Arranging an Enantioselective Aza-[2,3]-Wittig Rearrangement

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Abstract

The use of the aza-[2,3]-Wittig sigmatropic rearrangement in the synthesis of α,α-disubstituted α-amino acids has been investigated with the emphasis on obtaining enantioenriched rearrangement products. It was hoped that an enantioenriched precursor could form an axially chiral enolate which would impart chiral information on the product.

To access an axially chiral enolate, the rearrangement conditions of a known precursor **66** have been studied. Varying temperature had no effect on the enantioselectivity. Different bases were investigated with only KHMDS instigating rearrangement. Upon treatment with KHMDS, **66** rearranged to form the desired product as well as pyrrolidine **119**. The temperature of the rearrangement was varied; at lower temperatures only **119** was isolated.

A range of precursors with potential chelating groups has been synthesised. The effect of temperature on aza-[2,3]-Wittig rearrangement of these precursors was investigated; however, rearrangement did not occur at below temperatures of around - 40 ºC and this temperature was not low enough to provide an axially chiral enolate intermediate, as evidenced by the racemic nature of the rearrangement products.

The aza-[2,3]-Wittig rearrangement of amide precursor **63** was also investigated. The only product isolated upon treatment with KH and 18-crown -6 was pyrrolidine **158**.

Precursors **150** (derived from *tert*-leucine), and oxazoline **159** were subjected to rearrangement conditions. Deuterium quench studies showed that, in both cases, deprotonation had not occurred, possibly due to the sterically encumbered enolate that would form upon deprotonation.

Further investigations into the cyclisation of **66** showed that the probable mechanism was aza-[2,3]-Wittig rearrangement, followed by cyclisation. The resulting pyrrolidine was formed as a single diastereomer. Precursors **65**, **67** and **175** also underwent cyclisation in a similar manner. The relative stereochemistry of these pyrrolidines was determined by nOe experiments.

Studies of the mechanism of cyclisation of **63** were inconclusive. It is unknown whether pyrrolidine **158** is formed by an incomplete rearrangement or a fast rearrangement-cyclisation sequence.

The utility of the cyclisation was further demonstrated by Fleming oxidation of the dimethylphenylsilyl group and protiodesilylation of **119**.

Acknowledgements

I am indebted to Prof. Jim Anderson who has been a source of motivation and encouragement throughout my time in the Anderson group. I thank him for his enthusiasm and support. I am also grateful for the many lunches at the Vic and the Christmas parties which have provided so many fond memories.

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Abbreviations

The following abbreviations are used in the text:

Aib	Amino*iso*butyric acid
anal	analysis
app	Apparent
aq	Aqueous
Bn	Benzyl
Boc	*tert*-butoxycarbonyl
BOX	bis(oxazoline)
bp	Boiling point
br	Broad
18-C-6 / 18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
calcd	calculated
cat	Catalytic
Ch	1-amino-1-cyclohexylcarboxylic acid
COSY	Correlation spectroscopy
d	Doublet
DAST	Diethylaminosulfur trifluoride
DBAD	Dibenzyl azodicarboxylate

DCC	1,3-Dicyclohexylcarbodiimide
de	Diastereomeric excess
DEAD	Diethyl azodicarboxylate
DIBAL	Di*iso*butylaluminium hydride
DIPEA	Di*iso*propylethylamine
D-Iva	(-)-(*R*)-2-amino-2-methylbutyric acid
DMAP	4,4-dimethylaminopyridine
DME	Dimethoxyethane
DMF	Dimethylformamide
DMPU	*N,N'*-dimethyltetrahydropyrimidinone
DMSO	Dimethyl sulfoxide
DPPA	Diphenylphosphoryl azide
dr	Diastereomeric ratio
ee	Enantiomeric excess
Equiv	Equivalents
ES^+	Electrospray
Fmoc	9-fluorenylmethoxycarbonyl
h	Hour(s)
HMPA	Hexamethylphosphoric triamide
HOMO	Highest occupied molecular orbital
HPLC	High pressure liquid chromatography
HRMS	High resolution mass spectrometry
imid	Imidazole

IR	Infra-red
J	Coupling constant
KHMDS	Potassium hexamethyldisilazane
LDA	Lithium di*iso*propylamide
lit	Literature
LTMP	Lithium 2,2,6,6-tetramethylpiperidide
LUMO	Lowest unoccupied molecular orbital
m	Multiplet
m	*meta*
min	Minute(s)
MOM	Methoxymethyl
mp	Melting point
NBS	*N*-Bromosuccinimide
NMM	*N*-methylmorpholine
NMR	Nuclear magnetic resonance
nOe	Nuclear Overhauser effect
Np	Naphthyl
o	*ortho*
p	*para*
pet	petroleum
PDC	Pyridinium dichromate
PMB	*para*-Methoxybenzyl
ppm	Parts per million

q	Quartet
rt	Room temperature
s	Singlet
SAM	(*S*)-adenosyl-(*L*)-methionine
t	Triplet
TBAF	Tetra-*n*-butylammonium fluoride
TBAI	Tetra-*n*-butylammonium iodide
TBS	*tert*-Butyldimethylsilyl
THF	Tetrahydrofuran
tlc	Thin layer chromatography
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
VT	Variable temperature
wt	weight

1 Introduction

This project aimed to develop a synthetic route to α,α-disubstituted α-amino acids using an enantioselective aza-[2,3]-Wittig rearrangement as the key stereochemical determining step. We hoped to achieve this stereocontrol by creating an environment in which the reaction proceeds *via* an enolate possessing dynamic axial chirality. This would then be regenerated as central chirality in the rearrangement products. This introduction is divided into three parts: the importance and existing methods of synthesising α,α-disubstituted α-amino acids, a brief overview of [2,3]-sigmatropic rearrangements, in particular the aza-[2,3]-Wittig rearrangement, and, finally, a review of memory of chirality and its applications in organic synthesis.

1.1 Importance of α,α-disubstituted α-amino acids

α,α-Disubstituted α-amino acids represent an important class of non-proteinogenic α-amino acids. Peptides containing α,α-disubstituted α-amino acids often display significantly different chemical, biochemical and pharmacological properties, compared to peptides constructed from natural proteinogenic amino acids. This altered activity may result in beneficial

physiological effects and, therefore, α,α-disubstituted α-amino acids have been the subject of numerous studies.[1] The key features of peptides containing α,α-disubstituted α-amino acids are:

i) altered secondary and tertiary structure

In a peptide comprising of proteinogenic α-amino acids, the backbone conformation can be described by three torsion angles, ω, ψ and φ (**Figure 1.1**). The partial double bond character of the amide bond causes the amide to lie in a plane with ω usually close to 180 °.

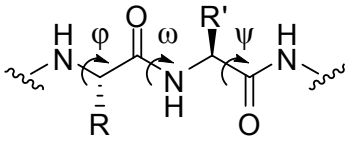


Figure 1.1

For amino acids other than glycine, the values of ψ and φ are restricted by the geometrical restraints imposed by the side chains and the carbonyl group. When the α-proton is substituted for an alkyl group, these restraints become further enhanced, severely limiting the values of ψ and φ. For example, α-amino*iso*butyric acid (Aib, **Figure 1.2**) is restricted to a small range of conformational space where ψ = ± 50 and φ = ± 50.[2] As a result, peptides containing Aib prefer folded conformations, generating either 3_{10} or α-helical secondary structures.[3] This folding property is thought to be

responsible for the membrane destabilisation exerted by peptaibols, a family of peptides isolated from soil fungi which is characterised by its high content of Aib residues.[4]

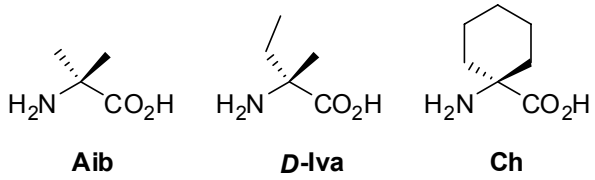


Figure 1.2: Examples of α,α-disubstituted α-amino acids

Other α,α-disubstituted α-amino acids, such as (-)-(*R*)-2-amino-2-methylbutyric acid (*D*-Iva, **Figure 1.2**) and 1-amino-1-cyclohexylcarboxylic acid (Ch, **Figure 1.2**) have a similar stabilising effect on 3_{10} and α-helical conformations.[5]

In addition to helical formation, the presence of α,α-disubstituted α-amino acids can promote other types of secondary conformation. α-Methylvaline[6] and α-methylphenylalanine[7] residues are much more efficient at forming β-turns and helices than their parent compounds, whereas diethylglycine[8] and di*iso*propylglycine are believed to induce an extended conformation.[9] Due to this ability to impart well-defined conformational constraints on a peptide backbone, α,α-disubstituted α-amino acids have played an important role in the design of peptide sequences with predetermined folding properties.

ii) resistance against enzymatic degradation

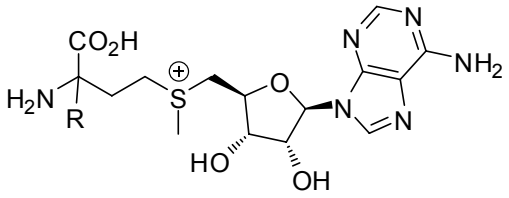
The development of efficient peptide drugs has focused on peptide analogues that can mimic the recognition and binding process of the parent peptide with the receptor site on the cell. However, analogues consisting of proteinogenic α-amino acids often have a short *in vivo* half-life and, due to degradation by peptidases, are not orally active. Peptides incorporating α,α-disubstituted α-amino acids may offer conformational stability against enzymatic degradation, without compromising the biological activity.

Antagonists for the pressor hormone angiotensin II have proved useful in the study of experimental hypertension and as possible clinical diagnostic tools.[10] In 1981, an analogue of angiotensin II, in which the tyrosine in position 4 was exchanged for a α-methyltyrosine residue, was studied.[11] Incubation with the peptidase α-chymotrypsin for 1 h indicated that no degradation had occurred; under the same conditions, angiotensin II was completely degraded to two components. In addition, the α-methylated analogue showed 92.6 ± 5.3 % pressor activity of angiotensin II.

iii) enzyme inhibition

α,α-Disubstituted α-amino acids are capable of acting as enzyme inhibitors, by imitating the ligand properties of their natural analogues, but preventing

the subsequent enzymatic reaction. Evidence for this is provided by: the inhibition of aspartate aminotransferase by α-methylaspartic acid;[12] the impediment of polyamine synthesis by the *S*-adenosyl-*L*-methionine (SAM) analogue **1** (**Figure 1.3**), which inhibits *S*-adenosyl-*L*-methionine decarboxylase;[13] the fact that α-methyltryptophan is a substrate for tryptophan hydrolase[14] and its 5-hydroxy derivative is known to be a potent inhibitor of the enzyme *in vivo*.[15]



SAM : R = H
1 : R = Me

Figure 1.3

iv) enhanced solubility

Insolubility of protected peptide fragments causes these substrates to be less amenable to further chain elongation. To overcome this problem, Narita *et al*. proposed partial replacement of alanine residues with the α,α-disubstituted α-amino acid, Aib.[16] They anticipated that this alteration would disturb the β-sheet structures and promote helical folding, a conformational transformation known to result in remarkable solubility improvement. This theory was tested on oligo(Leu)s containing Aib or alanine residues. All of

the peptides containing Aib were found to have high solubility in moderate- and high-polar organic solvents; however, peptides with no α,α-disubstituted α-amino acid residues were barely soluble in any of these solvents with the exception of HMPA.

1.2 Asymmetric synthesis of α,α-disubstituted α-amino acids

The growing interest in α,α-disubstituted α-amino acids has led to extensive research into the development of asymmetric methods of accessing these compounds. The construction of the fully substituted stereocentre continues to be a challenge and most approaches can be divided into four categories, depending on the bond which is formed in the asymmetric step (**Figure 1.4**).

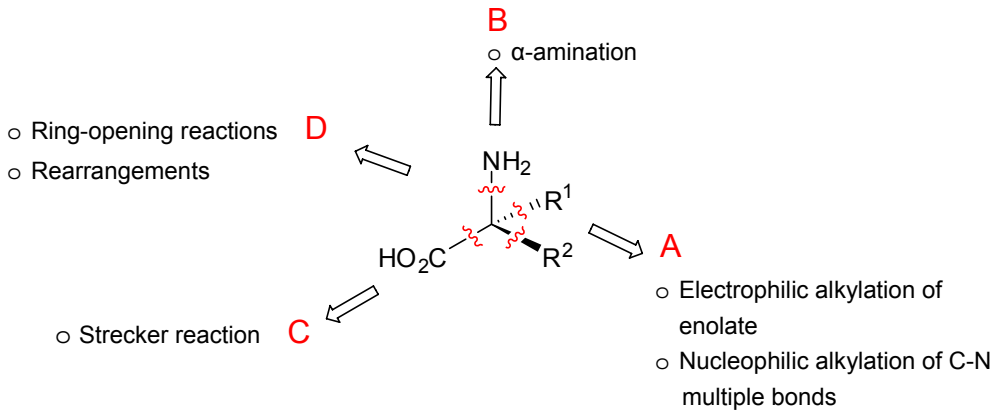


Figure 1.4: Possible approaches towards α,α-disubstituted α-amino acids

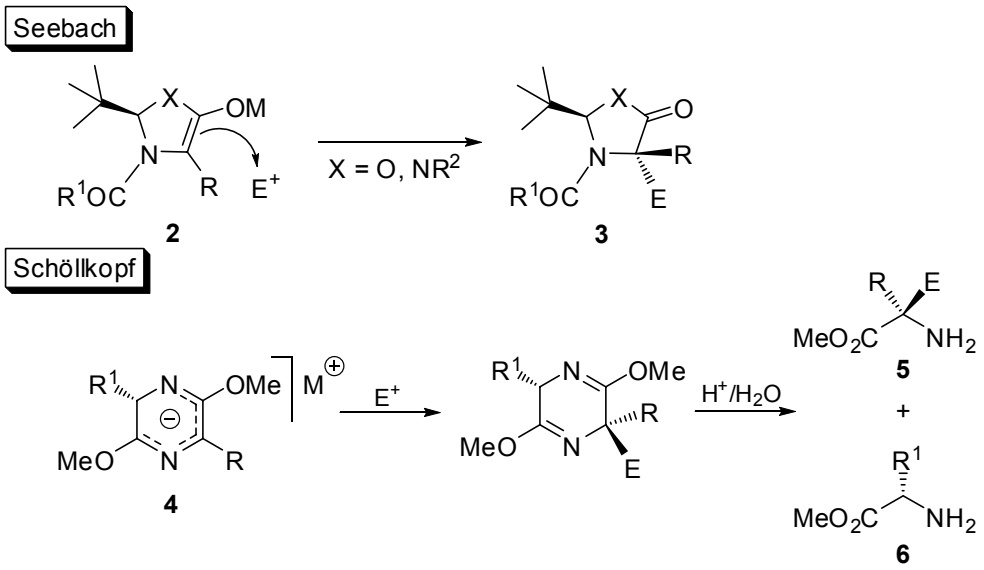
1.2.1 Path A - Addition of alkyl group R

Either of the alkyl groups on the quaternary centre of the α,α-disubstituted α-amino acid can be attached in an asymmetric manner. This can be achieved by electrophilic alkylation of amino acid enolate equivalents, or the nucleophilic alkylation of C-N multiple bonds.

i) electrophilic alkylation of enolates

This is by far the most common approach to the synthesis of α,α-disubstituted α-amino acids and encompasses the classic methods of both Seebach and Schöllkopf. The Seebach method proceeds through a chiral enolate **2** (**Scheme 1.1**).[17] The *tert*-butyl group determines the direction of approach of the electrophile and hence the configuration of the new chiral centre. A one-pot procedure allows the glycine derivative (**2**, R = H) to be alkylated twice; the asymmetry can be determined by the order of addition of the two electrophiles. Hydrolysis of the product **3** gives the free amino acids.

In a similar vein, the Schöllkopf method makes use of a metallated bislactim ether **4** which undergoes alkylation in a diastereoselective manner (**Scheme 1.1**).[18] The product can be hydrolysed at the imino ether groups, liberating the desired optically active disubstituted amino acid methyl ester **5** and the amino acid methyl ester **6**.



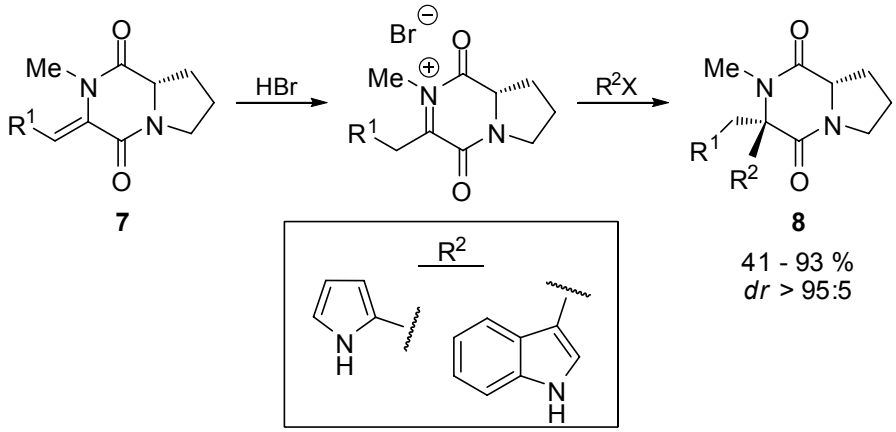
Scheme 1.1: The Seebach and Schöllkopf approaches to the synthesis of α,α-disubstituted α-amino acids

There are many other examples of this genre, the majority of which involve a cyclic enolate with a remote stereocentre to control the steric outcome of the reaction.[19] Also in this category is the work carried out by Kawabata and Fuji, but this will be discussed in more detail in **Section 3**.

ii) nucleophilic alkylation of C-N multiple bonds

Jin and Liebscher showed that *L*-proline-derived diketopiperazine **7** reacted in the presence of hydrogen bromide with nitrogen heterocycles to give disubstituted amino acid derivative **8** in more than 95:5 diastereoselectivity (**Scheme 1.2**).[20] The asymmetric synthesis of disubstituted amino acid derivatives has also been accomplished by nucleophilic addition to cyclic

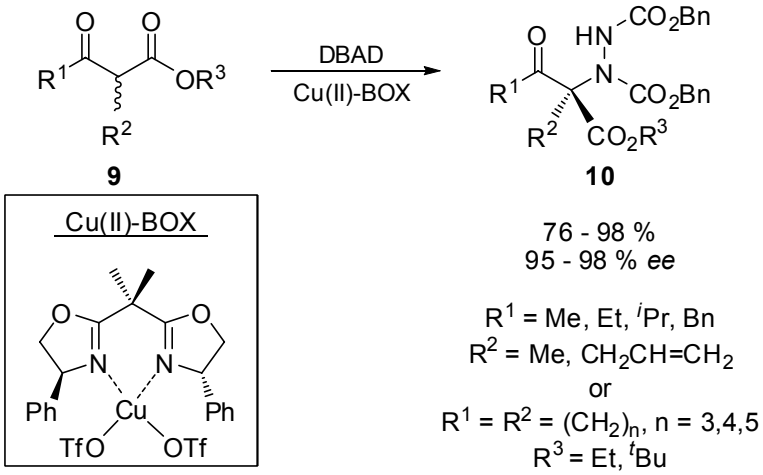
nitrones,[21] acyclic nitrones[22] and nitriles.[23] Employing a cyclic ketimine in the Mannich reaction has also proved successful.[24]



Scheme 1.2: Addition of *N*-heterocycles to diketopiperazines

1.2.2 Path B - α-Amination

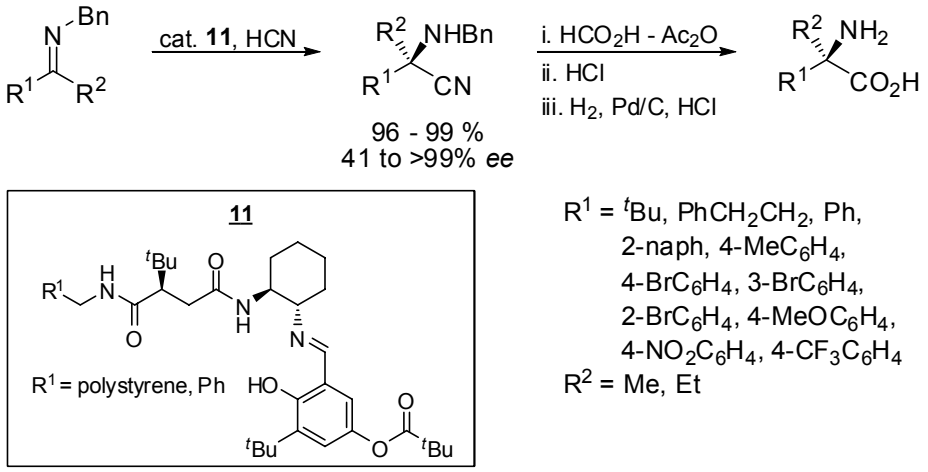
There have been several examples of α-amination of α-branched carbonyl compounds as a method of synthesising disubstituted amino acids.[25] The first general catalytic approach was reported by Jørgensen *et al.* in 2003.[26] Their method utilised Cu(II)-BOX complex in the reaction of different racemic α-alkyl-β-ketoesters **9** with diethyl azodicarboxylate (DEAD) and dibenzyl azodicarboxylate (DBAD). The products **10** were obtained in excellent yield and enantiomeric excess (**Scheme 1.3**).



