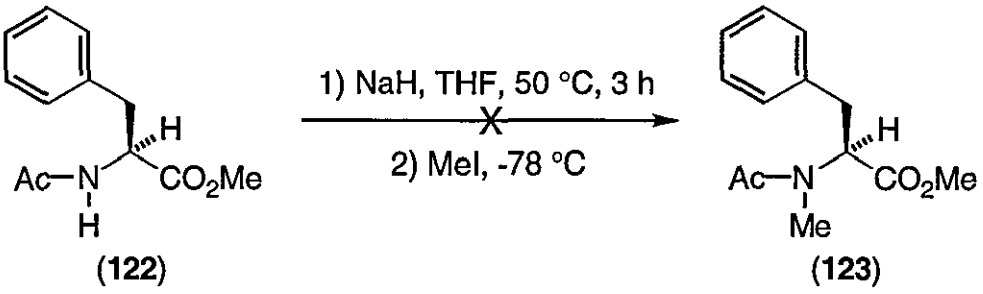
This proved to be the most problematic step in the synthesis of the radical precursors. Our plan was to alkylate the amino acid nitrogen with a 4-pentenyl group and therefore the aminyl radical produced could cyclise in a 5-*exo* manner (Scheme 106).



Scheme 106

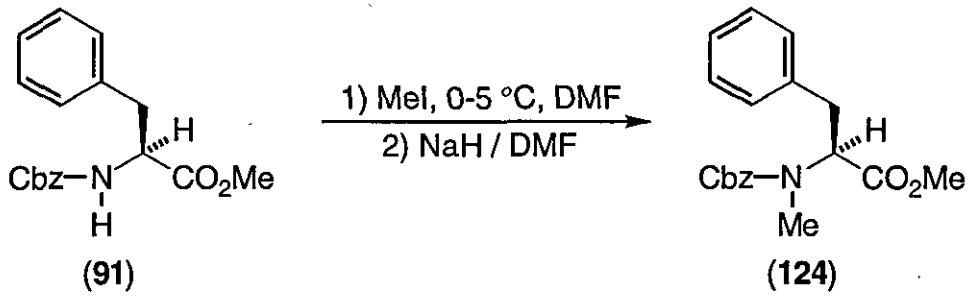
With the work that had been carried out on *N*-protected amino acids (section 2.1), the obvious answer was to alkylate and deprotect these derivatives. For instance, *N*-acetyl-*L*-phenylalanine methyl ester **122** was refluxed in tetrahydrofuran with sodium hydride, cooled and methyl iodide added. Unfortunately, no trace of *N*-alkylated compound **123** was isolated (Scheme 107). These reactions mirrored the problems that had been encountered in the attempted benzenesulfenylations of the protected amino acids in section 2.1. However, *N*-methylation was achieved in excellent yield by using the method devised by Benoiton and McDermott.[109] *N*-(benzyloxy-

carbonyl)-*L*-phenylalanine methyl ester **91** was cooled to 0-5 °C with methyl iodide in dimethylformamide. A sodium hydride/dimethylformamide suspension was syringed in and the reaction stirred at room temperature for 15 h to give *N*-methyl-*N*-(benzyloxy-carbonyl)-*L*-phenylalanine methyl ester **124** in 94 % yield (Scheme 108).



(122) (123)

Scheme 107

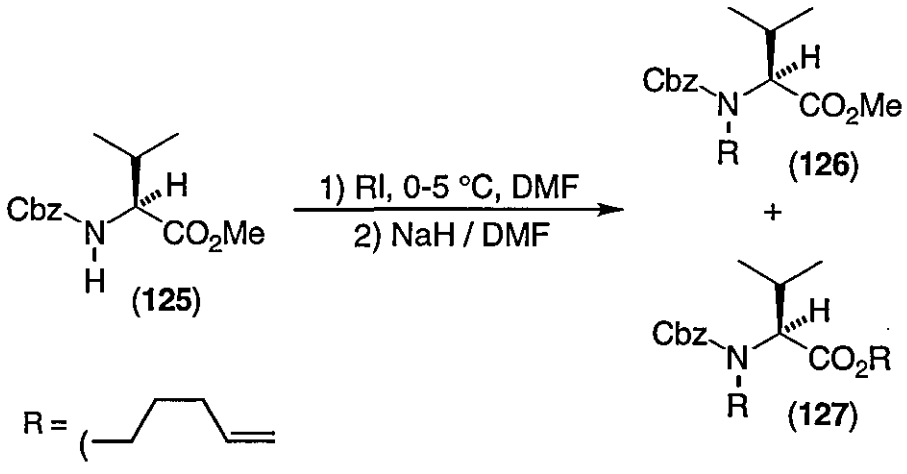


(91) (124)

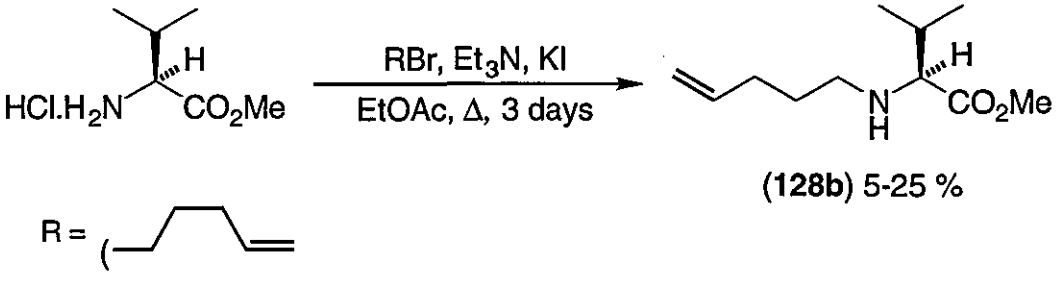
Scheme 108

The use of 5-bromopentene as alkylating agent, instead of methyl iodide, would therefore provide the desired product. *N*-(Benzyloxycarbonyl)-*L*-valine methyl ester **125** was reacted using the 5-bromopentene and *N*-alkylation occurred readily. Unfortunately, so did *trans*-esterification (Scheme 109) and the ensuing separation of the compounds, *N*-(benzyloxycarbonyl)-*N*-(pent-4-enyl)-*L*-valine methyl ester **126** and *N*-(benzyloxycarbonyl)-*N*-(pent-4-enyl)-*L*-valine pent-4-enyl ester **127**, proved troublesome. This route was finally abandoned when deprotection of the substrates caused further complications. For instance, the use of sodium in ammonia[110] removed the ester moiety and the use of hydrogen bromide in acetic acid,[111] somewhat unsurprisingly, resulted in addition of hydrogen bromide to the alkene and consequently loss of the double bond. A brief study into the use of tosyl derivatives, specifically *N*-tosyl-*L*-valine methyl ester, produced worse results! Formation of the *N*-tosyl-*L*-valine methyl ester from *L*-valine methyl ester hydrochloride and tosyl chloride was successful with an 89 % yield. However, the *N*-alkylation step never gave more

than trace amounts of product (by ^1H NMR spectroscopy), purification was not attempted and the reaction discontinued.



Scheme 109

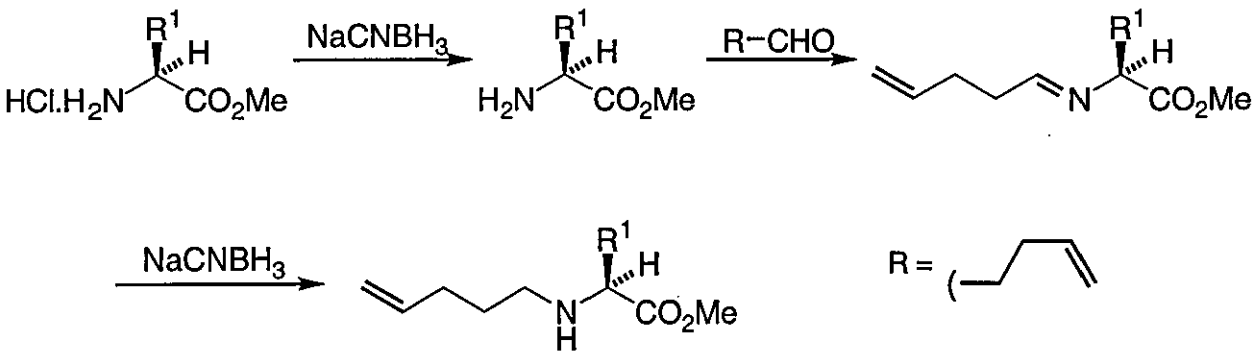


Scheme 110

A method devised within the Bowman group gave mono-*N*-alkylation of amines in good yield.[73] In this method, the amine was refluxed in ethyl acetate with 1 equivalent of the alkenyl bromide (alkylating reagent). The increased temperature facilitates the S_N2 reaction between amine and bromide to give the mono-alkylated product and hydrogen bromide. The excess triethylamine removes hydrogen bromide and the resultant hydrobromide salt precipitates out thus the reaction is forced to completion within a few hours. It was hoped that this method could be adapted to amino acids. The original method required refluxing for much longer (2-3 days) to produce some *N*-alkylated material but yields were improved by the introduction of potassium iodide. A Finkelstein type reaction converts the bromo compound into the more reactive iodo derivative. Thus, *L*-valine methyl ester hydrochloride was refluxed in ethyl acetate with 5-bromopentene, triethylamine and potassium iodide for 3 days to give *N*-(pent-4-enyl)-*L*-valine methyl ester **128b** in 5-25 % yield (Scheme 110). Extending

the period of reflux further than 3 days did not improve the yield but resulted in degradation of the compound and no improvement on 25 % was ever achieved. This method was applied to the amino acid, *L-tert*-leucine methyl ester, but no recoverable yield of *N*-alkylated product was obtained. Indeed, thin layer chromatography indicated that numerous compounds had formed. This suggested that degradation or other side reactions had occurred thus the method was deemed unsuitable as a general alkylation procedure.

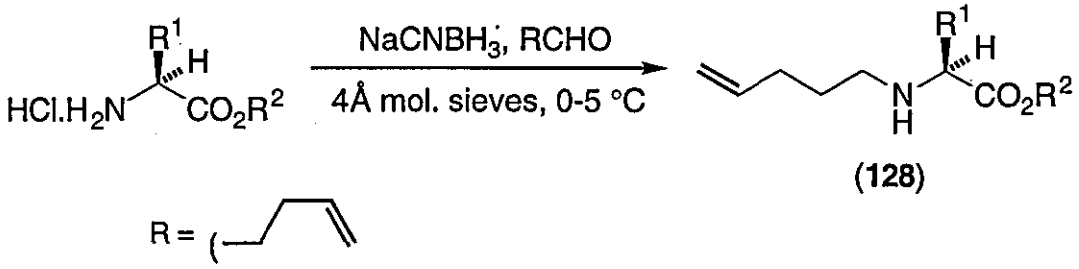
We next turned our attention to the use of reductive alkylation. By condensing the amino ester with a suitable aldehyde (4-penten-1-al was used) and reducing the resulting imine, the *N*-alkylated product could be obtained (Scheme 111).



Scheme 111

Several attempts involving imine formation (see section 3.2) followed by reduction using sodium borohydride proved unsuccessful and the answer was found in a "one pot" synthesis reported in the literature.[112] The amino methyl ester hydrochloride salts, 4-penten-1-al and 4Å molecular sieves in anhydrous methanol were cooled to 0-5 °C and sodium cyanoborohydride added and stirred overnight. An aqueous work-up gave the *N*-alkylated products **128a-d**. With the *tert*-butyl esters, two alterations in procedure were required to obtain the *N*-alkylated products **128e-h**. As the starting material was the free amine and not the hydrochloride salt, an improvement in yield was obtained when *p*-toluenesulfonic acid was added as an acid catalyst. Also, the solvent used was anhydrous acetonitrile as *trans*-esterification was noted with methanol as solvent. Similarly, the benzyl esters exhibited *trans*-esterification but, unlike their *tert*-butyl counterparts, the change in solvent had little effect. The reactions always produced benzyl alcohol as the major product and the alcohol was inseparable from the *N*-alkylated compounds using flash column chromatography. It was decided that further investigation using benzyl esters would only be appropriate if a more suitable method of *N*-alkylation was discovered. This

work has not, as yet, been carried out. The results for the *N*-alkylation of the methyl and *tert*-butyl ester derivatives are summarised in Scheme 112.



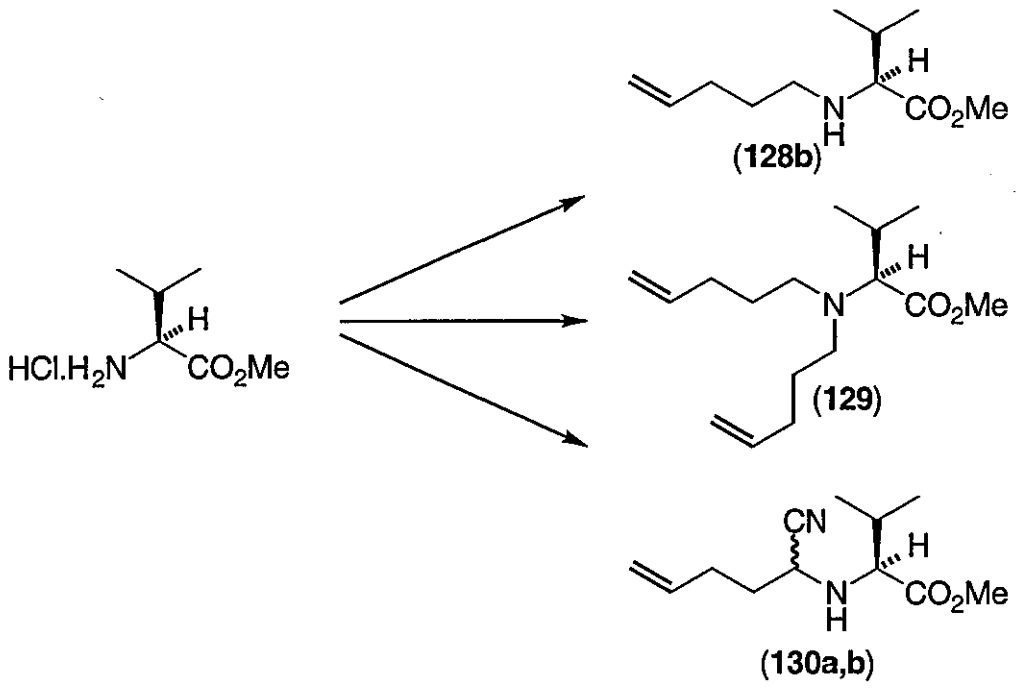
(128)

R =

Compound	R^1	R^2	Solvent	Yield, %
(128a)	Me	Me	MeOH	50-55
(128b)	*iso*-Pr	Me	MeOH	30-35
(128c)	Bn	Me	MeOH	30-50
(128d)	^{t}Bu	Me	MeOH	0-20
(128e)	Me	^{t}Bu	CH_3CN	20-35
(128f)	*iso*-Pr	^{t}Bu	CH_3CN	25-40
(128g)	Bn	^{t}Bu	CH_3CN	25-50
(128h)	^{t}Bu	^{t}Bu	CH_3CN	0-20

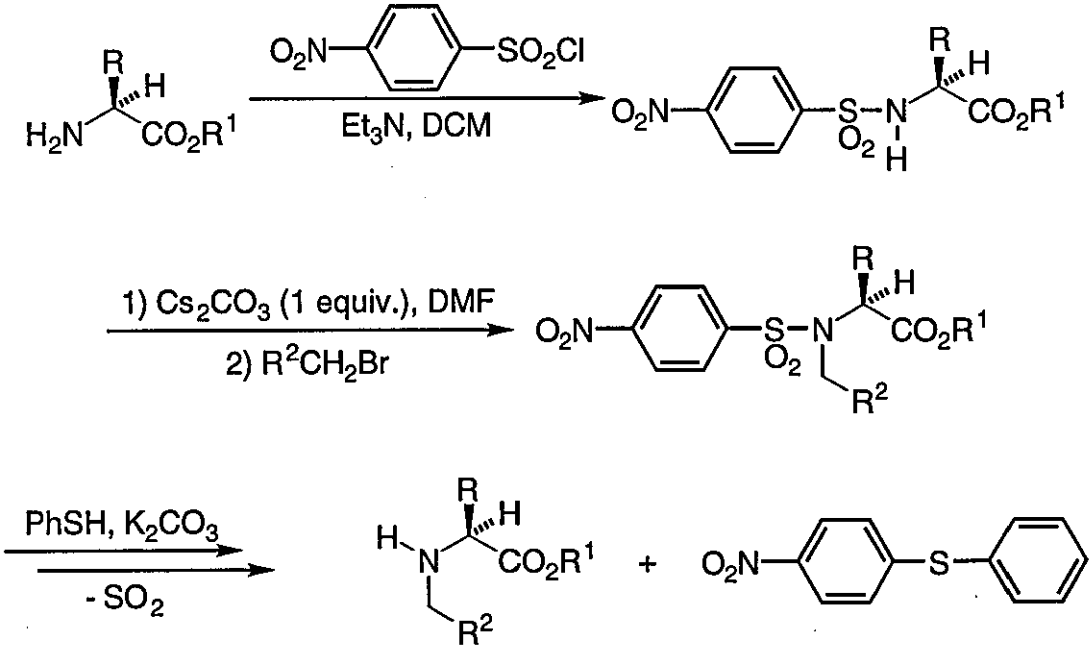
Scheme 112

There were several drawbacks with these methods. The yields varied from poor to moderate depending on the amino acid substrate. It was observed that as the size of the amino acid side-chain increased so the yield dropped and this may have been due to steric hindrance in the formation of the imine. Also, the consistency of yield for *N*-alkylation varied considerably for certain substrates, especially the *tert*-leucine derivatives. Dilution appeared to be a major factor in this problem as increased concentration of reactants resulted in lower yields. Finally, the *N*-alkylated product was one of many formed in the reaction and this resulted in tedious column chromatography. With *L*-valine methyl ester hydrochloride, for instance, it was possible to isolate three of the other compounds. They were the dialkylated product **129** and the two diastereomers **130a** and **130b** formed from the addition of hydrogen cyanide onto the imine double bond (Scheme 113). These were also formed with the other amino acids but isolation/identification was not carried out.



Scheme 113

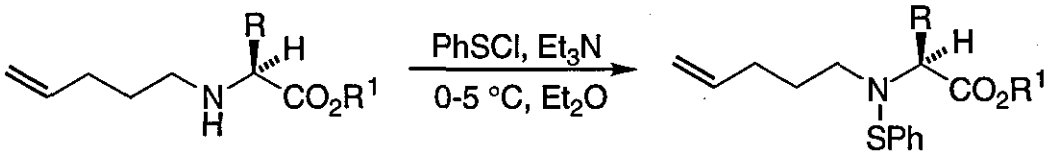
Work has continued within the group by Dr D. R. Coghlan on the *N*-alkylation of amino acids. The result has been the development of a method using the nitrobenzenesulfonamides of amino acids that allows mono *N*-alkylation in good to excellent yield (Scheme 114).[113]



Scheme 114

(iii) N-*Benzenesulfenylation of the* N-*alkylated α-Amino Acids*

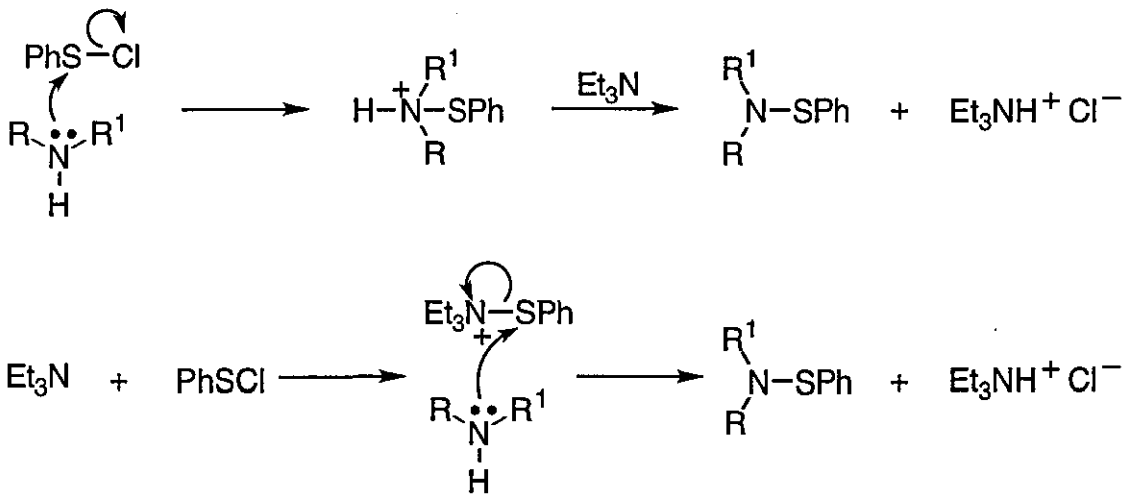
The sulfenamides **131a-e,g** were formed by the dropwise addition of benzenesulfenyl chloride to a stirred solution of the *N*-alkylated amino ester and triethylamine in anhydrous diethyl ether at 0-5 °C (Scheme 115).[73] Formation was through nucleophilic attack of the amine on the sulfur with the triethylamine acting as an acid acceptor and driving the reaction to completion. A possible alternative mechanism involves attack on the sulfur by the more nucleophilic triethylamine and subsequent reaction with the amine (Scheme 116). The method generally worked well but it was important to ensure that the reaction was dilute (*i.e.* at least 40 cm^3 of anhydrous diethyl ether per 1 g of *N*-alkylated amino acid) and that a combination of poor stirring and/or excess benzenesulfenyl chloride was avoided. This ensured that no benzenesulfenylation of the alkene or polymerisation of the sulfenamide occurred. Previously, sulfenamides of amines had been purified using TLC alumina chromatography as the compounds were unstable on silica. The effect of the α-carboxy ester group of the amino acid was to decrease the nucleophilicity of the nitrogen. This allowed partial stability on flash silica but no stability on TLC alumina! Consequently, the cleaner the benzenesulfenylation the better the purification was achieved using a "quick" column on silica.



(128) **(131)**

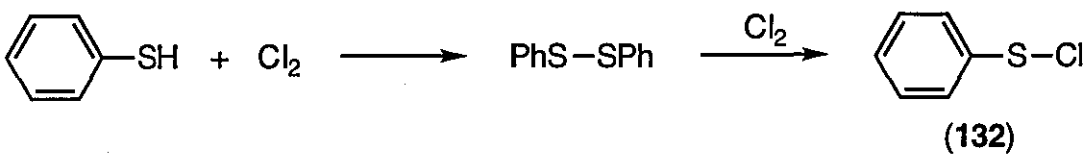
Compound	R	R^1	Yield, %
(128a)	Me	Me	90-95
(128b)	*iso*-Pr	Me	78-90
(128c)	Bn	Me	60-85
(128d)	^{t}Bu	Me	65-80
(128e)	Me	^{t}Bu	50-70
(128g)	Bn	^{t}Bu	65-80

Scheme 115



Scheme 116

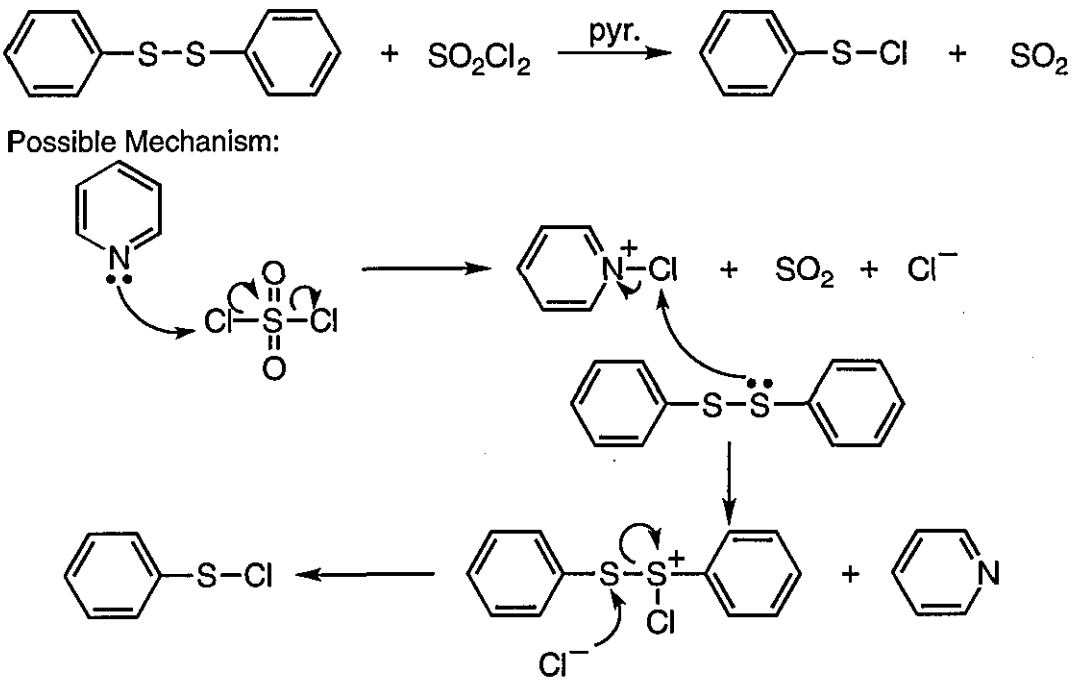
The benzenesulfenyl chloride **132** was originally prepared by the method of bubbling chlorine through a solution of thiophenol in light petroleum (Scheme 117).[114] The reaction proceeds *via* the formation of the white solid diphenyl disulfide, presumably formed from the initial oxidation of the thiol by the chlorine gas. As more chlorine is bubbled through, the white solid dissolves to give a red solution containing benzenesulfenyl chloride. The problems from using thiols, the possibility of the white solid altering/blocking the flow of chlorine gas and subsequent suck-back from the chlorine traps as well as the careful handling required during the work-up/distillation meant that this method was extremely troublesome.



(132)

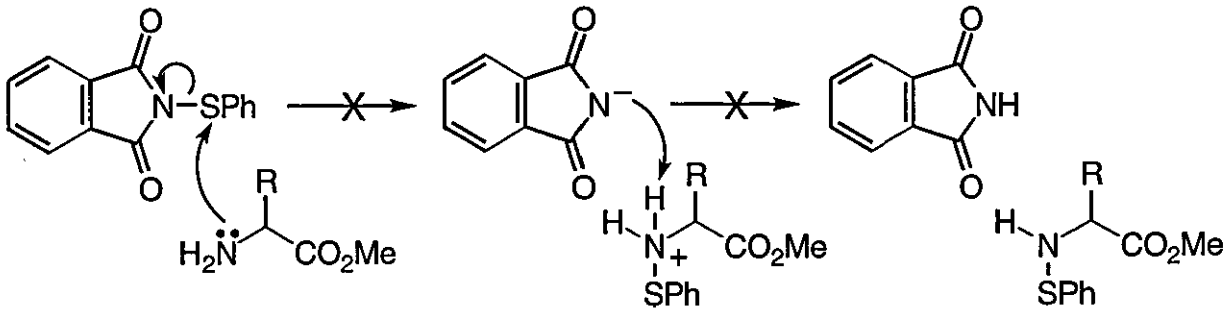
Scheme 117

Fortunately, it has since been superseded by the reaction of sulfuryl chloride with diphenyl disulfide (Scheme 118).[115] It has the advantages that the volume of benzenesulfenyl chloride produced can be accurately calculated and, therefore, no storage of the reagent is required, and the reaction is "user friendly" and requires only 45 minutes to complete rather than 1.5 days. Also, as the reagent **132** was fresh, the resulting sulfenamide was cleaner and purification easier.



Scheme 118

Unfortunately, *N*-(benzenesulfenyl)phthalimide was too unreactive to be of use for the *N*-benzenesulfenylation reaction and no sulfenamide was produced even after refluxing for several days (Scheme 119). The low nucleophilicity of the α-amino esters required that the benzenesulfenylation reagent was strongly electrophilic *e.g.* PhSCl. Secondly, the reaction between unsubstituted amines and *N*-(benzenesulfenyl) phthalimide is much slower than with PhSCl hence the lack of reaction was not unexpected.

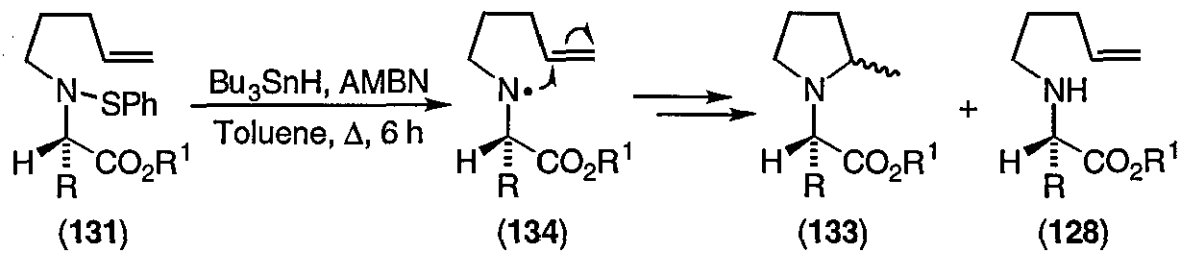


Scheme 119

2.2.2 Cyclisation Reactions of the *N*-alkylated Sulfenamide Precursors

Unlike their urethane counterparts, a blank reaction without tri-*n*-butyltin hydride showed that the sulfenamides were stable in refluxing toluene. The method of cyclisation, therefore, involved the syringe pump addition of a toluene solution of tri-*n*-butyltin hydride and AMBN over 6 h to a refluxing toluene solution of the sulfenamide.

During this research, the infuriating aspect for most of the synthetic work had been the ability for each amino acid to require slight variations in method/work-up for useful amounts of compound to be obtained. The work-up for the radical reactions was no exception! As the bulk of the amino acid increased, so its willingness to be extracted into 6 M hydrochloric acid decreased. Consequently, another method was necessary to separate the amine material from the tin impurities as column chromatography of the crude product achieved only partial separation. This was achieved by adding 1M HCl in ether to the crude (after removal of toluene) and passing the resultant mixture through a short column of flash silica with diethyl ether as eluant. The hydrochloride salts of the amine material remained at the top of the column whilst the tin impurities were flushed off. The amine material was obtained by adding triethylamine to the eluant, thus producing the free amine and allowing its passage through the silica column. The sulfenamides that were eventually synthesised using this adaption in order to obtain usable amounts of amine material for further purification were **131c-e,g**. One common problem with all the amine materials was their ability to "stick" to the flash silica during columning and therefore reduce the amount of product obtained. Flash silica had to be used as the use of TLC alumina proved ineffective at separation.

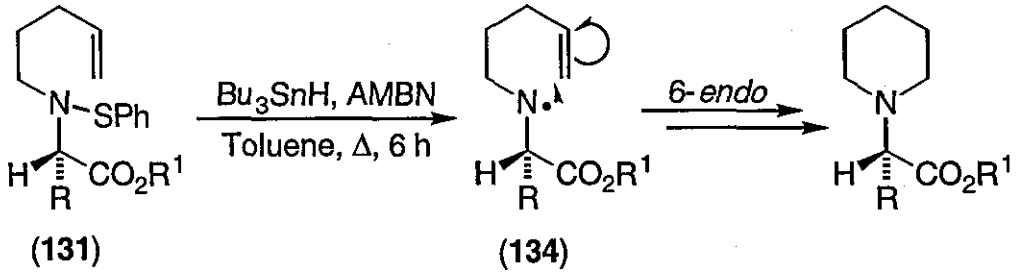


(131) **(134)** **(133)** **(128)**

Sulfenamide Precursor	R	R^1	Yield, % diastereomers **(133)**	uncyclised **(128)**	*d.e.*
(131a)	Me	Me	52, 30	11	27
(131b)	*iso*-Pr	Me	52, 19	27	46
(131c)	Bn	Me	48, 18	34	46
(131d)	^{t}Bu	Me	31, 21	36	20
(131e)	Me	^{t}Bu	58, 23	19	46
(131g)	Bn	^{t}Bu	64, 23	12	48

Scheme 120

The amino ester sulfenamides **131** were reacted with tri-*n*-butyltin hydride as described to yield mixtures of two diastereomers **133**, *via* 5-*exo* cyclisation, and uncyclised amino esters **128** (Scheme 120). Separation of the products proved problematic due to their similar R_F values. The minor diastereomer and uncyclised material co-eluted and were unseparable. The major diastereomer was isolated but in very low yield. Interestingly, analysis of the crude products using GC/MS indicated traces (<1 %) of 6-*endo* cyclisation (Scheme 121). The GC trace from analysis of the amine extraction indicated only 3 major amines and 1 minor amine. From the MS data, all 4 had the same molecular ion (*e.g. L*-valine derivative **b**) at 199, loss of CO_2Me at 140 and loss of isopropyl side chain at 156 but only two contained a peak at 184 which was indicative of loss of the methyl from the newly formed ring. The remaining two, 1 major and 1 minor amine, could only be uncyclised or 6-*endo* cyclised material. Since the uncyclised spectrum was known and correlated with the major component, the minor compound could only be 6-*endo* material. The isolation of this compound was never achieved though so the absolute certainty of this assignment is, presently, not possible. Sulfenamide **131d** was the exception, in terms of yield, with *ca.* 5 % of 6-*endo* cyclised material indicated. This was possibly due to larger steric hindrance for the 5-*exo* cyclisation, due to the *tert*-butyl group, than was experienced by the other intermediate aminyl radicals **134a-c,e,g**.



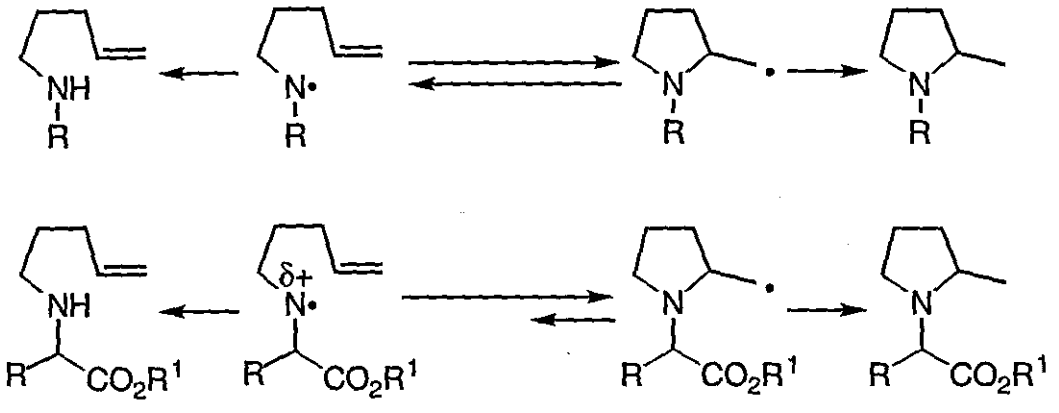
(131) **(134)**

Scheme 121

The yields and diastereomeric excesses of the cyclised/uncyclised products were calculated using ^1H NMR spectroscopy with the internal standard, 1,4-dinitrobenzene. The technique of GC/MS was also used to confirm the ^1H NMR spectroscopy results and a good correlation existed between the two. This was only possible as the cyclised/uncyclised products had a similar response to the flame ionisation detection used in GC/MS (the values stated are the average of three experiments). The one exception was with the products obtained from sulfenamide **131d** (*L-tert*-leucine derivative). Only GC/MS could be used as an increase in impurities resulting from the

radical reaction meant that the ratio for internal standard to product would have been inaccurate for the substrates to be measured.

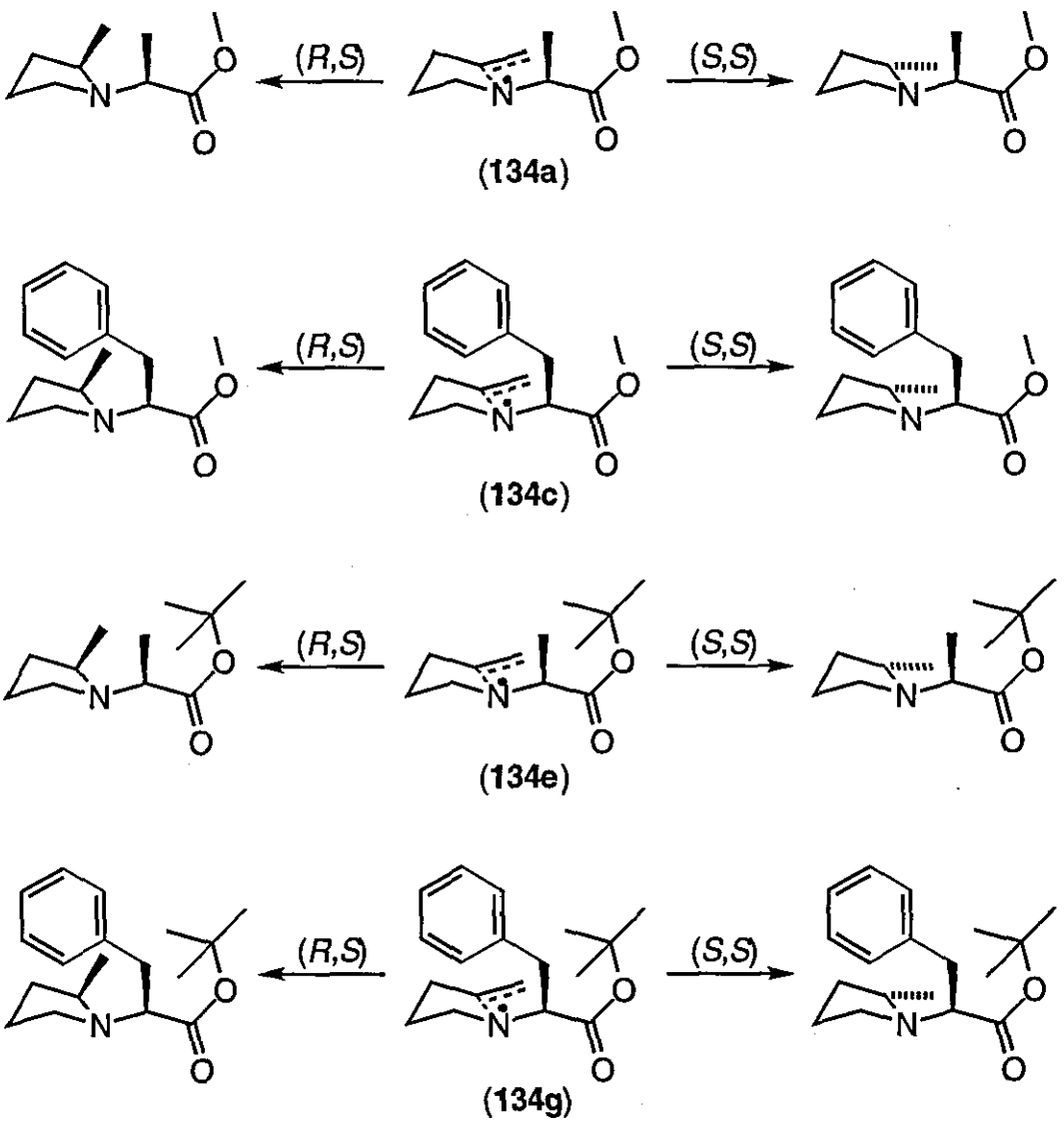
The relative yields of 5-*exo* cyclised products **133** to uncyclised α-amino esters **128** *via* intermediate aminyl radicals **134** are much higher than for the cyclisation of ordinary *N*-alkyl-4-pentenamines.[49] This would suggest that our prediction for the electron-withdrawing effect of the α-ester is correct. The ester moiety imparts a degree of electrophilicity to the intermediate aminyl radical **134** thereby facilitating faster cyclisation. The result could also be explained, however, by a decrease in the rate of the reverse ring-opening compared to that for *N*-alkyl-4-pentenamines (Scheme 122) but with the additional evidence from the H-abstraction described in section 2.1.4, our α-ester prediction is highly likely.



Scheme 122

The cyclisations show interesting diastereoselectivity of cyclisation for α-chiral aminyl radicals but it was not possible to increase the diastereoselectivity above *circa* 50 %. For the methyl esters **133**, the *d.e.* increased with the size of the amino acid side chain (Me < Bn, *iso*-Pr) as expected but dropped when the bulky *tert*-butyl group of the *tert*-leucine was present. This could be explained by the possible thermal degradation of the *tert*-leucine products leading to a false *d.e.* and the observed increase in impurities. Scheme 123 shows the aminyl radical transition states of the alanine derivative **134a** and the phenylalanine derivative **134c**. The size of the benzyl group in **134c** would influence the resultant *d.e.* of the reaction to a greater extent than the methyl group of the alanine derivative in **134a**. The effect of increasing the size of the ester moiety from methyl to *tert*-butyl improved the *d.e.* for the *L*-alanine substrate (**131a** versus **131e**) but the small increase observed with the *L*-phenylalanine derivative (**131c** versus **131g**) was within experimental error. Scheme 123 contains the aminyl radical transition states for both the *tert*-butyl esters of alanine **134e** and phenylalanine **134g**. It is possible that the *tert*-butyl

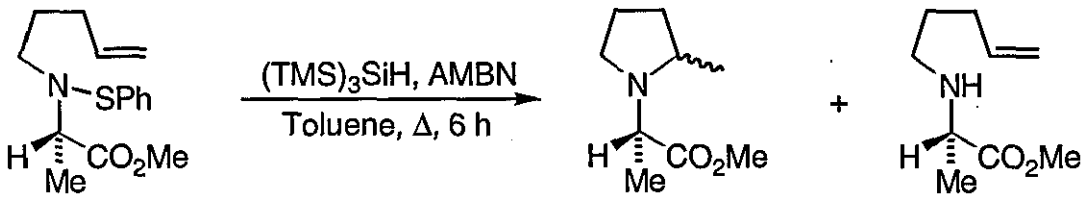
group could provide an additional steric hindrance towards formation of the 5-membered ring within the transition state of the alanine derivative (in addition to that already present from the alanine methyl group). In contrast, the benzyl group of the phenylalanine derivative **134g** would restrict rotation of the *tert*-butyl ester, thus reducing its effect within the transition state and therefore showing no improvement of *d.e.* on that obtained with the methyl ester.



Scheme 123

If the rate of hydrogen abstraction from the radical generating agent by the intermediate aminyl radical could be lowered then a higher yield of cyclisation and/or *d.e.* could be predicted. The reagent, *tris*-(trimethylsilyl)silane, is known to have a stronger Si-H bond than the Sn-H bond in tri-*n*-butyltin hydride.[116] For instance, the

absolute rate constant for H-abstraction by secondary alkyl radicals, $R^1R^2C\bullet$, is only 2.6 x 10^5 for the silane compared with 1.9 x 10^6 for the tin hydride. However, unexpectedly, the opposite was observed when the reaction with **131a** was repeated using *tris*-(trimethylsilyl)silane in place of tri-*n*-butyltin hydride. The yield of the cyclised diastereomers of methyl (2*S*)-(2-methyltetrahydro-1*H*-1-pyrrolyl)propanoate **133a** was only 21 % and 7 % (*d.e.* = 50 %) whereas the yield of *N*-(pent-4-enyl)-*L*-alanine methyl ester **128a** had increased to 72 % (Scheme 124). It was obvious that the *tris*-(trimethylsilyl)silane was less useful than the tri-*n*-butyltin hydride and was not investigated further.



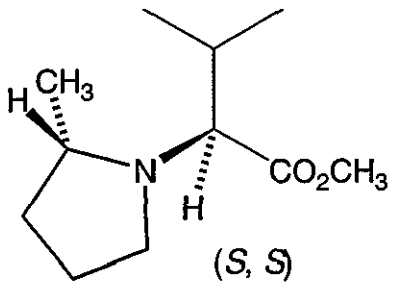
(131a) **(133a)** **(128a)**

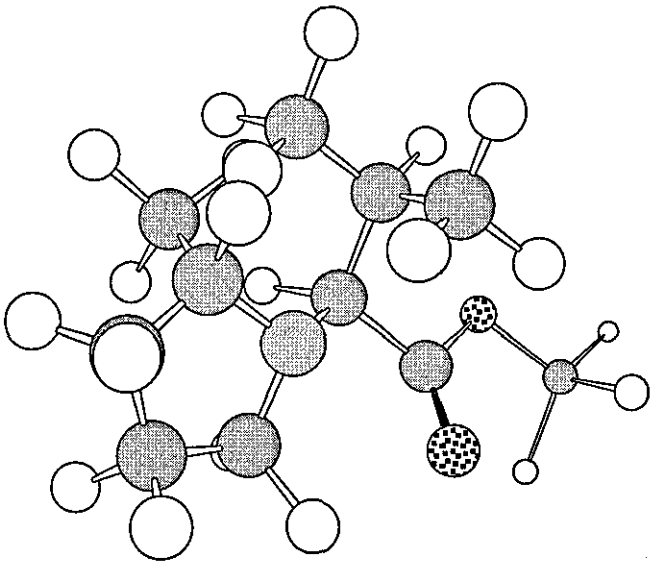
21 and 7 % yield
d.e. = 50 %

72 % yield

Scheme 124

The only disappointment with the cyclisations was that it had not been possible to discover the preferred stereochemistry of the cyclic products as they had all been oils. An obvious route to determine the absolute stereochemistry would be to convert one isomer to a crystalline derivative and analyse by X-ray crystallography. Unfortunately, manipulation of the isolated cyclised derivative proved fruitless. For instance, the attempts at hydride reduction of the ester moiety to obtain the alcohol resulted in either polymeric material or impure starting material being isolated. Consequently, we decided to use the MM2 molecular modelling package to obtain an "estimate" of the stereochemistry at the newly formed chiral centre. The cyclised product **133b** (*L*-valine methyl ester derivative) was entered into the package without defining the stereochemistry at the newly formed chiral centre (Scheme 125). The programming within the computer package had to define a 3D simulation of the structure hence its interpretation of the newly formed chiral centre within the model predicted an *S*-conformation. This use of MM2/Chem 3D programmes only provides a possible indication of the stereochemistry of the major isomer and further study is required to accurately determine the stereochemistry.





COMPUTER PREDICTION

Scheme 125

2.3 Summary of the Results for the Sulfenamide Derivatives

For convenience, the summary has been split into the two main sections discussed previously in the text (*i.e.* sections 2.1 and 2.2):

2.3.1 Summary of the Amino Acid Side Chain Research

Preparation of the *N*-benzenesulfenylated radical precursors was achieved in good yield for the non-amino acid and amino acid, with no amine protection, substrates. In contrast, the *N*-protected amino acids proved problematic. For amino acids containing an aromatic ring, the method of *N*-benzenesulfenylation devised was apparently only suitable for certain *L*-phenylalanine derivatives. The results of the cyclisations are summarised as follows:

ii) 5-*Exo* cyclisation of the aminyl radical of *N*-benzyloxycarbonyl-derived urethanes onto alkenes was shown.

iii) Cyclisation onto the aromatic ring of the compounds *N*-(benzenesulfenyl)-*N*-(benzyloxycarbonyl)-*L*-phenylalanine methyl ester and *N*-(benzenesulfenyl)-*L*-phenylalanine methyl ester was not achieved. Only uncyclised material was isolated.

iv) The 5-*exo* cyclisation of *N*-(benzenesulfenyl)-*N*-tosyl-*L*-phenylalanine methyl ester was also not achieved but an interesting radical cleavage was observed.

2.3.2 Summary of the *N*-Alkylated Amino Acid Research

Formation of the radical precursors was only hampered by the *N*-alkylation step. Both ester formation and *N*-benzenesulfenylation occurred in good to excellent yields. Reductive alkylation was the best general method used for *N*-alkylation of α-amino acids. The results of the cyclisations are summarised as follows:

i) 5-*Exo* cyclisations of aminyl radicals onto the alkene of the *N*-(pent-4-enyl) substituted α-amino acids were achieved in good yield.

