A NOVEL ROUTE TO CHIRAL UNSATURATED AMINES

A thesis submitted in partial fulfilment of the requirements of the degree of

Doctor of Philosophy

by

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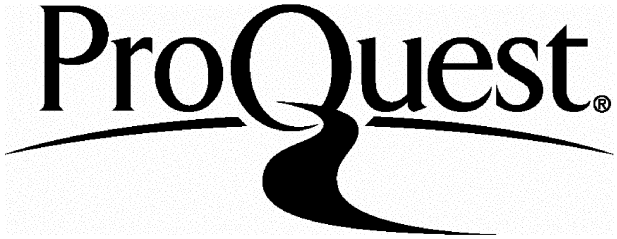

"If you come across error, rather than uprooting it or knocking it down, see if you can trim it patiently, allowing the light to shine upon the nucleus of good and truth that is usually not missing even in erroneous opinions."

Albino Luciani

Abstract

Recently, there has been much effort directed toward the synthesis of chiral unsaturated alcohols. One of the best methodologies requires the synthesis of a chiral 1,3-dioxolane, which is then ring-opened stereospecifically with a suitable organosilicon nucleophile. Removal of the auxiliary then reveals the desired homochiral alcohol. However, no analogous methodology exists for the preparation of homochiral unsaturated amines. The aim of this project is to develop a synthesis of these amines by ring opening of a chiral tetrahydro-1,3-oxazine; oxidation and removal of the chiral auxiliary would reveal the desired amine.

The synthesis of a suitable 1,3-amino alcohol chiral auxiliary is described. This was prepared by one-carbon homologation of (*S*)-alanine with sodium cyanide, and hydrolysis of the resulting nitrile. The chiral β-amino acid produced was then reduced.

The synthesis of tetrahydro-1,3-oxazines is described. These were prepared initially from direct condensation of the amino alcohol and an aldehyde, and later by an acetal exchange reaction between the amino alcohol and the relevant diethyl acetal. Information about the structure of the aminal has been determined. Attempted extension of the Noyori acetalisation to the preparation of tetrahydro-1,3-oxazines is also outlined.

The ring-opening reaction of tetrahydro-1,3-oxazines with allyltrimethylsilane is described. These reactions did not result in significant amounts of product being formed. Further work necessary is outlined.

Acknowledgements

Firstly, I would like to thank my supervisor, Dr. Alethea Tabor, whose help and guidance throughout this project has been invaluable.

Thanks are due to the past and present members of the Tabor group: Scott, Mick, Al, Martin and Emma for a stimulating environment in which to work. Thanks are particularly due to Mick and Al for helping with the proof reading of this thesis. The assistance of the technical staff at Edinburgh, UCL and the School of Pharmacy, University of London in running mass spectra and some NMR samples is acknowledged.

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Finally to my parents: without their support, the completion of this PhD would not have been possible.

Contents

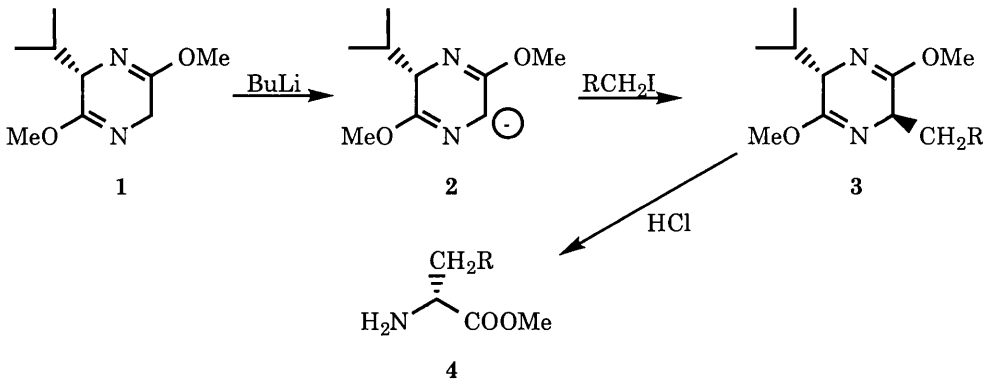
1. Introduction

1.1 Aim of the project

Many methods have recently been devised for the synthesis of enantiomerically pure amino acids and amines, and these generally rely on two types of reaction, either the reaction of the chiral enolate of an amino acid with an alkylating reagent, or the reaction of a chiral enolate with an electrophilic amine equivalent.

Schöllkopf *et al.* have described the use of the chiral pyrazine **1** (derived from the methyl esters of (*S*)-valine and glycine) to prepare substituted chiral glycine derived amino acids **4** (Scheme 1)[1].

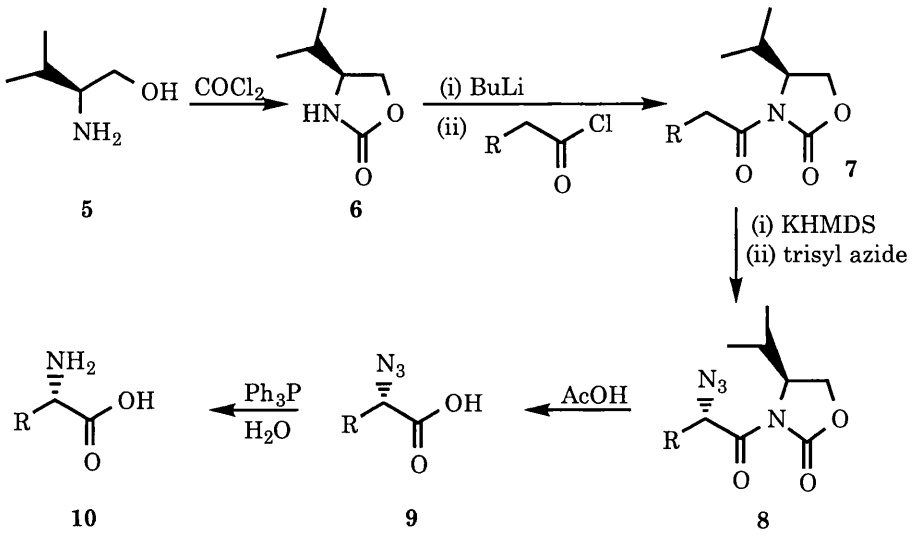
Scheme 1



Removal of a proton from **1** gave chiral enolate **2** which was then alkylated selectively from one side only to give the substituted pyrazine **3**. Cleavage of **3** with hydrochloric acid revealed the glycine derivative **4**.

An auxiliary with the chirality also derived from an amino acid has been described by Evans *et al.* (Scheme 2)[2].

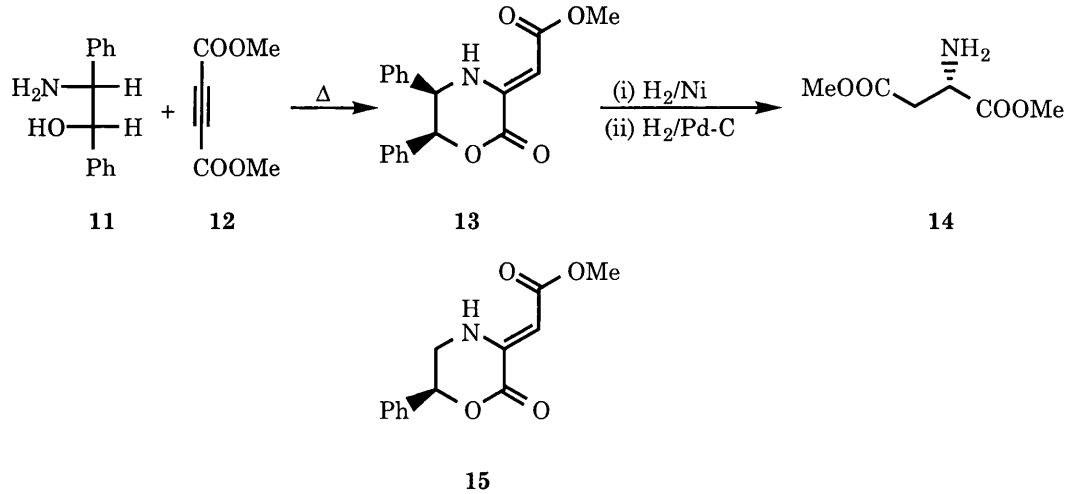
Scheme 2



Reaction of (*S*)-valinol **5** with phosgene gave the chiral oxazolidinone **6**, which was then acylated to give **7**. Removal of an α-proton from the side chain of **7**, followed by addition of triisopropylsulphonyl (trisyl) azide gave **8**, and cleavage of the chiral auxiliary followed by conversion of the azide to an amine revealed the amino acid **10**.

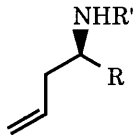
Various methods have also been invented for the preparation of chiral amines via catalytic hydrogenation. For example, (*S*)-aspartic acid methyl ester has been prepared as shown in Scheme 3[3].

Scheme 3



Condensation of *erythro*-(+)-1,2-diphenylethanolamine **11** with acetylene dicarboxylic acid methyl ester **12** gave cyclised 1,4-oxazine **13**, and catalytic hydrogenation revealed the aspartic acid **14** in excellent enantiomeric excess. On the other hand, reduction of oxazine **15** gave an e.e. of only 15%.

However, the reactions described above are unsuitable for the preparation of chiral unsaturated amines such as **16**.

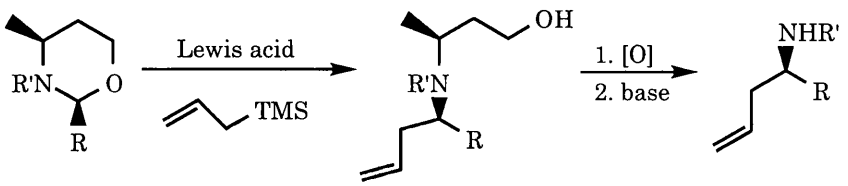


16

The catalytic hydrogenation reaction is unsuitable, as the unsaturated functionality would be destroyed, whilst the Schöllkopf approach shown in Scheme 1 gives only β-unsaturated-α-amino acids, with chain extension then being required to produce more complex carbon skeletons.

The objective of the project is to develop a novel methodology for the preparation of amines **16** via the Lewis acid mediated ring opening of chiral tetrahydro-1,3-oxazines (6-membered aminals) **17** with a nucleophile. In this project, allyl nucleophiles have been studied with the aim of synthesising homochiral homoallylic amines (Scheme 4).

Scheme 4



17 **18** **16**

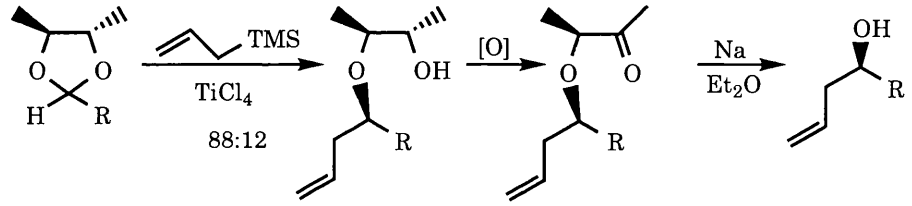
The ring opening reaction would give alcohol **18**, and oxidation and removal of the chiral auxiliary by a base catalysed retro-Michael reaction would reveal the

amine **16**. These reactions have not previously been described. However, extensive work has been carried out in two related fields: the preparation of chiral unsaturated alcohols by ring opening of cyclic 1,3-acetals, and amido alkylation of simple organometallics by chiral tetrahydro-1,3-oxazolidines (5-membered aminals). This work suggests that the reactions described in Scheme 4 should be successful, and is reviewed in the next section.

1.2.1 Ring opening of cyclic acetals

Chiral 1,3-acetals have become important in asymmetric synthesis, and in particular Johnson *et al.* have developed a key synthesis of homochiral unsaturated alcohols. A review of this field has recently appeared[4]. Initial studies were carried out on 5-membered 1,3-acetals (Scheme 5).

Scheme 5



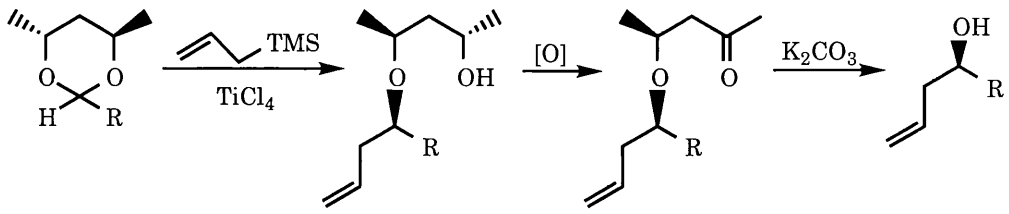
19 **20** **21** **22**

R= *n*-hexyl, cyclohexyl

Ring opening of the acetal **19** with allyltrimethylsilane and titanium tetrachloride gave ring opened ether **20**. Oxidation of the alcohol moiety of **20** gave ketone **21**, and then the chiral auxiliary was eliminated by sodium in refluxing ether to reveal the chiral unsaturated alcohol **22**. Unfortunately, the harsh conditions needed to removed the auxiliary reduced the synthetic utility of the process.

Subsequently, the ring opening reactions of the 6-membered acetals 23 were investigated (Scheme 6)[5].

Scheme 6



23 **24** **25** **22**

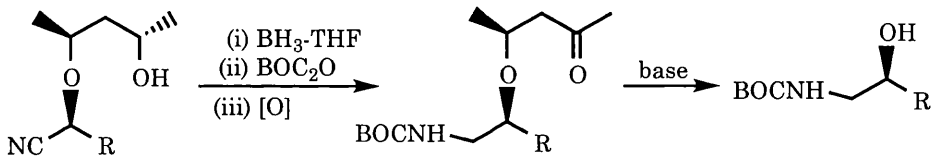
R= *n*-hexyl, cyclohexyl 89:11

Ring opening, and oxidation of the resulting alcohol (as before) gave ketone **25**. The auxiliary was removed by a base catalysed retro-Michael reaction to give the unsaturated alcohol **22**. In contrast to the reaction conditions employed in Scheme 5, the elimination process was very mild, and therefore the usefulness of the process was greatly improved. It was observed that acetal **23** underwent similar ring opening reactions with trimethylsilyl acetylene[6] and trimethylsilyl cyanide[7] to give chiral propargylic alcohols **26** and cyanohydrins **27** respectively.

26 **27**

Interestingly, the ether derived from the ring opening of acetal **23** with trimethylsilyl cyanide was also converted into an α-amino alcohol (Scheme 7).

Scheme 7



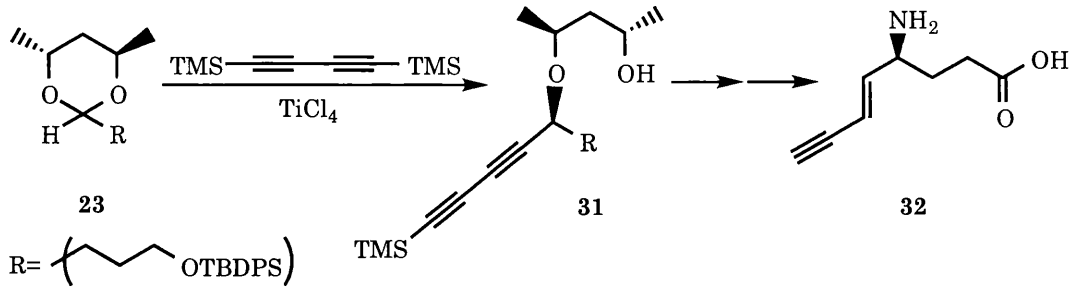
28 **29** **30**

R= Ph, *n*-$C_{11}H_{23}$

Reduction of the cyano group of **28**, followed by protection of the resulting amine, and oxidation of the alcohol moiety gave ketone **29**. Removal of the auxiliary (retro-Michael reaction) revealed the amino alcohol **30**.

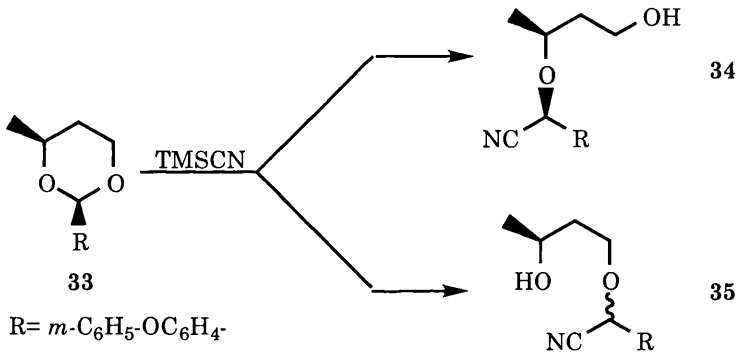
It has been shown that the ring opening reaction of acetal **23** can occur with multi unsaturated nucleophiles, for example Holmes *et al.* carried out the ring opening reaction of **23** with bis-trimethylsilyl butadiyne in their synthesis of a GABA-T inhibitor **32** (Scheme 8)[8].

Scheme 8



The ring opening reaction of acetal **33** (formed from (*S*)-butane-1,3-diol) with trimethylsilyl cyanide has also been investigated (Scheme 9)[9].

Scheme 9

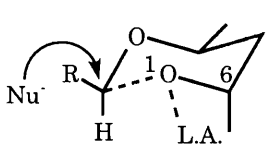


It was found that the diastereomeric ratio of the ring opened products **34** and **35** was extremely dependant on rate of addition of the reactants and the temperature - ratios between 1:1 and 99:1 were observed.

1.2.2 Mechanism of ring opening of cyclic acetals

As previously detailed, the ring opening of cyclic acetals with organosilicon reagents is Lewis acid mediated, and the first rationalisation of the reaction mechanism was made by considering the two possible intermediate complexes that can be formed during the reaction (Scheme 10)[4].

Scheme 10



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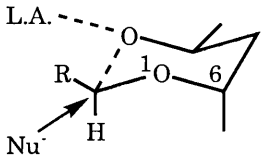


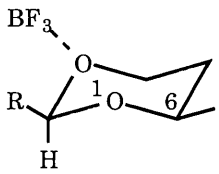
37

In complex **36**, the Lewis acid is co-ordinated to O_1. This has the effect of lengthening the C_2-O_1 bond and shortening the C_2-O_3 bond, thus reducing the steric interactions between the (axial) hydrogen of C_2 and the methyl group on C_6. The nucleophile then attacks in an anti manner, and the ring opened product is formed.

However, for complex **37**, the Lewis acid is co-ordinated to O_3, which lengthens the C_2-O_3 bond, and shortens the C_2-O_1 bond. This increases the steric interactions between the hydrogen on C_2 and the methyl group on C_6. The formation of this complex is therefore disfavoured.

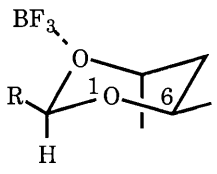
Unfortunately, this theory does not explain the unidirectional ring opening ring of acetals such as **33**. Denmark *et al.* have studied the boron trifluoride complexes **38** and **39** by ^{13}C NMR at -95°C, which were derived from acetals **40** and **41** (Scheme 11)[10].

Scheme 11



38

R= *n*-hexyl



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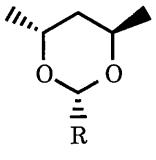

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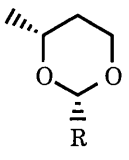

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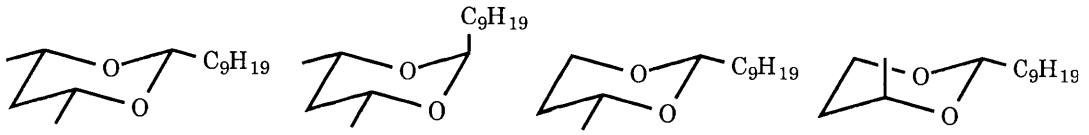
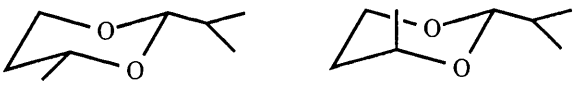
The ^{13}C NMR spectrum of **38** showed a single Lewis acid-acetal complex had formed, and an APT experiment showed C_4 was bonded to the complexed

oxygen. In a difference nOe experiment on complex **39,** a strong enhancement for the resonances of H_6 was observed when irradiating H_1. It was concluded that H_6 was axial and the substituent methyl was equatorial. For intermediate **39**, a single complex was also observed (^{13}C NMR), an a 2-D NMR experiment showed that C_4 was bonded to the complexed oxygen. It was postulated that on co-ordination of the Lewis acid, the oxygen atom rehybridises toward sp^2, giving a planar or weakly pyramidal state. This trigonal state experiences stronger eclipsing interactions with an equatorial group, and so co-ordination next to an axial substituent is preferred.

A recent study by Sammakia *et al.* on the ring opening reaction of acetals **42** to **47** has shown that the reaction mechanism depends to some extent on the stereochemistry of the particular acetal[11].



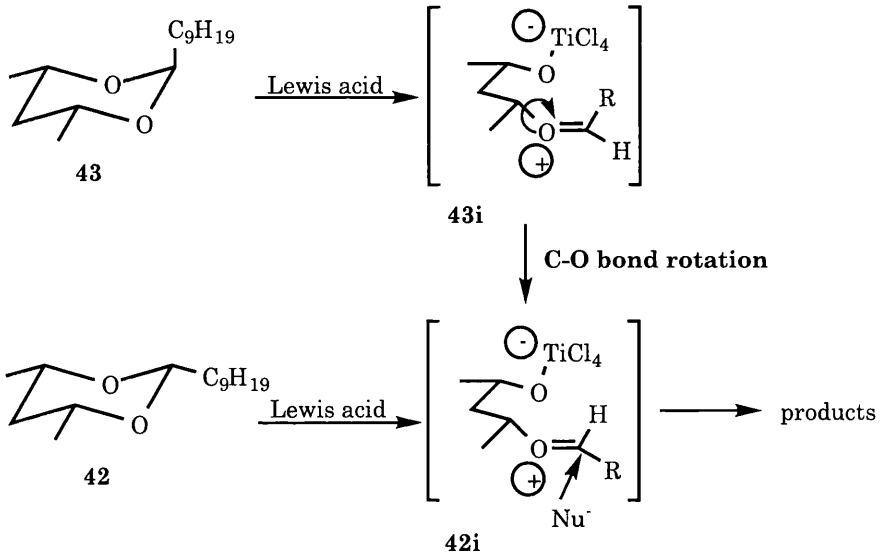
42 **43** **44** **45**



46 **47**

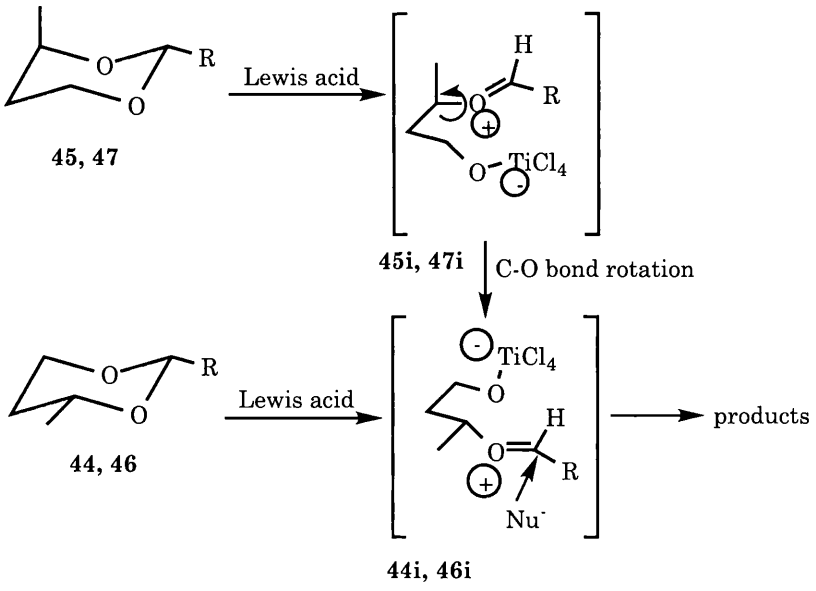
It was found that the ratio of diastereomers obtained from the ring opening of **42** and **43** was virtually identical. This was not the case for acetals **44** to **47**. For **44** and **46**, a high ratio of major:minor diastereomers was obtained, for **45** and **47** the ratio was low. It was evident that the mechanism for the reactions was not identical in each case. The mechanism for ring opening of **42** and **43** was rationalised as shown in Scheme 12.

Scheme 12



Co-ordination of the Lewis acid to **43** gives complex **43i** which then isomerises via a C-O bond rotation to give **42i** (also formed directly from acetal **42**). This isomerisation is faster than attack of the nucleophile, and so the diastereomeric ratio will be independent of the geometry of the starting acetal. However, this is not the case for acetals **45** and **47**. The mechanism of this ring opening was rationalised as shown in Scheme 13.

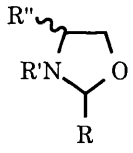
Scheme 13



The conformation of lowest energy is that where the substituent in the 2-position is equatorial, and the methyl group in the 4-position axial. Co-ordination of the Lewis acid gives complexes **45i** and **47i**. To isomerise, **45i** and **47i** must undergo rotation about the C-C and C-O bonds, which will be a higher energy process than the C-O bond rotation for complex **43i**. The ratio of diastereomers from the ring opening of **44** and **46** and **45** and **47** would be expected to be the same if this was the mechanism. However, this was found not to be the case - for acetals **45** and **47** the ratio was low, and for **44** and **46** it was high, indicating the direct displacement mechanism (Scheme 10) is operating for **44** and **46**.

1.3 Reactions of tetrahydro-1,3-oxazolidines

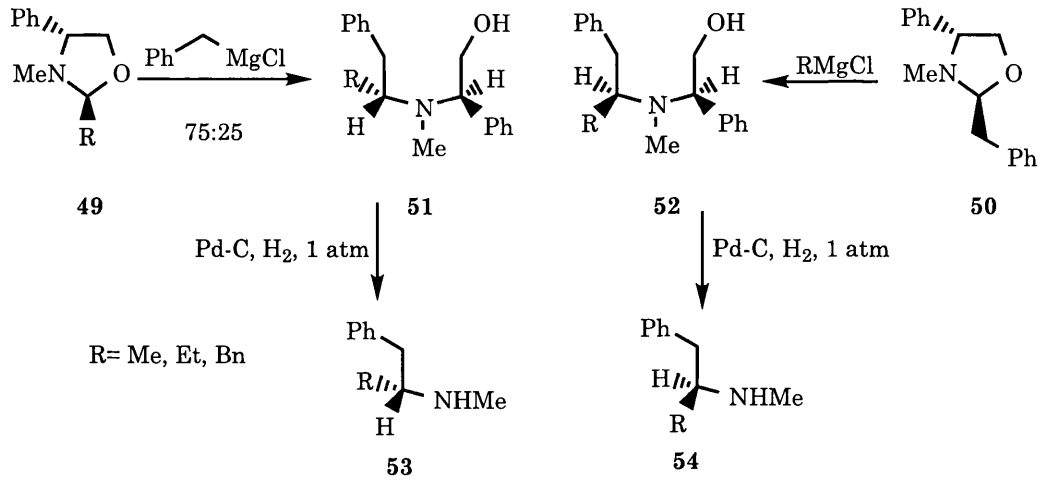
The ring opening and associated reactions of 5-membered ring systems **48** (tetrahydro-1,3-oxazolidines) have been extensively studied to determine their use as chiral synthons. This has been possible, since the chirality can be easily derived from α-amino acids, after they are reduced to amino alcohols.



48

For example, Takahashi *et al.* have described a novel route to both enantiomers of several chiral phenylethylamines, as shown in Scheme 14[12].

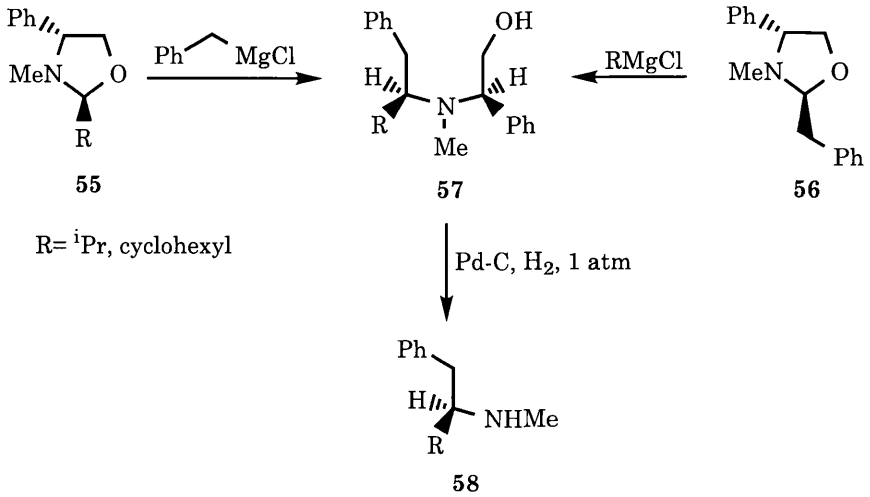
Scheme 14



Aminal **49**, derived from (*R*)-phenylglycinol, was ring opened with benzylmagnesium chloride to give alcohol **51**. Removal of the chiral auxiliary by catalytic hydrogenation revealed the (*R*)-amine **53**. The other enantiomer was prepared by ring opening of aminal **50** to give alcohol **52**. Catalytic hydrogenation of **52** gave the (*S*)-amine **54**.

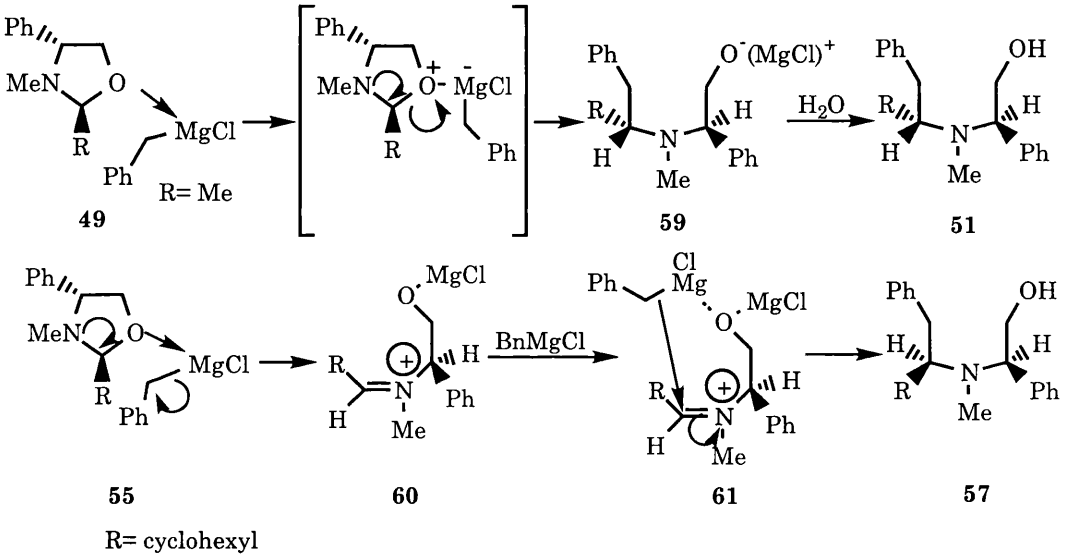
The R group was then changed to a bulkier substituent and a surprising result was obtained (Scheme 15).