Scheme 1.3: α-Amination of α-alkyl-β-ketoesters **9**

1.2.3 Path C - Addition of a 'CO_2H' synthon

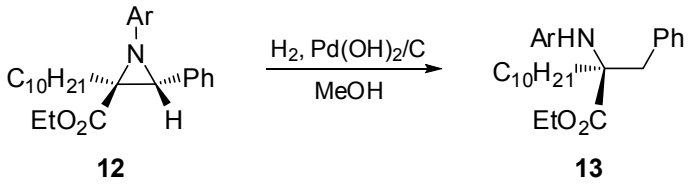
The development of the Strecker reaction in 1850 marked the first (racemic) amino acid synthesis.[27] When chiral ketimines are used in this reaction, α,α-disubstituted α-amino acids are obtained in high yields and good optical purities.[28] In 2000, the first catalytic asymmetric Strecker reaction of a ketimine was reported by Vachal and Jacobsen (**Scheme 1.4**).[29] The use of a Schiff base catalyst **11** allowed the preparation of disubstituted amino acids in essentially quantitative yield and moderate to excellent enantiomeric excess. Since this publication, several other examples of the catalytic asymmetric Strecker reaction have been reported for the synthesis of α,α-disubstituted α-amino acids.[30]



Scheme 1.4: Asymmetric catalytic Strecker synthesis of disubstituted amino acids

1.2.4 Path D - stereoselective ring-opening

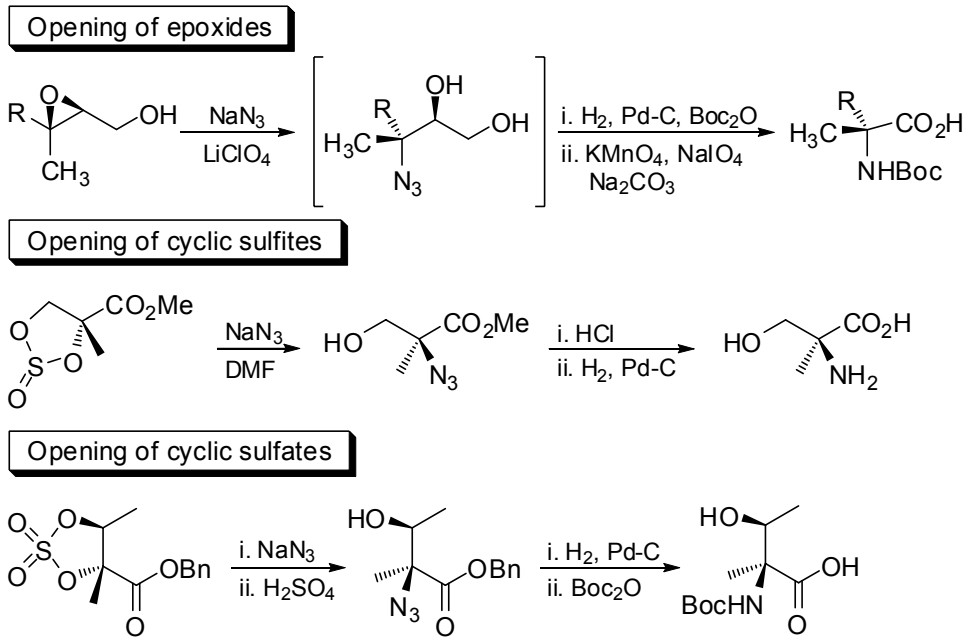
There have been various reports on the use of chiral azirines and aziridines as intermediates in the synthesis of α,α-disubstituted α-amino acids.[31] Satoh and Fukada adopted this approach from aziridines in the synthesis of phenylalanine derivative **13** (**Scheme 1.5**).[32]



12 **13**

Scheme 1.5: Stereoselective ring opening of chiral aziridine **12**

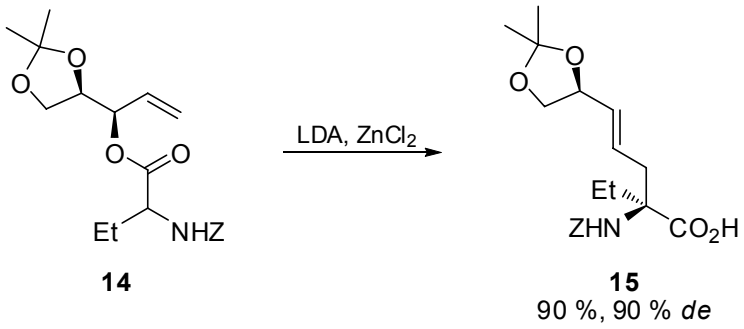
Optically pure α,α-disubstituted α-amino acids have also been accessed by the stereoselective ring-opening of epoxides,[33] cyclic sulfites,[34] and cyclic sulfates (**Scheme 1.6**).[31c]



Scheme 1.6: Ring-opening of epoxides, cyclic sulfites, and cyclic sulfates

1.2.5 Path D - rearrangements

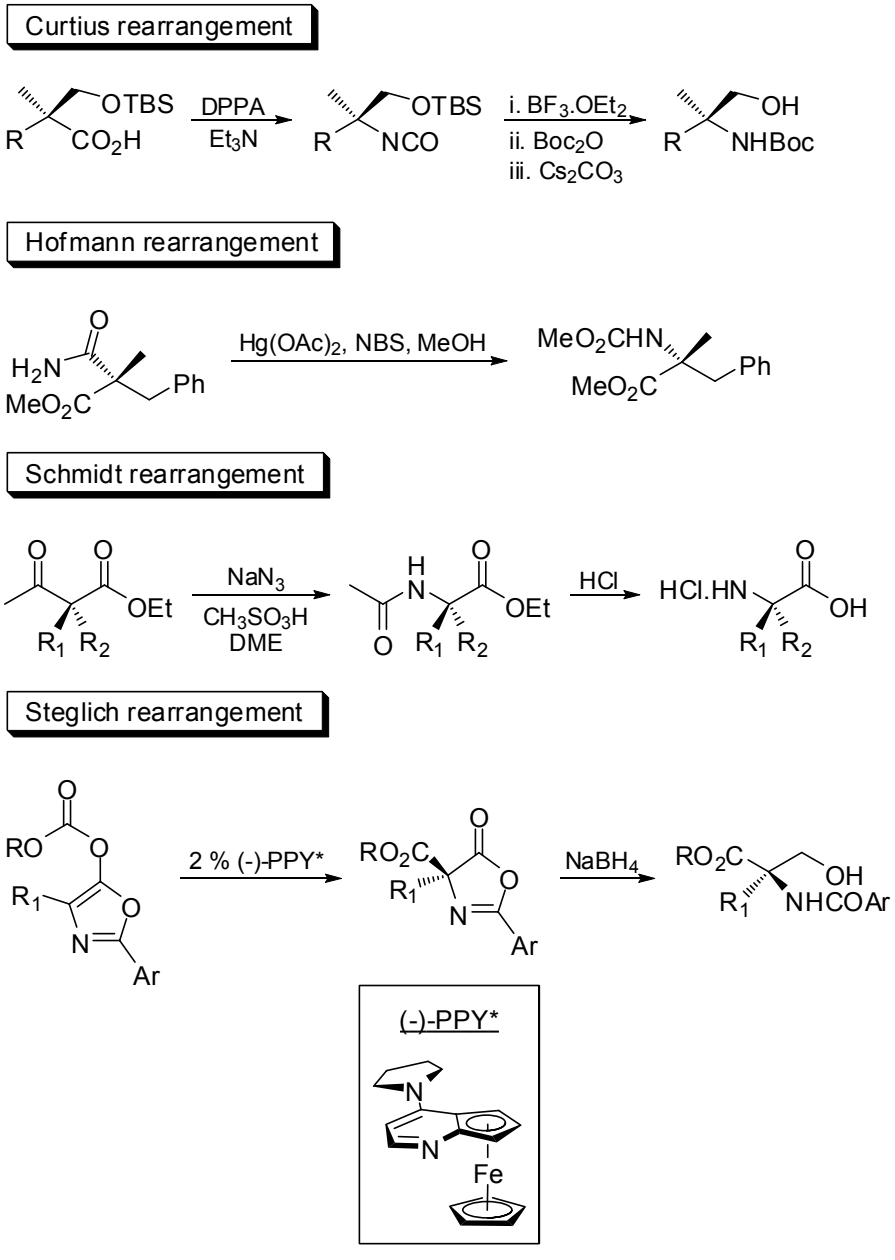
Kazmaier has shown that the Claisen rearrangement of chelated enolates is a useful route to α-alkylated amino acids.[35] Chiral ester **14** rearranged after treatment with LDA and chelation with a metal salt to give product **15** in high yield and with a high degree of chirality transfer (**Scheme 1.7**).



14 **15**
90 %, 90 % *de*

Scheme 1.7: Claisen rearrangement of chelated enolates

In addition to the Claisen rearrangement, the Curtius,[36] Hofmann,[37] Schmidt[38] and Steglich[39] rearrangements have all been used for the asymmetric synthesis of α,α-disubstituted α-amino acids (**Scheme 1.8**).



Scheme 1.8: Use of rearrangements in the asymmetric synthesis of α,α-disubstituted α-amino acids

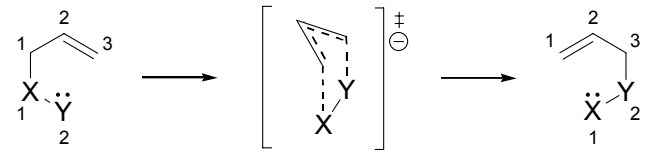
1.3 Summary

Optically active α,α-disubstituted α-amino acids have received increasing attention over the past few decades. Their unique biological properties and influences over peptide folding have made them valuable tools to probe the mechanism of enzyme reactions. The challenge of constructing the quaternary α centre with control of absolute stereochemistry has prompted many investigations into the synthesis of this class of non-proteinogenic amino acids.

2 Sigmatropic Rearrangements

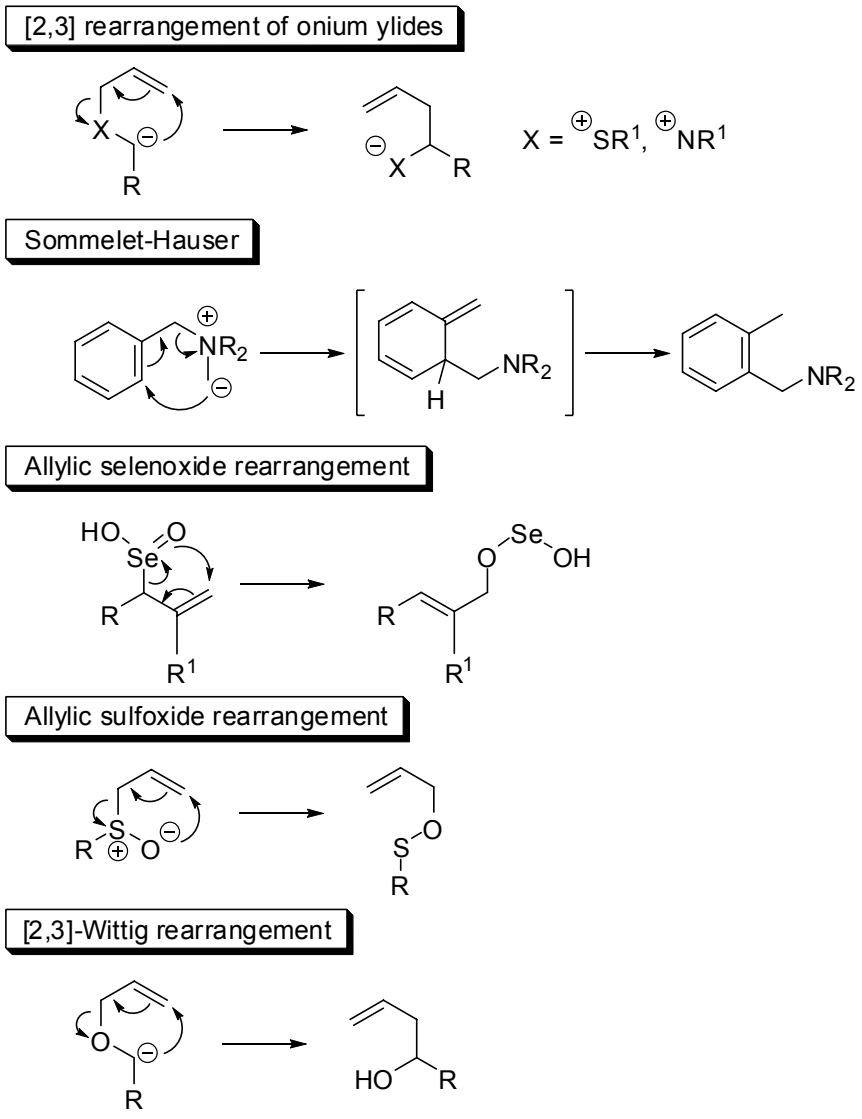
The development of new transformations that efficiently produce molecular complexity in a stereocontrolled fashion is an important aspect of contemporary organic synthesis. One of the most powerful methods for the stereocontrolled synthesis of organic compounds involves the use of sigmatropic rearrangements. These rearrangements occur through highly ordered cyclic transition states and, as the most favourable transition state geometry can often be anticipated from principles of conformational analysis, the stereochemical outcome is subject to prediction and control.

A sigmatropic rearrangement of order [i,j] is defined as the migration of a σ bond, flanked by one or more π electron systems, to a new position whose termini are i - 1 and j - 1 atoms removed from the original bonded loci, in an uncatalysed intramolecular process.[40]



Scheme 2.1: A general [2,3]-sigmatropic rearrangement

Of most importance to the work presented in this thesis is the [2,3]-sigmatropic rearrangement, which proceeds though a six-electron, five-membered transition state (**Scheme 2.1**). There are many variants of this type of rearrangement in terms of both the atom pair (X, Y) and the electronic state of Y (anion, non-bonding electron pair or ylide).

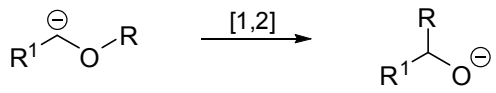


Scheme 2.2: Examples of [2,3]-sigmatropic rearrangements

Some well-known examples include the [2,3]-rearrangement of ammonium and sulfonium ylides,[41] the Sommelet-Hauser rearrangement,[42] the rearrangement of allylic selenoxides[43] and the rearrangement of allylic sulfoxides (**Scheme 2.2**).[44] One of the most studied rearrangements of this type is the [2,3]-Wittig rearrangement and this will be looked at in more detail.

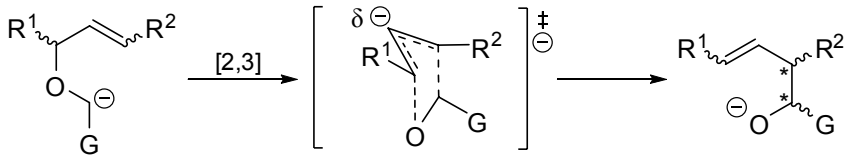
2.1 The [2,3]-Wittig Rearrangement

The rearrangement of ethers upon treatment with strong base is called the Wittig rearrangement (**Scheme 2.3**).[45] This [1,2] shift is believed to proceed *via* a radical-pair dissociation-recombination mechanism. In contrast, when R is allylic, a symmetry-allowed, concerted process ensues, with the predominant route now a [2,3]-shift (**Scheme 2.4**).[46]



Scheme 2.3: A general [1,2]-Wittig rearrangement

The [1,2]-Wittig may often compete with the [2,3]-Wittig rearrangement, to an extent that depends markedly upon substrate structure and reaction temperature.[47] It is generally accepted that the [1,2]-shift can be minimised or often completely suppressed at lower temperatures.[48]



Scheme 2.4: A general [2,3]-Wittig rearrangement

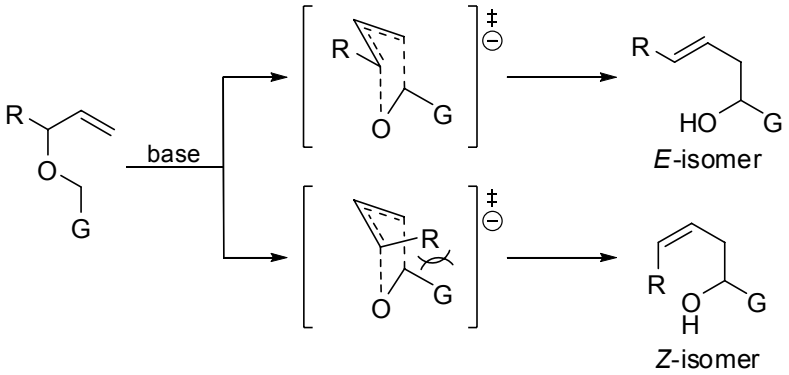
The synthetic utility of this reaction originates from the five-membered 'folded envelope' transition state through which the rearrangement is thought to proceed (**Scheme 2.4**, arbitrary arrangement of substituents shown in transition state). This is supported by molecular modelling experiments by Houk *et al.*,[49] which show the partially formed and the partially broken bonds almost eclipsing one another. These experiments also predict a build-up of negative charge on the central allyl carbon, in the transition state.