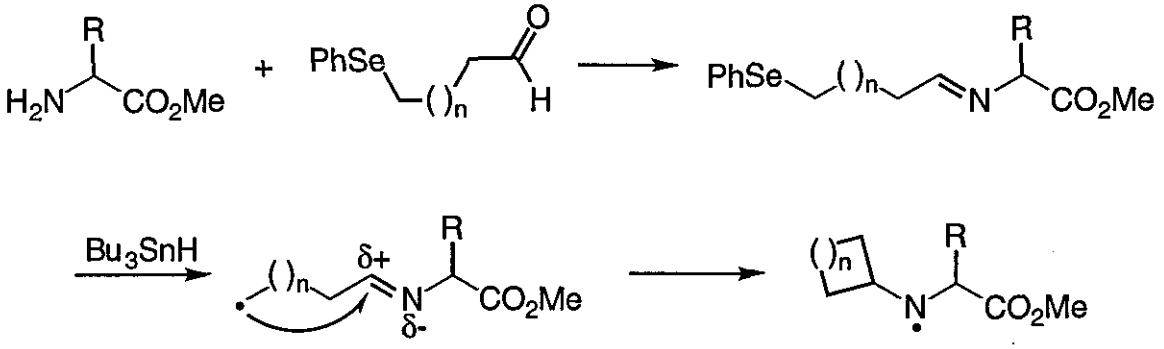
ii) The α-chiral centre of the amino acid induced diastereoselectivity on the newly formed chiral centres of the cyclised products. The *d.e.* increased with the size of the amino acid side chain to a maximum of *ca.* 50 %.

iii) The increase in ester size (OMe to O^{t}Bu) only increased the *d.e.* of the smallest amino acid used, *L*-alanine.

iv) Evidence of 6-*endo* cyclisation was observed using GC/MS analysis but no product was isolated.

THE PREPARATION AND GENERATION OF AMINYL RADICALS DERIVED FROM IMINE DERIVATIVES OF α-AMINO ACIDS

The formation of aminyl radicals from cyclisation onto imine derivatives of amines has been investigated within the research group with some success (see section 1.5.3).[98] We considered that this methodology could prove a useful alternative procedure to that of sulfenamides. In our earlier studies, imine derivatives had been successfully prepared from α-amino esters as intermediates in the reductive alkylation reaction (section 2.2.1). Our intention was to use α-amino acids as the amine starting material and condense with, initially, a ω-benzeneselenyl aldehyde before reacting under standard tri-*n*-butyltin hydride/AMBN conditions. We envisaged that the carboxymethyl group of the α-amino acid would encourage cyclisation onto the imine, the electron-withdrawing effect of the ester increasing the electropositivity of the imine carbon and thus favouring the subsequent cyclisation (Scheme 126). The eventual aim of this study was to use the aminyl radical thus generated for tandem cyclisations, *e.g.* onto an alkenyl side-chain to synthesise proline analogues (section 4.2).

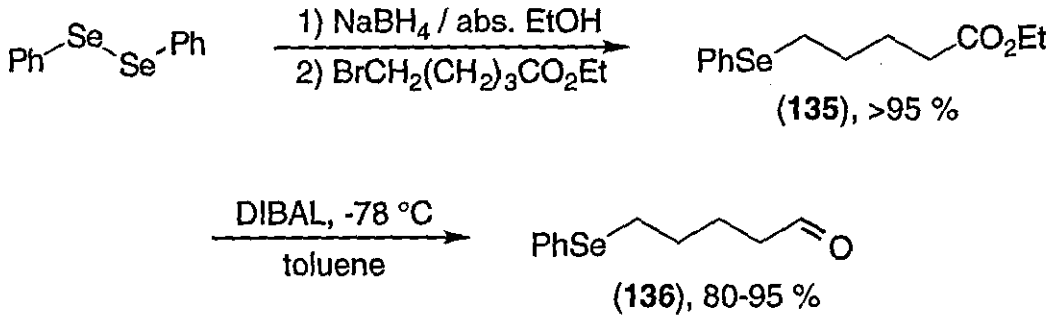


Scheme 126

3.1 Preparation of ω-Benzeneselenyl Aldehydes[98]

The general route used for the synthesis of these aldehydes involved the preparation of the suitable corresponding benzeneselenyl substituted ester and subsequent reduction to the aldehyde using diisobutylaluminium hydride (DIBAL). 5-Benzeneselenylpentanal **136** was synthesised using this method (Scheme 127). There are several methods available for the introduction of a benzeneselenyl group onto a molecule. The reaction of ethylbromovalerate (ω-bromoester) with the benzeneselenide nucleophile generated *in situ* by the borohydride reduction of diphenyl diselenide gave ethyl 5-benzeneselenylpentanoate **135** in excellent yield. The reaction mechanism proceeds by S_N2 substitution and the nucleophilic

selenium species is thought to be a complex between the benzeneselenide anion and borane: [$PhSe(BH_3)^-$].[117] The use of DIBAL, for reduction of the ester to the aldehyde[118], gave 5-benzeneselenylpentanal **136** in 80-95 % yield.

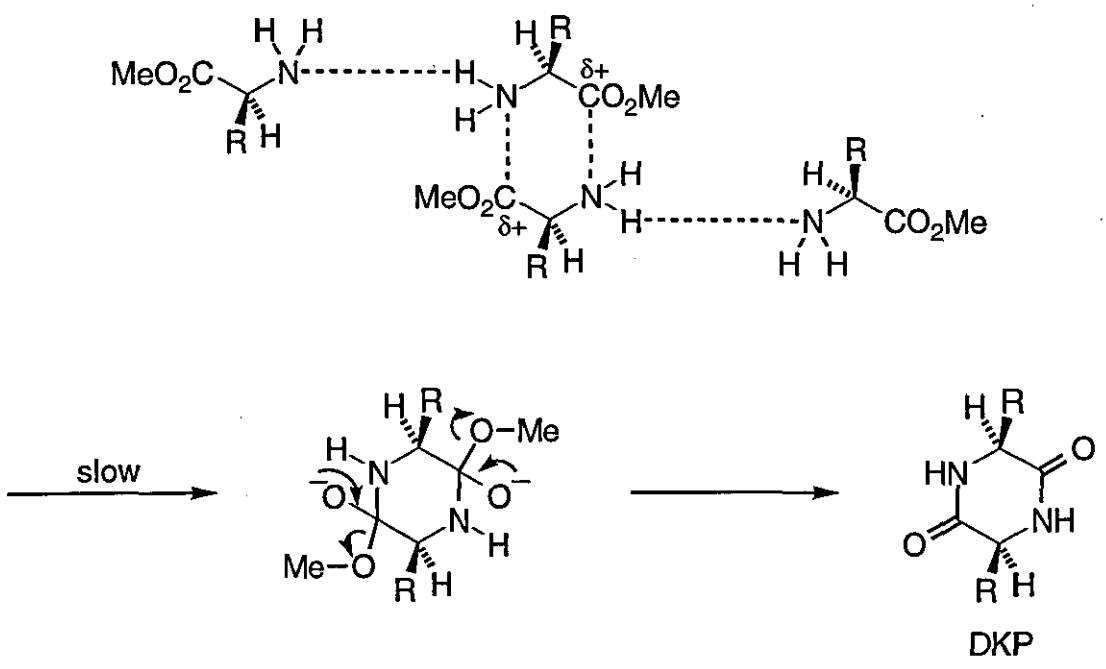


Scheme 127

The aldehyde **136** would lead to a possible 5-*exo* cyclisation (see section 3.2). Similarly, it was envisaged that the aldehyde 6-benzeneselenylhexanal could lead to a 6-*exo* cyclisation. The synthesis of 6-benzeneselenylhexanal would use the method detailed in Scheme 127 but, presently, the aldehyde has not been synthesised and no cyclisation studies have been undertaken.

3.2 Synthesis and Cyclisation of the Imine Derivatives

Neutralisation of the hydrochloride salts of the relevant α-amino esters would appear to be routine. Yields of the free amines were poor and variable, with yields being non-reproducible across a series of amino acid derivatives. Indeed, with *L*-alanine methyl ester hydrochloride, the resultant free amine was found to be very volatile and evaporation of the neutralisation mixture resulted in low yields, although with care this can be minimised. The best and most repeatable method of obtaining the free amine involved dissolving the acid salt in a minimum volume of water, adding anhydrous sodium carbonate until the pH was raised to 10 and then extracting with dichloromethane. The resultant free amine of the amino acid derivative (a colourless oil) was used almost immediately as, with time, the formation of diketopiperazine (DKP)/polymeric material occurred as indicated by the presence of a white solid (Scheme 128). This was also an unwanted impurity in the subsequent imine formation reaction. It was observed that DKP formation was most rapid with *L*-phenylalanine methyl ester.

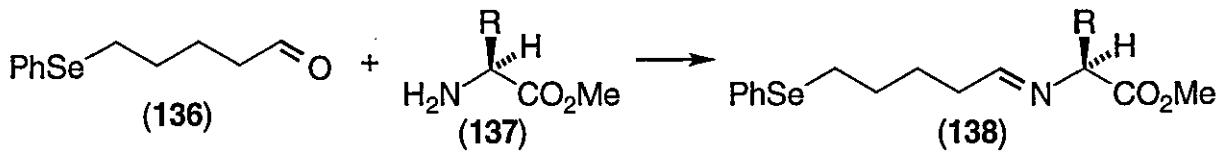


Scheme 128

Imines have been formed by a variety of methods for condensation between amine and aldehyde/ketone, *e.g.* the azeotropic removal of water[119] or the use of molecular sieves.[120] The use of the Dean-Stark azeotropic removal of water (toluene as solvent) proved unsatisfactory. Large amounts of impurities were formed and little or no imine was present (by ^{1}H NMR spectroscopy). The heating of the amine/aldehyde solution must have led to side-reactions occurring and therefore the resultant impurities. To avoid heating, the reactants were stirred in various solvents (*e.g.* dichloromethane, acetonitrile) with various drying agents (*e.g.* anhydrous $MgSO_4$, $CaSO_4$) with imine formation, at best, in about 30-40 % yield though the starting materials were still present. This was still unacceptable for the subsequent radical reaction as any side-reactions that might ensue with the impurities would only cause further purification problems later. Carrying out the condensation reaction using a Soxhlet apparatus, to pass "wet" low boiling solvent (the reactions were carried out in dichloromethane or diethyl ether) over freshly activated 4Å molecular sieves improved the yields of the imine but a long reflux time of 1-2 days increased the side reactions as encountered with the Dean-Stark reaction, although to a lesser degree.

The simplest of reactions was found to produce the best results. When one equivalent of 5-benzeneselenylpentanal **136** was added to the amino acid derivative **137**, an exothermic reaction was noted. This was found to be the formation of the required imine **138** (Scheme 129). No drying agents or acid catalysts were required and studies indicated that no further imine formation occurred after 1 h (by ^{1}H

NMR spectroscopy), even if a drying agent such as anhydrous $MgSO_4$ was subsequently added to force the equilibrium towards imine formation. Yields of imines still varied depending on the α-amino acid derivative used but the resulting reaction mixture contained only minor amounts of the two starting materials in addition to the imine. Consequently, no further purification was carried out and the crude carried through to the radical reaction. One other point of interest occurred during the formation of the imine. When the amine and aldehyde were stirred together, the initial ^1H NMR chemical shift of the imine C-H triplet was at about 7.5 ppm. Yet, when the mixture was stirred for more than a couple of hours, the triplet was reduced in size and a second triplet observed at 5.5 ppm. The 5.5 ppm triplet was the only one observed when the imine was formed using higher temperature techniques. It could be argued that the imine was equilibrating between its *cis/trans* isomers but no investigation into this was attempted. Previous work within the group had shown imine protons at both the 7.5 and 5.5 ppm values but both had not been observed in the same experiment.

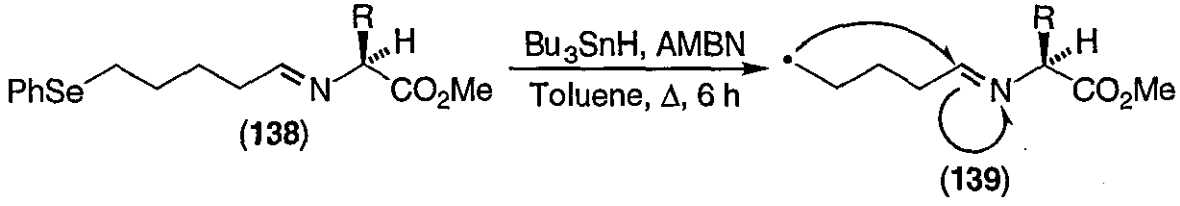


a compounds, R = Me
b compounds, R = *iso*-Pr
c compounds, R = Bn

Scheme 129

In contrast to all the previous radical reactions, the deoxygenation of the solution was carried out at room temperature rather than at elevated temperature for a minimum of 45 minutes. The addition of the tri-*n*-butyltin hydride/AMBN solution was started as the temperature of the imine solution approached 80 °C. Abstraction of the benzeneselenyl group by the tri-*n*-butyltin radical produced the radical **139** which underwent 5-*exo* cyclisation onto the imine bond and then subsequent H-abstraction from tri-*n*-butyltin hydride gave the *N*-(cyclopentyl)-*L*-amino esters **140** in good yield (Scheme 130). Separation of the amine products from the tin impurities was achieved by extraction as the hydrochloride salt into 6 M hydrochloric acid. GC/MS analysis of the amine material obtained after rebasification indicated that the cyclised compound was the major product for R = Me, Bn and the sole product for R = *iso*-Pr. No uncyclised compound was ever observed. Purification using flash column chromatography was necessary for the

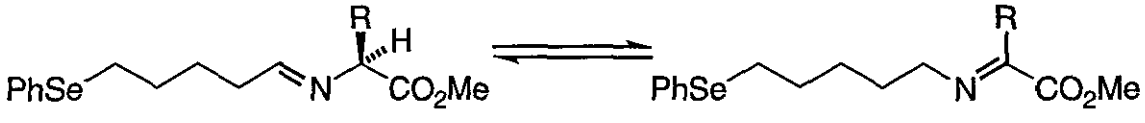
removal of baseline material and, although small volumes of flash silica were used, the overall yield of isolated product **140** was obviously reduced. The use of TLC alumina has not, as yet, been investigated. The higher yield of cyclised material obtained from the imine **138b** may have been due to the high purity of the precursor. This was the only reaction where characterisation of the imine was possible.



Imine Precursor	R	Yield, % **140**
138a	Me	45
138b	*iso*-Pr	68
138c	Bn	45

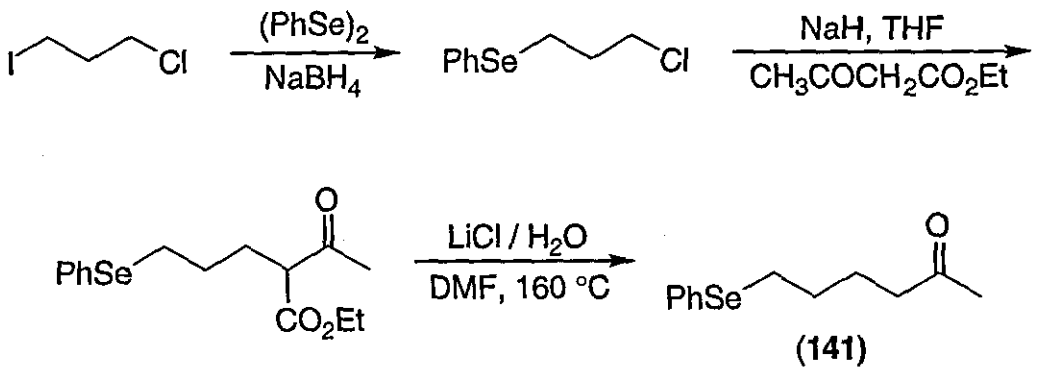
Scheme 130

In the formation of imines of α-amino acid derivatives, racemisation of the chiral centre could conceivably result from a 1,3-hydrogen shift from the α-centre onto the imine (Scheme 131). If this process had occurred then the optical rotations obtained from the cyclised amino acid derivatives would be zero due to the compound's racemic nature. This was found not to be the case as compounds **140b** and **140c** were shown to have optical rotations of -13.58 and +13.49 respectively, which indicated that, if racemisation had taken place, it was not 100 %.

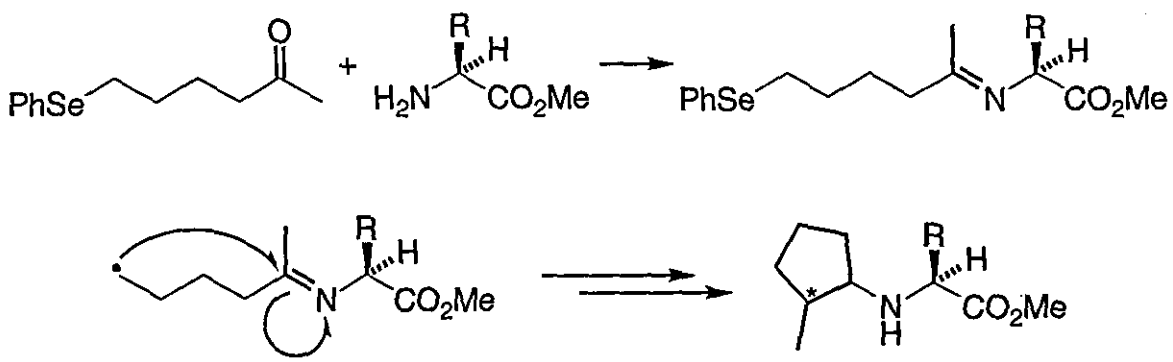


Scheme 131

Formation of the aminyl radical had been shown to be successful and two further areas could have been investigated but time did not allow for both to be researched. The first involved repeating the experiments with the ketone, 6-benzeneselenyl-2-hexanone **141**. Its synthesis has been documented (Scheme 132).[98] The iodide of 1-chloro-3-iodopropane is displaced by benzeneselenide and the resulting 1-(benzeneselenyl)-3-chloropropane added to the sodium salt of ethyl 3-oxobutanoate to give ethyl 2-acetyl-5-(benzeneselenyl)pentanoate. Cleavage of the ester group to yield the ketone is achieved by hydrolysis with lithium chloride in dimethylformamide/water followed by thermal decarboxylation. The condensation of the ketone with the α-amino acid derivative and then cyclisation would have indicated whether the chiral centre of the amino acid derivative had any effect on the newly formed chiral centre (Scheme 133). This has yet to be carried out.



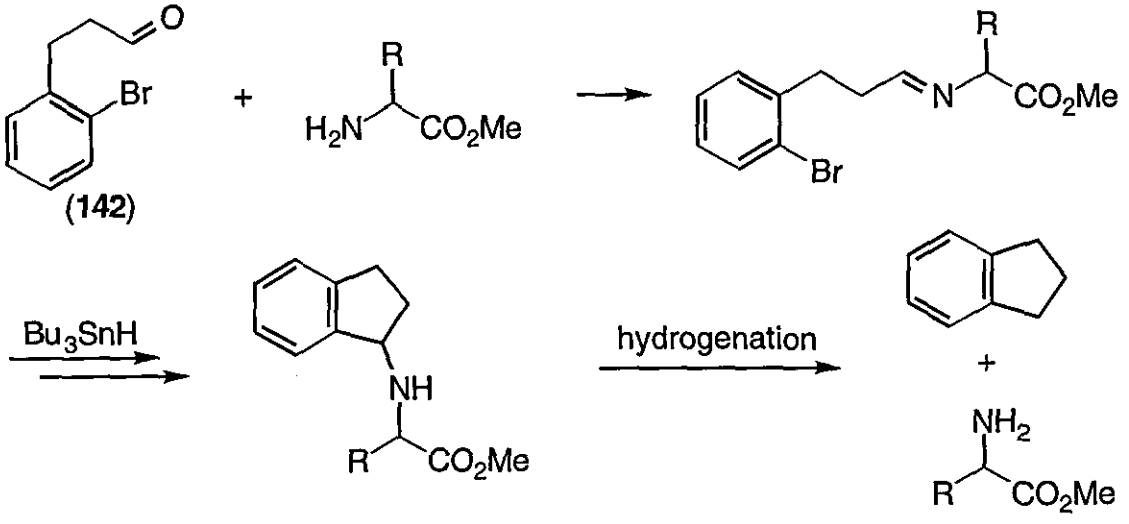
Scheme 132



Scheme 133

An alternative aldehyde would form the imine more easily. We first considered an aldehyde which, after cyclisation of the imine, would yield a moiety which could easily be removed. The use of the aldehyde **142** was considered. The indane ring could be readily cleaved from the amine using hydrogenation because it

would be a benzylic amine (Scheme 134). If a tandem cyclisation was employed (see section 4.2) then, after removal of the moiety, a new proline derivative would have been formed. This aldehyde would however not be any more reactive than the ω-benzeneselenyl aldehydes in the troublesome formation of imines. Therefore, we sought an alternative aldehyde source.

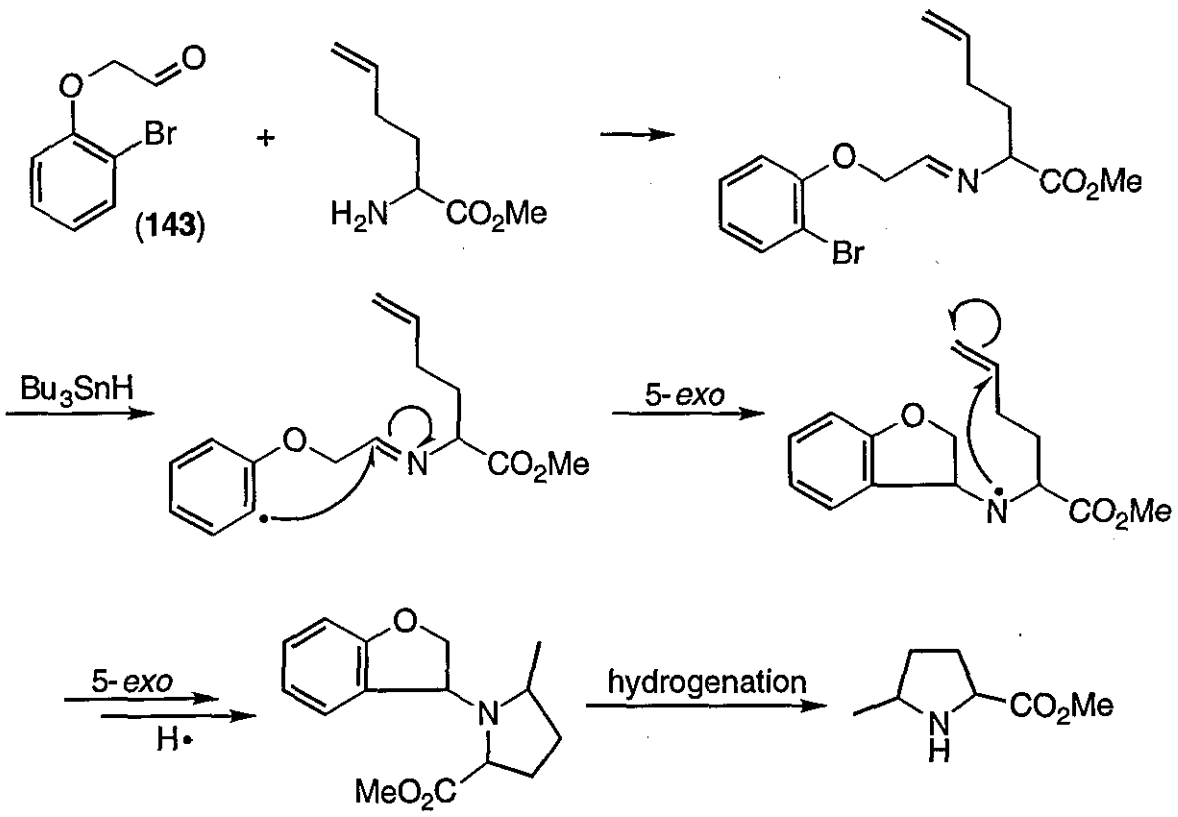


Scheme 134

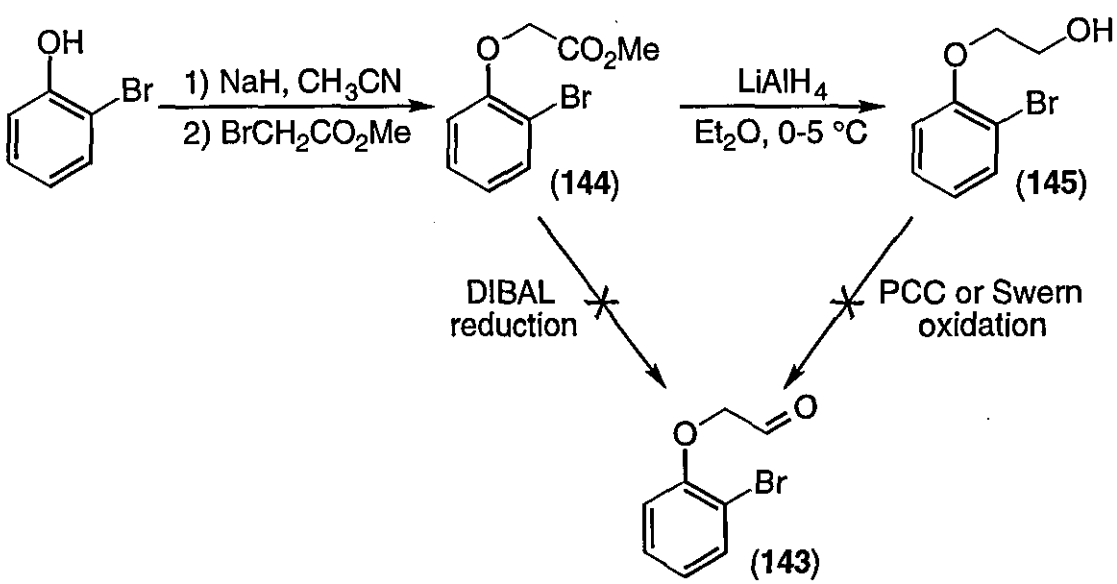
Use of the aldehyde, 2-(*o*-bromophenoxy)ethanal **143** could achieve the desired results. The α-aryloxy group would strongly enhance the electrophilicity of the aldehyde to facilitate imine formation as well as weakly enhance the electrophilicity of the cyclised aminyl radical, thereby facilitating faster aminyl cyclisation (*e.g.* Scheme 135). The indane group can also be easily removed by hydrogenation because the *C-N* bond to be cleaved is benzylic.

The synthesis of the aldehyde, 3-(*o*-bromophenyl)propanal (a carbon analogue of **143** and shown as **142** in scheme 134) has been documented.[121,122] Similarly, the aldehyde **143** could be synthesised by reduction of the corresponding ester by DIBAL or oxidation of the corresponding alcohol. Formation of methyl 2-(*o*-bromophenoxy)ethanoate **144** from the reaction between the phenolate salt of 2-bromophenol and methyl bromoacetate occurred in >90 % yield. Subsequent reduction to the alcohol **145** using lithium aluminium hydride also proceeds in high yield (Scheme 136). Unfortunately, obtaining the aldehyde **143** from either of the ester **144** or the alcohol **145** in any useful amount proved futile. Reduction of the ester **144** using DIBAL gave numerous products, as indicated by thin layer chromatography of the reaction mixture, and only trace amounts of any aldehyde could be detected using ^{1}H NMR spectroscopy. Oxidation of the alcohol **145** to the aldehyde **143** gave similar results. The mild oxidative reactions of pyridinium

chlorochromate (PCC) and Swern oxidation conditions were tried. Both gave greater amounts of an unknown aldehyde compound compared with the reduction method, the PCC method being the most encouraging, but the yield was still very low and impurities were numerous.

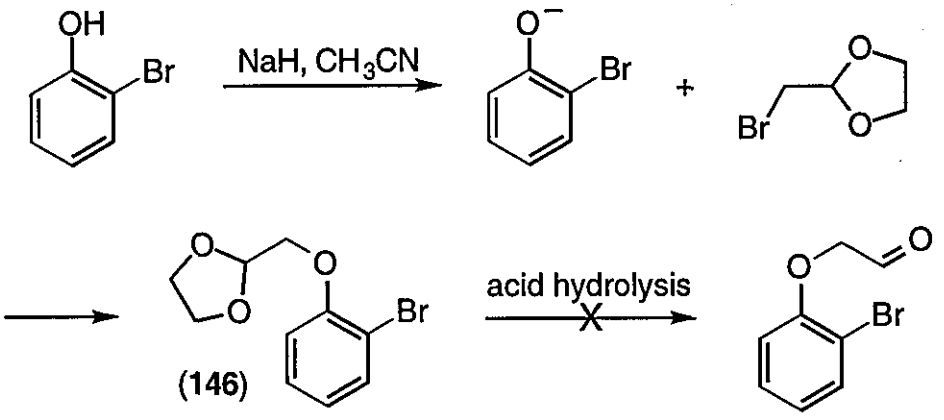


Scheme 135



Scheme 136

Our final attempt at synthesizing the aldehyde **143** involved reaction of the phenolate salt of 2-bromophenol with 2-bromomethyl-1,3-dioxolane to give the acetal 2-[2-(2-bromophenoxy)ethyl]-1,3-dioxolane **146** (Scheme 137). Hydrolysis of the acetal **146** using varying concentrations of hydrochloric acid did not yield the aldehyde but, instead, the acetal starting material was recovered. Stirring with concentrated hydrochloric acid for 1.5 days gave an unknown compound but no aldehyde was formed and, in this case, no aromaticity within the compound was present! ^{1}H NMR spectroscopy indicated that four types of CH_2 were present, two of which had electron-withdrawing components attached. ^{13}C NMR spectroscopy confirmed this and also showed that the electron-withdrawing elements were different (*e.g.* CH_2O and CH_2Cl). Only one compound was present using the techniques of thin layer chromatography and GC/MS. Interestingly, the MS data from the GC/MS, when compared with a MS library database, had a 90 % correlation with the MS of the compound 4-chlorobutanol. There was no obvious route for the synthesis of 4-chlorobutanol and the abscence of the OH peak expected at 2.65 ppm (^{1}H NMR spectrum)[123] would suggest that the unknown compound was not 4-chlorobutanol. Synthesis of the aldehyde **143** was discontinued due to lack of time.



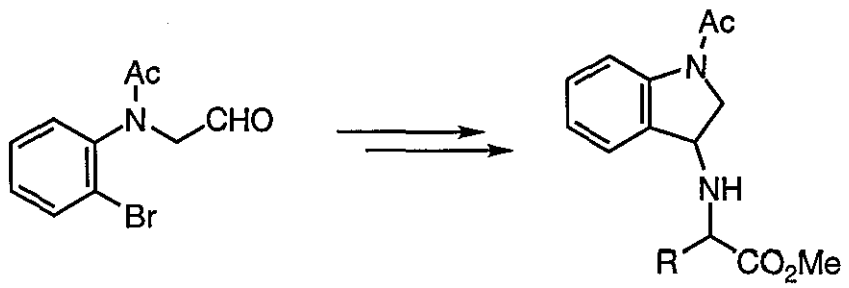
Scheme 137

3.3 Summary of the Results for the Imine Derivatives

Our initial results indicate that the methodology developed for the generation of aminyl radicals *via* cyclisation onto amino acid imines has provided a new synthetic procedure.

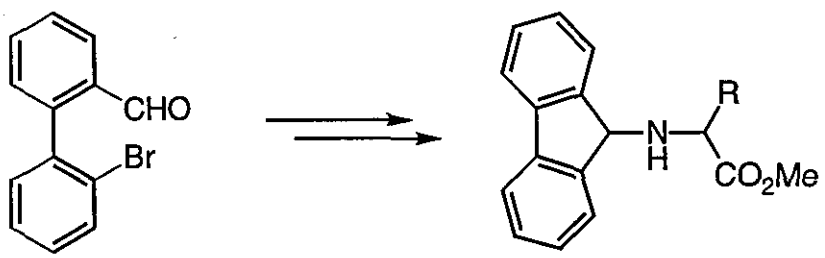
Further studies are required utilising aldehyde derivatives such as the described 2-(*o*-bromophenoxy)ethanal **143**. Research is underway within the research group to produce the nitrogen equivalent (*i.e.* nitrogen replacing the

oxygen), *N*1-(2-bromophenyl)-*N*1-(2-oxoethyl)acetamide, of the aldehyde **143** (Scheme 138).



Scheme 138

Synthesis of the reactive biphenyl aldehyde **147** is also underway within the group. Formation of imines is facile and the fluorenyl group should be easily removed (Scheme 139).

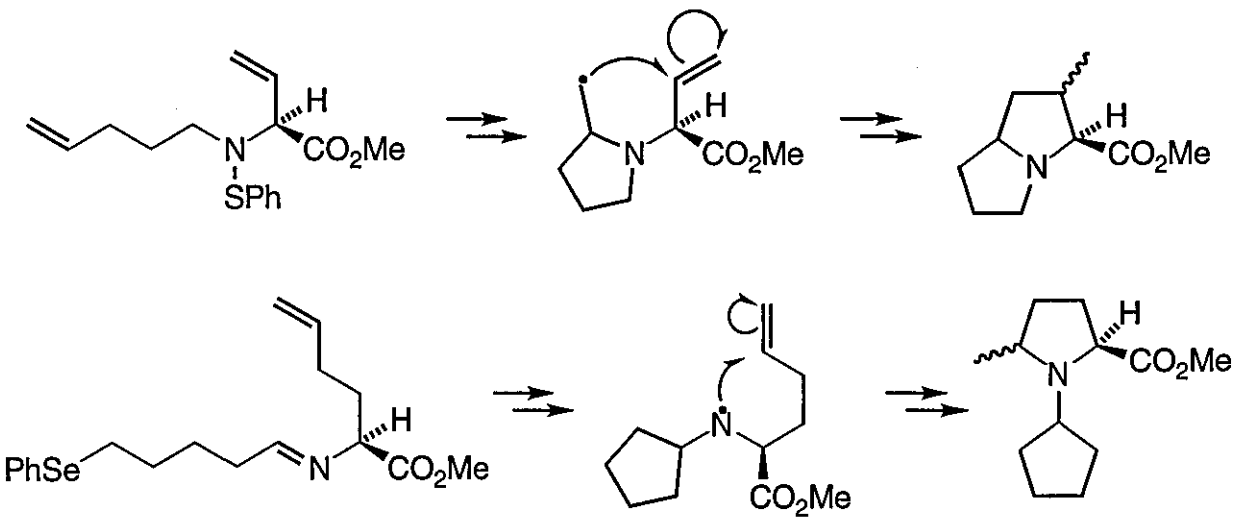


(147)

Scheme 139

TANDEM CYCLISATIONS UTILISING α-AMINO ACID DERIVATIVES

Having successfully cyclised the sulfenamide derivatives of *N*-(ω-alkenyl) α-amino acids and produced aminyl radicals from imine derivatives, the next step was to take both examples of monocyclisation and attempt tandem cyclisations (*e.g.* Scheme 140).



Scheme 140

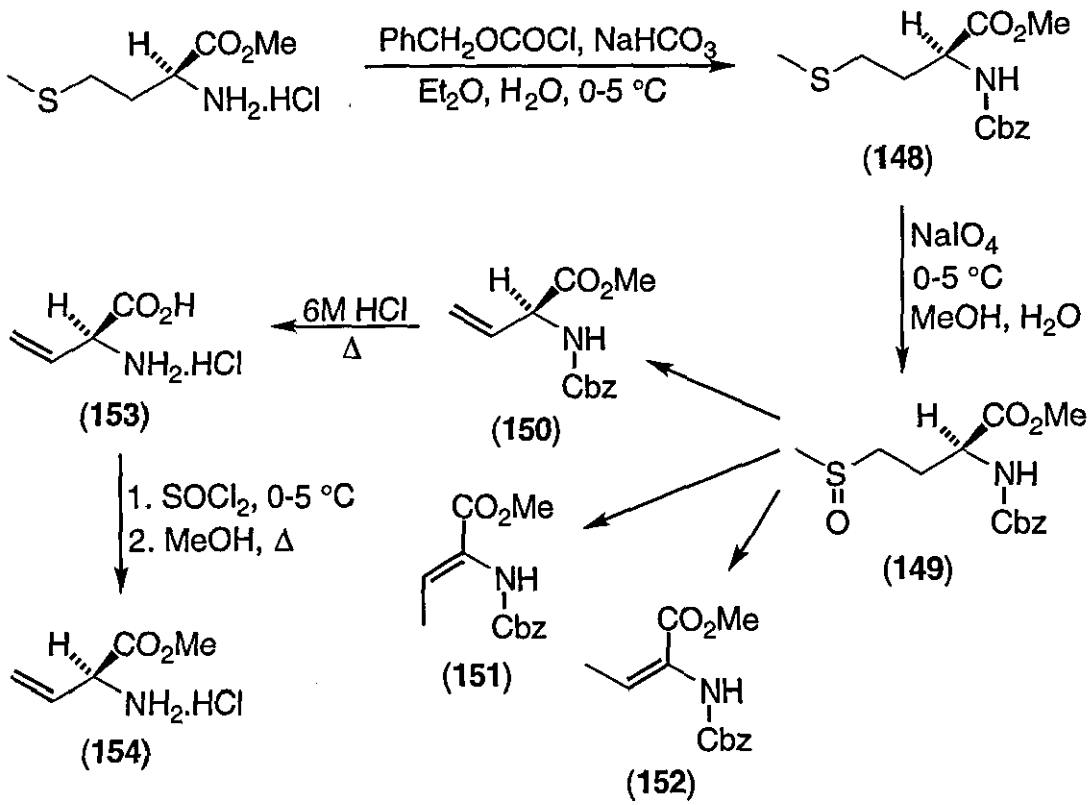
4.1 Tandem Cyclisations using Sulfenamide Derivatives

We had anticipated carrying out two tandem cyclisations using our *N*-alkylated derivatives, a 5-*exo*, 5-*exo* cyclisation and 5-*exo*, 6-*exo* cyclisation. The use of a 6-*exo* initial cyclisation was not attempted as the *N*-alkylation step of introducing a hex-5-enyl chain onto the amino acid had not been developed. In order to study the 5-*exo*, 5-*exo* cyclisation, the starting material required, before using our developed methods for *N*-alkylation and *N*-benzenesulfenylation, was the unnatural amino acid, *L*-vinylglycine methyl ester hydrochloride **154**.

The synthesis of *L*-vinylglycine from *L*-methionine methyl ester has been documented (Scheme 141) and our synthesis was carried out using this route.[124] The *L*-methionine methyl ester hydrochloride was protected using benzylchloroformate to give *N*-(benzyloxycarbonyl)-*L*-methionine methyl ester **148** in excellent yield. Oxidation of the urethane **148** using sodium periodate similarly gave an excellent yield in the formation of methyl *L*-2-(benzyloxycarbonylamino)-4-(methylsulfinyl)butanoate **149**. This sulfoxide was then heated using a Kugelrohr apparatus at 235 °C under reduced pressure (0.5 mmHg) causing sulfoxide elimination and subsequent distillation gave the desired product *N*-(benzyloxy-

carbonyl)-*L*-vinylglycine methyl ester **150** in moderate yield. This step was problematic as the sulfur-containing by-products needed careful handling due to their unpleasant smell. The complete separation of product from the potent smelling impurities was not possible through distillation alone. The separation was compounded further as the elimination not only produced the desired compound but led to the (*Z*) and (*E*) α,β-unsaturated isomers **151** and **152** in small yield. This led to a tedious chromatographic procedure using an increasing ratio of ethyl acetate to light petroleum as eluant in order that the *N*-(benzyloxycarbonyl)-*L*-vinylglycine methyl ester **150** was isolated in about 90-95 % purity.

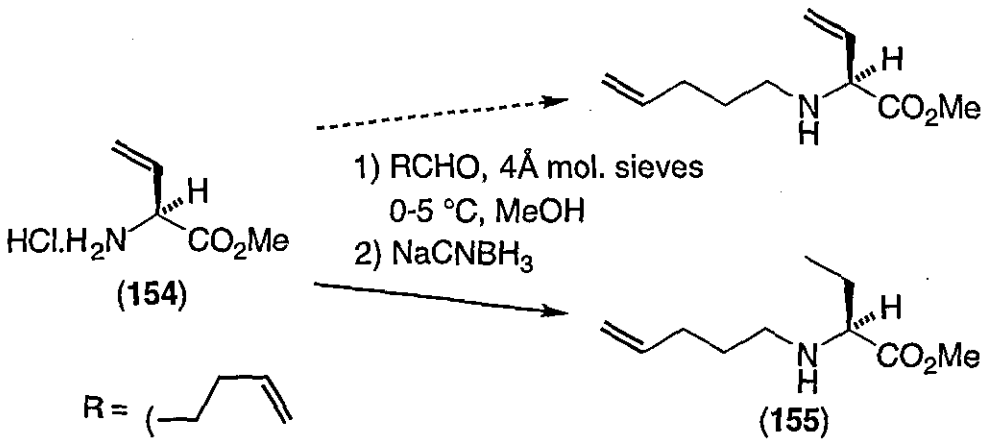
Removal of the benzyloxycarbonyl protecting group on the nitrogen of the amino acid was, of course, not possible using hydrogenation as this would have reduced the alkene as well. Unfortunately, the routine removal of benzyloxy-carbonyl groups would result in the loss of the alkene moiety. The harsh method used therefore was to reflux the urethane **150** in 6M hydrochloric acid! The deprotection also resulted in hydrolysis of the methyl ester, hence *L*-vinylglycine hydrochloride **153** was obtained in good yield.



Scheme 141

Esterification of the hydrochloride salt **153** to obtain *L*-vinylglycine methyl ester **154** was achieved by reaction with thionyl chloride at low temperature

followed by refluxing in methanol as solvent. The yield for this reaction was consistently low and perhaps the use of diazomethane (as described in section 2.1) would have been a better option.

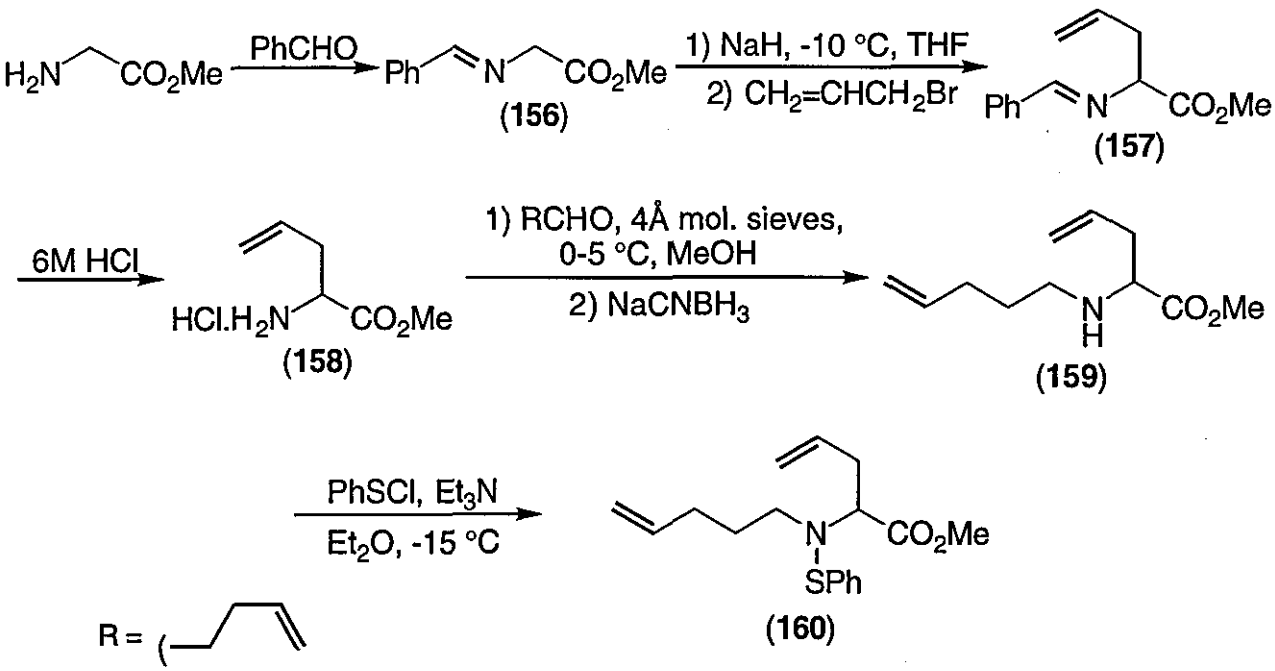


Scheme 142

Having finally synthesised our amino acid precursor, the *N*-alkylation was carried out using 4-pentenal and sodium cyanoborohydride as reported in section 2.2.1. (Scheme 142). The expected *N*-(pent-4-enyl)-*L*-vinylglycine methyl ester was not isolated and, instead, the compound methyl (2*S*)-2-(4-pentenylamino) butanoate **155** was produced in 25 % yield. The sodium cyanoborohydride has obviously reduced both imine and vinyl double bonds. Even when the amount of cyanoborohydride reagent added was controlled so that it was never in excess, the reduction of the vinyl double bond still occurred (although a small amount of the desired compound appeared to have formed, it was not possible to isolate it due to the numerous impurities). The use of sodium cyanoborohydride for the reduction of α,β-double bonds in amino acids has been documented.[125] The conditions required methanolic hydrogen chloride and this is not too dissimilar to the conditions present for the *N*-alkylation but there is no precedent for the reduction of β,γ-double bonds. There was no obvious answer as to why this process was occurring. Possibly, the conformation of the amino acid encouraged the reduction to occur but without further investigation, any answer would be speculative. Time restrictions meant that no further work was carried out on the 5-*exo*, 5-*exo* cyclisation.

The amino acid precursor for 5-*exo*, 6-*exo* cyclisation was synthesised as shown in Scheme 143. This procedure used the method devised by Stork *et al.*[126] followed by the reductive alkylation and *N*-benzenesulfenylation as used in section 2.2 and 2.3. Glycine methyl ester was condensed with benzaldehyde in good yield to give methyl 2-[(1-phenylmethylidene)amino]acetate **156**. Deprotonation at the

carbon α to the ester moiety with sodium hydride followed by quenching with allyl bromide yielded methyl 2-[(1-phenylmethylidene)amino]-4-pentenoate **157**. The method is such that only a racemic mixture of the desired amino acid could be obtained. Finally, hydrolysis of the imine **157** with 6M hydrochloric acid gave methyl 2-amino-4-pentanoate hydrochloride **158** as a brown and highly hygroscopic solid. Attempted purification of the solid *via* recrystallisation proved ineffective thus the crude brown solid was used for the next reaction. Reductive alkylation of the amino acid derivative **158** using sodium cyanoborohydride and 4-pentenal gave the expected methyl 2-(4-pentenylamino)-4-pentenoate **159** in at least 20 % yield. The dialkylated methyl 2-(di-4-pentenylamino)-4-pentenoate was also isolated but, unlike the *L*-vinylglycine derivative, there was no evidence for reduction of the double bond. The radical precursor methyl 2-[4-pentenyl(benzenesulfenyl)amino]-4-pentenoate **160** was isolated in 85 % yield by the reaction between **159** and benzenesulfenyl chloride.

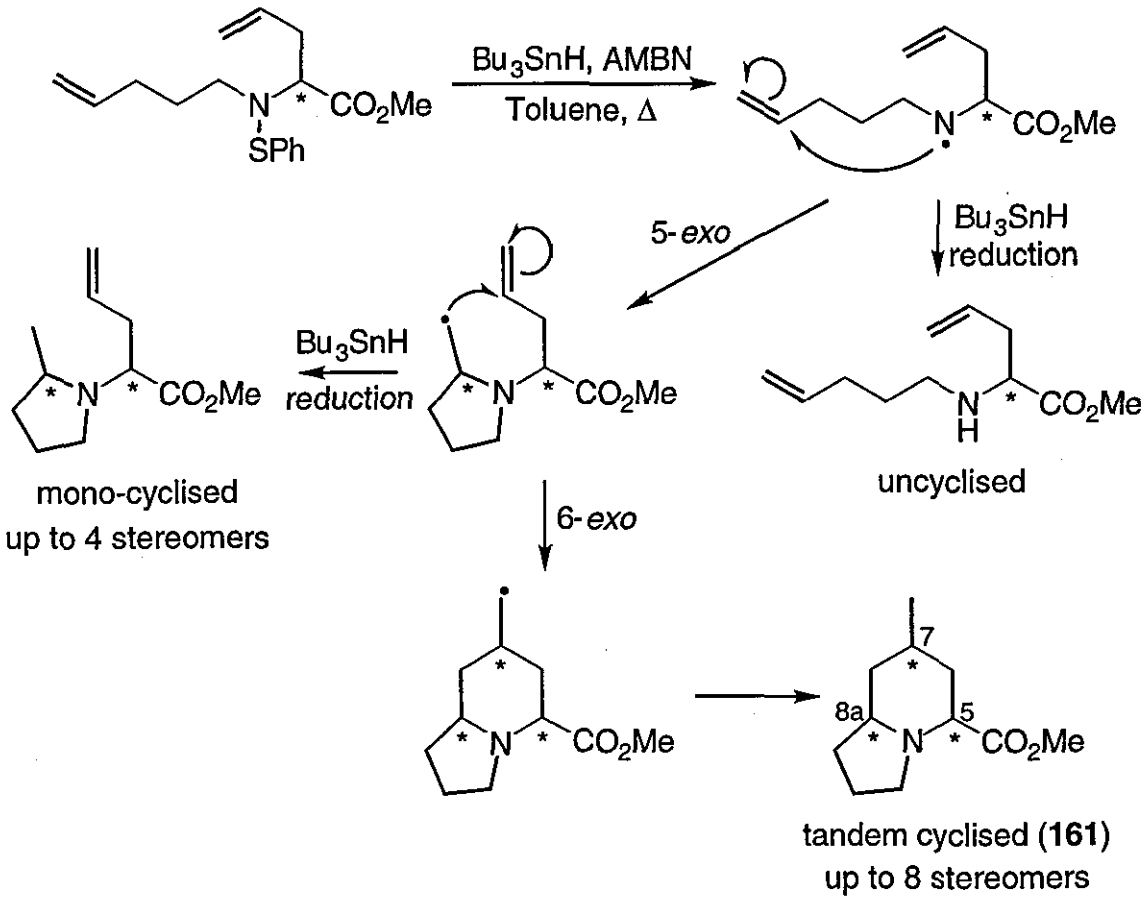


(156) (157) (158) (159) (160)

Scheme 143

Cyclisation of the radical precursor **160** was carried out using standard tri-*n*-butyltin hydride conditions. Addition of the tri-*n*-butyltin hydride/AMBN solution in toluene over 6 h to a refluxing toluene solution of **160** gave encouraging and conflicting results. The possible avenues of reaction are shown in Scheme 144. Apart from uncyclised material, up to 4 stereomers (2 pairs of enantiomers) of mono-cyclised material and 8 stereomers (4 pairs of enantiomers) could be synthesised during the radical reaction. In fact, only two diastereomers of methyl 7-

methylperhydro-5-indolizinecarboxylate **161** (from the 5-*exo*, 6-*exo* tandem cyclisation) were isolated in 5 % and 3 % yield.