Scheme 15



The ring opening reaction of aminals **55** and **56** using the bulkier Grignard reagents furnished the same diastereomeric alcohol (**57**), indicating a difference in reaction mechanism (Scheme 16).

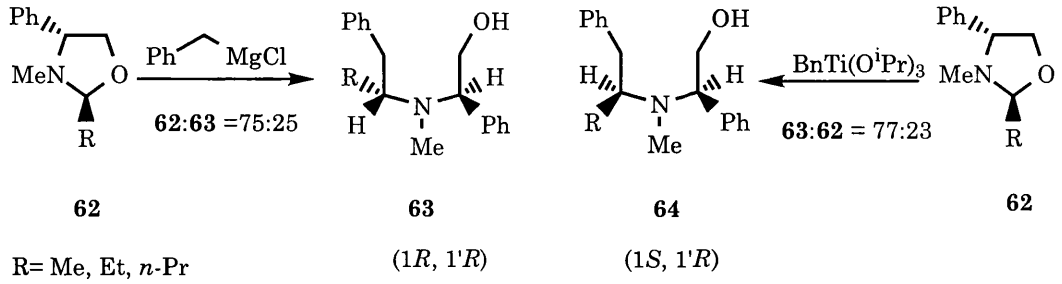
Scheme 16



Reaction of **49** with 1 equivalent of Grignard reagent gave an almost 100% yield of the ring opened product **51**, while 2 equivalents of Grignard were required to give the same yield from **55**. It was thought that in the former case, the Grignard reagent was attacking the ring in a concerted manner, while in the latter case, one molecule of Grignard reagent cleaved the ring, and the second attacked the intermediate immonium salt **61**. Subsequently, this mechanism was found to be in operation for ring opening reactions with magnesium bromide-type Grignard reagents[13].

The ring opening reaction of the aminal with other organometallics has also been investigated (Scheme 17)[14].

Scheme 17

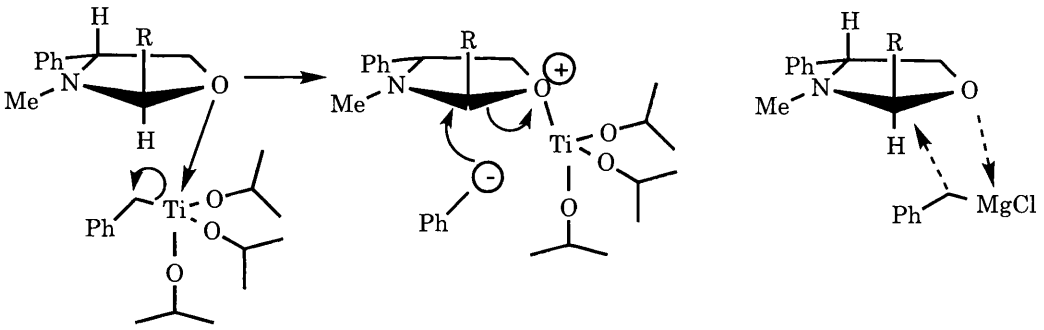


62 **63** **64** **62**

R= Me, Et, *n*-Pr (1*R*, 1'*R*) (1*S*, 1'*R*)

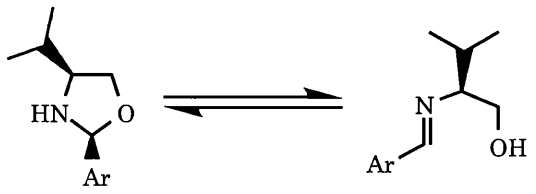
Ring opening of aminals **62** with benzylmagnesium chloride favoured the formation of the (1*S*,1'*R*) amino alcohols **63** as detailed earlier. However, reaction of **62** with benzyltitanium triisopropoxide gave the diastereomer (1*S*, 1'*R*) in good yield. This is because the benzyl moity of the titanium reagent attacks from the opposite side of the C-O bond[15] compared to the Grignard reagent (Scheme 18), and thus opposite diastereomers are formed.

Scheme 18



It has been noted that chiral oxazolidines **65** with an unprotected nitrogen atom can tautomerise to an imino alcohol **66**, with consequent equilibration between the two forms (Scheme 19)[16].

Scheme 19

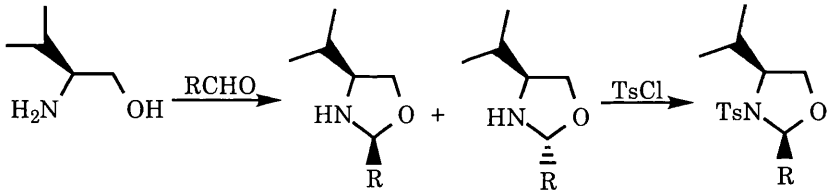


65 **66**

The position of the equilibrium depends on the bulk of the substituent attached to C_2.

If an unprotected amino alcohol is condensed with an aldehyde, the aminal formed is a mixture of diastereomers. For example, reaction of (*S*)-valinol with a range of aldehydes gives a mixture of oxazolidines **67**[17]. Interestingly, subsequent protection of the nitrogen atom with *p*-toluenesulphonyl chloride gave only a single diastereomer of **68** (Scheme 20)[18].

Scheme 20

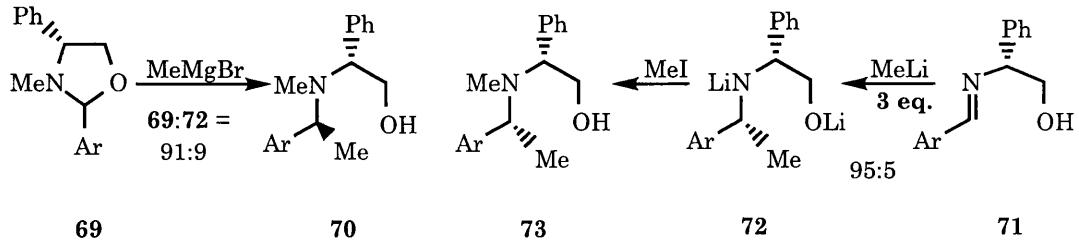


R= methyl, phenyl, cyclohexyl **67** **68**

single diastereomer

The addition of an organometallic reagent to imines and oxazolidines derived from the same amino alcohols and aldehydes has been exploited to give amines of opposite stereochemistries (Scheme 21)[19].

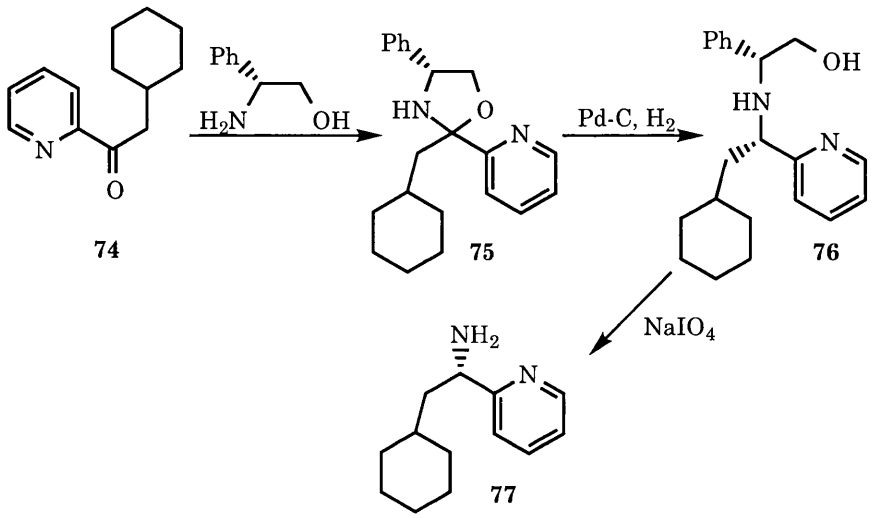
Scheme 21



Ring opening of the oxazolidine **69** with Grignard reagent gave (*R*,*S*) alcohol **70** (as before). Addition of methyllithium to imine **71** gave alcohol **72**. The surprising stereochemistry of this reaction can be attributed to a transition state resulting from chelation of the alkoxy substituent and imino nitrogen to the lithium atom, then the other MeLi attacks from the least hindered face. Methylation of the nitrogen of **72** gave (*R*,*R*) alcohol **73**. The (*R*,*R*) alcohols can also be derived from the addition of organocerium reagents[20].

These reactions have been used to prepare several types of chiral nitrogen containing compounds. For example, the synthesis of a novel chiral primary amine has been described (Scheme 22)[21].

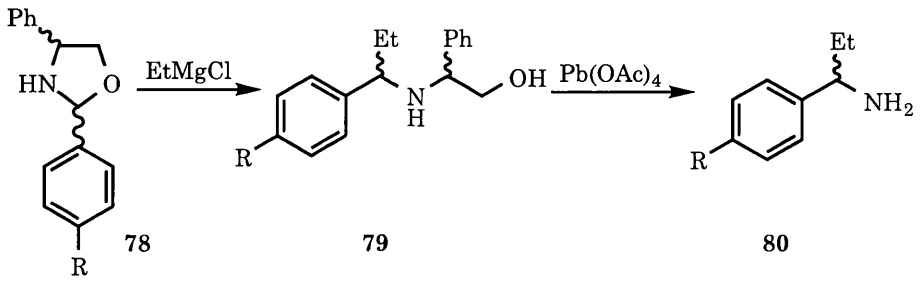
Scheme 22



Ketone **74** was condensed with (*R*)-phenylglycinol to give oxazolidine **75**, catalytic reduction gave alcohol **76** with very high diastereoselectivity. Removal of the auxiliary by periodate cleavage gave the target amine **77**. A similar periodate cleavage has recently been published by Pedrosa *et al.*[22]

The synthesis of α-alkylphenylethylamines has also been achieved (Scheme 23)[23].

Scheme 23

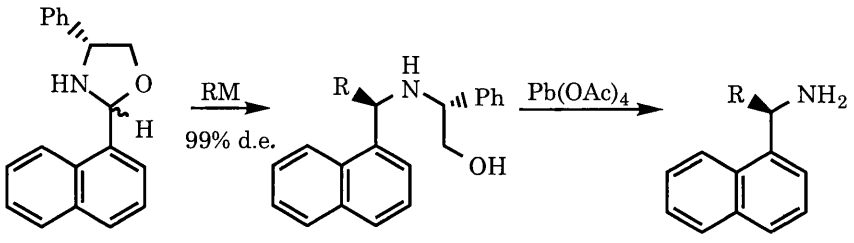


78 **79** **80**

R= H, Br, OMe

Ring opening of oxazolidine **78** gave alcohol **79**, and oxidative cleavage of the chiral auxiliary gave amine **80**. Either enantiomer of **80** could be prepared owing to the ready availability of both enantiomers of phenylglycinol. The ring opening of oxazolidines **81** with organometallic reagents has been used to prepare the related naphthalene derivatives (Scheme 24)[24].

Scheme 24

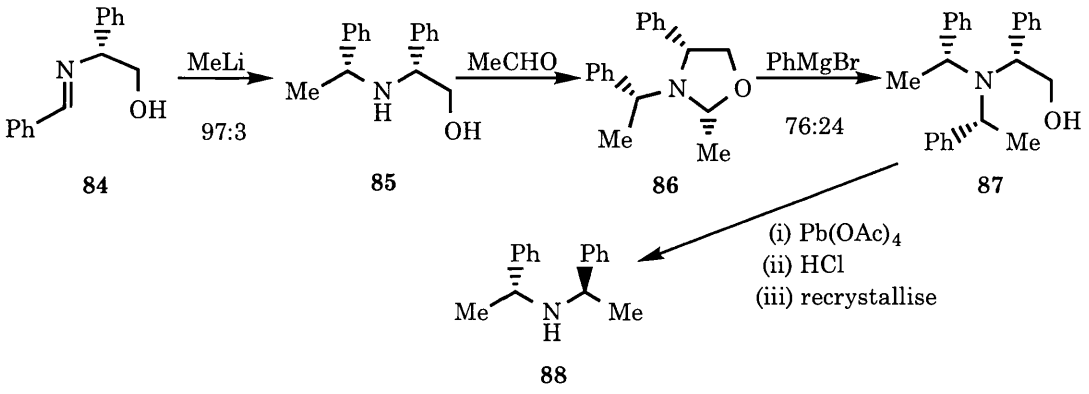


81 **82** **83**

R= Me, Et, *n*-Bu, Ph
M= Li, $CeCl_2$

Chiral secondary amines have also been prepared by this route, an example is shown in Scheme 25[25].

Scheme 25

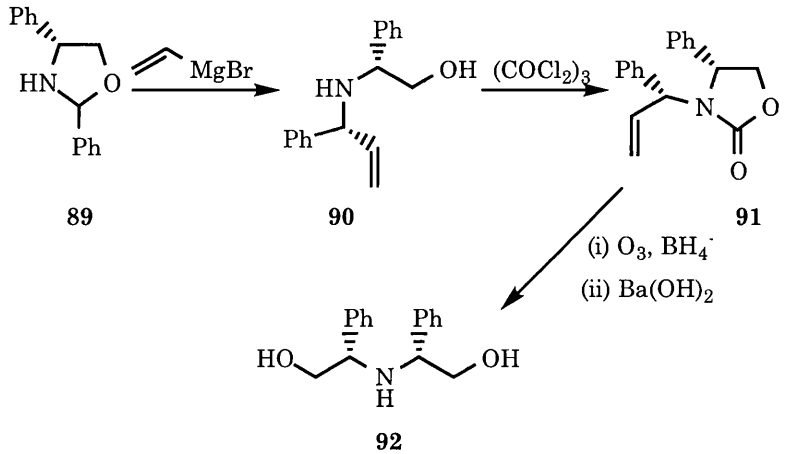


84 85 86 87 88

Addition of methyllithium to imine **84** gave alcohol **85** which was then condensed with acetaldehyde to give oxazolidine **86**. Ring opening of **86** with phenylmagnesium bromide gave alcohol **87**, and the chiral auxiliary was removed by oxidative cleavage to reveal amine **88**.

Synthesis of both diastereomers of a chiral diethanolamine has been carried out by Meyers *et al.* (Scheme 26)[26].

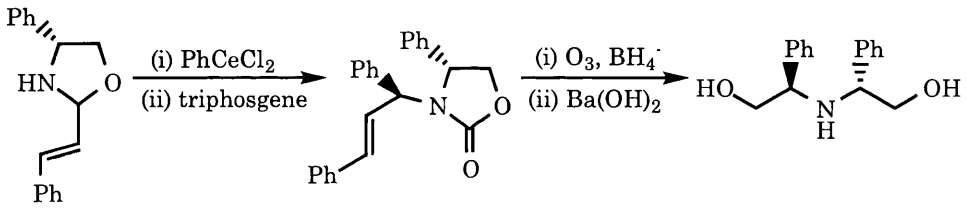
Scheme 26



89 90 91 92

Oxazolidine **89** was ring opened with vinylmagnesium bromide to give alcohol **90**, condensation of **90** with triphosgene gave chiral oxazolidinone **91**. Ozonolysis, reduction of the resulting aldehyde and hydrolysis of the oxazolidinone gave *meso* diol **92**. The C_2-symmetric diol was prepared (Scheme 27) by ring opening of oxazolidine **93** with an organocerium reagent. A similar series of reactions to those described in Scheme 24 furnished the desired diethanolamine **95** in excellent yield.

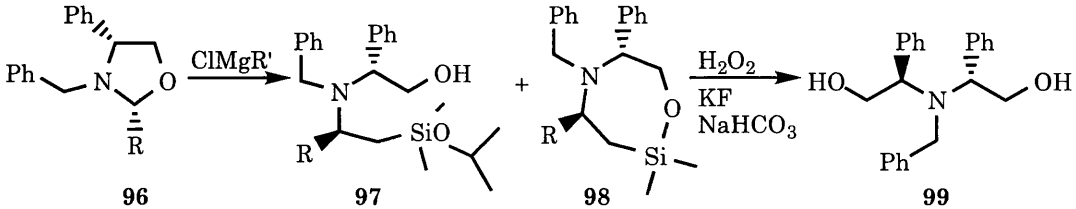
Scheme 27



93 **94** **95**

A more unusual preparation of a chiral diethanolamine has been described by Takahashi *et al.* (Scheme 28)[27].

Scheme 28



96 **97** **98** **99**

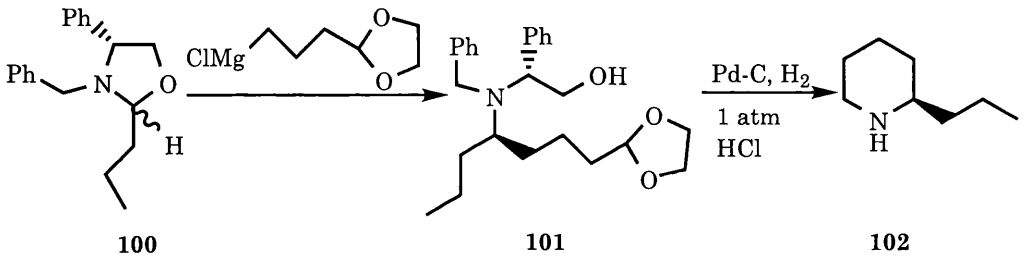
R= Ph, Me, *i*-Pr

2:1 to 7:1

Reaction of oxazolidine **96** with isopropyloxydimethylsilylmagnesium chloride gave not only ring opened alcohol **97** but cyclised product **98**. Oxidative cleavage of **97** and **98** furnished the diethanolamine **99** in good to excellent yield.

The previously described ring opening reactions have been used to prepare some naturally occurring amine compounds. For example, Takahashi *et al.* have prepared the naturally occurring alkaloids (*R*)-coniine **102** (Scheme 29) and (-)-dihydropinidine **106**[28].

Scheme 29

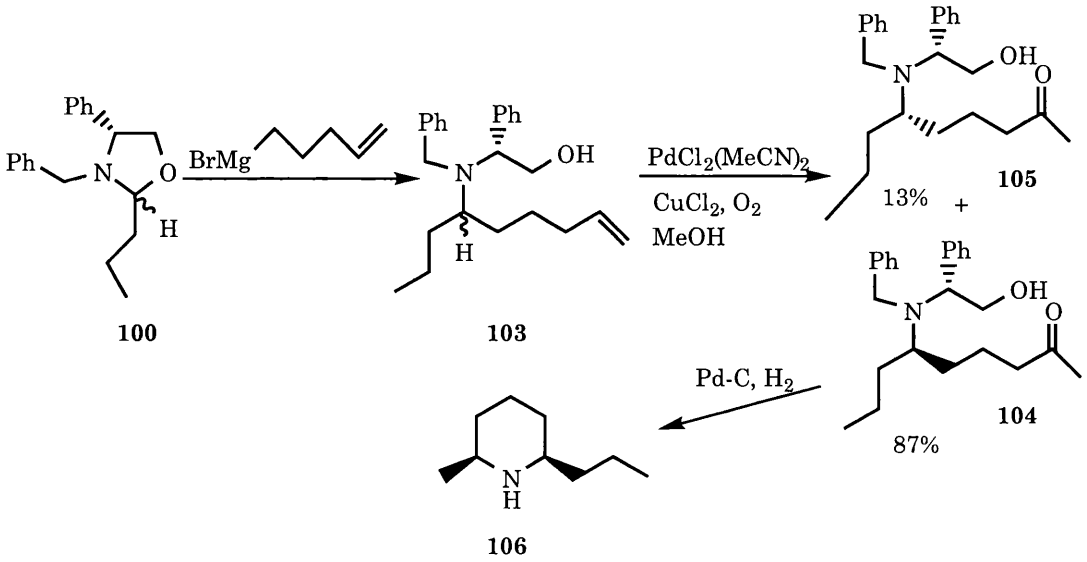


100 **101** **102**

Ring opening of oxazolidine **100** with Grignard reagent gave alcohol **101**, which was subjected to catalytic reduction to give (*R*)-coniine **102** in excellent yield.

In the dihydropinidine synthesis (Scheme 30), ring opening of oxazolidine **100** with a different Grignard reagent gave alcohol **103**. Submission of **103** to the Wacker reaction gave a mixture of ketones **104** and **105**, which were separated by flash chromatography. Catalytic hydrogenation of **104** gave dihydropinidine **106**.

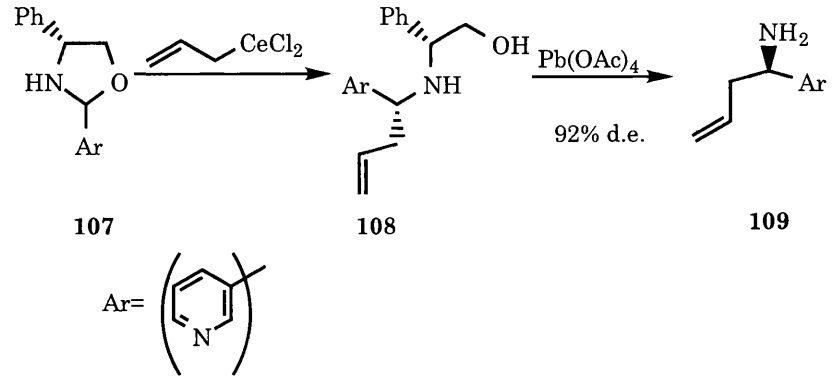
Scheme 30



100 **103** **105** **104** **106**

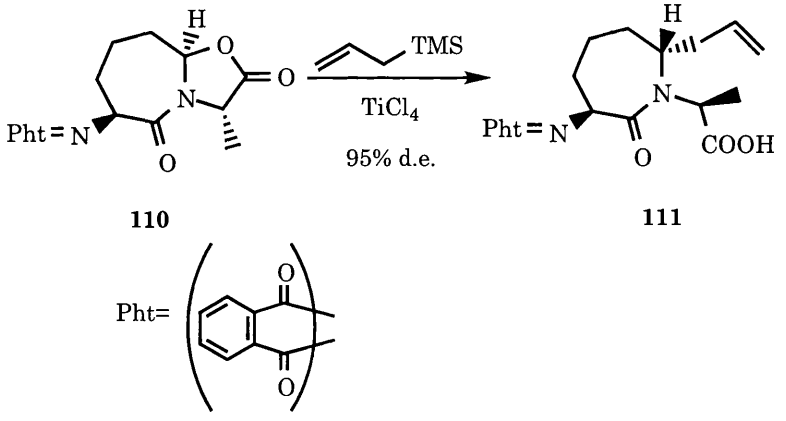
Pridgen *et al.* have described the preparation of homochiral unsaturated amines by ring opening of oxazolidines with unsaturated organometallic nucleophiles (Scheme 31)[29].

Scheme 31



Ring opening of **107** with allylcerium chloride gave alcohol **108**, cleavage of the auxiliary with lead tetra-acetate revealed unsaturated amine **109**. The allyl group has also been introduced successfully in the preparation of substituted Freidinger lactams (Scheme 32)[30].

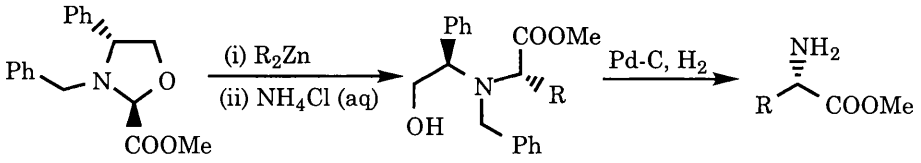
Scheme 32



Ring opening of azepinone **110** with allyltrimethylsilane and a Lewis acid gave the lactam **111** in good yield , with inversion of configuration.

Synthesis of novel amino acids has also been achieved using ring opening methodology (Scheme 33)[31].

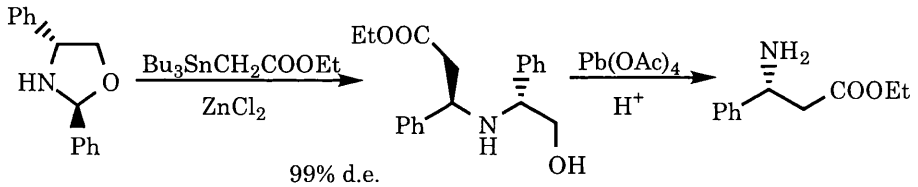
Scheme 33



112 **113** **114**

Ring opening of oxazolidine **112** with an organozinc reagent gave alcohol **113**, removal of the chiral auxiliary by catalytic hydrogenation furnished the amino acid ester **114**. Similarly, addition of ethyltributylstannylacetate to oxazolidine **115** gave alcohol **116** in very high diastereomeric excess (Scheme 34).

Scheme 34

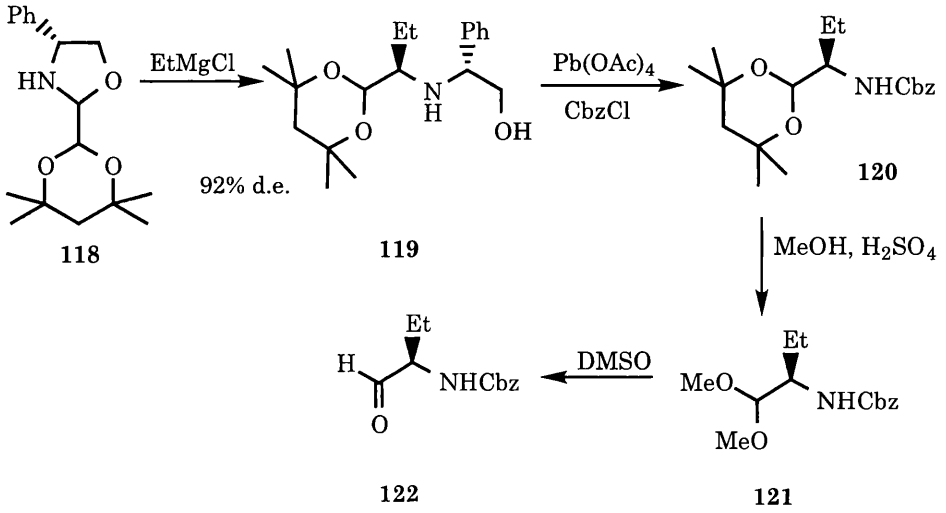


115 **116** **117**

Removal of the chiral auxiliary furnished the amino ester **117**[32].

The ring opening reaction has also been shown to be compatible with acetal protecting groups (Scheme 35)[33].

Scheme 35

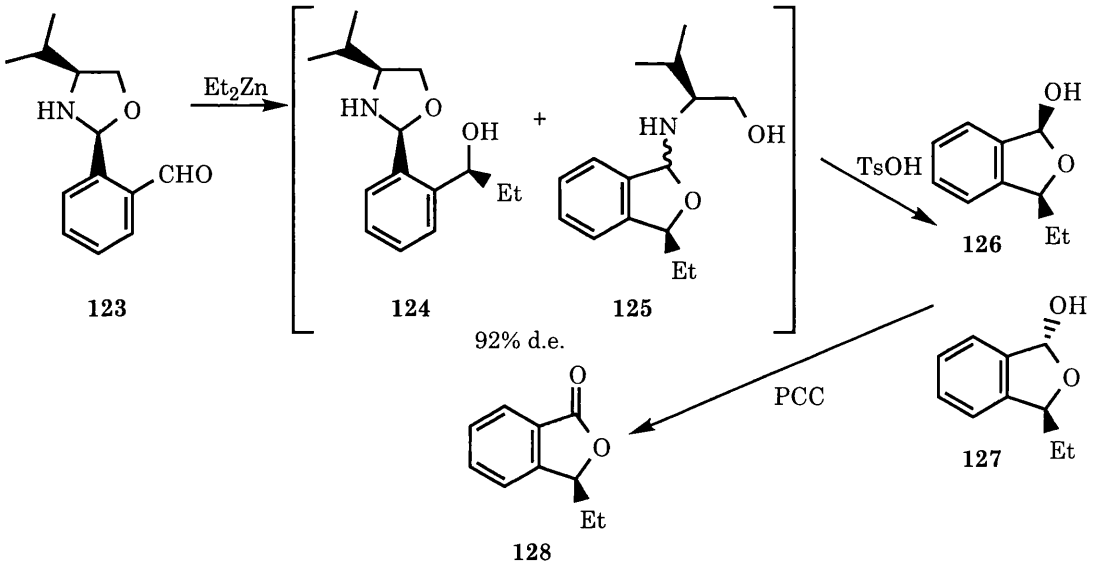


118 119 120 121 122

Ring opening of oxazolidine **118** with ethylmagnesium bromide gave alcohol **119** in very high diastereomeric excess. Removal of the auxiliary and protection of the resulting amine with benzyl chloroformate gave protected amino aldehyde **120**. An acetal exchange reaction gave acetal **121**, then deprotection of **121** with dimethylsulphoxide revealed the amino aldehyde **122**.

Interesting reactions where the oxazolidine ring itself has been used as a chiral template have also been investigated. An example of this is the preparation of chiral 3-substituted phthalides, shown in Scheme 36[34].

Scheme 36

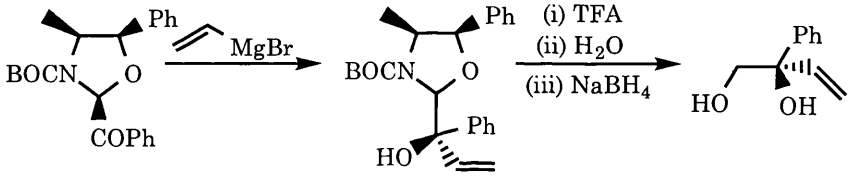


123 124 125 126 127 128

Ring opening of oxazolidine **123** with diethyl zinc furnished a mixture of **124** and **125**. Heating under reflux with *p*-toluenesulphonic acid removed the chiral auxiliary and gave a mixture of the alcohols **126** and **127**. Oxidation of the alcohols with pyridinium chlorochromate gave a single enantiomer of the phthalide **128**. It is interesting to note that **124** and **125** did not need to be separated - since the stereochemistry of the hydroxyl group in **126** and **127** does not affect the chiral purity of the final product.

A homochiral 1,2-diol has also been prepared using an oxazolidine ring as a chiral auxiliary (Scheme 37)[35].