Such an ordered transition state allows stereochemical information in the substrate to be imparted upon the products of the reaction and, therefore, the [2,3]-Wittig rearrangement may furnish products with predictable formation of specific alkene geometries and with control of both relative and absolute stereochemistry.

i) alkene geometry

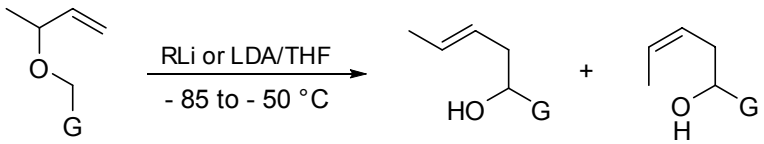
The [2,3]-Wittig rearrangement is capable of generating both (*E*)- and (*Z*)-alkenes. Examination of the transition state indicates that the (*E*)-isomer

should be formed predominantly, as the R group should adopt an *endo* position to avoid unfavourable pseudo-1,3-diaxial interactions with the anion-stabilising group, G (**Scheme 2.5**). This has been proven for a variety of substrates (**Scheme 2.6**).[46b]



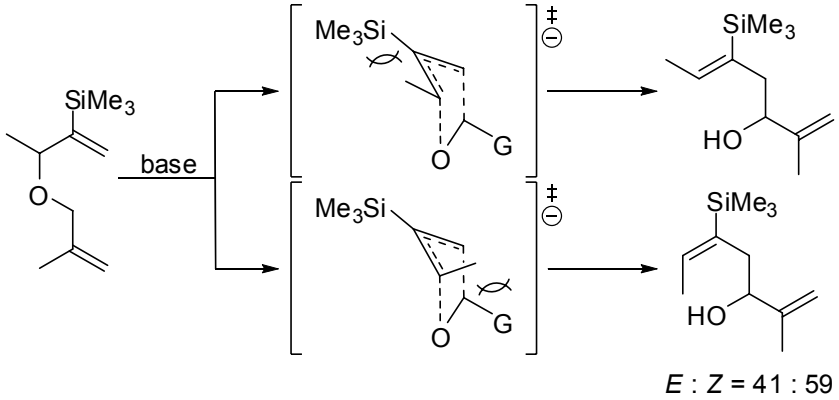
Scheme 2.5: Transition states for possible alkene geometries

When a substituent is present on the allyl moiety of the rearrangement precursor, selectivity of the alkene geometry decreases, undoubtedly due to the smaller energy differences between the transition states (**Scheme 2.7**).[50]



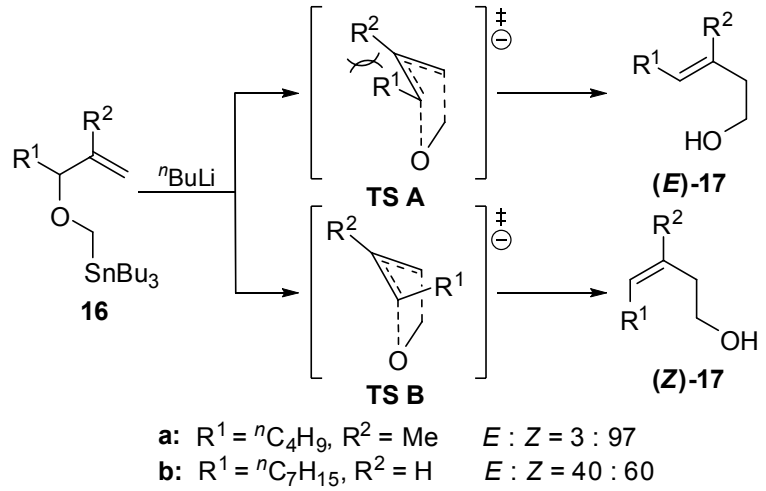
G	% of *E*
fluorenyl	100
$C(R)=CH_2$ (R = H, CH_3)	98
$C\equiv CR$ (R = H, CH_3, $SiMe_3$)	93 - 98
Ph	100
CO_2H	74
CO_2CH_3	78

Scheme 2.6: Alkene stereoselectivity



Scheme 2.7: Rearrangement of substrate with allyl substituent

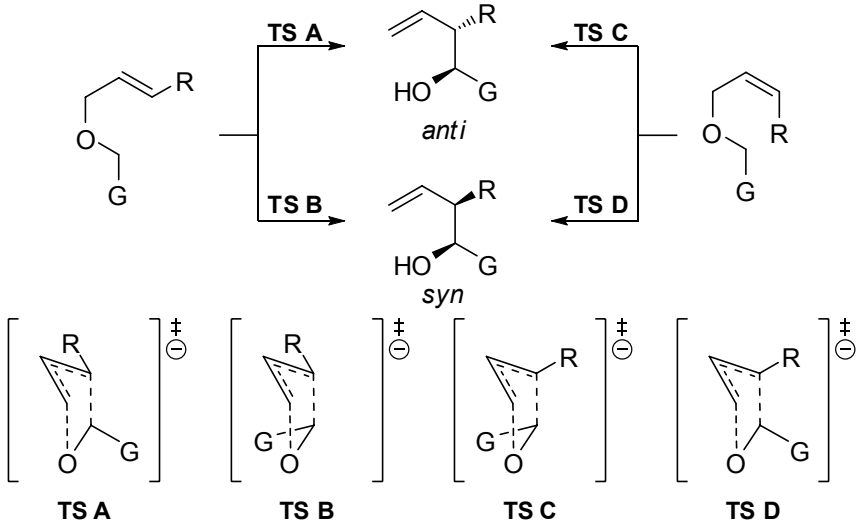
An exception to the *E* selectivity is provided by the rearrangement of tin-substituted ethers **16** (**Scheme 2.8**).[51] When R^1 is a butyl group and R^2 a methyl (**16a)**, the $A^{1,2}$ strain is greater than the steric interaction of the butyl group with the pseudoaxial proton of the methylene unit, enabling the rearrangement to proceed predominantly though transition state **B**. This affords the (*Z*)-homoallylic alcohol **17a** as the major product. This model was confirmed by the rearrangement of **16b** (R^1 = ^{n}heptyl, R^2 = H), which led to a 40:60 mixture of *E* : *Z* alkenes.



Scheme 2.8: [2,3]-Wittig rearrangement of tin-substituted ethers

ii) control of relative stereochemistry

The predictability and control of the relative stereochemistry of products furnished by the [2,3]-Wittig rearrangement of non-terminal alkenes are amongst its most valuable attributes. The diastereoselectivity of the reaction has been shown to be a direct consequence of the substrate alkene geometry and the preference of the anion-stabilising group, G, to adopt an *exo* or *endo* position within the transition state.[46b] As a general rule, with G preferentially adopting an *exo* position in the transition state, the (*E*)-substrate exhibits *anti* selectivity, whereas the (*Z*)-substrate furnishes *syn* products. This sense of selectivity is reversed when G is a π acceptor. In this case, G prefers to adopt an *endo* position in order to stabilise the build-up of negative charge on the central allyl carbon. The possible transition states and the products they afford are illustrated below **(Scheme 2.9).**



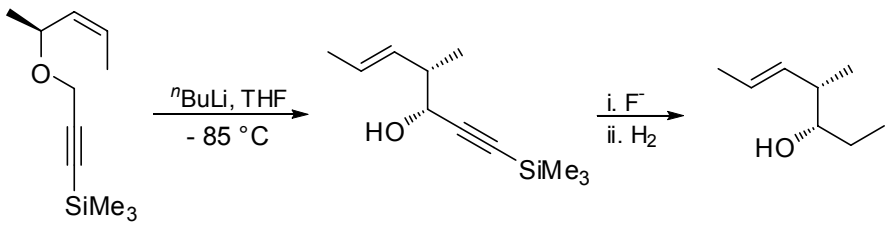
Scheme 2.9: Transition state models for the prediction of diastereoselectivity

iii) control of absolute stereochemistry

It has been shown that, as well as being highly diastereoselective, the [2,3]-Wittig rearrangement also has the potential to furnish homoallylic alcohols in high enantioselectivity.[46a] This control of absolute stereochemistry has been achieved in three ways: asymmetric transmission, asymmetric induction and the use of a chiral, non-racemic base or chiral ligand-bound metal reagents.

(a) asymmetric transmission

This method employs a chiral centre present in the starting material to transfer chiral information to the product. The original chirality is destroyed as the new chiral centres are formed. An example is shown by the rearrangement of **18**, which occurs with high diastereoselectivity and control of alkene geometry (**Scheme 2.10**).[52] Removal of the silicon group, followed by hydrogenation gave the insect pheromone **20** with the same degree of optical purity as the rearrangement substrate.



18 98 % *ee*

19 > 98 % *E*, > 98 % *syn*

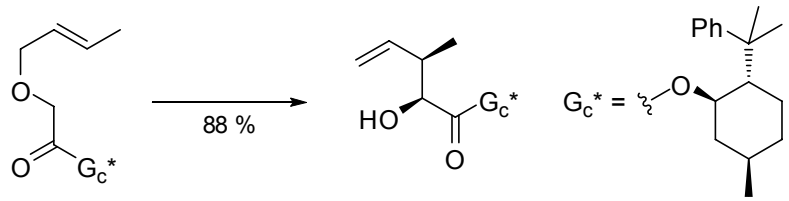
20 98 % *ee*

Scheme 2.10: Asymmetric rearrangement of **18**

As the stereochemical outcome can often be predicted, this method of asymmetric transmission has found wide application in the stereocontrolled synthesis of natural products.[53]

(b) asymmetric induction

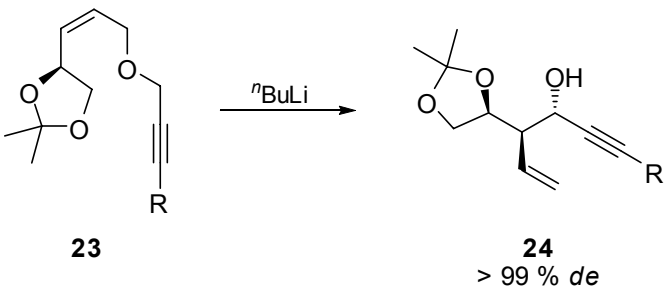
In this method a chiral auxiliary is used to provide the stereochemical information in the transition state of the rearrangement. The chiral auxiliary may be incorporated as the migrating terminus, thus allowing rearrangement to occur through a 'chiral enolate'.[54] This is exemplified by the rearrangement of **21** which contains the 8-phenylmenthol chiral auxiliary. The product was isolated in 88 % yield and 97 % *de* (**Scheme 2.11**).[54c]



21 **22** 97 % *de*

Scheme 2.11: Example of a chiral auxiliary-mediated asymmetric [2,3]-Wittig rearrangement

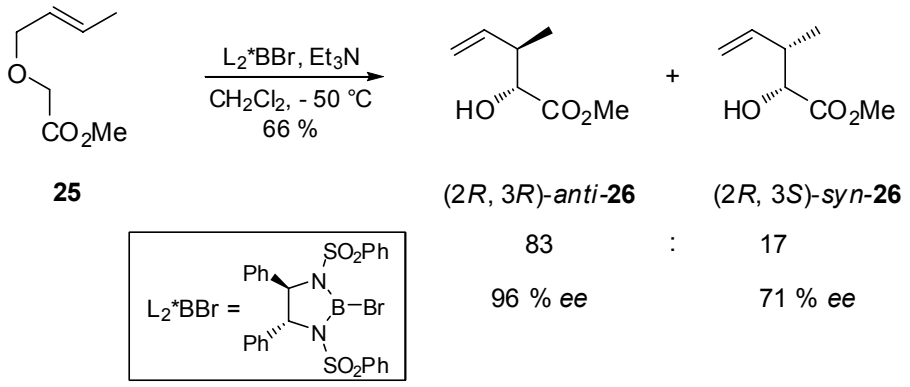
Alternatively, the chiral auxiliary may be included in the allyl moiety of the rearrangement substrate.[55] The rearrangement of **23** results in the formation of **24** essentially as a single stereoisomer (**Scheme 2.12**).[55a]



Scheme 2.12: [2,3]-Wittig rearrangement of **23**

(c) use of chiral, non-racemic base or chiral ligand-bound metal reagents

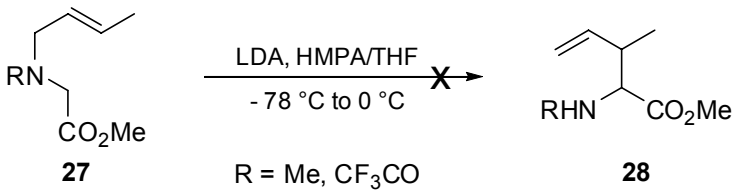
In this method, a chiral migrating terminus is generated in an enantioselective manner from an achiral substrate. For example, the rearrangement of **25** involves the formation of a chiral boron enolate with a chiral bis-sulfonamide ligand to provide **26** in high *ee*, and good *anti* diastereoselectivity (**Scheme 2.13**).[56]



Scheme 2.13: Enantioselective [2,3]-Wittig rearrangement of **25**

2.2 The aza-[2,3]-Wittig rearrangement

Although the [2,3]-Wittig rearrangement has long been a well-established procedure, its nitrogen analogue had, until recent years, received comparatively little attention. Nakai *et al*. attempted the aza-[2,3]-Wittig rearrangement of crotyl amine **27** (**Scheme 2.14**).[57] This substrate was submitted to the same reaction conditions used to initiate [2,3]-Wittig rearrangement of the corresponding ether.[58] Amine **27** failed to rearrange when treated with LDA at - 78 °C warming to room temperature, indicating that the aza-[2,3]-Wittig rearrangement was not as easily effected as its oxygen analogue.



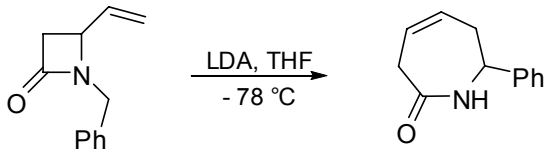
Scheme 2.14: Attempted aza-[1,2]-Wittig rearrangement of **27**

It may be conceived that the [2,3] rearrangement of an allylamine should proceed more readily than that of the analogous ether as the HOMO of an α-amino carbanion is higher in energy than that of an α-oxy carbanion, thus providing a more effective interaction with the LUMO of the allyl moiety. However, this is not the case, presumably because the main driving force for the rearrangement is the transfer of a negative charge from the α-carbon to

the more electronegative heteroatom. The lower stability and higher basicity of the resulting amide anion compared to the alkoxide anion could explain the observed reluctance of amines to undergo [2,3] rearrangement relative to their corresponding ethers.

2.2.1 Aza-[2,3]-Wittig rearrangement of cyclic substrates

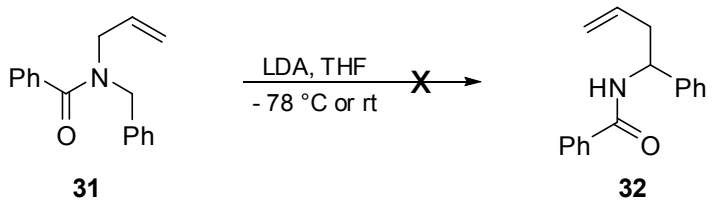
The first successful example of an aza-[2,3]-Wittig rearrangement was reported by Durst *et al*. in 1972.[59] Treatment of **29** with LDA at - 78 °C yielded the 7-membered lactam **30** in virtually quantitative yield (**Scheme 2.15**).



29 **30**

Scheme 2.15: First example of aza-[2,3]-Wittig rearrangement

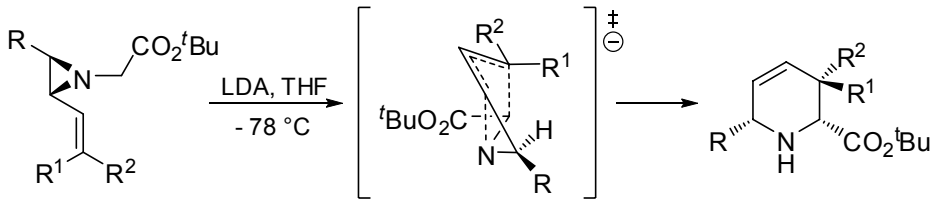
The ease of rearrangement was attributed to relief in ring strain in forming a seven-membered ring from a four-membered lactam. This theory was supported by the failure of an acyclic analogue **31** to undergo rearrangement when subjected to the same reaction conditions (**Scheme 2.16**).



31 **32**

Scheme 2.16: Attempted aza-[2,3]-Wittig rearrangement of **31**

In an analogous vein, the aza-[2,3]-Wittig rearrangement of aziridines has been reported independently by two groups. It is assumed again that the thermodynamic driving force for the reaction is provided by relief of ring strain. Somfai *et al*. have reported extensive investigations into the aza-[2,3]-Wittig rearrangement of both *cis*- and *trans*-2,3-disubstituted vinylaziridines.[60] Treatment of *trans*-vinylaziridine **33** with LDA at - 78 °C furnished the *cis*-tetrahydropyridine derivative **34** in high yields and diastereoselectivity (**Scheme 2.17**).



33 **34**

R = CH_2OBn, C_6H_{13}, ^{t}Bu,
R^1, R^2 = H, *E*-Me, *Z*-Me

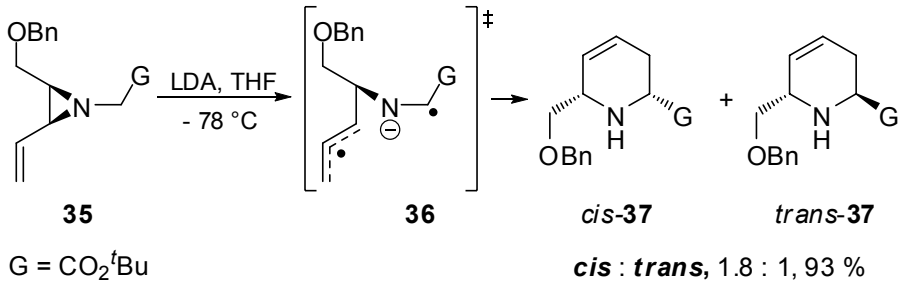
yields 92 - 98 %
single diastereomer

Scheme 2.17: Aza-[2,3]-Wittig rearrangement of *trans*-vinylaziridine **33**

The transition state depicted in **Scheme 2.17** is expected where the *tert*-butyl ester adopts an *endo* conformation, typical of a π-acceptor anion stabilising

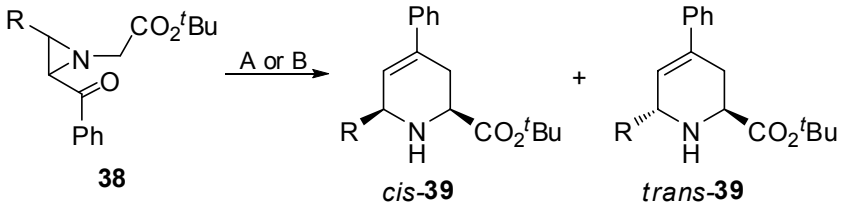
group. This methodology has been applied to the enantioselective synthesis of indolizidines 209D[60b,c] and 209B.[60c]

Under similar conditions, *cis*-vinylaziridines **35** undergo rearrangement to furnish a 1.8:1 mixture of *cis*- and *trans*-tetrahydropyridines **37** (**Scheme 2.18**).[60] This was explained by assuming cleavage of the initially formed anion into a diradical anion **36** which could then undergo non-selective ring closure to give the observed mixture of products.



Scheme 2.18: Aza-[2,3]-Wittig rearrangement of *cis*-vinylaziridine **35**

The aza-[2,3]-Wittig rearrangement of vinylaziridines has also been reported by the Coldham group, with similar results achieved.[61] During the course of this research, it was also discovered that a tandem Wittig olefination-aza-[2,3]-Wittig rearrangement could deliver tetrahydro-pyridines directly from 2-benzoylaziridines **38** (**Scheme 2.19**). It is assumed that the Wittig reaction gives the desired vinylaziridine which is then deprotonated by the second equivalent of Wittig reagent, allowing rearrangement to occur.