Scheme 144

Comparison of the ^{13}C NMR spectral data of compound **161** with known indolizine compounds indicated that a tandem cyclisation had occurred. Indolizines have been made previously within the research group (*e.g.* compounds **61** (section 1.5.2) and **75** (section 1.5.3) have already been mentioned).[73,98] The characteristic carbons on the indolizine **161** are 5-CH (CO_2Me substituted), 7-CH (Me substituted) and 8a-CH (ring junction carbon). Although, the substitution pattern of **161** is unlike anything in the literature, it can be concluded that the 5-CH should occur between 50 and 65 ppm. The diastereomers of **161** have 5-CH at 58 and 63 ppm respectively. A similar range of chemical shifts exists for the 8a-CH (55-70 ppm) and the diastereomers of **161** showed peaks at 56 and 58 ppm respectively. Compound **75** has no substitution at the 7-C and a chemical shift of 23 ppm. Apart from compound **61**, no other indolizine with an alkyl substitution at 7-C was found. Although, it is recognised that the chemical shift for 7-C in **61** (46 ppm) is somewhat higher than those for 7-C in the diastereomers of **161** (28 and 27 ppm respectively), it

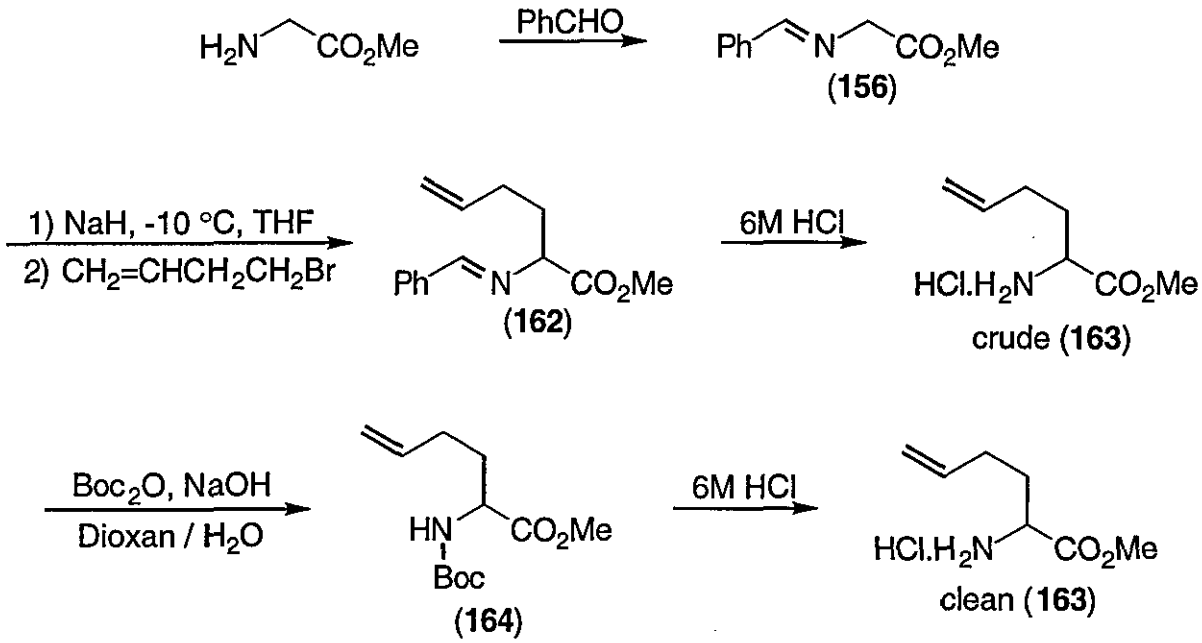
is concluded that compound **161** represents the most reasonable structure for these products.

No other identifiable compounds were isolated but the presence of further compounds was evident in our analysis. The ^1H NMR spectrum of the amine components, extracted from the crude product with hydrochloric acid, clearly showed the formation of up to 4 cyclised products (2 pairs of doublets at 1.75 and 0.75 ppm) which could have been mono-cyclised products, tandem cyclised products or a combination of both. The ^1H NMR spectrum also showed that uncyclised material was a minor component. The amount of alkenyl material present was in excess of uncyclised recovered **159** and this suggested that side reactions had occurred. The MS data obtained from the GC/MS analysis of the crude reaction mixture confirmed that uncyclised material (loss of the alkenyl side-chain of the amino acid at m/z 156) was a minor component. Trace amounts of mono-cyclised material were also indicated (loss of the alkenyl side-chain at m/z 156 and loss of methyl from newly-formed ring at m/z 182). But only three major amine components of equal size, corresponding to the tandem cyclisation products, were observed by GC/MS analysis! The expected fourth peak from the final pair of enantiomers was apparently not present. There are too many questions to be answered about this reaction and further study is required before any real conclusions can be determined. Unfortunately, time dictated that this was not possible and the reaction has not been repeated.

4.2 Tandem Cyclisations using Imine Derivatives

The amino acid precursor for the 5-*exo*, 5-*exo* cyclisation was synthesised using the method devised by Stork *et al* as described in section 4.1 (Scheme 145).[126] Glycine methyl ester was condensed with benzaldehyde in good yield to give methyl 2-[(1-phenylmethylidene)amino]acetate **156**. Deprotonation at the carbon α to the ester moiety with sodium hydride followed by quenching with 4-bromobut-1-ene yielded methyl 2-[(1-phenylmethylidene)amino]-5-hexenoate **162**. The method is such that only a racemic mixture of the desired amino acid could be obtained. Finally, hydrolysis of the imine **162** with 6M hydrochloric acid gave methyl 2-amino-5-hexenoate hydrochloride **163** as an orange and highly hygroscopic solid. Unlike the use of the crude material previously (section 4.1), it was imperative that the amino acid salt was pure before preparing the free amine for imine formation. This was achieved by protecting the amine of the amino acid with a *tert*-butoxycarbonyl group, purifying using flash column chromatography and then removing the protective group. Thus, the crude material containing methyl 2-amino-5-hexenoate hydrochloride **163** was reacted with *tert*-butyl dicarbonate to

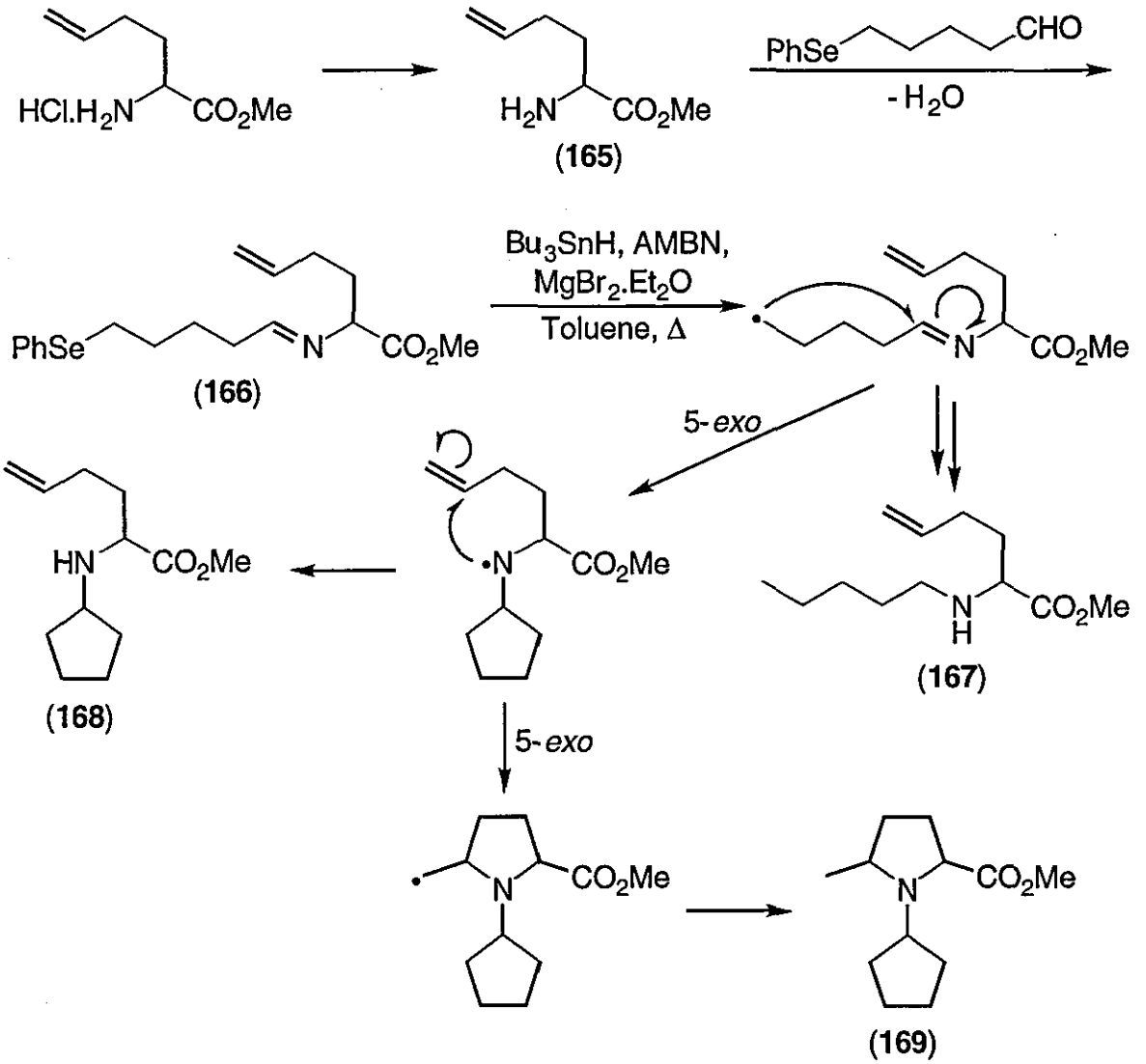
give methyl 2-[(*tert*-butoxycarbonyl)amino]-5-hexenoate **164** in 25 % yield. The purified amino acid **164** was stirred with 4M HCl in dioxan to give methyl 2-amino-5-hexenoate hydrochloride **163** as a cream solid in quantitative yield (Scheme 145).



Scheme 145

Unlike the use of the crude material previously (section 4.1), it was imperative that the amino acid salt was pure before preparing the free amine for imine formation. This was achieved by protecting the amine of the amino acid with a *tert*-butoxycarbonyl group, purifying using flash column chromatography and then removing the protective group. Thus, the crude material containing methyl 2-amino-5-hexenoate hydrochloride **163** was reacted with *tert*-butyl dicarbonate to give methyl 2-[(*tert*-butoxycarbonyl)amino]-5-hexenoate **164** in 25 % yield. The purified amino acid **164** was stirred with 4M HCl in dioxan to give methyl 2-amino-5-hexenoate hydrochloride **163** as a cream solid in quantitative yield (Scheme 145).

Imine formation was carried out as described in section 3.2. The free amine, methyl 2-amino-5-hexenoate **165**, was obtained *via* reaction of the hydrochloride salt with anhydrous potassium carbonate and condensed with 5-benzeneselenylpentanal **136** to give methyl 2-{[5-(benzeneselenyl)pentylidene] amino}-5-hexenoate **166**. To achieve better yields from tandem cyclisations using imines, Bowman *et al.* used 1 equivalent of the Lewis acid, magnesium bromide dietherate (see section 1.5.3).[98] Consequently, this was applied to our radical reaction and the possible reaction pathways are shown in Scheme 146.



Scheme 146

A solution of the imine **166** and magnesium bromide dietherate in anhydrous toluene was deoxygenated at room temperature for about 45 min and the reaction heated to reflux. As the reaction temperature reached 80 °C, a solution of tri-*n*-butyltin hydride/AMBN was syringed in over a total period of 6 h. Unfortunately, the cyclisation reaction was unsuccessful. Neither uncyclised material **167**, mono-cyclised product **168** nor tandem cyclised compound **169** were isolated. Indeed, the GC/MS studies of the crude reaction material indicated that only tin compounds were present! Extraction of the amines using hydrochloric acid gave an amine material whose ^{1}H NMR spectrum indicated that alkenyl material and one major MeO-containing compound was evident. Yet, purification of the 0.5 g of amine material using flash column chromatography gave only trace amounts of numerous compounds. The reaction obviously requires further investigation to

see whether the lack of isolated products and conflicting data was a "one-off" or the result of a more complex problem.

4.3 Summary of Results for Tandem Cyclisations

Our incomplete and unoptimised results show promise that these methodologies could be used to facilitate tandem reactions. Isolation of the tandem cyclised product methyl 7-methylperhydro-5-indolizinecarboxylate **161**, albeit in low yield, was encouraging. Considerable more study on improving reaction conditions is required, especially with the imine precursors where no identifiable amine products were isolated. This research is currently ongoing within the group.

EXPERIMENTAL

5.1 General Information

All solvents were distilled before use: light petroleum (refers to the fraction boiling between 40 °C and 60 °C), diethyl ether and ethyl acetate from calcium chloride; dichloromethane and toluene from phosphorous pentoxide; ethanol and methanol from magnesium and iodine. Anhydrous solvents (toluene, diethyl ether, dichloromethane *etc.*) were obtained from Aldrich Chemical Co. Ltd. Chemicals used in the work were obtained predominantly from Aldrich Chemical Co. Ltd. and Lancaster Synthesis Ltd. and were distilled or recrystallised as required.

Analytical thin layer chromatography was carried out using aluminium backed plates coated with Merck Kieselgel 60 GF_{254}. Plates were visualised under UV light (at 254 and/or 360 nm) or by staining with either potassium permanganate or ninhydrin dip, followed by heating. Flash column chromatography was carried out using Merck Kieselgel 60 H silica. Pressure, when required, was applied at the column head using hand bellows. Samples were applied as saturated solutions in an appropriate solvent.

Infra red spectra were recorded in the range 4000-600 cm^{-1} using a Nicolet 205 FT-IR Spectrometer, with internal calibration. ^{1}H and ^{13}C NMR spectra were recorded using either a Bruker AC250 or DPX400 Spectrometer. For the calculation of yields by ^{1}H NMR spectroscopy, *p*-dinitrobenzene was used as an internal standard.

Electron Impact (E.I.) mass spectra were recorded on a Kratos MS80 instrument. Chemical Ionisation (C.I.) and Fast Atom Bombardment (FAB) mass spectra were recorded on a VG Analytical ZAB-E instrument (EPSRC Mass Spectroscopy Service, Swansea). Elemental analyses were carried out on a Perkin Elmer 2400 CHN Elemental Analyser. Melting points were determined on a Leica Galen III Instrument.

5.2 Index of Experimental

5.3 Experimental for Chapter Two 102

1. Diazomethane Production
2. Preparation of *N*-(benzenesulfenyl)-*N*-(ethoxycarbonyl)cyclohexylamine **90** using benzenesulfenyl chloride
3. Preparation of *N*-(benzenesulfenyl)-*N*-(ethoxycarbonyl)cyclohexylamine **90** using *N*-(benzenesulfenyl)phthalimide
4. Reaction between *N*-(benzenesulfenyl)-*N*-(ethoxycarbonyl)cyclohexylamine **90** and tri-*n*-butyltin hydride
5. Preparation of *N*-(benzyloxycarbonyl)-*L*-phenylalanine methyl ester **91**
6. Attempted synthesis of *N*-(benzenesulfenyl)-*N*-(benzyloxycarbonyl)-*L*-phenylalanine methyl ester **92** using Newcomb's method
7. Preparation of *N*-(benzenesulfenyl)-*N*-(benzyloxycarbonyl)-*L*-phenylalanine methyl ester **92** using *n*-BuLi
8. Attempted introduction of the *N*-(benzyloxycarbonyl) protecting group to *N*-(benzenesulfenyl)-*L*-phenylalanine methyl ester **102**
9. Preparation of *N*-(benzenesulfenyl)-*N*-(benzyloxycarbonyl)-*L*-phenylalanine methyl ester **92** using NaH and dimethylformamide
10. Preparation of *N*-(benzyloxycarbonyl)-*O*-methyl-*L*-tyrosine methyl ester **93**
11. Attempted synthesis of *N*-(benzenesulfenyl)-*N*-(benzyloxycarbonyl)-*O*-methyl-*L*-tyrosine methyl ester **94**
12. Preparation of *N*-acetyl-*L*-phenylalanine methyl ester **95**
13. Attempted synthesis of *N*-acetyl-*N*-(benzenesulfenyl)-*L*-phenylalanine methyl ester
14. Reaction between *N*-(benzenesulfenyl)-*N*-(benzyloxycarbonyl)-*L*-phenylalanine methyl ester **92** and tri-*n*-butyltin hydride
15. Preparation of 3-(cyanopropyl)triphenylphosphonium bromide **96**
16. Preparation of (*Z*)-4-cyano-1-phenylbut-1-ene **97**
17. Preparation of (*Z*)-5-amino-1-phenylpent-1-ene **98**
18. Preparation of *N*-(benzyloxycarbonyl)-(*Z*)-5-amino-1-phenylpent-1-ene **99**
19. Preparation of *N*-(benzenesulfenyl)-*N*-(benzyloxycarbonyl)-(*Z*)-5-amino-1-phenylpent-1-ene **100**
20. Reaction between *N*-(benzenesulfenyl)-*N*-(benzyloxycarbonyl)-(*Z*)-5-amino-1-phenylpent-1-ene **100** and tri-*n*-butyltin hydride
21. Preparation of *N*-(benzenesulfenyl)-*L*-phenylalanine methyl ester **102** using benzenesulfenyl chloride

22. Preparation of *N*-(benzenesulfenyl)-*L*-phenylalanine methyl ester **102** using N-(benzenesulfenyl)phthalimide
23. Reaction between *N*-(benzenesulfenyl)-*L*-phenylalanine methyl ester **102** and tri-*n*-butyltin hydride
24. Preparation of *N*-tosyl-*L*-phenylalanine *tert*-butyl ester **104**
25. Preparation of *N*-(benzenesulfenyl)-*N*-tosyl-*L*-phenylalanine *tert*-butyl ester **105**
26. Reaction between *N*-(benzenesulfenyl)-*N*-tosyl-*L*-phenylalanine *tert*-butyl ester **105** and tri-*n*-butyltin hydride
27. Preparation of *N*-butoxycarbonyl-*L*-valine **115**
28. Preparation of *N*-butoxycarbonyl-*L*-valine benzyl ester **116**
29. Preparation of *L*-valine benzyl ester hydrochloride **117**
30. Preparation of *N*-(benzyloxycarbonyl)-*L*-valine **118b**
31. Preparation of *N*-(benzyloxycarbonyl)-*L*-valine *tert*-butyl ester **119b**
32. Preparation of *L*-valine *tert*-butyl ester **120b**
33. Preparation of *N*-(benzyloxycarbonyl)-*L-tert*-leucine **118d**
34. Preparation of *N*-(benzyloxycarbonyl)-*L-tert*-leucine *tert*-butyl ester **119d**
35. Preparation of *L-tert*-leucine *tert*-butyl ester **120d**
36. Preparation of *tert*-butyl N-*iso*propyl-(*iso*propylamino)methanimidate **121**
37. Preparation of *N*-(benzyloxycarbonyl)-*L*-alanine **118a**
38. Preparation of *N*-(benzyloxycarbonyl)-*L*-alanine *tert*-butyl ester **119a**
39. Preparation of *L*-alanine *tert*-butyl ester **120a**
40. Preparation of *N*-(benzyloxycarbonyl)-*L*-phenylalanine *tert*-butyl ester **119c**
41. Preparation of *L*-phenylalanine *tert*-butyl ester **120c**
42. Attempted synthesis of *N*-acetyl-*N*-methyl-*L*-phenylalanine methyl ester **123**
43. Preparation of *N*-(benzyloxycarbonyl)-*N*-methyl-*L*-phenylalanine methyl ester **124**
44. Preparation of *N*-(benzyloxycarbonyl)-*L*-valine methyl ester **125**
45. *N*-Alkylation of *N*-(benzyloxycarbonyl)-*L*-valine methyl ester **125** using 5-bromopentene
46. Attempted deprotection of *N*-(benzyloxycarbonyl)-N-(pent-4-enyl)-*L*-valine methyl ester **126** using sodium in ammonia
47. Deprotection of *N*-(benzyloxycarbonyl)-N-(pent-4-enyl)-*L*-valine methyl and pent-4-enyl ester mixture
48. Preparation of *N*-tosyl-*L*-valine methyl ester
49. Attempted *N*-alkylation of *N*-tosyl-*L*-valine methyl ester
50. Preparation of *N*-(pent-4-enyl)-*L*-valine methyl ester **128b** using 5-bromopentene
51. Attempted *N*-alkylation of *L-tert*-leucine methyl ester hydrochloride using 5-bromopentene
52. Preparation of *N*-(pent-4-enyl)-*L*-alanine methyl ester **128a**

53. Preparation of *N*-(pent-4-enyl)-*L*-valine methyl ester **128b** using reductive alkylation
54. Preparation of *N*-(pent-4-enyl)-*L*-phenylalanine methyl ester **128c**
55. Preparation of *N*-(pent-4-enyl)-*L*-*tert*-leucine methyl ester **128d**
56. Preparation of *N*-(pent-4-enyl)-*L*-alanine *tert*-butyl ester **128e**
57. Preparation of *N*-(pent-4-enyl)-*L*-valine *tert*-butyl ester **128f**
58. Preparation of *N*-(pent-4-enyl)-*L*-phenylalanine *tert*-butyl ester **128g**
59. Preparation of *N*-(pent-4-enyl)-*L*-*tert*-leucine *tert*-butyl ester **128h**
60. Attempted synthesis of *N*-(pent-4-enyl)-*L*-alanine benzyl ester
61. Preparation of *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-alanine methyl ester **131a**
62. Preparation of *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-valine methyl ester **131b**
63. Preparation of *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-phenylalanine methyl ester **131c**
64. Preparation of *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-*tert*-leucine methyl ester **131d**
65. Preparation of *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-alanine *tert*-butyl ester **131e**
66. Preparation of *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-phenylalanine *tert*-butyl ester **131g**
67. Benzenesulfenyl chloride **132** (method 1)
68. Benzenesulfenyl chloride **132** (method 2)
69. *N*-(benzenesulfenyl)phthalimide
70. Reaction between *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-alanine methyl ester **131a** and tri-*n*-butyltin hydride
71. Reaction between *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-valine methyl ester **131b** and tri-*n*-butyltin hydride
72. Reaction between *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-phenylalanine methyl ester **131c** and tri-*n*-butyltin hydride
73. Reaction between *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-*tert*-leucine methyl ester **131d** and tri-*n*-butyltin hydride
74. Reaction between *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-alanine *tert*-butyl ester **131e** and tri-*n*-butyltin hydride
75. Reaction between *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-phenylalanine *tert*-butyl ester **131g** and tri-*n*-butyltin hydride
76. Reaction between *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-alanine methyl ester **131a** and *tris*(trimethylsilyl)silane

5.4 Experimental for Chapter Three **152**

77. Preparation of ethyl 5-benzeneselenylpentanoate **135**

78. Preparation of 5-benzeneselenylpentanal **136**
79. Preparation of *L*-valine methyl ester **137b**
80. Preparation of *L*-phenylalanine methyl ester **137c**
81. Preparation of methyl (2*S*)-2-[5-(benzeneselenylpentylidene)amino]propanoate **138a**
82. Preparation of methyl (2*S*)-3-methyl-2-[5-(benzeneselenylpentylidene)amino] butanoate **138b**
83. Preparation of methyl (2*S*)-3-phenyl-2-[5-(benzeneselenylpentylidene)amino] propanoate **138c**
84. Reaction between methyl (2*S*)-2-[5-(benzeneselenylpentylidene)amino]propanoate **138a** and tri-*n*-butyltin hydride
85. Reaction between methyl (2*S*)-3-methyl-2-[5-(benzeneselenylpentylidene)amino] butanoate **138b** and tri-*n*-butyltin hydride
86. Reaction between methyl (2*S*)-3-phenyl-2-[5-(benzeneselenylpentylidene)amino] propanoate **138c** and tri-*n*-butyltin hydride
87. Preparation of methyl 2-(*o*-bromophenoxy)ethanoate **144**
88. Preparation of 2-(*o*-bromophenoxy)ethanol **145**
89. Attempted aldehyde formation from methyl 2-(*o*-bromophenoxy)ethanoate **144** using DIBAL
90. Attempted aldehyde formation from 2-(*o*-bromophenoxy)ethanol **145** using pyridinium chlorochromate
91. Attempted aldehyde formation from 2-(*o*-bromophenoxy)ethanol **145** using the Swern oxidation
92. Preparation of 2-[2-(2-bromophenoxy)ethyl]-1,3-dioxolane **146**
93. Hydrolysis of 2-[2-(2-bromophenoxy)ethyl]-1,3-dioxolane **146**

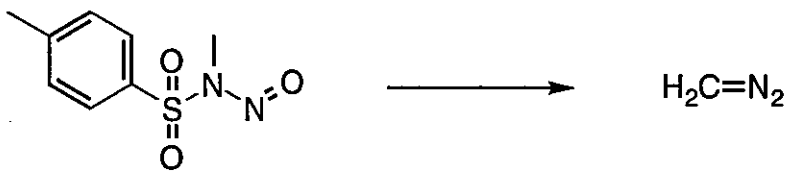
5.5 Experimental for Chapter Four **162**

94. Preparation of *N*-(benzyloxycarbonyl)-*L*-methionine methyl ester **148**
95. Preparation of methyl *L*-2-(benzyloxycarbonylamino)-4-(methylsulfinyl)butanoate **149**
96. Preparation of *N*-(benzyloxycarbonyl)-*L*-vinylglycine methyl ester **150**
97. Preparation of *L*-vinylglycine hydrochloride **153**
98. Preparation of *L*-vinylglycine methyl ester hydrochloride **154**
99. *N*-Alkylation of *L*-vinylglycine methyl ester hydrochloride **154**
100. Preparation of methyl 2-[(1-phenylmethylidene)amino]acetate **156**
101. Preparation of methyl 2-[(1-phenylmethylidene)amino]-4-pentenoate **157**
102. Preparation of methyl 2-amino-4-pentenoate hydrochloride **158**
103. Preparation of methyl 2-(4-pentenylamino)-4-pentenoate **159**

104. Preparation of methyl 2-[4-pentenyl(benzenesulfenyl)amino]-4-pentenoate **160**
105. Reaction between methyl 2-[4-pentenyl(benzenesulfenyl)amino]-4-pentenoate **160** and tri-*n*-butyltin hydride
106. Preparation of methyl 2-[(1-phenylmethylidene)amino]-5-hexenoate **162**
107. Preparation of methyl 2-amino-5-hexenoate hydrochloride **163** (crude)
108. Preparation of methyl 2-[(tert-butoxycarbonyl)amino]-5-hexenoate **164**
109. Preparation of methyl 2-amino-5-hexenoate hydrochloride **163** (pure)
110. Preparation of methyl 2-amino-5-hexenoate **165**
111. Preparation of methyl 2-{[5-(benzeneselenyl)pentylidene]amino}-5-hexenoate **166**
112. Reaction between methyl 2-{[5-(benzeneselenyl)pentylidene]amino}-5-hexenoate **166** and tri-*n*-butyltin hydride

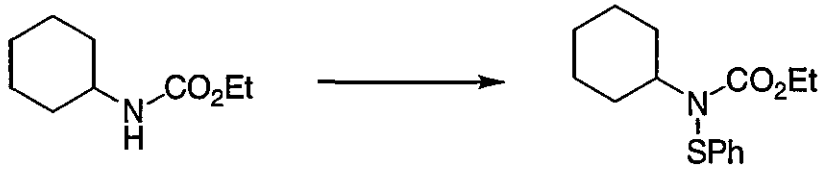
5.3 Experimental for Chapter Two

1. Diazomethane Production[127]



Potassium hydroxide (10 g), distilled water (24 cm^3) and ethanol (30 cm^3) were placed in a 500 ml round bottomed flask (set up for distillation) and heated to 50 °C. A solution of Diazald® (10 g) in diethyl ether (150 cm^3) was added dropwise and, on completion, the flask contents were heated to 65 °C. The distillate was collected until it contained no yellow colouration. The yellow diethyl ether distillate collected contained approximately 30 mmol of diazomethane.

2. *N*-(Benzenesulfenyl)-*N*-(ethoxycarbonyl)cyclohexylamine (90) using benzenesulfenyl chloride



(89) (90)

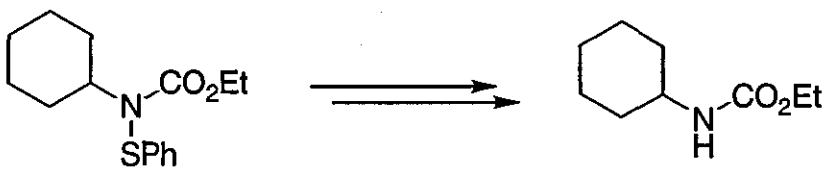
A solution of *N*-(ethoxycarbonyl)cyclohexylamine **89** (1.00 g, 5.84 mmol) in anhydrous tetrahydrofuran (5 cm^3) was syringed into a flask containing a mixture of sodium hydride (0.41 g, 16.92 mmol) and anhydrous tetrahydrofuran (20 cm^3) under nitrogen before stirring at 50 °C for 2 h. The flask was then cooled to -78 °C and benzenesulfenyl chloride added dropwise with stirring until the yellow colouration produced failed to decolourise. The reaction was allowed to return to room temperature whilst stirring for 30 min. Ethanol (1 cm^3) was added followed by diethyl ether (30 cm^3) and phosphate buffer solution (PBS, 0.05 M, pH = 7.0, 40 cm^3). The layers were separated and the PBS fraction extracted further with diethyl ether (2 x 20 cm^3) before combining the ether fractions. These were washed with distilled water (2 x 20 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness. Purification using flash column chromatography (ethyl acetate/light petroleum) gave the N-*(benzenesulfenyl)*-N-*(ethoxycarbonyl)cyclohexylamine* **90** (0.33 g, 20 %) as a yellow

oil; υ_{max}/cm^{-1} (neat) 3050, 2932, 2856, 1705, 738 and 690; δ_H (250 MHz, $CDCl_3$) 7.32-7.11 (5 H, m, ArH), 4.24 (2 H, q, *J* 7.2 Hz, CH_2O), 4.29-4.20 (1 H, m, CHN), 1.27 (3 H, t, *J* 7.1 Hz, CH_3) and 1.77-1.04 (10 H, m, cyclohexyl); δ_C (62.9 MHz, $CDCl_3$) 158.05 (urethane CO_2), 140.44 (ArC-S), 126.03, 125.79 and 123.68 (Ar-CH), 62.88 (CH_2O), 59.83 (CHN), 31.16, 25.53, 25.17 (cyclohexyl-CH_2) and 14.42 (CH_3); *m/z* 279.1293 [M^+ (100 %), $C_{15}H_{21}NO_2S$ requires 279.1293], 197 (45), 125 (32), 109 (48), 65 (29), 55 (32) and 41 (36).

3. *N*-(Benzenesulfenyl)-*N*-(ethoxycarbonyl)cyclohexylamine (90) using *N*-(benzenesulfenyl)-phthalimide

A solution of *N*-(ethoxycarbonyl)cyclohexylamine **89** (2.00 g, 11.68 mmol) in anhydrous tetrahydrofuran (15 cm^3) was syringed into a flask containing a mixture of sodium hydride (0.91 g, 38.00 mmol) and anhydrous tetrahydrofuran (25 cm^3) under nitrogen before stirring at 50 °C for 3 h. The flask was then cooled to -78 °C, *N*-(benzenesulfenyl)-phthalimide (3.01 g, 11.74 mmol) added and the reaction stirred for 1 h. The mixture was then returned to room temperature and stirred for a further 15 h. The mixture was filtered then evaporated to dryness and the yellow slurry recovered dissolved in light petroleum (20 cm^3), filtered again and evaporated to dryness. Purification using flash column chromatography (ethyl acetate/light petroleum) yielded the N-*(benzenesulfenyl)*-N-*(ethoxycarbonyl) cyclohexylamine* **90** (0.86 g, 26 %) as a yellow oil; see experiment 2 for data.

4. Reaction between *N*-(benzenesulfenyl)-*N*-(ethoxycarbonyl)cyclohexylamine (90) and tri-*n*-butyltin hydride



(90) **(89)**

A solution of *N*-(benzenesulfenyl)-*N*-(ethoxycarbonyl)cyclohexylamine **90** (205 mg, 0.73 mmol) in anhydrous toluene (100 cm^3) was refluxed under nitrogen at 110 °C for 1 h before injecting a solution (nitrogen purged for 30 min) of tri-*n*-butyltin hydride (0.26 cm^3, 0.97 mmol) and AIBN (41 mg, 0.25 mmol) in anhydrous toluene (25 cm^3) over 5 h using a syringe pump, then stirred for a further h before cooling and evaporating to dryness to give a yellow oil (1.07 g). TLC analysis of the crude

product showed that all the sulfenamide had been consumed. Using the internal standard, dimethoxybenzene, the crude material was identified by ^{1}H NMR spectroscopy to contain *N*-(ethoxycarbonyl)cyclohexylamine **89** in quantitative yield; δ_H (250 MHz, $CDCl_3$) 4.50 (1 H, br, NH), 3.99 (2 H, q, *J* 7.1 Hz, CH_2O), 3.40 (1 H, br, CHN), 1.94-1.89 (2 H, m, cyclohexyl-CH_2), 1.74-1.59 (4 H, m, cyclohexyl-CH_2), 1.43-1.04 (4 H, m, cyclohexyl-CH_2) and 1.24 (3 H, t, *J* 7.1 Hz, CH_3).

The data was consistent with that previously reported in the literature.[128]

5. *N*-(Benzyloxycarbonyl)-*L*-phenylalanine methyl ester (91)

(91)

A solution of *N*-(benzyloxycarbonyl)-*L*-phenylalanine (5.00 g, 16.70 mmol) in diethyl ether (100 cm^3) was cooled to 0-5 °C in an ice bath. Diazomethane (diethyl ether solution) was added dropwise until no effervescence was observed and a pale yellow colour remained. Nitrogen was bubbled through the solution until the yellow colour was no longer evident. The solution was evaporated to dryness to give *N*-(benzyloxycarbonyl)-*L*-phenylalanine methyl ester **91** (5.10 g, 94 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3339, 3032, 2954, 1722, 1527, 1216, 748 and 700; δ_H (250 MHz, $CDCl_3$) 7.35-7.09 (10 H, m, ArH), 5.30 (1 H, d, *J* 7.8 Hz, NH), 5.11 (2 H, s, CH_2O), 4.68 (1 H, q, *J* 8.0 Hz, CHN), 3.72 (3 H, s, OCH_3) and 3.17-3.09 (2 H, m, $PhCH_2$); δ_C (62.9 MHz, $CDCl_3$) 172.60 (ester CO_2), 155.80 (urethane CO_2), 137.14 and 136.52 (Ar-C), 129.19, 128.53, 128.44, 128.09, 127.99 and 127.06 (Ar-CH), 66.88 (CH_2O), 54.79 (CHN), 52.19 (OCH_3) and 38.16 ($PhCH_2$); *m/z* 313.1314 [M^+ (24 %), $C_{18}H_{19}NO_4$ requires 313.1314], 270 (27), 210 (28), 181 (30), 162 (95), 91 (100) and 65 (44).

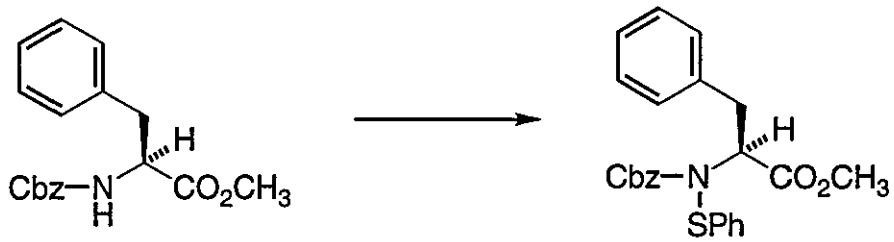
The data was consistent with that previously reported in the literature.[129]

6. Attempted synthesis of *N*-(benzenesulfenyl)-*N*-(benzyloxycarbonyl)-*L*-phenylalanine methyl ester (92) using Newcomb's method

A solution of *N*-(benzyloxycarbonyl)-*L*-phenylalanine methyl ester **91** (1.00 g, 3.34 mmol) in anhydrous tetrahydrofuran (5 cm^3) was syringed into a flask containing a mixture of sodium hydride (0.38 g, 15.83 mmol) and anhydrous tetrahydrofuran (20

cm^3) under nitrogen before stirring at 50 °C for 2 h. The flask was then cooled to -78 °C and benzenesulfenyl chloride added dropwise with stirring until the yellow colouration produced failed to decolourise. The reaction was allowed to return to room temperature whilst stirring for 30 min. Ethanol (1 cm^3) was added then the mixture evaporated to dryness. Diethyl ether (30 cm^3) and distilled water (15 cm^3) were added, the layers separated and the aqueous layer was extracted further with diethyl ether (1 x 20 cm^3). The organic fractions were combined, dried ($MgSO_4$), filtered and evaporated to dryness to give a brown solid. ^1H NMR spectroscopy of the crude solid indicated that the desired compound had not been made and this method was eventually discontinued.

7. *N*-(Benzenesulfenyl)-*N*-(benzyloxycarbonyl)-*L*-phenylalanine methyl ester (92) using *n*-BuLi



(91) **(92)**

A solution of *N*-(benzyloxycarbonyl)-*L*-phenylalanine methyl ester **91** (0.78 g, 2.49 mmol) in anhydrous tetrahydrofuran (25 cm^3) was placed in a flask under nitrogen and cooled to -78 °C. A 1.6 M hexane solution of *n*-BuLi (2.1 cm^3, 3.4 mmol) was added and the solution stirred for 30 min before the dropwise addition of benzenesulfenyl chloride (0.9 g, 6.6 mmol). On returning to room temperature, diethyl ether (50 cm^3) and phosphate buffer solution (PBS, 0.05 cm^3, pH = 7.0, 40 cm^3) were added and the layers separated. The PBS fraction was extracted with diethyl ether (2 x 20 cm^3), the ether fractions were combined, washed with distilled water (2 x 20 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness. Purification using flash column chromatography (ethyl acetate/light petroleum) yielded the N-*(benzenesulfenyl)*-N-*(benzyloxycarbonyl)*-L-*phenylalanine methyl ester* **92** (0.42 g, 40 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3031, 2952, 1744, 1710, 740 and 698; δ_H (250 MHz, $CDCl_3$) 7.35-7.04 (15 H, m, ArH), 5.21 (2 H, s, CH_2O), 5.13 (1 H, dd, *J* 9.5, 5.6 Hz, CHN), 3.51 (3 H, s, OCH_3) 3.38 (1 H, dd, *J* 14.4, 5.6 Hz, PhC*H*H) and 3.24 (1 H, dd, *J* 14.4, 9.5 Hz, PhCH*H*); δ_C (62.9 MHz, $CDCl_3$) 170.43 (ester CO_2), 157.84 (urethane CO_2), 137.22 (ArC-S), 136.86 and 135.91 (Ar-C), 129.03, 128.63, 128.41, 128.33, 128.14, 127.87, 127.50, 126.86 and 126.51 (Ar-CH), 68.95 (CH_2O), 65.65 (CHN), 52.05 (OCH_3) and 35.64

($PhCH_2$); *m/z* 421.1348 [M^+ (55 %), $C_{24}H_{23}NO_4S$ requires 421.1348], 378 (26), 312 (23), 286 (25) and 91 (100).

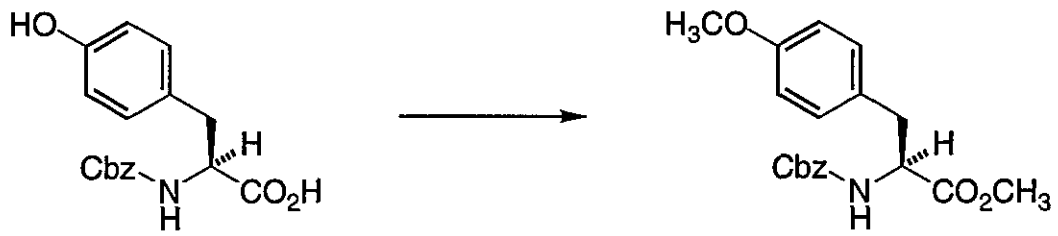
8. Attempted introduction of the N-(benzyloxycarbonyl) protecting group to *N*-(benzenesulfenyl)-*L*-phenylalanine methyl ester (102)

A solution of *N*-(benzenesulfenyl)-*L*-phenylalanine methyl ester **102** (0.86 g, 2.99 mmol) in anhydrous dimethylformamide (10 cm^3) was syringed into a flask containing sodium hydride (0.10 g, 4.20 mmol) at 0-5 °C (ice bath) under nitrogen and allowed to stir for 3 h. Benzylchloroformate (0.7 cm^3, 4.4 mmol) was added dropwise, the reaction stirred a further 15 min then phosphate buffer solution (PBS, 0.05 M, pH = 7.0, 50 cm^3) and diethyl ether (40 cm^3) added. The layers were separated and the PBS fraction was further extracted with diethyl ether (2 x 20 ml). The ether fractions were then combined and washed with distilled water (4 x 20 ml) and brine (saturated, 3 x 20 ml) before drying ($MgSO_4$) and filtering. Evaporation to dryness yielded a red oil (1.6 g) from which the ^1H NMR spectrum indicated that none of the expected *N*-(benzenesulfenyl)-*N*-(benzyloxycarbonyl)-*L*-phenylalanine methyl ester was present. This reaction was discontinued.

9. *N*-(Benzenesulfenyl)-*N*-(benzyloxycarbonyl)-*L*-phenylalanine methyl ester (92) using NaH and dimethylformamide

A solution of *N*-(benzyloxycarbonyl)-*L*-phenylalanine methyl ester **91** (1.00 g, 3.19 mmol) in anhydrous dimethylformamide (5 cm^3) was added dropwise by syringe into a flask containing sodium hydride (0.45 g, 18.75 mmol, freshly washed in light petroleum) at -30 °C under nitrogen. After stirring for 3 h, benzenesulfenyl chloride was added dropwise until the yellow colouration produced on addition ceased to decolourise. On returning to room temperature, diethyl ether (40 cm^3) and phosphate buffer solution (PBS, 0.05 M, pH = 7.0, 50 cm^3) were added to the reaction. The layers were separated and the PBS fraction was further extracted with diethyl ether (2 x 25 cm^3), all the ether fractions combined, washed with brine (saturated, 3 x 25 cm^3) and distilled water (5 x 25 cm^3) and dried ($MgSO_4$). Filtration followed by evaporation of the distillate to dryness allowed purification using flash column chromatography [dichloromethane/light petroleum (1:1)] to give *N*-(benzenesulfenyl)-*N*-(benzyloxycarbonyl)-*L*-phenylalanine methyl ester **92** (0.56 g, 42 %) as a colourless oil. The data obtained was identical to that in experiment 7.

10. *N*-(Benzyloxycarbonyl)-*O*-methyl-*L*-tyrosine methyl ester (93)



(93)

A solution of *N*-(benzyloxycarbonyl)-*L*-tyrosine (5.02 g, 15.92 mmol) in diethyl ether (100 cm^3) was cooled to 0-5 °C in an ice bath. Diazomethane (ether solution) was added until no effervescence occurred then a further equivalent volume of diazomethane solution was evaporated to dryness to give *N*-(benzyloxycarbonyl)-*O*-methyl-*L*-tyrosine methyl ester **93** (5.19 g, 95 %)as a colourless oil; υ_{max}/cm^{-1} (neat) 3416, 2954, 1743, 1702 and 699; δ_H (250 MHz, $CDCl_3$) 7.34 (5 H, br, benzyloxycarbonyl ArH), 7.02 (2 H, d, *J* 8.5 Hz, ArH *meta* to OMe), 6.81 (2 H, d, *J* 8.5 Hz, ArH *ortho* to OMe), 5.38 (1 H, d, *J* 7.9 Hz, NH), 5.10 (2 H, s, CH_2O), 4.63 (1 H, br d, *J* 7.3 Hz, CHN), 3.77 (3 H, s, CH_3O-Ar), 3.72 (3 H, s, OCH_3) and 3.12-2.92 (2 H, m, $PhCH_2$); δ_C (62.9 MHz, $CDCl_3$) 173.16 (ester CO_2), 158.43 (urethane CO_2), 156.28 (Ar-C-OMe), 136.78 and 136.25 (Ar-C), 130.20 (Ar-CH *meta* to OMe), 128.44, 128.08, 127.98 and 127.64 (Ar-CH), 113.98 (Ar-C *ortho* to OMe), 66.64 (CH_2O), 55.10 (CHN), 54.94 (CH_3O-Ar), 52.17 (OCH_3) and 37.25 ($PhCH_2$); *m/z* 343.1421 [M^+ (14 %), $C_{19}H_{21}NO_5$ requires 343.1420], 192 (88), 121 (100), 91 (84), 77 (31) and 65 (25).

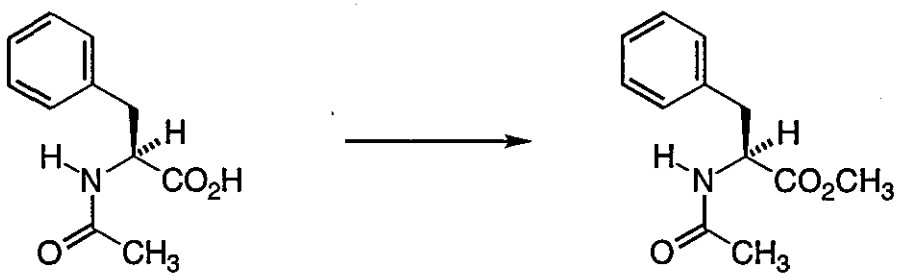
The compound has been previously reported in the literature.[130]

11. Attempted synthesis of *N*-(benzenesulfenyl)-*N*-(benzyloxycarbonyl)-*O*-methyl-*L*-tyrosine methyl ester

A solution of *N*-(benzyloxycarbonyl)-*O*-methyl-*L*-tyrosine methyl ester (1.00 g, 2.91 mmol) in anhydrous dimethylformamide (12 cm^3) was added dropwise by syringe to a flask under nitrogen containing sodium hydride (0.25 g, 10.42 mmol, washed in light petroleum). The reaction was stirred for 3 h at room temperature before cooling to -30 °C and adding benzenesulfenyl chloride dropwise by syringe until the yellow colour produced on addition failed to decolourise. Phosphate buffer solution (PBS, 0.05 M, pH = 7.0, 50 cm^3) and diethyl ether (50 cm^3) were added. The layers were separated and the PBS fraction was extracted further with diethyl ether (2 x 20 cm^3). The ether fractions were combined, washed with distilled water (5 x 20 cm^3) and brine (saturated, 3 x 20 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness to give an orange oil. Purification using flash column chromatography (30 %

dichloromethane/light petroleum increasing to dichloromethane) gave several isolated compounds. ^{1}H NMR spectroscopy indicated that the majority were due to side reactions of the benzenesulfenyl chloride and that, even though no starting material was present, only an impure trace amount of *N*-(benzenesulfenyl)-*N*-(benzyloxycarbonyl)-*O*-methyl-*L*-tyrosine methyl ester was produced.