Scheme 37



129 **130** **131**

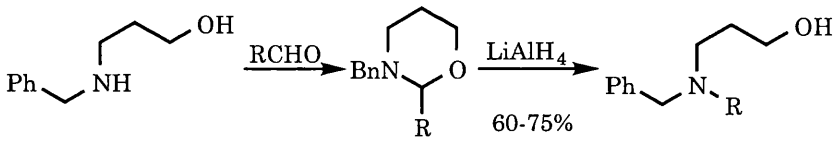
Addition of vinylmagnesium bromide to oxazolidine **129** gave alcohol **130**, cleavage of the oxazolidine with TFA, followed by reduction of the resulting aldehyde gave chiral alcohol **131**.

1.4 Ring opening of tetrahydro-1,3-oxazines

In contrast to the ring opening of 5-membered aminals, only a few reactions of tetrahydro-1,3-oxazines **18** (6-membered aminals) have been reported.

For example, Pedrosa *et al.* prepared 3-dialkylaminopropanols as shown in Scheme 38[36].

Scheme 38



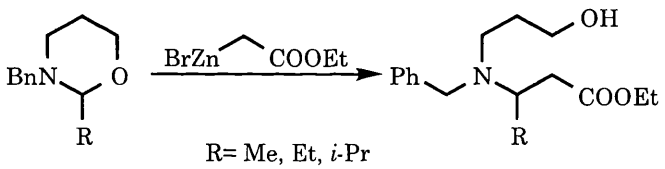
132 **133** **134**

R= Me, Et, n-C_8H_{17}, Ph

Condensation of 3-amino propanol **132** with a number of aldehydes gave aminals **133**. Ring opening with lithium aluminium hydride gave the products **134** in good yields.

Ring opening of aminals **133** (Scheme 39) with the Reformatsky reagent derived from ethyl 2-bromoacetate and zinc gave β-amino esters **135**[37].

Scheme 39

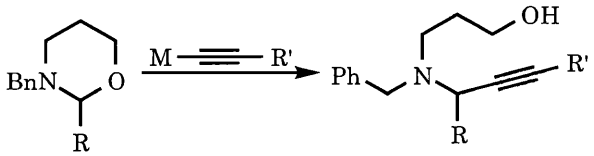


R= Me, Et, i-Pr

133 **135**

β-Amino acetylenes **136** have been prepared by ring opening of aminal **133** with alkynyl anions (Scheme 40)[38], however yields were at best only 60%.

Scheme 40

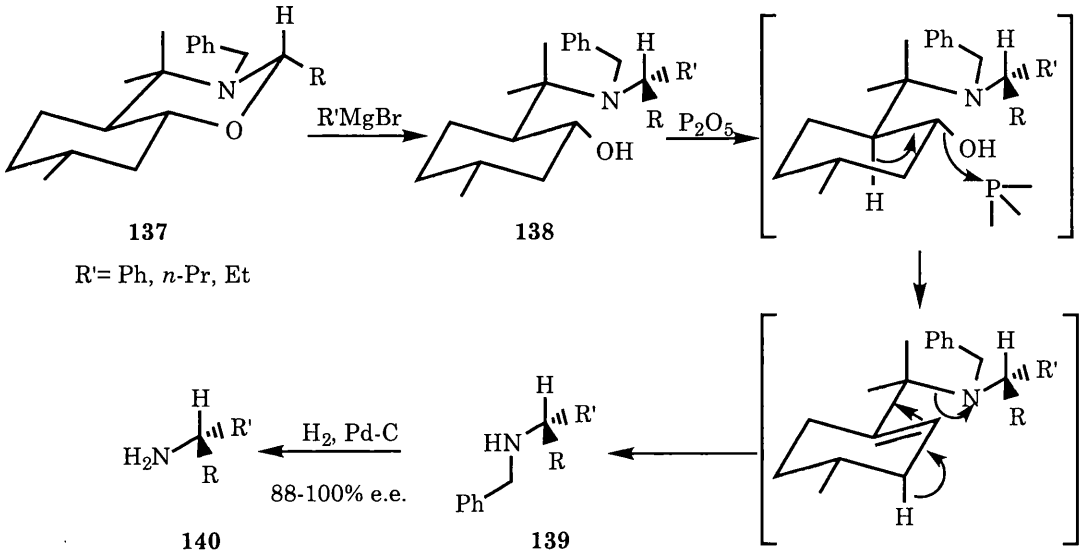


133 **136**

R= H, Ph R'= TMS, Ph M= F_2B, $(i\text{-PrO})_3Ti$

The preparation of a chiral amine has been achieved by ring opening of aminal **137** (Scheme 41)[22].

Scheme 41



Reaction of aminal **137** with Grignard reagent gave alcohol **138**. Elimination of the auxiliary gave amine **139**, which was then debenzylated by catalytic hydrogenation to give amine **140** in good to excellent e.e.

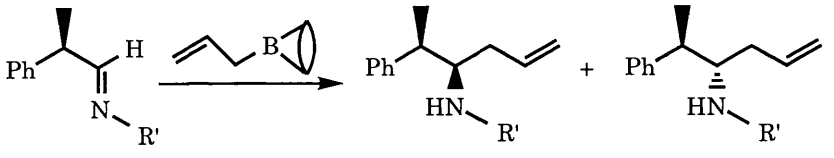
1.5 Preparation of homochiral unsaturated amines

Although the preparation of homochiral unsaturated amines by ring opening of 6-membered aminals (Scheme 4) has not been described, other methods have been invented , and these generally rely on the addition of an nucleophilic allyl eqivalent to a chiral imine.

For example, Yamamoto *et al.* described the addition of an allyl group using allyl 9-borabicyclo-[3.3.1]-nonane (allyl-9-BBN) to chiral imines with very high 1,2 and 1,3 asymmetric induction[39].

Treatment of imine **141** with allyl-9-BBN (1,2 induction) gave chiral amine **142** with excellent diastereoselectivity (Scheme 42).

Scheme 42

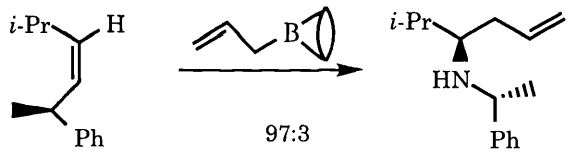


141 **142** **143**

R'= *n*-Pr, **141:142** = 96:4
R'= *i*-Pr, **141:142** = 100:0

Likewise, addition of allyl-9-BBN to the chiral imine **144** (Scheme 43) proceeded with very high 1,3-asymmetric induction.

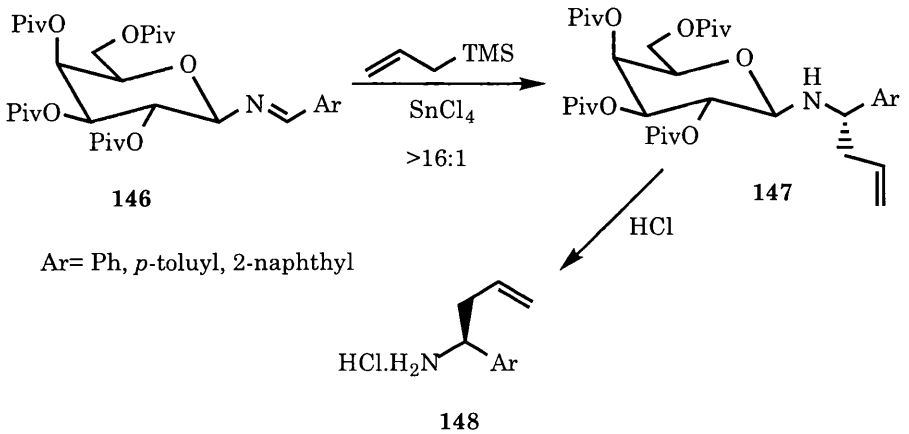
Scheme 43



144 **145**

Kunz *et al.* have used the imine **146** derived from galactopyranosylamine as a chiral auxiliary (Scheme 44)[40].

Scheme 44



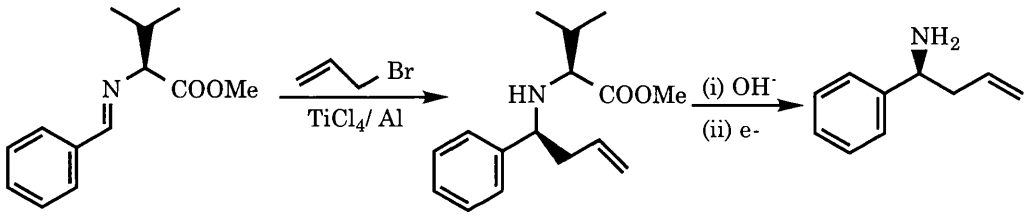
146 **147** **148**

Ar= Ph, *p*-toluyl, 2-naphthyl

Addition of allyltrimethylsilane to **146** in the presence of stannic chloride gave homoallylic amines **147** with excellent diastereoselectivity. The auxiliary was then cleaved to give amine **148**.

An imine **149** derived from (*S*)-valine has been used to prepare homochiral unsaturated amines by addition of allyl bromide mediated by a titanium/aluminium bimetal system to give ester **150** (Scheme 45)[41].

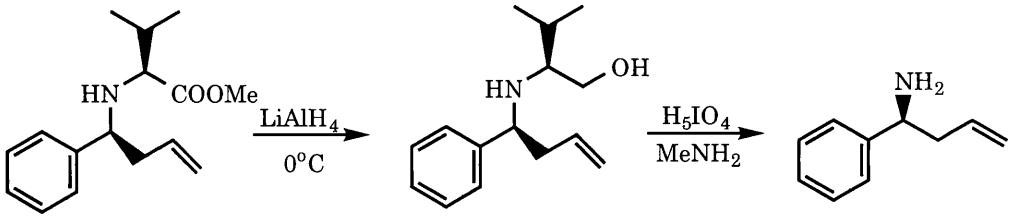
Scheme 45



149 **150** **151**

The auxiliary was then removed by electrolysis to reveal the homochiral amine. Savoia *et al.* later found that deprotection of **150** by electrolysis gave inconsistent results, so a new route was devised (Scheme 46)[42].

Scheme 46

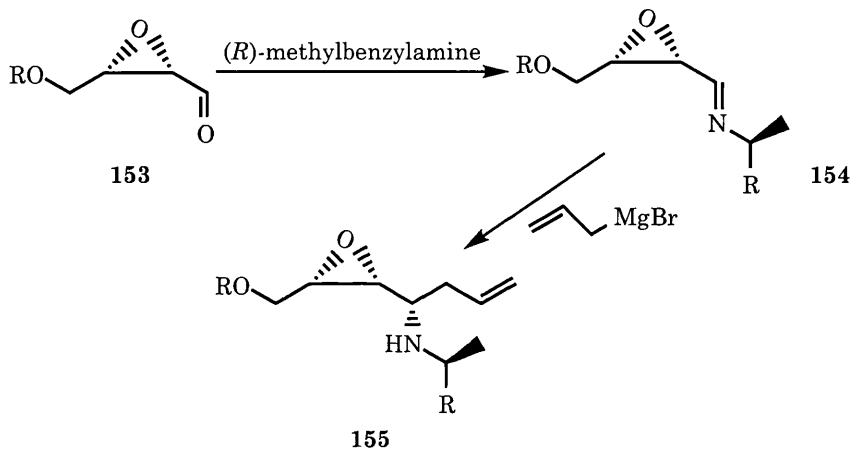


150 **152** **151**

Reduction of **150** with lithium aluminium hydride at low temperature furnished alcohol **152**. Oxidative cleavage with periodic acid in the presence of methylamine gave amine **151**.

Homochiral amines have been prepared by addition of Grignard reagents to α,β-epoxyimines **154**, which are prepared from epoxyaldehydes **153** and (*R*)-methylbenzylamine (Scheme 47)[43].

Scheme 47

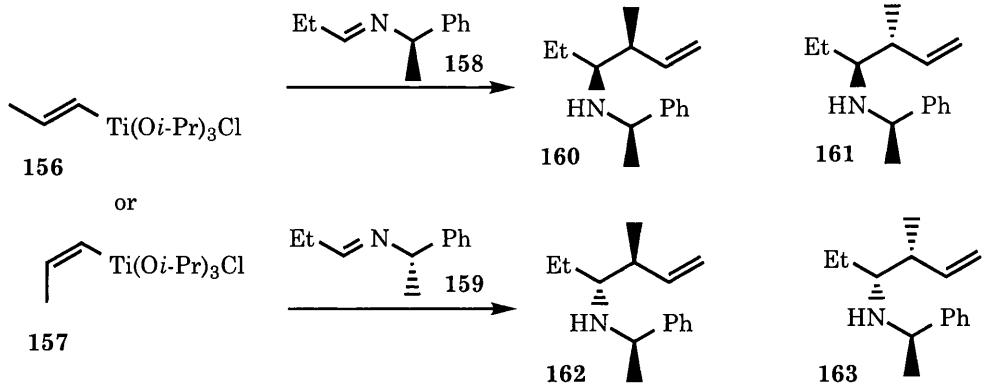


153 **154** **155**

Addition of allylmagnesium bromide to the imine **154** gave homochiral aminoepoxide **155**. Surprisingly, addition of allymagnesium bromide to the imine derived from **152** and (*S*)-methylbenzylamine also gave **155** - the stereochemistry on the nitrogen had no bearing on the outcome of the reaction.

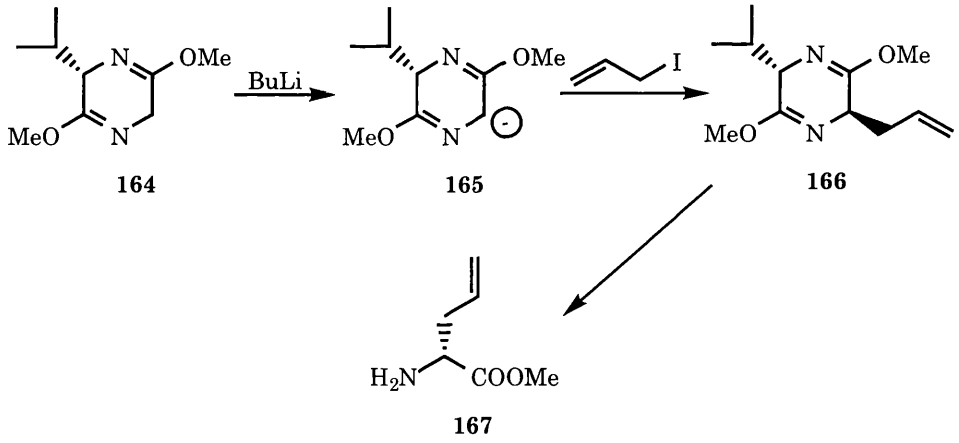
The reactions previously described can only yield monosubstituted homoallyic amines. Sato *et al.* found that the addition of organotitanium reagent **156** or **157** to imines **158** and **159** enabled all four stereoisomers of a disubstituted homoallylic amine to be prepared (Scheme 48)[44]. The imines **158** and **159** were prepared from methylbenzylamine as both enantiomers are cheap and readily available.

Scheme 48



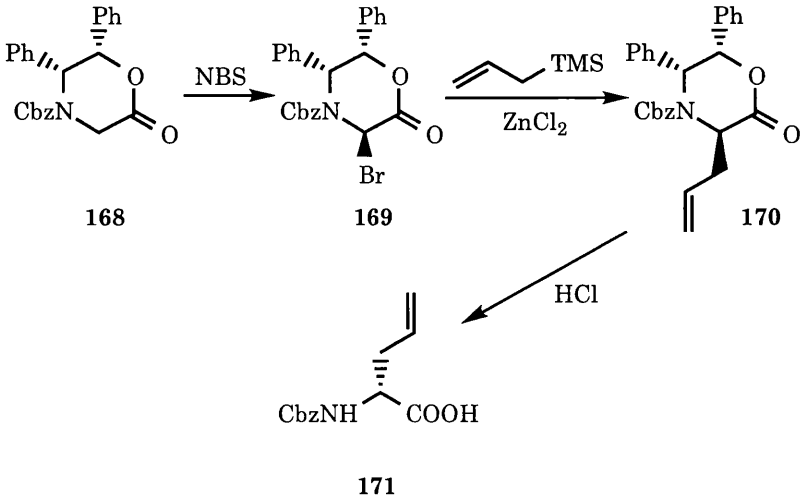
The Schöllkopf methodology has been used to prepare the chiral amino acid **167** (Scheme 49)[1].

Scheme 49



Addition of allyl iodide to enolate **165** and cleavage of the auxiliary from **166** gave **167** in excellent yield. Williams *et al.* have described the use of oxazinone **168** as a chiral auxiliary (Scheme 50)[45].

Scheme 50



168 **169** **170** **171**

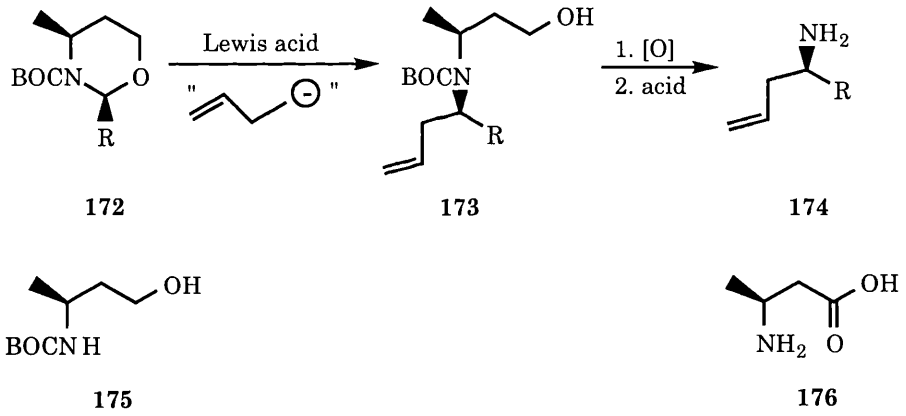
Bromination of **168** with N-bromosuccinamide gave **169**, which was then alkylated with allyltrimethylsilane to give **170**. Removal of the chiral auxiliary revealed the glycine derivative **171**.

2. Synthesis of the β-amino alcohol chiral auxiliary

2.1 Project overview

The objective of the project was to design a novel methodology for the preparation of chiral allylic amines. It was envisaged that these amines could be synthesised from chiral tetrahydro-1,3-oxazines (aminals) by ring opening with a nucleophilic allyl equivalent, then removal of the chiral auxiliary (Scheme 51).

Scheme 51



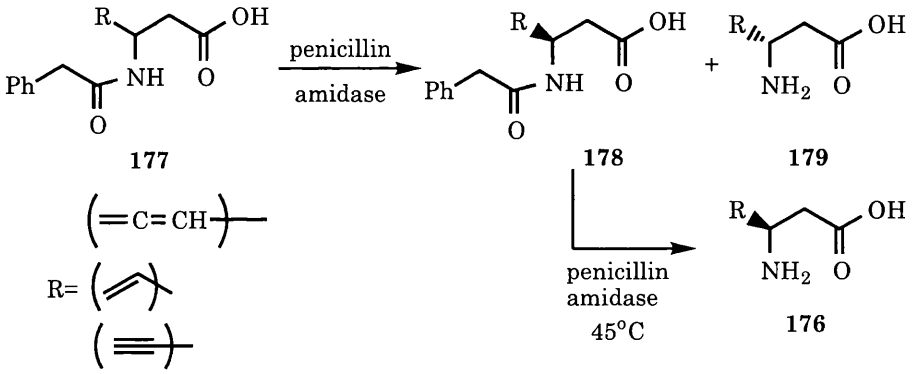
The aminal **172** is formally a condensation product of a 1,3-amino alcohol and an aldehyde, and therefore an efficient synthesis of the chiral amino alcohol **175** was required. It was thought that this alcohol could be prepared from the corresponding chiral amino acid **176** and accordingly, methods for preparing **176** were investigated.

In this chapter, literature methods for preparing amino acids such as **176** will first be reviewed, then the methods used during this project discussed.

2.2 Resolution of racemates by enzymatic and crystallisation methods

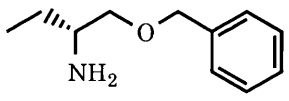
Margolin has recently described the resolution of a number of racemic GABA inhibitors into both enantiomers by enzymatic resolution (Scheme 2)[46].

Scheme 52



The phenylacetyl-protected racemic acid was subjected to hydrolysis by penicillin amidase in a pH7 buffer at room temperature, which exclusively deprotected the (*S*)-enantiomer of racemate **177** to give **179**. The (*R*)-enantiomer **176** was revealed by hydrolysis of **178** with the same enzyme at higher temperature. Pig kidney esterase has also been used to affect a similar transformation of trifluoroacetyl-protected 3-aminobutanoic acid[47]. The use of enzymatic resolution methods is not widespread, and indeed studies in our laboratory[48] using *candida cylindracea* lipase to resolve the enantiomers of 3-aminobutanoic acid have so far proved unsuccessful.

The resolution of amino acids has also been carried out by resolution of diastereomeric salts[49]. Brown *et al.* have used the O-benzyl ether derivative of (*R*)-2-aminobutan-1-ol **180** as a chiral base to resolve racemic phenylglycine and tyrosine.



180

The diastereomeric salts derived from **180** were separated by fractional crystallisation. Each salt was then acidified, which revealed the chiral amino acid. An advantage of this synthesis is that the chiral base **180** could be recycled, however the disadvantage was that several crystallisations were necessary before the diastereomeric salts were enantiomerically pure, and hence yields of the chiral amino acids were low.

There have been several synthetic methods devised for the preparation of β-amino acids and these are described in more detail below.

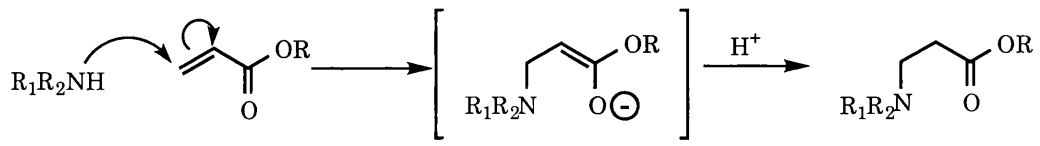
2.3 Synthesis of β-amino acids

Although not as widespread in nature as α-amino acids, β-amino acids are still important, and exist in many different natural products[50]. As a result there has been much effort directed toward developing stereoselective syntheses of these acids.

2.3.1 Michael addition of an amine equivalent to an α,β-unsaturated carbonyl

One of the conceptually simplest methods for the preparation of β-amino acids and their derivatives is the Michael addition of an amine equivalent to an α,β-unsaturated carbonyl group **181** which gives adduct **182** (Scheme 53).

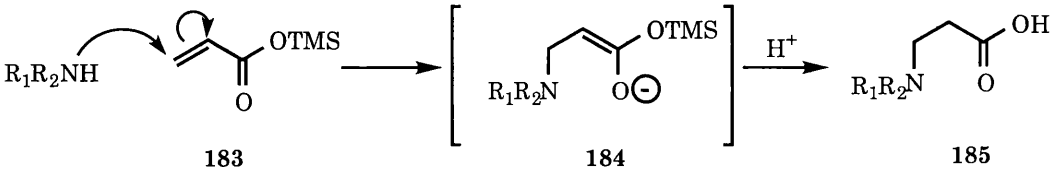
Scheme 53



181 **182**

For example, Kwiatkowski *et al.* recently described a synthesis of β-alanine derivatives, which were prepared from the addition of secondary amines to trimethylsilyl acrylate **183** (Scheme 54) to give the trimethylsilyl esters **184** which were then hydrolysed in situ to reveal the amino acid **185**[51].

Scheme 54

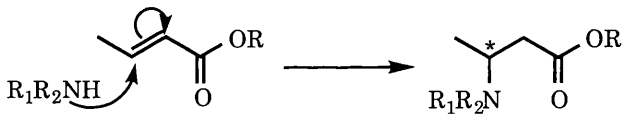


183 **184** **185**

An advantage of this synthesis is that there is no acid or base catalysis for the Michael addition, which improves substrate compatibility in other parts of a complicated molecule.

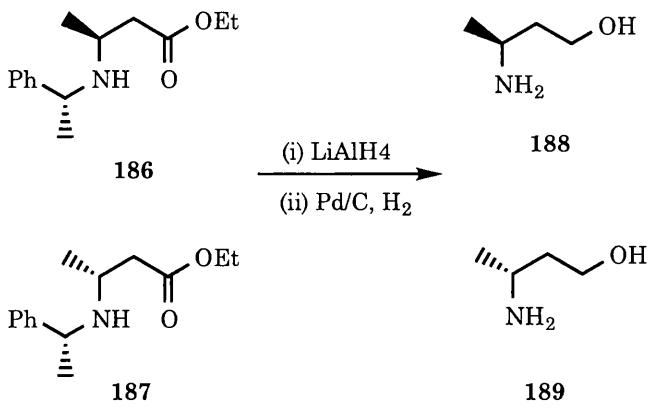
If the α,β-carbonyl compound is substituted at the β-position, a new chiral centre will be created on addition of the amine equivalent (Scheme 55).

Scheme 55



One of the earliest attempts to exploit this for the preparation of chiral β-amino acids was made by Kinas *et al.* who prepared a diastereomeric mixture of esters from the amine 1-(*S*)-methylbenzylamine and ethyl crotonate (Scheme 56)[52].

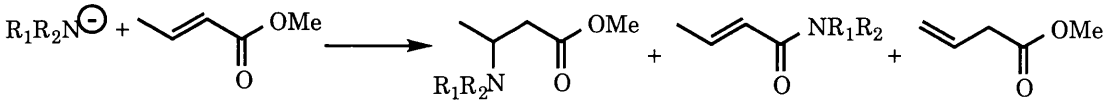
Scheme 56



The diastereomers **186** and **187** were separated by flash chromatography, the ester reduced and the auxiliary removed by catalytic hydrogenation to reveal the chiral amino alcohols **188** and **189**. Unfortunately, due to the reversibility of the Michael addition, the yield of the diastereomers was low, at about 30%.

To overcome this difficulty, the lithium amide instead of the free amine can be used for the Michael addition (Scheme 57), as this reaction is not reversible[53].

Scheme 57



190a,b,c **191a,b,c** **192a,b,c**

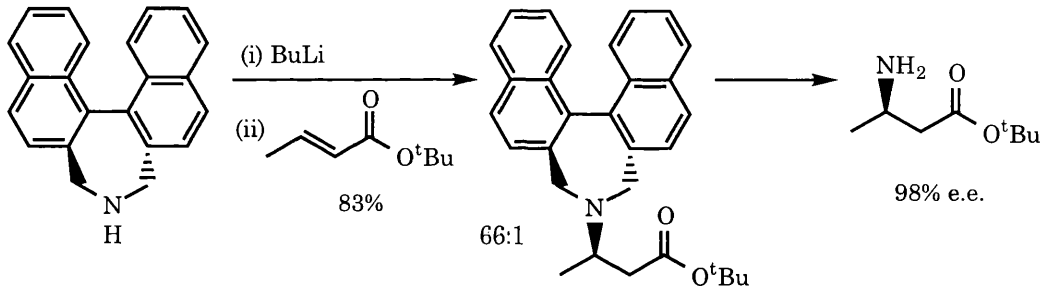
a: R_1=R_2= isopropyl
b: R_1=H, R_2=Bn
c: R_1=Bn, R_2=trimethylsilyl

Unfortunately, depending on the substituents on the nitrogen atom, poor regioselectivity is observed and varying amounts of **190**, **191** and **192** are obtained. Indeed, Yamamoto *et al.* found that addition of LDA to methyl

crotonate gave a low yield of **190a,** and significant amounts of **192a**, while addition of lithium benzylamide gave **191b** as the majority product[53]. However, addition of lithium benzyltrimethylsilyl amide gave exclusively **192c** in high yield.

Attempts to control the enantioselective and regioselective addition of the lithium amide have centred on using chiral secondary amines and variation of the ester group to obtain good diastereomeric excesses. For example, Hawkins *et al.* used the lithium amide of **193** to add to *t*-butyl crotonate in DME to give exclusively 1,3 addition and high d.e. (Scheme 58)[54].

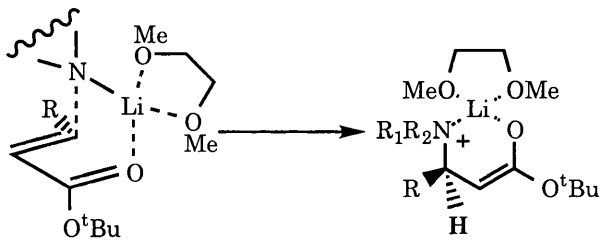
Scheme 58



193 **194** **195**

Removal of the auxiliary from **194** by catalytic hydrogenation in the presence of morpholine revealed the free amino ester **195**. The addition of the amide is thought to proceed via a 6-membered transition state **196** (Scheme 59), where the given enantiomer of the amide approaches the least hindered face of the olefin to give complex **197**.

Scheme 59

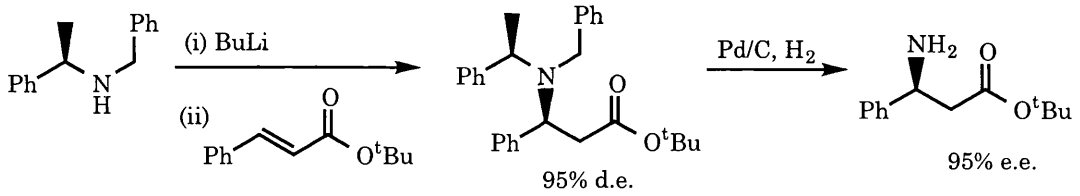


196 **197**

It was also found that Z-olefins gave the opposite diastereomer compared to E-olefins.

Another approach to enantioselective addition of lithium amides has recently been described by Davies *et al.* (Scheme 60)[55].

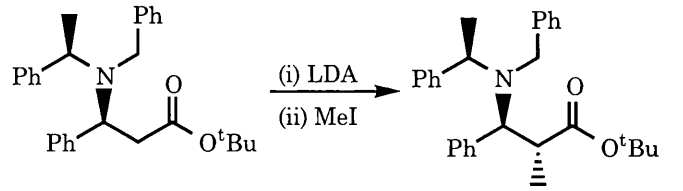
Scheme 60



198 **199** **200**

The lithium amide derived from the chiral amine **198** was added to *t*-butyl cinnamate to give the Michael adduct **199** in high yield and excellent diastereomeric excess. Removal of the benzyl groups by catalytic hydrogenation revealed the chiral amino ester **200**. This methodology has also been extended to the synthesis of α-substituted-β-amino acids (Scheme 61)[56].