R	Conditions[a]	T (°C)	Yield (%)	*cis*:*trans*
Ph	A	0	-	-
Me	B	rt	57	100 : 0
Bu	B	rt	55	100 : 0
^{i}Pr	B	rt	66	100 : 0
^{i}Pr	B	0	50	100 : 0
^{i}Pr	B	40	33	71 : 29
^{i}Pr	A	0	31	58 : 42

[a] A = NaH, DMSO; B = BuLi, DME

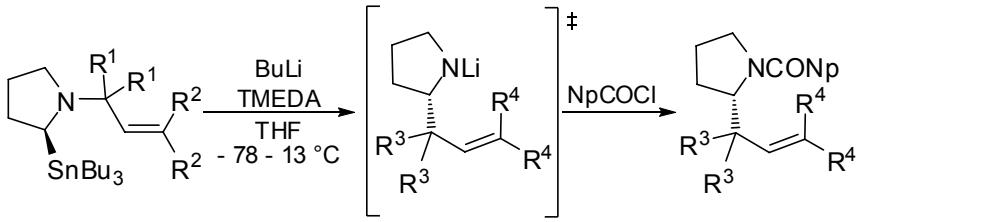
Scheme 2.19: Tandem Wittig olefination-aza-[2,3]-Wittig rearrangement

2.2.2 Aza-[2,3]-Wittig rearrangement of acyclic substrates

Promotion of an acyclic aza-[2,3]-Wittig rearrangement proved to be considerably more challenging. Early attempts resulted in either no rearrangement or the formation of [1,2]-rearrangement products.[62,63]

Aside from the work carried out in our group, which will be discussed in **Sections 2.2.3** to **2.2.5**, there have been other reports of moderately successful aza-[2,3]-Wittig rearrangement of acyclic substrates. Gawley *et al*. investigated a nitrogen analogue of the [2,3]-Still-Wittig rearrangement (**Scheme 2.20**).[64] Transmetallation of enantioenriched stannane **40** with BuLi

at - 78 °C, followed by warming to 13 °C resulted in the formation of the pyrrolidine anion **41**. This was then quenched with α-naphthoyl chloride, to yield the naphthamide **42** in 64 % and 48 % *ee*.



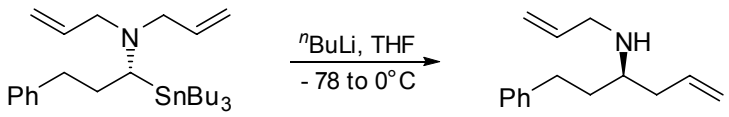
40a: $R^1 = R^2 = H$
b: $R^1 = D$; $R^2 = H$
c: $R^1 = H$; $R^2 = D$
d: $R^1 = H$; $R^2 = Me$

41

42a: $R^3 = R^4 = H$, 64 %, 48 % *ee*
b: $R^3 = H$; $R^4 = D$
c: $R^3 = D$; $R^4 = H$
d: $R^3 = H$; $R^4 = Me$, 32 %, 8 % *ee*

Scheme 2.20: Aza-Still-Wittig rearrangement of **40**

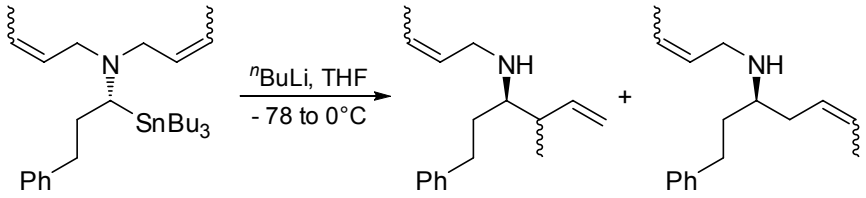
To ascertain the mechanistic pathway of this reaction, regioselectively deuterated substrates **40b** and **40c** were prepared and subjected to the rearrangement conditions. Assuming that the only operative mechanisms are the [1,2] and [2,3] rearrangements, it was established that 53 % of the rearrangement proceeded *via* the [2,3] pathway and 47 % *via* the [1,2] shift. This partially accounts for the diminished optical purity of the product **42a**, as the [1,2]-rearrangement is known to be non-selective. It was considered that the low enantioselectivity could also be attributed to partial racemisation of the organolithium intermediate at the temperature required for rearrangement to occur. Rearrangement of **40d** occurred exclusively *via* the [1,2]-pathway to afford virtually racemic **42d**, indicating the importance of steric influence on the reaction.



43 **44**, 50 %, 48 % *ee*

Scheme 2.21: Aza-Wittig rearrangement of **43**

Another report by Tomooka and Nakai investigated the rearrangement of precursor **43** (**Scheme 2.21**).[65] As in the previous report by Gawley *et al.*,[64] the low *ee* is attributed to the possible racemisation of the lithiated intermediate, as well as both the [1,2] and the [2,3] pathways being in operation. Further proof of this is shown by the rearrangement of crotyl precursor **45** which resulted in the [1,2] and [2,3] adducts being formed in 34 and 45 % respectively (**Scheme 2.22**).



45 **46**, 45 % **47**, 34 %

Scheme 2.22: Aza-Wittig rearrangement of **45**

Recent *ab initio* calculations by Houk *et al.* suggest that the aza-[2,3]-Wittig rearrangement proceeds *via* a homolytic cleavage-recombination pathway in the gas-phase.[66] However, the stereochemical outcome of the rearrangements outlined above and the results obtained in our group would suggest that the aza-[2,3]-Wittig rearrangement occurs *via* some type of concerted mechanism. This difference may be explained by the effect of the solvent in the experimental reactions.

2.2.3 Development of an acyclic diastereoselective aza-[2,3]-Wittig rearrangement

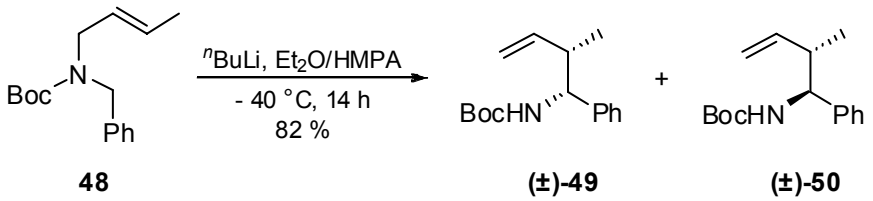
The aza-[2,3]-Wittig rearrangements of acyclic substrates discussed in **Section 2.2.2** all suffered from the major drawback of competing [2,3] and [1,2] pathways. This prompted our group to investigate the rearrangement with a view to eliminating the [1,2] pathway. The investigation began with a carefully designed precursor **48** (**Scheme 2.23**), with the following key features:

i. *The nitrogen protecting group* - an electron-withdrawing group (Boc) was used to stabilise the nitrogen anion formed upon [2,3] rearrangement thus increasing the thermodynamic driving force for the reaction.

ii. *The migrating group* - this had to be an anion-stabilising group to direct deprotonation α to nitrogen without stabilising the resulting anion to an extent that rearrangement did not occur.

iii. *A regiochemical marker* - the methyl group of the allyl moiety was necessary to differentiate [2,3] rearrangement products from potential [1,2] products.

Upon treatment with strong base, precursor **48** underwent aza-[2,3]-Wittig rearrangement to furnish the diastereoisomers **49** and **50** in a 3:2 ratio (**Scheme 2.23**).[67] No [1,2]-rearrangement products were observed.



Scheme 2.23: Aza-[2,3]-Wittig rearrangement of **48**

Proof of stereochemistry was provided by conversion of products **49** and **50** to *N*-Boc-*iso*leucine methyl ester. Comparison of NMR data confirmed that the minor diastereoisomer had the same relative stereochemistry of the natural *L*-isomer of the amino acid.

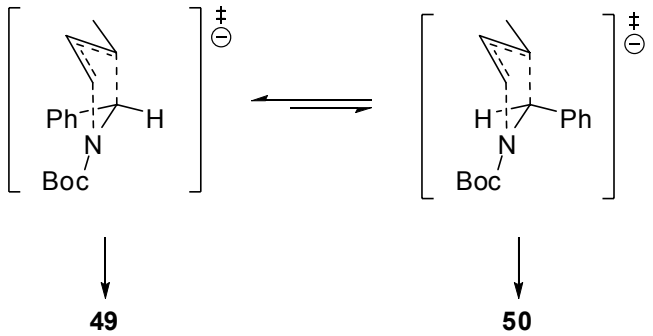
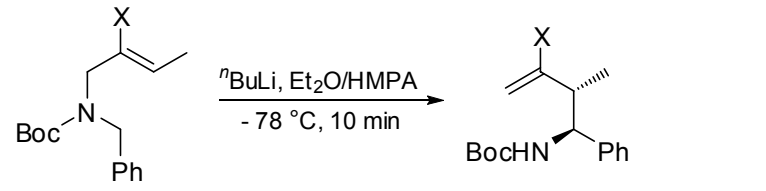


Figure 2.1: Transition state models for the aza-[2,3]-Wittig rearrangement of **48**

This result was in line with the transition state model proposed for the [2,3]-Wittig rearrangement. The poor diastereoselectivity of the rearrangement was attributed to small differences in the energies of the *endo* and *exo* transition states (**Figure 2.1**).

The small build up of negative charge predicted at the central vinyl carbon in the transition state of the [2,3]-Wittig rearrangement[49] prompted the design of a precursor containing an anion-stabilising group at this position. Due to the well-documented ability of silicon to stabilise α negative charge,[68] a trimethylsilyl group was incorporated at the C_2 position (**51**, **Scheme 2.24**).[69]



51 X = TMS
53 X = $SiMe_2Ph$

52 X = TMS, 88 %, *dr* > 20:1
54 X = $SiMe_2Ph$, 81 %, *dr* > 20:1

Scheme 2.24: Silicon-assisted aza-[2,3]-Wittig rearrangement

When treated with ^{n}BuLi in THF at - 78 °C, precursor **51** (X = TMS) underwent rearrangement in 88 % yield and > 20:1 *dr*. Examination of the transition state (**Figure 2.2**) and spectral evidence suggested that the major diastereoisomer was *anti*-**52**; however, this could not be substantiated due to

the reluctance of the vinyl silane to undergo protiodesilylation under the reported conditions.[70]

To overcome this issue, other groups which could potentially stabilise α negative charge were screened, including dimethylphenylsilyl, phenyl, phenylthio, sulfoxide and sulfone substituents[71] and a tri-*n*butyltin group.[72] While the phenyl and phenylthio substituents had a decreased effect on the diastereoselectivity of the reaction (*syn*:*anti* 1:7 and 1:4 respectively), the sulfur derivatives were found to be incompatible with the reaction conditions. The dimethylphenylsilyl group (**53**, **Scheme 2.24**) was found to be efficient, producing **54** in 81 % yield with complete diastereoselectivity. It was also easily removed after rearrangement using TBAF in DMSO,[73] allowing the relative stereochemistry to be unambiguously confirmed by comparison of NMR spectrum with **50**.

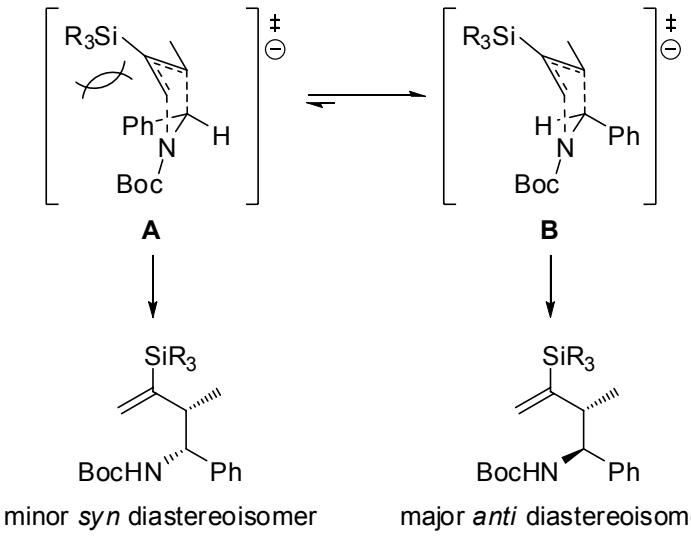
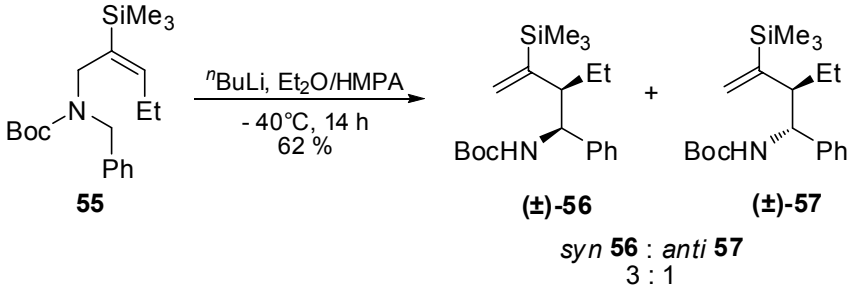


Figure 2.2: Transition state models for the silicon-assisted rearrangement

The increase in diastereoselectivity can be explained by the prohibitive pseudo-1,3-diaxial interaction between the migrating group and the silyl group, shown in transition state **A** (**Figure 2.2**). This induces the rearrangement to occur *via* transition state **B**, leading to the *anti* product.

Studies of the scope and limitations of the rearrangement have shown that a wide range of precursors, varying in alkene configuration, alkene substitution and migrating group, undergo aza-[2,3]-Wittig rearrangement.

i) alkene geometry



Scheme 2.25: Aza-[2,3]-Wittig rearrangement of *Z*(C)-alkene **55**

The aza-[2,3]-Wittig rearrangement of *Z*(C)-alkenes has also been achieved (**Scheme 2.25**).[74] The rearrangement of **55** occurred in 62 % yield with a diastereomeric ratio of 3:1 in favour of the *syn* product **56**. This diminished diastereoselectivity in comparison with the *E*(C)-alkenes can be attributed to competing steric interactions present in each of the two possible transition states **A** and **B** (**Figure 2.3**).

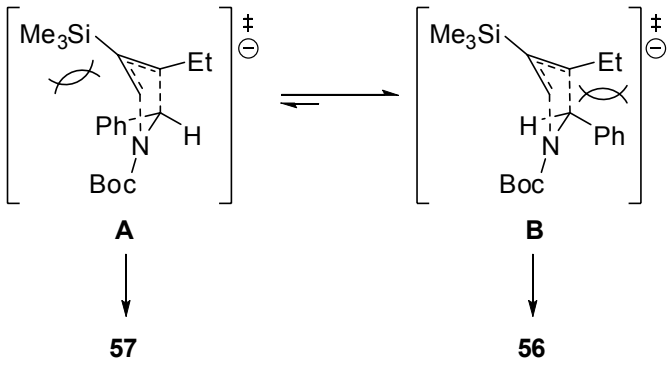
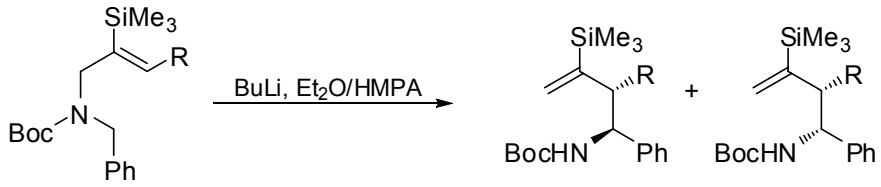


Figure 2.3: Possible transition states for the rearrangement of **55**

The pseudo-1,3-diaxial interaction between the phenyl group and the silyl moiety in **A** would appear to be more important than the 1,2 interaction between the phenyl ring and the ethyl substituent in **B** in controlling the sense of diastereoselectivity in this rearrangement.

ii) alkene substitution



Precursor	R	Yield (%)	*dr* (*anti*:*syn*)
51	Me	88	> 20:1
58a	Et	92	18:1
58b	^{i}Pr	94	11:1
58c	H	78	-

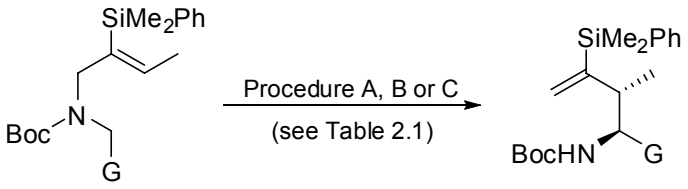
Scheme 2.26: Variation of alkene substitution

It has been shown that primary and secondary alkyl substituents give good rearrangements in terms of yield and diastereoselectivity (**Scheme 2.26**).[69] Rearrangement of a terminal alkene precursor **58c** (R = H, **Scheme 2.26**) has also been shown to occur in 78 % yield.

iii) migrating group

A range of precursors **59a-l** were synthesised, varying in anion-stabilising group, G. Rearrangement of these precursors was investigated (**Scheme 2.27**) with strong bases ^{n}BuLi or LDA in THF with HMPA cosolvent at - 78 °C and warming to - 40 °C or room temperature for 14 h.[75] The results are summarised in **Table 2.1**.

These results allow the definition of a level of stabilisation for the carbanion above which rearrangement does not occur. By comparing the pK_a data of G-CH_3 compounds, it can be proposed that anion-stabilising groups G that exert a pK_a of less than ~ 22 on an adjacent methyl group do not facilitate the rearrangement.



59a-l **(±)-60a-l**

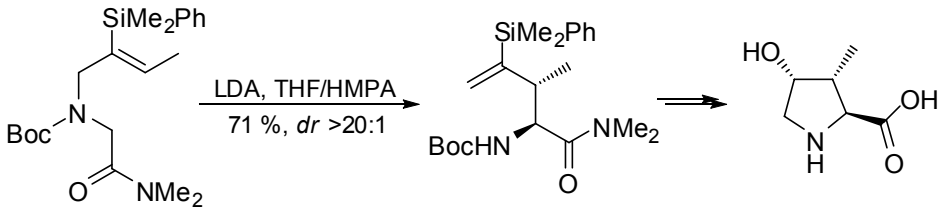
Scheme 2.27: Variation of migrating group

Precursor	G	Conditions[a]	Yield (%)	*dr* (*anti*:*syn*)
59a	CO_2H	B	15	> 20:1
59b	CO_2Me	B	70	> 20:1
59c	$CONMe_2$	C	71	> 20:1
59d	oxazoline	A	70	> 20:1
59e	CN	B	67	3: 1
59f	C≡C-Me	A[b]	43	10: 1
59g	C≡C-TMS	B	77	10: 1
59h	CON(OMe)Me	B/C	20,[c] 22[d]	-
59i	COPh	B/C	100[d]	-
59j	COMe	B/C	70[d]	-
59k	CHO	B/C	0	-
59l	$SnBu_3$	A	92[e]	-

[a] General procedures: (A) ^{n}BuLi, THF/HMPA (4:1), - 78 °C to - 40 °C, 14 h; (B) as A but LDA (C) as B but warming to rt, 3h. [b] ^{t}BuLi. [c] de-*N*-methoxylated precursor **59h**. [d] starting material. [e] protodestannylated precursor **59l**.