12. *N*-Acetyl-*L*-phenylalanine methyl ester (95)



(95)

A solution of *N*-acetyl-*L*-phenylalanine (5.79 g, 27.95 mmol) in methanol (50 cm^3) was cooled to 0-5 °C in an ice bath. Diazomethane (diethyl ether solution) was added dropwise until no effervescence was observed and a pale yellow colour remained. Nitrogen was bubbled through the solution until the yellow colour was no longer evident. The solution was evaporated to dryness to give *N*-acetyl-*L*-phenylalanine methyl ester **95** (6.06 g, 97 %) as a white solid, m.p. 86-88 °C (lit.[132] 89-90 °C); υ_{max}/cm^{-1} (nujol mull) 3302, 3024, 2948, 1722, 1681, 745 and 692; δ_H (250 MHz, $CDCl_3$) 7.25 (3 H, m, *p*- and *m*-ArH), 7.08 (2 H, m, *o*-ArH), 6.06 (1 H, d, *J* 8.0 Hz, NH), 4.88 (1 H, dt, *J* 7.8, 3.6 Hz, CHN), 3.71 (3 H, s, OCH_3), 3.17-3.09 (2 H, dd, *J* 5.7, 4.5 Hz, $PhCH_2$) and 1.91 (3 H, s, $OCCH_3$); δ_C (62.9 MHz, $CDCl_3$) 172.04 (ester CO_2), 169.56 (amide CO_2), 135.77 (Ar-C), 129.20, 128.50 and 127.05 (Ar-CH), 53.04 (CHN), 52.23 (OCH_3), 37.76 ($PhCH_2$) and 23.03 (CH_3).

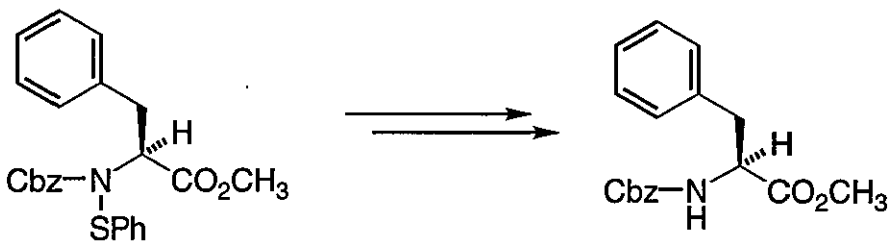
The method has been previously reported in the literature.[131] The compound data was reported elsewhere and it is consistent with the results presented here.[133]

13. Attempted synthesis of *N*-acetyl-*N*-(benzenesulfenyl)-*L*-phenylalanine methyl ester

A mixture of *N*-acetyl-*L*-phenylalanine methyl ester **95** (0.99 g, 4.80 mmol), anhydrous dimethylformamide (30 ml) and sodium hydride was cooled to -30 °C under nitrogen. After stirring for 3 h, benzenesulfenyl chloride was added dropwise until the yellow colouration produced on addition ceased to decolourise. The

mixture was returned to room temperature and stirred overnight. Diethyl ether (40 cm^3) and phosphate buffer solution (PBS, 0.05 M, pH = 7.0, 50 cm^3) were added to the reaction. The layers were separated and the PBS fraction was further extracted with diethyl ether (2 x 25 cm^3), all the ether fractions were combined, washed with brine (saturated, 3 x 25 cm^3) and distilled water (5 x 25 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness. Purification using flash column chromatography (dichloromethane/light petroleum (1:1) gave several fractions as colourless oils. ^1H NMR spectroscopy indicated that none of the desired compound was present.

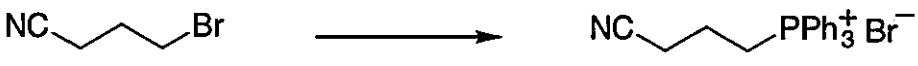
14. Reaction between *N*-(benzenesulfenyl)-*N*-(benzyloxycarbonyl)-*L*-phenylalanine methyl ester (92) and tri-*n*-butyltin hydride



(92) **(91)**

A solution of *N*-(benzenesulfenyl)-*N*-(benzyloxycarbonyl)-*L*-phenylalanine methyl ester **92** (396 mg, 0.94 mmol) in anhydrous toluene (200 cm^3) was stirred under nitrogen at 80 °C for 90 min before injecting a solution (nitrogen purged for 45 min) of tri-*n*-butyltin hydride (0.50 cm^3, 1.86 mmol) and AIBN (62 mg, 0.38 mmol) in anhydrous toluene (25 cm^3) over 5 h using a syringe pump, then stirred for a further 45 min before cooling and evaporating to dryness. Purification using flash column chromatography (ethyl acetate/light petroleum) yielded *N*-(benzyloxy-carbonyl)-*L*-phenylalanine methyl ester **91** (122 mg, 41 %) as a colourless oil (see experiment 5 for data). No other identifiable *L*-phenylalanine derivatives were isolated.

15. 3-(Cyanopropyl)triphenylphosphonium bromide (96)[73]

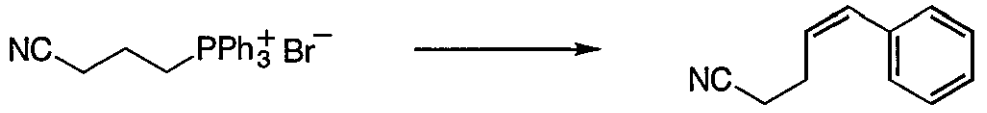


(96)

A solution of 3-bromopropyl cyanide (25.03 g, 0.17 mol) and triphenylphosphine (46.14 g, 0.17 mol) in toluene (500 cm^3) was refluxed for 72 h. On cooling, colourless crystals of the product were filtered off, washed with cold toluene and dried to yield

the 3-cyanopropyltriphenylphosphonium bromide **96** (46.29 g, 78 %), m.p. 215-217 °C; δ_H (250 MHz, $CDCl_3$) 7.85 (15 H, m, ArH), 4.14 (2 H, m, CH_2PPh_3), 3.11 (2 H, t, *J* 9.2 Hz, CH_2CN) and 1.96 (2 H, m, $CH_2CH_2CH_2$); δ_C (62.9 MHz, $CDCl_3$) 132.86 (Ar-C), 130.65, 128.98 (Ar-CH), 119.19 (CN), 117.53 (Ar-CH), 21.85 (CH_2PPh_3), 19.79 (CH_2CN) and 17.94 ($CH_2CH_2CH_2$).

16. (Z)-4-Cyano-1-phenylbut-1-ene (97)

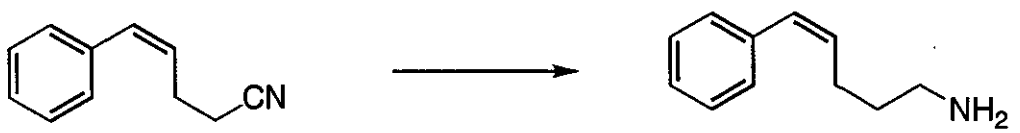


(96) **(97)**

To a mixture of sodium hydride (2.65 g, 0.11 mol, freshly washed with light petroleum) in anhydrous tetrahydrofuran (200 cm^3) under nitrogen was added 4-cyanobutylphosphonium bromide **96** (45.26 g, 0.11 mol) over a 20 min period. This was stirred for 1 h before the dropwise addition of benzaldehyde (3.90 g, 0.04 mol). After a further 20 h stirring, the mixture was poured onto ice/water (200 cm^3) and acidified to pH = 2 with 2 M hydrochloric acid. The product was extracted with diethyl ether (3 x 50 cm^3), the ether extracts combined, dried ($MgSO_4$), filtered and evaporated to dryness. Purification using flash column chromatography (diethyl ether/light petroleum) gave the (Z)-4-cyano-1-phenylbut-1-ene **97** (4.64 g, 80 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3475, 3058, 3023, 2931, 2246, 768 and 701; δ_H (250 MHz, $CDCl_3$) 7.53-7.32 (2 H, m, ArH), 7.28-7.22 (3 H, m, ArH), 6.61 (1 H, d, *J* 11.5 Hz, PhCH=), 5.64 (1 H, dt, *J* = 11.5, 7.1 Hz, =C*H*CH_2), 2.65 (2 H, dt, *J* 7.2, 1.7 Hz, =CCH_2) and 1.61 (2 H, t, *J* 7.1 Hz, CH_2N); δ_C (62.9 MHz, $CDCl_3$) 136.94 (Ar-C), 132.57 (PhCH=), 128.89, 127.65 (Ar-CH), 125.98 (=$CHCH_2$), 119.61 (CN), 24.77 (=CCH_2) and 17.97 (CH_2CN). *m/z* 157.0890 [M^+ (23 %), $C_{11}H_{11}N$ requires 157.0891], 126 (16), 117 (100), 91 (22), 51 (14) and 39 (15).

The method has been previously reported in the literature.[73] The compound data was reported elsewhere and it is consistent with the results presented here.[134]

17. (Z)-5-Amino-1-phenylpent-1-ene (98)



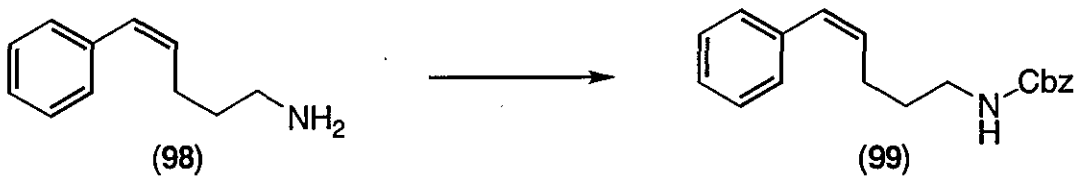
(97) **(98)**

A solution of (Z)-4-cyano-1-phenylbut-1-ene **97** (1.93 g, 12.24 mmol) in anhydrous diethyl ether (10 cm^3) was added dropwise by syringe to a suspension of lithium

aluminium hydride (0.61 g, 15.27 mmol) in anhydrous diethyl ether (30 cm^3) at 0-5 °C (ice bath) under nitrogen and stirred for 1 h. Dilute sodium hydroxide was added until effervescence ceased and the product extracted into dichloromethane (2 x 30 cm^3). The combined organic extracts were washed with distilled water (2 x 30 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness to yield (Z)-5-amino-1-phenylpent-1-ene **98** (1.83 g, 92 %) as a yellow slurry; υ_{max}/cm^{-1} (neat) 3368, 3303, 2928, 756 and 699; δ_H (250 MHz, $CDCl_3$) 7.37-7.19 (5 H, m, ArH), 6.44 (1 H, d, *J* 11.6 Hz, PhCH=), 5.73-5.59 (1 H, m, =C*H*CH_2), 2.72 (2 H, t, *J* 9.6 Hz, CH_2N), 2.37-2.30 (2 H, m, =CCH_2), 1.61 (2 H, quintet, *J* 7.4 Hz, $CH_2CH_2CH_2$) and 1.55 (2 H, br, NH_2); δ_C (62.9 MHz, $CDCl_3$) 132.27 (Ar-C), 129.16, 128.64, 128.08, 126.81 and 126.47 (Ar- and alkenyl-CH), 41.71 (CH_2N), 33.87 (=CCH_2) and 25.84 ($CH_2CH_2CH_2$).

The method has been previously reported in the literature.[73] The compound data was reported elsewhere and it is consistent with the results presented here.[135]

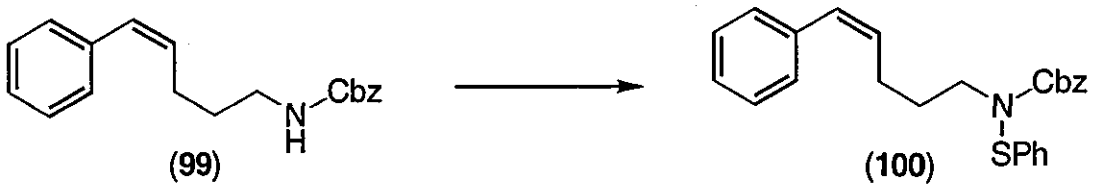
18. *N*-(Benzyloxycarbonyl)-(Z)-5-amino-1-phenylpent-1-ene (99)



(98) (99)

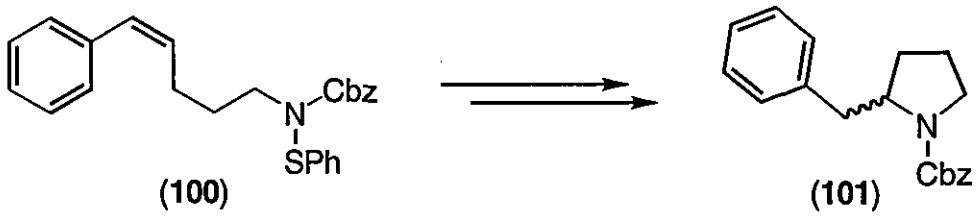
A solution of (Z)-5-amino-1-phenylpent-1-ene **98** (1.79 g, 11.18 mmol) in anhydrous dichloromethane (20 cm^3) was cooled in an ice bath to 0-5 °C under nitrogen and benzylchloroformate (2.0 cm^3, 13.4 mmol) added dropwise. Triethylamine (3.6 cm^3, 22.4 mmol) was subsequently added dropwise and the reaction stirred for 30 min before the addition of distilled water (30 cm^3). The product was extracted with dichloromethane (2 x 20 cm^3), the organic extracts combined and washed with distilled water (2 x 15 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness. Purification using flash column chromatography (80 % dichloromethane/light petroleum) gave N-*(benzyloxycarbonyl)*-(Z)-*5-amino-1-phenylpent-1-ene* **99** (2.41 g, 72 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3422, 3338, 2935, 1699 and 699; δ_H (250 MHz, $CDCl_3$) 7.38-7.24 (10 H, m, ArH), 6.48 (1 H, d, *J* 11.6 Hz, PhCH=), 5.72-5.55 (1 H, m, =C*H*CH_2), 5.10 (2 H, s, CH_2O), 4.71 (1 H, br, NH), 3.22 (2 H, q, *J* 6.7 Hz, CH_2N), 2.39-2.32 (2 H, m, =CCH_2) and 1.67 (2 H, quintet, *J* 7.3 Hz, $CH_2CH_2CH_2$); δ_C (62.9 MHz, $CDCl_3$) 156.31 (urethane CO_2), 137.35 (Ar-C), 131.44, 129.71, 128.63, 128.44, 128.14, 128.00, 126.95, 126.61 and 125.92 (Ar- and alkenyl-CH), 66.52 (CH_2N), 40.57 (=CCH_2) and 25.61 ($CH_2CH_2CH_2$); *m/z* 296.1644 [MH^+ (16 %), $C_{19}H_{22}NO_2$ requires 296.1650], 298 (14), 217 (100), 90 (80), 63 (32) and 39 (16).

19. *N*-(Benzenesulfenyl)-*N*-(benzyloxycarbonyl)-(Z)-5-amino-1-phenylpent-1-ene (100)



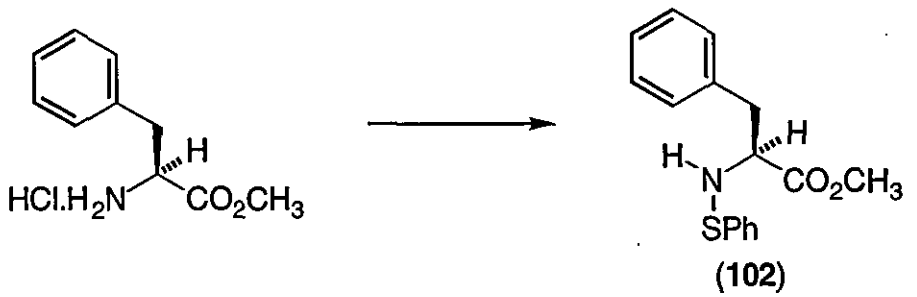
A solution of *N*-(benzyloxycarbonyl)-(Z)-5-amino-1-phenylpent-1-ene **99** (1.02 g, 3.47 mmol) in anhydrous tetrahydrofuran (25 cm^3) was placed in a flask under nitrogen and cooled to -78 °C. A 1.6 M hexane solution of *n*-BuLi (3.3 cm^3, 5.2 mmol) was added and the solution stirred for 10 min before the dropwise addition of benzenesulfenyl chloride. Addition was stopped when the yellow colouration produced failed to decolourise. The mixture was warmed to room temperature, diethyl ether (30 cm^3) and phosphate buffer solution (PBS, 0.05 cm^3, pH = 7.0, 30 cm^3) were added and the layers separated. The PBS fraction was extracted with diethyl ether (2 x 20 cm^3) then the ether fractions were combined, washed with distilled water (2 x 20 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness. Purification using flash column chromatography (40 % dichloromethane/light petroleum) yielded N-*(benzenesulfenyl)*-N-*(benzyloxycarbonyl)*-(Z)-*5-amino-1-phenylpent-1-ene* **100** (0.92 g, 66 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3058, 2939, 1702, 738 and 697; δ_H (250 MHz, $CDCl_3$) 7.41-7.22 (15 H, m, ArH), 6.49 (1 H, d, *J* 11.6 Hz, PhCH=), 5.68 (1 H, dt, *J* 11.7, 7.2 Hz, =C*H*CH_2), 5.28 (2 H, s, CH_2O), 3.70 (2 H, t, *J* 7.3 Hz, CH_2N), 2.44-2.36 (2 H, m, =CCH_2) and 1.89 (2 H, m, $CH_2CH_2CH_2$); δ_C (62.9 MHz, $CDCl_3$) 157.77 (urethane CO_2), 138.23 (Ar-C-S), 137.44 (Ar-*C*-C=C), 136.05 (Ar-*C*-CH_2O), 131.58, 129.59, 129.52, 129.08, 128.73, 128.49, 128.18, 128.14, 127.88, 126.96, 126.74, 126.62, 126.00 and 124.88 (Ar- and alkenyl-CH), 68.62 (CH_2O), 53.52 (CH_2N), 28.92 (=CCH_2) and 25.64 ($CH_2CH_2CH_2$); *m/z* (CI) 404.1684 [MH^+ (100 %), $C_{25}H_{26}NO_2S$ requires 404.1684], 360 (48), 312 (21), 204 (28), 160 (37), 143 (48), 108 (59) and 91 (88).

20. Reaction between *N*-(benzenesulfenyl)-*N*-(benzyloxycarbonyl)-(Z)-5-amino-1-phenylpent-1-ene (100) and tri-*n*-butyltin hydride



A solution of *N*-(benzenesulfenyl)-*N*-(benzyloxycarbonyl)-(Z)-5-amino-1-phenylpent-1-ene **100** (448 mg, 1.11 mmol) in anhydrous toluene (200 cm^3) was stirred under nitrogen at 80 °C for 90 min before injecting a solution (nitrogen purged for 45 min) of tri-*n*-butyltin hydride (0.40 cm^3, 1.48 mmol) and AIBN (55 mg, 0.33 mmol) in anhydrous toluene (25 cm^3) over 5 h using a syringe pump, then stirred for a further 2 h before cooling, stirring overnight and evaporating to dryness. Purification using flash column chromatography (15 % ethyl acetate/light petroleum) yielded *benzyl 2-benzyl-1-pyrrolidinecarboxylate* **101** (164 mg, 50 %) as a colourless oil and as a 1:1 mix of inseparable rotamers; υ_{max}/cm^{-1} (neat) 3043, 2988, 2912, 1702, 733 and 692; δ_H (250 MHz, $CDCl_3$) 7.46-7.36 (5 H, m, urethane ArH), 7.29-7.22 (4 H, m, ArH), 7.13-7.10 (1 H, m, ArH), 5.22 (2 H, s, CH_2O), 4.15 (1 H, br, CHN), (2 H, br, CH_2N), 3.24 (rotamer 1, 1 H, br d, *J* 12.9 Hz, PhC*H*H), 3.06 (rotamer 2, 1 H, br d, *J* 10.3 Hz, PhC*H*H), 2.70-2.56 (rotamers 1 and 2, 1 H, m, PhCH*H*) and 1.77 (4 H, br, $CHCH_2CH_2$+$CH_2CH_2CH_2$); δ_C (62.9 MHz, $CDCl_3$) rotamer 1, 155.36 (urethane CO_2), 139.37 (Ar-C-CH_2CO_2), 137.59 (Ar-C), 130.01, 129.80, 128.92, 128.81, 128.78, 128.49, 128.43, 128.32, 128.25, 126.70 and 126.63 (Ar-CH), 66.92 (CH_2O), 59.71 (CHN), 47.02 (CH_2N), 39.85 ($PhCH_2CH$), 29.29 ($CHCH_2CH_2$) and 23.88 ($CH_2CH_2CH_2$); rotamer 2, 155.25 (urethane CO_2), 139.28 (Ar-C-CH_2CO_2), 137.33 (Ar-C), 130.01, 129.80, 128.92, 128.81, 128.78, 128.49, 128.43, 128.32, 128.25, 126.70 and 126.63 (Ar-CH), 67.40 (CH_2O), 59.24 (CHN), 47.28 (CH_2N), 41.02 ($PhCH_2CH$), 30.13 ($CHCH_2CH_2$) and 23.08 ($CH_2CH_2CH_2$); *m/z* 296.1650 [MH^+ (3 %), $C_{19}H_{22}NO_2$ requires 296.1650], 204 (44), 160 (40), 91 (100), 65 (18) and 39 (10).

21. *N*-(Benzenesulfenyl)-*L*-phenylalanine methyl ester (102) using Benzenesulfenyl Chloride



(102)

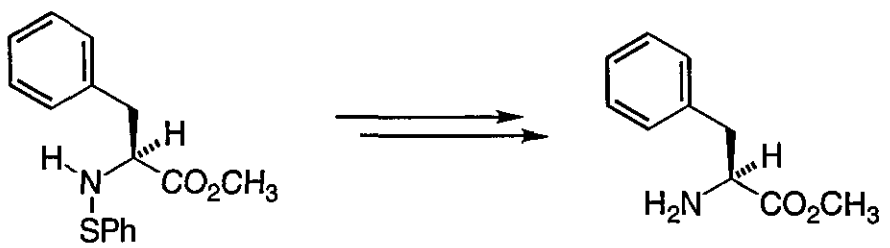
To a solution of *L*-phenylalanine methyl ester hydrochloride (1.00 g, 4.64 mmol) in anhydrous diethyl ether (50 cm^3) was added triethylamine (13 cm^3, 93 mmol, dried over KOH). This was cooled to 0-5 °C in an ice bath before adding a solution of benzenesulfenyl chloride (1.1 g, 7.6 mmol) in anhydrous diethyl ether (10 cm^3) over 30 min. Filtration and evaporation to dryness yielded an orange slurry (1.8 g). The

crude material contained a pair of diastereomers of the title compound in a 4:1 ratio but attempts at purification of the compound resulted in degradation of the product. Consequently, the crude mix was used as the *N*-(benzenesulfenyl)-*L*-phenylalanine methyl ester **102**; δ_H (250 MHz, $CDCl_3$) major diastereomer, 7.37-7.05 (10 H, m, ArH), 3.78 (1 H, dd, *J* 7.7, 5.4 Hz, CHN), 3.70 (3 H, s, OCH_3), 3.30 (1 H, d, *J* 8.3 Hz, NH), 3.16 (1 H, dd, *J* 13.7, 5.4 Hz, PhC*H*H) and 2.96 (1 H, dd, *J* 13.7, 7.7 Hz, PhCH*H*); minor diastereomer, 7.37-7.05 (10 H, m, ArH), 3.72 (1 H, dd, *J* 7.7, 5.4 Hz, CHN), 3.72 (3 H, s, OCH_3), 3.30 (1 H, d, *J* 8.3 Hz, NH), 3.20-3.13 (1 H, m, PhC*H*H) and 3.02-2.93 (1 H, m, PhCH*H*); δ_C (62.9 MHz, $CDCl_3$) major diastereomer, 173.75 (ester CO_2), 141.62 (Ar-C-S), 136.56 (Ar-C), 129.34-123.53 (Ar-CH), 65.86 (CHN), 52.03 (OCH_3) and 39.43 ($PhCH_2$); minor diastereomer, 173.75 (ester CO_2), 141.62 (Ar-C-S), 136.56 (Ar-C), 129.34-123.53 (Ar-CH), 66.08 (CHN), 52.13 (OCH_3) and 39.56 ($PhCH_2$).

22. *N*-(Benzenesulfenyl)-*L*-phenylalanine methyl ester (102) using *N*-(benzenesulfenyl)phthalimide

A solution of *L*-phenylalanine methyl ester (1.01 g, 5.58 mmol) and *N*-(benzenesulfenyl)phthalimide (1.43 g, 5.58 mmol) in anhydrous dichloromethane (30 cm^3) was refluxed for 4 days. The orange solution formed was cooled to room temperature and evaporated to dryness to give a red oil. The use of thin layer chromatography and ^1H NMR spectroscopy indicated that starting materials, desired product (one diastereomer only observed) and several impurities were present. This was no improvement on using benzenesulfenyl chloride hence the synthesis of **102** was discontinued using this route.

23. Reaction between *N*-(benzenesulfenyl)-*L*-phenylalanine methyl ester (102) and tri-*n*-butyltin hydride

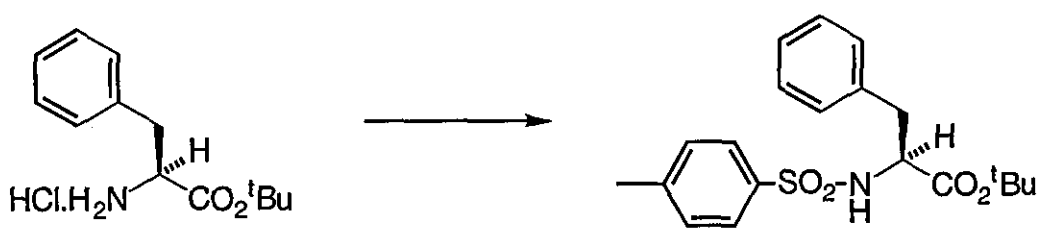


(102) **(103)**

A solution of *N*-(benzenesulfenyl)-*L*-phenylalanine methyl ester **102** (crude material, 476 mg, 1.66 mmol max.) in anhydrous toluene (200 cm^3) was stirred under nitrogen at 80 °C for 90 min. A solution (nitrogen purged for 45 min) of tri-*n*-

butyltin hydride (0.50 cm^3, 1.86 mmol) and AIBN (82 mg, 0.50 mmol) in anhydrous toluene (25 cm^3) was added slowly over 5 h using a syringe pump. The solution was stirred for a further 45 min, cooled and evaporated to dryness. Dichloromethane (5 cm^3) and 6 M hydrochloric acid (10 cm^3) were added, the layers separated and the organic layer further extracted with 6 M hydrochloric acid (2 x 10 cm^3). The acid fractions were combined, washed with light petroleum (2 x 10 cm^3) and the pH raised to 10 by the addition of 4 M sodium hydroxide solution before extraction using dichloromethane (4 x 20 cm^3). The dichloromethane fractions were combined, washed with distilled water (1 x 20 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness to give pure *L*-phenylalanine methyl ester **103** (124 mg, minimum of 42 % yield) as a colourless oil; the data obtained was identical to that stated in experiment 80 and was consistent with that previously reported in the literature.[136]

24. *N*-Tosyl -*L*-phenylalanine *tert*-butyl ester (104)



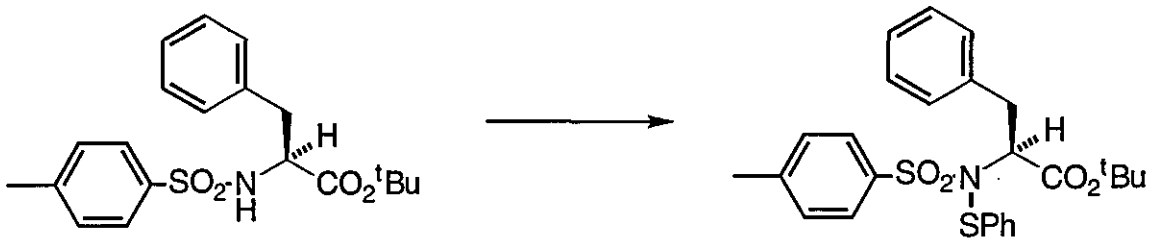
(104)

A solution of *L*-phenylalanine *tert*-butyl ester hydrochloride (1.00 g, 3.88 mmol) in dimethylformamide (15 cm^3) was cooled to 0-5 °C in an ice bath and triethylamine (1.62 cm^3, 11.64 mmol) added. Tosyl chloride (0.74 g, 3.88 mmol) was introduced and the reaction stirred at 0-5 °C for 1 h before stirring overnight at room temperature. Evaporation to dryness resulted in a white solid which was taken up in diethyl ether (30 cm^3) and distilled water (30 cm^3), the layers separated and the organic layer washed with citric acid (5% m/v solution, 10 cm^3), distilled water (10 cm^3), sodium hydrogencarbonate (1.0 M, 10 cm^3) and brine (saturated, 10 cm^3). The organic layer was dried ($MgSO_4$), filtered and evaporated to dryness. Purification using flash column chromatography (15% ethyl acetate/hexane, 1% triethylamine) and recrystallization (ethyl acetate/hexane) yielded the *N*-tosyl-*L*-phenylalanine *tert*-butyl ester **104** (1.27 g, 87 %) as white needle-like crystals, m.p. 117.0-117.2 °C; (Found: C, 63.69; H, 6.73; N, 3.76. $C_{20}H_{25}NO_4S$ requires C, 63.98; H, 6.71; N, 3.73); υ_{max}/cm^{-1} (Nujol mull) 3295, 2927, 2853, 1714, 1350 and 1162; δ_H (400 MHz, $CDCl_3$) 7.60-7.57 (2 H, m, ArH ortho to SO_2), 7.19-7.14 (5 H, m, ArH), 7.07-7.05 (2 H, m, ArH

ortho to CH_3), 5.07 (1 H, d, *J* 9.2 Hz, NH), 4.00 (1 H, dt, *J* 9.2, 6.2 Hz, CHN), 2.98-2.88 (2 H, m, $PhCH_2$), 2.31 (3 H, s, tosyl CH_3) and 1.10 (9 H, s, Me_3); δ_C (100.6 MHz, $CDCl_3$) 169.70 (CO_2), 143.34 (tosyl Ar-C, SO_2 substituted), 136.89 (phenylalanine Ar-C), 135.25 (tosyl Ar-C, CH_3 substituted), 129.56, 128.26, 126.97 (phenylalanine Ar-CH), 129.49 (tosyl Ar-C *ortho* to CSO_2), 127.16 (tosyl Ar-C *ortho* to CCH_3), 82.52 (CO), 56.64 (CHN), 39.63 (CH_2), 27.53 (Me_3) and 21.31 (tosyl CH_3); *m/z* 375.1497 [M^+ (12 %), $C_{20}H_{25}NO_4S$ requires 375.1504], 274 (100), 228 (61), 155 (74), 91 (79) and 57 (36).

The compound has been previously reported in the literature.[137]

25. *N*-(Benzenesulfenyl) -*N*-tosyl -*L*-phenylalanine *tert*-butyl ester (105)

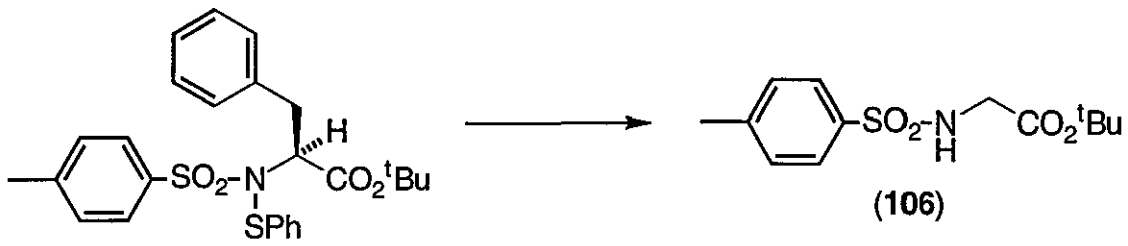


(104) **(105)**

A mixture of *N*-tosyl-*L*-phenylalanine *tert*-butyl ester **104** (0.87 g, 2.31 mmol), sodium hydride (60% dispersion in mineral oil, 0.29 g, 7.38 mmol) and anhydrous dimethylformamide (40 cm^3) were stirred for 5 h at -30 °C (acetone/dry ice bath used). The dropwise addition of benzenesulfenyl chloride at - 30 °C was continued until the yellow colouration produced was persistant for several minutes. This was allowed to stir for 1 h whilst the reaction returned to room temperature. The mixture was taken up in diethyl ether (30 cm^3) and distilled water (30 cm^3), the layers separated and the aqueous layer extracted further with diethyl ether (2 x 20 cm^3). The organic layers were combined and the dimethylformamide washed out with distilled water (3 x 20 cm^3) and saturated brine (3 x 20 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness. Purification using flash column chromatography (60 % dichloromethane/hexane) yielded the N-*(benzenesulfenyl)*-N-*tosyl*-L-*phenylalanine* tert-*butyl ester* **105** (0.75 g, 67 %) as a thick colourless gum; υ_{max}/cm^{-1} (neat) 3063, 3030, 2979, 2931, 1736, 1354 and 1163; δ_H (400 MHz, $CDCl_3$) 7.66 (2 H, br, ArH *ortho* to SO_2), 7.33 (2 H, br, ArH *ortho* to CH_3), 7.16-7.14 (5 H, m, phenylalanine ArH), 7.11-7.09 (3 H, m, benzenesulfenyl ArH), 6.99-6.97 (2 H, m, benzenesulfenyl ArH), 5.06 (1 H, br t, *J* 6.2 Hz, CHN), 3.20-3.14 (1 H, m, PhCH*H*), 3.01-2.95 (1 H, m, PhC*H*H), 2.31 (3 H, s, tosyl CH_3) and 1.08 (9 H, s, Me_3); δ_C (100.6 MHz; $CDCl_3$) 168.50 (CO_2), 143.95 (tosyl Ar-C, SO_2 substituted), 138.04 (benzenesulfenyl Ar-C), 136.51 (phenylalanine Ar-C), 135.78 (tosyl Ar-C, CH_3 substituted), 129.32, 129.08, 128.61, 128.26, 128.20, 127.29, 126.69, 126.47 (Ar-CH), 82.19 (CO), 65.00 (CHN), 36.91 (CH_2),

27.52 (Me_3) and 21.43 (tosyl CH_3); *m/z* 483.1557 [M^+ (68 %), $C_{26}H_{29}NO_4S_2$ requires 483.1538], 382 (67), 328 (26), 272 (30), 228 (80), 155 (23), 109 (41) and 91 (100).

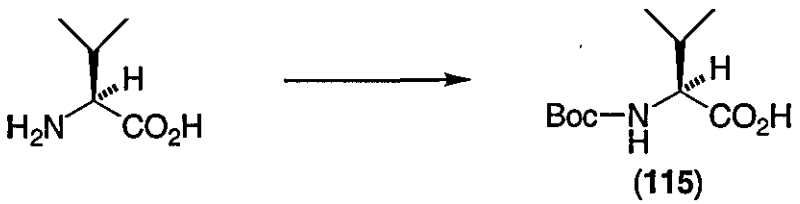
26. Reaction between *N*-(benzenesulfenyl)-*N*-tosyl-*L*-phenylalanine *tert*-butyl ester (105) and tri-*n*-butyltin hydride



(105) (106)

A solution of *N*-(benzenesulfenyl)-*N*-tosyl-*L*-phenylalanine *tert*-butyl ester **105** (297 mg, 0.61 mmol) in anhydrous toluene (200 cm^3) was deoxygenated for 90 min at 80 °C before injecting a solution of tri-*n*-butyltin hydride (0.23 cm^3, 0.82 mmol) and AIBN (33 mg, 0.20 mmol) in anhydrous toluene (20 cm^3) over 5 h using a syringe pump. The reaction was cooled and stirred overnight at room temperature, the tin residues were removed using flash column chromatography (10% ethyl acetate/ light petroleum increasing to ethyl acetate to retrieve tosyl compounds), the tin free fractions were combined, evaporated to dryness and purified using flash column chromatography (20 % diethyl ether/light petroleum) to give *N*-tosylglycine *tert*-butyl ester **106** (48 mg, 28 %) as a white powder, m.p. 110.0-110.5 °C (lit.[138] 109 °C); υ_{max}/cm^{-1} (Nujol mull) 3190, 2905, 2836 and 1742; δ_H (250 MHz, $CDCl_3$) 7.75 (2 H, d, *J* 8.3 Hz, ArH ortho to SO_2), 7.31 (2 H, d, *J* 8.1 Hz, ArH ortho to CH_3), 4.98 (1 H, br, NH), 4.98 (2 H, d, *J* 5.4, CH_2N), 2.42 (3 H, s, tosyl CH_3) and 1.35 (9 H, s, Me_3); δ_C (100.6 MHz, $CDCl_3$) 175.44 (CO_2), 151.43 (tosyl Ar-C, SO_2 substituted), 143.84 (tosyl Ar-C, CH_3 substituted), 137.37 (tosyl Ar-CH *ortho* to SO_2), 134.98 (tosyl Ar-CH *ortho* to CH_3), 90.62 (CO), 52.37 (CH_2N), 35.45 (Me_3) and 29.20 (tosyl CH_3); *m/z* 285.1030 [M^+ (8 %), $C_{13}H_{19}NO_4S$ requires 285.1035], 184 (45), 155 (52), 91 (56), 65 (20), 57 (100) and 41 (27). *N*-tosyl-*L*-phenylalanine *tert*-butyl ester **104** (82 mg, 35 %) was also isolated (see experiment 24 for data).

27. *N*-Butoxycarbonyl-*L*-valine (115)



(115)

L-Valine (20.82 g, 0.18 mol) was dissolved in sodium hydroxide solution (14.40 g in 150 cm^3 distilled water) and di-*tert*-butyl dicarbonate (44.31 g, 0.20 mmol) in dioxan (150 cm^3) was added with vigorous stirring. The reaction was stirred at room temperature for 3 h before evaporating to low volume, dissolving in water (300 cm^3, ensure solution is basic) and washing with diethyl ether (3 x 75 cm^3). The solution was acidified to pH = 2 with conc. hydrochloric acid and extracted with dichloromethane (3 x 100 cm^3). The organic fractions were combined , washed with saturated brine (2 x 50 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness to give the *N*-butoxycarbonyl-*L*-valine **115** (37.3 g, 97 %) as a thick colourless oil; υ_{max}/cm^{-1} (neat) 3318, 2972, 2935, 2878 and 1717; δ_H (400 MHz, $CDCl_3$) rotamer 1, 10.92 (1 H, br, CO_2H), 5.07 (1 H, d, *J* 9.0 Hz, NH), 4.24 (1 H, dd, *J* 9.0, 4.5 Hz, CHN), 2.21-2.14 (1 H, m, isopropyl CH), 1.42 (9 H, br s, Me_3), 0.97 (3 H, d, *J* 6.7 Hz, CH_3), 0.90 (3 H, d, *J* 6.8 Hz, CH_3); rotamer 2, 10.92 (1 H, br, CO_2H), 6.33 (1 H, d, *J* 7.4 Hz, NH), 4.40-3.96 (br m, CHN), 2.21-2.14 (1 H, m, isopropyl CH), 1.42 (9 H, br s, Me_3), 0.96 (3 H, d, *J* value obscured, CH_3) and 0.92 (3 H, d, *J* value obscured, CH_3); δ_C (100.6 MHz, $CDCl_3$) rotamer 1, 177.02 (acid-C), 155.85 ($RNHCO_2R$), 80.03 ($COMe_3$), 58.45 (CHN), 31.03 (isopropyl CH), 28.27 (Me_3), 18.98 (isopropyl CH_3), 17.46 (isopropyl CH_3); rotamer 2, 177.02 (acid-C), 156.95 ($RNHCO_2R$), 81.55 ($COMe_3$), 60.10 (CHN), 31.03 (isopropyl CH), 28.27 (Me_3), 18.98 (isopropyl CH_3) and 17.46 (isopropyl CH_3); *m/z* 172.1340 [M-CO_2H (38 %), $C_9H_{18}NO_2$ requires 172.1338] 217 (6), 172 (38), 116 (58), 72 (44) and 57 (100).

The data was consistent with that previously reported in the literature.[139]

28. *N*-Butoxycarbonyl-*L*-valine benzyl ester (116)

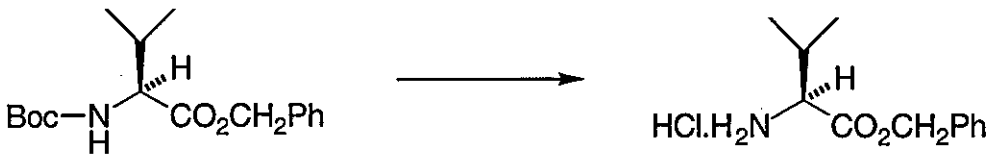
(115) **(116)**

A mixture of *N*-butoxycarbonyl-*L* -valine **115** (6.58 g, 30.28 mmol), dimethylformamide (60 cm^3, dried over 4Å molecular sieves), potassium carbonate (4.40g, 31.84 mmol) and benzyl bromide (4.00 cm^3, 33.03 mmol) were stirred at 50 °C for 4 h. The reaction was cooled, evaporated to dryness and dissolved in ethyl acetate (50 cm^3). This was washed with citric acid (5% m/v, 2 x 40 cm^3), distilled water (2 x 40 cm^3) and saturated brine (2 x 40 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness to give the *N*-butoxycarbonyl-*L*-valine benzyl ester **116** (9.19 g, 99 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3443, 3373, 2968, 1740, 1716, 752 and 698; δ_H

(400 MHz, $CDCl_3$) 7.35-7.31 (5 H, m, ArH), 5.18 (1 H, d, *J* 12.3 Hz, C*H*HO), 5.12 (1 H, d, *J* 12.2 Hz, CH*H*O), 5.03 (1 H, d, *J* 8.9 Hz, NH), 4.26 (1 H, dd, *J* 9.1, 4.6 Hz, CHN), 2.19-2.10 (1 H, m, isopropyl CH), 1.42 (9 H, br s, Me_3), 0.92 (3 H, d, *J* 6.9 Hz, isopropyl CH_3) and 0.83 (3 H, d, *J* 6.9 Hz, isopropyl CH_3); δ_C (100.6 MHz, $CDCl_3$) 172.14 (ester-CO_2), 155.59 ($RNHCO_2R$), 135.39 (Ar-C), 128.45, 128.26, 128.22 (Ar-CH), 79.61 ($OCMe_3$), 66.74 (CH_2O), 58.51 (CHN), 31.20 (isopropyl CH), 28.20 (Me_3), 18.87 (isopropyl CH_3) and 17.39 (isopropyl CH_3); *m/z* 307.1775 [M^+ (4 %), $C_{17}H_{25}NO_4$ requires 307.1783], 172 (82), 116 (84), 91 (85), 72 (84), 57 (100) and 41 (13).

The data was consistent with that previously reported in the literature.[140]

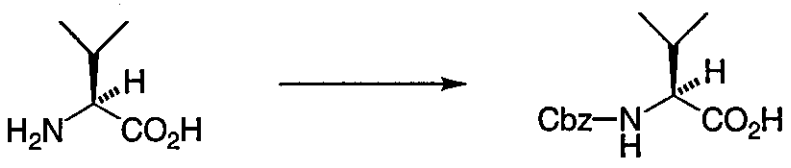
29. *L*-Valine benzyl ester hydrochloride (117)



(116) **(117)**

N-Butoxycarbonyl-*L*-valine benzyl ester **116** (9.09 g, 29.56 mmol) was dissolved in ethyl acetate (100 cm^3) and 4 M HCl in dioxan solution (60 cm^3, excess) added. After stirring for 3 h, starting material was still evident by thin layer chromatography and a further 10 cm^3 of 4 M HCl/dioxan added before stirring overnight. The reaction was evaporated to low volume, ethyl acetate added and this process continued until the *L*-valine benzyl ester hydrochloride **117** (6.49 g, 90 %) was obtained as a white powder, m.p. 138-140 °C (lit.[141] 138-139 °C); (Found: C, 59.24; H, 7.46; N, 5.74. $C_{12}H_{18}NO_2Cl$ requires C, 59.13; H, 7.44; N, 5.75); υ_{max}/cm^{-1} (Nujol mull) 2950, 2916, 2851, 2639 and 1742; δ_H (400 MHz, $CDCl_3$) 8.89 (3 H, br s, NH_3^+), 7.36-7.27 (5 H, m, ArH), 5.25 (1 H, d, *J* 12.1 Hz, C*H*HO), 5.15 (1 H, d, *J* 12.1 Hz, CH*H*O), 3.98 (1 H, d, *J* 3.6 Hz, CHN), 2.48-2.40 (1 H, m, isopropyl CH), 1.08 (3 H, d, *J* 7.0 Hz, CH_3) and 1.06 (3 H, d, *J* 7.1 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 168.29 (CO_2), 134.63 (quaternary Ar-C), 128.52 (Ar-CH), 67.82 (CH_2O), 58.45 (CHN), 29.87 (isopropyl CH), 18.24 (CH_3) and 18.16 (CH_3); *m/z* (free base, FAB) 208.1345 [MH^+, (100 %), $C_{12}H_{18}NO_2$ requires 208.1337], 91 (41) and 72 (100).

30. *N*-(Benzyloxycarbonyl)-*L*-valine (118b)



(118b)

L-Valine (20.18 g, 0.17 mol) was dissolved in aqueous sodium hydroxide (6.89 g, 0.17 mol in 120 cm^3 distilled water) and cooled to 0-5 °C in an ice bath. A simultaneous dropwise addition of benzyl chloroformate (38.83 cm^3, 0.26 mol) and 4 M sodium hydroxide solution (65 cm^3, 0.26 mol) was followed by stirring at room temperature for 1.5 h. The aqueous solution was washed with diethyl ether (3 x 50 cm^3), acidified to pH = 2 with conc. hydrochloric acid, extracted with dichloromethane (3 x 50 cm^3) and the organic fractions combined. These were washed with saturated brine (2 x 50 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness to give the *N*-(benzyloxy carbonyl)-*L*-valine **118b** (40.49 g, 94 %) as a thick colourless oil; υ_{max}/cm^{-1} (neat) 3324, 2969 and 1719; δ_H (400 MHz, $CDCl_3$) rotamer 1, 10.49 (1 H, brd, CO_2H), 7.36-7.33 (5 H, m, ArH), 5.41 (1 H, d, *J* 9.1 Hz, NH), 5.10 (2 H, d, *J* 3.2 Hz, CH_2O), 4.35 (1 H, dd, *J* 9.1, 4.6 Hz, CHN), 2.27-2.19 (1 H, m, isopropyl CH), 0.99 (3 H, d, *J* 6.9 Hz, CH_3) and 0.91 (3 H, d, *J* 6.9 Hz, CH_3), rotamer 2, 10.49 (1 H, brd, CO_2H), 7.32-7.29 (5 H, m, ArH), 6.47 (1 H, d, *J* 8.5 Hz, NH), 5.14 (2 H, brd s, CH_2O), 4.17 (1 H, dd, *J* 8.3, 4.8 Hz, CHN), 2.27-2.19 (1 H, m, isopropyl CH), 0.97 (3 H, d, *J* value obscured, CH_3) and 0.93 (3 H, d, *J* value obscured, CH_3); δ_C (100.6 MHz, $CDCl_3$) rotamer 1, 176.74 (acid-C), 156.39 ($RNHCO_2R$), 136.03 (Ar-C), 128.46, 128.15, 128.06 (Ar-CH), 67.14 (CH_2O), 58.85 (CHN), 30.96 (isopropyl CH), 17.27 (CH_3) and 16.91 (CH_3), rotamer 2, 176.49 (acid-C), 157.18 ($RNHCO_2R$), 135.58 (Ar-C), 127.65, 127.61, 126.99 (Ar-CH), 67.61 (CH_2O), 59.63 (CHN), 30.81 (isopropyl CH), 17.27 (CH_3) and 16.91 (CH_3); *m/z* 251.1157 [M^+ (16 %), $C_{13}H_{17}NO_4$ requires 251.1164], 162 (21), 108 (54), 91 (100) and 65 (15).