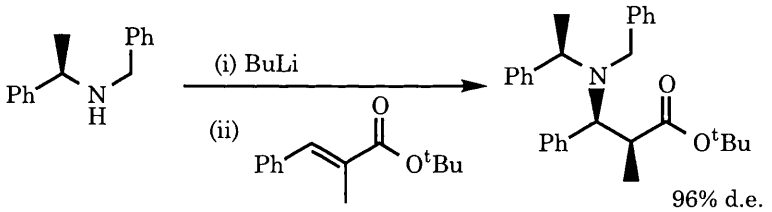
Scheme 61



199 **201**

Deprotonation of the α-position of Michael adduct **199** with LDA followed by trapping of the resulting anion with methyl iodide gave the α-substituted (*2R, 3R*) amino ester **201** with excellent diastereoselectivity. To prepare the (*2S,3R*) derivative, the lithium amide of **198** was added to *t*-butyl-2-methyl-cinnamate (Scheme 62) to give Michael adduct **202** in high yield and diastereomeric excess.

Scheme 62



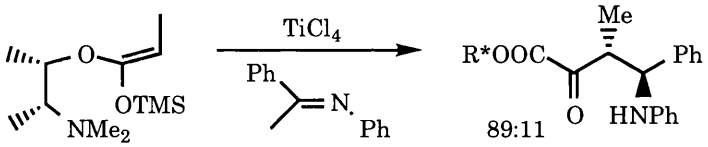
198 **202**

2.3.2 Nucleophilic addition to imines

Another methodology which has received much attention for the preparation of β-amino acids is the nucleophilic addition of organometallic reagents or enolates to imines or imine equivalents.

Several workers have exploited the addition of chiral silyl ketene acetals to imines, promoted by various catalysts. Gennari *et al.* have reacted the chiral silyl ketene **203** with benzylidene in the presence of titanium tetrachloride to give amino ester **204** in good yield and excellent d.e. (Scheme 63)[57].

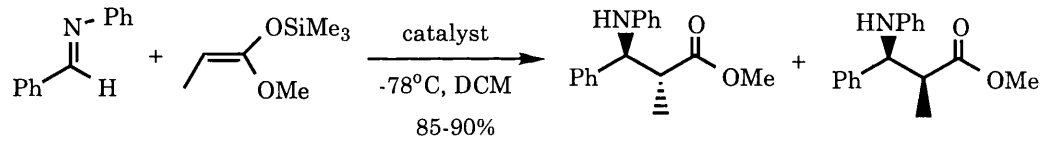
Scheme 63



203 **204**

Mukaiyama *et al.* took this approach further in their search for an efficient catalyst for their synthesis of β-amino acids by screening a number of metal salts in order to determine their effectiveness as Lewis acids (Scheme 64)[58].

Scheme 64

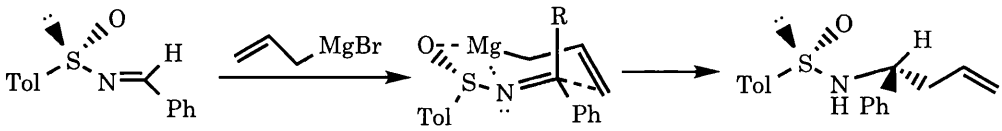


205 **206** **207** **208**

Reaction of imine **205** and ketene silyl acetal **206** with an inorganic salt as catalyst gave esters **207** and **208**. The two best catalysts were found to be iron (II) iodide and trityl hexachloroantimonate, both of these gave the esters **207** and **208** in high yield, and the anti:syn ratio was 92:8.

Nucleophilic additions to chiral sulphinimines have also received much attention. For example Hua *et al.*[15] showed (Scheme 65) that addition of allylmagnesium bromide to chiral sulphinimine **209** proceeds via intermediate **210** to give **211** in almost quantitative yield and >95% d.e.[59]

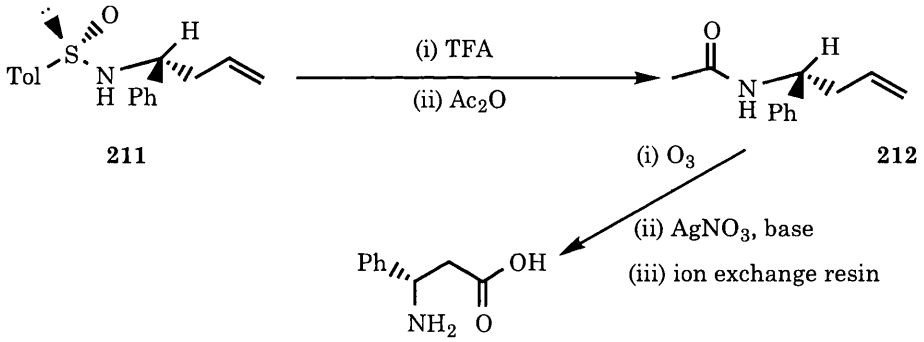
Scheme 65



209 **210** **211**

To convert to the β-amino acids the tosyl group of **211** was removed with trifluoroacetic acid, then reaction with acetic anhydride gave **212** (Scheme 66).

Scheme 66

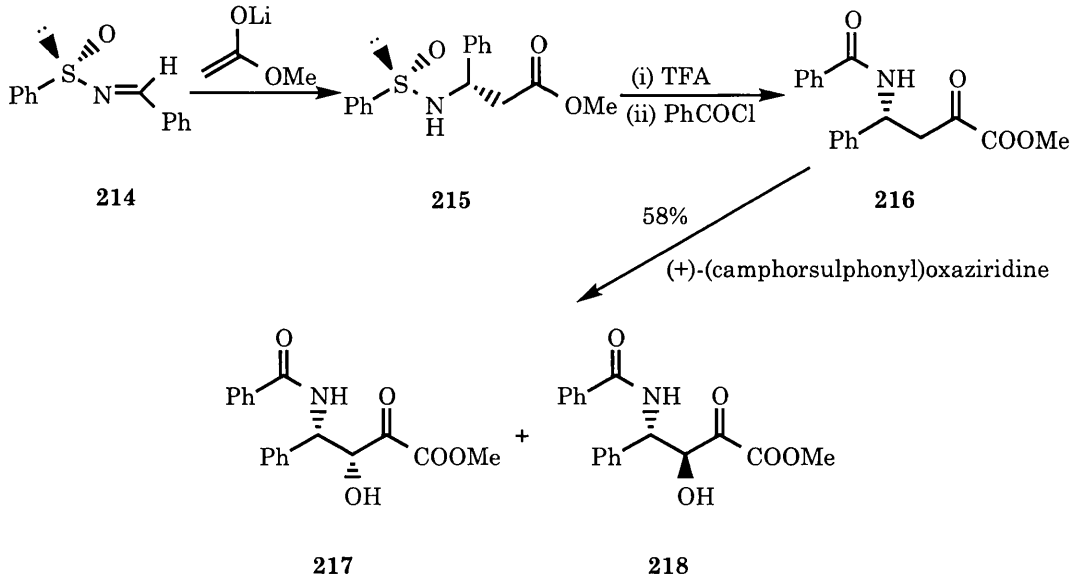


211 **212** **213**

A series of standard transformations was then used to enable amine **212** to be converted to amino acid **213** in excellent yield.

Davis *et al.* have recently used this methodology to prepare the C-13 side chain of taxol (Scheme 67)[60]. Protected acid **215** was prepared by addition of the lithium enolate of methyl acetate to sulphinimine **214**. The sulphonyl moiety of **215** was cleaved with TFA and reaction with benzoyl chloride gave **216**.

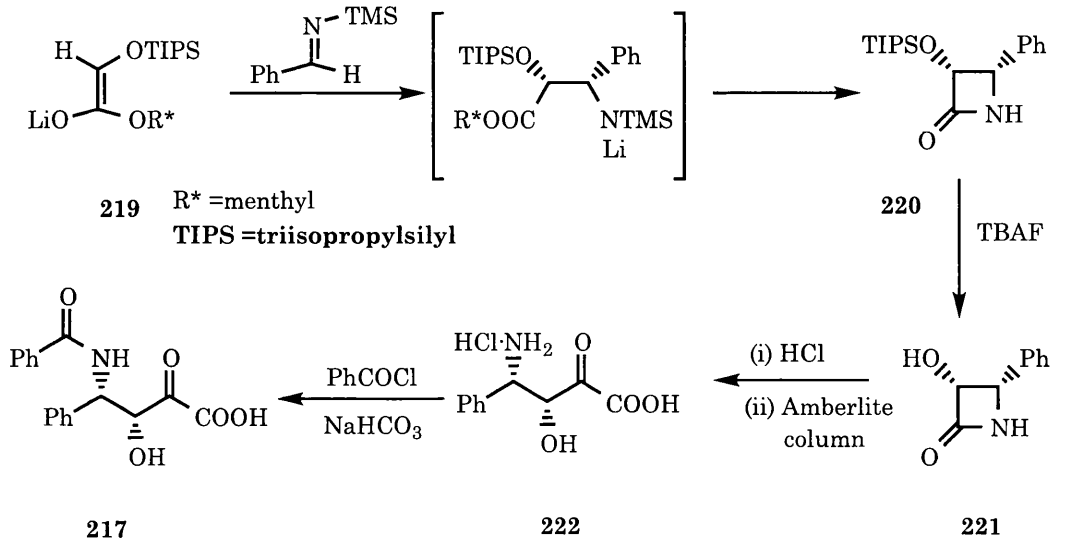
Scheme 67



Hydroxylation of the enolate dianion of **216** with (+)-(camphorsulphonyl)oxaziridine in the presence of lithium chloride gave a syn:anti mixture of α–OH acids in good yield. This mixture was purified by flash chromatography to give the C-13 taxol side chain **217** in good yield and excellent e.e.

Ojima *et al.* have prepared acid **217** by a different imine addition reaction (Scheme 68)[61].

Scheme 68

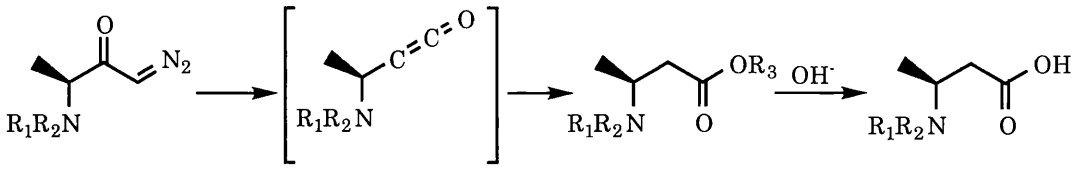


The lithiated enolate **219** with menthol as the chiral auxiliary was added to the imine to give an intermediate which spontaneously cyclised to the β-lactam **220**. Removal of the TIPS group gave lactam **221** and opening of the lactam with HCl furnished the amino acid hydrochloride **222** which was immediately N-protected to give the taxol side chain **217**.

2.3.3 Homologation of α-amino acids

α-Amino acids are abundant in nature, and thus much effort has been directed toward extending the carbon chain by one atom to give the corresponding β-amino acids. This has generally been accomplished by the Arndt-Eistert reaction (Scheme 69), which proceeds via a diazoketone intermediate **223**. This then undergoes the Wolff rearrangement to give first a ketene **224**, then a β-amino acid ester **225** which is then saponified to reveal the free acid **226**. The free acid can be prepared directly if water is used as the solvent for this reaction.

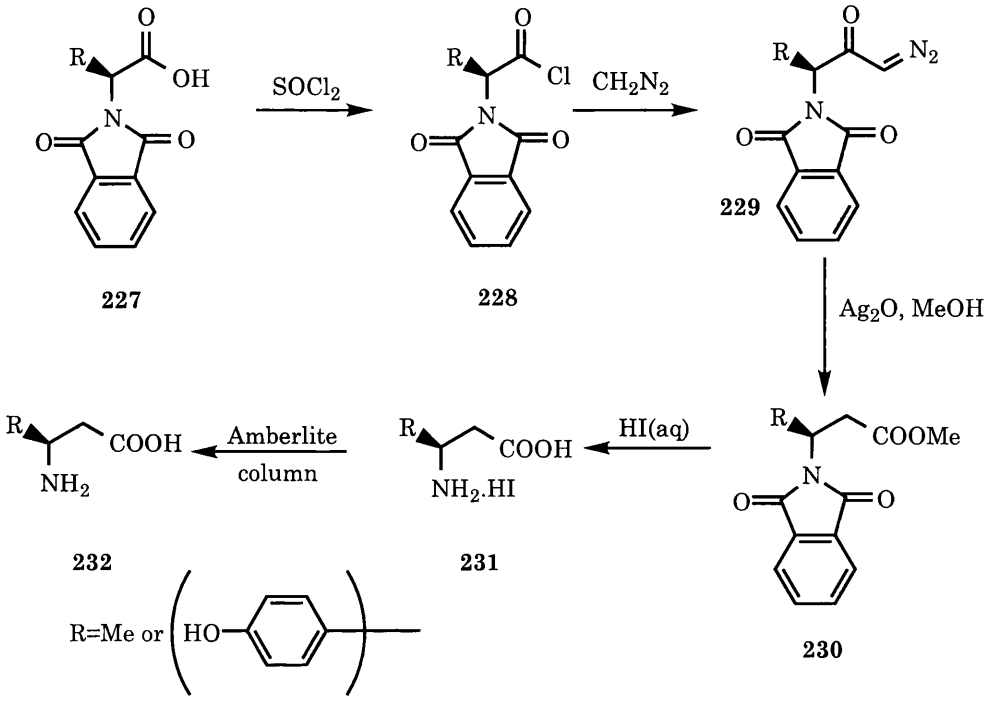
Scheme 69



223 **224** **225** **226**

In general, there are two main methods of preparing the diazoketone intermediate: via the acid chloride, or the mixed anhydride of the α-amino acid. These procedures have been documented in the literature and a number of protecting groups for the nitrogen have been used. For example, Balenovic *et al.* prepared the β-amino acid derivative of tyrosine and the β-amino acid derivative of alanine and leucine by way of the N-phthalimido acid chlorides of the amino acids (Scheme 70)[62-64].

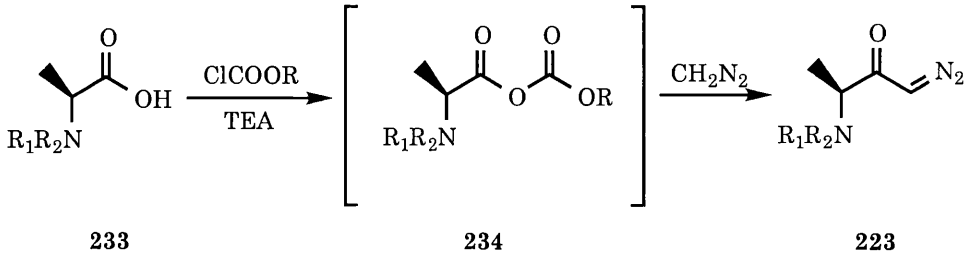
Scheme 70



The acid chloride **228** was stirred with diazomethane to give the diazoketone **229** in good yield. Induction of the Wolff rearrangement by silver oxide gave the ester **230**. The ester was hydrolysed and the N-phthalimide protecting group removed with hydriodic acid to give the amino acid hydro-iodide **231**, the free amino acid **232** was revealed by passing the hydro-iodide through a column of ion-exchange resin.

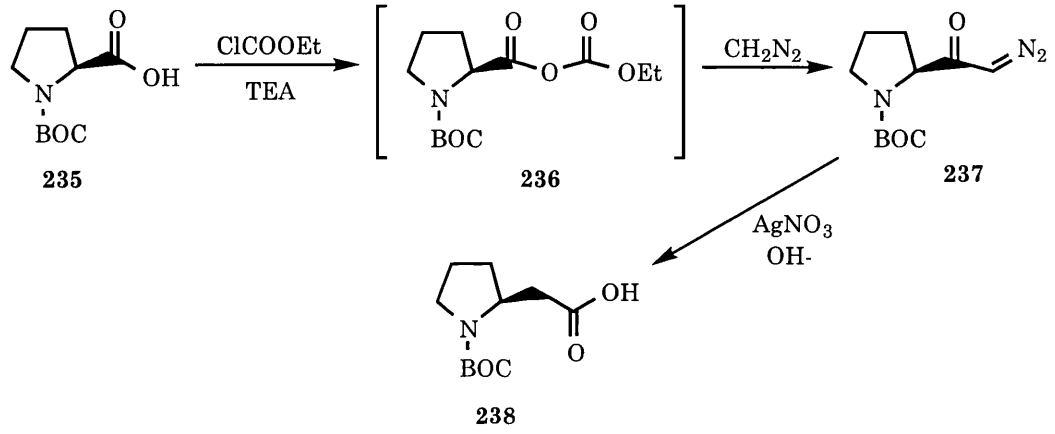
In more recent papers, the diazoketone has been prepared by way of a mixed anhydride intermediate (Scheme 71).

Scheme 71



For example, Ondetti *et al.* prepared β-proline from N-BOC proline as shown in Scheme 72[65]. Reaction of N-BOC proline **235** with ethyl chloroformate gave mixed anhydride **236**, which was then added to a solution of diazomethane to give **237**. Induction of the Wolff rearrangement revealed acid **238**.

Scheme 72



235 **236** **237** **238**

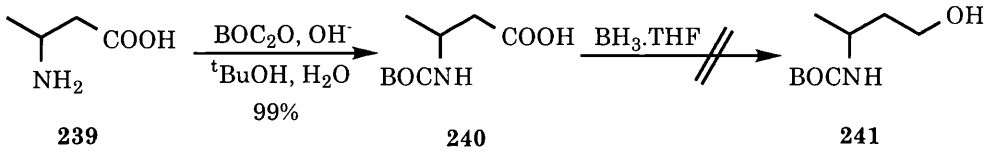
Balasfini *et al.* have prepared N-Cbz proline using the same procedure as Ondetti above[66], and Plucinska *et al.* prepared a series of β-amino acids with both Cbz and BOC protection[67]. The melting points and optical rotations of the diazoketones prepared differed significantly from those reported in earlier papers. This discrepancy was attributed to varying amounts of methyl ester of the α-amino acid being present as a contaminant (formed due to small quantities of water being present in the reaction).

None of these synthetic strategies looked optimal for the preparation of the chiral auxiliary **175**, so it was therefore necessary to design a new synthetic methodology.

2.4 Preparation of racemic N-BOC 3-aminobutan-1-ol (241)

To optimise the conditions of ring formation and aminal ring opening, racemic amino alcohol **241** was required for the preliminary experiments. At first, it was thought that a protected amino acid could be reduced, and this reaction was attempted as shown in Scheme 73.

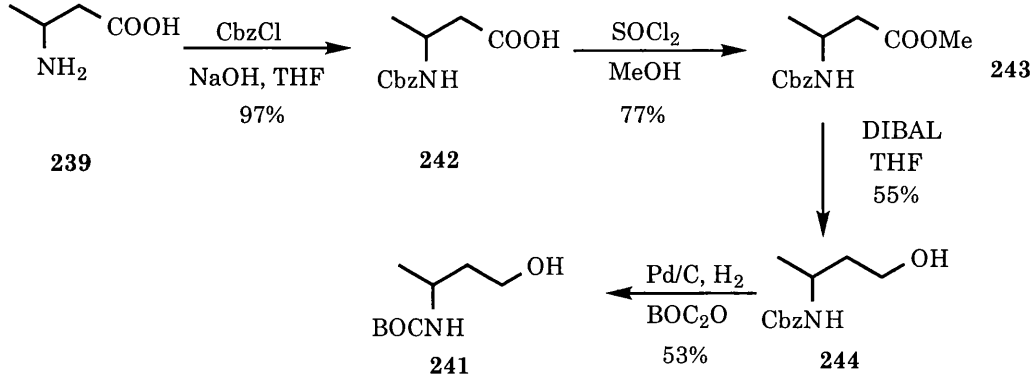
Scheme 73



Commercially available 3-amino-butanoic acid **239** was protected in quantitative yield, to give **240**[68]. Attempted reduction of **240** with borane-THF complex proved to be unsuccessful, in contrast to a previous report[69].

The racemic N-BOC amino alcohol was initially prepared as outlined in Scheme 74[69].

Scheme 74



3-Amino butanoic acid **239** was N-protected using benzyl chloroformate to give acid **242**, then this was esterified with methanol and thionyl chloride to give the

ester **243**. Reduction of the ester with DIBAL in toluene gave the protected amino alcohol **244** and catalytic hydrogenation of alcohol **244** in the presence of di-*t*-butyl-dicarbonate furnished the desired N-BOC protected amino alcohol **241**[71].

The two main disadvantages of this strategy are the large number of steps required and the low overall yield of alcohol **241** obtained, so this synthesis was abandoned.

It was envisaged that direct preparation of alcohol **241** by reduction of 3-amino butanoic acid **239**, and protection of the resulting 3-amino butan-1-ol without purification would provide a better route to the required amino alcohol.

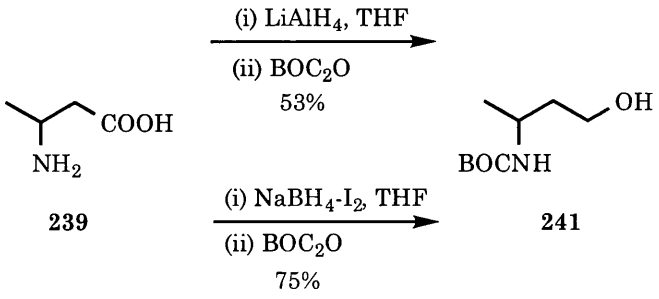
The earliest report of the successful preparation of amino alcohols from amino acids was by Karrer *et al.* who prepared leucinol, alaninol and phenylalaninol by reduction of the relevant amino acid ester with sodium in absolute ethanol[72]. In a subsequent report, Karrer prepared a range of amino alcohols by reduction of the amino acids ester with lithium hydride in ether[73].

Later, it was shown that the free amino acid could be reduced directly by lithium aluminium hydride[74], and variations of this reduction became standard. Other reductions have been reported[75], but proved to be difficult to reproduce, used noxious chemicals or used high cost materials.

Recently, two reports have been published concurrently, which utilise sodium borohydride as the reducing agent. Ahito *et al.* have used a sodium borohydride-sulphuric acid complex for the reduction[76], and Meyers *et al.* used sodium borohydride-iodine as the reducing agent[77]. The former method has the advantage that the solvent (THF) does not need to be rigorously dried.

Therefore, two separate methods were attempted (Scheme 75).

Scheme 75

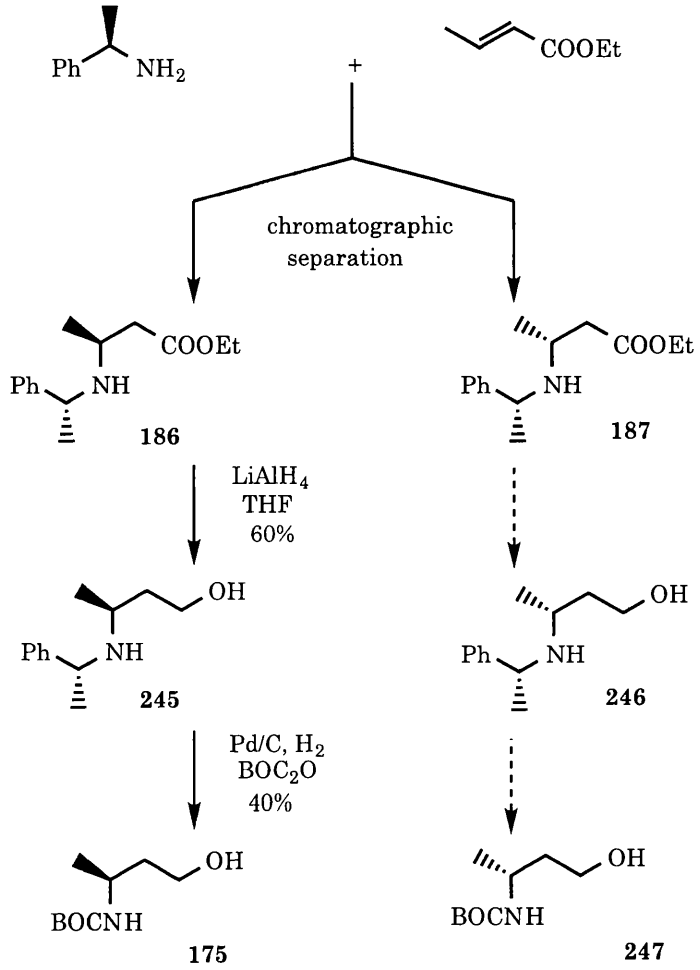


Reduction of the amino acid **239** with lithium aluminium hydride[74] in THF and protection of the nitrogen without further purification furnished alcohol **241** in a best yield of 53%. However, considerable difficulty was encountered in removing aluminium salts after workup, this caused the yield of **241** obtained to vary widely. Instead, the amino acid was reduced using the method of Meyers[77] (sodium borohydride-iodine in THF) and after workup the free amino alcohol was protected without further purification to give the desired product **241** in excellent yield. This route was used for all subsequent preparations of **241**.

2.5 Preparation of 3-(*S*)-N-BOC amino butan-1-ol (175)

For the ring opening methodology described in section 4.2 to be useful, a preparation of chirally pure N-BOC protected amino alcohol had to be devised. Initially, chiral amino alcohol **175** was prepared following the method of Kinas[52], and this is outlined in Scheme 76.

Scheme 76



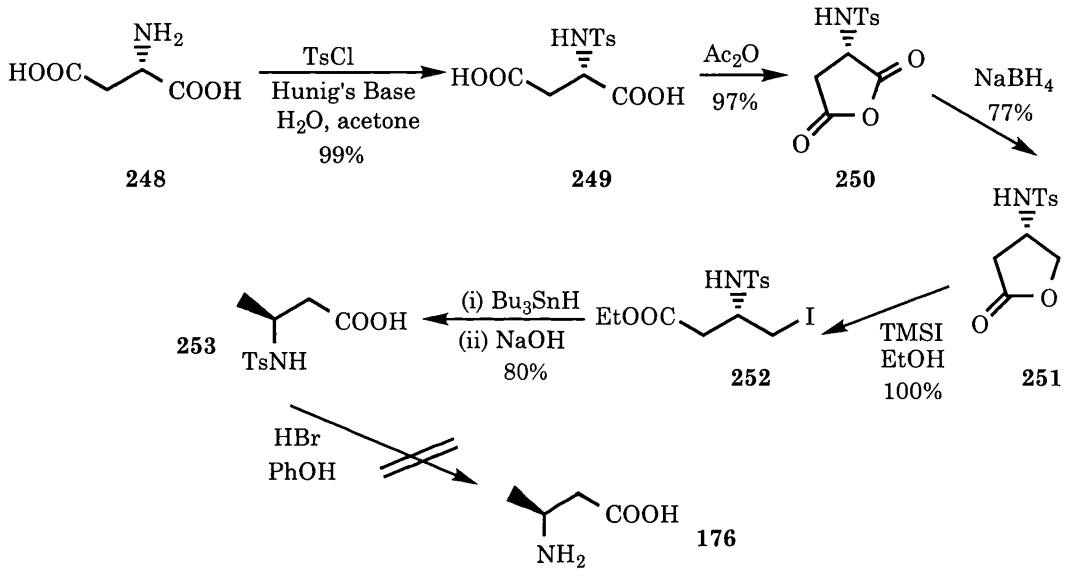
1-(*S*)-Methylbenzylamine was condensed with ethyl crotonate in a Michael reaction, by refluxing in ethanol. This gave a mixture of diastereomers **186** and **187** which were separated by flash chromatography, then (*S*,*S*) ester **186** was reduced using lithium aluminium hydride to give alcohol **245**, catalytic hydrogenation of **245** in the presence of di-*t*-butyl dicarbonate gave the required N-BOC amino alcohol 175[78] in low overall yield. A similar sequence using (*R*,*S*) ester **187** would have yielded alcohol **247**, but these reactions were not performed.

This synthesis was abandoned for two reasons. Firstly, the esters **186** and **187** proved very difficult to separate effectively, so only small quantities could be

prepared at any given time, and secondly the low overall yield and large number of steps made the process very inefficient.

A second method used to prepare the chiral auxiliary was the method of Jefford[79], outlined in Scheme 77.

Scheme 77

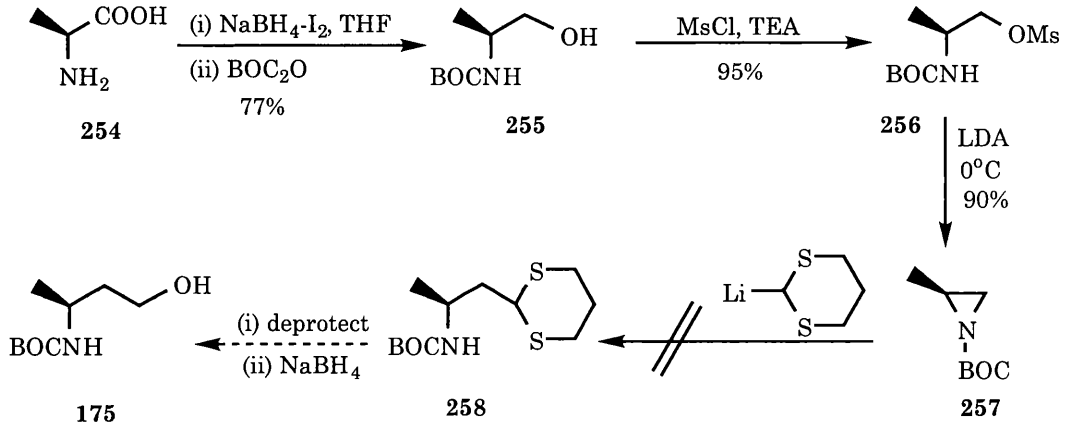


(*S*)-Aspartic acid **248** was N-tosylated in quantitative yield to give **249**, and this was cyclised with acetic anhydride to give the succinate derivative **250**. This was then selectively reduced to the lactone **251** using sodium borohydride, and lactone **251** was ring opened with trimethylsilyliodide to give the ester **252**. The iodine was removed by reduction with tributyltin hydride, then the ester saponified to reveal N-tosylated-β-amino acid **253**.

Unfortunately, it proved impossible to remove the tosyl group from **253**, in contrast to published work[80]. Heating of acid **253** under reflux with concentrated aqueous hydrogen bromide and phenol gave none of the desired product **176**, and only starting material was recovered, so this synthesis was also abandoned.

A third synthetic strategy tried is outlined in Scheme 78.