Table 2.1: Scope of substituents G on aza-[2,3]-Wittig rearrangement

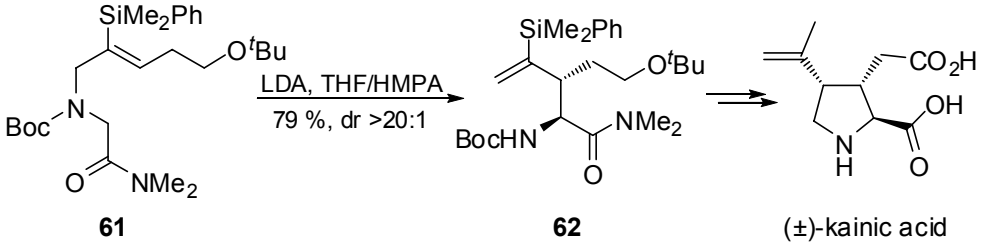
2.2.4 Applications of the aza-[2,3]-Wittig rearrangement



59c **60c** (±)-HyMePro

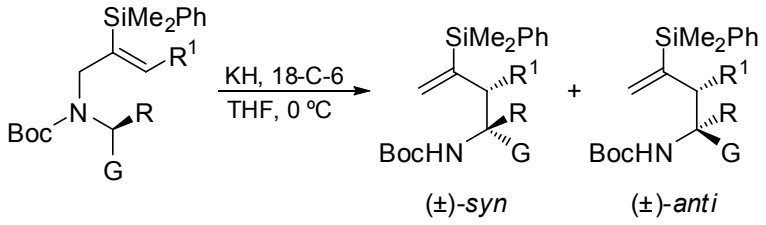
Scheme 2.28: Synthesis of (2*S**,3*R**,4*R**)-4-hydroxy-3-methylproline

The aza-[2,3]-Wittig rearrangement has been employed in the synthesis of two natural products, (2*S**,3*R**,4*R**)-4-hydroxy-3-methylproline (**Scheme 2.28**)[76] and (±)-kainic acid (**Scheme 2.29**).[77] In both cases, the aza-[2,3]-Wittig rearrangement was used as the key stereochemical determining step.



Scheme 2.29: Synthesis of (±)-kainic acid

There has also been considerable success using the aza-[2,3]-Wittig rearrangement in the diastereoselective synthesis of α,α-disubstituted α-amino acids (**Scheme 2.30**).[78]



Entry	Precursor	G	R	R^1	Yield (%)	*dr* (*syn*:*anti*)
1	**63**	$CONEt_2$	Me	Me	77	< 1:20
2	**64**	$CONEt_2$	Me	H	76	-
3	**65**	CO_2Me	Me	Me	77	~ 7:1
4	**66**	CO_2Me	^{i}Pr	Me	72	> 20:1
5	**67**	CO_2Me	Bn	Me	75	~ 1:1

Scheme 2.30: Formation of α,α-disubstituted α-amino acids.

Precursor **63** derived from alanine diethylamide (entry 1) underwent rearrangement with high *anti* selectivity. This rearrangement was also successful for the terminal alkene precursor **64** (entry 2). Diethylamide precursors with increased steric bulk at the α-position (R = ^{i}Pr, Bn, Ph) could not be deprotonated due to steric inhibition of resonance. To reduce the $A^{1,3}$ strain in the reactive intermediate, the corresponding methyl ester derivatives were synthesised. The alanine methyl ester precursor **65** underwent rearrangement in *dr* of 7:1 in favour of the *syn* product (entry 3); the valine derivative **66** gave a diastereoselectivity of > 20:1 also in favour of the *syn* product (entry 4); the phenylalanine derivative **67** rearranged in a surprisingly unselective manner (entry 5). Aside from the phenylalanine methyl ester **67**, these rearrangements can be explained by examining the competing interaction in the transition state (**Figure 2.4**). The larger group (R or G) will prefer to adopt the less hindered *exo* position, in order to minimise pseudo-1,3-diaxial interaction with the silyl group.

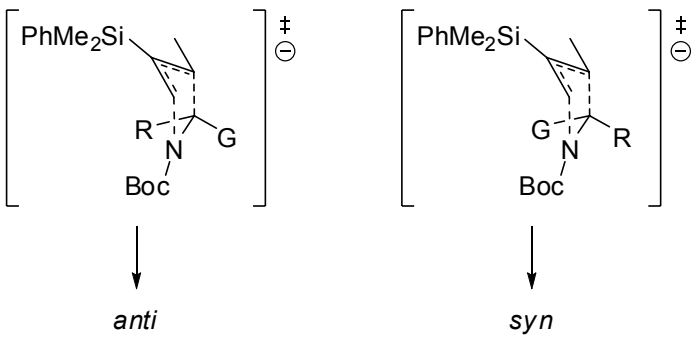


Figure 2.4: Transition state models for aza-[2,3]-Wittig rearrangement of **63 - 66**

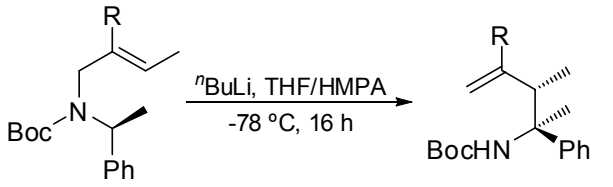
2.2.5 Development of an asymmetric aza-[2,3]-Wittig rearrangement

Although the aza-[2,3]-Wittig rearrangement has been shown to be highly versatile and diastereoselective, attempts at obtaining enantioenriched rearrangement products have proven less successful. The methods attempted and their results are outlined below:

i) asymmetric transmission

Rearrangement products **69** and **71** (**Scheme 2.31**) have been isolated[79] and shown to have significant specific rotations (- 31.2 and - 20.3 10^{-1} deg cm^2 g^{-1} respectively). However, measurement of enantioselectivity proved difficult as separation of a number of derivatives by chiral HPLC was not possible and derivatisation with a number of chiral groups was low yielding and ambiguous.

Investigations into the aza-[2,3]-Wittig rearrangement of enantioenriched precursors led to the synthesis of precursors possessing a stereogenic centre in the allyl moiety.[80] The rearrangement of these precursors was studied; the ester-stabilised anions of valine and serine derivatives **72** and **74** were the most successful with up to 66 % yield, 10:1 alkene (*E*)-stereoselectivity and 70 % *ee* (**Scheme 2.32**).

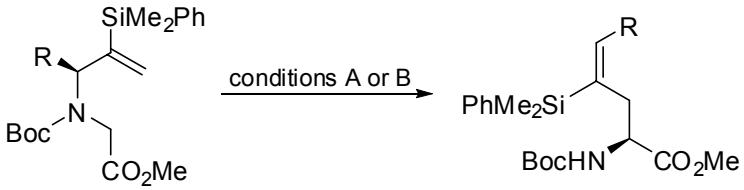


68 R = TMS
70 R = $SiMe_2Ph$

69 R = TMS
71 R = $SiMe_2Ph$

Scheme 2.31: Aza-[2,3]-Wittig rearrangement of **68** and **70**

A methyl group at the stereogenic centre of the rearrangement precursor was determined to be inadequate at controlling alkene selectivity and enantioselectivity. It has therefore been established that there is a limitation of steric bulk at the stereogenic centre; the substituent must be bulky enough to dictate alkene selectivity, but not too large to compromise the directing effect of the silyl group on the anion-stabilising group.



72 R = ^{i}Pr
74 R = OMOM

73 R = ^{i}Pr
75 R = OMOM

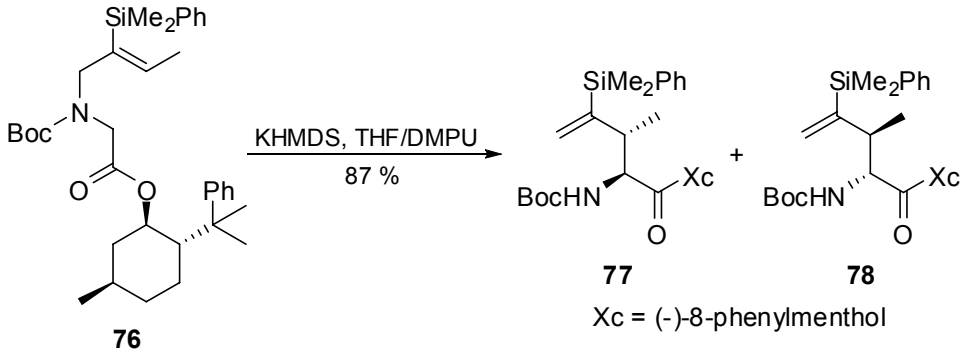
Precursor	R	Conditions[a]	Yield (%)	*ee* (%)	*E*:*Z*
72	^{i}Pr	A	66	70	10:1
74	OMOM	B	65	65[b]	10:1

[a] (A) KH, 18-crown-6, THF, rt, 3h (B) LDA, THF/HMPA, 0°C, 10 min [b] *ee* of starting material was 87 %

Scheme 2.32: Aza-[2,3]-Wittig rearrangement of enantioenriched precursors **72** and **74**

ii) asymmetric induction

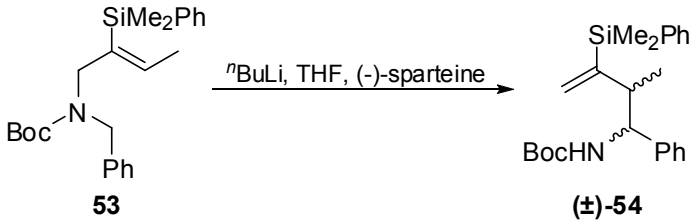
Owing to the success of asymmetric induction in the [2,3]-Wittig rearrangement,[54] a wide range of chiral auxiliaries were surveyed in the aza-[2,3]-Wittig rearrangement.[81] An (-)-8-phenylmenthol ester was found to be the most effective, furnishing the rearrangement product in 87 % yield, with complete *anti* selectivity and 3:1 diastereoselectivity with respect to the auxiliary (**Scheme 2.33**). This method has been used to synthesise intermediates that complete formal asymmetric syntheses of (+)-HyMePro and (-)-kainic acid.



Scheme 2.33: The use of chiral auxiliaries in the aza-[2,3]-Wittig rearrangement.

iii) use of chiral, non-racemic base or chiral ligand-bound metal reagent

Enantioselective deprotonation of achiral precursors has been unsuccessful thus far. No enantioselectivity was observed when rearrangement precursor **53** was treated with either a chiral base or an achiral base and chiral additive (**Scheme 2.34**).[82]



53 **(±)-54**

Scheme 2.34: Attempted enantioselective aza-[2,3]-Wittig rearrangement.

Rearrangement of the benzylic anion of **53** occurs at temperatures above -40 °C, and it is thought that at this temperature, the rate of racemisation is faster than the rate of rearrangement.

2.3 Summary

The aza-[2,3]-Wittig rearrangement has been developed to provide homoallylic amines. Previous work in our group has shown that a wide range of precursors, varying in migrating group alkene geometry and substitution, undergo rearrangement in high yields and excellent diastereoselectivities. The rearrangement has been used in the racemic synthesis of 4-hydroxy-3-methylproline, kainic acid and α,α-disubstituted α-amino acid derivatives. Attempts to control the absolute stereochemistry of the rearrangement have proven less successful; it is our aim to develop a flexible methodology that will allow for the formation of a range of α,α-disubstituted α-amino acid derivatives, in an enantioselective manner.

3 Axially Chiral Enolates by Memory of Chirality

3.1 Concept

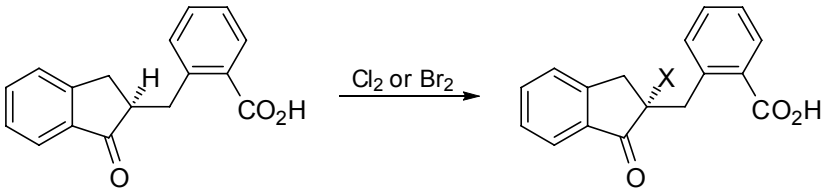
A stereogenic centre α to a carbonyl group should be lost upon enolisation as the tetrahedral sp^3 carbon becomes a planar sp^2 carbon centre. In the absence of a chiral environment, often provided by the use of chiral electrophiles, chiral ligands or chiral auxiliaries, reaction of the enolate with an electrophile would be expected to yield a racemic product. However, chirality of the carbonyl compound may be regenerated without the use of any external chiral sources; this phenomenon is referred to as memory of chirality.

One mechanism of asymmetric enolate alkylation reactions is the use of dynamic conformational chirality (rather than static central chirality) to control the stereochemical approach of the electrophile. To achieve this, the substrate structure and reaction conditions must be carefully considered in order to introduce a degree of atropisomerism to the reactive intermediate. The next section will consider the origins of this concept and some of the

most recent successful examples of asymmetric alkylation of axially chiral enolates.

3.2 Previous examples

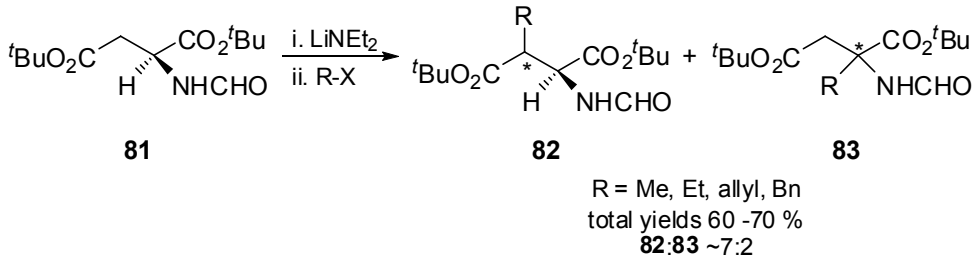
In 1913, Leuchs reported that the halogenation of ketone **79** using chlorine or bromine resulted in the formation of optically active ketones **80a** and **80b** (**Scheme 3.1**).[83] This surprising result prompted Marquet *et al.* to further investigate the mechanism of the reaction.[84] By optimising the concentration of the reagents, they isolated product **80a** with an optical purity of 35 %. It would appear that chiral information of the original ketone is retained in the intermediate enol in this reaction.



79 **80a**, X = Cl
80b, X = Br

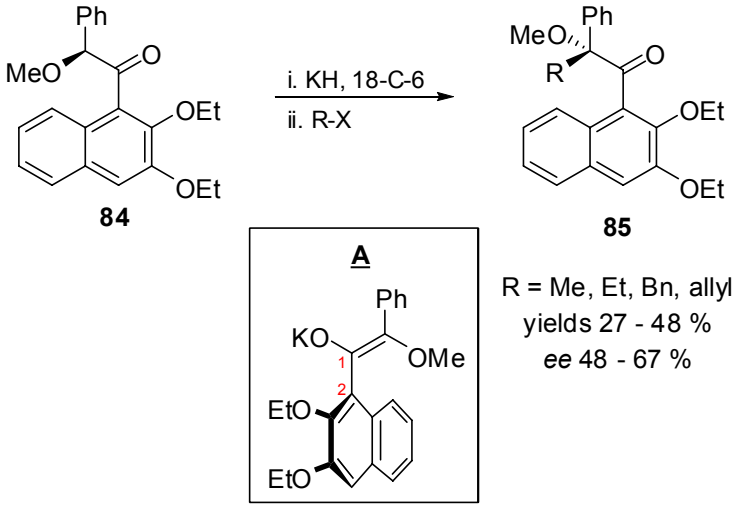
Scheme 3.1: Formation of optically active ketones **80**

In 1981, Seebach *et al*. also demonstrated this effect with the alkylation of di-*tert*-butyl (*S*)-*N*-formylaspartate **81**. The reaction provided not only enantiomerically pure β-alkylated product **82**, but 15 % of α-alkylated product **83** in 60 % *ee* (**Scheme 3.2**).[85]



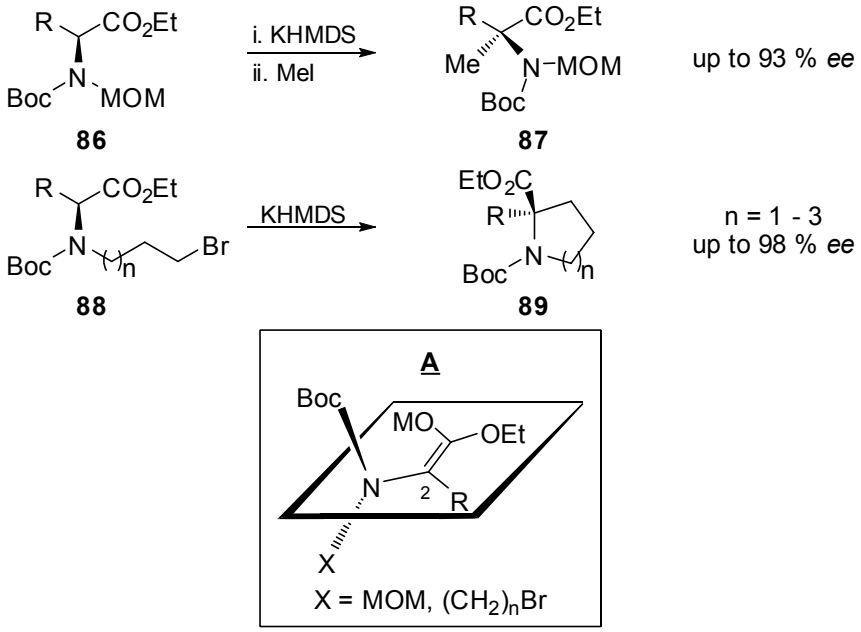
Scheme 3.2: Asymmetric alkylation of **81**

Since these early examples, pioneering work has been carried out in this area by Kawabata and Fuji. They have shown that the alkylation of chiral ketones such as **84** can occur in an enantioselective manner without any additional chiral source (**Scheme 3.3**).[86] It was proposed that the central chirality in ketone **84** is transferred to axial chirality about the C_1-C_2 bond of the intermediate enolate **A**. This is then regenerated as central chirality in the product **85** by reaction of the chiral enolate with the electrophile.



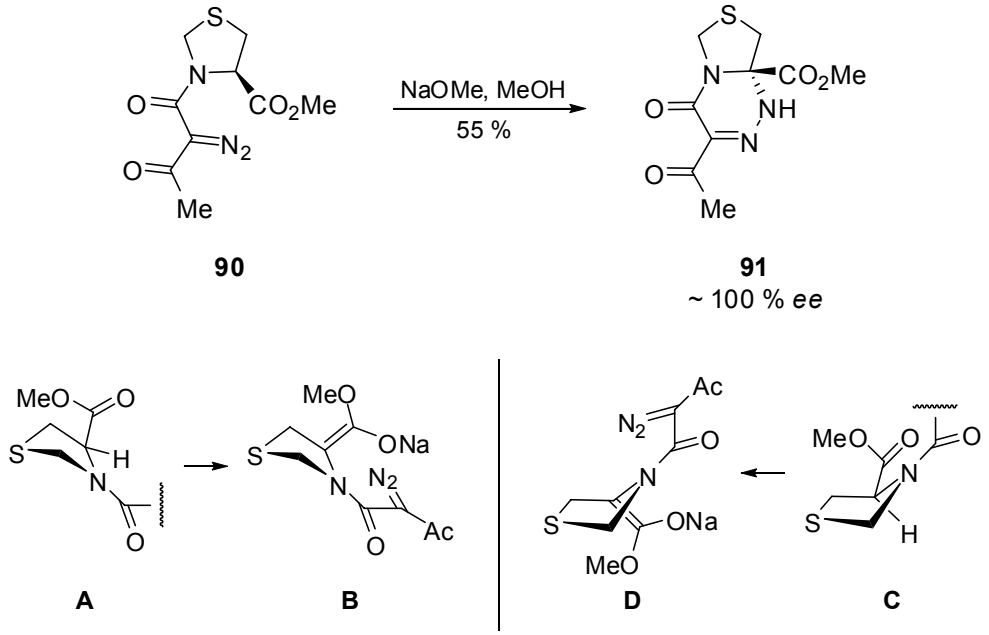
Scheme 3.3: Enantioselective alkylation of ketone **84**

Kawabata and Fuji have extended this methodology to include the asymmetric alkylation of α-amino acids to produce α,α-disubstituted α-amino acid derivatives (**Scheme 3.4**).[87] After surveying a range of protecting groups, they found that *N*-Boc-*N*-MOM-protected amino acid derivatives **86** underwent alkylation in up to 93 % *ee*. This method has been applied to the α-alkylation of derivatives of phenylalanine, tyrosine, tryptophan, histidine, valine, leucine and isoleucine. An intramolecular variant of the reaction has also been developed, furnishing proline derivatives **89** in up to 98 % *ee*. In both of these cases, the authors propose that the reactions proceed through enolate intermediate **A** which exhibits dynamic axial chirality along the C_2-N axis (**Scheme 3.4**). In the alkylation of **86**, the electrophile approaches from the sterically less demanding face (MOM) of the enolate double bond.