The data was consistent with that previously reported in the literature.[142]

31. *N*-(Benzyloxycarbonyl)-*L*-valine *tert*-butyl ester (119b)

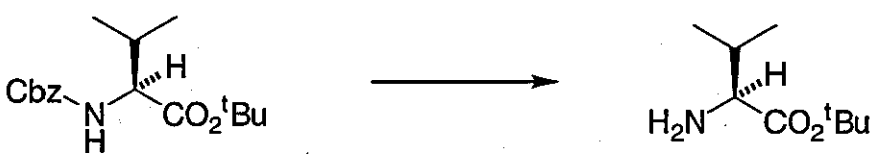
(118b) **(119b)**

N-(Benzyloxycarbonyl)-*L*-valine **118b** (5.59 g, 22.24 mmol) was dissolved in sieve dried dimethylformamide (100 cm^3) in the presence of benzyltriethylammonium chloride (5.11 g, 22.26 mmol). Anhydrous potassium carbonate (79.91 g, 0.58 mol) and *tert*-butyl bromide (123 cm^3, 1.07 mol) were added and the mixture stirred at 55 °C for 24 h. The inorganics were dissolved in distilled water (300 cm^3) and the mixture extracted with ethyl acetate (2 x 100 cm^3 + 1 x 50 cm^3). The organic fractions were combined, washed with distilled water (3 x 50 cm^3) and brine (3 x 50 cm^3),

dried ($MgSO_4$), filtered and evaporated to dryness. Purification using flash column chromatography (10 % ethyl acetate/hexane) gave the *N*-(benzyloxycarbonyl)-*L*-valine *tert*-butyl ester **119b** (5.71 g, 84 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3348, 2965 and 1722; δ_H (400 MHz, $CDCl_3$) 7.36-7.28 (5 H, m, ArH), 5.28 (1 H, br d, *J* 8.7 Hz, NH), 5.10 (2 H, br s, CH_2O), 4.18 (1 H, dd, *J* 9.0, 4.4 Hz, CHN), 2.18-2.10 (1 H, m, $CHMe_2$), 1.45 (9 H, s, ester Me_3), 0.95 (3 H, d, *J* 6.9 Hz, CH_3) and 0.88 (3 H, d, *J* 6.9 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 170.98 (ester-CO_2), 156.14 ($RNHCO_2R$), 136.35 (Ar-C), 128.39, 127.98, 127.96 (Ar-CH), 81.79 (CO), 66.77 (CH_2O), 59.26 (CHN), 31.36 ($CHMe_2$), 27.97 (ester Me_3), 18.76 (CH_3) and 17.31 (CH_3); *m/z* 307.1775 [M^+ (2 %), $C_{17}H_{25}NO_4$ requires 307.1783], 251 (26), 206 (74), 162 (90), 91 (100) and 57 (38).

The method has been previously reported in the literature.[107] The compound data was reported elsewhere and it is consistent with the results presented here.[143]

32. *L*-Valine *tert*-butyl ester (120b)

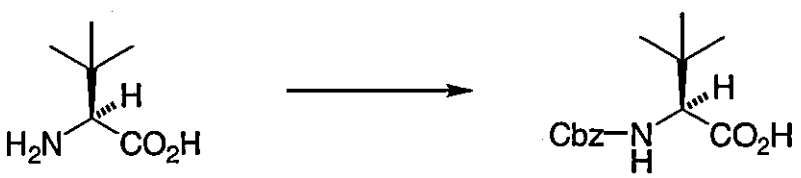


(119b) **(120b)**

A solution of *N*-(benzyloxycarbonyl)-*L*-valine *tert*-butyl ester **119b** (5.65 g, 18.39 mmol) in methanol (60 cm^3) was flushed with nitrogen whilst adding 10 % palladium on carbon (0.60 g). The reaction was then shaken under hydrogen until thin layer chromatography indicated that hydrogenolysis was complete, filtered and evaporated to dryness to give *L*-valine *tert*-butyl ester **120b** (2.89 g, 91 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3380, 2972, 2958, 2887 and 1722; δ_H (400 MHz, $CDCl_3$) 3.14 (1 H, d, *J* 4.7 Hz, CHN), 2.01-1.93 (1 H, m, $CHMe_2$), 1.43 (11 H, br, ester Me_3 + NH_2), 0.95 (3 H, d, *J* 6.9 Hz, CH_3) and 0.87 (3 H, d, *J* 6.8 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 81.06 (CO), 60.67 (CHN), 32.49 ($CHMe_2$), 28.78 (Me_3), 19.61 (CH_3) and 17.39 (CH_3).

The compound has been previously reported in the literature.[144]

33. *N*-(Benzyloxycarbonyl)-*L*-*tert*-leucine (118d)

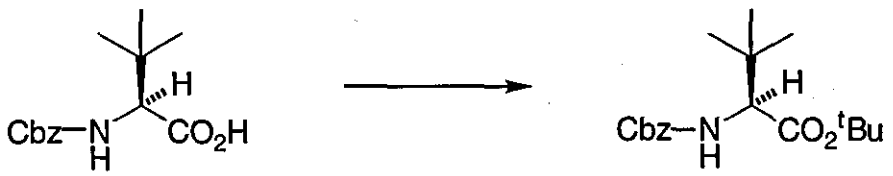


(118d)

L-tert-Leucine (25.06 g, 0.19 mmol) was dissolved in aqueous sodium hydroxide solution (7.62 g in 150 cm^3 distilled water) and cooled to 0-5 °C in an ice bath. A simultaneous dropwise addition of benzyl chloroformate (42.96 cm^3, 0.29 mmol) and sodium hydroxide solution (11.44 g in 70 cm^3 distilled water) at 0-5 °C was followed by overnight stirring at room temperature. The solution was washed with diethyl ether (3 x 50 cm^3), acidified with conc. hydrochloric acid (pH=2) and extracted with dichloromethane (3 x 50 cm^3). The dichloromethane fractions were combined, washed with saturated brine (2 x 50 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness to give the *N*-(benzyloxycarbonyl)-*L-tert*-leucine **118d** (48.98 g, 97 %) as a thick colourless oil; υ_{max}/cm^{-1} (neat) 3500-3300, 2964, 2910, 1708 and 1701; δ_H (400 MHz, CD_3OD) 7.36-7.32 (5 H, m, ArH), 5.06 (2 H, s, CH_2O), 3.94 (1 H, s, CHN) and 0.99 (9 H, s, Me_3); δ_C (100.6 MHz, CD_3OD) 177.13 (CO_2H), 158.50 ($RNHCO_2R$), 138.30 (Ar-C), 129.46, 129.01, 128.92 (Ar-CH), 67.61 (CH_2O), 65.33 (CHN), 35.04 (CMe_3) and 27.34 (Me_3); *m/z* 266.1405 [MH^+ (38 %), $C_{14}H_{19}NO_4$ requires 266.1392], 256 (34), 220 (38), 209 (47), 148 (46), 108 (74), 91 (100), 79 (62) and 57 (63).

The compound has been previously reported in the literature.[145]

34. *N*-(Benzyloxycarbonyl)-*L-tert*-leucine *tert*-butyl ester (119d)



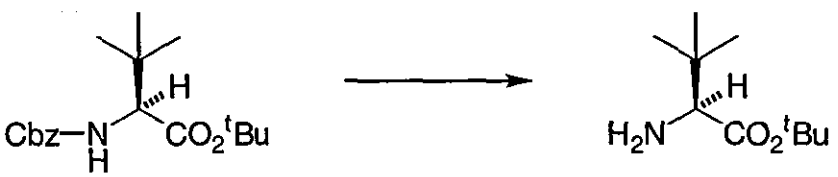
(118d) **(119d)**

N-(Benzyloxycarbonyl)-*L-tert*-leucine **118d** (6.02 g, 22.69 mmol) was dissolved in sieve dried dimethylformamide (100 cm^3) in the presence of benzyltriethylammonium chloride (5.26 g, 22.90 mmol). Anhydrous potassium carbonate (82.69 g, 0.60 mol) and *tert*-butyl bromide (130 cm^3, 1.09 mol) were added and the mixture stirred at 55 °C for 24 h. The inorganics were dissolved in distilled water (300 cm^3) and the mixture extracted with ethyl acetate (2 x 100 cm^3 + 1 x 50 cm^3). The organic fractions were combined, washed with distilled water (3 x 50 cm^3) and brine (3 x 50 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness. Purification using flash column chromatography (10 % ethyl acetate/hexane) gave the *N*-(benzyloxycarbonyl)-*L-tert*-leucine *tert*-butyl ester **119d** (4.68 g, 64 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3438, 3358, 2953 and 1721; δ_H (400 MHz, $CDCl_3$) 7.36-7.33 (5 H, m, ArH), 5.35 (1 H, br d, *J* 9.3 Hz, NH), 5.13-5.06 (2 H, m, CH_2O), 4.05 (1 H, d,

J 9.6 Hz, CHN), 1.46 (9 H, s, ester Me_3) and 0.97 (9 H, s, Me_3); δ_C (100 MHz, $CDCl_3$) 170.61 (ester-CO_2), 156.08 ($RNHCO_2R$), 136.29 (Ar-C), 128.43, 128.05, 128.02 (Ar-CH), 81.86 (CO), 66.83 (CH_2O), 62.42 (CHN), 34.84 (CMe_3), 27.97 (ester Me_3) and 26.49 (Me_3); *m/z* 322.2031 [MH^+ (15 %), $C_{18}H_{28}NO_4$ requires 322.2018], 266 (57), 222 (14), 176 (13), 91 (100) and 57 (14).

The method has been previously reported in the literature.[107] The compound was reported elsewhere in the literature.[146]

35. *L*-tert-Leucine *tert*-butyl ester (120d)



(119d) **(120d)**

A mixture of *N*-(benzyloxycarbonyl)-*L*-*tert*-leucine *tert*-butyl ester **119d** (4.53 g, 14.11 mmol), 10 % palladium on carbon catalyst (0.5 g) and methanol (50 cm^3) were hydrogenated (hydrogen balloon) for 4 h before filtering and evaporating to dryness to give the *L*-*tert*-leucine *tert*-butyl ester **120d** (2.14 g, 81 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3391, 2976, 2966, 2936, 2908 and 1725; δ_H (400 MHz, $CDCl_3$) 2.98 (1 H, s, CHN), 1.48 (2 H, s, NH_2), 1.43 (9 H, s, ester (Me_3) and 0.93 (9 H, s, (Me_3); δ_C (100 MHz, $CDCl_3$) 174.08 (CO_2), 80.63 (CO), 63.87 (CHN), 34.23 (CMe_3), 28.01 (ester Me_3) and 26.30 (Me_3); *m/z* (FAB) 188.1650 [MH^+ (58 %, $C_{10}H_{21}NO_2$ requires 188.1651], 116 (52), 86 (100) and 75 (26).

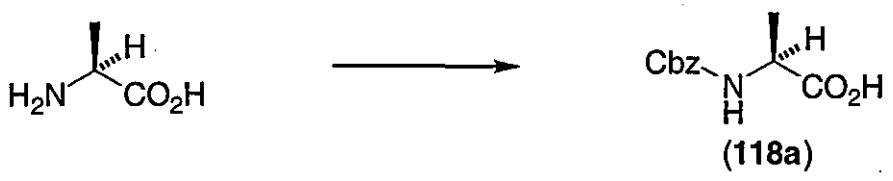
The compound has been previously reported in the literature.[146]

36. Preparation of *tert*-butyl *N*-isopropyl-(isopropylamino)methanimidate (121)

(121)

A mixture of *N,N'*-diisopropylcarbodiimide (7.32 g, 56.56 mmol), *tert*-butanol (5.05 g, 67.83 mmol) and copper (I) chloride (0.06 g, 0.57 mmol) was stirred under nitrogen overnight to give a black suspension containing *tert*-butyl *N*-isopropyl-(isopropyl-amino)methanimidate **121**. The mixture formed was used as the crude. No purification was attempted.

37. *N*-(Benzyloxycarbonyl)-*L*-alanine (118a)

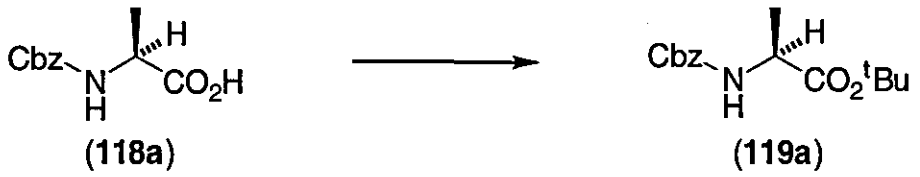


(118a)

A solution of *L*-alanine (25.16 g, 0.28 mol) in aqueous sodium hydroxide (11.30 g, 0.28 mol in 150 cm^3 of distilled water) was cooled to 0-5 °C in an ice bath. A simultaneous dropwise addition of benzylchloroformate (63.65 cm^3, 0.42 mol) and aqueous sodium hydroxide (16.94 g, 0.42 mol in 80 cm^3 of distilled water) at 0-5 °C was followed by stirring overnight at room temperature. The mixture was washed with diethyl ether (3 x 50 cm^3), the pH lowered to 2 with concentrated hydrochloric acid and the organics extracted with dichloromethane (3 x 50 cm^3). The organic fractions were combined, washed with brine (saturated, 2 x 50 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness to yield *N*-(benzyloxycarbonyl)-*L*-alanine **118a** (61.60 g, 98 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3326, 3065, 3034, 2984, 2941 and 1701; δ_H (400 MHz, CD_3OD) 7.36-7.32 (5 H, m, ArH), 5.06 (2 H, s, CH_2O), 4.15 (1 H, q, *J* 7.3 Hz, CHN) and 1.36 (3 H, d, *J* 7.2 Hz, CH_3); δ_C (100 MHz, CD_3OD) 177.57 (ester-CO_2), 158.32 ($RNHCO_2R$), 138.24 (Ar-C), 129.46, 128.99, 128.81 (Ar-CH), 67.55 (CH_2O), 51.39 (CHN) and 18.27 (CH_3); *m/z* (FAB) 246.0754 [$(M+Na)^+$ (77 %), $C_{11}H_{13}NO_4Na$ requires 246.0743], 115 (86), 91 (52) and 47 (100), (EI) 178 (20), 140 (63), 56 (24), 44 (100) and 41 (48).

The data was consistent with that previously reported in the literature.[147]

38. *N*-(Benzyloxycarbonyl)-*L*-alanine *tert*-butyl ester (119a)



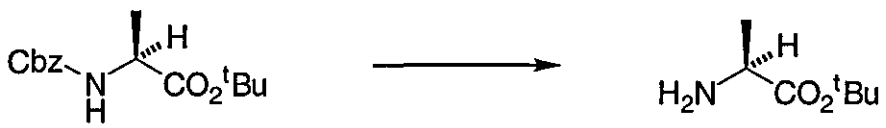
(118a) **(119a)**

To a solution of *N*-(benzyloxycarbonyl)-*L*-alanine **118a** (6.23 g, 27.91 mmol) in anhydrous dichloromethane (25 cm^3) under nitrogen was added crude *tert*-butyl *N*-isopropyl-(isopropylamino)methanimidate **121** (from reaction described in experiment 36) and the reaction stirred overnight. The reaction was poured into light petroleum (100 cm^3), filtered through celite and evaporated to dryness to give a green oil (5.13 g). Purification using flash column chromatography (15 % ethyl

acetate/light petroleum) yielded *N*-(benzyloxycarbonyl)-*L*-alanine *tert*-butyl ester **119a** (3.82 g, 49 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3340, 3034, 2979, 2937 and 1723; δ_H (400 MHz, $CDCl_3$) 7.40-7.34 (5 H, m, ArH), 5.40 (1 H, br, NH), 5.14 (2 H, s, CH_2O), 4.32-4.25 (1 H, m, CHN), 1.49 (9 H, s, Me_3) and 1.40 (3 H, d, *J* 7.1 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 172.57 (ester-CO_2), 155.97 ($RNHCO_2R$), 136.85 (Ar-C), 128.87, 128.47 (Ar-CH), 82.26 (CO), 67.14 (CH_2O), 50.59 (CHN), 28.33 (Me_3) and 19.26 (CH_3); *m/z* 280.1549 [M^+ (8 %), $C_{15}H_{21}NO_4$ requires 280.1549], 224 (29), 178 (23), 134 (44), 108 (20), 91 (100), 65 (20), 57 (57) and 41 (21).

The data was consistent with that previously reported in the literature.[148]

39. *L*-Alanine *tert*-butyl ester (120a)

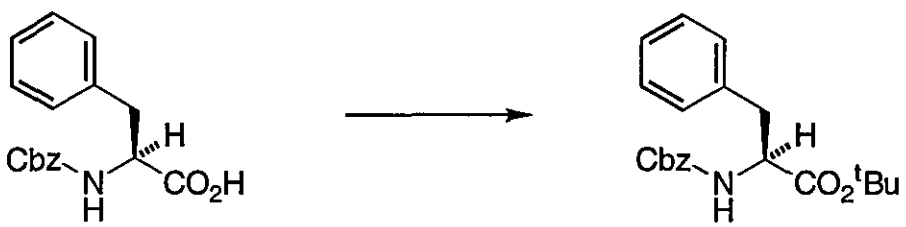


(119a) **(120a)**

A solution of *N*-(benzyloxycarbonyl)-*L*-alanine *tert*-butyl ester **119a** (3.82 g, 13.68 mmol) in methanol (40 cm^3) was flushed with nitrogen whilst adding 10 % palladium on carbon (0.30 g). The reaction was then shaken under hydrogen until thin layer chromatography indicated that hydrogenolysis was complete, filtered and evaporated to dryness to give *L*-alanine *tert*-butyl ester **120a** (1.87 g, 94 %) as a colourless oil; δ_H (250 MHz, $CDCl_3$) 3.41 (1 H, q, *J* 7.0 Hz, CHN), 1.58 (2 H, br, NH_2), 1.46 (9 H, s, ester Me_3) and 1.29 (3 H, d, *J* 7.1 Hz, CH_3).

The compound has been previously reported in the literature.[144]

40. *N*-(Benzyloxycarbonyl)-*L*-phenylalanine *tert*-butyl ester (119c)



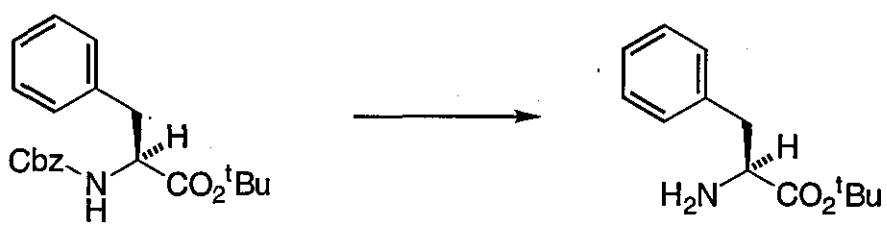
(118c) **(119c)**

To a solution of *N*-(benzyloxycarbonyl)-*L*-phenylalanine **118c** (5.01 g, 16.58 mmol) in anhydrous dichloromethane (20 cm^3) under nitrogen was added crude *tert*-butyl *N*-

isopropyl-(isopropylamino)methanimidate **121** (prepared as described in experiment 36 from *N,N'*-diisopropylcarbodiimide (4.68 g, 36.12 mmol), *tert*-butanol (3.47 g, 36.14 mmol) and copper (I) chloride (0.05 g, 0.50 mmol)) and the reaction stirred overnight. The reaction was poured into light petroleum (150 cm^3), filtered through celite and evaporated to dryness to give a green oil (5.03 g). Purification using flash column chromatography (20 % ethyl acetate/light petroleum) yielded *N*-(benzyloxycarbonyl)-*L*-phenylalanine *tert*-butyl ester **119c** (3.62 g, 61 %) as a white solid, m.p. 78.5-80 °C (lit.[149] 79-80 °C); (Found: C, 70.70; H, 6.98; N, 4.13. $C_{21}H_{25}NO_4$ requires C, 70.96; H, 7.09; N, 3.94); υ_{max}/cm^{-1} (neat) 3340, 3065, 3032, 2979, 2939, 1734, 1716, 1698, 746 and 699; δ_H (400 MHz, $CDCl_3$) 7.39-7.33 (5 H, m, ArH), 7.31-7.26 (3 H, m, amino acid ArH), 7.19 (2 H, d, *J* 7.7 Hz, amino acid *o*-ArH), 5.29 (1 H, d, *J* 7.5 Hz, NH), 5.17-5.12 (2 H, m, CH_2O), 4.58 (1 H, apparent q, *J* 7.5 Hz, CHN), 3.12 (2 H, d, *J* 5.9 Hz, $PhCH_2$) and 1.44 (9 H, s, Me_3); δ_C (100 MHz, $CDCl_3$) 170.96 (ester-CO_2), 156.00 ($RNHCO_2R$), 136.80, 136.48 (Ar-C), 131.82, 129.92, 129.68, 129.24, 129.18, 128.90, 128.79, 128.53, 128.48, 127.34 (Ar-CH), 82.70 (CO), 67.23 (CH_2O), 55.60 (CHN), 38.85 (CH_2CHN) and 28.33 (Me_3); *m/z* 356.1855 [MH^+ (6 %), $C_{21}H_{26}NO_4$ requires 356.1862], 210 (36), 148 (24), 92 (37), 91 (100), 65 (28), 57 (48) and 41 (35).

The data was consistent with that previously reported in the literature.[150]

41. *L*-Phenylalanine *tert*-butyl ester (120c)



(119c) **(120c)**

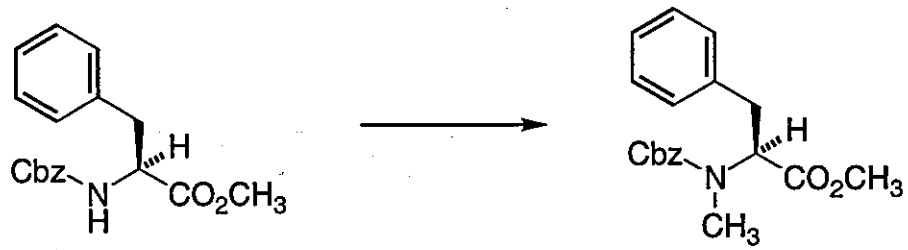
A solution of *N*-(benzyloxycarbonyl)-*L*-phenylalanine *tert*-butyl ester **119c** (3.48 g, 9.79 mmol) in methanol (50 cm^3) was flushed with nitrogen whilst adding 10 % palladium on carbon (0.50 g). The reaction was then shaken under hydrogen until thin layer chromatography indicated that hydrogenolysis was complete, filtered and evaporated to dryness to give *L*-phenylalanine *tert*-butyl ester **120c** (2.16 g, 98 %) as a colourless oil; δ_H (250 MHz, $CDCl_3$) 7.33-7.21 (5 H, m, ArH), 3.61 (1 H, dd, *J* 7.6, 5.7 Hz, CHN), 3.05 (1 H, dd, *J* 13.6, 5.6, PhC*H*H), 2.84 (1 H, dd, *J* 13.5, 7.8 Hz, PhCH*H*), 1.55 (2 H, s, NH_2) and 1.43 (9 H, s, ester Me_3).

The data was consistent with that previously reported in the literature.[151]

42. Attempted synthesis of *N*-acetyl-*N*-methyl-*L*-phenylalanine methyl ester (123)

A mixture of sodium hydride (0.12 g, 3.00 mmol, 60 % emulsion in oil), *N*-acetyl-*L*-phenylalanine methyl ester **122** (0.50 g, 2.40 mmol) and anhydrous tetrahydrofuran (40 ml) were placed in a flask under nitrogen and refluxed for 3 h at 50 °C. The mixture was cooled to -78 °C and methyl iodide (0.3 ml, 6.0 mmol) added dropwise by syringe before stirring for 30 min and returning to room temperature. Diethyl ether (50 ml) and phosphate buffer solution (PBS, 0.05 M, pH = 7.0, 40 ml) were added, the layers were then separated and the PBS fraction was extracted further with diethyl ether (2 x 20 ml). The ether fractions were combined, washed with water (2 x 20 ml) and dried ($MgSO_4$). Filtration and evaporation to dryness gave a colourless oil. Purification using flash column chromatography yielded a colourless oil. The ^1H NMR spectrum indicated that no phenylalanine derivative was present. The oil was identified as the emulsion oil from the sodium hydride. This reaction was discontinued.

43. *N*-(Benzyloxycarbonyl)-*N*-methyl-*L*-phenylalanine methyl ester (124)



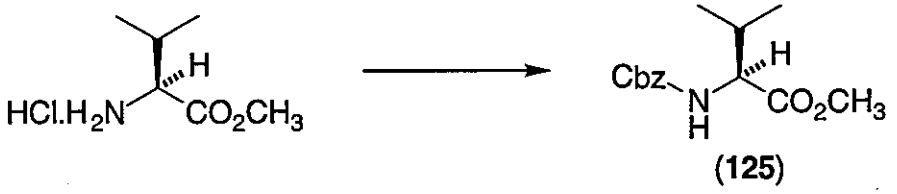
(91) **(124)**

A solution of *N*-(benzyloxycarbonyl)-*L*-phenylalanine methyl ester **91** (1.08 g, 3.21 mmol) in anhydrous dimethylformamide (30 cm^3) and methyl iodide (1.7 ml, 27 mmol) was cooled to 0-5 °C under nitrogen. A suspension of sodium hydride (0.18 g, 7.50 mmol, freshly washed in light petroleum) in anhydrous dimethylformamide (10 cm^3) was added dropwise then the reaction returned to room temperature and stirred for 15 h. Phosphate buffer solution (PBS, 0.05 M, pH = 7.0, 50 cm^3) and diethyl ether (40 cm^3) were added and the fractions separated. The PBS fraction was washed with diethyl ether (2 x 30 cm^3), then the combined ether fractions were washed with distilled water (5 x 20 cm^3), brine (saturated, 3 x 20 cm^3), dried ($MgSO_4$) and filtered. Evaporation to dryness yielded a pair of rotamers of *N*-(benzyloxycarbonyl)-*N*-methyl-*L*-phenylalanine methyl ester **124** (0.99 g, 94 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3036, 2952, 1743, 1701, 753 and 700; δ_H (250 MHz, $CDCl_3$) major rotamer, 7.40-7.18 (10 H, m, ArH), 5.10 (2 H, s, CH_2O), 5.00 (1 H, dd, *J* 14.4, 5.4 Hz, CHN), 3.75 (3 H, s,

OCH_3), 3.05 (2 H, t, *J* 11.0 Hz, $PhCH_2$) and 2.82 (3 H, s, NCH_3); minor rotamer, 7.40-7.18 (10 H, m, ArH), 5.04 (2 H, s, CH_2O), 4.80 (1 H, dd, *J* 10.6, 4.9 Hz, CHN), 3.68 (3 H, s, OCH_3), 3.33 (2 H, dt, *J* 14.6, 5.3 Hz, $PhCH_2$) and 2.84 (3 H, s, NCH_3); δ_C (62.9 MHz, $CDCl_3$) major rotamer 171.82 (ester CO_2), 156.74 (urethane CO_2), 137.07-126.61 (Ar-C and Ar-CH), 67.14 (CH_2O), 60.21 (CHN), 52.22 (OCH_3), 35.23 ($PhCH_2$) and 31.63 (NCH_3); minor rotamer 171.36 (ester CO_2), 155.91 (urethane CO_2), 137.07-126.61 (Ar-C and Ar-CH), 67.33 (CH_2O), 60.63 (CHN), 52.22 (OCH_3), 35.23 ($PhCH_2$) and 32.13 (NCH_3); *m/z* 327.1471 [M^+ (unknown %), $C_{19}H_{21}NO_4$ requires 327.1471], mass spectrum details unavailable.

The method has been previously reported in the literature.[109]

44. *N*-(Benzyloxycarbonyl)-*L*-valine methyl ester (125)

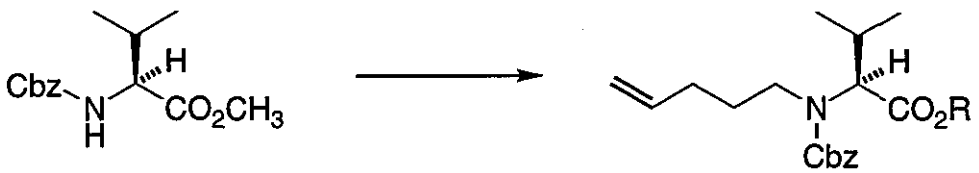


(125)

To a mixture of *L*-valine methyl ester hydrochloride (5.01 g, 29.89 mmol), ethyl acetate (50 cm^3) and distilled water (15 cm^3) was added sodium hydrogencarbonate (8.03 g, 80.22 mmol). The mixture was stirred for 5 min before the addition of benzyl chloroformate (5.8 cm^3, 38.6 mmol) over a 10 min period and then stirred for a further 3 h. The reaction layers were separated and the organic layer washed with 2 M hydrochloric acid (1 x 30 cm^3), distilled water (1 x 30 cm^3), 2 M sodium hydrogencarbonate solution (1 x 30 cm^3) and brine (saturated, 1 x 30 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness. Hexane (25 cm^3) was added, the crystals formed were recovered by filtration and washed with cold hexane. The hexane filtrate was evaporated to dryness and the hexane addition repeated. The white, feather-like crystals obtained were *N*-(benzyloxycarbonyl)-*L*-valine methyl ester **125** (7.59 g, 96 %), m.p. 56.4-56.7 °C (*lit.*[152] 55.5-56.5 °C); υ_{max}/cm^{-1} (neat) 3358, 2928, 1748 and 1712; δ_H (250 MHz, $CDCl_3$) 7.36 (5 H, br, ArH), 5.30 (1 H, br, NH), 5.12 (2 H, s, CH_2O), 4.68 (1 H, dd, *J* 9.0, 4.8 Hz, CHN), 3.74 (3 H, s, OCH_3), 2.14 (1 H, m, $CHMe_2$), 0.97 (3 H, d, *J* 6.8 Hz, CH_3) and 0.90 (3 H, d, *J* 6.9 Hz, CH_3); δ_C (62.9 MHz, $CDCl_3$) 172.50 (ester CO_2), 156.25 (urethane CO_2), 136.82 (Ar-C), 128.43, 128.06 and 128.02 (Ar-CH), 66.91 (CH_2O), 59.01 (CHN), 52.00 (OCH_3), 31.19 ($CHMe_2$), 18.85 (CH_3) and 17.49 (CH_3); *m/z* 265.1313 [M^+ (5 %), $C_{14}H_{19}NO_4$ requires 2265.1314], 206 (8), 162 (14), 108 (19), 91 (100), 65 (15) and 39 (14).

The data was consistent with that previously reported in the literature.[129]

45. *N*-Alkylation of *N*-(benzyloxycarbonyl)-*L*-valine methyl ester (125) using 5-bromopent-1-ene



(125) **(126)**, R = CH_3

(127), R = $(CH_2)_3CH{=}CH_2$

A mixture of *N*-(benzyloxycarbonyl)-*L*-valine methyl ester **125** (1.99 g, 7.49 mmol), 5-bromopent-1-ene (3.2 ml, 27.01 mmol) and anhydrous dimethylformamide (5 ml) was cooled to 0-5 °C (ice bath) under nitrogen. A suspension of sodium hydride (0.51 g, 21.32 mmol, freshly washed in light petroleum) in anhydrous dimethylformamide (10 cm^3) was added dropwise then the reaction returned to room temperature and stirred for 24 h. Phosphate buffer solution (PBS, 0.05 M, pH = 7.0, 50 cm^3) and diethyl ether (50 cm^3) were added and the fractions separated. The PBS fraction was washed with diethyl ether (2 x 20 cm^3), then the combined ether fractions were washed with distilled water (5 x 20 cm^3), brine (saturated, 3 x 20 cm^3), dried ($MgSO_4$) and filtered. Evaporation to dryness gave an orange oil. Purification using flash column chromatography (15 % ethyl acetate/light petroleum) gave a pair of diastereomers of N-*(benzyloxycarbonyl)*-N-*(pent-4-enyl)*-L-*valine methyl ester* **126** (0.73 g, 29 % isolated yield) as a colourless oil; υ_{max}/cm^{-1} (neat) 3058, 2965, 1743 and 1704; δ_H (250 MHz, $CDCl_3$) major diastereomer, 7.36-7.30 (5 H, m, ArH), 5.80-5.57 (1 H, br, =CH), 5.17 (2 H, s, CH_2O), 5.07-4.89 (2 H, br, $=CH_2$), 4.32 (1 H, d, *J* 10.5 Hz, CHN), 3.70 (3 H, s, OCH_3), 3.30-3.20 (2 H, m, CH_2N), 2.31-2.20 (1 H, m, $CHMe_2$), 2.13-1.95 (2 H, br, CH_2-C=C), 1.83-1.56 (2 H, br, $CH_2CH_2CH_2$), 0.98 (3 H, d, *J* 6.3 Hz, CH_3) and 0.88 (3 H, d, *J* 5.7 Hz, CH_3); minor diastereomer, 7.36-7.30 (5 H, m, ArH), 5.80-5.57 (1 H, br, =CH), 5.17 (2 H, s, CH_2O), 5.07-4.89 (2 H, br, $=CH_2$), 4.05 (1 H, d, *J* 10.1 Hz, CHN), 3.62 (3 H, s, OCH_3), 3.30-3.20 (2 H, m, CH_2N), 2.31-2.20 (1 H, m, $CHMe_2$), 2.13-1.95 (2 H, br, CH_2-C=C), 1.83-1.56 (2 H, br, $CH_2CH_2CH_2$), 0.98 (3 H, d, *J* 6.3 Hz, CH_3) and 0.88 (3 H, d, *J* 5.7 Hz, CH_3); δ_C (62.9 MHz, $CDCl_3$) major diastereomer 171.78 (ester CO_2), 156.22 (urethane CO_2), 137.64 (=CH), 136.50 (Ar-C), 128.35, 127.88, 127.73 (Ar-CH), 114.84 ($=CH_2$), 67.65 (CH_2O), 64.85 (CHN), 51.69 (OCH_3), 45.81 (CH_2N), 31.12 (CH_2C=C), 27.79 ($CHMe_2$), 27.17 ($CH_2CH_2CH_2$), 20.22 (CH_3) and 18.98 (CH_3); minor diastereomer 172.16 (ester CO_2), 157.19 (urethane CO_2), 137.64 (=CH), 136.50 (Ar-C), 128.35, 127.88, 127.73 (Ar-CH), 114.84 ($=CH_2$), 67.86 (CH_2O), 64.31 (CHN), 51.69 (OCH_3), 44.39 (CH_2N), 31.12 (CH_2C=C), 28.04 ($CH_2CH_2CH_2$), 27.79 ($CHMe_2$), 19.85

(CH_3) and 18.79 (CH_3); *m/z*, CI, 334.2018 [MH^+ (100 %), $C_{19}H_{28}NO_4$ requires 334.2018], 243 (8), 200 (10), 159 (19), 108 (19) and 91 (11).

The pair of diastereomers of N-*(benzyloxycarbonyl)*-N-*(pent-4-enyl)*-L-*valine pent-4-enyl ester* **127** (0.28 g, 10 % isolated yield) were also isolated as a colourless oil; υ_{max}/cm^{-1} (neat) 3053, 2975, 2925, 1749 and 1707; δ_H (250 MHz, $CDCl_3$) major diastereomer, 7.33-7.28 (5 H, m, ArH), 5.79-5.62 (2 x 1 H, br, 2 x =CH), 5.14 (2 H, s, $PhCH_2O$), 5.03-4.90 (2 x 2 H, br, 2 x $=CH_2$), 4.25 (1 H, d, *J* 10.3 Hz, CHN), 4.12-3.98 (2 H, br, CH_2O), 3.30-3.18 (2 x 2 H, br, CH_2N), 2.31-2.24 (1 H, m, $CHMe_2$), 2.19-1.85 (2 x 2 H, br, CH_2-C=C), 1.75-1.53 (2 x 2 H, br, $CH_2CH_2CH_2$), 0.97 (3 H, d, *J* 6.2 Hz, CH_3) and 0.87 (3 H, d, *J* 5.8 Hz, CH_3); minor diastereomer, 7.33-7.28 (5 H, m, ArH), 5.79-5.62 (2 x 1 H, br, 2 x =CH), 5.14 (2 H, s, CH_2O), 5.03-4.90 (2 x 2 H, br, 2 x $=CH_2$), 4.12-3.98 (3 H, m, CH_2O+CHN), 3.30-3.18 (2 x 2 H, br, CH_2N), 2.31-2.24 (1 H, m, $CHMe_2$), 2.19-1.85 (2 x 2 H, br, CH_2-C=C), 1.75-1.53 (2 x 2 H, br, $CH_2CH_2CH_2$), 0.97 (3 H, d, *J* 6.2 Hz, CH_3) and 0.87 (3 H, d, *J* 5.8 Hz, CH_3); δ_C (62.9 MHz, $CDCl_3$) major diastereomer 172.03 (ester CO_2), 156.24 (urethane CO_2), 137.64 (ester =CH), 137.15 (=CH), 136.58 (Ar-C), 128.32, 127.85, 127.74 (Ar-CH), 115.29 (ester $=CH_2$), 114.79 ($=CH_2$), 67.21 (CH_2O), 64.82 (CHN), 64.09 (ester CH_2O), 44.85 (CH_2N), 31.12 (CH_2C=C), 29.86 (ester CH_2C=C), 27.99 ($CH_2CH_2CH_2$), 27.56 ($CHMe_2$), 27.24 (ester $CH_2CH_2CH_2$), 19.96 (CH_3) and 18.92 (CH_3); minor diastereomer 172.83 (ester CO_2), 157.08 (urethane CO_2), 137.64 (ester =CH), 137.15 (=CH), 136.58 (Ar-C), 128.32, 127.85, 127.74 (Ar-CH), 115.29 (ester $=CH_2$), 114.79 ($=CH_2$), 67.21 (CH_2O), 65.13 (CHN), 64.09 (ester CH_2O), 46.12 (CH_2N), 31.12 (CH_2C=C), 29.86 (ester CH_2C=C), 27.99 ($CH_2CH_2CH_2$), 27.56 ($CHMe_2$), 27.24 (ester $CH_2CH_2CH_2$), 20.25 (CH_3) and 18.92 (CH_3); *m/z*, CI, 388.2488 [MH^+ (100 %), $C_{23}H_{34}NO_4$ requires 388.2488], 334 (10), 274 (12), 230 (11), 108 (22) and 91 (14).

46. Attempted deprotection of *N*-(benzyloxycarbonyl)-*N*-(pent-4-enyl)-*L*-valine methyl ester (126) using sodium in ammonia[110]

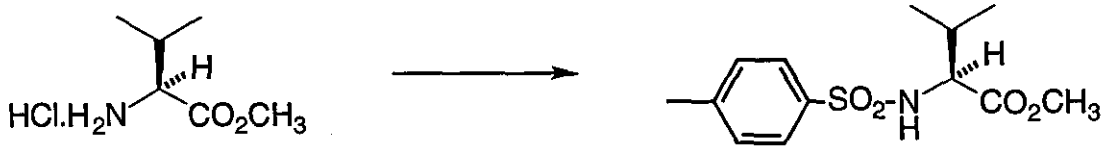
Ammonia was condensed into a flask containing *N*-(benzyloxycarbonyl)-*N*-(pent-4-enyl)-*L*-valine methyl ester **126** (0.83 g, 2.25 mmol) at -78 °C using a dry ice/acetone bath. Sodium metal, cleaned using a methanol then light petroleum wash, was added in small pieces with stirring until the blue colouration produced on addition failed to decolourise. Ammonium chloride was then added to quench the reaction (blue colouration removed) and the reaction allowed to warm to room temperature before the addition of ethyl acetate (20 cm^3) and distilled water (20 cm^3). The layers were separated, the aqueous layer further extracted with ethyl acetate (2 x 10 cm^3) and then the organic fractions combined. These were washed with distilled water (1 x 10 cm^3) and brine (1 x 10 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness to

give a colourless oil (0.50 g). ^{1}H NMR spectroscopy indicated that the expected deprotection had not taken place and that there was significant loss of the ester moiety. Further purification was not attempted.

47. Deprotection of *N*-(benzyloxycarbonyl)-*N*-(pent-4-enyl)-*L*-valine methyl and pent-4-enyl ester mixture[111]

A solution of *N*-(benzyloxycarbonyl)-*N*-(pent-4-enyl)-*L*-valine methyl ester **126** and *N*-(benzyloxycarbonyl)-*N*-(pent-4-enyl)-*L*-valine pent-4-enyl ester **127** (0.50 g, crude material from experiment 45, 1.34 mmol max.) in 33 % hydrogen bromide/acetic acid (1.0 cm^3, 3.9 mmol) was stirred for an hour. Distilled water (20 cm^3) and diethyl ether (20 cm^3) were added, the layers were separated and the ether layer extracted further with distilled water (2 x 15 cm^3). The aqueous fractions were combined, washed with diethyl ether (1 x 10 cm^3) and the pH of the solution raised to 10 with anhydrous sodium carbonate. The product was then extracted with dichloromethane (4 x 20 cm^3), the organic fractions combined, dried ($MgSO_4$), filtered and evaporated to dryness to give a colourless oil (0.36 g). Purification using flash column chromatography (10 % ethyl acetate/light petroleum) gave one major fraction (68 mg) and baseline material only. ^{1}H NMR spectroscopy of the fraction indicated that the deprotection had been successful but that addition of hydrogen bromide to the alkene moiety had also occurred. This method was therefore unsuitable and not pursued.

48. *N*-Tosyl-*L*-valine methyl ester



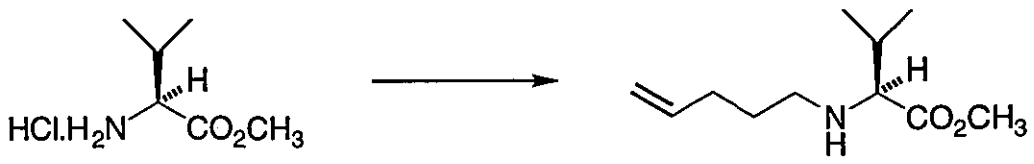
A mixture of *L*-valine methyl ester hydrochloride (1.00 g, 5.97 mmol) in anhydrous dimethylformamide (15 cm^3) was cooled to 0-5 °C (ice bath) under nitrogen. Triethylamine (2.5 cm^3, 18 mmol, dried over KOH) then tosyl chloride were added and the reaction stirred at 0-5 °C for 2 h. On returning to room temperature, the reaction was stirred overnight before adding ethyl acetate (20 cm^3) and distilled water (20 cm^3). The layers were separated and the aqueous layer extracted further with ethyl acetate (3 x 20 cm^3) before combining the organic fractions. These were washed with 2 M sodium hydrogencarbonate (1 x 30 cm^3), distilled water (2 x 30 cm^3) and brine (saturated, 3 x 30 cm^3), dried ($MgSO_4$), filtered and evaporated to

dryness. Purification using flash column chromatography (25 % ethyl acetate/light petroleum) gave *N*-tosyl-*L*-valine methyl ester (1.50 g, 89 %) as a white solid, m.p. 77.5-78.5 °C (lit.[153] 75-76 °C); υ_{max}/cm^{-1} (neat) 3263, 2923, 2872 and 1740; δ_H (250 MHz, $CDCl_3$) 7.72-7.67 (2 H, d, *J* 8.3 Hz, ArH *ortho* to SO_2), 7.28-7.25 (2 H, d, *J* 8.3 Hz, ArH *ortho* to Me), 5.18 (1 H, d, *J* 10.1 Hz, NH), 3.71 (1 H, dd, *J* 10.1, 5.1 Hz, CHN), 3.43 (3 H, s, OCH_3), 2.40 (3 H, s, Ph-CH_3), 2.07-1.94 (1 H, m, $CHMe_2$), 0.93 (3 H, d, *J* 6.8 Hz, CH_3) and 0.87 (3 H, d, *J* 6.9 Hz, CH_3); δ_C (62.9 MHz, $CDCl_3$) 171.70 (ester CO_2), 143.50 (Ar-C- SO_2), 136.22 (Ar-C-CH_3), 129.46 (Ar-CH *ortho* to SO_2), 127.24 (Ar-CH *ortho* to Me), 60.98 (CHN), 52.06 (OCH_3), 31.54 ($CHMe_2$), 21.43 (Ph-CH_3), 18.84 (CH_3) and 17.40 (CH_3); *m/z* 286.1119 [MH^+ (51 %), $C_{13}H_{20}NO_4S$ requires 286.1113], 268 (48), 240 (50), 226 (100), 155 (50), 91 (75) and 65 (29).

49. Attempted *N*-alkylation of *N*-tosyl-*L*-valine methyl ester

A solution of *N*-tosyl-*L*-valine methyl ester (0.21 g, 0.74 mmol) and 5-bromopent-1-ene (0.36 cm^3, 2.95 mmol) in anhydrous dimethylformamide (5 cm^3) was cooled to 0-5 °C in an ice bath under nitrogen. A suspension of sodium hydride (0.53 g, 2.21 mmol, freshly washed in light petroleum) in anhydrous dimethylformamide (5 cm^3) was added dropwise and the reaction mixture stirred for 2 h at 0-5 °C before returning the reaction to room temperature and stirring for another 24 h. Ethyl acetate (30 cm^3) and distilled water (30 cm^3) were added, the layers separated and the aqueous layer extracted further with ethyl acetate (2 x 20 cm^3). The organic fractions were combined, washed with distilled water (4 x 20 cm^3) and brine (saturated, 3 x 20 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness to give a colourless oil (0.35 g). TLC indicated that several products had been made. ^1H NMR spectroscopy showed that the desired compound was present in very low yield. Further purification was not attempted.

50. *N*-(Pent-4-enyl)-*L*-valine methyl ester (128b) using 5-bromopentene



(128b)

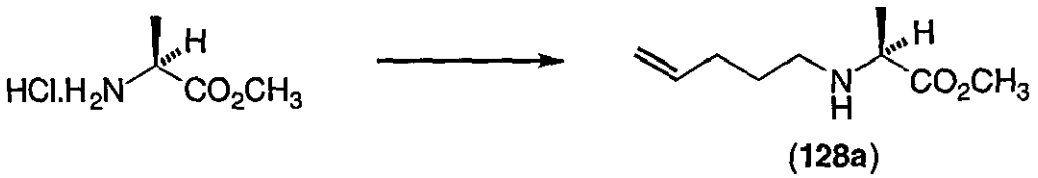
A mixture of *L*-valine methyl ester hydrochloride (3.77 g, 28.72 mmol), sieve dried triethylamine (40 cm^3, 10 equivalents), potassium (I) iodide (2.38 g, 14.36 mmol) and sieve dried ethyl acetate (100 cm^3) was stirred under nitrogen and brought to reflux.

5-bromopent-1-ene (3.5 cm^3, 28.72 mmol) was added and the solution refluxed for 3 days. After 24 and 48 h, further additions of 5-bromopent-1-ene (0.8 cm^3, 6.56 mmol) were made. The mixture was filtered and evaporated to dryness. Purification using flash column chromatography (15 % ethyl acetate/light petroleum) yielded the N-*(pent-4-enyl)*-L-*valine methyl ester* **128b** (0.87 g, 15 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3334, 3079, 2961 and 1737; δ_H (400 MHz, $CDCl_3$) 5.82-5.72 (1 H, ddt, *J* 16.9, 10.3, 6.6 Hz, =CH), 5.00-4.89 (2 H, m, $=CH_2$), 3.66 (3 H, s, OCH_3), 2.93 (1 H, d, *J* 6.3 Hz, CHN), 2.59-2.52 and 2.41-2.34 (2 x 1 H, m, CH_2N), 2.08-2.03 (2 H, m, $CH_2C=C$), 1.84 (1 H, octet, *J* 6.7 Hz, $CHMe_2$), 1.61-1.45 (3 H, m, $CH_2CH_2CH_2$ + NH), 0.92 (3 H, d, *J* 6.8 Hz, CH_3) and 0.90 (3 H, d, *J* 6.8 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 175.75 (CO_2), 138.37 (=CH), 114.43 ($=CH_2$), 67.38 (OCH_3), 51.12 (CHN), 48.00 (CH_2N), 31.54 ($CHMe_2$), 31.54 ($CH_2C=C$), 29.25 ($CH_2CH_2CH_2$), 19.04 (CH_3) and 16.66 (CH_3); *m/z* 198.1495 [$(M-H)^+$ (8 %), $C_{11}H_{20}NO_2$ requires 198.1494], 156 (53), 140 (100), 102 (26), 84 (19), 69 (22) and 41 (28).