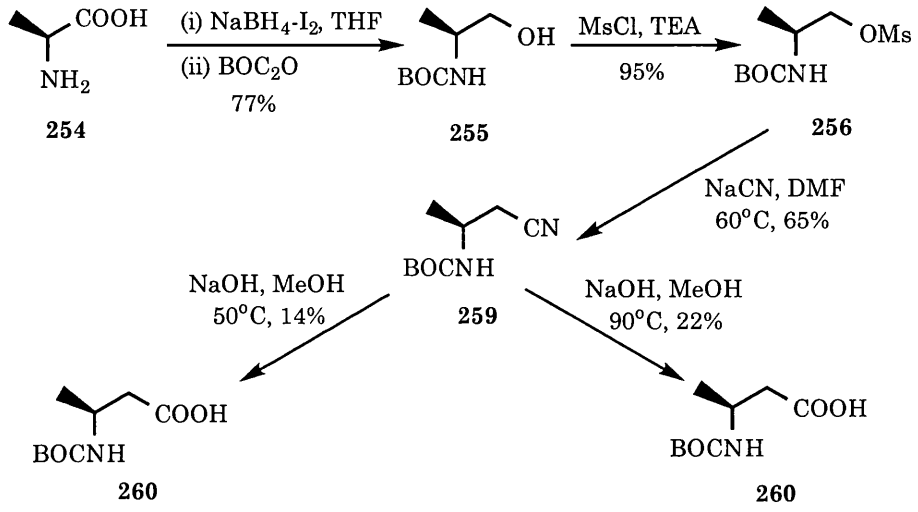
Scheme 78



(*S*)-Alanine **254** was reduced using the method of Meyers[77], and subsequently N-protection of the resulting amino alcohol without further purification furnished N-BOC-(*S*)-alaninol **255**[81] in very good yield. The protected alaninol **255** was O-mesylated with methanesulphonyl chloride and triethylamine, then treatment of the resulting mesylate **256**[82] with lithium di-isopropylamide furnished the chiral N-BOC aziridine **257**[83] in excellent yield. It was envisaged that the aziridine could be ring opened with a lithiated dithiane exclusively at the least hindered position to give the protected N-BOC amino aldehyde **258**, which could then be deprotected and the aldehyde reduced to reveal the desired N-BOC amino alcohol **175**. Unfortunately, no ring opening of the aziridine was observed, however it has been found that thianes can be difficult to lithiate effectively[84], this is a possible explanation for the failure of the reaction.

A fourth synthetic strategy is outlined in Scheme 79.

Scheme 79



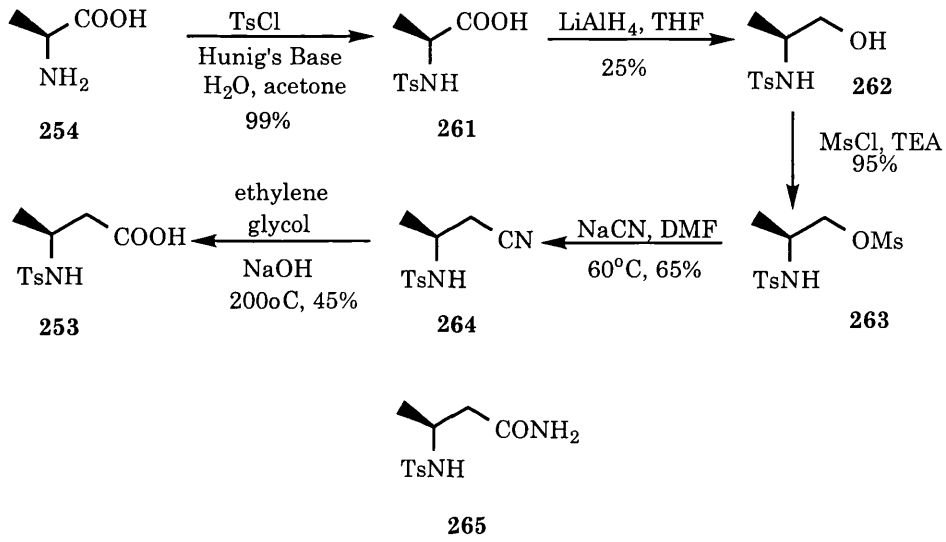
(*S*)-Alanine **254** was reduced using the method of Meyers[77], and protection of the resulting amino alcohol gave N-BOC-(*S*)-alaninol **255**[80]. This was then mesylated using methanesulphonyl chloride and triethylamine to give **256**[82]. The mesylate was displaced by heating with sodium cyanide in DMF at 60°C to give nitrile **259**[81v] in good yield. Interestingly, it was found that this reaction does not proceed well in DMSO, the usual solvent for this reaction. Heating of the reaction mixture above 60°C caused severe side reactions, with consequent low recovery of nitrile. It was also found to be necessary to purify the nitrile at this stage to prevent difficulty in separating the desired protected amino alcohol **175** from residual alaninol at the end of the synthetic sequence. With **259** in hand, efforts were then directed to converting the nitrile moiety to either an acid or aldehyde functionality.

Firstly, the nitrile was subjected to hydrolysis by methanolic sodium hydroxide at 50°C, and after workup, furnished 3-(*S*)-N-BOC-amino butanoic acid **260**[85] in 14% yield. Hydrolysis at 90°C (the maximum temperature possible

before thermal decomposition of the BOC group begins) gave acid **260** in 22% yield.

To obtain more data about the susceptibility of the nitrile to hydrolysis, the N-tosyl nitrile **264** was prepared as outlined in Scheme 80.

Scheme 80



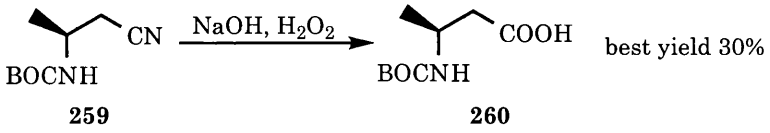
(*S*)-Alanine **253** was protected quantitatively with *p*-toluenesulphonyl chloride to give protected acid **261**[86] which was reduced with lithium aluminium hydride to give N-tosyl amino alcohol **262**[87]. The amino alcohol **262** was then subjected to mesylation to give **263** and substitution with sodium cyanide gave nitrile **264**[88].

Nitrile **264** was then subjected to hydrolysis using sodium hydroxide in refluxing ethylene glycol (200°C) to give 3-(*S*)-N-tosyl-amino butanoic acid **253** in 45% yield. TLC analysis of the reaction mixture showed that all the nitrile had been consumed, and a mass spectrum of the residue left after removal of the acid from the reaction mixture showed the presence of amide **265**. It was therefore evident that the nitrile was quickly being hydrolysed to the amide, but the amide only partially hydrolysed to the acid **253**.

A milder form of hydrolysis, using basic hydrogen peroxide has been shown by Danieli *et al.*[89] to give an excellent yield of the desired acid.

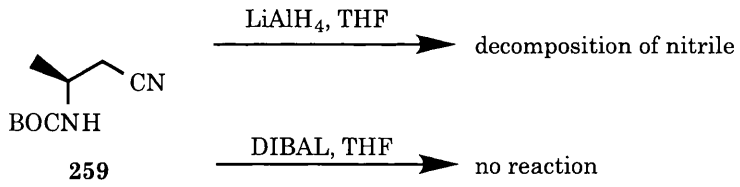
Unfortunately, this reaction proved very difficult to optimise for nitrile **259**, some runs gave a poor yield of acid **260** (up to 30%), while others resulted in extensive decomposition of the nitrile **259** and no discernible products were recovered (Scheme 81).

Scheme 81



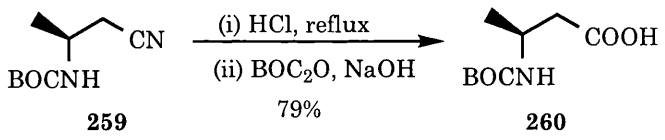
Therefore, attempts to hydrolyse nitrile **259** were abandoned and efforts were then concentrated on reducing the nitrile group to an aldehyde functionality which could then easily be reduced to give the desired alcohol **175**. This was attempted using lithium aluminium hydride, which caused decomposition of the nitrile. With DIBAL, no reaction occurred at any temperature[90], and starting material was recovered (Scheme 82)

Scheme 82



Heating of nitrile **259** under reflux with concentrated hydrochloric converted the nitrile functionality to a carboxylic acid group but also resulted in removal of the BOC group (Scheme 83). The nitrogen was reprotected with BOC_2O after removing ammonia from the reaction mixture (failure to remove ammonia caused side reactions when the reprotection was attempted).

Scheme 83

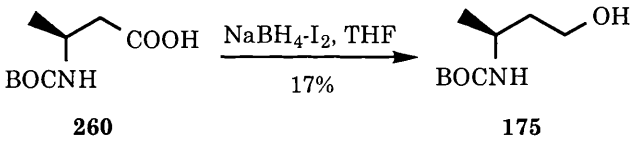


259 **260**

This furnished the N-BOC-protected amino acid **260** in excellent yield, and pure enough to be used in subsequent reactions.

Acid **260** was subjected to the Meyers reduction[77] in an attempt to convert the acid to protected amino alcohol **175** (Scheme 84).

Scheme 84

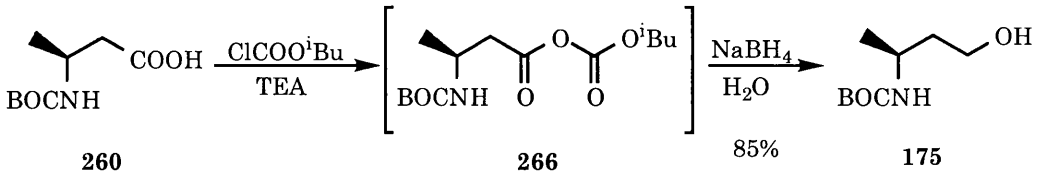


260 **175**

This resulted in extensive decomposition of the BOC group, with only a small amount of **175** being recovered .

The acid **260** was reduced by first converting to the mixed anhydride **266** with isobutyl chloroformate, then **266** was reduced by the addition of sodium borohydride give the desired amino alcohol **175** in excellent yield (Scheme 85).

Scheme 85

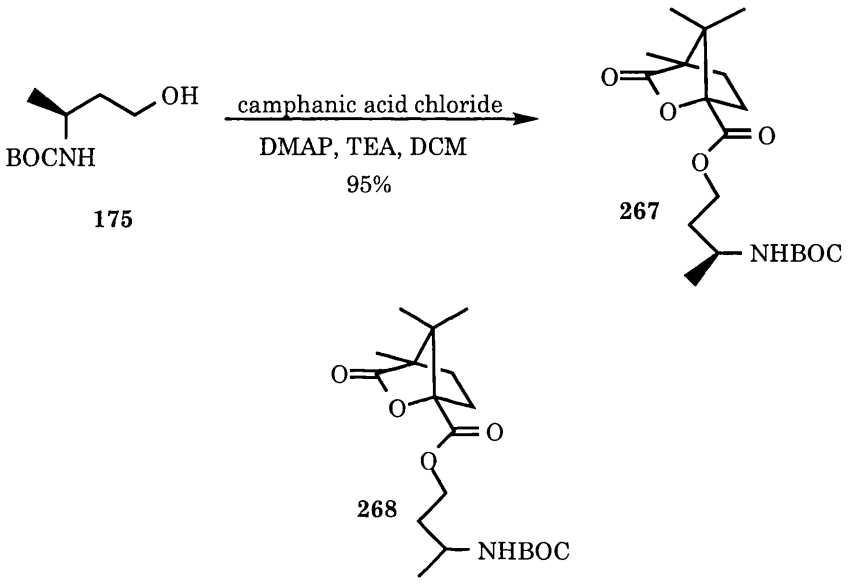


260 **266** **175**

To check the chiral purity of **174** it was necessary to prepare a derivative so that examination by NMR spectroscopy and HPLC could take place. Reaction of chiral

amino alcohol **175** with camphanic acid chloride proceeded cleanly and in high yield to give the camphanic ester **267** (Scheme 86).

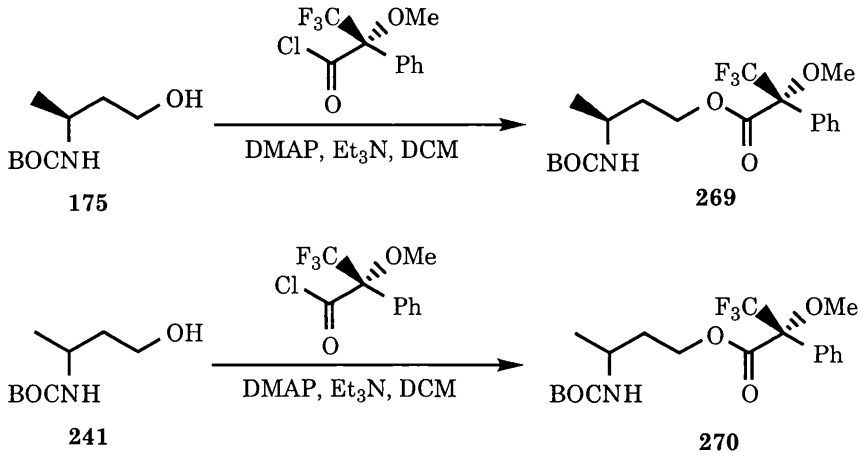
Scheme 86



Examination of the ^{1}H NMR spectrum of the diastereomeric camphanate esters **268** derived from the racemic amino alcohol **241** showed clear splitting of some of the peaks, but the second diasteromer could not be seen in the NMR spectrum of **267**, indicating a diastereomeric ratio of at least 95:5.

Lack of a UV-active chromophore in **267** made HPLC analysis difficult, therefore chiral amino alcohol **175** and the racemic amino alcohol **241** were converted to their Moshers esters **269** and **270** respectively (Scheme 87)[91].

Scheme 87



175 **269**

241 **270**

Examination of the HPLC trace of the diastereomers **270** derived from the racemic alcohol **241** showed two clear peaks, the second peak could not be seen on the trace of **269**, thereby indicating the enantiomeric purity of **175** was at least 99.9%.

2.6 Summary

In conclusion, the racemic auxiliary **241** has been prepared in excellent yield by reduction of 3-amino butanoic acid with sodium borohydride, followed by protection with di-*t*-butyl-dicarbonate. A novel route has been devised to prepare the chiral auxiliary **175**.

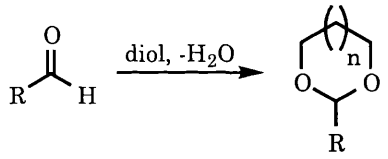
Both these alcohols were used to form aminals, this is detailed in the next chapter.

3. Synthesis of tetrahydro-1,3-oxazines

3.1 Overview and synthetic strategy

An acetal is a condensation product of an aldehyde and an alcohol, and the use of a diol in the condensation results in a ring structure **271** (n=0 or 1) These compounds are termed 1,3-dioxolanes (n=0) or 1,3-dioxanes (n=1) (Scheme 88). A review detailing a number of methods for formation of acetals has appeared in *Synthesis*[92].

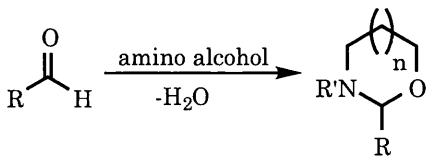
Scheme 88



271

If, instead of a diol, an amino alcohol is used, then compounds **272** are produced (Scheme 89), named tetrahydo-1,3-oxazolidines (5-membered ring, n=0) and tetrahydro-1,3-oxazines (6-membered ring, n=1).

Scheme 89

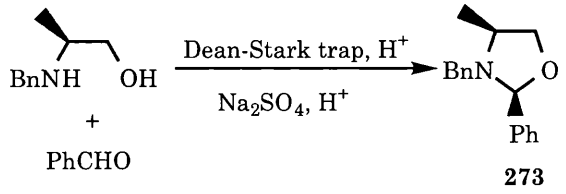


272

These are much less stable than the corresponding acetals, but it has been shown that the stability of the ring can be increased if the nitrogen is protected with an electron-withdrawing group[93].

Two main methods have been used for removal of water from an aminal formation reaction. Heating of stoichiometric amounts of aldehyde and amino alcohol under reflux in a Dean-Stark trap, with acid catalysis, gave the aminal **273** in high yield (Scheme 90)[24].

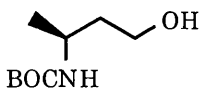
Scheme 90



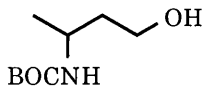
273

The dehydration has also been effected at room temperature, using magnesium or sodium sulphate to remove the water[94]. In both these transformations, the nitrogen was protected with either a benzyl or a benzyloxycarbonyl group.

No preparations of 6-membered aminals from amino alcohols with N-BOC protection have been described, however it was envisaged that a series of aminals derived from amino alcohol **175** or **241** (i.e. chiral or racemic) could be prepared using either of the methods described above.



175

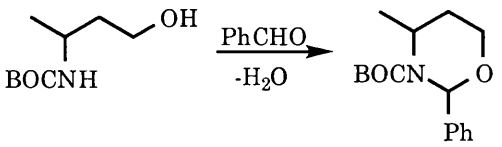


241

3.2 Preparation of aminals by direct condensation

The first ring formation experiments were carried out with racemic 3-N-BOC-amino alcohol **241** and benzaldehyde, to give the aminal **274** (Scheme 91).

Scheme 91



241 **274**

A range of conditions of dehydration and acid catalyst were tried, and these are summarised in Table 1.

Table 1

Aldehyde Equivalents	Solvent	Acid	Dehydration Method	Yield of aminal (%)
1	benzene	TsOH	Dean-Stark trap	25
1	toluene	TsOH	Dean-Stark trap	16
5	benzene	TsOH	Dean-Stark trap	29
1	benzene	PPTS	Dean-Stark trap	0
1	benzene	TsOH	Na_2SO_4	20
5	benzene	TsOH	Na_2SO_4	40
1	benzene	TsOH	molecular sieves	20
5	benzene	TsOH	molecular sieves	24

Unfortunately, in most cases yields of the aminals were low. In almost all reactions, TLC analysis showed that both aldehyde and amino alcohol **241** were still present in the reaction mixture, but large amounts of baseline material had also formed. No reaction was seen when using the weak acid PPTS as the catalyst.

This outcome is surprising in view of the results of other workers detailed in section 3.1. There are several possible reasons for this. Firstly, the acid used to induce the condensation appears also to have caused cleavage of the

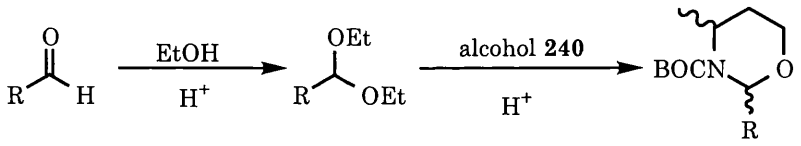
BOC group. Aminals with the nitrogen protected with a Cbz group have been shown to form in high yield using this method[70]. Data obtained for the analogous O,O-acetals show that 6-membered rings are less stable than 5-membered[95]. It is possible that this is also true for aminals as well. Finally, most 5-membered aminals that appear in the literature have been prepared using an aromatic aldehyde, which increases the stability of the ring.

The direct formation of aminals was therefore abandoned.

3.3 Preparation of tetrahydro-1,3-oxazines by acetal exchange

At this point it was decided to try a different approach to the formation of the aminals and this is shown in Scheme 92.

Scheme 92



275 **276**

The aldehyde is protected as its diethyl acetal **275**, and this acetal is heated under reflux with amino alcohol **241** in a Dean-Stark trap to furnish the required products **276**.

The aldehydes were converted to their diethyl acetals **275** in good to excellent yields, by solution in an ethanol/ether mixture, using *p*-toluene sulphonic acid as the catalyst, with sodium sulphate to remove the water (Table 2). In general, after workup, the acetals did not need further purification.

Table 2

R	Dehydration agent	Yield of diethylacetal (%)
n-propyl **277**[96]	sodium sulphate	91
cyclohexyl **278**[97]	sodium sulphate	93
benzyl **279**[98]	sodium sulphate	65

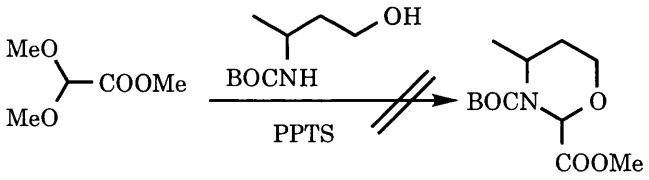
The acetals were heated under reflux with amino alcohol **241** and PPTS in a Dean and Stark trap to give the desired aminals in good to excellent yields with little decomposition (Table 3). The major:minor product ratio varied between 75:25 and 96:4

Table 3

R	Yield of aminal (%)
n-propyl **280**	75
cyclohexyl **281**	90
benzyl **282**	65
phenyl **274**	70

This acetal exchange methodology was tried using a dimethyl acetal in an attempt to discover whether this would offer any improvement in yield. Yields obtained were low, probably due to the greater stability of the dimethyl acetal, and indeed the reaction failed completely when attempting to prepare aminal **284** from methyl dimethoxyacetate **283** (Scheme 93).

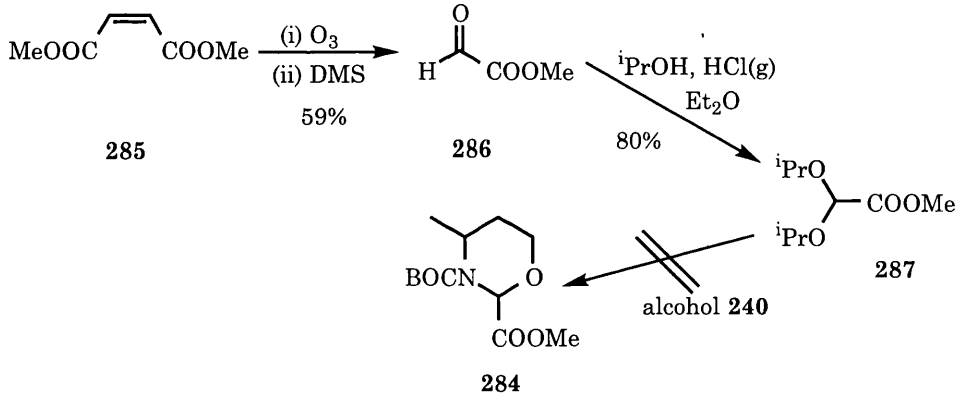
Scheme 93



283 **284**

To determine whether this particular reaction failed due to the use of the dimethyl acetal, methyl di-isopropyloxyacetate was prepared as shown in Scheme 94.

Scheme 94



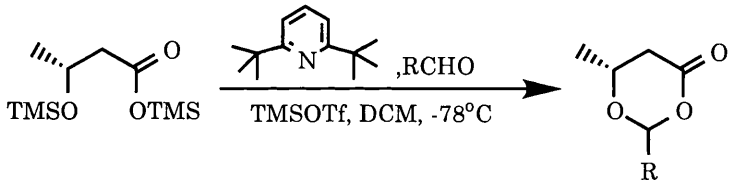
285 **286** **287** **284**

Dimethyl maleate **285** was subjected to ozonolysis then the resulting ozonide was reduced without isolation to give methyl glyoxalate **286**[99]. This was then protected by stirring with isopropanol in ether, while bubbling hydrogen chloride through the mixture. This gave methyl di-isopropyloxyacetate **287** in good yield. Unfortunately no reaction occurred on refluxing **287** with amino alcohol **241** in a Dean-Stark trap, and only starting amino alcohol **241** was recovered.

3.4 Preparation of aminals using the Noyori acetalisation

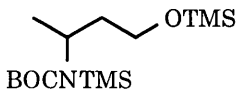
An interesting, mild acetal formation reaction was recently described by Noyori[100], and further elaborated by Schreiber[101]. This reaction involves coupling of a bis(trimethylsilyl)hydroxy acid **288** with an aldehyde to give acetal **289**, and is remarkable in that the reaction takes place at very low temperature (Scheme 95).

Scheme 95



288 R= *n*-heptyl **289**

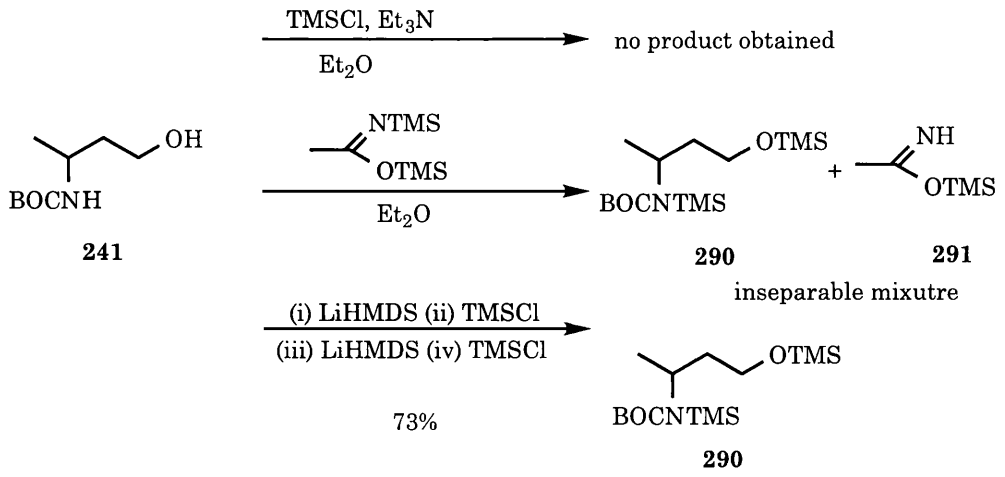
It was envisaged that the Noyori reaction could be applied to the formation of aminals. This would provide a route to prepare those aminals derived from unstable aldehydes (i.e. those which could not be converted to their diethyl acetals). Extension of this methodology to the formation of aldehydes therefore required that bis(trimethylsilyl) 3-N-BOC amino butanol **290** be prepared.



290

This proved to be more difficult than expected, and the various reactions tried are shown in Scheme 96.

Scheme 96

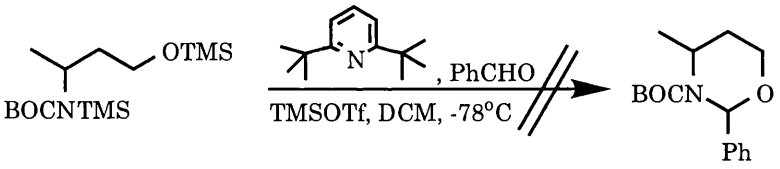


Reaction of amino alcohol **241** with trimethylsilyl chloride, and triethylamine caused extensive decomposition of **241**, and no products or starting material were recovered. Reaction of **241** with bis(trimethylsilyl)acetamide gave a quantitative yield of **290** as evidenced by NMR spectroscopy, however the product proved impossible to separate from the mono(trimethylsilyl)acetamide byproduct **291**. Surprisingly, bis(trifluoromethylsilyl)acetamide, a stronger silylating agent, did not give a quantitative conversion to **290** (NMR).

Deprotonation of amino alcohol **241** with one equivalent of lithium hexamethyldisilazide, followed by addition of one equivalent of trimethylsilylchloride (carried out twice) gave the desired di-silylated amino alcohol **290** in very good yield. Purification was effected by the removal of the lithium chloride by-product by filtration, and removal of the solvent.

Unfortunately, when **290** was subjected to the Noyori acetalisation with benzaldehyde, no product **274** was observed (Scheme 97).

Scheme 97

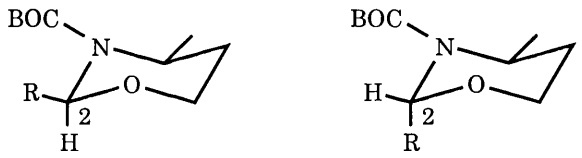


290 **274**

However the reaction was performed only once, and thus it is entirely possible that success will be obtained after optimisation of conditions.

3.5 The structure of tetrahydro-1,3-oxazines

After workup, and analysis by ^1H NMR, the aminals that had been prepared appeared to be mixtures of diastereomers **292** and **293** - two sets of peaks for the acetal proton were seen in each case.



292 **293**

R= *n*-Pr, cyclohexyl, Bn, Ph

The ratio of major:minor product varied between 96:4 and 70:30 depending on the nature of R and the reaction time - a longer reflux gave more of the minor product. This seemed to indicate that the thermodynamic diastereomer was **293**, with the substituent R axial.

It was thought that determination of the C_2-H_2 coupling constant would enable the structure of the major product to be determined - the coupling constant for an axial C-H coupling should be 140Hz and 150Hz for an equatorial coupling. The aminal that was studied was the cyclohexyl derivative **281**.

A 100MHz ^{13}C-^{1}H coupled spectrum was obtained and is shown in Figure 1. Unfortunately, the resonances of the two products were not separated, however a 150MHz spectrum gave good separation (Figure 2).