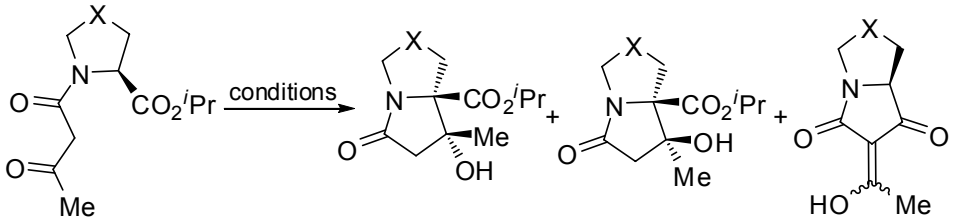
Scheme 3.4: Asymmetric synthesis of α,α-disubstituted α-amino acid derivatives *via* memory of chirality

In 1991, Stoodley *et al.* demonstrated the principle of memory of chirality in the cyclisation of thiazolidine **90**, which proceeds with retention of configuration (**Scheme 3.5**).[88] It is suggested that compound **90** undergoes deprotonation to give the enolate **B**, which is favoured over its enantiomer **D**. This is attributed to the greater ease in attaining the geometry **A** required for deprotonation, compared with the geometry **C**, which suffers from a disfavoured $A^{1,3}$ interaction between the acyl substituent and the methyl ester. The high degree of optical purity observed in the products infers that the intramolecular trapping of enolate **B** by the highly electrophilic diazo group occurs more rapidly than racemisation.



Scheme 3.5: Asymmetric cyclisation of **90**

This group have also shown that thiaproline, oxaproline and proline derivatives **92a-c** undergo aldol cyclisations in an asymmetric manner (**Scheme 3.6**).[89] HPLC analysis of compounds **93a** and **94a** showed these products were formed in 99 % *ee*. Similarly, the *ees* of **93c** and **94c** were determined to be 87 %. Attempts to determine the *ees* of aldol products **93b** and **94b** were unproductive; however, derivatisation studies showed that the aldol cyclisations occurred in 96 % *ee*.



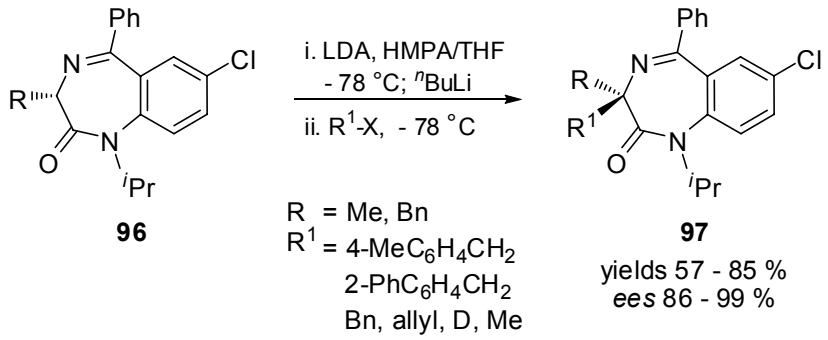
Compound	X	Conditions[a]	Yield (%)	Ratio **93**:**94**:**95**
92a	S	A	68	69:23:8
92b	O	B	63	70:30:0
92c	CH_2	C	35	55:19:26

[a] General procedures: (A) KCN (150 mol %), MeOH, 2 h (B) K_2CO_3, H_2O (C) KCN (300 mol %), ^{i}PrOH, reflux, 24 h

Scheme 3.6: Memory of chirality in aldol cyclisations of **92a-c**

The Carlier group have also made use of the inversion barrier of cyclic systems to prevent racemisation in the enantioselective synthesis of quaternary 1,4-benzodiazepin-2-ones *via* memory of chirality.[90] The products **97** were obtained in up to 85 % yield and 99 % *ee* (**Scheme 3.7**).

The bulky N_1 substituent (^{i}Pr) confers conformational stability to the intermediate enolate; the activation free energy for ring inversion at 195 K was calculated to be 17.5 kcal/mol, which corresponds to a racemisation $t_{1/2}$ (195 K) value of 970 h (compared to values of 12.4 kcal/mol and 0.11 min for the *N*-Me substrate).

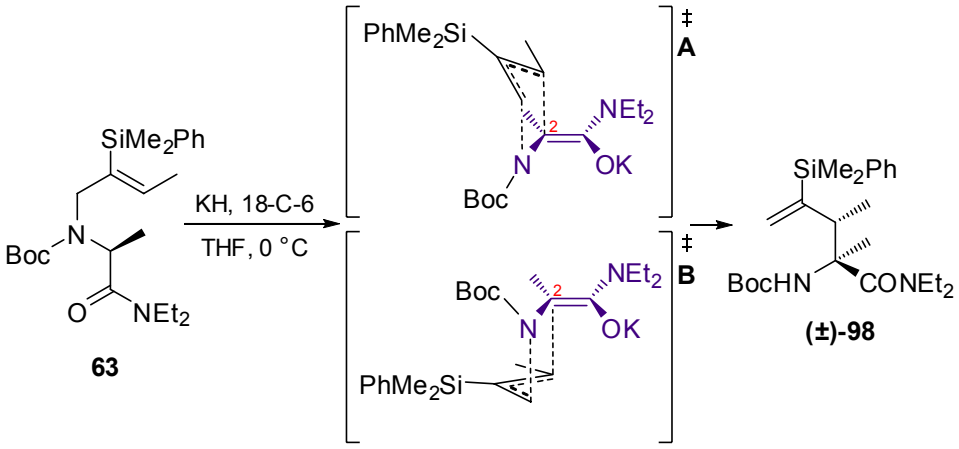


Scheme 3.7: Enantioselective synthesis of quaternary 1,4-benzodiazepin-2-ones

3.3 Introducing the memory of chirality concept to the aza-[2,3]-Wittig rearrangement

This aim of this project was to investigate the conditions of the aza-[2,3]-Wittig rearrangement of enantioenriched precursors in order to promote the rearrangement to occur through an axially chiral enolate intermediate. The rearrangement of precursors derived from alanine, phenylalanine and valine methyl esters has already been established (**Scheme 2.30**);[78] however, in the previous work, only racemic products were obtained. This is presumably

because, under the conditions of the reaction, racemisation of the enolate occurred at a greater rate than the rearrangement. Using the rearrangement of **63** as an example, this would allow equal access to transition states **A** and **B** (arbitrary conformation of enolate, **Scheme 3.8**).

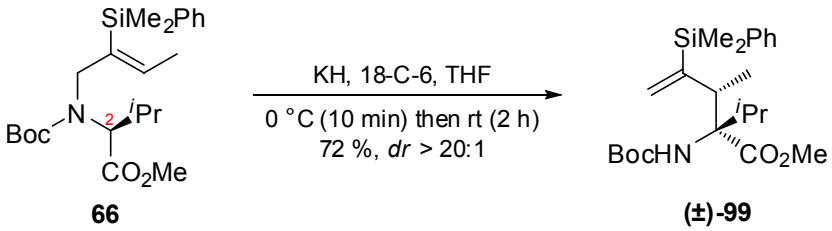


Scheme 3.8: Racemisation of enolate during the rearrangement of **63**

If conditions could be optimised to prevent free rotation around the C_2-N bond, rearrangement would occur from one face of the enolate only, resulting in the formation of enantioenriched products.

4 Investigations into Axially Chiral Enolates

To begin our investigations into axially chiral enolates as intermediates in the aza-[2,3]-Wittig rearrangement, we decided to explore the rearrangement of a known precursor. Previous studies had shown that precursors derived from alanine, phenylalanine and valine methyl esters underwent aza-[2,3]-Wittig rearrangement to form α,α-disubstituted α-amino acid derivatives (**Scheme 2.30**) in good yields.[78] As discussed in **Section 3.3**, no enantioselectivity was observed in these rearrangements; however, we hoped to develop reaction conditions that would enable rearrangement to occur from one face only of an axially chiral enolate. The valine-based precursor **66** was chosen as this had previously shown the highest diastereoselectivity upon rearrangement (**Scheme 4.1**) and it was thought that the *iso*propyl group, as the largest substituent, would have the greatest chance of inducing atropisomerism around the C_2-N bond.

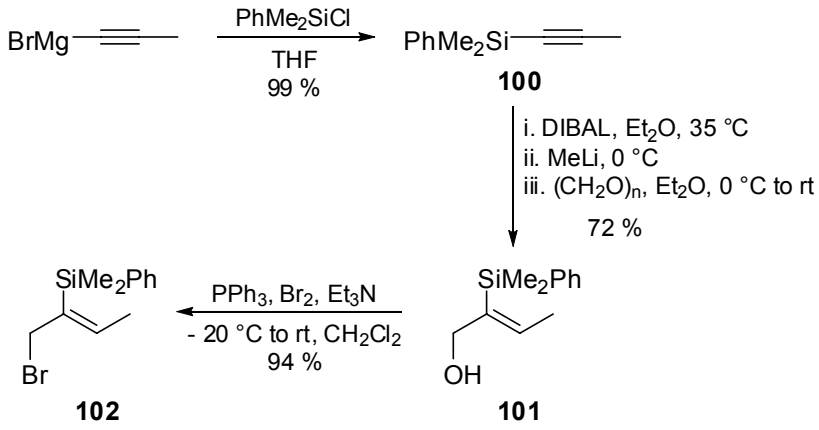


66 **(±)-99**

Scheme 4.1: Previous conditions established for rearrangement of **66**

4.1 Studies of valine-derived precursor 66

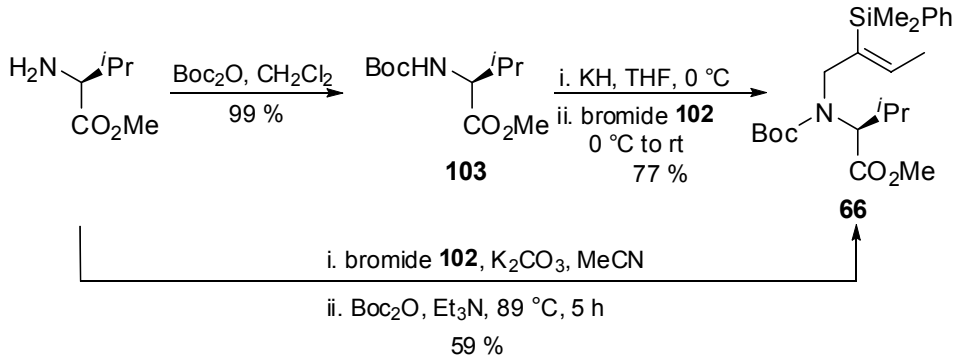
4.1.1 Synthesis of precursor 66



Scheme 4.2: Preparation of bromide **102**

Initially, precursor **66** was prepared according to the previously established protocol.[78] This commenced with the formation of bromide **102** (**Scheme 4.2**). Reaction of propynylmagnesium bromide with chlorodimethylphenylsilane gave the silyl alkyne **100**. Hydroalumination using DIBAL, followed by formation of the *ate* complex with MeLi and reaction with paraformaldehyde furnished crotyl alcohol **101**. This then underwent bromination using triphenylphosphine dibromide, generated *in situ*, to yield the desired bromide **102** in an overall yield of 67 %. Boc protection of (*L*)-valine methyl ester, followed by deprotonation with potassium hydride and alkylation with bromide **102** provided precursor **66** in 76 % yield over two steps (**Scheme 4.3**). The precursor could also be

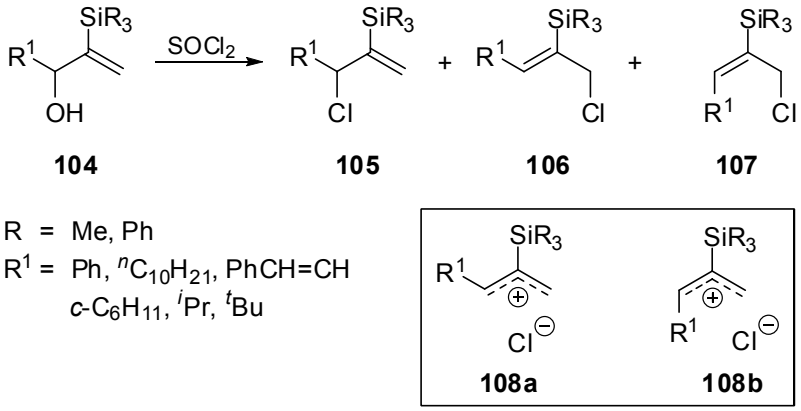
accessed by alkylation of (*L*)-valine methyl ester with bromide **102**, followed by Boc protection, to give **66** in 59 % yield over two steps (**Scheme 4.3**).



Scheme 4.3: Preparation of precursor **66**

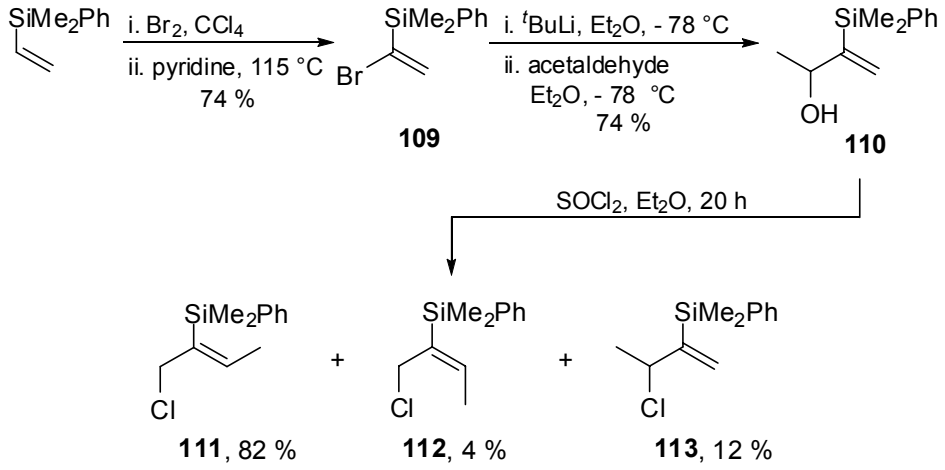
Although this was an effective route to the desired precursor, the discontinued availability of neat DIBAL required in the hydroalumination of alkyne **100** proved problematic. Previous work had shown that the concentration of reagents in the hydroalumination step was of paramount importance: the reaction proceeded in higher yields as the concentration was increased. The reaction was attempted using a 1 M solution of DIBAL in THF; however, after heating the reaction to reflux for 5 days, tlc analysis showed that there was still unreacted starting material. Using this method, alcohol **101** was obtained in 17 % yield. As this step was central to the synthesis of all of our precursors for the aza-[2,3]-Wittig rearrangement, this low yield was unacceptable and we were therefore compelled to develop an alternative synthetic route.

Chan *et al.* showed that treatment of allylic alcohol **104** with thionyl chloride resulted in the formation of chlorides **105 - 107** (**Scheme 4.4**).[91] The relative proportions of each chloride depended on the structure of **104**, as well as the reaction solvent and temperature.



Scheme 4.4: Formation of chlorides **105 - 107**

It was found that the rearranged chlorides **106** and **107** were formed to a greater extent, often to the exclusion of **105** if chlorination was carried out in a polar solvent, such as Et_2O, or at a high temperature. These observations are consistent with an ionic mechanism for the allylic rearrangement. A polar solvent would encourage the formation of an intimate ion pair (**108**), which would allow the regioselective addition of the chloride ion. The rearrangement furnishes predominantly the *Z*-isomer **106** with the *E*-isomer **107** present in most cases in < 10 %. The authors suggest that the transoid configuration of the intermediate carbocation **108a** is more stable than the cisoid configuration **108b**, accounting for the observed stereoselectivity.

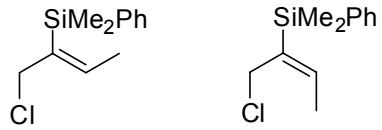


Scheme 4.5: Synthesis of chlorides **111** - **113**

Following this example, alcohol **110**, which had previously been used in our group,[71] was synthesised (**Scheme 4.5**). Dimethylphenylvinylsilane underwent bromination, followed by elimination to yield bromide **109** in 74 %. Halogen-lithium exchange gave the α-silyl anion which was reacted with acetaldehyde to give the desired alcohol in 74 % yield. Using Et_2O as the reaction solvent, the allylic rearrangement was carried out to yield chlorides **111** - **113** in 20 h as an inseparable mixture in a 20:1:3 ratio. In an attempt to improve this ratio, the reaction was carried out under reflux conditions. After 2 h, tlc analysis indicated complete consumption of alcohol **110**; after purification, chlorides **111** - **113** were obtained in 91 % yield but in a lower ratio of 12:1:2.

Determination of alkene geometry of the major compound was achieved by graduated nOe experiments. By virtue of the multiplicity and electronic

effects of the substituents, the peaks for the major compound were assigned as: δ 0.52 (6H, s, Si(C*H*$_3$)$_2$), 1.68 (3H, d, *J* = 7.1 Hz, CHC*H*$_3$), 4.22 (2H, s, C*H*$_2$Cl), 6.57 (1H, q, *J* = 7.0 Hz, C*H*CH$_3$), 7.38 - 7.62 (5H, m, Ar*H*). The corresponding peaks for the minor double bond isomer were assigned as: δ 0.52 (6H, s, Si(C*H*$_3$)$_2$), 1.87 (3H, d, *J* = 6.8 Hz, CHC*H*$_3$), 4.19 (2H, s, C*H*$_2$Cl), 6.19 (1H, q, *J* = 6.7 Hz, C*H*CH$_3$), 7.38 - 7.62 (5H, m, Ar*H*). Irradiation of the signal at δ 6.56, corresponding to the vinylic proton of the major compound induced an enhancement at δ 4.22, assigned as C*H*$_2$Cl of the major compound, and at δ 1.68, assigned as CHC*H*$_3$. This suggests that the alkene geometry of the major compound is *Z*, and is therefore the structure assigned as **111** (**Figure 4.1**). To confirm this, irradiation of the signal at δ 6.19, corresponding to the alkene proton of the minor compound induced an enhancement solely at δ 1.87, assigned as CHC*H*$_3$ of the minor isomer. Thus, the alkene geometry of the minor double bond isomer is assumed to be *E* (**112**, **Figure 4.1**).