51. Attempted N-alkylation of *L-tert*-leucine methyl ester hydrochloride using 5-bromopentene

A mixture of *L-tert*-leucine methyl ester hydrochloride (4.24 g, 23.32 mmol), sieve dried triethylamine (33 cm^3, 10 equivalents), potassium (I) iodide (1.96 g, 0.5 equivalents) and sieve dried ethyl acetate (100 cm^3) was stirred under nitrogen and brought to reflux. 5-bromopent-1-ene (2.9 cm^3, 23.32 mmol) was added and the solution refluxed for 3 days. After 24 and 48 h, further additions of 5-bromopent-1-ene (0.5 cm^3, 4.10 mmol) were made. The mixture was filtered and evaporated to dryness. Purification using flash column chromatography (15 % ethyl acetate/light petroleum) yielded numerous unidentifiable compounds. This reaction was discontinued.

52. *N*-(Pent-4-enyl)-*L*-alanine methyl ester (128a)



(128a)

A mixture of *L*-alanine methyl ester hydrochloride (2.37 g, 16.97 mmol), freshly activated 4Å molecular sieves (17 g), 4-penten-1-al (1.73 cm^3, 16.97 mmol) and sieve dried methanol (40 cm^3) was cooled to 0-5 °C in an ice bath before adding sodium cyanoborohydride (2.24 g, 33.93 mmol) and stirring for 1.5 h. The reaction was

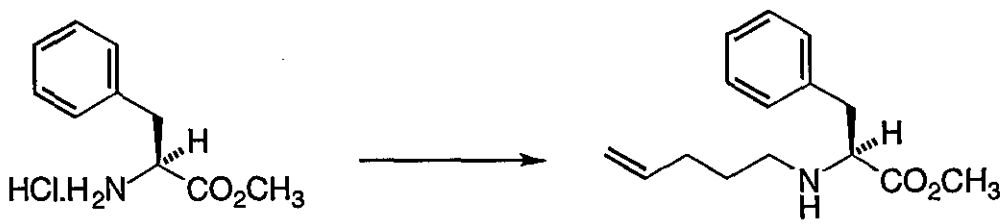
warmed to room temperature, stirred for 2.5 h, filtered and evaporated to dryness. Hydrochloric acid (1 M) was added (pH reduced to 2) and the aqueous solution washed with dichloromethane (2 x 20 cm^3). Anhydrous potassium carbonate (pH increased to 10) was introduced and the aqueous mixture extracted with ethyl acetate (3 x 25 cm^3), the organic solvent was dried ($MgSO_4$), filtered and evaporated to dryness to give a colourless oil (3.33 g). Purification using flash column chromatography (40 % ethyl acetate/hexane) gave the N-*(pent-4-enyl)*-L-*alanine methyl ester* **128a** (1.41 g, 48 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3330, 3078, 2978, 2934, 2842 and 1740; δ_H (400 MHz, $CDCl_3$) 5.81-5.71 (1 H, ddt, *J* 17.1, 10.3 and 6.6 Hz, =CH), 5.00-4.89 (2 H, m, $=CH_2$), 3.68 (3 H, s, OCH_3), 3.30 (1 H, q, *J* 7.0 Hz, CHN), 2.58-2.52 (1H, m, C*H*HN), 2.48-2.42 (1 H, m, CH*H*N), 2.08-2.02 (2 H, m, $CH_2C=C$), 1.62-1.48 (3 H, m, $CH_2CH_2CH_2$ + NH) and 1.25 (3 H, d, *J* 7.0 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 176.13 (CO_2), 138.16 (=CH), 114.54 ($=CH_2$), 56.53 (OCH_3), 51.55 (CHN), 47.33 (CH_2N), 31.27 ($CH_2C=C$), 29.25 ($CH_2CH_2CH_2$) and 18.95 (CH_3); *m/z* 172.1338 [MH^+ (8 %), $C_9H_{18}NO_2$ requires 172. 1338], 116 (86), 112 (100), 88 (79), 69 (87), 56 (94) and 44 (90). The dialkylated N, N-*bis(pent-4-enyl)*-L-*alanine methyl ester* **129a** (0.33 g, 8 %) was obtained as a colourless oil; υ_{max}/cm^{-1} (neat) 3078, 2979, 2936, 2843 and 1738; δ_H (400 MHz, $CDCl_3$) 5.85-5.74 (2 H, ddt, *J* 17.0, 10.3 and 6.7 Hz, =CH), 5.02-4.90 (4 H, m, $=CH_2$), 3.66 (3 H, s, OCH_3), 3.49 (1 H, q, *J* 7.1 Hz, CHN), 2.59-2.52 (2 H, m, C*H*HN and C*H*HN), 2.49-2.43 (2 H, m, CH*H*N and CH*H*N), 2.08-1.97 (4 H, m, $CH_2C=C$), 1.55-1.43 (4 H, m, $CH_2CH_2CH_2$) and 1.23 (3 H, d, *J* 7.0 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 174.44 (CO_2), 138.62 (=CH), 114.27 ($=CH_2$), 58.20 (OCH_3), 50.95 (CHN), 50.60 (CH_2N), 31.24 ($CH_2C=C$), 27.99 ($CH_2CH_2CH_2$) and 15.12 (CH_3); *m/z* 239.1881 [M^+ (40 %), $C_{14}H_{25}NO_2$ requires 239.1885], 184 (92), 180 (100), 156 (21), 130 (81), 112 (84), 72 (31), 69 (63), 56 (82) and 41 (88).

53. *N*-(Pent-4-enyl)-*L*-valine methyl ester (128b) using reductive alkylation

A mixture of *L*-valine methyl ester hydrochloride (4.01 g, 23.70 mmol), freshly activated 4Å molecular sieves (24 g), 4-penten-1-al (2.41 cm^3, 23.70 mmol) and anhydrous methanol (40 cm^3) was cooled to 0-5 °C in an ice bath before adding sodium cyanoborohydride (3.14 g, 47.40 mmol) and stirring for 1 h. The reaction was returned to room temperature and stirred for 3 h, filtered and evaporated to dryness. Hydrochloric acid (2 M) was added (pH reduced to 2) and the aqueous solution washed with ethyl acetate (2 x 25 cm^3). Anhydrous potassium carbonate (pH increased to 10) was introduced and the aqueous mixture extracted with ethyl acetate (4 x 25 cm^3). The organic solution was dried ($MgSO_4$), filtered and evaporated to dryness to give a colourless oil. Purification using flash column chromatography

(15 % ethyl acetate/light petroleum) gave the N-*(pent-4-enyl)*-L-*valine methyl ester* **128b** (1.35 g, 28 %) as a colourless oil; see experiment 50 for compound data. Two diastereomers of N-*(1-cyanopent-4-enyl)*-L-*valine methyl ester* **130a** (0.06 g, 12 %) and **130b** (0.03 g, 6 %) were also isolated as colourless oils; υ_{max}/cm^{-1} (neat) diastereomer **130a**, 3339, 3054, 2943 and 1733, diastereomer **130b**, 3331, 3062, 2921 and 1736; δ_H (400 MHz, $CDCl_3$) diastereomer **130a**, 5.70 (1 H, ddt, *J* 17.0, 10.6, 6.5 Hz, =CH), 5.06-4.96 (2 H, m, $=CH_2$), 3.71 (3 H, s, OCH_3), 3.37 (1 H, t, *J* 5.2 Hz, (CN)CHN), 2.96 (1 H, d, *J* 4.8 Hz, CHN), 2.30-2.14 (2 H, m, $CH_2C=C$), 1.89-1.77 (3 H, m, CH_2CHN + $CHMe_2$), 1.67 (1 H, br, NH), 0.88 (3 H, d, *J* 7.0 Hz, CH_3) and 0.85 (3 H, d, *J* 6.9 Hz, CH_3), diastereomer **130b**, 5.73 (1 H, ddt, *J* 17.1, 10.4, 6.7 Hz, =CH), 5.08-4.97 (2 H, m, $=CH_2$), 3.73 (1 H, t, *J* 5.0 Hz, (CN)CHN), 3.69 (3 H, s, OCH_3), 3.23 (1 H, d, *J* 4.7 Hz, CHN), 2.32-2.15 (2 H, m, $CH_2C=C$), 1.99-1.90 (1 H, m, $CHMe_2$), 1.86-1.74 (2 H, m, CH_2CHN), 1.66 (1 H, br, NH), 0.93 (3 H, d, *J* 7.0 Hz, CH_3) and 0.86 (3 H, d, *J* 6.9 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) diastereomer **130a**, 174.32 (CO_2), 136.11 (=CH), 119.78 (CN), 116.37 ($=CH_2$), 65.85 (CHN), 51.73 (CHN(CN)), 49.74 (OCH_3), 33.12 ($CH_2C=C$), 31.96 ($CHMe_2$), 29.44 (CH_2CHN), 18.99 (CH_3) and 17.94 (CH_3), diastereomer **130b**, 174.41 (CO_2), 136.17 (=CH), 119.71 (CN), 116.39 ($=CH_2$), 64.52 (CHN), 51.81 (CHN(CN)), 48.99 (OCH_3), 32.63 ($CH_2C=C$), 31.52 ($CHMe_2$), 29.60 (CH_2CHN), 19.25 (CH_3) and 17.92 (CH_3); *m/z* diastereomer **130a**, 225.1577 [$(M+H)^+$ (5 %), $C_{12}H_{21}N_2O_2$ requires 225.1603], 204 (18), 182 (17), 165 (88), 138 (100), 94 (30), 84 (44), 72 (65), 55 (56) and 41 (73), diastereomer **130b**, mass spectrum not available.

54. *N*-(Pent-4-enyl)-*L*-phenylalanine methyl ester (128c)

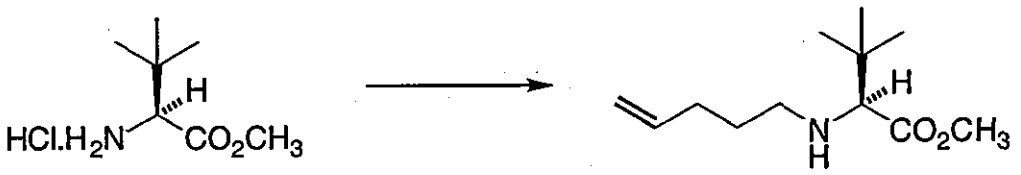


(128c)

A mixture of *L*-phenylalanine methyl ester hydrochloride (6.10 g, 28.28 mmol), freshly activated 4Å molecular sieves (29 g), 4-penten-1-al (2.88 cm^3, 28.28 mmol) and anhydrous methanol (80 cm^3) was cooled to -20 °C in an acetone/dry ice bath under nitrogen before adding sodium cyanoborohydride (3.75 g, 56.56 mmol) and stirring for 1 h. The reaction was warmed to room temperature and stirred overnight before filtering and evaporating to dryness. On the addition of hydrochloric acid (2 M), the pH was reduced to 2, then anhydrous potassium

carbonate was introduced and the pH increased to 10. The aqueous mixture was extracted with ethyl acetate (4 x 25 cm^3). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated to dryness to give a pale green oil. Purification using flash column chromatography (5 % ethyl acetate/1 % methanol/ dichloromethane) gave N-*(pent-4-enyl)*-L-*phenylalanine methyl ester* **128c** (3.50 g, 50 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3328, 3065, 2976, 2932, 2850 and 1737; δ_H (400 MHz, $CDCl_3$) 7.33-7.20 (5 H, m, ArH), 5.85-5.75 (1 H, ddt, *J* 17.1, 10.4 and 6.8 Hz, =CH), 5.05-4.94 (2 H, m, $=CH_2$), 3.67 (3 H, s, OCH_3), 3.54 (1 H, t, *J* 6.8 Hz, CHN), 2.98 (2 H, d, *J* 6.9 Hz, $PhCH_2$), 2.67-2.61 (1 H, m, C*H*HN), 2.53-2.47 (1 H, m, CH*H*N), 2.10-2.04 (2 H, m, CH_2C=C) and 1.65-1.54 (3 H, m, $CH_2CH_2CH_2$ + NH); δ_C (100 MHz, $CDCl_3$) 175.48 (CO_2), 138.67 (=CH), 137.90 (Ar-C), 129.53, 128.78, 127.06 (Ar-CH), 115.06 ($=CH_2$), 63.47 (CHN), 51.91 (OCH_3), 47.92 (CH_2N), 40.12 ($PhCH_2$), 31.67 (CH_2C=C) and 29.58 ($CH_2CH_2CH_2$); *m/z* 247.1574 [M^+ (10 %), $C_{15}H_{21}NO_2$ requires 247.1572], 188 (25), 156 (100), 102 (38), 96 (20), 91 (42), 69 (53) and 41 (79).

55. *N*-(Pent-4-enyl)-*L-tert*-leucine methyl ester (128d)



(128d)

A mixture of *L-tert*-leucine methyl ester hydrochloride (2.51 g, 13.80 mmol), freshly activated 4Å molecular sieves (14 g), 4-penten-1-al (1.41 cm^3, 13.80 mmol) and anhydrous methanol (60 cm^3) was cooled to 0-5 °C in an ice bath under nitrogen before adding sodium cyanoborohydride (1.83 g, 27.60 mmol) and stirring for 1 h. The reaction was warmed to room temperature and stirred overnight before filtering and evaporating to dryness. On the addition of hydrochloric acid (4 M), the pH was reduced to 2, then anhydrous potassium carbonate was introduced and the pH increased to 10. The aqueous mixture was extracted with ethyl acetate (4 x 20 cm^3). The organic extracts were combined, dried ($MgSO_4$), filtered and evaporated to dryness. Purification using flash column chromatography (1 % diethyl ether/ dichloromethane) gave N-*(pent-4-enyl)*-L-tert-*leucine methyl ester* **128d** (0.87 g, 30 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3341, 3078, 2954 and 1734; δ_H (250 MHz, $CDCl_3$) 5.88-5.78 (1 H, ddt, *J* 17.0, 10.3 and 6.6 Hz, =CH), 5.03-4.91 (2 H, m, $=CH_2$), 3.69 (3 H, s, OCH_3), 2.85 (1 H, s, CHN), 2.61-2.51 (1H, m, C*H*HN), 2.41-2.31 (1 H, m, CH*H*N), 2.13-2.04 (2 H, m, CH_2C=C), 1.59-1.46 (3 H, m, $CH_2CH_2CH_2$ + NH) and 0.94 (9 H, s, Me_3); δ_C (100 MHz, $CDCl_3$) 176.21 (CO_2), 138.47 (=CH), 114.43 ($=CH_2$), 70.53

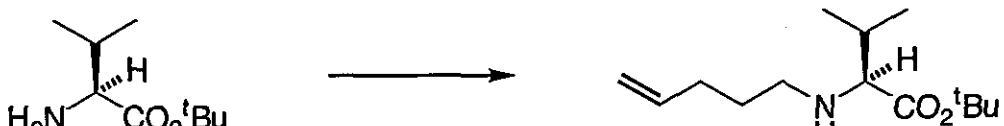
(CHN), 50.89 (OCH_3), 48.29 (CH_2N), 33.86 (CMe_3), 31.27 ($CH_2C{=}C$), 29.22 ($CH_2CH_2CH_2$) and 26.62 (Me_3); *m/z* (CI) 214.1807 [MH^+ (100 %), $C_{12}H_{24}NO_2$ requires 214.1807], 146 (100), 86 (17), 74 (44), 46 (77) and 44 (36).

56. *N*-(Pent-4-enyl)-*L*-alanine *tert*-butyl ester (128e)

(120a) **(128e)**

A mixture of *L*-alanine *tert*-butyl ester **120a** (0.98 g, 6.74 mmol), freshly activated 4Å molecular sieves (7 g), 4-penten-1-al (0.67 cm^3, 6.74 mmol), *para*-toluenesulfonic acid (85 mg, 0.5 mmol) and anhydrous methanol (40 cm^3) was stirred for 1.5 h. The reaction was cooled to 0-5 °C in an ice bath under nitrogen before adding sodium cyanoborohydride (0.56 g, 8.53 mmol) and stirring for 1 h. The reaction was warmed to room temperature and stirred overnight before filtering and evaporating to dryness. Distilled water (20 cm^3) was added, the pH increased to 10 with anhydrous potassium carbonate and the organics extracted with ethyl acetate (4 x 10 cm^3). The organic extracts were combined, washed with brine (saturated, 2 x 10 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness. Purification using flash column chromatography (30 % ethyl acetate/dichloromethane) gave the N-*(pent-4-enyl)*-L-*alanine* tert-*butyl ester* **128e** (0.46 g, 30 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3336, 2978, 2924 and 1729; δ_H (400 MHz, $CDCl_3$) 5.89-5.78 (1 H, ddt, *J* 17.1, 10.3, 6.6 Hz, =CH), 5.07-4.96 (2 H, m, $=CH_2$), 3.21 (1 H, q, *J* 7.0 Hz, CHN), 2.65-2.59 (1 H, m, C*H*HN), 2.55-2.49 (1 H, m, CH*H*N), 2.13-2.09 (2 H, m, $CH_2C{=}C$), 1.69 (1 H, br, NH), 1.67-1.57 (2 H, m, $CH_2CH_2CH_2$), 1.50 (9 H, s, Me_3) and 1.27 (3 H, d, *J* 7.0 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 175.71 (CO_2), 138.77 (=CH), 115.04 ($=CH_2$), 81.20 (CO), 57.77 (CHN), 47.83 (CH_2N), 31.86 ($CH_2C{=}C$), 29.82 ($CH_2CH_2CH_2$), 28.47 (Me_3) and 19.53 (CH_3); *m/z* 214.1805 [M^+ (26 %), $C_{12}H_{24}NO_2$ requires 214.1807], 158 (29), 112 (100), 69 (33), 56 (40), 41 (72) and 27 (27).

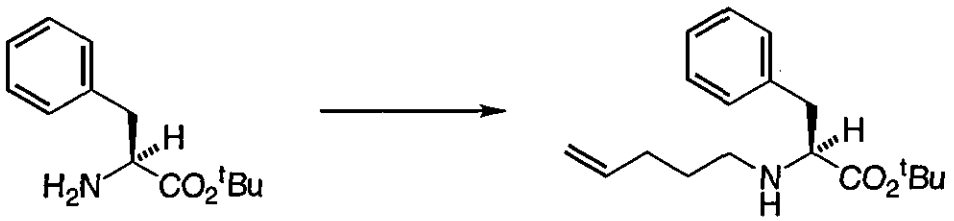
57. *N*-(Pent-4-enyl)-*L*-valine *tert*-butyl ester (128f)



(120b) **(128f)**

A mixture of *L*-valine *tert*-butyl ester **120b** (0.20 g, 1.15 mmol), anhydrous acetonitrile (20 cm^3), 4-pentenal (0.12 cm^3, 1.15 mmol) and 4Å molecular sieves (2 g) was stirred under nitrogen for 4 h before adding sodium cyanoborohydride (0.08 g, 1.15 mmol) and allowing to stir overnight. The reaction mixture was filtered, evaporated to dryness and 1 M hydrochloric acid added until the pH of the solution was 2. Anhydrous potassium carbonate was then added until the pH was raised to 10 and the organics extracted with ethyl acetate (3 x 30 cm^3). The organic fractions were combined, dried ($MgSO_4$), filtered and evaporated to dryness to give a green oil (0.25 g). Purification using flash column chromatography (10 % ethyl acetate/ dichloromethane) gave the N-*(pent-4-enyl)*-L-*valine* tert-*butyl ester* **128f** (0.11 g, 39 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3320, 2968, 2932 and 1726; δ_H (400 MHz, $CDCl_3$) 5.78 (1 H, ddt, *J* 17.0, 10.3, 6.7 Hz, =CH), 5.01-4.89 (2 H, m, $=CH_2$), 2.78 (1 H, d, *J* 6.1 Hz, CHN), 2.62-2.55 (1 H, m, C*H*HN), 2.43-2.37 (1 H, m, CH*H*N), 2.10-2.04 (2 H, m, $CH_2C=C$), 1.81 (1 H, octet, *J* 6.8 Hz, $CHMe_2$), 1.60-1.47 (3 H, m, $CH_2CH_2CH_2$ + NH), 1.45 (9 H, s, ester Me_3), 0.92 (3 H, d, *J* 6.9 Hz, CH_3) and 0.90 (3 H, d, *J* 6.7 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 174.62 (CO_2), 138.45 (=CH), 114.35 ($=CH_2$), 80.56 (CO), 67.87 (CHN), 47.93 (CH_2N), 31.60 ($CHMe_2$), 31.33 ($CH_2C=C$), 29.31 ($CH_2CH_2CH_2$), 28.07 (ester Me_3), 17.00 (CH_3) and 16.74 (CH_3); *m/z* (FAB) 242.2113 [MH^+ (53 %), $C_{14}H_{28}NO_2$ requires 242.2120], 186 (100), 140 (25), 72 (18) and 57 (16).

58. *N*-(Pent-4-enyl)-*L*-phenylalanine *tert*-butyl ester (128g)

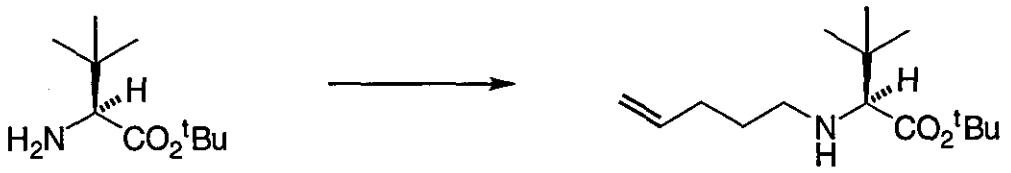


(120c) **(128g)**

A mixture of *L*-phenylalanine *tert*-butyl ester **120c** (1.07 g, 4.84 mmol), freshly activated 4Å molecular sieves (10 g), 4-penten-1-al (0.49 cm^3, 4.85 mmol), *para*-toluenesulfonic acid (82 mg, 0.5 mmol) and anhydrous methanol (40 cm^3) was stirred for 1.5 h. The reaction was cooled to 0-5 °C in an ice bath under nitrogen, sodium cyanoborohydride (0.42 g, 6.30 mmol) added and the reaction stirred for 1 h. The reaction was warmed to room temperature and stirred overnight before filtering and evaporating to dryness. Distilled water (20 cm^3) was added, the pH increased to 10 with anhydrous potassium carbonate and the organics extracted with ethyl acetate (4 x 10 cm^3). The organic extracts were combined, washed with brine (saturated, 2 x 10 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness.

Purification using flash column chromatography (3 % ethyl acetate/ dichloromethane) gave the N-*(pent-4-enyl)*-L-*phenylalanine* tert-*butyl ester* **128g** (0.55 g, 39 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3327, 3064, 3029, 2977, 2931 and 1726; δ_H (400 MHz, $CDCl_3$) 7.32-7.22 (5 H, m, ArH), 5.86-5.76 (1 H, ddt, *J* 17.0, 10.2 and 6.7 Hz, =CH), 5.04-4.95 (2 H, m, $=CH_2$), 3.41 (1 H, dd, *J* 7.7, 6.5 Hz, CHN), 2.97 (1 H, dd, *J* 13.5, 7.7 Hz, PhC*H*H), 2.88 (1 H, dd, *J* 13.5, 6.5 Hz, PhCH*H*), 2.68-2.62 (1 H, m, C*H*HN), 2.56-2.49 (1 H, m, CH*H*N), 2.11-2.05 (2 H, m, $CH_2C=C$), 1.66-1.49 (3 H, m, $CH_2CH_2CH_2$ + NH) and 1.37 (9 H, s, Me_3); δ_C (100 MHz, $CDCl_3$) 174.45 (CO_2), 138.75 (=CH), 138.04 (Ar-C), 129.77, 128.59, 126.86 (Ar-CH), 115.02 ($=CH_2$), 81.37 (CO), 63.88 (CHN), 47.85 (CH_2N), 40.28 ($PhCH_2$), 31.75 ($CH_2C=C$), 29.68 ($CH_2CH_2CH_2$) and 28.37 (Me_3); *m/z* 289.2034 [M^+ (100 %), $C_{18}H_{27}NO_2$ requires 289.2042], 233 (57), 197 (38), 187 (60), 141 (50), 90 (43), 57 (40) and 41 (39).

59. *N*-(Pent-4-enyl)-*L*-*tert*-leucine *tert*-butyl ester (128h)

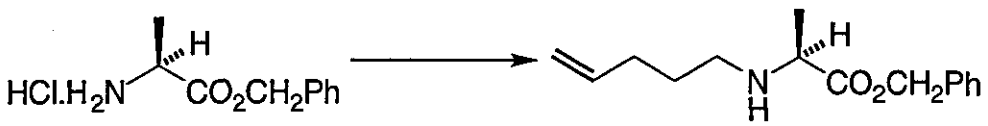


(120d) **(128h)**

A mixture of *L*-*tert*-leucine *tert*-butyl ester **120d** (0.54 g, 2.86 mmol), anhydrous acetonitrile (55 cm^3), 4-pentenal (0.28 cm^3, 2.86 mmol) and 4Å molecular sieves (9.5 g) was stirred under nitrogen for 7 h before adding sodium cyanoborohydride (0.19 g, 2.86 mmol) and allowing to stir overnight. The reaction mixture was filtered, evaporated to dryness and 4 M hydrochloric acid added until the pH of the solution was 2 then the aqueous mixture washed with ethyl acetate (3 x 20 cm^3). Anhydrous potassium carbonate was then added until the pH was raised to 10 and the organics extracted with ethyl acetate (4 x 20 cm^3). The organic fractions were combined, washed with brine (saturated, 1 x 20 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness. Purification using flash column chromatography (5 % ethyl acetate/ dichloromethane) gave the N-*(pent-4-enyl)*-L-tert-*leucine* tert-*butyl ester* **128h** (0.15 g, 20 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3343, 2977, 2959, 2934 and 1725; δ_H (400 MHz, $CDCl_3$) 5.83 (1 H, ddt, *J* 17.0, 10.3, 6.6 Hz, =CH), 5.05-4.94 (2 H, m, $=CH_2$), 2.73 (1 H, s, CHN), 2.62-2.57 (1 H, m, C*H*HN), 2.45-2.39 (1 H, m, CH*H*N), 2.12-2.08 (2 H, m, $CH_2C=C$), 1.57-1.50 (3 H, m, $CH_2CH_2CH_2$ + NH), 1.49 (9 H, s, ester Me_3) and 0.97 (9 H, s, amino acid Me_3); δ_C (100 MHz, $CDCl_3$) 175.10 (CO_2), 139.03 (=CH), 114.87 ($=CH_2$), 81.10 (CO), 71.45 (CHN), 48.60 (CH_2N), 34.26 ($C(Me)_3$), 31.79 ($CH_2C=C$), 29.74 ($CH_2CH_2CH_2$), 28.60 (ester Me_3) and 27.20 (amino acid Me_3); *m/z* 256.2273 [MH^+ (5

%), $C_{15}H_{30}NO_2$ requires 256.2276], 154 (100), 142 (54), 88 (15), 69 (23), 57 (17) and 41 (19).

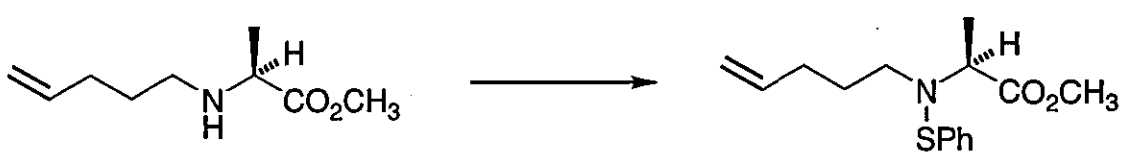
60. Attempted synthesis of *N*-(pent-4-enyl)-*L*-alanine benzyl ester



1) A mixture of *L*-alanine benzyl ester hydrochloride (4.03 g, 18.70 mmol), freshly activated 4Å molecular sieves (19 g), 4-penten-1-al (1.90 cm^3, 18.70 mmol) and sieve dried methanol (50 cm^3) was cooled to 0-5 °C in an ice bath before adding sodium cyanoborohydride (2.47 g, 37.40 mmol) and stirring for 1 h. The reaction was returned to room temperature and stirred for 2 h, filtered and evaporated to dryness. Hydrochloric acid (1 M)was added (pH reduced to 2) followed by anhydrous potassium carbonate (pH increased to 10) and the aqueous mixture was extracted with ethyl acetate (3 x 25 cm^3). The organic solvent was dried ($MgSO_4$), filtered and evaporated to dryness to give a colourless oil (4.98 g). Flash column chromatography (40 % ethyl acetate/hexane) gave several products. ^1H NMR spectroscopy indicated benzyl alcohol as the major product. *Trans*-esterification appeared to have occurred resulting in an inseparable mixture of amino acid substrates.

2) A mixture of *L*-alanine benzyl ester hydrochloride (1.11 g, 5.17 mmol), freshly activated 4Å molecular sieves (6 g), sieve dried acetonitrile (50 cm^3), 4-penten-1-al (0.53 cm^3, 5.17 mmol) and sodium cyanoborohydride (0.68 g, 10.33 mmol) was reacted as detailed in the previous reaction. The reaction was stirred for 3.5 h at room temperature before work-up gave a green oil (1.59 g). Flash column chromatography gave several products. ^1H NMR spectroscopy indicated no *trans*-esterification but benzyl alcohol was still the major product. The number of impurities were still high.

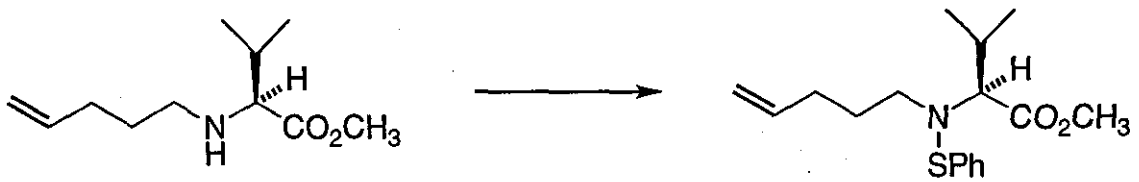
61. *N*-(Benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-alanine methyl ester (131a)



(128a) **(131a)**

A solution of *N*-(pent-4-enyl)-*L*-alanine **128a** (0.83 g, 4.87 mmol) and triethylamine (16 cm^3, >20 equivalents, dried over KOH) in anhydrous diethyl ether (40 cm^3) was cooled to 0-5 °C in an ice bath under nitrogen using oven dried glassware. Benzenesulfenyl chloride was added dropwise until thin layer chromatography indicated that conversion was complete. The reaction mixture was filtered and the filtrate evaporated to dryness to give a yellow oil. Purification by flash column chromatography (50 % dichloromethane/light petroleum + 2 % triethylamine) gave the N-*(benzenesulfenyl)*-N-*(pent-4-enyl)*-L-*alanine methyl ester* **131a** (1.00 g, 74 %) as a yellow oil; υ_{max}/cm^{-1} (neat) 3073, 2988, 2949, 2863 and 1741; δ_H (400 MHz, $CDCl_3$) 7.28 (4 H, s, ArH), 7.10-7.06 (1 H, m, ArH), 5.80-5.70 (1 H, ddt, *J* 17.0, 10.2 and 6.6 Hz, =CH), 4.99-4.90 (2 H, m, $=CH_2$), 3.88 (1 H, q, *J* 7.1 Hz, CHN), 3.71 (3 H, s, OCH_3), 3.17-3.10 and 3.05-2.98 (2 x 1 H, m, CH_2N), 2.06-2.01 (2 H, m, $CH_2C=C$), 1.75-1.67 (2 H, m, $CH_2CH_2CH_2$) and 1.45 (3 H, d, *J* 7.1 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 173.84 (CO_2), 143.20 (Ar-C), 138.09 (=CH), 128.40 (*m* - Ar-CH), 124.74 (*o* - Ar-CH), 122.64 (*p* - Ar-CH), 114.70 ($=CH_2$), 64.25 (OCH_3), 57.51 (CH_2N), 51.65 (CHN), 31.06 ($CH_2C=C$), 27.85 ($CH_2CH_2CH_2$) and 16.62 (CH_3); *m/z* 279.1293 [M^+ (60 %), $C_{15}H_{21}NO_2S$ requires 279.1293], 220 (100), 166 (15), 152 (14), 109 (37) and 56 (15).

62. *N*-(Benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-valine methyl ester (131b)

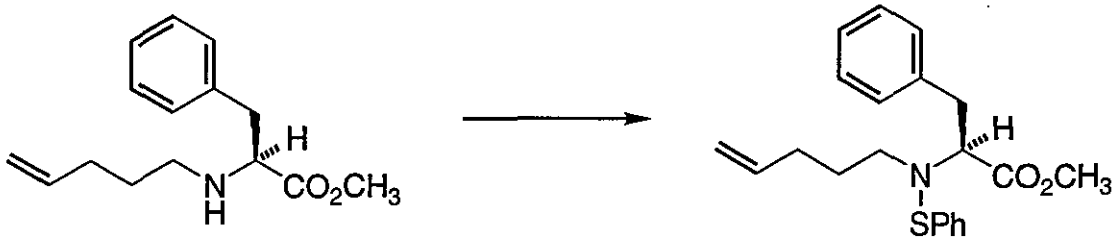


(128b) **(131b)**

A solution of *N*-(pent-4-enyl)-*L*-valine methyl ester **128b** (1.00 g, 4.99 mmol) and triethylamine (14 cm^3, 20 equivalents, dried over KOH) in anhydrous diethyl ether (40 cm^3) were cooled to 0-5 °C in an ice bath under nitrogen using oven dried glassware. Benzenesulfenyl chloride was added dropwise until thin layer chromatography indicated that conversion was complete. This was filtered and evaporated to dryness to give a yellow oil. Purification by flash column chromatography (40 % dichloromethane/light petroleum + 2 % triethylamine) gave the N-*(benzenesulfenyl)*-N-*(pent-4-enyl)*-L-*valine methyl ester* **131b** (1.19 g, 78 %) as a yellow oil; υ_{max}/cm^{-1} (neat) 3077, 2965, 2874, 1738, 739 and 693; δ_H (400 MHz, $CDCl_3$) 7.26 (4 H, s, ArH), 7.13-7.06 (1 H, m, ArH), 5.82-5.72 (1 H, ddt, *J* 16.9, 10.3 and 6.7 Hz, =CH), 5.01-4.92 (2 H, m, $=CH_2$), 3.63 (3 H, s, OCH_3), 3.30 (1 H, d, *J* 9.9 Hz, CHN), 3.08 (2 H, ddd, *J* 8.7, 7.0, 1.8 Hz, CH_2N), 2.30-2.21 (1 H, m, $CHMe_2$), 2.07-2.01 (2 H, m,

$CH_2C{=}C$), 1.84-1.65 (2 H, m, $CH_2CH_2CH_2$), 1.01 (3 H, d, *J* 6.7 Hz, CH_3) and 0.87 (3 H, d, *J* 6.6 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 173.10 (CO_2), 142.01 (Ar-C), 138.06 (=CH), 128.42 (*m* - Ar-CH), 125.16 (*o* - Ar-CH), 123.78 (*p* - ArCH), 114.71 ($=CH_2$), 76.05 (OCH_3), 55.67 (CH_2N), 51.14 (CHN), 31.05 ($CH_2C{=}C$), 28.94 ($CHMe_2$), 27.71 ($CH_2CH_2CH_2$), 20.37 (CH_3) and 19.40 (CH_3); *m/z* 307.1613 [M^+ (31 %), $C_{17}H_{25}NO_2S$ requires 307.1606], 264 (20), 248 (100), 210 (15), 109 (23), 69 (12) and 41 (21).

63. *N*-(Benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-phenylalanine methyl ester (131c)



(128c) **(131c)**

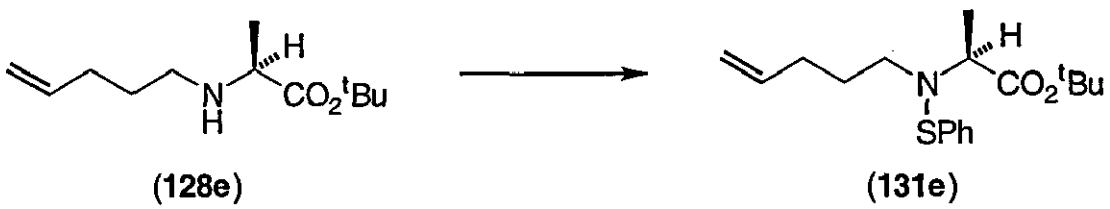
A solution of *N*-(pent-4-enyl)-*L*-phenylalanine methyl ester **128c** (1.00 g, 4.06 mmol) and triethylamine (12 cm^3, >20 equivalents, dried over KOH) in anhydrous diethyl ether (50 cm^3) was cooled to -15 °C in an acetone/dry ice bath under nitrogen using oven dried glassware. Benzenesulfenyl chloride was added dropwise until thin layer chromatography indicated that conversion was complete. The reaction mixture was stirred at room temperature for 1 h, filtered and the filtrate evaporated to dryness to give an orange oil. Purification by flash column chromatography (30 % dichloromethane/light petroleum + 2 % triethylamine) gave N-*(benzenesulfenyl)*-N-*(pent-4-enyl)*-L-*phenylalanine methyl ester* **131c** (1.29 g, 90 %) as a pale yellow oil; υ_{max}/cm^{-1} (neat) 3062, 2949, 2860 and 1736; δ_H (400 MHz, $CDCl_3$) 7.31-7.10 (10 H, m, ArH), 5.82-5.72 (1 H, ddt, *J* 17.0, 10.2 and 6.6 Hz, =CH), 5.03-4.95 (2 H, m, $=CH_2$), 4.08 (1 H, dd, *J* 8.3, 6.9 Hz, CHN), 3.62 (3 H, s, OCH_3), 3.31-3.26 (1 H, m, J_{ABX} 14.1, 8.3, 6.8 Hz, PhC*H*H), 3.20-3.08 (3 H, m, PhCH*H*+CH_2N), 2.03-1.99 (2 H, m, $CH_2C{=}C$), 1.72-1.62 (2 H, m, $CH_2CH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 173.25 (CO_2), 142.59 (Ar-C-S), 138.54 (=CH), 138.27 (Ar-C), 129.78, 129.64, 126.91, 125.43, 123.75 (Ar-CH), 115.21 ($=CH_2$), 71.32 (CHN), 52.07 (OCH_3), 47.94 (CH_2N), 37.29 ($PhCH_2$), 31.21 ($CH_2C{=}C$) and 28.06 ($CH_2CH_2CH_2$); *m/z* 355.1605 [M^+ (8 %), $C_{21}H_{25}NO_2S$ requires 355.1606], 296 (15), 264 (39), 218 (53), 188 (17), 156 (56), 109 (100), 91 (44), 77 (21), 65 (45), 51 (23) and 41 (81).

64. *N*-(Benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-*tert*-leucine methyl ester (131d)

(128d) **(131d)**

A solution of *N*-(pent-4-enyl)-*L*-*tert*-leucine **128d** (0.33 g, 1.55 mmol) and triethylamine (4.4 cm^3, >20 equivalents, dried over KOH) in anhydrous diethyl ether (40 cm^3) was cooled to -15 °C in an acetone/dry ice bath under nitrogen using oven dried glassware. Benzenesulfenyl chloride was added dropwise until thin layer chromatography indicated that conversion was complete. The reaction mixture was stirred at room temperature for 1 h, filtered and the filtrate evaporated to dryness to give an orange oil. Purification using flash column chromatography (30 % dichloromethane/light petroleum + 2 % triethylamine) gave N-*(benzene-sulfenyl)*-N-*(pent-4-enyl)*-L-tert-*leucine methyl ester* **131d** (0.40 g, 80 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3075, 2952, 2868 and 1737; δ_H (400 MHz, $CDCl_3$) 7.32-7.29 (4 H, m, ArH), 7.18-7.14 (1 H, m, ArH), 5.87-5.77 (1 H, ddt, *J* 16.9, 10.2 and 6.6 Hz, =CH), 5.06-4.96 (2 H, m, $=CH_2$), 3.69 (3 H, s, OCH_3), 3.65 (1 H, s, CHN), 3.29-3.13 (2 H, m, CH_2N), 2.10-2.04 (2 H, m, $CH_2C=C$), 1.90-1.77 (2 H, m, $CH_2CH_2CH_2$) and 1.10 (9 H, s, Me_3); δ_C (100 MHz, $CDCl_3$) 172.02 (CO_2), 141.68 (Ar-C-S), 138.15 (=CH), 128.35, 125.49, 124.45 (Ar-CH), 114.69 ($=CH_2$), 79.10 (CHN), 56.83 (CH_2N), 50.93 (OCH_3), 35.69 (CMe_3), 31.06 ($CH_2C=C$), 28.03 ($CH_2CH_2CH_2$) and 27.86 (Me_3); *m/z* 321.1765 [M^+ (35 %), $C_{18}H_{27}NO_2S$ requires 321.1762], 264 (100), 210 (43), 136 (15), 118 (11), 109 (47), 96 (20), 69 (45), 57 (30) and 41 (97).

65. *N*-(Benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-alanine *tert*-butyl ester (131e)

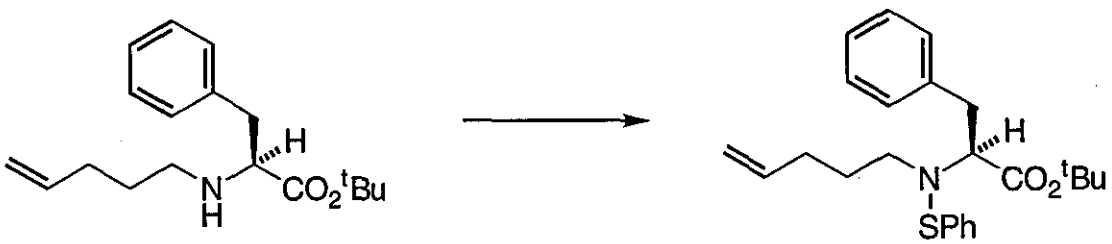


(128e) **(131e)**

A solution of *N*-(pent-4-enyl)-*L*-alanine *tert*-butyl ester **128e** (0.59 g, 2.76 mmol) and triethylamine (8 cm^3, >20 equivalents, dried over KOH) in anhydrous diethyl ether (40 cm^3) was cooled to -15 °C in an acetone/dry ice bath under nitrogen using oven

dried glassware. Benzenesulfenyl chloride was added dropwise until thin layer chromatography indicated that conversion was complete. The reaction mixture was stirred at room temperature for 1 h before filtering and evaporating to dryness to give an orange oil. Purification by flash column chromatography (20 % dichloromethane/light petroleum + 2 % triethylamine) gave N-*(benzenesulfenyl)*-N-*(pent-4-enyl)*-L-*alanine* tert-*butyl ester* **131e** (0.62 g, 70 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3074, 2979, 2935 and 1731; δ_H (400 MHz, $CDCl_3$) 7.31 (4 H, s, ArH), 7.12-7.08 (1 H, m, ArH), 5.83-5.73 (1 H, ddt, *J* 17.0, 10.2 and 6.6 Hz, =CH), 5.02-4.93 (2 H, m, $=CH_2$), 3.78 (1 H, q, *J* 7.2 Hz, CHN), 3.18 (1 H, m, C*H*HN), 3.07-3.00 (1 H, m, CH*H*N), 2.10-2.04 (2 H, m, $CH_2C=C$), 1.78-1.72 (2 H, m, $CH_2CH_2CH_2$), 1.52 (9 H, s, Me_3) and 1.44 (3 H, d, *J* 7.1 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 173.29 (CO_2), 144.34 (Ar-C-S), 138.67 (=CH), 128.84, 124.94, 122.71 (Ar-CH), 115.12 ($=CH_2$), 81.72 (CO), 65.43 (CHN), 47.95 (CH_2N), 31.63 ($CH_2C=C$), 28.51 (Me_3), 28.34 ($CH_2CH_2CH_2$) and 17.06 (CH_3); *m/z* 321.1761 [M^+ (8 %), $C_{18}H_{27}NO_2S$ requires 321.1762], 220 (100), 109 (22), 57 (23) and 41 (29).

66. *N*-(Benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-phenylalanine *tert*-butyl ester (131g)



(128g) **(131g)**

A solution of *N*-(pent-4-enyl)-*L*-phenylalanine *tert*-butyl ester **128g** (0.52 g, 1.81 mmol) and triethylamine (6 cm^3, >20 equivalents, dried over KOH) in anhydrous diethyl ether (30 cm^3) was cooled to -15 °C in an acetone/dry ice bath under nitrogen using oven dried glassware. Benzenesulfenyl chloride was added dropwise until thin layer chromatography indicated that conversion was complete. The reaction mixture was stirred at room temperature for 1 h before filtering and evaporating to dryness to give an orange oil. Purification using flash column chromatography (5 % dichloromethane/light petroleum + 2 % triethylamine) gave N-*(benzenesulfenyl)*-N-*(pent-4-enyl)*-L-*phenylalanine* tert-*butyl ester* **131g** (0.62 g, 86 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3062, 3029, 2977, 2932, 2863 and 1732; δ_H (400 MHz, $CDCl_3$) 7.29-7.07 (10 H, m, ArH), 5.83-5.72 (1 H, ddt, *J* 17.0, 10.2 and 6.7 Hz, =CH), 5.02-4.94 (2 H, m, $=CH_2$), 3.99 (1 H, t, *J* 7.5 Hz, CHN), 3.25 (1 H, dd, *J* 14.1, 7.3 Hz,

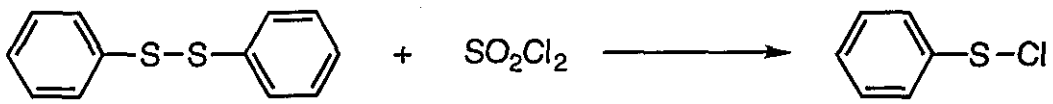
PhC*H*H), 3.16-3.08 (3 H, m, PhCH*H*+CH_2N), 2.06-2.01 (2 H, m, CH_2C=C), 1.78-1.63 (2 H, m, $CH_2CH_2CH_2$) and 1.44 (9 H, s, Me_3); δ_C (100 MHz, $CDCl_3$) 172.12 (CO_2), 143.45 (Ar-C-S), 138.59 (=CH), 138.45 (Ar-C), 129.76, 128.76, 128.64, 126.76, 125.06, 123.13 (Ar-CH), 115.13 (=CH_2), 81.94 (CO), 71.89 (CHN), 48.91 (CH_2N), 37.46 ($PhCH_2$), 31.55 (CH_2C=C), 28.40 (Me_3) and 28.06 ($CH_2CH_2CH_2$); *m/z* 397.2050 [MH^+ (7 %), $C_{24}H_{31}NO_2S$ requires 397.2075], 296 (44), 188 (29), 110 (50), 91 (69), 57 (72), 41 (100) and 29 (24).

67. Benzenesulfenyl chloride (132) (method 1)[114]

(132)

To a solution of benzenethiol (30 cm^3) in light petroleum (300 cm^3) under nitrogen was bubbled through chlorine gas. Initially, a white solid formed which slowly dissolved to an orange red solution. Chlorine was bubbled through for a further 10 min before flushing nitrogen through the system for 30 min. The light petroleum was distilled off and the resulting red solution distilled under reduced pressure (56 °C at 2 mmHg) to give benzenesulfenyl chloride **132** in excellent yield as a red liquid. No further purification was necessary; υ_{max}/cm^{-1} (neat) 3061, 1879, 1474 and 1440; δ_H (250 MHz, $CDCl_3$) 7.62 (2 H, m, ArH) and 7.35 (3 H, m, ArH); δ_C (62.9 MHz, $CDCl_3$) 135.54 (Ar-C-S), 131.68, 130.18 and 129.35 (Ar-CH).

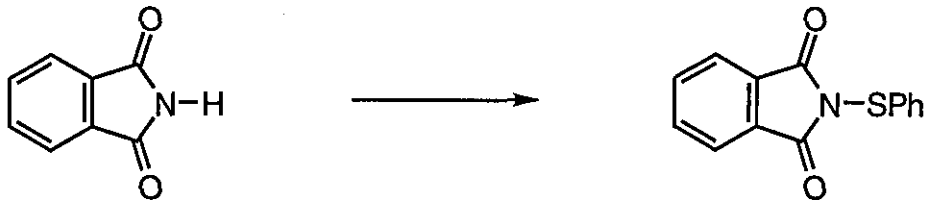
68. Benzenesulfenyl chloride (132) (method 2)[115]



(132)

To a solution of diphenyl disulfide (1.36 g, 6.14 mmol) in anhydrous dichloromethane (25 cm^3) under nitrogen was added pyridine (1 drop, catalytic). A 1.0 M dichloromethane solution of sulfuryl chloride (6.8 cm^3, 1.1 equivalents) was syringed in before refluxing the mixture for 30 min. On cooling, the resultant red dichloromethane solution contained benzenesulfenyl chloride **132** (12.28 mmol) and was used without further purification.