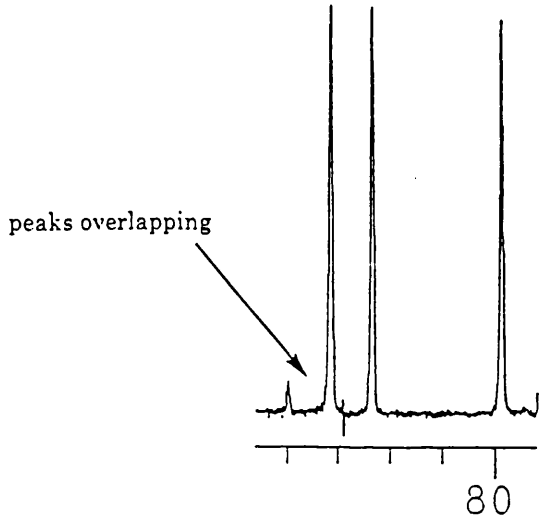


Figure 1 - 100MHz ^{13}C-^{1}H coupled spectrum of acetal carbon 2

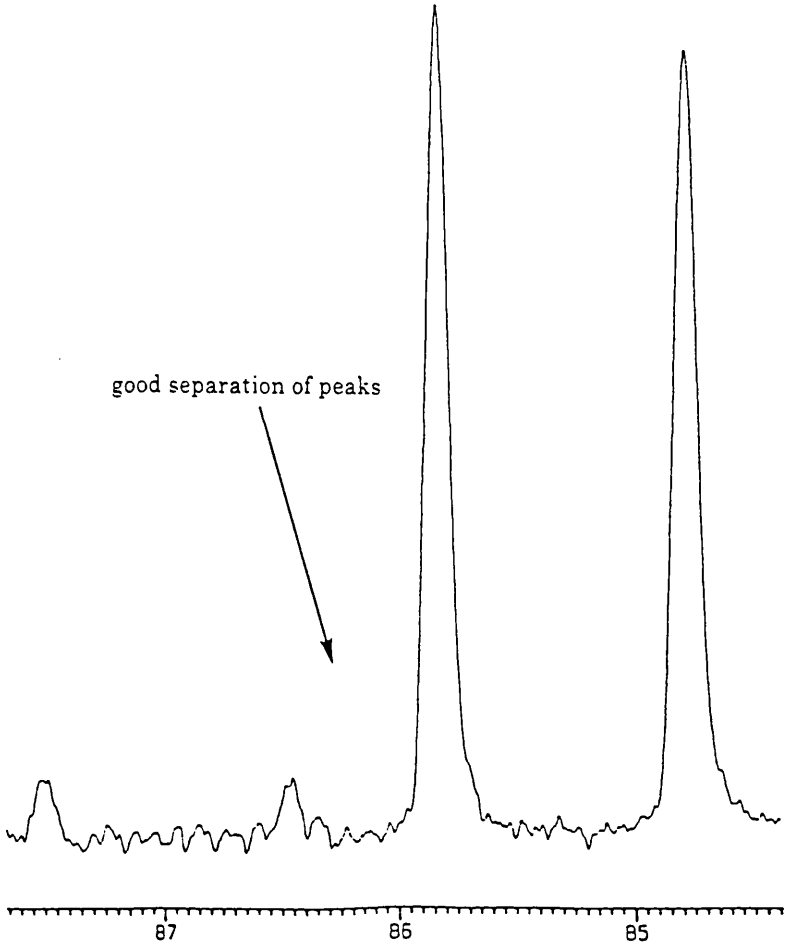
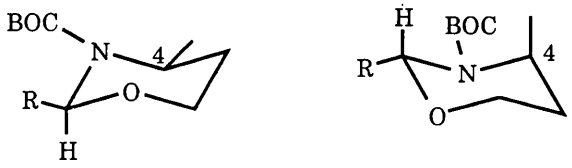


Figure 2 - 150MHz ^{13}C-^{1}H coupled spectrum of acetal carbon 2

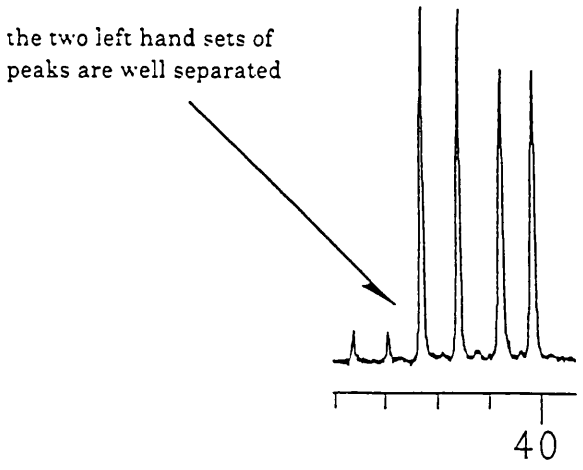
Analysis of the spectrum (Figure 2) provided a surprising result. The coupling constants of both sets of peaks are the same (142.1Hz), indicating that R is equatorial in both products! It was then thought that the structure of the products was **294** or **295** - where the methyl group at the 4-position of the ring was either equatorial or axial.



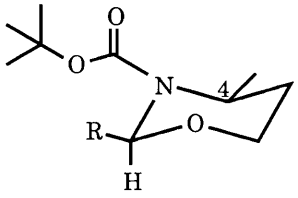
294 **295**

R= *n*-Pr, cyclohexyl, Bn, Ph

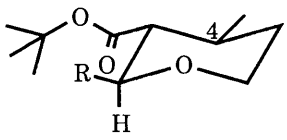
Analysis of the 100MHz ^{13}C-^{1}H spectrum of the C_4-H_4 resonance (Figure 3) again showed that the coupling constant was the same (141.4Hz), indicating that the methyl group was equatorial in both cases.



It was postulated that the different products were due to two different positions in space of the BOC group due to restricted rotation of the C-N bond (**296** and **297**).



296



297

The energy barrier for interconversion appears to be overcome by heating. Longer reaction times when synthesising the aminal did not give significantly lower yields, but did decrease major to minor product ratio, from *c.* 96:4 to *c.* 75:25.

3.6. Summary

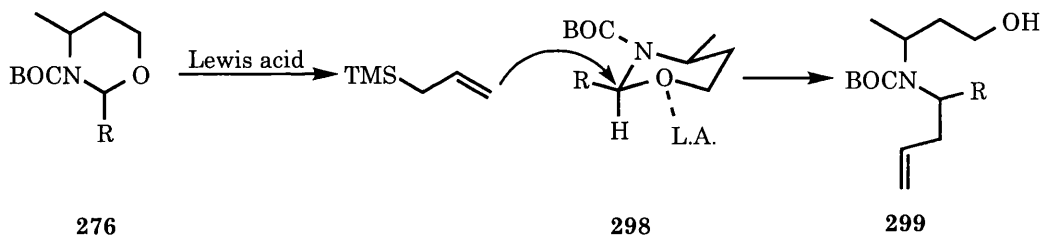
In conclusion, a new, novel method has been devised to prepare N-BOC protected aminals in high yield, which avoids the use of a strong acid catalyst. Analysis of the structure of the cyclohexane derived aminal **281** has been carried out and a surprising result obtained. A novel preparation of a bis(trimethylsilyl) amino alcohol has also been developed.

4. Ring opening of tetrahydro-1,3-oxazines

4.1 Synthetic strategy

With the aminal in hand it was planned to carry out the ring opening reaction in the manner described in Scheme 98

Scheme 98

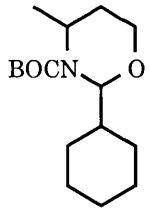


276 **298** **299**

It was envisaged that co-ordination of the Lewis acid would take place exclusively at the oxygen atom of the aminal **276** to give complex **298**, and attack of the organosilane nucleophile would then proceed at one face exclusively, with preferential cleavage of the C-O bond to give the alcohol **299**.

4.2 Ring opening of tetrahydro-1,3-oxazines

A range of solvents, Lewis acids and conditions were tried, and the results are summarised in Table 4. These reactions were carried out using the aminal derived from cyclohexane carboxaldehyde **281**.

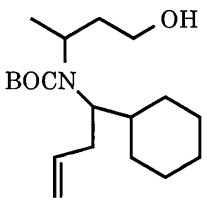


281

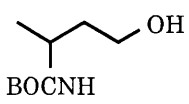
Table 4

Lewis Acid	Nucleophile Equivalents	Nucleophile	Temp (°C)	Solvent	Time	Yield of ring-opened aminal **300** (%)
$TiCl_4$	3.17		-78	DCM	20 mins.	0
$TiCl_4$	3.17		0	DCM	20 secs.	10
$SnBr_4$	8		-78	DCM	5 mins.	8
$SnBr_4$	8		0	DCM	20 secs.	25
$SnBr_4$	8		30	THF	45 mins.	11
$Ti(OiPr)_4$	8		30	THF	45 mins.	0
$BF_3.OEt_2$	4		30	THF	3 hrs.	0
$BF_3.OEt_2$	4		30	THF	45 mins.	see text

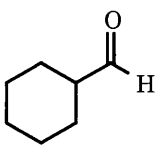
In general, all of these reaction conditions failed to give any appreciable amount of ring opened alcohol **300**, instead on workup amino alcohol **241** and aldehyde **301** were recovered.



300

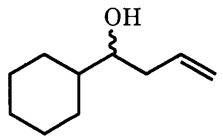


241



301

This suggests that Lewis acid complexation is taking place, but that the nucleophile is not strong enough to open the ring. On workup, a water molecule acts as a nucleophile, and the Lewis acid-aminal complex then decomposes. An interesting exception to this is detailed in entry 8, where the isolated product is alcohol **302**.

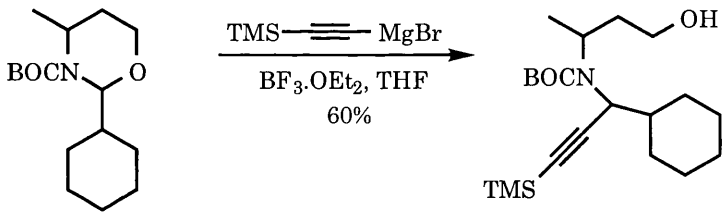


302

4.3 Future research

As discussed in section 4.2, it is evident that the allyl trimethylsilane nucleophile is not strong enough to attack the Lewis acid-aminal complex. Other work within our group[102] has shown that the aminal **281** can be ring opened using acetylenic Grignard reagents (Scheme 99) to give alcohol **303**.

Scheme 99



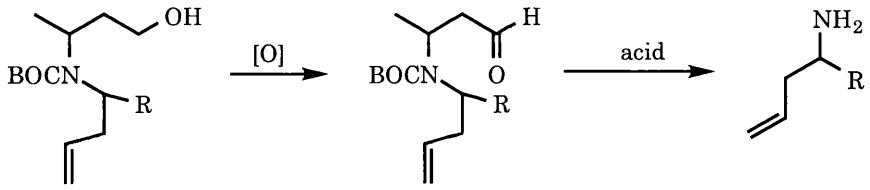
281 **303**

However as detailed previously (Table 4, entry 8) these conditions for ring opening with acetylenic Grignards gave alcohol **302** instead of the desired product when used with allylmagnesium bromide. It is evident that

allylmagnesium bromide is too strong a nucleophile, and therefore more experiments will have to be carried out using a range of other organometallics.

It is envisaged that once the ring opening has been optimised, the auxiliary would be eliminated as shown in Scheme 100. Oxidation of the alcohol functionality of **299** would give aldehyde **304**, and refluxing with dilute acid would induce the retro-Michael reaction to give the amine **305** (Scheme 50).

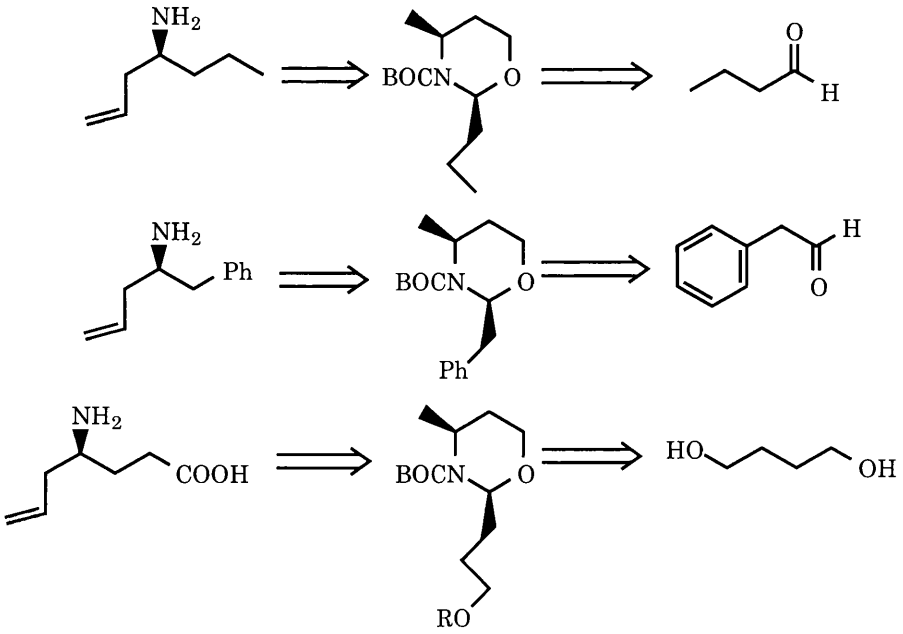
Scheme 100



297 **302** **303**

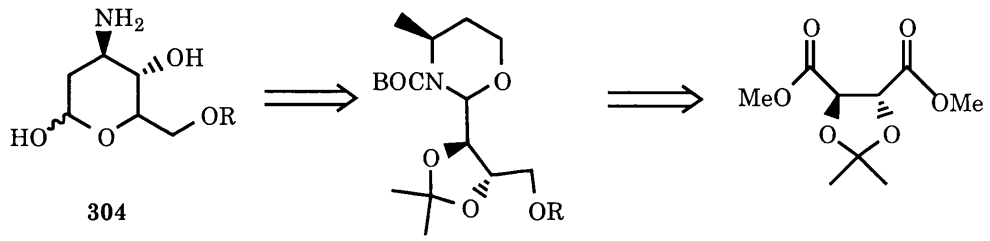
This has already been shown to work[102].Once the ring opening and elimination conditions have been optimised, some simple targets could be prepared (for examples, see Scheme 101) in order to demonstrate the effectiveness of the methodology.

Scheme 101



A more interesting target would be amino sugar **304** derived from tartaric acid (Scheme 102).

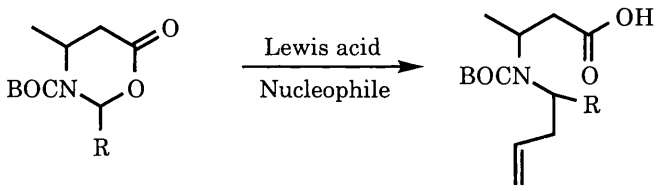
Scheme 102



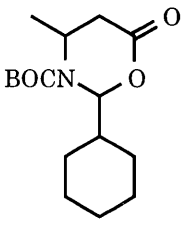
304

A possible way to eliminate the oxidation step in the synthesis of the amines is to use aminals **307** derived from 3-(*S*)-N-BOC-amino butanoic acid and the relevant aldehyde (Scheme 103). Ring opening would then give acid **308** from which the auxiliary could be eliminated directly, without the need for an oxidation step.

Scheme 103



307 **308**



309

These aminals have not previously been reported. However, during work on the synthesis of the aminals detailed in chapter 3, 'oxidised' aminal **309** was prepared, albeit in poor yield. This problem could be overcome using the modified Noyori acetalisation detailed in chapter 3.

5. Experimental

The following abbreviations have been used:

BOC	*t*-butoxycarbonyl
BOC_2O	di-*t*-butyl-dicarbonate
DCM	dichloromethane
DIBAL	diisobutylaluminium hydride
DMF	dimethylformamide
DMSO	dimethylsulphoxide
EtOAc	ethyl acetate
PPTS	pyridinium *p*-toluenesulphonate
RT	room temperature
TEA	triethylamine
TMS	trimethylsilyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TsOH	*p*-toluenesulphonic acid

Ether refers to diethyl ether. Brine refers to a saturated aqueous solution of sodium chloride. Rochelle Salt solution refers to a saturated aqueous solution of sodium potassium *L*-tartrate.

Infra-red spectra were recorded on a Perkin Elmer 1600 series FT-IR spectrometer, and the samples were prepared as thin films or as nujol mulls.

^1H NMR spectra were recorded on Jeol PMX60ST (60MHz), Bruker WP200SY (200MHz), Varian VXR200 (200MHz), Bruker WH360 (360MHz) and Varian VXR400 (400MHz) instruments using chloroform as an internal deuterium lock. The chemical shift for each signal is given in units of δ relative to tetramethylsilane where δ=0. The multiplicity of the signals is indicated as s -

singlet, d - doublet, t - triplet, q - quartet, m - multiplet, dd - doublet of doublets, dt - doublet of triplets, etc.

^{13}C NMR spectra were recorded on Bruker WP200SY (50MHz), Varian VXR400 (100MHz) and Bruker AMX600 (150MHz) instruments, using internal deuterium lock and proton decoupling, except where indicated. The chemical shift data is given in units of δ relative to tetramethylsilane where $\delta=0$.

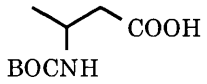
FAB mass spectra were recorded by the Edinburgh University mass spectrometry service, UCL mass spectrometry service and the School of Pharmacy, University of London on Kratos MS-50TC, ZAB 1000 and VG-50SAE instruments respectively.

Optical rotations were performed by Alex Drake, Birkbeck College London on a Perkin Elmer 141 polarimeter.

TLC was carried out on precoated 0.25 mm thick Merck 60 F_{254} silica plates. Visualisation was by absorption of u.v. light or by development with basic potassium permanganate solution. Flash chromatography was carried out using Merck Kieselgel 60 (230-400 mesh) and Merck neutral alumina (100-125 mesh)[103].

Reagents and solvents were purified where necessary by standard techniques[104]. All solvents were used dry unless otherwise stated. All glassware was dried overnight in an oven at 125°C unless otherwise stated. Benzaldehyde diethyl acetal was obtained from Alastair Rae, UCL.

3-(1,1-Dimethylethyloxycarbonylamino)-butanoic acid **240**[68]



To a solution of 3-amino butanoic acid **239** (1.00 g/9.70 mmol) in sodium hydroxide solution (1 M, 11 ml) was added *t*-butanol, and the mixture stirred for 5 min. BOC_2O (2.11 g/9.71 mmol/1 eq) was added dropwise over 5 min, and the mixture was stirred at RT for 20 hrs.

The reaction mixture was extracted with hexane (2 x 3 ml) and the organic phase was extracted with saturated $NaHCO_3$ (3 x 3 ml). The combined aqueous layers were cooled to 0°C and acidified to pH1 with potassium hydrogen sulphate solution (2.24 g/0.16 mmol in 15 ml H_2O). The solution was extracted with ether (4 x 25 ml), the combined organic layers washed with brine (30 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a clear oil. Purification by crystallisation from hexane gave the title compound as a white solid (1.95 g/9.61 mmol/99 %), m.p 76-78°C.

^1H NMR ($CDCl_3$, 400MHz): δ 1.25 (3H, d, J 6.7Hz, $C\underline{H}_3CH$), 1.45 (9H, s, $(C\underline{H}_3)_3C$), 2.55 (2H, m, $C\underline{H}_2COOH$), 4.05 (1H, m, $CH_3C\underline{H}$), 4.93 (1H, bs, $N\underline{H}$)

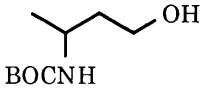
^{13}C NMR ($CDCl_3$, 100MHz): δ 20.40, 28.37, 40.23, 43.45, 79.71, 155.20, 176.90

υ_{max} (cm^{-1}): 3416, 3236, 1720, 1707, 1404, 1164 (nujol mull)

Found: (M^++H) 204.1226, $C_9H_{18}NO_4$ requires 204.1236

m/z 204 (M^++H, 55 %) 148 (65) 130 (30)

3-(1,1-Dimethylethyloxycarbonylamino)-butan-1-ol **241**[71]



(i) To a solution of borane-THF complex in THF (2 ml/2 mmol) at 0°C was added dropwise over 30 min a solution of acid **240** (0.20 g/1.00 mmol) in THF (1 ml). The mixture was then stirred for 2 hrs.

The reaction was quenched by addition of acetic acid in methanol (10 %, 1 ml), the solvent removed *in vacuo* and the residue redissolved in EtOAc (10 ml). The solution was washed with HCl (10 ml/1 M), water (10 ml), saturated NH_4CO_3 (10 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a clear, viscous oil. Examination of the oil by TLC and NMR spectroscopy showed no trace of the desired product.

(ii) To a solution of alcohol **244** (p82) (0.21 g/0.93 mmol) in methanol (15 ml) was added BOC_2O (0.26 g/1.20 mmol/1.3 eq) and palladium on carbon (40 mg). The mixture was stirred under a hydrogen atmosphere for 5 hrs.

The reaction mixture was filtered, and the solvent removed *in vacuo* to give a clear viscous oil. Purification by flash chromatography on silica gel (1:1 EtOAc/ hexane) gave the title compound as a white solid (96 mg/0.509 mmol/ 53 %).

(iii) 3-Amino butanoic acid **239** (1.05 g/9.70 mmol) was suspended in THF (7 ml) under nitrogen and lithium aluminium hydride (0.37 g/9.70 mmol/1 eq) added slowly. The mixture was then heated under reflux for 2 hrs.

The reaction was quenched by sequential addition of NaOH solution (1.2 ml, 2M), water (1.5 ml) and NaOH solution (2M, 4.6 ml). The aluminium salts were removed by filtration, and washed with THF (2 x 10 ml). The solvent was removed *in vacuo* from the combined organic layers to give a white paste, which

was then redissolved in water (20 ml). The solution was basified to pH12 (2M NaOH) and BOC_2O (2.23 g/10.18 mmol/1.05 eq) added. The mixture was then stirred for 18 hrs.

The reaction mixture was extracted with DCM (3 x 25 ml) then the combined organic layers washed with brine (25 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a viscous yellow oil. Purification by flash chromatography on silica gel (1:1 EtOAc/ hexane) gave the title compound as a white solid (0.97 g/5.14 mmol/53 %

(iv) To a suspension of 3-amino butanoic acid **239** (2.13 g/20.6 mmol) in THF (60 ml) under nitrogen at 0°C was added sodium borohydride (1.86 g/49.4 mmol/2.4 eq). Iodine (5.43 g) in THF (14 ml) was added dropwise, until the solution was colourless and effervescence had ceased. The mixture was then heated under reflux for 18 hrs.

The reaction was cooled to room temperature, and methanol added slowly until effervescence had ceased. The solvent was removed *in vacuo* to give a white paste which was then redissolved in water (100 ml). The solution was basified to pH12 (2M NaOH) and BOC_2O (6.54 g/30.0 mmol/1.45 eq) added. The mixture was then stirred for 18 hrs.

The reaction mixture was extracted with DCM (3 x 75 ml) then the combined organic layers washed with brine (75 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a clear viscous oil. Purification by flash chromatography on silica gel (1:1 EtOAC/ hexane) gave the title compound as a white solid (2.92 g/15.450 mmol/75 %).

m.p. 59-60°C. (lit.[71] 56°C)

R_f 0.27 (1:1 EtOAc/ hexane)

^1H NMR ($CDCl_3$, 200MHz): δ 1.09 (3H, J 6.7Hz, $C\underline{H}_3CH$), 1.35 (9H, s, $(C\underline{H}_3)_3C$), 1.68 (2H, m, $C\underline{H}_2CH_2OH$), 3.55 (2H, m, $CH_3C\underline{H}$), 3.74 (2H, m, $C\underline{H}_2OH$), 4.74 (1H, d, J 8.6Hz, $N\underline{H}$)

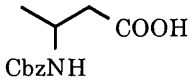
^{13}C NMR ($CDCl_3$, 50MHz): δ 21.07, 28.09, 40.16, 42.91, 58.61, 79.25, 156.45

υ_{max} (cm^{-1}): 3284, 1672, 1546, 1278, 1167 (nujol mull)

Found: (M^++H) 190.1443, $C_9H_{20}NO_3$ requires 190.1443

m/z 190 (M^++H, 60 %) 134 (100) 90 (80) 56 (100) 28 (70).

3-(Benzyloxycarbonylamino)-butanoic acid **242**[70]

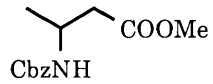


To a suspension of 3-amino butanoic acid **239** (0.40 g/1.90 mmol) in NaOH solution (4 M, 75 ml) and THF at 0°C was added dropwise benzyl chloroformate (0.55 ml/1.90 mmol/1 eq). The mixture was stirred at room temperature for 16 hrs.

EtOAc (15 ml) was added and the layers separated. The aqueous layer was acidified with HCl (2 M, 7 ml) and extracted with EtOAc (3 x 30 ml). The combined organic layers were washed with brine (30 ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to give the title compound as an off-white solid (0.43 g/1.84 mmol/97 %), m.p. 122-124°C (lit.[70] 122-124°C, lit[70ii] 126°C, lit[70iii] 129-130°C, lit[70iv] 122°C), which was sufficiently pure to be used in the subsequent reaction.

^1H NMR ($CDCl_3$, 200MHz): δ 1.25 (3H, d, J 6.7Hz, $C\underline{H}_3CH$), 2.56 (2H, d, J 5.3Hz, $C\underline{H}_2COOH$), 4.11 (1H, m, $CH_3C\underline{H}$), 5.00 (2H, s, Ar-$C\underline{H}_2$), 5.26 (1H, bs, N<u>H</u>), 7.34 (5H, m, Ar-<u>H</u>)

3-(Benzyloxycarbonylamino)-butanoic acid methyl ester **243**[70]



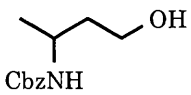
To a solution of acid **242** (3.10 g/12.00 mmol) in methanol (25 ml) at 0°C under nitrogen was added thionyl chloride (1.48 ml) over 15 min. The mixture was allowed to warm to room temperature and stirred for 16 hrs.

The solvent was removed *in vacuo*, and the residue was redissolved in DCM (25 ml). The solution was washed with NaOH solution (2 M, 2 x 10 ml), water (10 ml), brine (10 ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to give a yellow oil. Purification by flash chromatography on silica gel (10% EtOAc/ DCM) gave the title compound as a white solid (2.32 g/9.24 mmol/77 %), m.p. 41-44°C (lit.[70] 41-43°C).

R_f 0.58 (10% EtOAc/ hexane)

^1H NMR ($CDCl_3$, 360MHz): δ 1.22 (3H, d, J 6.7Hz, $C\underline{H}_3CH$), 2.51 (2H, d, J 5.3Hz, $C\underline{H}_2COOCH_3$), 3.65 (3H, s, $COOC\underline{H}_3$), 4.09 (1H, m, $CH_3C\underline{H}$), 5.07 (2H, s, Ar-$C\underline{H}_2$), 5.25 (1H, s, N$\underline{H}$), 7.31 (5H, m, Ar-$\underline{H}$)

3-(Benzyloxycarbonylamino)-butan-1-ol **244**[70]



To a solution of ester **243** (1.00 g/9.97 mmol) in THF (25 ml) at -78°C under nitrogen was added DIBAL solution (1M in THF, 11.91 ml/1.2 eq) dropwise over 10 min. The mixture was stirred for 1 hr at -78°C, then warmed to 0°C and stirred for a further hour.

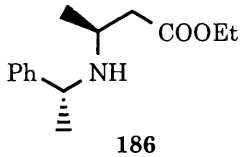
The reaction mixture was cooled to -78°C and quenched with HCl (2 M, 8 drops). The mixture was then poured into Rochelle Salt solution (15 ml) and extracted with ethyl acetate (3 x 25 ml). The combined organic layers were washed with brine (25 ml), dried ($MgSO_4$) and the solvent removed *in vacuo* to

give a viscous yellow oil. Purification by flash chromatography on silica gel (1:1 EtOAc/ hexane) gave the title compound as a white solid (0.49 g/2.18 mmol/ 55 %), m.p. 57-59°C (lit.[70] 58-60°C).

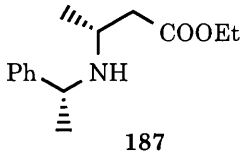
R_f 0.18 (1:1 EtOAc/ hexane)

^{1}H NMR ($CDCl_3$, 200MHz): δ 1.11 (3H, d, J 6.6Hz, $C\underline{H}_3CH$), 1.36 (1H, m, $C\underline{H}_aH_a'CH_2OH$), 1.76 (1H, m, $CH_a\underline{H}_a'CH_2OH$), 3.72 (2H, m, $C\underline{H}_2OH$), 3.85 (1H, m, $CH_3C\underline{H}$), 5.02 (2H, s, Ar-$C\underline{H}_2$), 5.39 (2H, d, J 8.3Hz, N$\underline{H}$), 7.33 (5H, m, Ar-$\underline{H}$)

3-(*S*,*R*)-N-[1(*S*)-methylbenzyl]-butanoic acid ethyl ester **186**,**187**[52]



186



187

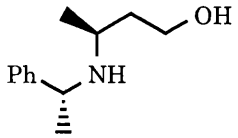
To a solution of ethyl crotonate (6.25 g/54.8 mmol) in ethanol (12.5 ml) was added 1-(*S*)-methylbenzylamine (5.54 g/45.7 mmol/0.83 eq) and the mixture heated under reflux for 6 hrs.

The solvent was removed *in vacuo* to give a clear oil. Purification by Kugelrohr distillation (205°C/15 mmHg) gave the title compounds as a mixture of diastereomers (3.20 g/13.71 mmol/30 %). The (S,S) diastereomer **186** was separated from the mixture as needed by flash chromatography on silica gel (1:1 EtOAc/ hexane).

R_f 0.28 (1:1 EtOAc/ hexane)

^{1}H NMR ($CDCl_3$, 400MHz): δ 1.03 (3H, d, J 6.5Hz, $C\underline{H}_3CH$), 1.24 (3H, t, J 7.1Hz, $C\underline{H}_3CH_2O$), 1.30 (3H, d, J 6.5Hz, $CHPhC\underline{H}_3$), 2.30 (2H, m, $C\underline{H}_2CH_2O$), 2.96 (1H, sextuplet, J 5.5Hz, $CH_3C\underline{H}$), 3.86 (1H, q, J 6.5Hz, $C\underline{H}PhCH_3$), 4.11 (2H, q, J 7.14Hz, $CH_3C\underline{H}_2O$), 7.27 (5H, m, Ar-$\underline{H}$), identical to compound prepared in the literature.

3-(*S*)-N-[1-(*S*)-Methylbenzyl]-butan-1-ol **245**[52]

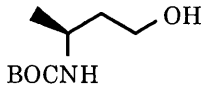


To a solution of ester **186** (0.61 g/2.62 mmol) in THF (3 ml) under nitrogen was added slowly lithium aluminium hydride (0.11 g/2.88 mmol/1.1 eq) and the mixture heated under reflux for 5 hrs.

The reaction was quenched by dropwise addition of NaOH solution (10 M, 2 ml), ether added, and the reaction filtered. The aluminium salts were washed with ether (2 x 3 ml), the combined organic layers were dried (KOH) and the solvent removed *in vacuo* to give a yellow oil. Purification by flash chromatography on silica gel (1:1 EtOAc/hexane) gave the title compound as a clear oil (0.302 g/1.57 mmol/60 %).

^{1}H NMR ($CDCl_3$, 400MHz): δ 1.08 (3H, d, J 6.5Hz, $C\underline{H}_3CH$), 1.35 (3H, d, J 6.6Hz, $CHPhC\underline{H}_3$), 1.42 (1H, m, $C\underline{H}_aH_{a'}$), 1.78 (1H, m, $CH_a\underline{H}_{a'}$), 2.96 (1H, m, $CH_3C\underline{H}$), 3.86 (3H, m, $C\underline{H}_2OH$ and $C\underline{H}PhCH_3$), identical to compound prepared in the literature

3-(S)-(1,1-Dimethylethyloxycarbonylamino)-butan-1-ol **175**[78]



(i) To a solution of alcohol **245** (p84) (0.64 g/3.49 mmol) in ethanol (6 ml) was added palladium on carbon (40 mg) and BOC_20 (0.76 g/3.49 mmol/1 eq), and the mixture stirred under a hydrogen atmosphere for 18 hrs.

The reaction mixture was filtered and the solvent removed *in vacuo* to give a yellow oil. Purification by flash chromatography on silica gel (1:1 EtOAc/ hexane) gave the title compound as a white solid (0.26 g/1.39 mmol/40 %).

(ii) To a solution of acid **260** (3.00 g/15.9 mmol) (p94) in THF (40 ml) under nitrogen was added sodium borohydride (1.20 g/31.7 mmol). Iodine (2.01 g) in THF (7ml) was added dropwise until the solution was colourless and effervescence had ceased. The mixture was then heated under reflux for 18 hrs.