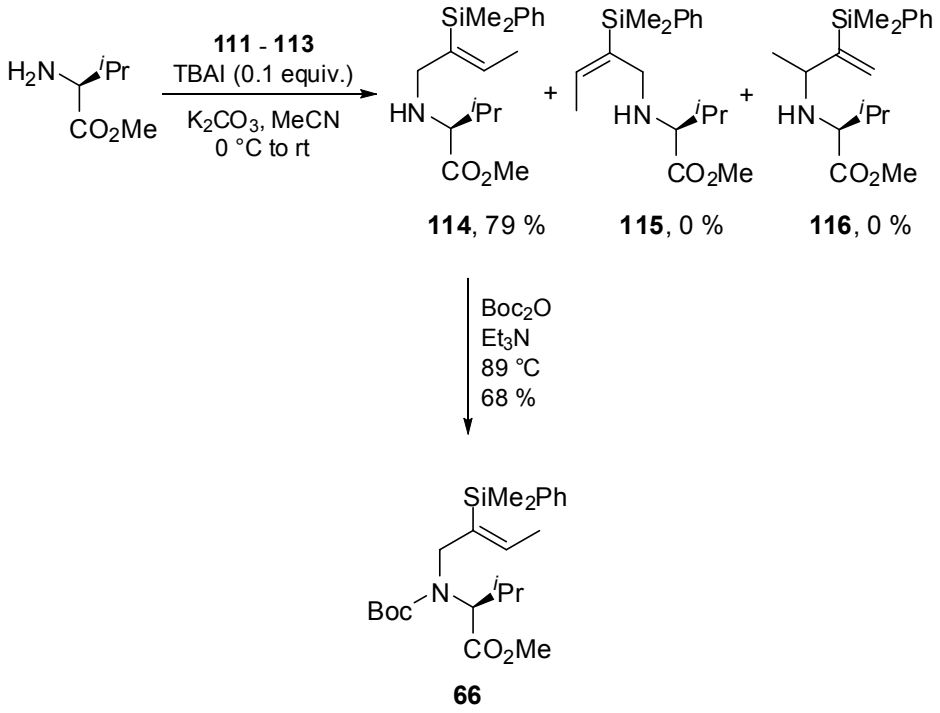


111 **112**

Figure 4.1

When (*L*)-valine methyl ester was subjected to the alkylation conditions used previously for bromide **102** (K_2CO_3, MeCN, 14 h), no products were

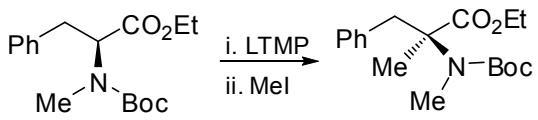
observed and, upon work-up, only starting materials were recovered. It was postulated that this may have been due to the inferior propensity of chloride to act as a leaving group. The reaction was therefore repeated in the presence of a catalytic amount of TBAI. Pleasingly, the desired product **114** was obtained in 79 % yield (**Scheme 4.6**). Neither the *E* isomer **115** nor secondary amine **116** was isolated. Boc protection of **114** using di-*tert*-butyldicarbonate with Et_3N as solvent, under reflux conditions, gave precursor **66** in 68 % yield.



Scheme 4.6: Alkylation of (*L*)-valine methyl ester with chloride **111**

4.1.2 Aza-[2,3]-Wittig rearrangement of 66

Kawabata and Fuji *et al*. demonstrated that the dynamic axial chirality of the enolates of their amino acid derivatives was markedly related to temperature as evidenced by studies on the alkylation of **117** (**Scheme 4.7**).[87b] Although the enolate was configurationally stable for at least an hour at - 78 ºC (entries 1 - 3), it rapidly loses its chirality as the temperature is increased.



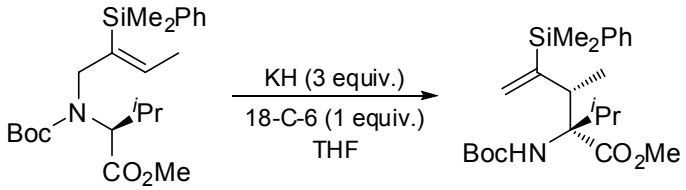
117 **118**

Entry	Conditions for enolate formation	Yield (%)	*ee* (%)
1	- 78 ºC, 0 min	9	74
2	- 78 ºC, 15 min	40	82
3	- 78 ºC, 60 min	28	81
4	- 78 ºC, 15 min, then - 40 ºC, 15 min	39	10
5	- 78 ºC, 15 min, then rt, 45 min	26	~ 0

Scheme 4.7: Temperature dependence of axially chiral enolates

With this in mind, the rearrangement of **66** was carried out at lower temperatures, using the conditions already established (**Scheme 4.8**). As the temperature was lowered, the rate of rearrangement decreased significantly; at - 40 ºC (entry 5), no rearrangement occurred at all and only degradation products were observed. Unfortunately, no significant specific rotations

were observed for the rearrangement products that were isolated, suggesting that the products were racemic.

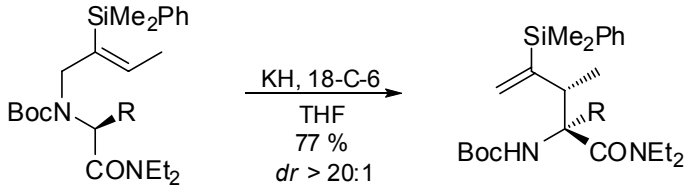


66 **(±)-99**

Entry	T (ºC)	Time (h)	Yield of **99** (%)
1	0	4	76
2	- 10	8	72
3	- 20	48	74
4	- 35	72	69
5	- 40	96	0

Scheme 4.8: Aza-[2,3]-Wittig rearrangement of **66**

Previous work on the aza-[2,3]-Wittig rearrangement of α-substituted α-amino acid-based precursors had shown that the only base that would promote rearrangement of **63** (R = Me) was KH, in the presence of 18-crown-6 (**Scheme 4.9**).[78]



63, R = Me **(±)-98**, R = Me

Scheme 4.9: Rearrangement of amide **63**

When R = ^{i}Pr or Bn, rearrangement had not occurred; this was explained by the steric inhibition of resonance experienced upon enolate formation (**Figure 4.2**). As the nature of R had been limited to Me by the diethylamide group, attention had turned to the methyl ester analogues as they suffer from significantly less $A^{1,3}$ strain.

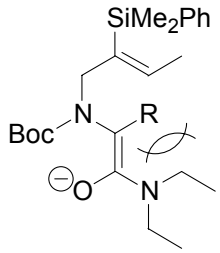
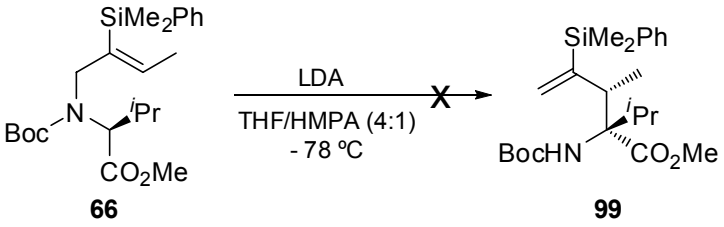


Figure 4.2

No other bases had been tested in the rearrangement of the methyl ester analogues as precursors with R = Me, ^{i}Pr, Bn had all undergone rearrangement under the conditions established for the amide series (3 equiv. KH, 1 equiv. 18-crown-6, THF, 0 ºC to rt). We were interested to see if other bases would be able to generate a more reactive or even axially chiral enolate.

The use of LDA had previously been effective in the aza-[2,3]-Wittig rearrangement so precursor **66** was subjected to a solution of LDA in THF/HMPA (4:1) at - 78 ºC (**Scheme 4.10**). Unfortunately, under these conditions, the precursor appeared to degrade to a number of

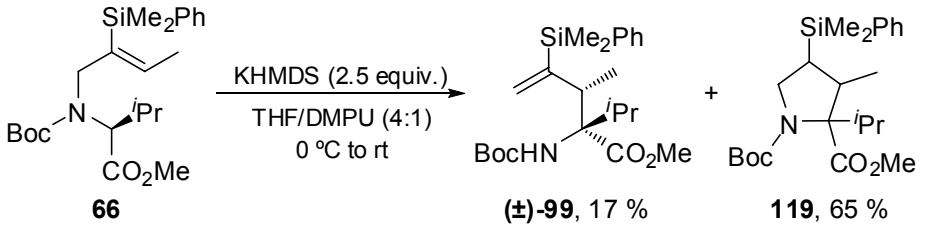
indistinguishable products. The reaction was repeated at 0 ºC with a similar outcome.



66 **99**

Scheme 4.10: Attempted rearrangement of **66** using LDA

Precursor **66** was also subjected to a solution of KHMDS in an attempt to initiate aza-[2,3]-Wittig rearrangement. The conditions used had been optimised by previous work in the group. A solution of KHMDS (2.5 equiv. of 0.5 M solution in toluene) was added to precursor **66** in THF/DMPU (4:1) at 0 ºC and the reaction allowed to warm to rt. After 2 h, tlc analysis indicated that the precursor had all been consumed and two products had formed. The reaction was worked up and purified by flash column chromatography to yield the rearrangement product **99** in 17 % yield. This was found to be racemic. The major product was determined to be pyrrolidine **119** which was obtained in 65 % yield (**Scheme 4.11**). This will be discussed further in **Section 5.1**.



66 **(±)-99**, 17 % **119**, 65 %

Scheme 4.11: Rearrangement of **66** with KHMDS

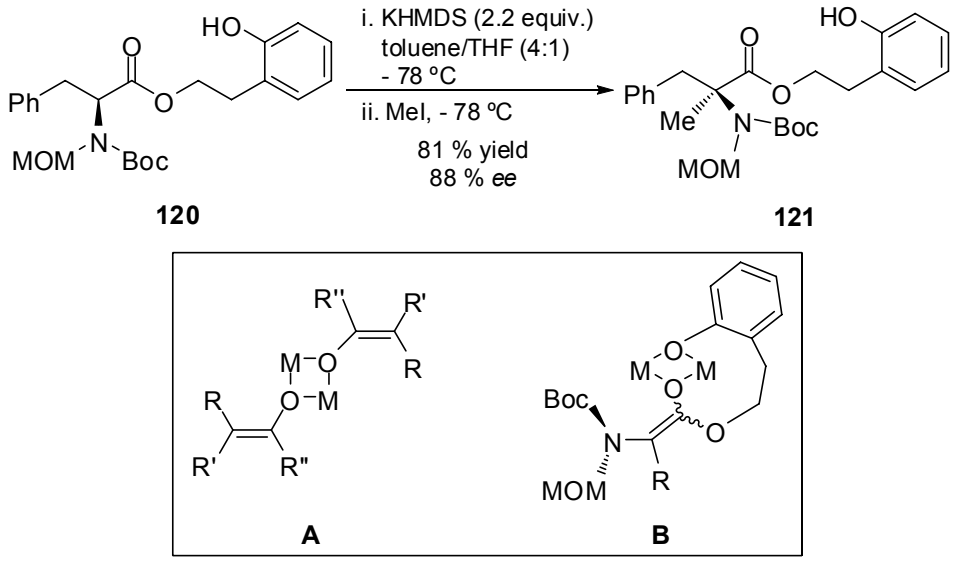
The effect of temperature on the rearrangement of **66** with KHMDS was also investigated, maintaining all other conditions constant (**Table 4.1**). The rearrangement product **99** of the reaction at 0 ºC (entry 1) showed no optical activity, suggesting that the product was racemic. At lower temperatures, the only product formed was pyrrolidine **119**. At - 45 ºC (entry 3), no reaction was observed. The reaction was repeated at - 78 ºC, and was quenched with MeOD after 1 h. Work-up and purification by flash column chromatography afforded the pure precursor **66**, which was shown to have 90 % deuterium incorporated α to the ester functionality (in protiated **66** this proton appears at δ 3.70 - 4.45). Interestingly, the deuterated precursor **66** exhibited a specific rotation of - 25.7 10^{-1} deg cm^2 g^{-1} (compared to - 39.5 10^{-1} deg cm^2 g^{-1} for protiated **66**), which suggested a higher degree of atropisomerism in the intermediate enolate at this low temperature.

Entry	T (ºC)	Time (h)	Yield of **99** (%)	Yield of **119** (%)
1	0	14	9	64
2	- 40	48	0	52
3	- 45	96	0	0

Table 4.1: Effect of temperature on rearrangement of **66** using KHMDS

These results suggest that deprotonation does occur at lower temperatures; however, the resulting anion does not undergo rearrangement. Therefore, a different approach was needed in order to enhance the stability of a potentially chiral enolate against racemisation.

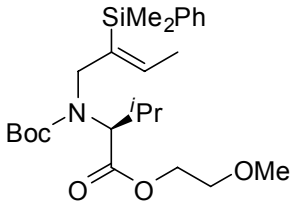
4.2 Precursors with potential chelating groups



Scheme 4.12: Alkylation of **120**

Kawabata and Fuji *et al*. have shown that amino acid derivatives with pendant chelating groups can be alkylated in high *ee* (**Scheme 4.12**).[92] Enolates generally form aggregates consisting of an oxygen-metal bond framework (**A**, **Scheme 4.12**).[93] The complexity of the aggregates is due to the intermolecular association of enolate subunits. Kawabata and Fuji *et al*.

suggest that the formation of a stable intramolecular aggregate, such as **B** (**Scheme 4.12**), simplifies the aggregate intermediates and affects the stereoselectivity of the reaction by enhancing the stability of the chiral enolate against racemisation. Experimental evidence showed that the half-life of racemisation of the enolate of **120** was roughly estimated to be 80 min at - 40 °C, compared to that of the corresponding ethyl ester of around 7 min at - 40 °C. We were interested to see if this principle could also be applied to our rearrangement and decided to explore the synthesis and rearrangement of **122** (**Figure 4.3**).

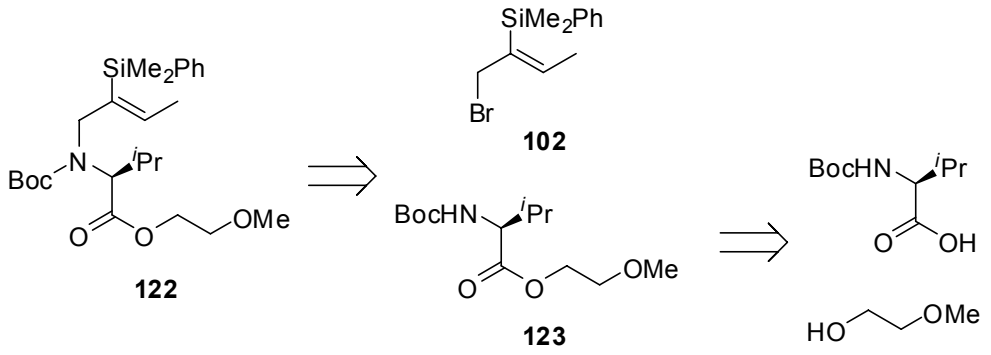


122

Figure 4.3

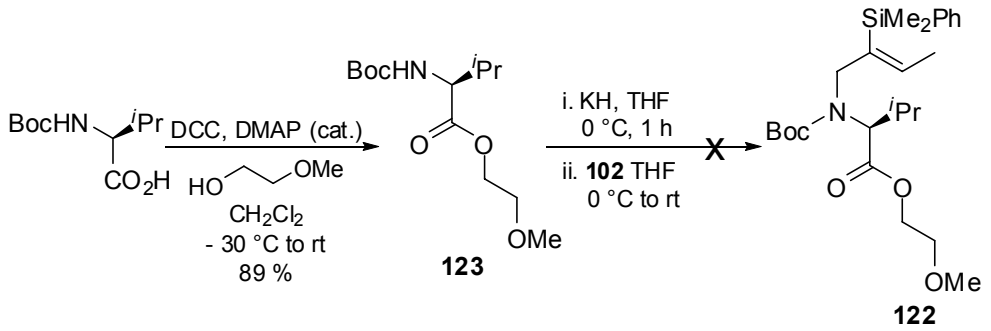
4.2.1 Synthesis of precursor 122

Retrosynthetically, **122** could be accessed from the alkylation of the potassium salt of **123** with bromide **102**. Esterification of Boc-(*L*)-valine with 2-methoxyethanol would provide **123** (**Scheme 4.13**).



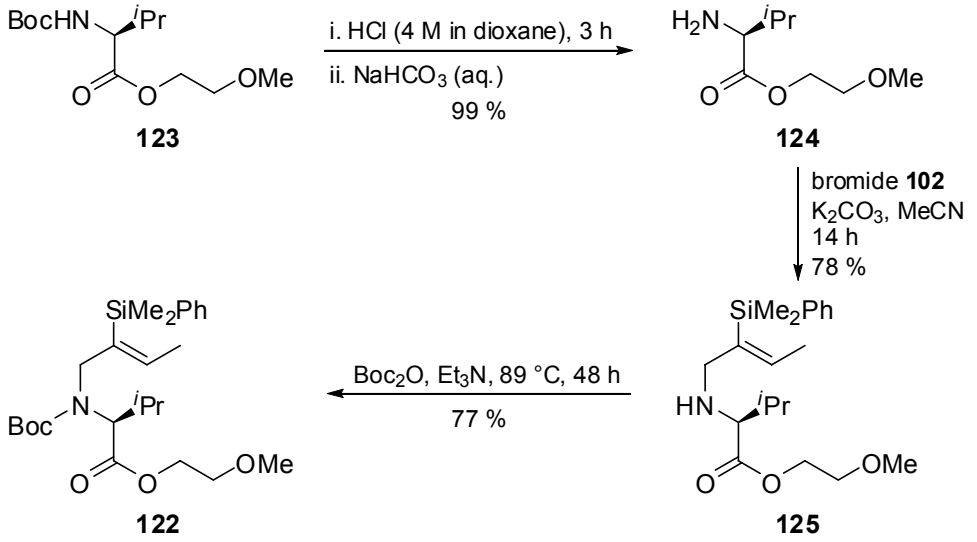
Scheme 4.13: Retrosynthetic analysis of **122**

Esterification of Boc-(*L*)-valine with 2-methoxyethanol in the presence of DCC and catalytic DMAP occurred in 89 % yield (**Scheme 4.14**). Treatment of ester **123** with potassium hydride, followed by bromide **102** resulted in no reaction. As this reaction proceeds well with the corresponding methyl ester, it was thought that, upon deprotonation, the pendant methoxy group may be co-ordinating to the potassium. This intramolecular coordination may confer stability, rendering the species less reactive towards bromide **102**.



Scheme 4.14: Attempted synthesis of precursor **122**

It was decided to first remove the Boc-protecting group using HCl to yield amine **124** in 99 % yield after basic work-up (**Scheme 4.15**). Alkylation of **124** furnished secondary amine **125** and re-introduction of the Boc group gave precursor **122** in 53 % overall yield (**Scheme 4.15**).