69. *N*-(Benzenesulfenyl)phthalimide[88]



Benzenesulfenyl chloride (34.6 g, 0.31 mol) was added dropwise over 20 min to a solution of phthalimide (45.6 g, 0.31 mol) and triethylamine (37.6 g, 0.37 mol) in anhydrous diethyl ether (200 cm^3). The resultant mixture was filtered and evaporated to dryness to give a white solid. Recrystallisation from ethanol yielded pure *N*-(benzenesulfenyl)phthalimide (41.9 g, 53 %) as white crystals, m.p. 158-160 °C (lit.[154] 160-161 °C); υ_{max}/cm^{-1} (Nujol mull) 1605, 1465, 715 and 685; δ_H (250 MHz, $CDCl_3$) 7.84-7.77 (4 H, m, phthalimide Ar-H) and 7.25-7.20 (5 H, m, SPh Ar-H).

70. Reaction between *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-alanine methyl ester (131a) and tri-*n*-butyltin hydride

(131a) **(133a)**

A solution of *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-alanine methyl ester **131a** (773 mg, 2.77 mmol) in anhydrous toluene (300 cm^3) was refluxed under nitrogen for 1 h before injecting a solution of tri-*n*-butyltin hydride (1.15 cm^3, 4.15 mmol) and AMBN (277 mg, 1.38 mmol) in anhydrous toluene (25 cm^3) over 6 h using a syringe pump. The reaction was cooled and stirred overnight at room temperature. After evaporating to low volume, the amine products were extracted into hydrochloric acid (6 M, 10 cm^3) and washed with diethyl ether (3 x 5 cm^3). Anhydrous potassium carbonate (pH increased to 10) was added and the free amines extracted with dichloromethane (3 x 5 cm^3). The organic solution was dried ($MgSO_4$), filtered and evaporated to dryness to give a yellow oil. Purification using flash column chromatography (40 % ethyl acetate/light petroleum) gave the major cyclised diastereomer *methyl 2(S)-2-(2-methyltetrahydro-1H-1-pyrrolyl)propanoate* **133a** (20

mg, 5 % isolated yield) as a pale yellow oil; υ_{max}/cm^{-1} (neat) 2962, 2872 and 1738; δ_H (400 MHz, $CDCl_3$) 3.65 (3 H, s, OCH_3), 3.61 (1 H, q, *J* 7.2 Hz, CHN), 3.02-2.97 (1 H, m, ring CHN), 2.77-2.69 (2 H, m, CH_2N), 1.92-1.83 (1 H, m, C*H*HCHN), 1.42-1.33 (1 H, m, CH*H*CHN), 1.78-1.61 (2 H, m, $CH_2CH_2CH_2$), 1.33 (3 H, d, *J* 7.2 Hz, CH_3) and 1.04 (3 H, d, *J* 6.1 Hz, ring CH_3); δ_C (100.6 MHz, $CDCl_3$) 175.56 (CO_2), 58.00 (CHN), 57.59 (ring CHN), 52.75 (OCH_3)), 49.00 (CH_2N), 35.06 ($CH_2CH(Me)N$), 23.85 ($CH_2CH_2CH_2$), 20.94 (CH_3) and 18.93 (ring CH_3); *m/z* 171. 1266 [M^+ (12 %), $C_9H_{17}NO_2$ requires 171.1259], 112 (100), 91 (18), 69 (24) and 41 (20).

GC/MS and ^1H NMR (internal standard, dinitrobenzene) of the crude gave yields of cyclised material as 52 % major diastereomer, 30 % minor diastereomer (d.e. = 27) and a yield of 11 % for uncyclised product.

71. Reaction between *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-valine methyl ester (131b) and tri-*n*-butyltin hydride

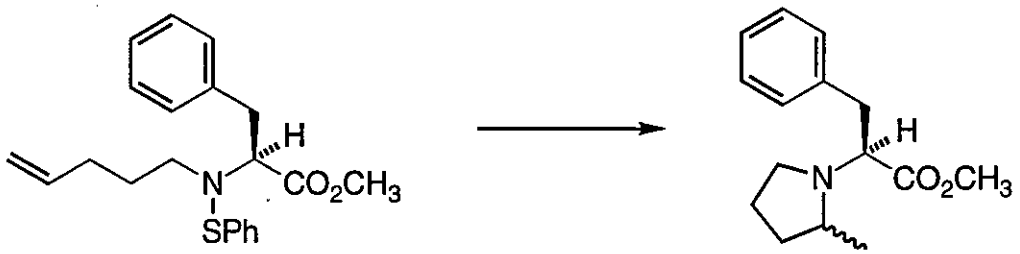
(131b) **(133b)**

A solution of *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-valine methyl ester **131b** (491 mg, 1.60 mmol) in anhydrous toluene (300 cm^3) was refluxed under nitrogen for 1 h before injecting a solution of tri-*n*-butyltin hydride (1.00 cm^3, 3.73 mmol) and AMBN (178 mg, 0.90 mmol) in anhydrous toluene (25 cm^3) over 6 h using a syringe pump. The reaction was cooled and stirred overnight at room temperature. After evaporating to dryness, the amine products were extracted into hydrochloric acid (6 M, 10 cm^3) and washed with diethyl ether (3 x 5 cm^3). Anhydrous potassium carbonate (pH increased to 10) was added and the free amines extracted with dichloromethane (3 x 5 cm^3). The organic solution was dried ($MgSO_4$), filtered and evaporated to dryness to give a yellow oil. Purification using TLC neutral alumina column chromatography (50 % dichloromethane/light petroleum) gave the major cyclised diastereomer *methyl 2(S)-3-methyl-2-(2-methyltetrahydro-1H-1-pyrrolyl) butanoate* **133b** (30 mg, 9 % isolated yield) as a pale yellow oil; υ_{max}/cm^{-1} (neat) 2962, 2872 and 1734; δ_H (400 MHz, $CDCl_3$) 3.66 (3 H, s, OCH_3), 3.01 (1 H, d, *J* 10.5 Hz, CHN), 2.93-2.84 (1 H, m, ring CHN), 2.74-2.62 (1 H, m, C*H*HN), 2.56-2.46 (1 H, m, CH*H*N), 2.06-1.94 (1 H, m, C*H*HCHN), 1.89-1.76 (2 x 1 H, m, CH*H*CHN + $CHMe_2$), 1.41-1.22 (2 H, m, $CH_2CH_2CH_2$), 1.05 (3 H, d, *J* 5.9 Hz, ring CH_3), 0.97 (3 H, d, *J* 6.6 Hz, CH_3) and

0.87 (3 H, d, *J* 6.5 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 173.14 (CO_2), 67.84 (CHN), 56.34 (OCH_3), 50.71 (ring CHN), 46.37 (CH_2N), 33.34 ($CH_2CH(Me)N$), 28.74 ($CHMe_2$), 23.85 ($CH_2CH_2CH_2$), 20.46 (ring CH_3), 20.07 (CH_3) and 19.52 (CH_3); *m/z* 199.1575 [M^+ (6 %), $C_{11}H_{21}NO_2$ requires 199.1572], 156 (46), 140 (100), 124 (12), 110 (11), 96 (8), 84 (14), 69 (20) and 41 (32).

GC/MS and ^1H NMR (internal standard, dinitrobenzene) of the crude gave yields of cyclised material as 52 % major diastereomer, 19 % minor diastereomer (d.e. = 46) and a yield of 27 % for uncyclised product.

72. Reaction between *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-phenylalanine methyl ester (131c) and tri-*n*-butyltin hydride



(131c) **(133c)**

A solution of *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-phenylalanine methyl ester **131c** (528 mg, 1.49 mmol) in anhydrous toluene (280 cm^3) was refluxed under nitrogen for 1 h before injecting a solution of tri-*n*-butyltin hydride (0.55 cm^3, 1.98 mmol) and AMBN (149 mg, 0.74 mmol) in anhydrous toluene (20 cm^3) over 5 h using a syringe pump. The reaction was cooled and stirred overnight at room temperature. After evaporating to dryness, hydrogen chloride solution (1 M in diethyl ether, 10 cm^3) was added and the tin compounds removed using flash column chromatography (diethyl ether). The amine products were recovered off the column, once TLC indicated no further tin impurities, by eluting with 10 % triethylamine/diethyl ether. The fractions obtained were combined and evaporated to dryness to give a yellow oil (257 mg). Purification using flash column chromatography (5 % ethyl acetate/light petroleum) gave the major cyclised diastereomer *methyl 2(S)-2-(2-methyltetrahydro-1H-1-pyrrolyl)-3-phenylpropanoate* **133c** (43 mg, 12 % isolated yield) as a pale yellow oil; υ_{max}/cm^{-1} (neat) 2961, 2892 and 1732; δ_H (400 MHz, $CDCl_3$) 7.32-7.20 (5 H, m, ArH), 3.80 (1 H, dd, *J* 9.2, 6.1 Hz, CHN), 3.61 (3 H, s, OCH_3), 3.19-3.11 (2 H, m, C*H*HN + PhC*H*H), 3.01-2.97 (1 H, dd, J_{ABX} 13.4, 6.1 Hz, PhCH*H*), 2.88-2.82 (1 H, dt, *J* 16.8, 8.4 Hz, CH*H*N), 2.72-2.67 (1 H, m, ring CHN), 1.96-1.88 (1 H, m, C*H*HCH(Me)N), 1.80-1.69 (2 H, m, $CH_2CH_2CH_2$), 1.45-1.36 (1

H, m, CH*H*CH(Me)N) and 1.06 (3 H, d, *J* 6.0 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 171.42 (CO_2), 137.74 (Ar-C), 128.18, 127.37, 125.44 (Ar-CH), 61.90 (CHN), 55.45 (OCH_3), 49.83 (ring CHN), 46.19 (CH_2N), 36.77 ($PhCH_2$), 32.09 ($CH_2CH(Me)N$), 21.10 ($CH_2CH_2CH_2$) and 18.00 (CH_3); *m/z* 247.1573 [M^+ (3 %), $C_{15}H_{21}NO_2$ requires 247.1572], 188 (62), 156 (100), 91 (15), 69 (15) and 41 (24).

GC/MS and ^1H NMR (internal standard, dinitrobenzene) of the crude gave yields of cyclised material as 48 % major diastereomer, 18 % minor diastereomer (d.e. = 46) and a yield of 34 % for uncyclised product.

73. Reaction between *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L-tert*-leucine methyl ester (131d) and tri-*n*-butyltin hydride

(131d) **(133d)**

A solution of *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L-tert*-leucine methyl ester **131d** (212 mg, 0.66 mmol) in anhydrous toluene (300 cm^3) was refluxed under nitrogen for 1 h before injecting a solution of tri-*n*-butyltin hydride (0.24 cm^3, 0.88 mmol) and AMBN (66 mg, 0.33 mmol) in anhydrous toluene (25 cm^3) over 6 h using a syringe pump, then cooled and stirred overnight at room temperature. After evaporating to dryness, hydrogen chloride solution (1 M in diethyl ether, 10 cm^3) was added and the tin compounds removed using flash column chromatography (diethyl ether). The amine products were recovered off the column, once TLC indicated no further tin impurities, by eluting with 10 % triethylamine/diethyl ether. The fractions obtained were combined and evaporated to dryness to give a yellow oil (80 mg). Purification using flash column chromatography (5 % ethyl acetate/light petroleum) gave the cyclised compound *methyl 2(S)-3,3-dimethyl-2-(2-methyl tetrahydro-1H-1-pyrrolyl)butanoate* **133d** (5 mg, 4 % isolated yield) as a pale yellow oil; υ_{max}/cm^{-1} (neat) 2962, 2884 and 1733; δ_H (400 MHz, $CDCl_3$) 3.65 (3 H, s, OCH_3), 3.13 (1 H, s, CHN), 3.08-2.99 (1 H, m, ring CHN), 2.79-2.71 (2 H, m, CH_2N), 2.12-2.04 (1 H, m, C*H*HCHN), 1.71-1.62 (1 H, m, CH*H*CHN), 1.50-1.33 (2 H, m, $CH_2CH_2CH_2$), 0.98 (3 H, d, *J* 6.0 Hz, ring CH_3) and 0.89 (9 H, s, Me_3); δ_C (100.6 MHz, $CDCl_3$) 172.56 (CO_2), 73.19 (CHN), 52.44 (OCH_3), 50.52 (ring CHN), 47.32 (CH_2N), 33.71 ($CH_2CH(Me)N$), 31.92 (CMe_3), 25.04 ($CH_2CH_2CH_2$), 24.92 (Me_3) and 19.24 (ring CH_3); *m/z* 213.1725 [M^+

(3 %), $C_{12}H_{23}NO_2$ requires 213.1729], 156 (100), 154 (48), 124 (16), 96 (11), 69 (22) and 41 (13).

GC/MS and ^1H NMR (internal standard, dinitrobenzene) of the crude gave yields of cyclised material as 35 % major diastereomer, 24 % minor diastereomer (*d.e.* = 20) and a yield of 41 % for uncyclised product.

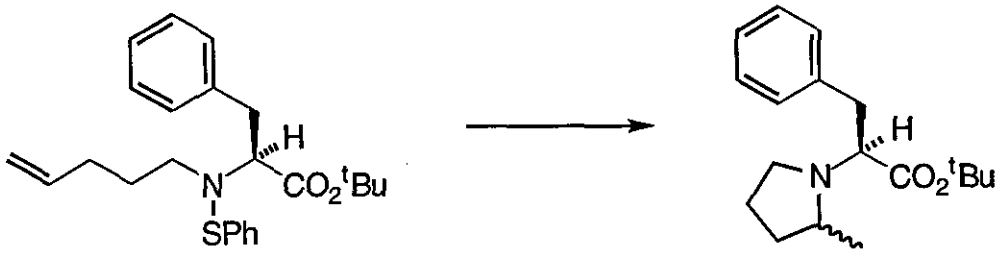
74. Reaction between *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-alanine *tert*-butyl ester (131e) and tri-*n*-butyltin hydride

(131e) **(133e)**

A solution of *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-alanine *tert*-butyl ester **131e** (311 mg, 0.97 mmol) in anhydrous toluene (280 cm^3) was refluxed under nitrogen for 1 h. A solution of tri-*n*-butyltin hydride (0.36 cm^3, 1.29 mmol) and AMBN (97 mg, 0.48 mmol) in anhydrous toluene (20 cm^3) was added by injection over 5 h using a syringe pump. The reaction was refluxed for a further hour, cooled and stirred overnight at room temperature. After evaporating to dryness, hydrogen chloride solution (1 M in diethyl ether, 10 cm^3) was added and the tin compounds removed using flash column chromatography (diethyl ether). The amine products were recovered off the column, once TLC indicated no further tin impurities, by eluting with 10 % triethylamine/diethyl ether. The fractions obtained were combined and evaporated to dryness to give a yellow oil (132 mg). Purification using flash column chromatography (10 % ethyl acetate/light petroleum) gave the major cyclised diastereomer tert-*butyl 2(S)2-(2-methyltetrahydro-1*H*-1-pyrrolyl) propanoate* **133e** (18 mg, 9 % isolated yield) as a pale yellow oil; υ_{max}/cm^{-1} (neat) 2968, 2873 and 1725; δ_H (400 MHz, $CDCl_3$) 3.46 (1 H, q, *J* 7.2 Hz, CHN), 2.98-2.92 (1 H, dt, *J* 8.7, 4.2 Hz, C*H*HN), 2.81-2.74 (2 H, m, CH*H*N+ring CHN), 1.88-1.81 (1 H, m, C*H*HCH(Me)N), 1.67-1.56 (2 H, m, $CH_2CH_2CH_2$), 1.43-1.36 (1 H, m, CH*H*CH(Me)N), 1.39 (9 H, s, Me_3), 1.26 (3 H, d, *J* 7.3 Hz, CH_3) and 1.02 (3 H, d, *J* 6.0 Hz,ring CH_3); δ_C (100.6 MHz, $CDCl_3$) 173.13 (CO_2), 80.95 (CO), 56.49 (CHN), 56.44 (ring CHN), 46.98 (CH_2N), 33.57 ($CH_2CH(Me)N$), 28.70 (Me_3), 22.32 ($CH_2CH_2CH_2$), 19.30 (CH_3) and 17.62 (ring CH_3); *m/z* (CI) 214.1807 [MH^+ (25 %), $C_{12}H_{24}NO_2$ requires 214.1807], 212 (61), 192 (37), 156 (26), 112 (28), 86 (43), 84 (100) and 46 (34).

GC/MS and ^{1}H NMR (internal standard, dinitrobenzene) of the crude gave yields of cyclised material as 58 % major diastereomer, 23 % minor diastereomer (*d.e.* = 45) and a yield of 19 % for uncyclised product.

75. Reaction between *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-phenylalanine *tert*-butyl ester (131g) and tri-*n*-butyltin hydride

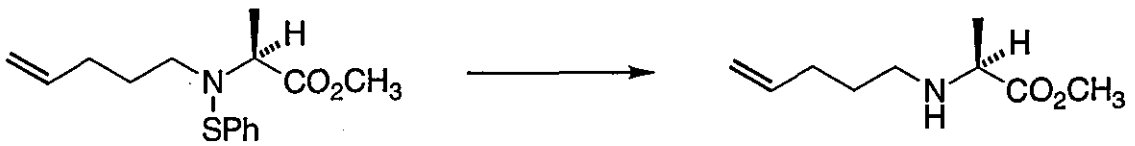


(131g) **(133g)**

A solution of *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-phenylalanine *tert*-butyl ester **131g** (317 mg, 0.80 mmol) in anhydrous toluene (280 cm^3) was refluxed under nitrogen for 1 h. A solution of tri-*n*-butyltin hydride (0.30 cm^3, 1.06 mmol) and AMBN (80 mg, 0.40 mmol) in anhydrous toluene (20 cm^3) was added by injection over 5 h using a syringe pump, refluxed for a further hour then cooled and stirred overnight at room temperature. After evaporating to dryness, hydrogen chloride solution (1 M in diethyl ether, 10 cm^3) was added and the tin compounds removed using flash column chromatography (diethyl ether). The amine products were recovered off the column, once TLC indicated no further tin impurities, by eluting with 10 % triethylamine/diethyl ether. The fractions obtained were combined and evaporated to dryness to give a yellow oil (159 mg). Purification using flash column chromatography (4 % ethyl acetate/light petroleum) gave the major cyclised diastereomer tert-*butyl 2(S)-2-(2-methyltetrahydro-1H-1-pyrrolyl)-3-phenyl propanoate* **133g** (25 mg, 11 % isolated yield) as a pale yellow oil; υ_{max}/cm^{-1} (neat) 2967, 2870 and 1723; δ_H (400 MHz, $CDCl_3$) 7.29-7.21 (5 H, m, ArH), 3.68 (1 H, dd, *J* 9.6, 5.9 Hz, CHN), 3.16-3.10 (2 H, m, C*H*HN + PhC*H*H), 2.97-2.91 (2 H, m, PhCH*H*+ CH*H*N), 2.82-2.75 (1 H, m, ring CHN), 1.95-1.86 (1 H, m, C*H*HCH(Me)N), 1.84-1.64 (3 H, m, $CH_2CH_2CH_2$+CH*H*CH(Me)N), 1.37 (9 H, s, Me_3) and 1.08 (3 H, d, *J* 6.0 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) 171.48 (CO_2), 139.79 (Ar-C), 129.62, 128.46, 126.54 (Ar-CH), 81.08 (CO), 63.43 (CHN), 56.58 (ring CHN), 47.12 (CH_2N), 38.13 ($PhCH_2$), 33.37 ($CH_2CH(Me)N$), 28.60 (Me_3), 22.36 ($CH_2CH_2CH_2$) and 19.14 (CH_3); *m/z* (CI) 290.2120 [MH$^+$ (30 %), $C_{18}H_{28}NO_2$ requires 290.2120], 188 (27), 168 (20), 86 (28), 84 (60), 74 (26), 58 (33), 46 (100) and 44 (39).

GC/MS and ^{1}H NMR (internal standard, dinitrobenzene) of the crude gave yields of cyclised material as 64 % major diastereomer, 23 % minor diastereomer (*d.e.* = 27) and a yield of 12 % for uncyclised product.

76. Reaction between *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-alanine (131a) and *tris*(trimethylsilyl)silane



(131a) **(128a)**

A solution of *N*-(benzenesulfenyl)-*N*-(pent-4-enyl)-*L*-alanine methyl ester **131a** (485 mg, 1.74 mmol) in anhydrous toluene (250 cm^3) was refluxed under nitrogen for 1 h before injecting a solution of *tris*(trimethylsilyl)silane (0.66 cm^3, 2.08 mmol) and AMBN (174 mg, 0.87 mmol) in anhydrous toluene (25 cm^3) over 6 h using a syringe pump. The reaction was cooled and stirred overnight at room temperature before evaporating to dryness to give a yellow oil. GC/MS and ^{1}H NMR (internal standard, dinitrobenzene) of the crude gave yields of cyclised material as 21 % major diastereomer, 7 % minor diastereomer (*d.e.* = 50) and a yield of 72 % for uncyclised product. Isolation of the products was unnecessary.

5.4 Experimental for Chapter Three

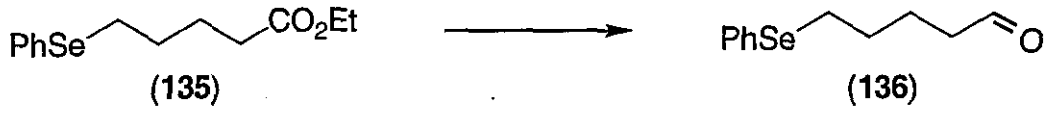
77. Ethyl 5-benzeneselenylpentanoate (135)[98]

(135)

To a solution of diphenyl diselenide (3.96 g, 12.43 mmol) in absolute ethanol (100 cm^3) at 0-5 °C (ice bath) under nitrogen was added sodium borohydride (1.44 g, 37.30 mmol) and the reaction stirred for 30 min. A solution of ethylbromovalerate (5.78 g, 27.35 mmol) in absolute ethanol (10 cm^3) was syringed in and the reaction stirred overnight before quenching with 2 M hydrochloric acid (10 cm^3) and evaporating to low volume. The solution was extracted with diethyl ether (3 x 10 cm^3) and the ether extracts combined, washed with sodium hydrogencarbonate solution

(saturated, 1 x 10 cm^3) and brine (saturated, 1 x 10 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness. Purification using flash column chromatography (30 % dichloromethane/light petroleum) yielded ethyl 5-benzeneselenylpentanoate **135** (7.26 g, 100 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3057, 2935, 1736, 1576, 1477, 1437 and 739; δ_H (250 MHz, $CDCl_3$) 7.47 (2 H, m, *ortho* ArH), 7.24 (3 H, m, ArH), 4.10 (2 H, q, *J* 7.1 Hz, CH_2O), 2.90 (2 H, t, *J* 7.0 Hz, CH_2Se), 2.29 (2 H, t, *J* 7.1 Hz, CH_2CO_2), 1.76-1.70 (4 H, m, CH_2CH_2Se + $CH_2CH_2CO_2$) and 1.23 (3 H, t, *J* 7.1 Hz, CH_3); δ_C (62.9 MHz, $CDCl_3$) 173.15 (CO_2), 132.46 (Ar-CH), 130.20 (Ar-C), 128.97, 126.68 (Ar-CH), 60.19 (CH_2O), 33.65 (CH_2CO_2), 29.52 (CH_2Se), 27.21 (CH_2CH_2Se), 25.03 ($CH_2CH_2CO_2$) and 25.03 (CH_3); *m/z* 286.0460 [M^+ (9 %), $C_{13}H_{18}O_2Se$ requires 286.0472], 157 (15), 129 (75), 101 (92), 83 (48), 77 (27) and 55 (70).

78. 5-Benzeneselenylpentanal (136)[98]



(135) **(136)**

To a solution of 1.0 M DIBAL-H (18.37 cm^3, 18.37 mmol) in anhydrous toluene (25 cm^3) at -78 °C (acetone/dry ice bath) under nitrogen was added a solution of ethyl 5-benzeneselenylpentanoate **135** (2.10 g, 7.35 mmol) in anhydrous toluene (10 cm^3) ensuring that the internal reaction temperature never rose above -65 °C. The reaction was stirred at -78 °C until thin layer chromatography indicated that no starting material was present. A solution of acetic acid (1.06 cm^3, 18.37 mmol) in anhydrous toluene (10 cm^3) was added dropwise (reaction kept below -65 °C), the reaction warmed to 0 °C and distilled water (5 cm^3) added before warming to room temperature. Sodium carbonate was added until no effervescence was observed then ethyl acetate (30 cm^3) was added and the reaction mixture filtered before evaporating to dryness. Purification using flash column chromatography (dichloromethane) yielded 5-benzeneselenylpentanal **136** (1.70 g, 96 %) as a pale green oil; υ_{max}/cm^{-1} (neat) 3055, 2937, 1720, 1577, 1479 and 1439; δ_H (250 MHz, $CDCl_3$) 9.72 (1 H, s, CHO), 7.48 (2 H, m, *ortho* ArH), 7.25 (3 H, m, ArH), 2.89 (2 H, t, *J* 7.6 Hz, CH_2Se), 2.42 (2 H, t, *J* 6.9 Hz, CH_2CHO) and 1.75-1.68 (4 H, m, CH_2CH_2Se + $CH_2CH_2CO_2$); δ_C (62.9 MHz, $CDCl_3$) 202.03 (CO), 132.58 (Ar-CH), 130.20 (Ar-C), 129.02, 126.78 (Ar-CH), 43.15 (CH_2CHO), 29.46 (CH_2Se), 27.28 (CH_2CH_2Se) and 22.05 (CH_2CH_2CHO); *m/z* 242.0224 [M^+ (19 %), $C_{11}H_{13}OSe$ requires 242.0210], 158 (61), 108 (77), 91 (46), 85 (38), 79 (83), 69 (100) and 55 (46).

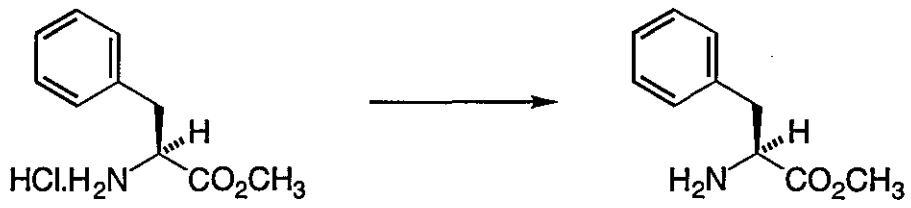
79. *L*-Valine methyl ester (137b)

(137b)

To a solution of *L*-valine methyl ester hydrochloride (1.00 g, 5.97 mmol) in distilled water (10 cm^3) was added anhydrous potassium carbonate until the pH was raised to 10. The free amine was extracted with dichloromethane (3 x 10 cm^3), the organic extracts combined, dried ($MgSO_4$), filtered and evaporated to dryness to give the *L*-valine methyl ester **137b** (0.67 g, 85 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3391, 3324, 2963, 2876 and 1738; δ_H (400 MHz, $CDCl_3$) 3.66 (3 H, s, OCH_3), 3.23 (1 H, d, *J* 5.0 Hz, CHN), 1.95 (1 H, dqq, *J* 6.9, 6.8, 5.1 Hz, $CHMe_2$), 1.38 (2 H, br, NH_2), 0.91 (3 H, d, *J* 6.9 Hz, CH_3) and 0.84 (3 H, d, *J* 6.8 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 175.86 (CO_2), 59.84 (CHN), 51.49 (OCH_3), 32.02 ($CHMe_2$), 19.09 (CH_3) and 17.06 (CH_3); *m/z* 131.0946 [M^+ (3 %), $C_6H_{13}NO_2$ requires 131.0946], 88 (80), 72 (100) and 55 (60).

The data was consistent with that previously reported in the literature.[155]

80. *L*-Phenylalanine methyl ester (137c)

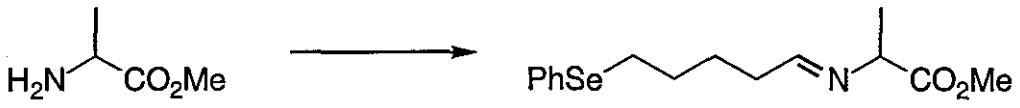


(137c)

To a solution of *L*-phenylalanine methyl ester hydrochloride (1.50 g, 6.95 mmol) in distilled water (30 cm^3) was added sodium hydrogencarbonate until effervescence ceased. The amine was extracted into dichloromethane (3 x 15 cm^3), the organic fractions were then combined, washed with distilled water (1 x 20 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness to give the *L*-phenylalanine methyl ester **137c** (1.25 g, 100 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3378, 3310, 3029, 2952, 1736, 747 and 702; δ_H (250 MHz, $CDCl_3$) 7.32-7.15 (5 H, m, ArH), 3.72 (1 H, dd, *J* 7.8, 5.3 Hz, CHN), 3.69 (3 H, s, OCH_3), 3.07 (1 H, dd, *J* 13.5, 5.2 Hz, PhC*H*H), 2.84 (1 H, dd, *J* 13.5, 7.9 Hz, PhCH*H*) and 1.52 (2 H, s, NH_2); δ_C (62.9 MHz, $CDCl_3$) 175.32 (ester CO_2), 137.15 (Ar-C), 129.18, 128.47 and 126.73 (Ar-CH), 55.73 (CHN), 51.86 (OCH_3) and 40.99 ($PhCH_2$).

The data was consistent with that previously reported in the literature.[136]

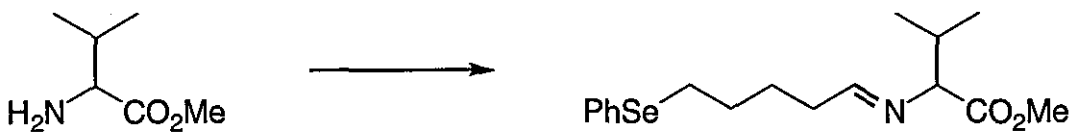
81. Methyl (2*S*)-2-[5-(benzeneselenylpentylidene)amino]propanoate (138a)



(138a)

A mixture of *L*-alanine methyl ester (0.18 g, 1.70 mmol) and 5-benzeneselenylpentan-1-al (0.24 g, 1.01 mmol) was stirred for 1 h before adding dichloromethane (3 cm^3). The solution was dried ($MgSO_4$), filtered and evaporated to dryness to give crude methyl (2*S*)-2-[5-(benzeneselenylpentylidene)amino] propanoate **138a** (0.30 g) as a pale green oil. No further purification was attempted as ^1H NMR spectroscopy indicated that the imine had been made.

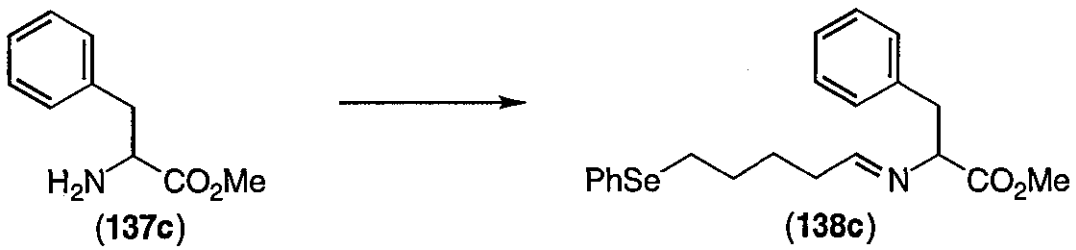
82. Methyl (2*S*)-3-methyl-2-[5-(benzeneselenylpentylidene)amino]butanoate (138b)



(137b) **(138b)**

A mixture of *L*-valine methyl ester **137b** (0.15 g, 1.16 mmol) and 5-benzeneselenylpentan-1-al (0.27 g, 1.11 mmol) was stirred for 1 h before adding dichloromethane (3 cm^3). The solution was dried ($MgSO_4$), filtered and evaporated to dryness to give crude methyl (2*S*)-3-methyl-2-[5-(benzeneselenylpentylidene) amino]butanoate **138b** (0.39 g) as a pale green oil. No further purification was required as ^1H NMR spectroscopy indicated that only trace amounts of starting material were present; υ_{max}/cm^{-1} (neat) 3071, 3056, 2958, 2870, 1736 and 1663; δ_H (400 MHz, $CDCl_3$) 7.59 (1 H, t, *J* 5.1 Hz, CH=N), 7.49-7.44 (2 H, m, ArH), 7.28-7.23 (3 H, m, ArH), 3.73 (3 H, s, OCH_3), 3.40 (1 H, d, *J* 7.2 Hz, CHN), 2.91 (2 H, t, *J* 6.9 Hz, CH_2Se), 2.37-2.27 (2 H, m, CH_2CH=N), 1.81-1.66 (5 H, m, CH_2CH_2Se + CH_2CH_2CH=N + $CHMe_2$), 0.88 (3 H, d, *J* 6.8 Hz, CH_3) and 0.85 (3 H, d, *J* 6.8 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 176.29 (CO_2), 143.65 (CH=N), 140.04 (Ar-C-Se), 133.00, 130.69, 127.16 (Ar-CH), 80.74 (CHN), 60.35 (OCH_3), 35.64 (CH_2Se), 31.74 ($CHMe_2$), 30.15 (CH_2CH=N), 27.83 (CH_2CH_2Se), 26.57 (CH_2CH_2CH=N), 18.98 (CH_3) and 17.64 (CH_3); *m/z* 356.0059 [MH^+ (10 %), $C_{17}H_{26}NO_2Se$ requires 356.1128], 296 (18), 225 (16), 198 (31), 170 (14), 138 (19), 132 (20), 88 (35), 72 (100) and 55 (47).

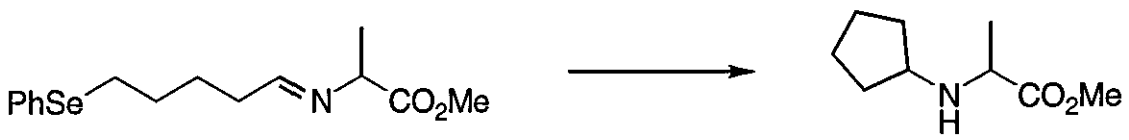
83. Methyl (2*S*)-3-phenyl-2-[5-(benzeneselenylpentylidene)amino]propanoate (138c)



(137c) **(138c)**

A mixture of *L*-phenylalanine methyl ester **137c** (0.18 g, 1.00 mmol) and 5-benzeneselenylpentan-1-al (0.25 g, 1.03 mmol) was stirred for 1 h before adding dichloromethane (3 cm^3). The solution was dried ($MgSO_4$), filtered and evaporated to dryness to give crude methyl (2*S*)-3-phenyl-2-[5-(benzeneselenylpentylidene) amino]propanoate **138c** (0.41 g) as a pale green oil. No further purification was attempted as ^1H NMR spectroscopy indicated that the imine had been made.

84. Reaction between methyl (2*S*)-2-[5-(benzeneselenylpentylidene)amino] propanoate (138a) and tri-*n*-butyltin hydride

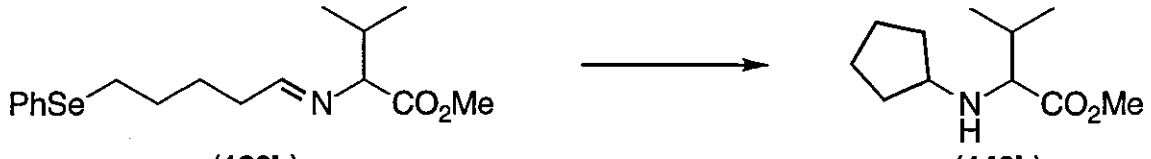


(138a) **(140a)**

A solution of methyl (2*S*)-2-[5-(benzeneselenylpentylidene)amino]propanoate **138a** (0.30 g, 0.90 mmol) in anhydrous toluene (200 cm^3) was deoxygenated at room temperature for 90 min before heating to reflux and injecting a solution of tri-*n*-butyltin hydride (0.33 cm^3, 1.20 mmol) and AMBN (0.09 g, 0.45 mmol) in anhydrous toluene (20 cm^3) over 5 h using a syringe pump. The reaction was cooled then stirred overnight before adding 6 M hydrochloric acid (20 cm^3) and stirring for 2 h. The layers were separated and the organic layer extracted further with 6 M hydrochloric acid (2 x 10 cm^3). The acid fractions were combined, the pH raised to 10 with anhydrous potassium carbonate and the free amine extracted with dichloromethane (3 x 10 cm^3). The organic fractions were combined, dried ($MgSO_4$), filtered and evaporated to dryness. Purification using flash column chromatography (80 % ethyl acetate /light petroleum) gave N-*cyclopentyl*-L-*alanine methyl ester* **140a** (0.07 g, 45 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3330, 2954, 2870 and 1738; δ_H

(400 MHz, $CDCl_3$) 3.65 (3 H, s, OCH_3), 3.32 (1 H, q, *J* 6.9 Hz, CHN), 2.94 (1 H, pentet, *J* 6.8 Hz, ring CHN), 1.83-1.68 (2 x 1 H, m, $CH_{A1}H_{A2}CHN + CH_{B1}H_{B2}CHN$), 1.67-1.56 (2 x 1 H, m, $CH_{C1}H_{C2}CH_2CHN + CH_{D1}H_{D2}CH_2CHN$), 1.51-1.42 (2 x 1 H, m, $CH_{C1}H_{C2}CH_2CHN + CH_{D1}H_{D2}CH_2CHN$), 1.34-1.18 (2 x 1 H, m, $CH_{A1}H_{A2}CHN + CH_{B1}H_{B2}CHN$), 1.20 (3 H, d, J 6.9 Hz, CH_3) and 0.84 (1 H, br, NH); δ_C (100 MHz, $CDCl_3$) 177.18 (CO_2), 58.41 (CHN), 55.77 (ring CHN), 52.12 (OCH_3), 33.99 (C_AH_2CHN), 33.21 (C_BH_2CHN), 24.36 ($C_CH_2CH_2CHN$), 24.31 ($C_DH_2CH_2CHN$) and 19.99 (CH_3); *m/z* 172.1340 [MH^+ (10 %), $C_9H_{18}NO_2$ requires 172.1337], 112 (100), 84 (12), 44 (57) and 41 (16).

85. Reaction between methyl (2*S*)-3-methyl-2-[5-(benzeneselenylpentylidene) amino]butanoate (138b) and tri-*n*-butyltin hydride

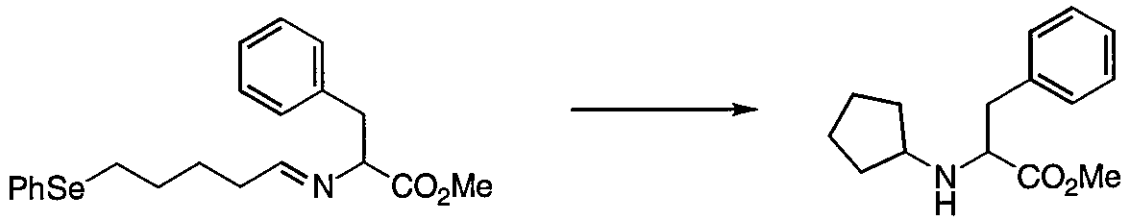


(138b) **(140b)**

A solution of methyl (2*S*)-3-methyl-2-[5-(benzeneselenylpentylidene)amino] butanoate **138b** (0.36 g, 1.02 mmol) in anhydrous toluene (200 cm^3) was deoxygenated at room temperature for 90 min before heating to reflux and injecting a solution of tri-*n*-butyltin hydride (0.33 cm^3, 1.20 mmol) and AMBN (0.09 g, 0.45 mmol) in anhydrous toluene (20 cm^3) over 5 h using a syringe pump. The reaction was cooled, stirred overnight and evaporated to dryness. Diethyl ether (5 cm^3) and 6 M hydrochloric acid (5 cm^3) were added and the ether layer was extracted further with 6 M hydrochloric acid (2 x 3 cm^3). The acid fractions were combined, washed with diethyl ether (3 x 5 cm^3) then the pH raised to 10 with the addition of anhydrous potassium carbonate before extracting with dichloromethane (4 x 5 cm^3). The organic fractions were combined, dried ($MgSO_4$), filtered and evaporated to dryness. Purification using flash column chromatography (40 % ethyl acetate/ dichloromethane) gave N-*cyclopentyl*-L-*valine methyl ester* **140b** (0.14 g, 68 %) as a pale yellow oil, $[\alpha]_D^{25}$ -13.58 (c = 3.00, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3332, 2957, 2871 and 1737; δ_H (400 MHz, $CDCl_3$) 3.64 (3 H, s, OCH_3), 2.93 (1 H, d, *J* 6.2 Hz, CHN), 2.86 (1 H, pentet, *J* 5.9 Hz, ring CHN), 1.76 (1 H, octet, *J* 6.6 Hz, $CHMe_2$), 1.75-1.55 (4 x 1 H, m, $CH_{A1}H_{A2}CHN + CH_{B1}H_{B2}CHN + CH_{C1}H_{C2}CH_2CHN + CH_{D1}H_{D2}CH_2CHN$), 1.51-1.37 (2 x 1 H, m, $CH_{C1}H_{C2}CH_2CHN + CH_{D1}H_{D2}CH_2CHN$), 1.29-1.17 (2 x 1 H, m, $CH_{A1}H_{A2}CHN + CH_{B1}H_{B2}CHN$), 0.86 (3 H, d, *J* 6.2 Hz, CH_3) and 0.84 (3 H, d, *J* 6.5 Hz,

CH_3); δ_C (100 MHz, $CDCl_3$) 176.74 (CO_2), 66.45 (CHN), 58.82 (ring CHN), 51.71 (OCH_3), 34.21 (C_AH_2CHN), 32.94 (C_BH_2CHN), 32.13 ($CHMe_2$), 24.27 ($C_CH_2CH_2CHN$), 24.18 ($C_DH_2CH_2CHN$), 19.51 (CH_3) and 19.20 (CH_3); *m/z* 200.1609 [M^+ (96 %), $C_{11}H_{22}NO_2$ requires 200.1650], 156 (68), 140 (100), 88 (62), 72 (69), 55 (31), 41 (39), 28 (19) and 15 (20).

86. Reaction between methyl (2*S*)-3-phenyl-2-[5-(benzeneselenylpentylidene) amino]propanoate (138c) and tri-*n*-butyltin hydride

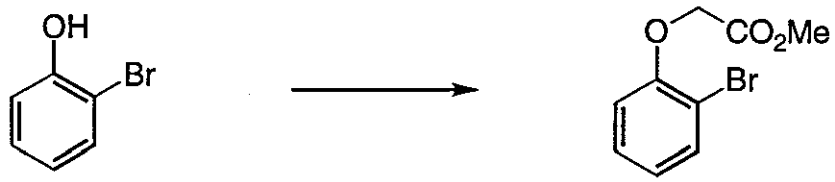


(138c) **(140c)**

A solution of methyl (2*S*)-3-phenyl-2-[5-(benzeneselenylpentylidene)amino] propanoate **138c** (0.41 g, 1.01 mmol) in anhydrous toluene (200 cm^3) was deoxygenated at room temperature for 90 min before heating to reflux and injecting a solution of tri-*n*-butyltin hydride (0.37 cm^3, 1.34 mmol) and AMBN (0.10 g, 0.50 mmol) in anhydrous toluene (20 cm^3) over 5 h using a syringe pump. The reaction was cooled, stirred overnight and evaporated to dryness. Diethyl ether (5 cm^3) and 6 M hydrochloric acid (5 cm^3) were added and the ether layer was extracted further with 6 M hydrochloric acid (2 x 3 cm^3). The acid fractions were combined, washed with diethyl ether (3 x 5 cm^3) and the pH raised to 10 with the addition of anhydrous potassium carbonate before extracting with dichloromethane (4 x 5 cm^3).The organic fractions were combined, dried ($MgSO_4$), filtered and evaporated to dryness. Purification using flash column chromatography (40 % ethyl acetate/ dichloromethane) gave N-*cyclopentyl*-L-*phenylalanine methyl ester* **140c** (0.11 g, 45 %) as a pale yellow oil, $[\alpha]_D^{25}$ +13.49 (c = 1.80, $CHCl_3$); υ_{max}/cm^{-1} (neat) 3319, 2952, 2868 and 1737; δ_H (400 MHz, $CDCl_3$) 7.22-7.09 (5 H, m, ArH), 3.54 (3 H, s, OCH_3), 3.48 (1 H, t, *J* 7.1 Hz, CHN), 2.91 (1 H, pentet, *J* 6.6 Hz, ring CHN), 2.86 (2 H, t, *J* 7.0 Hz, $PhCH_2$), 1.89 (1 H, br, NH), 1.79-1.47 (4 x 1 H, m, $CH_{A1}H_{A2}CHN$ + $CH_{B1}H_{B2}CHN$ + $CH_{C1}H_{C2}CH_2CHN$ + $CH_{D1}H_{D2}CH_2CHN$), 1.46-1.35 (2 x 1 H, m, $CH_{C1}H_{C2}CH_2CHN$ + $CH_{D1}H_{D2}CH_2CHN$) and 1.30-1.12 (2 x 1 H, m, $CH_{A1}H_{A2}CHN$ + $CH_{B1}H_{B2}CHN$); δ_C (100 MHz, $CDCl_3$) 175.87 (CO_2), 137.78 (Ar-C), 129.52, 128.70, 127.04 (Ar-CH), 62.32 (CHN), 58.57 (ring CHN), 55.18 (OCH_3), 40.42 ($PhCH_2$), 33.98 (C_AH_2CHN), 32.83 (C_BH_2CHN), 24.14 ($C_CH_2CH_2CHN$) and 24.11 ($C_DH_2CH_2CHN$); *m/z* 248.1664 [M^+ (44

%), $C_{15}H_{22}NO_2$ requires 248.1650], 188 (38), 156 (100), 120 (34), 88 (78), 69 (26) and 41 (39).

87. Methyl 2-(*o*-bromophenoxy)ethanoate (144)

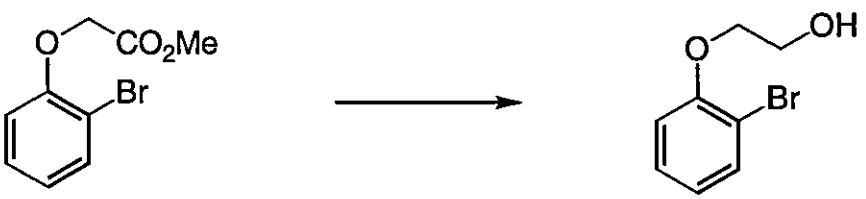


(144)

To a solution of 2-bromophenol (3.95 g, 22.37 mmol) in anhydrous acetonitrile (10 cm^3) under nitrogen was added sodium hydride (freshly washed in light petroleum) until effervescence ceased. The reaction mixture was evaporated to dryness to give a cream solid and then a solution of methyl bromoacetate (3.71 g, 23.49 mmol) in anhydrous acetonitrile (10 cm^3) was syringed in under nitrogen. After stirring overnight, the mixture was filtered through celite and evaporated to dryness to give methyl 2-(*o*-bromophenoxy)ethanoate **144** (5.13g, 94 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3066, 3003, 2953, 2850 and 1763; δ_H (400 MHz, $CDCl_3$) 7.56 (1 H, dd, *J* 7.9, 1.5 Hz, ArH *ortho* to Br), 7.25 (1 H, dt, *J* 8.1, 1.6 Hz, ArH *para* to O), 6.90 (1 H, dt, *J* 7.6, 1.2 Hz, ArH *para* to Br), 6.81 (1 H, dd, *J* 8.2, 1.1 Hz, ArH *ortho* to O), 4.72 (2 H, s, CH_2O) and 3.81 (3 H, s, CH_3O); δ_C (100 MHz, $CDCl_3$) 168.45 (CO_2), 154.12 (Ar-C-O), 133.66 (Ar-CH *ortho* to Br), 128.36 (Ar-CH *para* to O), 123.04 (Ar-CH *para* to Br), 113.66 (Ar-CH *ortho* to O), 112.40 (Ar-C-Br), 66.19 (CH_2O) and 52.23 (CH_3O); *m/z* 244.7435 [M^+ (52 %), $C_9H_{10}BrO_2$ requires 244.9814], 246 (50), 185 (29), 165 (100), 157 (27), 69 (28) and 45 (34).