The reaction was cooled to room temperature, and methanol added slowly until effervescence had ceased, then the solvent was removed *in vacuo* to give a white paste. Water (20 ml) and DCM (20 ml) were added and the layers separated. The aqueous layer was extracted with DCM (3 x 20 ml) then the combined organic layers washed with brine (20 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a clear viscous oil. Purification by flash chromatography on silica gel (1:1 EtOAc/hexane) gave the title compound as a white solid (0.48 g/2.58 mmol/17 %).

(iii) To a solution of acid **260** (1.50 g/7.39 mmol) and TEA (1.03 ml/7.39 mmol/1 eq) in THF (9 ml) under nitrogen was added isobutyl chloroformate (0.95 ml/7.39 mmol/1.1 eq), the mixture stirred for 15 min, filtered and the filtrate stored at 0°C. This solution was added dropwise to a suspension of sodium borohydride (0.73 g/19.2 mmol/2.6 eq) in water (10 ml) at 0°C and the mixture stirred for 2 hrs.

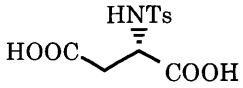
The reaction mixture was washed with $NaHCO_3$ solution (10 ml), brine (10 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a clear oil. Purification by flash chromatography on silica gel (1:1 EtOAc/hexane) gave the title compound as a white solid (1.19 g/6.29 mmol/85 %).

m.p. 59-60°C. (lit.[78i] 56°C)

$[\alpha]_D$ 13.1° (DCM) (2.284 mg/ ml) (lit.[78i] 10.2° ($CHCl_3$) (0.5 g/100 ml), lit.[78ii] 11.4° ($CHCl_3$) (1.8 g/100 ml))

All other spectra were identical to those reported for racemic alcohol **241** (p79)

(*S*)-N-(*p*-Toluenesulphonyl)-aspartic acid **249**[79]

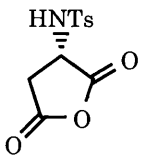


To a solution of (*S*)-aspartic acid (6.00 g/45.0 mmol) in sodium hydroxide solution (3.60 g/45.0 mmol/1 eq in 48 ml H_2O) was added diisopropylethylamine (Hünig's Base) (8.61 ml/49.5 mmol/1.1 eq), *p*-toluenesulphonyl chloride (8.57 g/45.0 mmol/1 eq) and acetone (48 ml). The mixture was then stirred for 18 hrs.

The reaction mixture was washed with ether (2 x 15 ml) and the combined washings were extracted with NaOH solution (5 %, 10 ml). The combined basic aqueous were cooled to -10°C, acidified to pH 1 with concentrated HCl and extracted with ether (4 x 20 ml) The combined organic layers were washed with water (2 x 20 ml), brine (20 ml), dried (Na_2SO_4) and the solvent removed in vacuo to give the title compound as a white solid (12.78 g/44.5 mmol/99 %), m.p.112-114°C (lit.[79] 113-114°C), which was pure by NMR analysis.

^{1}H NMR (acetone-d_6, 400MHz): δ 2.37 (3H, s, Ar-C<u>H</u>$_3$), 2.75 (2H, d, J 5.5Hz, C<u>H</u>$_2$COOH), 3.58 (2H, m, CHC<u>H</u>$_2$), 4.25 (1H, t, J 5.5Hz, C<u>H</u>COOH), 7.33 (2H, d, J 8.1Hz, Ar-<u>H</u>), 7.77 (2H, d, J 8.1Hz, Ar-<u>H</u>)

(*S*)-N-(*p*-Toluenesulphonyl)-aspartic anhydride **250**[79]

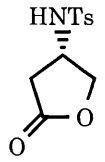


The protected acid **249** (12.56 g/43.8 mmol) was dissolved in acetic anhydride (100 ml) and stirred for 18 hrs.

The acetic anhydride was then removed *in vacuo* to give the title compound as a white solid (11.42 g/42.4 mmol/97 %), m.p. 126-128°C (lit.[79] 126-128°C), which was pure by NMR analysis.

^{1}H NMR ($CDCl_3$, 400MHz): δ 2.46 (3H, s, Ar-C$\underline{H}_3$), 3.11 (1H, dd, J_{aa} 19.3Hz, J_{ab} 7.3Hz, C$\underline{H}_a$H$_{a'}$), 3.36 (1H, dd, J_{aa} 19.3Hz, J_{ab} 9.5Hz, CH$_a\underline{H}_{a'}$), 4.47 (1H, m, C$\underline{H}$N), 5.51 (1H, bs, N$\underline{H}$), 7.37 (2H, d, J 8.0Hz, Ar-$\underline{H}$), 7.78 (2H, d, J 8.0Hz, Ar-$\underline{H}$)

4,5-Dihydro-4-(*S*)-(*p*-toluenesulphonylamino)-furan-2-(3H)-one **251**[79]



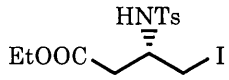
To a suspension of $NaBH_4$ (1.30 g/34.3 mmol) in THF (70 ml) at 0°C under nitrogen was added dropwise a solution of anhydride **250** (9.24 g/34.4 mmol/1 eq) in THF (70 ml). The mixture was stirred at 0°C for 2 hrs and at RT for 1 hr.

The reaction mixture was acidified to pH2 with concentrated HCl, then the THF removed *in vacuo*. Water (45 ml) was added and the mixture extracted with EtOAc (8 x 45 ml). The combined organic layers were dried (Na_2SO_4) and the solvent removed *in vacuo* to give a yellow oil. The oil was dissolved in benzene (100 ml), *p*-toluenesulphonic acid (46 mg) added, and the mixture heated under reflux in a Dean and Stark trap for 4 hrs.

The reaction mixture was filtered through a silica plug, and the solvent was removed *in vacuo* to give the title compound as a white solid (6.67 g/26.1 mmol/76 %), m.p. 111-112°C (lit.[79] 111-113°C), which was pure by NMR analysis.

^{1}H NMR ($CDCl_3$, 400MHz): δ 2.38 (1H, dd, J_{aa} 17.8Hz, J_{ab} 4.7Hz, C$\underline{H}_a$H$_{a'}$CO), 2.44 (3H, s, Ar-C$\underline{H}_3$), 2.64 (1H, dd, J_{aa} 17.8Hz, J_{ab} 7.8Hz, CH$_a\underline{H}_{a'}$CO), 4.15 (2H, m, C$\underline{H}_2$O), 5.94 (1H, d, J 6.9Hz, N$\underline{H}$), 7.33 (2H, d, J 8.1Hz, Ar-$\underline{H}$), 7.74 (2H, d, J 8.1Hz, Ar-$\underline{H}$)

4-Iodo-3-(*S*)-(*p*-toluenesulphonylamino)-butanoic acid ethyl ester **252**[79]

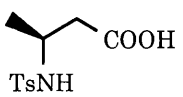


To a solution of lactone **251** (0.56 g/2.19 mmol) in DCM (8 ml) at 0°C under nitrogen was added ethanol (0.65 ml) and trimethylsilyliodide (0.89 ml). The mixture was stirred at RT for 6 hrs, then ethanol (0.65 ml) and trimethylsilyliodide (0.89 ml) were added, and the mixture stirred for a further 12 hrs at RT.

Ethanol (2.5 ml) was added, stirring continued for 30 min, then water (5 ml) and DCM (8 ml) were added, the layers separated, and the aqueous layer extracted with DCM (3 x 15 ml). The combined organic layers were washed with sodium thiosulphate solution (5 %, 15 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give the title compound as a white solid (0.86 g/2.19 mmol/100 %), m.p. 116-118°C (lit.[79] 117-118°C) which was pure by NMR analysis.

^{1}H NMR ($CDCl_3$, 400MHz): δ 1.21 (3H, t, J 7.2Hz, C$\underline{H}_3$CH$_2$O), 2.43 (3H, s, Ar-C$\underline{H}_3$), 2.58 (1H, dd, J_{aa} 15.5Hz, J_{ab} 6.2Hz, C$\underline{H}_a$H$_a$'CO), 2.67 (1H, dd, J_{aa} 15.5Hz, J_{ab} 5.3Hz, CH$_a\underline{H}_a$'CO), 3.24 (1H, m, C$\underline{H}_a$H$_a$'I), 3.37 (1H, dd, J_{aa} 14.7Hz, J_{ab} 4.2Hz, CH$_a\underline{H}_a$'I), 3.55 (1H, m, C$\underline{H}$N), 4.05 (2H, m, C$\underline{H}_2$O), 5.39 (1H, d, J 9.0Hz, N$\underline{H}$), 7.31 (2H, d, J 8.0Hz, Ar-$\underline{H}$), 7.76 (2H, d, J 8.0Hz, Ar-$\underline{H}$)

3-(*S*)-(*p*-Toluenesulphonylamino)-butanoic acid **253**[79]



(i) To a solution of the ester **252** (0.86 g/2.19 mmol) in benzene (20 ml) was added tri-*n*-butyltin hydride (0.61 ml/2.32 mmol/1.05 eq) and AIBN (19 mg/0.116 mmol/0.05 eq). The mixture was then heated under reflux for 2 hrs.

The reaction mixture was washed with saturated potassium fluoride solution (10 ml), filtered and the layers separated. The organic layer was dried (Na_2SO_4) and the solvent removed *in vacuo* to give a yellow oil. The oil was dissolved in methanolic sodium hydroxide (2M, 5ml in 3 ml of methanol) and stirred at 50°C for 2 hrs.

The reaction mixture was cooled, acidified to pH 1 with concentrated HCl and brine (20 ml) added. The mixture was extracted with ether (4 x 20 ml), the combined organic layers dried (Na_2SO_4) and the solvent removed *in vacuo* to give a viscous oil. Purification by recrystallisation from hexane gave the title compound as a white solid (0.450 g/1.76 mmol/80 %).

(ii) To a solution of the nitrile **264** (p97) (2.12 g/8.92 mmol) in ethylene glycol (45 ml) was added sodium hydroxide (5.01 g/0.12 mol). The mixture was then heated under reflux for 2 hrs.

The reaction was cooled to RT, diluted with water, cooled to 0°C, acidified to pH 1 with HCl (1M), and the mixture extracted with ether (2 x 50 ml). The combined organic layers were washed with brine (30 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a yellow solid. Purification by recrystallisation from hexane gave the title compound as a white solid (0.726 g/4.013 mmol/45 %).

$[\alpha]_D$ 23.4 (DCM) (2.013 mg/ml) (lit.[79] 25.8° ($CHCl_3$) (1.1 g/100 ml))

m.p. 124-126°C (lit.[79] 125-126°C)

^1H NMR ($CDCl_3$, 400MHz): δ 1.16 (3H, d, J 6.7Hz, $C\underline{H}_3CH$), 2.43 (3H, s, Ar-$C\underline{H}_3$), 2.51 (2H, d, J 5.3Hz, $C\underline{H}_2COOH$), 3.71 (1H, m, $CH_3C\underline{H}$), 5.40 (1H, bs, N$\underline{H}$), 7.31 (2H, d, J 8.4Hz, Ar-$\underline{H}$), 7.76 (2H, d, J 8.4Hz, Ar-$\underline{H}$)

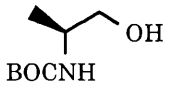
Attempted preparation of 3-(*S*)-amino butanoic acid **176**

To a solution of acid **253** (0.62 g/2.41 mmol) in concentrated hydrobromic acid solution (6 ml) was added phenol (20 mg), and the mixture heated under

reflux for 90 min. The mixture was then cooled, water (15 ml) added, and extracted with EtOAc (2 x 15 ml). The solvent was removed from the aqueous layer *in vacuo* to give a orange semi-solid residue. The residue was dissolved in propylene oxide (6 ml) and ethanol (10 ml), and the mixture refluxed for 2 hr.

The solvent was removed *in vacuo* to give an orange solid (0.42 g) Examination of its 1H NMR spectrum showed only the presence of starting material. No evidence of deprotection could be seen.

2-(S)-(1,1-Dimethylethyloxycarbonylamino)-propanol **255**[81]



To a suspension of (*S*)-alanine **254** (3.66 g/41.2 mmol) in THF (80 ml) was added sodium borohydride (3.72 g/98.8 mmol/2.4 eq). Iodine (10.9 g) in THF (20 ml) was added dropwise, until the solution was colourless and effervescence had ceased. The mixture was then heated under reflux for 18 hrs.

The reaction was cooled to room temperature, and methanol added slowly until effervescence had ceased. The solvent was removed *in vacuo* to give a white paste which was then redissolved in water (100 ml). The solution was basified to pH12 (2M NaOH) and BOC_2O (8.98 g/41.2 mmol/1 eq) added. The mixture was then stirred for 18 hrs.

The reaction mixture was extracted with DCM (3 x 80 ml) then the combined organic layers washed with brine (80 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give the title compound as a white solid (5.55 g/31.7 mmol/77 %), m.p. 45-48°C (lit. [81i] 53-54, lit.[81ii] 58.8-59.8, lit.[81iii] 59-60, lit.[81iv] 59-60, lit. [81v] 59-61)

$[\alpha]_D$ -5.6° (DCM) (2.502 mg/ml) (lit.[68] -1.0° ($CHCl_3$) (1.3 g/100 ml), lit.[81i] -11.6° ($CHCl_3$) (0.6 g/100 ml), lit.[81iii] -8.8° ($CHCl_3$) (1.0 g/100 ml), lit.[81v] -8.9°, ($CHCl_3$) (1.01 g/100 ml))

R_f 0.22 (1:1 EtOAc/ hexane)

^{1}H NMR ($CDCl_3$, 400MHz): δ 1.14 (3H, d, J 6.8Hz, C$\underline{H}_3$CH), 1.45 (9H, s, (C$\underline{H}_3$)$_3$C), 3.50 (1H, dd, J_{aa} 11.0Hz, J_{ab} 6.2Hz, C$\underline{H}_a$H$_{a'}$OH), 3.65 (1H, dd, J_{aa} 11.0Hz, J_{ab} 3.65Hz, CH$_a\underline{H}_{a'}$OH), 3.75 (1H, m, CH$_3$C$\underline{H}$), 4.65 (1H, m, N$\underline{H}$)

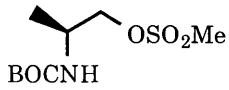
^{13}C NMR ($CDCl_3$, 100MHz): δ 17.33, 28.40, 48.55, 67.27, 79.53, 156.28

υ_{max} (cm^{-1}): 3356, 1680, 1526, 1377, 1170 (nujol mull)

Found: (M^++H) 176.1280, $C_8H_{18}NO_3$ requires 176.1287

m/z 176 (M^++H, 75 %) 157 (15) 120 (100)

2-(S)-(1,1-dimethylethyloxycarbonylamino)-1-(methanesulphonyloxy)-propane **256**[82]



To a solution of alcohol **255** (11.53 g/65.9 mmol) and TEA (27.50 ml/197.6 mmol/3 eq) in DCM (40 ml) at 0°C under nitrogen was added dropwise methanesulphonyl chloride (10.20 ml/131.7 mmol/ 2 eq). The mixture was then stirred for 1 hr.

The reaction mixture was poured into saturated aqueous ammonium chloride (100 ml) and the layers separated. The organic layer was washed with $NaHCO_3$ solution (100 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give the title compound as a yellow solid (15.83 g/62.6 mmol/95 %), which was used immediately without further purification.

^{1}H NMR ($CDCl_3$, 400MHz): δ 1.23 (3H, d, J 7.0Hz, C$\underline{H}_3$CH), 1.44 (9H, s, (C$\underline{H}_3$)$_3$C), 3.03 (3H, s, OSO_2CH_3), 3.95 (1H, m, CH$_3$C$\underline{H}$), 4.17 (2H, m, C$\underline{H}_2$O), 4.65 (1H, bs, N$\underline{H}$)

2-(S)-Methyl-N-(1,1-dimethylethyloxycarbonyl)-aziridine **257**[83]

To a solution of diisopropylamine (1.15 ml/7.91 mmol) in ether (5 ml) at -20°C under nitrogen was added *n*-butyllithium solution (7.91 ml/7.91 mmol/1 eq). The cooling bath was removed and the mixture was stirred for 30 min. The LDA solution was added dropwise via cannula to a solution of mesylate **256** (2.00 g/7.91 mmol/1 eq) in ether (15 ml), and the mixture was then stirred for 45 min.

The reaction mixture was poured into saturated ammonium chloride solution, the layers separated, and the aqueous layer extracted with ether (2 x 20 ml). The combined organic layers were dried (Na_2SO_4) and the solvent removed *in vacuo* to give the title compound as a clear yellow oil (0.86 g/5.48 mmol/70 %), which was used immediately without further purification.

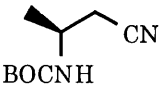
^{1}H NMR ($CDCl_3$, 400MHz): δ 1.25 (3H, d, J 4.8Hz, C$\underline{H}_3$), 1.44 (9H, s, (C$\underline{H}_3$)$_3$C), 1.86 (1H, d, J 4.0Hz, C$\underline{H}_a$H$_{a'}$), 2.23 (1H, d, J 8.1Hz, CH$_a\underline{H}_{a'}$), 2.41 (1H, m, C$\underline{H}$N)

Attempted preparation of thiane **258**

To a solution of 1,3-dithiane (0.17 g/1.42 mmol) in THF (3 ml) at -23°C under nitrogen was added *n*-butyllithium solution (0.56 ml/1.42 mmol/1 eq). The mixture was stirred for 1 hr, then cooled to -78°C. To this solution was added dropwise aziridine **257** (0.22 g/1.42 mmol/1 eq) and the mixture stirred for 1 hr at -78°C and 1 hr at 0°C.

The reaction was quenched with water (5 ml) and extracted with EtOAc (3 x 15 ml). The combined organic layers were washed with brine (20 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a yellow solid (0.264 g). Examination of the NMR spectrum of the solid showed only the presence of starting materials.

3-(S)-(1,1-dimethylethyloxycarbonylamino)-butyronitrile **259**[81v]



To a solution of mesylate **256** (p91) (10.28 g/40.6 mmol) in DMF (200 ml) under nitrogen was added sodium cyanide (14.92 g/304.5 mmol/7.5 eq), and the mixture stirred at 60°C for 90 min.

The reaction mixture was diluted with ether (200 ml), and passed through an alumina plug. The solvent was then removed *in vacuo* to give a yellow solid. Purification by flash chromatography on silica gel (30% EtOAc/ hexane) gave the title compound as an off-white solid (4.86 g/26.4 mmol/65 %), m.p. 67-69°C (lit.[81v] 69-70°C)

$[\alpha]_D$ -94.3° (DCM) (1.41 mg/ml) (lit.[81v] -87° ($CHCl_3$) (1.00 g/100 ml))

R_f 0.25 (25% EtOAc/ hexane)

^1H NMR ($CDCl_3$, 400MHz): δ (3H, d, J 7.0Hz, $C\underline{H}_3CH$), 1.42 (9H, s, $(C\underline{H}_3)_3C$), 2.51 (1H, dd, J_{aa} 16.6Hz, J_{ab} 4.1Hz, $C\underline{H}_aH_{a'}CN$), 2.73 (1H, bdd, $CH_a\underline{H}_{a'}CN$), 3.93 (1H, m, $CH_3C\underline{H}$), 4.75 (1H, bs, $N\underline{H}$).

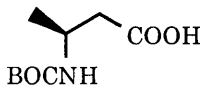
^{13}C NMR ($CDCl_3$, 100MHz): δ 19.50, 25.13, 28.12, 43.20, 80.10, 117.36, 154.84

υ_{max} (cm^{-1}): 3366, 2246, 1683, 1514, 1167 (nujol mull)

Found: (M^++H) 185.1293, $C_9H_{17}N_2O_2$ requires 185.1290

m/z 185 (M^++H, 42 %) 129 (100)

3-(S)-(1,1-Dimethylethyloxycarbonylamino)-butanoic acid **260**[85]



(i) To a solution of the nitrile **259** (7.47 g/40.6 mmol) in methanol (300 ml) was added NaOH solution (2M, 250 ml). The mixture was then stirred at 50°C for 5 hrs.

The reaction mixture was cooled to RT and the methanol removed *in vacuo*. The solution was cooled to 0°C, and acidified to pH 1 with HCl (1M). The solution was extracted with ether (3 x 50 ml), the combined organic layers were then dried (Na_2SO_4) and the solvent removed *in vacuo* to give a yellow oil. Purification by crystallisation from hexane gave the title compound as a white solid (1.19 g/6.21 mmol/14 %).

(ii) The above hydrolysis was also carried out at 90°C, and a yield of 22% (1.87 g/9.23 mmol) was obtained.

(iii) To a suspension of nitrile **259** (817.7 mg/4.44 mmol) in sodium hydroxide solution (20 %, 6.7 ml) was added hydrogen peroxide solution (30% in H_2O, 6.2 ml) and the mixture stirred at 60°C for 15 min. Methanol was then added, and the mixture refluxed for 2 hrs.

The reaction mixture was cooled to RT, water (30 ml) added, cooled to 0°C and the mixture extracted with ether (3 x 30 ml). The combined organic layers were dried (Na_2SO_4) and the solvent removed *in vacuo* to give a clear oil. Purification by recrystallisation from hexane gave the product as a white solid in a best yield of 30% (270 mg). This procedure gave widely varying yields.

(iv) Concentrated hydrochloric acid (15 ml) was added dropwise to solid nitrile **259** (2.014 g/10.946 mmol) until effervescence had ceased. The mixture was then heated under reflux for 6 hrs.

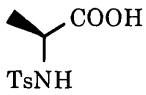
The reaction was cooled to RT, and basified to pH 12 with NaOH solution (4M). The solvent was removed *in vacuo* to give a white paste, which was then redissolved in water (25 ml) and BOC_2O (2.39 g/10.9 mmol/1 eq) added. The mixture was then stirred for 18 hrs.

The reaction mixture was extracted with hexane (4 ml), the aqueous layer cooled to 0°C, acidified to pH 4 with HCl (1M) and extracted with ether (3 x 30 ml). The combined organic layers were dried (Na_2SO_4) and the solvent removed *in vacuo* to give a yellow oil. Purification by recrystallisation from hexane gave the title compound as a white solid (1.75 g/8.65 mmol/79 %)

$[\alpha]_D$ -22.8° (DCM) (2.06 mg/ ml) (lit.[85] -214.1° ($CHCl_3$) (1.0 g/100 ml)

All spectra were identical to those obtained for racemic acid **240** (p78)

(S)-N-(p-Toluenesulphonyl)-alanine **261**[86]



To a solution of (*S*)-alanine (17.80 g/0.20 mol) in sodium hydroxide solution (8.0 g/0.20 mol/1 eq in 214 ml H_2O) was added Hünig's base (38.27 ml/0.22 mol/1.1 eq), *p*-toluenesulphonyl chloride (42.4 g/0.22 mol/1.1 eq) and acetone (214 ml). The mixture was then stirred at RT for 18 hrs.

The reaction mixture was washed with ether (2 x 75 ml) and the combined washings were extracted with NaOH solution (5 %, 50 ml). The combined basic aqueous layers were cooled to -10°C, acidified to pH 1 with concentrated HCl and extracted with ether (4 x 80 ml) The combined organic layers were washed with water (2 x 80 ml), brine (80 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give the title compound as a white solid (48.11 g/0.20 mol/99 %), m.p. 119-121°C (lit.[86i] 131-132°C, lit.[86ii] 132-133°C, lit.[86iii] 134-135°C, lit.[86iv] 135-136°C, lit.[86v] 135-136°C), which was pure by NMR analysis.

$[\alpha]_D$ -27.5° (DCM) (2.126 mg/ ml) (lit.[86vi] -10.8° (DCM) (1.01 g/100 ml)

^{1}H NMR ($CDCl_3$, 400MHz): δ 1.41 (3H, d, 7.0Hz, $C\underline{H}_3CH$), 2.42 (3H, s, Ar-$C\underline{H}_3$), 4.00 (1H, m, $CH_3C\underline{H}$), 5.39 (1H, d, J 8.4Hz, N$\underline{H}$), 7.30 (2H, d, J 7.8Hz, Ar-$\underline{H}$), 7.74 (2H, d, J 7.8Hz, Ar-$\underline{H}$)

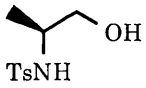
^{13}C NMR ($CDCl_3$, 100MHz): δ 19.53, 21.60, 51.20, 127.18, 129.82, 136.64, 143.98, 176.78

υ_{max}(cm^{-1}): 3267, 2728, 1712, 1654. 1342, 1149 (nujol mul)

Found: (M^++H) 244.0640, $C_{10}H_{14}NO_4S$ requires 244.0644

m/z 244 (M^++H, 75 %) 226 (15) 198 (100) 155 (70) 116 70)

2-(S)-(p-Toluenesulphonylamino)-propanol **262**[87]



To a solution of acid **261** (10.00 g/41.16 mmol) in THF (250 ml) was added slowly lithium aluminium hydride (3.91 g/102.8 mmol/2.5 eq) and the mixture heated under reflux for 4 hrs.

The reaction was cooled to RT, and quenched by dropwise addition of water (20 ml). The solution was filtered and the precipitate of aluminium salts was washed with ethyl acetate (2 x 100 ml). The combined organic layers were washed with brine (100 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a yellow solid. Purification by flash chromatography on silica gel (1:1 EtOAc/hexane) gave the title compound as a white solid (5.56 g/27.1 mmol/59 %), m.p. 55-57°C (lit.[87] 58-60°C)

$[\alpha]_D$ -22.7° (DCM) (1.917 mg/ ml)

R_f 0.35 (1:1 EtOAc/ hexane)

^{1}H NMR ($CDCl_3$, 400MHz): δ 1.02 (3H, d, J 6.6Hz, $C\underline{H}_3CH$), 2.43 (3H, s, Ar-$C\underline{H}_3$), 3.38 (1H, m, $CH_3C\underline{H}$), 3.44 (1H, m, $C\underline{H}_aH_{a'}O$), 3.57 (1H, dd, J_{aa} 11.0Hz, J_{ab} 3.6Hz, $CH_a\underline{H}_{a'}O$), 7.31 (2H, d, J 8.3Hz, Ar-$\underline{H}$), 7.78 (2H, d, J 8.3Hz, Ar-$\underline{H}$)

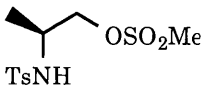
^{13}C NMR ($CDCl_3$, 100MHz): δ 17.54, 21.59, 51.52, 66.21, 127.10, 129.80, 137.55, 143.54

$\upsilon_{max}(cm^{-1})$: 3491, 3180, 1303, 1159, 976 (nujol mull)

Found: (M^++H) 230.0857, $C_{10}H_{16}NO_3S$ requires 230.0851

m/z 230 (M^++H, 100 %) 198 (25) 155 (50) 139 (30)

2-(S)-(p-Toluenesulphonylamino)-1-(methanesulphonyloxy)-propane **263**

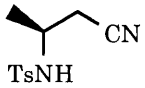


To a solution of alcohol **262** (3.59 g/15.6 mmol) and TEA (6.58 ml/47.0 mmol) in DCM (20 ml) at 0°C was added dropwise methanesulphonyl chloride (2.42 ml/31.33 mmol). The mixture was then stirred for 1 hr.

The reaction mixture was poured into saturated aqueous ammonium chloride (20 ml) and the layers separated. The organic layer was washed with $NaHCO_3$ solution (20 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give the title compound as a yellow solid (4.44 g/14.5 mmol/92 %), which was used immediately without further purification.

^1H NMR ($CDCl_3$, 400MHz): δ 1.13 (3H, d, J 7.0Hz, $C\underline{H}_3CH$), 2.44 (3H, s, Ar-$C\underline{H}_3$), 3.01 (3H, s, $SO_2C\underline{H}_3$), 3.62 (1H, m, $CH_3C\underline{H}$), 4.11 (2H, m, $C\underline{H}_2O$), 5.07 (1H, d, J 7.9Hz, N$\underline{H}$), 7.33 (2H, d, J 8.3Hz, Ar-$\underline{H}$), 7.77 (2H, m, J 8.3Hz, Ar-$\underline{H}$)

3-(S)-(p-Toluenesulphonylamino)-butyronitrile **264**[88]



To a solution of mesylate **263** (4.44 g/14.5 mmol) in DMF (40 ml) under nitrogen was added sodium cyanide (5.67 g/115.7 mmol/7.5 eq), and the mixture stirred at 60°C for 90 min.

The reaction mixture was diluted with ether (200 ml), and passed through an alumina plug. The solvent was then removed *in vacuo* to give a yellow solid. Purification by flash chromatography on silica gel (30% ether/hexane) gave the title compound as a white solid (2.116 g/8.918 mmol/62 %), m.p. 69-70°C.

$[\alpha]_D$ -67.5° (DCM) (2.241 mg/ ml)

^1H NMR ($CDCl_3$, 400MHz): δ 1.23 (3H, d, J 6.7Hz, $C\underline{H}_3CH$), 2.44 (3H, s, Ar-$C\underline{H}_3$), 2.57 (2H, m, $C\underline{H}_2CN$), 3.62 (1H, m, $CH_3C\underline{H}$), 5.14 (1H, d, J 7.6Hz, N<u>H</u>), 7.33 (2H, d, J 8.1Hz, Ar-<u>H</u>), 7.77 (2H, d, J 8.1Hz, Ar-<u>H</u>)

^{13}C NMR ($CDCl_3$, 100MHz): 20.24, 21.78, 26.31, 46.25, 117.01, 127.04, 130.01, 137.01, 144.04

$\upsilon_{max}(cm^{-1})$: 3253, 2251, 1725, 1340, 1148, 1094 (nujol mull)

Found: (M^++H) 239.0859, $C_{11}H_{15}N_2O_2S$ requires 239.0854

m/z 239 (M^++H, 75 %) 230 (30) 198 (100) 155 (95) 137 (50)

Attempted reduction of 3-(S)-(1,1-dimethylethyloxycarbonylamino)-butyronitrile **259**

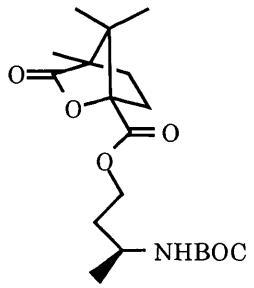
(i) To a solution of nitrile **259** (p93) (1.000 g/5.435 mmol) in THF (5 ml) under nitrogen was added lithium aluminium hydride (0.309 g/8.018 mmol/1.45 eq) and the mixture heated under reflux for 2 hrs.

The reaction was quenched by dropwise addition of water (1ml), the solution filtered and the precipitate washed with ether (3 x 10 ml). The combined organic layers were dried (Na_2SO_4) and the solvent removed *in vacuo* to give a clear oil, hwever no product or starting material could be identified.