The compound has been previously reported in the literature.[156]

88. 2-(*o*-Bromophenoxy)ethanol (145)



(144) **(145)**

A solution of 2-(*o*-bromophenoxy)ethanoate **144** (1.03 g, 4.18 mmol) in anhydrous diethyl ether (20 cm^3) was cooled to 0-5 °C under nitrogen and lithium aluminium hydride (0.17 g, 4.18 mmol) added. The reaction was stirred for 1 h then 2 M sodium

hydroxide added dropwise until effervescence ceased. The mixture was filtered, dried ($MgSO_4$), filtered and evaporated to dryness to give 2-(*o*-bromophenoxy) ethanol **145** (0.79 g, 88 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3388, 3064, 2938, 2876, 1248, 1054 and 750; δ_H (400 MHz, $CDCl_3$) 7.47 (1 H, dd, *J* 7.9, 1.5 Hz, ArH *ortho* to Br), 7.19 (1 H, dt, *J* 7.7, 1.5 Hz, ArH *para* to O), 6.85 (1 H, dd, *J* 8.1, 1.2 Hz, ArH *ortho* to O), 6.79 (1 H, dt, *J* 7.7, 1.1 Hz, ArH *para* to Br), 4.07 (2 H, t, *J* 4.3 Hz, CH_2OH), 3.91 (2 H, t, *J* 4.4 Hz, CH_2O) and 2.10 (1 H, br, OH); δ_C (100 MHz, $CDCl_3$) 155.39 (Ar-C-O), 133.79 (Ar-CH *ortho* to Br), 128.97 (Ar-CH *para* to O), 122.93 (Ar-CH *para* to Br), 114.41 (Ar-CH *ortho* to O), 113.01 (Ar-C-Br), 71.21 (CH_2OH) and 61.69 (CH_2O); *m/z* 215.9788 [M^+ (25 %), $C_8H_9BrO_2$ requires 215.9786], 218 (25), 174 (72), 172 (73), 138 (31), 94 (100), 77 (29), 65 (27) and 45 (28).

The data was consistent with that previously reported in the literature.[157]

89. Attempted aldehyde formation from methyl 2-(*o*-bromophenoxy)ethanoate 144 using DIBAL-H

To a solution of 1.0 M DIBAL-H (9.32 cm^3, 9.32 mmol) in anhydrous toluene (30 cm^3) at -78 °C (acetone/dry ice bath) under nitrogen was added a solution of methyl 2-(*o*-bromophenoxy)ethanoate **144** (0.91 g, 3.73 mmol) in anhydrous toluene (10 cm^3) ensuring that the internal reaction temperature never rose above -65 °C. The reaction was stirred at -78 °C until thin layer chromatography indicated that no starting material was present. A solution of acetic acid (0.54 cm^3, 9.32 mmol) in anhydrous toluene (10 cm^3) was added dropwise (reaction kept below -65 °C), the reaction warmed to 0 °C and distilled water (5 cm^3) added before warming to room temperature. Sodium carbonate was added until effervescence ceased and then ethyl acetate (20 cm^3) was added before filtering and evaporating to dryness to give a yellow oil (1.06 g). ^1H NMR spectroscopy indicated that only a minor amount of any aldehyde was present. Impurities made purification difficult and the reaction was discontinued.

90. Attempted aldehyde formation from 2-(*o*-bromophenoxy)ethanol (145) using pyridinium chlorochromate

A solution of methyl 2-(*o*-bromophenoxy)ethanol **145** (0.81 g, 3.74 mmol) in anhydrous dichloromethane (5 cm^3) was syringed into a flask containing dried, crushed 4Å molecular sieves (5 g), pyridinium chlorochromate (0.82 g, 3.74 mmol) and anhydrous dichloromethane (25 cm^3) under nitrogen. The reaction was stirred for 1 h, filtered through celite, filtered through flash silica and evaporated to

dryness to give a thick pale yellow gum (0.28 g). The use of thin layer chromatography indicated that several products had been made. Unfortunately, there were only trace amounts of any aldehyde present (determined using ^{1}H NMR spectroscopy) and time has not permitted further investigation.

91. Attempted aldehyde formation from 2-(*o*-bromophenoxy)ethanol (145) using the Swern Oxidation

Dimethylsulfoxide (0.48 cm^3, 6.67 mmol) in anhydrous dichloromethane (3 cm^3) was added dropwise over 5 min to a solution of oxalyl chloride (0.30 cm^3, 3.34 mmol) in anhydrous dichloromethane (15 cm^3) at -78 °C. The mixture was stirred for 10 min before a solution of methyl 2-(*o*-bromophenoxy)ethanol **145** (0.66 g, 3.03 mmol) in anhydrous dichloromethane (3 cm^3) was added dropwise over 5 min. The mixture was stirred for a further 10 min and then triethylamine (2.14 cm^3, 15.17 mmol) added. After stirring for 15 min, the mixture was warmed to 0 °C then distilled water (15 cm^3) added. The layers were separated and the aqueous layer extracted further with dichloromethane (2 x 10 cm^3). The organic fractions were combined, washed with water (2 x 10 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness to give a thick colourless gum (0.52 g). The use of thin layer chromatography indicated that several products had been made. Unfortunately, there were only trace amounts of any aldehyde present (determined using ^{1}H NMR spectroscopy) and time has not permitted further investigation.

92. 2-[2-(2-Bromophenoxy)ethyl]-1,3-dioxolane (146)

(146)

To a solution of 2-bromophenol (1.08 g, 6.12 mmol) in anhydrous acetonitrile (10 cm^3) was added sodium hydride (freshly washed in light petroleum) until effervescence ceased. The reaction mixture was evaporated to dryness to give a cream solid and then a solution of 2-bromomethyl-1,3-dioxolane (0.66 cm^3, 6.12 mmol) in anhydrous acetonitrile (10 cm^3) was syringed in under nitrogen. After stirring overnight, the mixture was filtered through celite and evaporated to dryness to give 2-[2-(2-bromophenoxy)ethyl]-1,3-dioxolane **146** (1.15 g, 73 %) as a

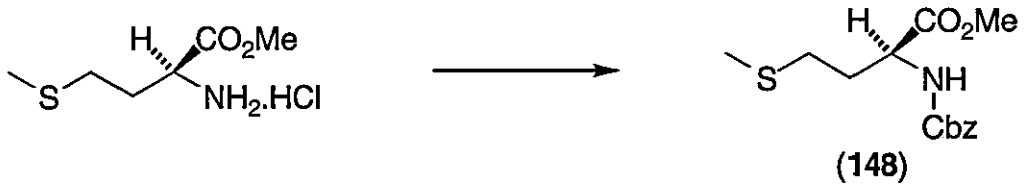
yellow oil; δ_H (400 MHz, $CDCl_3$) 7.20 (1 H, dd, *J* 7.8, 1.7 Hz, ArH *ortho* to Br), 6.82 (1 H, dt, *J* 8.0, 1.6 Hz, ArH *para* to O), 6.56 (1 H, dd, *J* 8.1, 1.5 Hz, ArH *ortho* to O), 6.12 (1 H, dt, *J* 7.8, 1.5 Hz, ArH *para* to Br), 5.06 (1 H, t, *J* 4.0 Hz, CHO), 4.02-3.94 (2 H, m, OCH_2CH_2O), 3.91-3.83 (2 H, m, OCH_2CH_2O) and 3.31 (2 H, d, *J* 4.2 Hz, OCH_2CHO); δ_C (100.6 MHz, $CDCl_3$) 164.29 (Ar-C-O), 130.60 (Ar-CH *ortho* to Br), 127.37 (Ar-CH *para* to O), 118.88 (Ar-CH *para* to Br), 113.97 (Ar-C-Br), 111.49 (Ar-CH *ortho* to O), 64. 53 (OCH_2CH_2O) and 31.36 (OCH_2CHO).

93. Hydrolysis of 2-[2-(2-bromophenoxy)ethyl]-1,3-dioxolane (146)

Concentrated hydrochloric acid (3 cm^3) was stirred with a solution of 2-[2-(2-bromophenoxy)ethyl]-1,3-dioxolane **146** in diethyl ether (5 cm^3) for 1.5 days. The layers were separated and the organic layer dried ($MgSO_4$), filtered and evaporated to dryness to give an unknown colourless oil; υ_{max}/cm^{-1} (neat) 3321, 2944 and 2873; δ_H (400 MHz, $CDCl_3$) 3.69 (2 H, t, *J* 6.33 Hz), 3.58 (2 H, t, *J* 6.42 Hz), 1.91-1.83 (2 H, m) and 1.77-1.66 (2 H, m); δ_C (100.6 MHz, $CDCl_3$) 62.08 (CH_2), 44.92 (CH_2), 29.94 (CH_2) and 29.05 (CH_2); m/z 90 (10), 84 (9), 71 (46), 55 (75), 42 (100), 41 (44) and 31 (87).

5.5 Experimental for Chapter Four

94. *N*-(Benzyloxycarbonyl)-*L*-methionine methyl ester (148)[124]

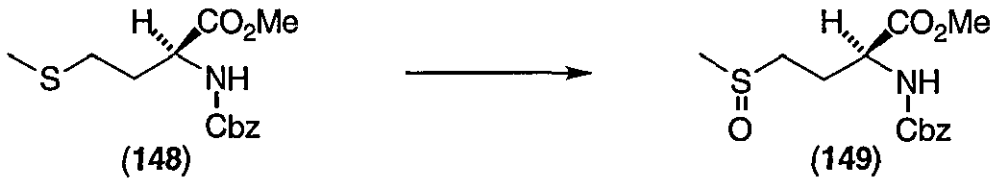


(148)

A solution of *L*-methionine methyl ester hydrochloride (10.00 g, 50.08 mmol) and sodium hydrogencarbonate (25.06 g, 0.30 mol) in distilled water (70 cm^3) and diethyl ether (70 cm^3) was cooled to 0-5 °C in an ice bath. Benzyl chloroformate (8.28 cm^3, 55.08 mmol) was added dropwise over 30 min then the reaction returned to room temperature and stirred overnight. The two layers were separated and the aqueous layer extracted further with diethyl ether (2 x 30 cm^3). The organic fractions were combined, washed with 1 M hydrochloric acid (2 x 30 cm^3), distilled water (2 x 30 cm^3) and brine (1 x 30 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness to give *N*-(benzyloxycarbonyl)-*L*-methionine methyl ester **148** (14.31 g, 96 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3336, 3033, 2953, 2918 and 1723; δ_H (400 MHz, $CDCl_3$) 7.43-7.29 (5 H, m, ArH), 5.53 (1 H, br, NH), 5.19 (2 H, s, CH_2O), 4.53 (1 H, m, CHN), 3.78 (3 H, s, OCH_3), 2.56 (2 H, t, *J* 7.3 Hz, CH_2S), 2.19-2.12 (1 H, m, *CH*HCHN), 2.06-1.97

(1 H, m, CH*H*CHN) and 2.11 (3 H, s, SCH_3); δ_C (100 MHz, $CDCl_3$) 172.77 (CO_2), 156.22 ($RNHCO_2R$), 136.51 (Ar-C), 129.03, 128.52 (Ar-CH), 67.39 (CH_2O), 53.48 (CHN), 52.81 (CH_3O), 32.28 (CH_2S), 30.20 (CH_2CHN) and 15.75 (SCH_3); *m/z* 297.1033 [M^+ (3 %), $C_{14}H_{19}NO_4S$ requires 297.1035], 162 (19), 145 (29), 91 (100) and 61 (23).

95. Methyl *L*-2-(benzyloxycarbonylamino)-4-(methylsulfinyl)butanoate (149)[124]



A solution of *N*-(benzyloxycarbonyl)-*L*-methionine methyl ester **148** (3.12 g, 10.49 mmol) in methanol (40 cm^3) was cooled to 0-5 °C in an ice bath and a solution of sodium periodate (2.49 g, 10.49 mmol) in distilled water (40 cm^3) added. The reaction was returned to room temperature, stirred overnight and then filtered through celite. Dichloromethane (30 cm^3) was added and the layers separated. The aqueous layer was extracted further with dichloromethane (2 x 20 cm^3) then the organic fractions were combined, washed with distilled water (1 x 30 cm^3) and brine (1 x 30 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness to give methyl *L*-2-(benzyloxycarbonylamino)-4-(methylsulfinyl)butanoate **149** (3.28 g, 100 %) as a thick colourless gum and as a pair of diastereomers; υ_{max}/cm^{-1} (neat) 3345, 3025, 2949, 1730, 1716 and 1063; δ_H (400 MHz, $CDCl_3$) 7.52-7.31 (5 H, m, ArH), 5.68 or 5.60 (1 H, d, *J* 6.7 Hz, NH), 5.12 (2 H, s, CH_2O), 4.50 (1 H, br, CHN), 3.78 (3 H, s, OCH_3), 2.85-2.76 or 2.74-2.64 (2 H, m, CH_2S), 2.57 or 2.56 (3 H, s, SCH_3), 2.47-2.34 (2 x 1 H, m, C*H*HCHN) and 2.24-2.09 (2 x 1 H, m, CH*H*CHN); δ_C (100 MHz, $CDCl_3$) 172.15 (CO_2), 151.82 ($RNHCO_2R$), 136.04 (Ar-C), 128.59, 128.18 (Ar-CH), 67.23 (CH_2O), 52.86 (CHN), 52.82 (CH_3O), 50.64 (CH_2S), 46.53 (CH_2CHN) and 38.63 (SCH_3); *m/z* 313.0984 [M^+ (3 %), $C_{14}H_{19}NO_5S$ requires 393.0984], 190 (8), 146 (11), 114 (18), 91 (100) and 65 (9).

96. *N*-(Benzyloxycarbonyl)-*L*-vinylglycine methyl ester (150)[124]

The methyl *L*-2-(benzyloxycarbonylamino)-4-(methylsulfinyl)butanoate **149** (8.00 g, 25.52 mmol) was placed in a Kugelrohr apparatus and distilled under reduced

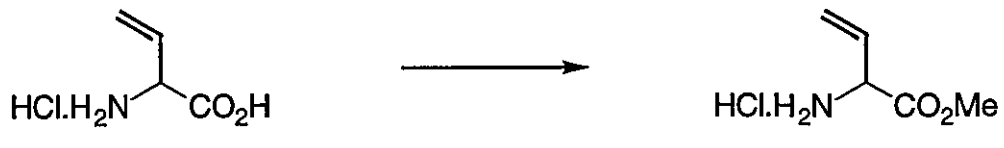
pressure (235 °C, 0.5 mmHg) into a cooled Kugelrohr bulb as a yellow oil. Purification using flash column chromatography (20 % ethyl acetate/light petroleum increasing to 35 % ethyl acetate/light petroleum) yielded *N*-(benzyloxycarbonyl)-*L*-vinylglycine methyl ester **150** (4.31 g, 68 %) as a pale yellow oil; υ_{max}/cm^{-1} (neat) 3341, 3065, 3033, 2954, 1734, 1718, 741 and 699; δ_H (400 MHz, $CDCl_3$) 7.21-7.14 (5 H, m, ArH), 5.79-5.71 (1 H, m, =CH), 5.33 (1 H, br, NH), 5.21 (1 H, dd, *J* 17.1, 1.8 Hz, =C*H*H), 5.13 (1 H, dd, *J* 10.1, 1.8 Hz, =CH*H*), 4.98 (2 H, s, CH_2O), 4.79 (1 H, br, CHN) and 3.61 (3 H, s, CH_3O); δ_C (100 MHz, $CDCl_3$) 171.29 (CO_2), 155.94 ($RNHCO_2R$), 136.56 (Ar-C), 132.72 (=CH), 128.94, 128.62, 128.54 (Ar-CH), 118.19 ($=CH_2$), 67.54 (CH_2O), 56.53 (CHN) and 53.13 (CH_3O); *m/z* 250.1079 [MH^+ (13 %), $C_{13}H_{16}NO_4$ requires 250.1079], 116 (18), 108 (23), 106 (18), 74 (57), 46 (100) and 44 (39).

97. *L*-Vinylglycine hydrochloride (153)[124]

(150) **(153)**

A mixture of *N*-(benzyloxycarbonyl)-*L*-vinylglycine methyl ester **150** (3.48 g, 13.96 mmol) and 6 M hydrochloric acid (50 cm^3) was refluxed for 2 h then cooled and washed with dichloromethane (4 x 25 cm^3). After evaporation to dryness, the solid formed was refluxed in acetone (30 cm^3) for 2 h then cooled, filtered and the solid dried under reduced pressure to give *L*-vinylglycine hydrochloride **153** (1.41 g, 73 %) as a cream solid, m.p. 182-183 °C; υ_{max}/cm^{-1} (nujol mull) 2916, 1980 and 1732; δ_H (400 MHz, D_2O) 5.98 (1 H, ddd, *J* 17.4, 10.4, 7.2 Hz, =CH), 5.58-5.53 (2 H, m, $=CH_2$) and 4.59 (1 H, d, *J* 7.3 Hz, CHN); δ_C (100 MHz, $CDCl_3$) 170.97 (CO_2), 128.38 (=CH), 123.45 ($=CH_2$) and 55.52 (CHN); *m/z* 102.0555 [$(M-Cl)^+$ (43 %), $C_4H_8NO_2$ requires 102.0555], 56 (100), 54 (26), 44 (46), 36 (68) and 28 (82).

98. *L*-Vinylglycine methyl ester hydrochloride (154)[124]



(153) **(154)**

A solution of *L*-vinylglycine hydrochloride **153** (1.38 g, 10.05 mmol) in anhydrous methanol (50 cm^3) was cooled to -20 °C before adding thionyl chloride (0.89 cm^3, 12.06 mmol) dropwise ensuring that the internal reaction temperature never rose above -10 °C. The reaction was then stirred at room temperature for 30 min before refluxing for a further 4 h. The reaction was cooled, evaporated to dryness and dichloromethane (20 cm^3) added. The resultant mixture was filtered and evaporated to dryness to give *L*-vinylglycine methyl ester **154** (1.02 g, 67 %) as a thick pale brown gum; δ_H (400 MHz, $CDCl_3$) 8.92 (3 H, br, NH_3^+), 6.09 (1 H, ddd, *J* 17.3, 10.7, 7.1 Hz, =CH), 5.72 (1 H, d, *J* 17.2 Hz, =C*H*H), 5.54 (1 H, d, *J* 10.4 Hz, =CH*H*), 4.78 (1 H, d, *J* 6.8 Hz, CHN) and 3.76 (3 H, s, OCH_3).

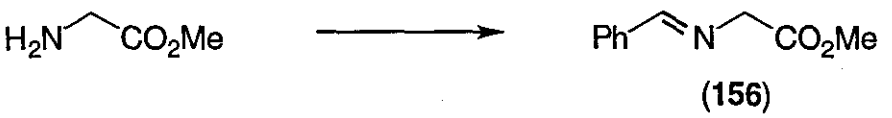
99. *N*-Alkylation of *L*-vinylglycine methyl ester hydrochloride (154)

(154) **(155)**

A mixture of *L*-vinylglycine methyl ester hydrochloride **154** (0.47 g, 3.12 mmol), freshly activated 4Å molecular sieves (5 g), 4-penten-1-al (0.32 cm^3, 3.12 mmol) and anhydrous methanol (25 cm^3) was cooled to 0-5 °C under nitrogen before adding sodium cyanoborohydride (0.21 g, 3.17 mmol). The reaction was stirred for 1 h and sodium cyanoborohydride (0.08 g, 1.2 mmol) added again. After stirring for another h, a further addition (0.05 g, 0.8 mmol) was made then the reaction returned to room temperature and stirred overnight. The reaction was filtered and evaporated to dryness then distilled water (20 cm^3) was added, the pH increased to 10 with anhydrous potassium carbonate and the organics extracted with ethyl acetate (4 x 10 cm^3). The organic fractions were combined, washed with brine (saturated, 2 x 10 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness. Purification using flash column chromatography (20 % ethyl acetate/light petroleum) yielded *methyl (2S)-2-(4-pentenylamino)butanoate* **155** (0.14 g, 25 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3332, 3077, 2934 and 1735; δ_H (400 MHz, $CDCl_3$) 5.74 (1 H, ddt, *J* 17.0, 10.3, 6.7 Hz, =CH), 4.97-4.86 (2 H, m, $=CH_2$), 3.65 (3 H, s, CH_3O), 3.11 (1 H, t, *J* 6.5 Hz, CHN), 2.56-2.49 (1 H, m, CH*H*N), 2.44-2.37 (1 H, m, C*H*HN), 2.07-1.99 (2 H, m, $CH_2C=C$), 1.65-1.43 (5 H, m, $CH_2CH_2CH_2$ + CH_2CHN + NH) and 0.86 (3 H, t, *J* 7.4 Hz, CH_3); δ_C (100 MHz, $CDCl_3$) 176.28 (CO_2), 138.74 (=CH), 115.04 ($=CH_2$), 63.21 (CHN), 51.92 (CH_3O), 48.04 (CH_2N), 31.77 ($CH_2C=C$), 29.71 ($CH_2CH_2CH_2$), 26.94 (CH_2CHN) and 10.51 (CH_3); *m/z*

185.1421 [M^+ (10 %), $C_{10}H_{19}NO_2$ requires 185.1416], 184 (21), 155 (20), 133 (22), 57 (100), 51 (26), 41 (40), 28 (29) and 18 (66).

100. Methyl 2-[(1-phenylmethylidene)amino]acetate (156)



(156)

A mixture of glycine methyl ester (20.00 g, 0.22 mol) and benzaldehyde (23.82 g, 0.22 mol) was stirred at room temperature for 3 h then dichloromethane (500 cm^3) added. The resultant solution was washed with brine (2 x 100 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness to give methyl 2-[(1-phenylmethylidene)amino] acetate **156** (37.79 g, 95 %) as a viscous pale yellow oil; υ_{max}/cm^{-1} (neat) 2953, 2880 and 1748; δ_H (250 MHz, $CDCl_3$) 8.27 (1 H, s, CH=N), 7.79-7.75 (2 H, m, Ar-H), 7.42-7.40 (3 H, m, Ar-H), 4.40 (2 H, s, CH_2) and 3.76 (3 H, s, OCH_3); δ_C (62.9 MHz, $CDCl_3$) 170.4 (CO_2), 165.3 (CH=N), 135.4 (Ar-C), 131.2, 128.5, 128.4 (Ar-CH), 61.9 (CH_2) and 52.0 (CH_3); *m/z* 178 (4), 162 (24), 118 (78), 104 (12), 91 (100), 77 (10), 74 (21) and 65 (10).

The data was consistent with that previously reported in the literature.[158]

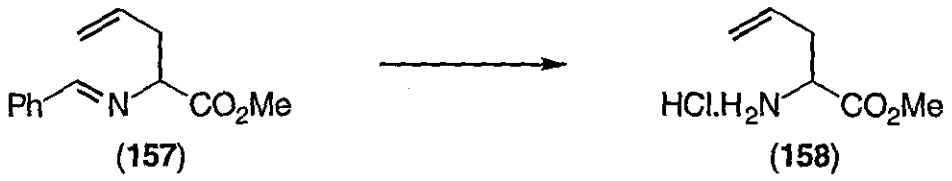
101. Methyl 2-[(1-phenylmethylidene)amino]-4-pentenoate (157)

(156) **(157)**

To a solution of methyl 2-[(1-phenylmethylidene)amino]acetate **156** (5.00 g, 28.32 mmol) in anhydrous tetrahydrofuran (100 cm^3) under nitrogen at -40 °C was added sodium hydride (0.68 g, 28.32 mmol, freshly washed in light petroleum) and the reaction temperature raised to -10 °C. After stirring for 1 h, allyl bromide (2.45 cm^3, 28.32 mmol) was added dropwise, ensuring that the temperature never rose above -5 °C, and stirred for a further 3 h at -10 °C. On returning to room temperature, the reaction was stirred overnight, filtered and evaporated to dryness to give a yellow oil (6.08 g) containing methyl 2-[(1-phenylmethylidene)amino]-4-pentenoate **157**. No further purification was attempted; δ_H (250 MHz, $CDCl_3$) 8.27 (1 H, s, CH=N), 7.68 (2 H, d, *J* 7.9 Hz, *o*-ArH), 7.45-7.34 (3 H, m, ArH), 5.75 (1 H, ddt, *J* 17.2, 10.1, 7.9 Hz, CH=C), 5.15-5.06 (2 H, m, $=CH_2$), 4.06 (1 H, dd, *J* 8.0, 5.8 Hz, CHN), 3.76 (3 H, s, OCH_3) and 1.92-1.73 (2 H, m, $CH_2C=C$).

The method has been previously reported in the literature.[159]

102. Methyl 2-amino-4-pentenoate hydrochloride (158)

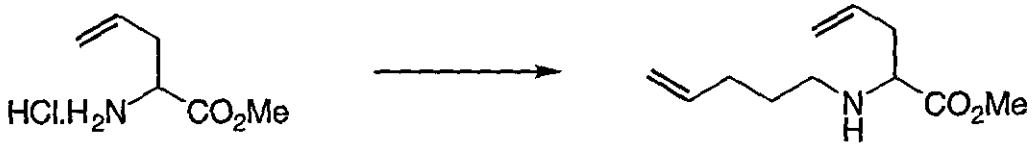


(157) **(158)**

A mixture of unpurified methyl 2-[(1-phenylmethylidene)amino]-4-pentenoate **157** (6.00 g) and 6 M hydrochloric acid (40 cm^3) was stirred for 3 h then washed with diethyl ether (3 x 20 cm^3). The aqueous solution was evaporated to low volume, methanol (10 cm^3) added and then evaporated to dryness. The addition of methanol (10 cm^3) and evaporation to dryness was repeated 3 times to give the crude hydrochloride salt **158** (4.56 g) as a brown solid.

The data was consistent with that previously reported in the literature.[160]

103. Methyl 2-(4-pentenylamino)-4-pentenoate (159)

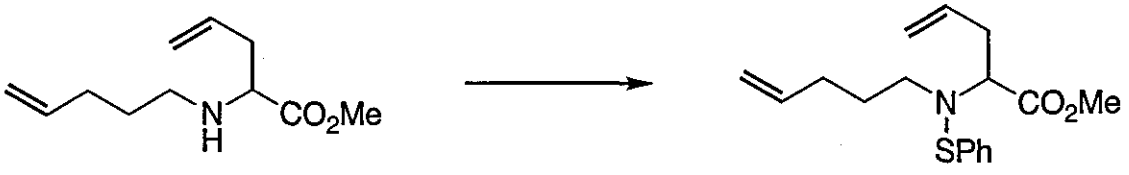


(158) **(159)**

A mixture of crude methyl 2-amino-4-pentenoate hydrochloride **158** (4.56 g, 35.06 mmol maximum), freshly activated 4Å molecular sieves (28 g), 4-penten-1-al (3.57 cm^3, 35.06 mmol) and anhydrous methanol (80 cm^3) was cooled to -20 °C in an acetone/dry ice bath under nitrogen before adding sodium cyanoborohydride (4.64 g, 70.12 mmol) and stirring for 1 h. The reaction was warmed to room temperature and stirred overnight before filtering and evaporating to dryness. Distilled water (30 cm^3) was added, the pH increased to 10 with anhydrous potassium carbonate and the organics extracted with ethyl acetate (3 x 20 cm^3). The organic extracts were dried ($MgSO_4$), filtered and evaporated to dryness. Purification using flash column chromatography (2 % ethyl acetate/dichloromethane) gave *methyl 2-(4-pentenyl-amino)-4-pentenoate* **159** (1.24 g, 22 % minimum) as a colourless oil; υ_{max}/cm^{-1} (neat) 3331, 3077, 2978, 2932, 2844 and 1737; δ_H (400 MHz, $CDCl_3$) 5.87-5.72 (2 x 1 H, m, 2 x =CH), 5.16-4.95 (2 x 2 H, m, 2 x $=CH_2$), 3.74 (3 H, s, OCH_3), 3.35 (1 H, t, *J* 6.5 Hz, CHN), 2.68-2.48 (2 H, m, CH_2N), 2.45-2.41 (2 H, m, CH_2CHN), 2.13-2.08 (2 H, m,

CH_2C=C), 1.89 (1 H, br, NH) and 1.67-1.52 (2 H, m, $CH_2CH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 175.26 (CO_2), 138.44 (amino acid =CH), 133.74 (side chain =CH), 118.13 (amino acid $=CH_2$), 114.85 (side chain $=CH_2$), 61.27 (CHN), 51.75 (OCH_3), 47.67 (CH_2N), 37.81 (CH_2CHN), 31.51 (side chain CH_2C=C) and 29.38 ($CH_2CH_2CH_2$); *m/z* 197.1413 [M^+ (8 %), $C_{11}H_{19}NO_2$ requires 197.1416], 188 (31), 142 (78), 93 (35), 79 (33), 67 (41), 55 (100), 41 (86), 27 (30) and 15 (23). The dialkylated *methyl 2-(di-4-pentenylamino)-4-pentenoate* (0.47 g, 5 %) was also isolated as a colourless oil; υ_{max}/cm^{-1} (neat) 3077, 2933, 2857 and 1736; δ_H (400 MHz, $CDCl_3$) 5.90-5.77 (3 x 1 H, m, 3 x =CH), 5.12-4.92 (3 x 2 H, m, 3 x $=CH_2$), 3.70 (3 H, s, OCH_3), 3.42 (1 H, t, *J* 7.5 Hz, CHN), 2.72-2.62 (2 x 1 H, m, 2 x *CH*HN), 2.55-2.45 (3 x 1 H, m, 2 x CH*H*N + amino acid *CH*HC=C), 2.40-2.33 (1 H, m, amino acid CH*H*C=C), 2.19-2.01 (2 x 2 H, m, 2 x side chain CH_2C=C) and 1.60-1.47 (2 x 2 H, m, side chain $CH_2CH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 173.58 (CO_2), 139.10 (amino acid =CH), 135.63 (side chain =CH), 117.09 (side chain $=CH_2$), 114.81 (amino acid $=CH_2$), 63.76 (CHN), 51.30 (CH_2N), 51.75 (OCH_3), 34.68 (CH_2CHN), 31.72 (side chain CH_2C=C) and 28.38 ($CH_2CH_2CH_2$); *m/z* 265.2037 [M^+ (56 %), $C_{16}H_{27}NO_2$ requires 265.2042], 223 (100), 205 (90), 169 (41), 115 (27), 55 (20) and 41 (86).

104. Methyl 2-[4-pentenyl(benzenesulfenyl)amino]-4-pentenoate (160)

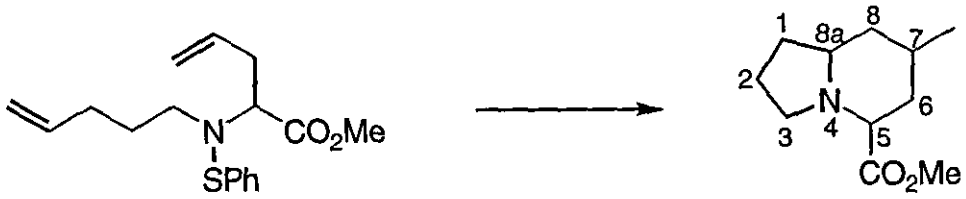


(159) **(160)**

A solution of methyl 2-(4-pentenylamino)-4-pentenoate **159** (0.86 g, 4.38 mmol) and triethylamine (12 cm^3, 20 equivalents, dried over KOH) in anhydrous diethyl ether (50 cm^3) was cooled to -15 °C in an acetone/dry ice bath under nitrogen using oven dried glassware. Benzenesulfenyl chloride (dichloromethane solution) was added dropwise until thin layer chromatography indicated that conversion was complete. The reaction mixture was stirred at room temperature for 1 h before filtering and evaporating to dryness to give an orange oil. Purification by flash column chromatography (25 % dichloromethane/light petroleum + 2 % triethylamine) gave *methyl 2-[4-pentenyl(benzenesulfenyl)amino]-4-pentenoate* **160** (1.13 g, 85 %) as a pale yellow oil; υ_{max}/cm^{-1} (neat) 3075, 2978, 2942, 2861, 1741, 739 and 692; δ_H (400 MHz, $CDCl_3$) 7.34-7.29 (4 H, m, ArH), 7.15-7.12 (1 H, m, ArH), 5.90-5.74 (2 x 1 H, m, 2 x =CH), 5.15-4.92 (2 x 2 H, m, 2 x $=CH_2$), 3.83 (1 H, dd, *J* 7.9, 6.9 Hz, CHN), 3.73 (3 H, s, OCH_3), 3.19-3.07 (2 H, m, CH_2N), 2.73-2.58 (2 H, m, CH_2CHN), 2.08 (2 H, q, *J* 7.3 Hz, CH_2C=C) and 1.78-1.72 (2 H, m, $CH_2CH_2CH_2$); δ_C (100 MHz, $CDCl_3$) 173.34 (CO_2),

142.89 (Ar-C-S), 138.55 (amino acid =CH), 134.98 (side chain =CH), 128.89, 125.19, 123.81 (Ar-CH), 117.94 (amino acid $=CH_2$), 115.25 (side chain $=CH_2$), 69.66 (CHN), 57.59 (CH_2N), 52.08 (OCH_3), 35.65 (CH_2CHN), 31.52 (side chain $CH_2C=C$) and 28.21 ($CH_2CH_2CH_2$); *m/z* 305.1458 [M^+ (55 %), $C_{17}H_{23}NO_2S$ requires 305.1449], 264 (70), 246 (45), 210 (44), 109 (48), 69 (43), 55 (25) and 41 (100).

105. Reaction between methyl 2-[4-pentenyl(benzenesulfenyl)]amino]-4-pentenoate (160) and tri-*n*-butyltin hydride



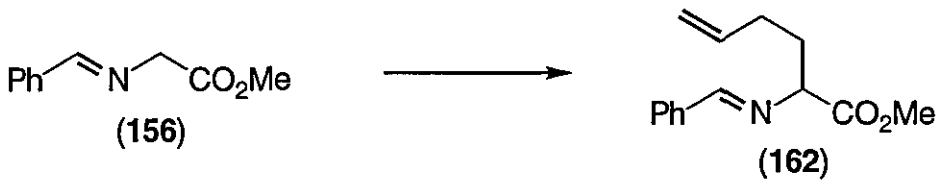
(160) **(161)**

A solution of methyl 2-[4-pentenyl(benzenesulfenyl)]amino]-4-pentenoate **160** (328 mg, 1.07 mmol) in anhydrous toluene (300 cm^3) was refluxed under nitrogen for 1 h before injecting a solution of tri-*n*-butyltin hydride (0.40 cm^3, 1.43 mmol) and AMBN (108 mg, 0.54 mmol) in anhydrous toluene (25 cm^3) over 6 h using a syringe pump. The reaction was cooled and stirred overnight at room temperature. After evaporating to low volume, the amine products were extracted into hydrochloric acid (6 M, 3 x 3 cm^3) and washed with diethyl ether (3 x 3 cm^3). Anhydrous potassium carbonate (pH increased to 10) was added and the free amines extracted with dichloromethane (4 x 3 cm^3). The organic solution was dried ($MgSO_4$), filtered and evaporated to dryness to give a yellow oil. Purification using flash column chromatography (40 % ethyl acetate/light petroleum) led to the isolation of two diastereomers of the tandem cyclised compound *methyl 7-methylperhydro-5-indolizinecarboxylate* **161**(10 mg, 5 % isolated yield and 6 mg, 3 % isolated yield respectively) as pale yellow oils; υ_{max}/cm^{-1} (neat) diastereomer 1, 2955, 2913, 2877 and 1740, diastereomer 2, 2955, 2913, 2875 and 1751; δ_H (400 MHz, $CDCl_3$) diastereomer 1, 3.65 (1 H, dd, *J* 5.9, 1.7 Hz, 5-CH), 3.50 (3 H, s, OCH_3), 2.96-2.84 (1 H, m, 8a-CH), 2.78 (1 H, dt, *J* 8.5, 3.6 Hz, 3-C*H*H), 2.60-2.54 (1 H, m, 6-C*H*H), 1.81-1.41 (6 x 1 H, m, 1-CH*H*, 2-CH_2, 3-C*H*H, 6-CH*H* and 7-CH), 1.41-1.25 (1 H, m, 8-C*H*H), 1.18-1.01 (1 H, m, 1-C*H*H), 0.74 (3 H, d, *J* 6.5 Hz, CH_3) and 0.72-0.57 (1 H, m, 8-CH*H*), diastereomer 2, 3.76 (3 H, s, OCH_3), 3.27-3.22 (1 H, m, 5-CH), 3.06 (1 H, apparent d, *J* 11.6 Hz, 8a-CH), 2.30-1.45 (11 H, m, 1-CH_2, 2-CH_2, 3-CH_2, 6-CH_2, 7-CH and 8-CH_2) and 1.06 (3 H, d, *J* 7.4 Hz, CH_3); δ_C (100.6 MHz, $CDCl_3$) diastereomer 1, 173.69 (CO_2), 58.42 (5-C), 56.24 (8a-C), 51.33 (OCH_3), 49.58 (3-C), 40.13 (8-C), 36.24 (2-C), 31.26 (1-C), 27.66 (7-C), 22.46 (CH_3)

and 21.69 (6-C), diastereomer 2, 172.62 (CO_2), 62.93 (5-C), 58.09 (8a-C), 52.56 (3-C), 52.32 (OCH_3), 36.24 (8-C), 35.93 (2-C), 30.24 (1-C), 26.74 (7-C), 20.84 (6-C) and 18.52 (CH_3); *m/z* diastereomer 1, 196.1335 [$(M-H)^+$ (3 %), $C_{11}H_{18}NO_2$ requires 196.1337], 138 (100), 96 (65), 69 (84), 54 (22), 41 (74), 27 (39) and 15 (31), diastereomer 2, 197.1396 [M^+ (2 %), $C_{11}H_{18}NO_2$ requires 1197.1416], 138 (100), 96 (80), 54 (18), 41 (46), 27 (22) and 15 (20).

GC/MS and ^1H NMR spectroscopy of the crude product indicated that further products had been made but these, as of yet, have not been isolated.

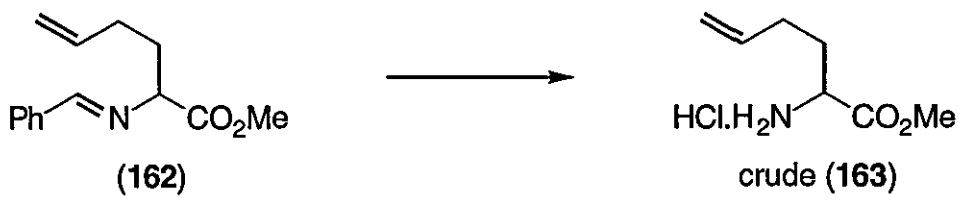
106. Methyl 2-[(1-phenylmethylidene)amino]-5-hexenoate (162)[161]



(156) **(162)**

To a solution of methyl 2-[(1-phenylmethylidene)amino]acetate **156** (5.00 g, 28.22 mmol) in anhydrous tetrahydrofuran (100 cm^3) under nitrogen at -40 °C was added sodium hydride (0.68 g, 28.22 mmol, freshly washed in light petroleum) and the reaction temperature raised to -10 °C. After stirring for 1 h, 4-bromobut-1-ene (2.95 cm^3, 28.32 mmol) was added dropwise, ensuring that the temperature never rose above -5 °C, and stirred for a further 3 h at -10 °C. On returning to room temperature, the reaction was stirred overnight, filtered and evaporated to dryness to give an orange oil (6.08 g) containing methyl 2-[(1-phenylmethylidene)amino]-5-hexenoate **162**. No further purification was attempted; δ_H (250 MHz, $CDCl_3$) 8.28 (1 H, s, CH=N), 7.81-7.77 (2 H, m, ArH), 7.47-7.38 (3 H, m, ArH), 5.75 (1 H, m, CH=C), 5.10-4.98 (2 H, m, $=CH_2$), 4.06 (1 H, t, *J* 5.2 Hz, CHN), 3.76 (3 H, s, OCH_3), 2.16-2.06 (2 H, m, CH_2CHN) and 1.88-1.83 (2 H, m, $CH_2C=C$).

107. Methyl 2-amino-5-hexenoate hydrochloride (163), (crude)



(162) crude **(163)**

A mixture of unpurified methyl 2-[(1-phenylmethylidene)amino]-5-hexenoate **162** (0.98 g) and 6 M hydrochloric acid (40 cm^3) was stirred for 3 h then washed with diethyl ether (3 x 20 cm^3). The aqueous solution was evaporated to low volume,

methanol (10 cm^3) added and then evaporated to dryness. The addition of methanol (10 cm^3) and evaporation to dryness was repeated 3 times to give the crude hydrochloride salt **163** (0.79 g) as an orange solid.

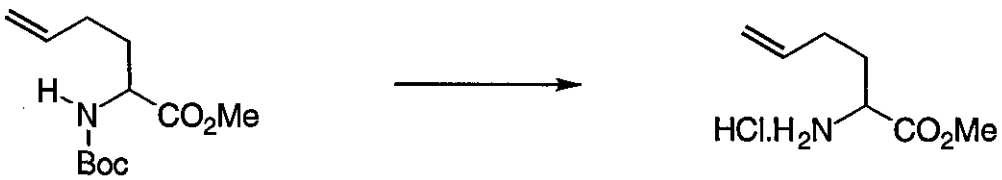
108. Methyl 2-[(*tert*-butoxycarbonyl)amino]-5-hexenoate (164)

crude (**163**) (**164**)

Solutions of *tert*-butyl dicarbonate (1.04 g, 4.76 mmol) in dioxan (10 cm^3) and sodium hydroxide (0.35 g, 8.64 mmol) in distilled water (10 cm^3) were added simultaneously to the crude hydrochloride salt of methyl 2-amino-5-hexenoate **163** (1.00 g, 4.32 mmol) and the reaction stirred overnight. The mixture was evaporated to low volume and the organics extracted with dichloromethane (3 x 10 cm^3). The organic fractions were combined, washed with brine (saturated, 2 x 10 cm^3), dried ($MgSO_4$), filtered and evaporated to dryness. Purification using flash column chromatography (3 % ethyl acetate/dichloromethane) yielded methyl 2-[(*tert*-butoxycarbonyl)amino]-5-hexenoate **164** (0.27 g, 29 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3365, 3079, 2979, 2955, 2933, 1747 and 1714; δ_H (400 MHz, $CDCl_3$) 5.86-5.76 (1 H, ddt, *J* 17.0, 10.4, 6.6 Hz), 5.10-5.01 (2 H, m, $=CH_2$), 4.36 (1 H, br, CHN), 3.76 (3 H, s, OCH_3), 2.19-2.11 (2 H, m, $CH_2C=C$), 1.97-1.89 (1 H, m, C*H*HCHN), 1.79-1.70 (2 x 1 H, m, CH*H*CHN + NH) and 1.47 (9 H, s, Me_3); δ_C (100.6 MHz, $CDCl_3$) 175.72 (ester CO_2), 157.75 (CO_2NH), 139.40 (=CH), 118.12 ($=CH_2$), 82.33 (CO), 55.46 (CHN), 54.66 (OCH_3), 34.54 (CH_2CHN), 31.91 ($CH_2C=C$) and 30.77 (Me_3); *m/z* 243.1476 [M^+ (5 %), $C_{12}H_{21}NO_4$ requires 243.1471], 188 (25), 143 (21), 128 (39), 84 (91), 67 (23), 57 (100), 41 (44) and 29 (24).

The data was consistent with that previously reported in the literature.[162]

109. Methyl 2-amino-5-hexenoate hydrochloride (163), (pure)



(**164**) pure (**163**)

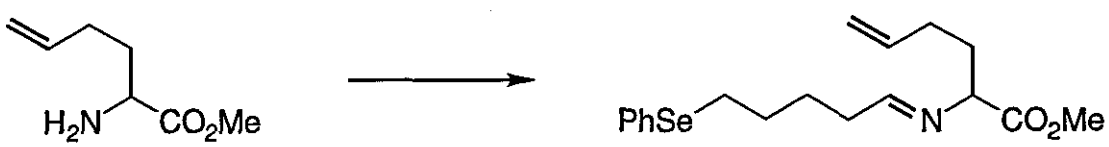
A solution of methyl 2-[(*tert*-butoxycarbonyl)amino]-5-hexenoate **164** (0.79 g) in ethyl acetate (10 cm^3) was stirred overnight with 4M HCl in dioxan (6 cm^3). The solution was evaporated to low volume, ethyl acetate (10 cm^3) added and then evaporated to dryness. The addition of ethyl acetate (10 cm^3) and evaporation to dryness was repeated 3 times to give *methyl 2-amino-5-hexenoate hydrochloride* **163** (0.58 g, 100 %) as a white solid, m.p. 88-90 °C; (Found: C, 46.91; H, 7.88; N, 7.72. $C_7H_{14}ClNO_2$ requires C, 46.80; H, 7.86; N, 7.80); υ_{max}/cm^{-1} (nujol mull) 3390, 2924, 2850 and 1753; δ_H (400 MHz, $CDCl_3$) 8.83 (3 H, br, NH_3^+), 5.81 (1 H, ddt, *J* 17.0, 10.4, 6.3 Hz), 5.17 (1 H, d, *J* 17.1, =C*H*H), 5.06 (1 H, d, *J* 10.2 Hz, =CH*H*), 4.18 (1 H, br, CHN), 3.83 (3 H, s, OCH_3) and 2.42-2.15 (4 H, m, $CH_2C{=}C$ + CH_2CHN); δ_C (100.6 MHz, $CDCl_3$) 170.26 (ester CO_2), 136.32 (=CH), 117.06 ($=CH_2$), 53.58 (CHN), 53.10 (OCH_3), 29.95 ($CH_2C{=}C$) and 29.41 (CH_2CHN); *m/z* 180.0794 [MH^+ (94 %), $C_7H_{14}ClNO_2$ requires 180.0791], 144 (34), 120 (54), 106 (55), 91 (83), 84 (100), 36 (60) and 30 (48).

110. Methyl 2-amino-5-hexenoate (165)

(163) **(165)**

To a solution of methyl 2-amino-5-hexenoate hydrochloride **163** (0.31 g, 1.71 mmol) in distilled water (5 cm^3) was added anhydrous potassium carbonate until the pH was raised to 10. The free amine was extracted with dichloromethane (3 x 5 cm^3), the organic extracts combined, dried ($MgSO_4$), filtered and evaporated to dryness to give the methyl 2-amino-5-hexenoate **165** (0.22 g, 91 %) as a colourless oil; υ_{max}/cm^{-1} (neat) 3384, 3076, 2953, 2859 and 1733; δ_H (400 MHz, $CDCl_3$) 5.84 (1 H, ddt, *J* 17.0, 10.2, 6.6 Hz, =CH), 5.12-5.01 (2 H, m, $=CH_2$), 3.76 (3 H, s, OCH_3), 3.51 (1 H, dd, *J* 7.5, 5.4 Hz, CHN), 2.23-2.17 (2 H, m, $CH_2C{=}C$), 1.95-1.80 (1 H, m, C*H*HCHN) and 1.75-1.61 (3 H, m, CH*H*CHN + NH_2); δ_C (100 MHz, $CDCl_3$) 176.80 (CO_2),137.87 (=CH), 115.81 (CH_2), 54.23 (CHN), 52.38 (OCH_3), 34.37 ($CH_2C{=}C$) and 30.24 (CH_2CHN).

111. Methyl 2-{[5-(benzeneselenyl)pentylidene]amino}-5-hexenoate (166)



(165) **(166)**

A mixture of methyl 2-amino-5-hexenoate **165** (0.18 g, 1.26 mmol) and 5-benzeneselenylpentan-1-al (0.33 g, 1.37 mmol) was stirred for 1 h before adding dichloromethane (3 cm^3). The solution was dried ($MgSO_4$), filtered and evaporated to dryness to give crude methyl 2-{[5-(benzeneselenyl)pentylidene]amino}-5-hexenoate **166** (0.48 g) as a pale green oil. No further purification was attempted as ^1H NMR spectroscopy indicated that the imine had been made.

112. Reaction between methyl 2-{[5-(benzeneselenyl)pentylidene]amino}-5-hexenoate (166) and tri-*n*-butyltin hydride

A solution of methyl 2-{[5-(benzeneselenyl)pentylidene]amino}-5-hexenoate **166** (0.47 g, 1.54 mmol) and magnesium bromide dietherate (0.40 g, 1.56 mmol) in anhydrous toluene (250 cm^3) was deoxygenated at room temperature for 90 min before heating to reflux and injecting a solution of tri-*n*-butyltin hydride (0.49 cm^3, 1.76 mmol) and AMBN (0.13 g, 0.66 mmol) in anhydrous toluene (20 cm^3) over 6 h using a syringe pump. The reaction was cooled, stirred overnight and evaporated to dryness. Diethyl ether (5 cm^3) and 6 M hydrochloric acid (5 cm^3) were added and the ether layer was extracted further with 6 M hydrochloric acid (2 x 3 cm^3). The acid fractions were combined, washed with diethyl ether (3 x 5 cm^3) and the pH raised to 10 with the addition of anhydrous potassium carbonate before extracting with dichloromethane (4 x 5 cm^3).The organic fractions were combined, dried ($MgSO_4$), filtered and evaporated to dryness. Purification using flash column chromatography (ethyl acetate/light petroleum) led to trace amounts of numerous unidentifiable compounds. The reaction has not been repeated to date.

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