(ii) To a solution of nitrile **259** (p93) (0.75 g/4.08 mmol) in DCM at -78°C was added DIBAL solution (1M in toluene, 2.93 ml/4.40 mmol/1.08 eq) and the mixture stirred for 30 min. The cooling bath was then removed and the mixture stirred at RT for a further 5 hrs.

The reaction was quenched by dropwise addition of water (1 ml), poured into Rochelle Salt solution, DCM (15 ml) added and the layers separated. The aqueous layer was extracted with DCM, then the combined organic layers were washed with brine (30 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a white solid, which was shown by NMR analysis to be the starting material.

Preparation of camphanate ester **267** of alcohol **175**



To a solution of alcohol **175** (28.5 mg/0.151 mmol), TEA (0.05 ml/0.38 mmol/2.5 eq) and DMAP (5 mg) in DCM (3 ml) was added (+)-camphanic acid chloride (63.5 mg/0.29 mmol/1.9 eq) in DCM (2 ml) and the mixture stirred for 18 hr.

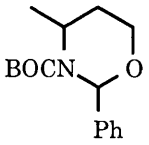
The reaction mixture was washed with water (3 x 4 ml), $NaHCO_3$ solution (5 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give the product as a clear viscous oil (54.1 mg/0.41 mmol/94 %). Examination of the ^1H NMR spectrum of the camphanate showed the presence of one diastereomer:

^1H NMR ($CDCl_3$, 400MHz): δ 0.95 (single peak, single diastereomer), 1.04 (3H, single peak, single diastereomer), 1.10 (3H, singlet), 1.17 (3H, d, J 6.7Hz, $C\underline{H}_3CH$), 1.41 (9H, s, $(CH_3)_3C$), 1.62-1.80 (2H, m), 1.86 (2H, m, $C\underline{H}_2CH_2O$), 2.05 (1H, m), 3.78 (1H, m, $CH_3C\underline{H}$), 4.25 (2H, m, $C\underline{H}_2O$), 6.50 (1H, bs, $N\underline{H}$)

The same reaction, carried out with racemic alcohol **241** (p79) gave a similar oil, but with doubling of some peaks:

^{1}H NMR ($CDCl_3$, 400MHz): δ 0.95, 0.96 (two singlets, two diastereomers), 1.04, 1.05 (3H, two singlets, two diastereomers), 1.09 (3H, singlet), 1.16 (3H, d, J 6.7Hz, $C\underline{H}_3CH$), 1.41 (9H, s, $(CH_3)_3C$), 1.62-1.80 (2H, m), 1.86 (2H, m, $C\underline{H}_2CH_2O$), 2.05 (1H, m), 3.78 (1H, m, $CH_3C\underline{H}$), 4.25 (2H, m, $C\underline{H}_2O$), 6.50 (1H, bs, N<u>H</u>)

3-(1,1-Dimethylethyloxycarbonyl)-4-methyl-2-phenyl-2,4,5,6-tetrahydro-1,3-oxazine **274**



(i) To a solution of amino alcohol **241** (p79) (0.31 g/1.65 mmol) in benzene (12 ml) was added benzaldehyde (0.16 ml/1.65 mmol/1 eq) and TsOH (15 mg). The mixture was heated under reflux in a Dean and Stark trap for 4 hrs.

The reaction mixture was poured into $NaHCO_3$ solution (5 ml) and extracted with ether (3 x 10 ml). The combined organic layers were washed with brine (20 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a yellow oil. Purification by flash chromatography on silica gel (4 % EtOAc/toluene) gave the title compound as a white solid (0.11 g/0.41 mmol/25 %).

(ii) The above conditions were employed using 5 equivalents (0.37 ml/8.25 mmol) of aldehyde to give the title compound as a white solid (0.13 g/0.48 mmol/29 %).

(iii) To a solution of amino alcohol **241** (p79) (0.31 g/1.65 mmol) in toluene (12 ml) was added benzaldehyde (0.16 ml/1.65 mmol) and TsOH (15 mg). The mixture was heated under reflux in a Dean and Stark trap for 4 hrs.

The reaction mixture was poured into $NaHCO_3$ solution (5 ml) and extracted with ether (3 x 10 ml). The combined organic layers were washed with brine (20 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a yellow

oil. Purification by flash chromatography on silica gel (4 % EtOAc/toluene) gave the title compound as a white solid (72.8 mg/0.27 mmol/16 %).

(iv) To a solution of amino alcohol **241** (p79) (0.31 g/1.65 mmol) in benzene (12 ml) was added benzaldehyde (0.16 ml/1.65 mmol/1 eq) and PPTS (15 mg). The mixture was heated under reflux in a Dean and Stark trap for 4 hrs.

The reaction mixture was poured into $NaHCO_3$ solution (5 ml) and extracted with ether (3 x 10 ml). The combined organic layers were washed with brine (20 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a yellow oil. No trace of the product was evident by NMR and TLC analysis.

(v) To a solution of amino alcohol **241** (p79) (0.31g/1.65 mmol) in benzene (12 ml) was added benzaldehyde (0.16 ml/1.65 mmol), TsOH (15 mg) and Na_2SO_4 (3 g). The mixture was stirred at RT for 4 hrs.

The reaction mixture was poured into $NaHCO_3$ solution (5 ml) and extracted with ether (3 x 10 ml). The combined organic layers were washed with brine (20 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a yellow oil. Purification by flash chromatography on silica gel (4 % EtOAc/toluene) gave the title compound as a white solid (90.8 mg/0.33 mmol/20 %).

(vi) The aboved conditions were employed using 5 equivalents (0.37 ml/8.25 mmol) of aldehyde to give the title compound as a white solid (0.18 g/0.66 mmol/40 %).

(vii) To a solution of amino alcohol **241** (p79) (0.31g/1.65 mmol) in benzene (12 ml) was added benzaldehyde (0.16 ml/1.65 mmol/1 eq), TsOH (15 mg) and molecular sieves (4 g). The mixture was stirred at RT for 4 hr.

The reaction mixture was poured into $NaHCO_3$ solution (5 ml) and extracted with ether (3 x 10 ml). The combined organic layers were washed with

brine (20 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a yellow oil. Purification by flash chromatography on silica gel (4 % EtOAc/toluene) gave the title compound as a white solid (90.4 mg/0.33 mmol/20 %).

(viii) The above conditions were employed using 5 equivalents (0.37 ml/8.25 mmol) of aldehyde to give the title compound as a white solid (0.11 g/0.39 mmol/24 %).

(ix) To a solution of the amino alcohol **241** (p79) (0.201 g/1.058 mmol) and benzaldehyde diethyl acetal (0.190 g/1.058 mmol) in benzene (12 ml) was added PPTS (10 mg) and the mixture heated under reflux in a Dean and Stark trap for 1 hr.

The reaction mixture was poured into $NaHCO_3$ solution (10 ml) and extracted with ether (3 x 15 ml). The combined organic layers were washed with brine (20 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a yellow oil. Purification by flash chromatography on neutral alumina (4% EtOAc/toluene) gave the title compound as a white solid (0.135 g/0.556 mmol/70 %).

m.p. 48-49°C

R_f 0.23 (5% EtOAc/ toluene)

^1H NMR ($CDCl_3$, 200MHz): δ 0.99 (3H, d, J 7.0Hz, $C\underline{H}_3CH$), 1.47 (9H, s, $(C\underline{H}_3)_3C$), 1.66-1.90 (1H, m, $CH_3CHC\underline{H}_aH_{a'}$), 2.00-2.20 (1H, m, $CH_3CHCH_a\underline{H}_{a'}$), 3.69-3.82 (1H, m, $CH_aC\underline{H}_eO$), 3.88-4.02 (1H, m, $C\underline{H}_aCH_eO$), 4.42-4.50 (1H, m, $CH_3C\underline{H}$), 6.68 (1H, s, $NC\underline{H}O$), 7.29-7.34 (5H, m, Ar-$\underline{H}$)

^{13}C NMR ($CDCl_3$, 50 MHz): δ 20.46, 28.25, 29.38, 44.56, 57.36, 80.16, 80.99, 82.00, 126.04-128.03, 140.11

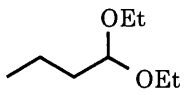
$\upsilon_{max}(cm^{-1})$: 1702, 1355, 1177, 1058, 723

Found: $(M^+ + H)$ 278.1756, $C_{16}H_{24}NO_3$ requires 278.1756

m/z 278 (M^++H, 55 %), 178 (100) 134 (50)

Preparation of aldehyde diethyl acetals:

n-Butyraldehyde diethyl acetal **277**[96]



To a solution of butyraldehyde (4.0 ml/44.1 mmol) in ether (30 ml) was added ethanol (10 ml), TsOH (1.69 g/8.88 mmol/0.2 eq) and Na_2SO_4 (5 g). The mixture was stirred at RT for 5 hrs.

The reaction mixture was poured into $NaHCO_3$ solution and the layers separated. The aqueous layer was washed with ether (30 ml), the combined organic layers were then washed with brine (40 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give the title compound as a clear mobile oil (5.88 g/40.41 mmol/90 %), b.p. 52°C/ 27mmHg (lit.[96i] 142°C/ 760mmHg, lit.[96ii] 145°C/ 760mmHg), which was pure by NMR analysis.

R_f 0.48 (4% EtOAc/ toluene)

^1H NMR ($CDCl_3$, 200 MHz): δ 0.89 (3H, t, J 7.1 Hz, $C\underline{H}_3CH_2CH_2$), 1.17 (6H, t, J 7.1Hz $C\underline{H}_3CH_2O$), 1.25-1.75 (4H, m, $CH_3C\underline{H}_2C\underline{H}_2$), 3.38-3.85 (4H, m, $CH_3C\underline{H}_2O$), 4.46 (1H, t, J 5.6Hz, $OC\underline{H}O$)

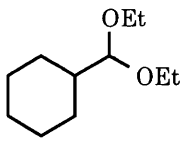
^{13}C NMR ($CDCl_3$, 63MHz): δ 13.46, 14.83, 17.62, 35.23, 60.32, 102.28

υ_{max} (cm^{-1}): 3467, 2962, 2874, 1461 (thin film)

Found: no (M^++H) peak observed

m/z 127 (100) 111 (25) 101 (65) 97 (10)

Cyclohexanecarboxaldehyde diethyl acetal **278**[97]



The above procedure was carried out using cyclohexanecarboxaldehyde (3.0 ml/24.81 mmol) to give the title compound as a clear mobile oil (4.29 g/23.1 mmol/93 %), b.p. 79°C/ 17mm Hg (lit.[97] 97°C/20mm Hg), which was pure by NMR analysis

R_f 0.50 (4% EtOAc/ toluene)

^1H NMR ($CDCl_3$, 200MHz): δ 1.18 (6H, t, J 7.3 Hz, $C\underline{H}_3CH_2O$), 0.85- 1.10 and 1.45- 1.92 (11H, 2 x m, cyclohexyl ring protons), 3.40- 3.80 (4H, m, $CH_3C\underline{H}_2O$), 4.10 (1H, d, J 7.1Hz, $OC\underline{H}O$)

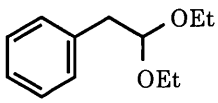
^{13}C NMR ($CDCl_3$, 63 MHz): δ 15.00, 25.54, 26.16, 27.92, 40.44, 61.26, 106.45

υ_{max} (cm^{-1}): 2974, 2924, 2682, 1734, 1449 (thin film)

Found: (M^++Na) 209.1517, $C_{11}H_{22}O_2Na$ requires 209.1513

m/z 209 (M^++Na, 25 %) 179 (90) 173 (100) 141 (65)

Phenylacetaldehyde diethyl acetal **279**[98]



The above procedure was carried out using phenylacetaldehyde (3. 0 ml/37.30 mmol) to give the title compound as a clear mobile oil (3.730 g/29.458 mmol/79 %), b.p. 155-160°C/26 mm Hg (lit.[98] 91-92°C/18 mm Hg) which was pure by NMR analysis.

R_f 0.54 (1:1 EtOAc/ hexane)

^{1}H NMR ($CDCl_3$, 400MHz): δ 1.19 (6H, t, J 7.0 Hz, 2x $C\underline{H}_3CH_2O$), 2.96 (2H, dd, J_{aa} 1.8 Hz, J_{ab} 5.6Hz, Ar-$C\underline{H}_2$), 3.47 (2H, m, 2x $OC\underline{H}_aCH_b$), 3.70 (2H, m, 2x $OCH_aC\underline{H}_b$), 4.66 (1H, t, J 5.6 Hz, $OC\underline{H}O$), 7.27 (5H, m, Ar-$\underline{H}$)

^{13}C NMR ($CDCl_3$, 100 MHz): δ 15.29, 40.93, 61.90, 103.91, 126.29, 128.21, 129.60, 137.38

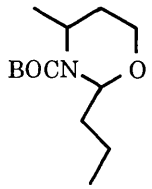
υ_{max} (cm^{-1}): 3736, 2975, 2360, 1127, 1060, 824 (thin film)

Found: (M^++H) 194.1303 $C_{12}H_{18}O_2$ requires 194.1307

m/z 194 (M^+ 25 %) 176 (60) 154 (100) 121 (60) 103 (55).

Preparation of tetrahydro-1,3-oxazines (acetal exchange):

3-(1,1-Dimethylethyloxycarbonyl)-4-methyl-2-(n-propyl)-2,4,5,6-tetrahydro-1,3-oxazine **280**



To a solution of the amino alcohol **241** (p79) (0.15 g/0.79 mmol) and *n*-butyraldehyde diethyl acetal (0.12 g/0.79 mmol/1 eq) in benzene (12 ml) was added PPTS (10 mg) and the mixture heated under reflux in a Dean and Stark trap for 1 hr.

The reaction mixture was poured into $NaHCO_3$ solution (10 ml) and extracted with ether (3 x 15 ml). The combined organic layers were washed with brine (20 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a yellow oil. Purification by flash chromatography on neutral alumina (4% EtOAc/toluene) gave the title compound as a clear mobile oil (0.135 g/0.556 mmol/70 %). An attempt to measure the atmospheric boiling point of the aminal resulted in decomposition at 110-111°C

R_f 0.30 (4 % EtOAc/ toluene)

^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.92 (3H, t, J 7.1 Hz, $C\underline{H}_3CH_2CH_2$), 1.26 (3H, d, J 7.0 Hz, $C\underline{H}_3CH$), 1.43 (9H, s, $(C\underline{H}_3)_3C$), 1.44-2.06 (6H, m, $CH_3CHC\underline{H}_2$

and $CH_3C\underline{H}_2C\underline{H}_2$), 3.51-3.61 (1H, m, $CH_a\underline{H}_{a'}O$), 3.82-3.97 (1H, m, $C\underline{H}_aH_{a'}O$), 5.35 (1H, dd, J 4.3 Hz, NC<u>H</u>O)

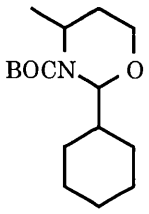
^{13}C NMR ($CDCl_3$, 63 MHz): δ 13.61, 18.80, 28.28, 29.56, 37.76, 43.44, 56.16, 79.50, 82.30, 153.44

υ_{max} (cm^{-1}): 3350, 2964, 2873, 1693, 1451 (thin film)

Found (M^++H) 244.1929, $C_{13}H_{26}NO_3$ requires 244.1913

m/z 244 (M^++H, 20 %) 144 (80) 55 (100).

3-(1,1-Dimethylethyloxycarbonyl)-4-methyl-2-cyclohexyl-2,4,5,6-tetrahydro-1,3-oxazine **281**



The above procedure was carried out using cyclohexanecarboxaldehyde diethyl acetal (0.21 g/1.61 mmol) to give the title compound as a white solid (0.354 g/1.448 mmol/90 %), m.p. 48-50°C.

R_f 0.32 (4 % EtOAc/ toluene)

^1H NMR ($CDCl_3$, 200MHz): δ 0.90-1.22, 1.55-2.15 (13H, 2 x m, cyclohexyl ring protons and $CH_3CHC\underline{H}_2$), 1.28 (3H, d, J 7.1 Hz, $C\underline{H}_3CH$), 1.44 (9H, s, $(C\underline{H}_3)_3C$), 3.52-3.62 (1H, m, $CH_a\underline{H}_eO$), 3.83-3.96 (1H, dt, J_{aa} 11.0Hz, J_{ab} 3.0Hz), 4.35-4.44 (1H, m, $CH_3C\underline{H}$), 5.13 (1H, d, NC<u>H</u>O)

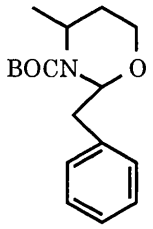
^{13}C NMR ($CDCl_3$, 63 MHz): δ 20.67, 25.73, 25.99, 26.16, 28.28, 29.56, 40.85, 43.72, 56.05, 79.60, 85.32, 154.20

υ_{max} (cm^{-1}): 2670, 2360, 1698 (nujol mull)

Found: (M^++H) 284.2238, $C_{16}H_{30}NO_3$ requires 284.2226

m/z 284 (M^++H, 50 %) 184 (70) 144 (70) 58 (100)

3-(1,1-Dimethylethyloxycarbonyl)-4-methyl-2-benzyl-2,4,5,6-tetrahydro-1,3-oxazine **282**



The above procedure was carried out using phenylacetaldehyde diethyl acetal (0.20 g/1.06 mmol) to give the title compound as an off-white solid (0.22 g/0.74 mmol/70 %), m.p 51-53°C.

^{1}H NMR ($CDCl_3$, 400MHz): δ 1.38 (3H, d, J 7.0Hz, C$\underline{H}_3$CH), 1.46 (9H, s, $(CH_3)_3C$), 1.55 (1H, m, CHC$\underline{H}_a$H$_{a'}$), 2.10 (1H, m, CHCH$_a\underline{H}_{a'}$), 2.97 (1H, dd, J_{aa} 12.0Hz, J_{ab} 3.3Hz, Ar-C$\underline{H}_a$H$_{a'}$), 3.17 (1H, m, Ar-CH$_a\underline{H}_{a'}$), 3.62 (1H, m, C$\underline{H}_a$H$_{a'}$O), 4.08 (1H, m, CH$_a\underline{H}_{a'}$O), 4.42 (1H, m, CH$_3$C$\underline{H}$), 5.51 (1H, dd, J_{ae} 3.4Hz, J_{aa} 9.0Hz, NC$\underline{H}$O), 7.27 (5H, m, Ar-$\underline{H}$)

^{13}C NMR ($CDCl_3$, 100MHz): δ 21.94, 28.43, 29.43, 40.42, 43.63, 56.98, 80.08, 84.29, 126.45, 128.41, 128.46, 129.09, 137.88

υ_{max} (cm^{-1}): 1707, 1353, 1175 (nujol mull)

Found: (M^++H) 292.1923, $C_{17}H_{26}NO_3$ requires 292.1913

m/z 292 (M^++H, 10%) 200 (30) 192 (80) 144 (100)

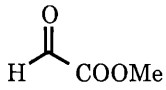
Attempted preparation of aminal **284**

(i) The above procedure was carried out using methyl dimethoxyacetate (0.13 ml/1.06 mmol), but no reaction was seen, and only starting materials were recovered.

(ii) To a solution of the amino alcohol **241** (p79) (0.20 g/1.06 mmol) and methyl di-isopropyloxyacetate (p108) (93.1 mg g/1.06 mmol/1 eq) in benzene (12 ml) was added PPTS (10 mg) and the mixture refluxed under Dean and Stark conditions for 1 hr.

The reaction mixture was poured into $NaHCO_3$ solution (10 ml) and extracted with ether (3 x 15 ml). The combined organic layers were washed with brine (20 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a yellow oil. No title compound could be identified from this mixture, and only starting amino alcohol was recovered.

Methyl glyoxalate **286**[99]

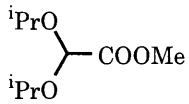


A solution of dimethyl maleate (6.16 ml/52.0 mmol) in DCM (25 ml) under nitrogen was cooled to -78°C and ozone passed through the solution for 2 hrs. Nitrogen was then passed through the solution until all colour had been removed. Dimethyl sulphide (15 ml) was added and the mixture stirred for 1 hr while being allowed to warm to RT.

The solvent was removed by blowing with nitrogen to give the crude title compound as a clear, very viscous oil. The required amount of material required was distilled from this oil immediately before use.

^1H NMR ($CDCl_3$, 200MHz): δ 3.87 (3H, s, $C\underline{H}_3O$), 9.38 (1H, s, $C\underline{H}O$), identical to compound prepared by the literature procedure.

Methyl di-isopropyloxyacetate **287**



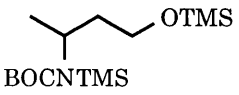
To a solution of freshly distilled methyl glyoxalate (1.75 g/19.9 mmol) in cyclohexane (125 ml) under nitrogen was added isopropanol (21 ml) and Na_2SO_4 (20 g). Hydrogen chloride gas was passed through the mixture for 3 hrs.

The reaction mixture was filtered, and sodium carbonate added until effervescence had ceased. The solution was filtered and the solvent removed *in*

vacuo to give a clear oil. Purification by Kugelrohr distillation gave the title compound as a clear oil (3.01 g/15.9 mmol/80 %), b.p. 75°C/20 mmHg, which was used immediately without further purification.

^{1}H NMR ($CDCl_3$, 400MHz): δ 1.21 (12H, m, 4x $C\underline{H}_3CH$), 3.77 (3H, s, $C\underline{H}_3O$), 3.92 (2H, m, 2x $OC\underline{H}(CH_3)_2$), 4.93 (1H, s, $OC\underline{H}O$)

Bis(trimethylsilyl)-3-(1,1-dimethylethyloxycarbonylamino)-butan-1-ol **290**



(i) To a solution of amino alcohol **241** (p79) (0.27 g/1.43 mmol) in ether (5 ml) under nitrogen was added TEA (0.41 ml/2.929 mmol/2 eq) and trimethylsilyl chloride (0.37 ml/2.93 mmol/2 eq). The mixture was then stirred at RT for 90 min.

The reaction mixture was filtered, and the solvent removed *in vacuo* to give a yellow oil. Analysis by TLC and NMR showed that extensive decomposition of the starting material had occurred.

(ii) To a solution of alcohol **241** (p79) (0.10 g/0.53 mmol) in ether (7 ml) under nitrogen was added bistrimethylsilylacetamide (0.26 ml/1.06 mmol/2 eq) and the mixture stirred at RT for 90 min.

The solvent was then removed *in vacuo* to give a clear oil. Analysis by NMR showed a 1:1 mixture of the title compound and O-trimethylsilyl acetamide. Attempts to separate the components of the mixture by distillation resulted in decomposition of the product.

(iii) To a solution of hexamethyldisilazane (0.52 ml/2.15 mmol) in THF (3 ml) at 0°C under nitrogen was added *n*-butyllithium solution (2.5M in THF, 0.94 ml/2.35 mmol/1.1 eq) and the mixture stirred for 15 min. This procedure was

carried out twice, and both solutions of lithium hexamethyldisilazide (LiHMDS) were stored at 0°C under nitrogen.

One portion of LiHMDS solution was cooled to -78°C, a solution of alcohol **241** (p79) (0.42 g/2.24 mmol) in THF (3 ml) added dropwise, and the mixture stirred for 15 min. Trimethylsilylchloride (0.57 ml/2.24 mmol/1 eq) was added dropwise, the cooling bath removed, and the mixture stirred for 15 min. The solution was then re-cooled to -78°C, the second portion of LiHMDS added dropwise, and stirring continued for 15 min. Trimethylsilylchloride (0.57 mmol/2.24 mmol/1 eq) was added dropwise, the cooling bath removed, and the mixture stirred for 15 min.

The solvent was removed *in vacuo* to give a yellow oil containing a precipitate. The crude product was dissolved in DCM (5 ml), filtered, and the solvent removed *in vacuo* to give a yellow oil, which was dried on a Schenk line for 18 hrs. This gave the title compound as a clear yellow oil (0.54 g/1.63 mmol/73 %) which was used immediately without further purification.

R_f 0.80 (1:1 EtOAc/ hexane)

^{1}H NMR ($CDCl_3$, 400 MHz): δ 0.05 (9H, s, $(C\underline{H}_3)_3SiO$), 0.17 (9H, s, $(C\underline{H}_3)_3SiN$), 1.09 (3H, d, J 6.6 Hz, $C\underline{H}_3CH$), 1.38 (9H, s, $(C\underline{H}_3)_3C$), 1.44-1.75 (2H, m, $CH_3CHC\underline{H}_2$), 3.50-3.75 (2H, m, $C\underline{H}_2O$)

Attempted preparation of 3-(1,1-dimethylethyloxycarbonyl)-4-methyl-2-benzyl-2,4,5,6-tetrahydro-1,3-oxazine **282** using a Noyori acetalisation

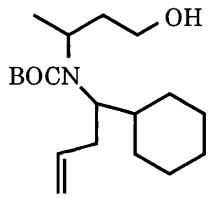
To a solution of silylated alcohol **290** (0.54 g/1.62 mmol), phenylacetaldehyde (0.17 ml/1.52 mmol/0.93 eq) and 2,6-di-*t*-butylpyridine (7.8 µl) at -78°C under nitrogen was added trimethylsilyl triflate (11.7 µl) and the mixture stirred for 3 hrs.

Methanol (0.1 ml) and TEA (0.1 ml) were added, and the reaction warmed to room temperature. The solvent was then removed *in vacuo* to give a yellow

oil, but examination of the oil by TLC and NMR spectroscopy showed no trace of the desired product.

3-[N-(1-allyl-1-cyclohexyl)-N-(1,1-dimethylethyloxycarbonylamino)]-butan-1-ol

300



(i) To a solution of aminal **281** (p106) (50 mg/0.19 mmol) and allyl trimethylsilane (0.11 ml/0.68 mmol/3.17 eq) in DCM (3 ml) at -78°C under nitrogen was added titanium tetrachloride (1M in DCM, 0.26 ml/1.41 eq) and the mixture stirred for 20 min.

The reaction was poured into saturated ammonium chloride, DCM (7 ml) added and the layers separated. The organic layer was washed with brine, dried (Na_2SO_4) and the solvent removed *in vacuo* to give a clear gum. No product could be identified.

(ii) A reaction was carried out at 0°C for 20 sec using the above quantities of reactants to give a clear oil. Purification by flash chromatography on neutral alumina gave the title compound as a clear oil (6 mg/18.6 μmol/10 %)

(iii) To a solution of aminal **281** (p106) (50 mg/0.19 mmol) and allyl trimethylsilane (0.23 ml/1.49 mmol/8 eq) in DCM (3 ml) at -78°C under nitrogen was added tin tetrabromide (1 M in DCM, 0.28 ml/1.5 eq) and the mixture stirred for 5 min. Water (1 ml) was then added, the reaction warmed quickly to RT and EtOAc (3 ml) added. The layers were separated, the organic layer washed with brine (3 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a

clear oil. Purification by flash chromatography on neutral alumina gave the title compound as a clear oil (5 mg/14.8 μmol/8 %).

(iv) A reaction was carried out at 0°C for 20 sec using the above quantities of reactants to give the title compound as a clear oil (15 mg /46.5 μmol/25 %).

(v) To a solution of aminal **281** (p106) (50 mg/0.19 mmol) and allyl trimethylsilane (0.23 ml/1.49 mmol/8 eq) in THF (3 ml) at RT under nitrogen was added tin tetrabromide (1 M in DCM, 0.28 ml/1.5 eq) and the mixture stirred for 45 min. Water (1 ml) and EtOAc (6 ml) were then added. The layers were separated, the organic layer washed with brine (3 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a clear oil. Purification by flash chromatography on neutral alumina gave the title compound as a clear oil (6.6 mg/20.5 μmol/8 %).

(vi) To a solution of aminal **281** (p106) (50 mg/0.19 mmol) and allyl trimethylsilane (0.23 ml/1.49 mmol/8 eq) in THF (3 ml) at RT under nitrogen was added titanium isopropoxide (0.12 ml/0.42 mmol/1.5 eq) and the mixture stirred for 45 min.

Water (1 ml) and DCM (4 ml) were then added. The layers were separated, the organic layer washed with brine (3 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a clear gum. No products could be identified.

(vii) To a solution of aminal **281** (p106) (50 mg/0.19 mmol) and allyl trimethylsilane (0.23 ml/1.49 mmol/8 eq) in THF (5 ml) at RT under nitrogen was added boron trifluoride etherate (0.05 ml/0.32 mmol/1.15 eq) and the mixture stirred for 3 hr.

Water (1 ml) and DCM (4 ml) were then added. The layers were separated, the organic layer washed with brine (3 ml), dried (Na_2SO_4) and the solvent removed *in vacuo* to give a clear gum. No products could be identified.

(viii) To a solution of aminal **281** (p106) (75 mg/0.28 mmol) and allyl magnesium bromide (1M in ether, 1.17 ml/4 eq) in THF under nitrogen was added boron trifluoride etherate (0.05 ml/0.32 mmol/1.15 eq). The mixture was then stirred at room temperature for 45 min.

The reaction was poured into saturated ammonium chloride solution (5 ml) and the layers separated. The organic layer was washed with brine, dried (Na2SO4) and the solvent removed in vacuo to give not the title compound, but alcohol **302** (13.3 mg/86.5 μmol/31 %).

decomposition point 85-86°C.

R_f 0.36 (4% EtOAc/ hexane)

^1H NMR ($CDCl_3$, 200MHz): δ 0.83-1.10, 1.52-1.85 (13H, 2xm, cyclohexyl ring protons and $C\underline{H}_2CH_2OH$), 1.14 (3H, d, J 6.5Hz, $C\underline{H}_3CH$), 1.42 (9H, s, $(C\underline{H}_3)_3C$), 2.25 (2H, m, $CH_2=CHC\underline{H}_2$), 3.00 (1H, q, J 5.6Hz, $NC\underline{H}CH$), 3.35-3.92 (3H, m, $C\underline{H}_2O$ and $CH_3C\underline{H}$), 5.05 (2H, m, $C\underline{H}_2=CH$), 5.81 (1H, m, $CH_2=C\underline{H}$)

^{13}C NMR ($CDCl_3$, 100MHz): δ 20.89, 26.38, 26.43, 28.26, 28.49, 28.92-29.51, 33.90, 35.33, 36.32, 40.93, 45.10, 67.14, 84.07, 116.67, 135.66

$\upsilon_{max}(cm^{-1})$: 3354, 3073, 2975, 1698, 1504, 1248, 1176, 1076

Found: $(M^+ + H)$ 326.2690, $C_{19}H_{36}NO_3$ requires 326.2695

m/z 326 (M^++H, 35 %) 226 (30) 184 (5) 134 (35)

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