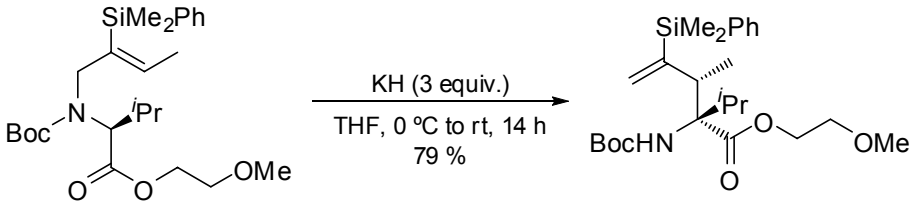


Scheme 4.15: Synthesis of precursor **122**

4.2.2 Aza-[2,3]-Wittig rearrangement of 122

Using KHMDS as the base, precursor **122** was subjected to the same reaction conditions used for aza-[2,3]-Wittig rearrangement of **66** (2.5 equiv. KHMDS, THF/DMPU, 0 ºC to rt). Rearrangement did not occur; the only products isolated appeared to be degraded starting material. Precursor **122** was then subjected to KH (3 equiv.) in THF at 0 °C to rt and, under these conditions, rearrangement occurred to form **126** in 79 % yield,

essentially as a single diastereoisomer (**Scheme 4.16**). Product **126** was found to be optically inactive. It was assumed that the relative stereochemistry would be the same as that previously determined for the valine methyl ester-derived rearrangement product **99**.[78]



122 **(±)-126**

Scheme 4.16: Rearrangement of **122**

The rearrangement was carried out at lower temperatures (**Table 4.2**). It was found that below 0 ºC, 18-crown-6 was necessary to enable rearrangement to occur.

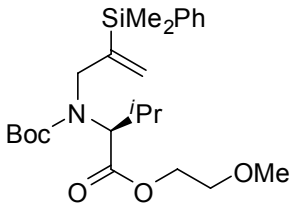
Entry	T (ºC)	18-crown-6 (equiv.)	Time (h)	Yield of **126** (%)
1	0	0	18	72
2	- 40	1	48	59
3	- 45	1	96	0

Table 4.2: Effect of temperature on aza-[2,3]-Wittig rearrangement of **122**

As the temperature was lowered, the rate of rearrangement became slower. The yields also decreased as the longer reaction times resulted in increased side product formation, although it was not possible to characterise these

impurities. Measurements of the $[\alpha]_D$ of the rearrangement products suggested that they were racemic. Below - 40 ºC, rearrangement did not occur. When the temperature of the reaction was lowered by only 5 ºC to - 45 ºC, only unreacted **122** was recovered from the reaction. In this case, a solution of precursor **122** and 18-crown-6 in THF was cooled to - 45 ºC and added *via* cannula to a stirred suspension of KH, which had also been cooled to - 45 ºC. The lack of reaction may have been due to the failure of the base to deprotonate the precursor at the lower temperature. Alternatively, deprotonation may have occurred; however, the enolate may have had insufficient energy to rearrange at - 45 ºC.

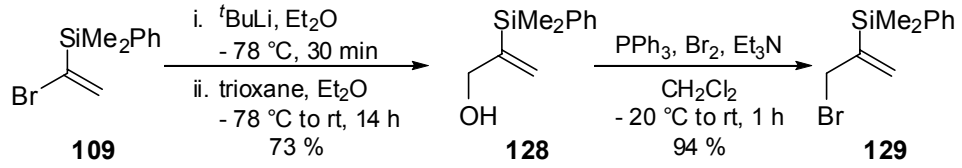
4.2.3 Synthesis of precursor 127



127

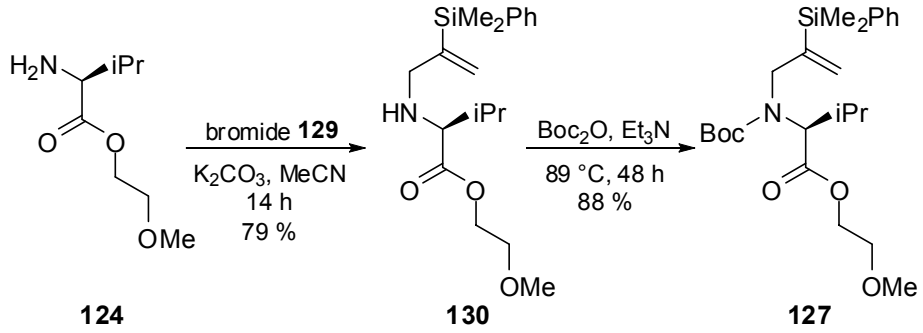
Figure 4.4

To determine the effect of alkene substitution, precursor **127** was synthesised (**Figure 4.4**). The terminal vinyl precursor would result in the formation of only one new stereocentre in the rearranged product, thus simplifying the reaction.



Scheme 4.17: Synthesis of allyl bromide **129**

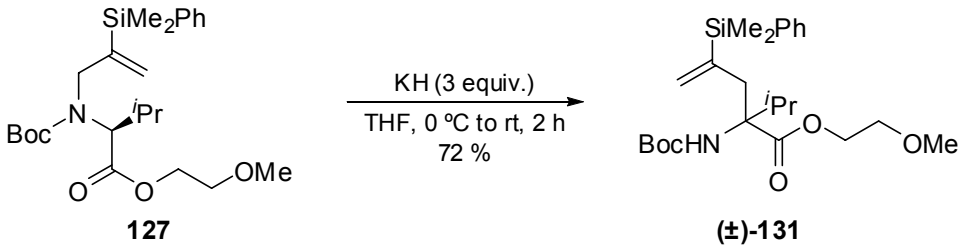
Bromide **129** was prepared by our previously established procedure (**Scheme 4.17**).[94] Vinyl bromide **109** was subjected to halogen-lithium exchange. Reaction of the resultant organolithium with trioxane yielded alcohol **128** in 73 % yield. Bromination furnished the desired allyl bromide **129** in 94 % yield. Alkylation of amine **124** with bromide **129**, followed by Boc protection gave the desired terminal alkene precursor **127** in 70 % over two steps (**Scheme 4.18**).



Scheme 4.18: Synthesis of terminal alkene precursor **127**

4.2.4 Aza-[2,3]-Wittig rearrangement of 127

Precursor **127** underwent rearrangement when treated with KH (3 equiv.) at 0 ºC then warmed to room temperature for 2 h (**Scheme 4.19**). Product **131** was obtained in 72 %. Measurement of $[\alpha]_D$ suggested that no chirality had been transferred.



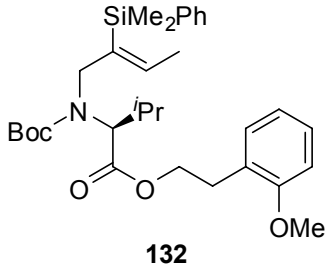
Scheme 4.19: Rearrangement of **127**

Again, the rearrangement was carried out at lower temperatures (**Table 4.3**). Similar results to those shown by the rearrangement of precursors **66** and **122** were obtained: no rearrangement was observed below - 40 °C and measurement of $[\alpha]_D$ suggested that the rearrangement products obtained were racemic. When the temperature of the reaction was lowered to - 45 ºC, only unreacted **127** was recovered from the reaction. Lowering the temperatue may have prohibited deprotonation of the precursor; however, it was also possible that the enolate was formed but did not possess sufficient energy to undergo rearrangement. The failure of the rearrangement of precursors with a methoxyethyl ester group to exhibit any chirality transfer prompted us to investigate other potential chelating groups.

Entry	T (ºC)	18-crown-6 (equiv.)	Time (h)	Yield of **131** (%)
1	0	0	72	0
2	0	1	24	72
3	- 40	1	72	45
4	- 45	1	96	0

Table 4.3: Effect of temperature on rearrangement of **127**

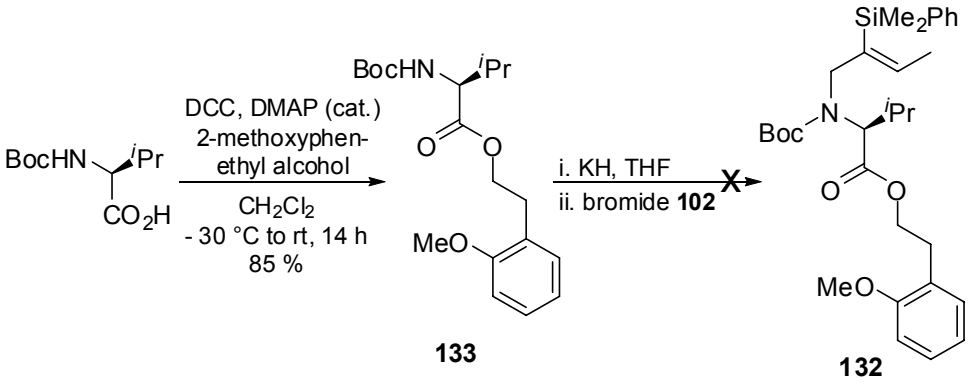
4.2.5 Synthesis of precursor 132



132

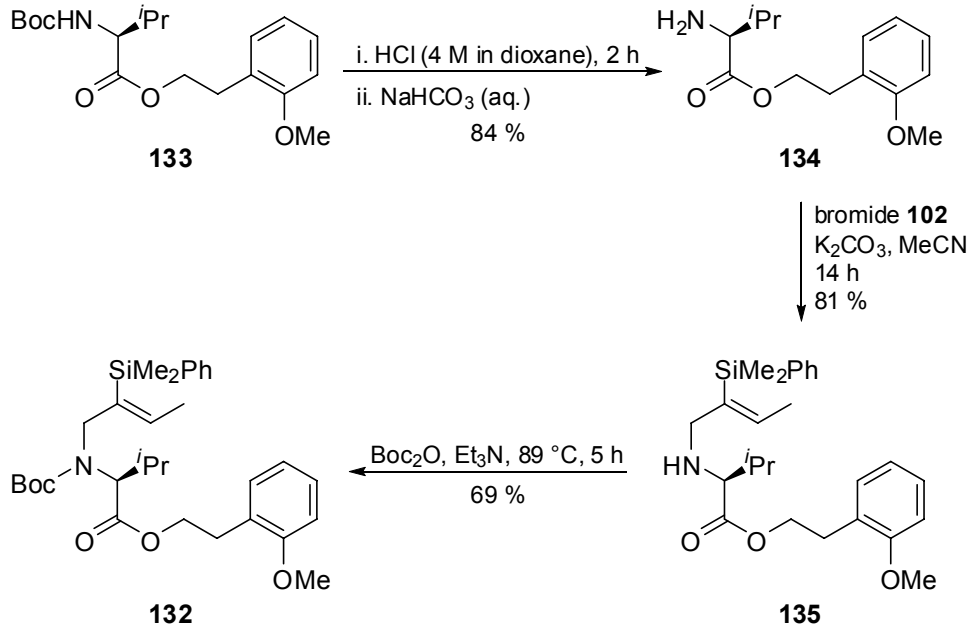
Figure 4.5

Precursor **132** with a methoxyphenethyl ester group was chosen as the next target for our investigation into the effect of temperature on the aza-[2,3]-Wittig rearrangement (**Figure 4.5**). It was postulated that this precursor could be synthesised by a similar route to that used for the synthesis of **122**.



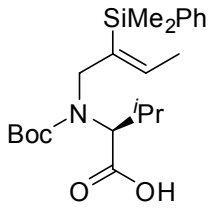
Scheme 4.20: Attempted synthesis of **132**

Accordingly, Boc-(*L*)-valine underwent esterification with 2-methoxyphenethyl alcohol in 85 % yield (**Scheme 4.20**). As observed in the synthesis of **122** (**Scheme 4.14**), attempted alkylation of the potassium salt of **133** with bromide **102** was unsuccessful.



Scheme 4.21: Synthesis of precursor **132**

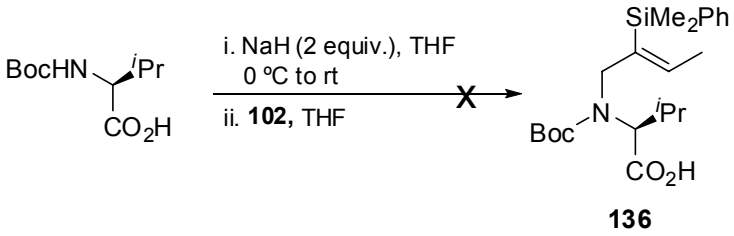
To overcome this, the Boc group was removed under acidic conditions to give the primary amine **134** in 84 % yield after a basic work-up (**Scheme 4.21**). Alkylation of **134** with crotyl bromide **102** furnished the secondary amine **135**, which underwent Boc protection to give the desired precursor **132** in 69 % yield. Although we were able to access the required precursor by this approach, it seemed a lengthy route and did not allow for the convenient synthesis of any analogues. To fully investigate a range of precursors with potential chelating groups, a more concise route was needed. It was thought that acid **136** (**Figure 4.6**) could be a common intermediate to access a range of esters.



136

Figure 4.6

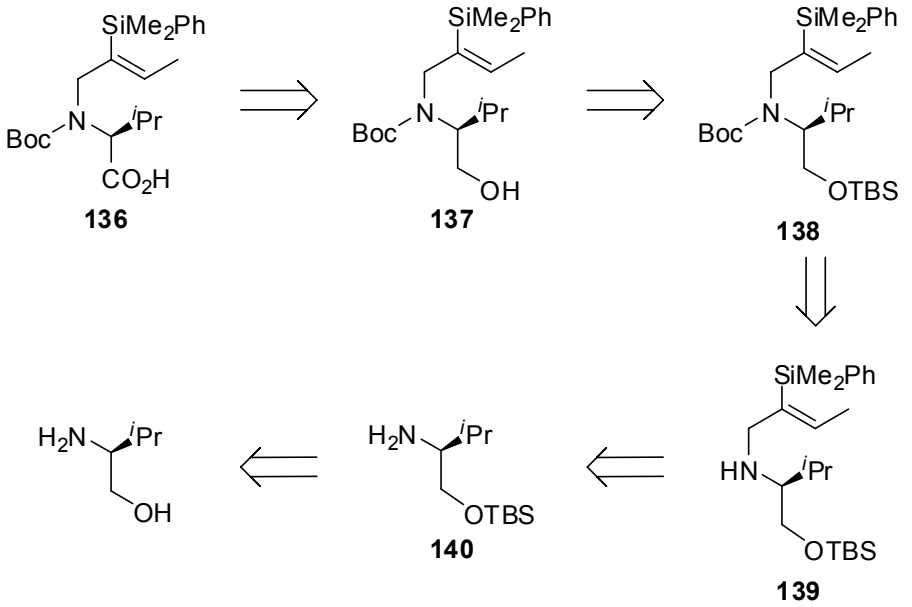
The simplest approach for the synthesis of acid **136** was direct alkylation of Boc-(*L*)-valine with bromide **102**; however, attempts to alkylate the Boc-(*L*)-valine di-anion were unsuccessful, with only unreacted Boc-(*L*)-valine and degradation products isolated (**Scheme 4.22**).



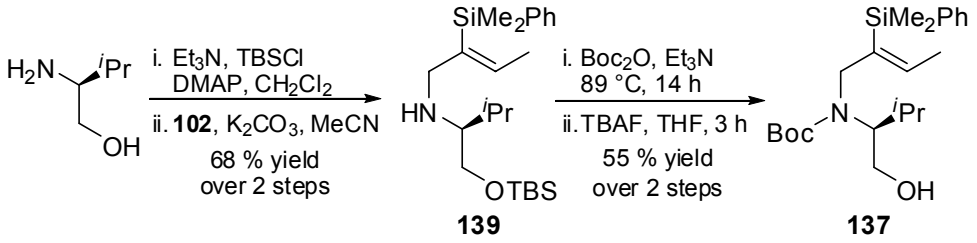
136

Scheme 4.22: Attempted synthesis of **136**

Retrosynthetically, acid **136** could be obtained from alcohol **137**, which in turn could be synthesised from the TBS-protected alcohol **138**. This could be accessed by Boc protection of secondary amine **139**, which could be attained by TBS protection and alkylation of commercially available (*L*)-valinol (**Scheme 4.23**).

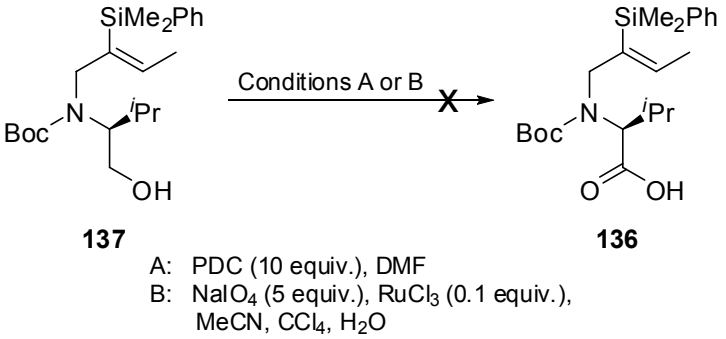


Scheme 4.23: Retrosynthetic analysis of acid **136**



Scheme 4.24: Synthesis of alcohol **137**

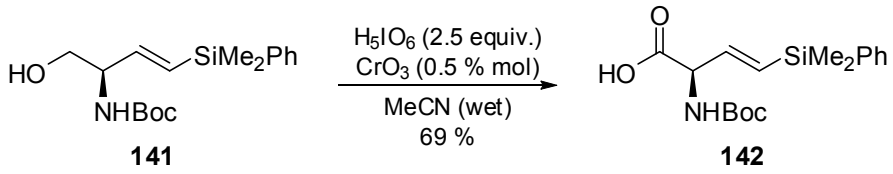
The synthesis of alcohol **137** proceeded as expected. Commercially available (*L*)-valinol underwent TBS protection, followed by alkylation, Boc protection and TBS deprotection to furnish **137** in 37 % overall yield (**Scheme 4.24**).



Scheme 4.25: Attempted oxidation of **137**

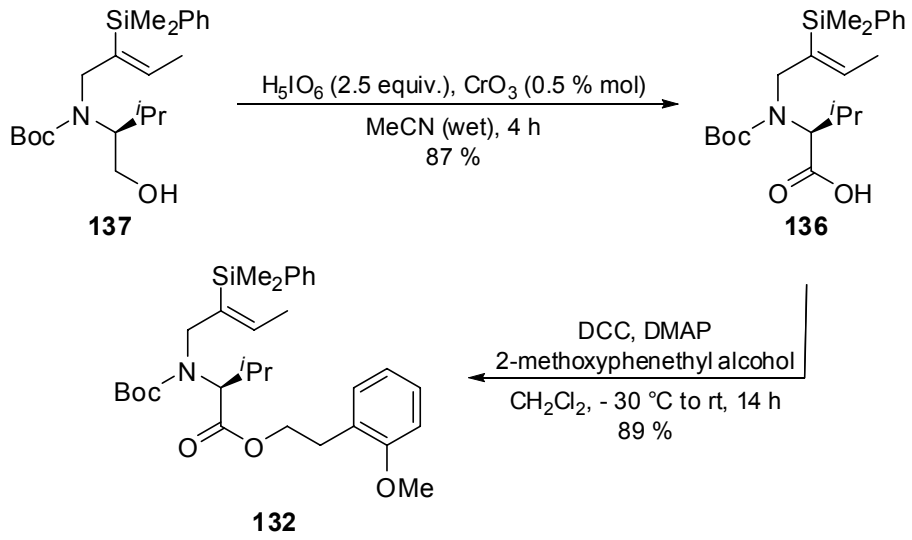
In 1997, Matsunaga *et al.* showed that Boc-amino alcohols could be oxidised directly to their corresponding acids by PDC.[95] Carrying out the same procedure on alcohol **137** resulted in the degradation of the starting material to a number of indistinguishable products (**Scheme 4.25**). Degradation was also observed when the oxidation was attempted with

sodium periodate and catalytic ruthenium trichloride, a protocol published by Young *et al.* for the oxidation of Boc-amino alcohols (**Scheme 4.25**).[96] A further search of the literature showed that Reginato *et al*. had used the method published by Zhao *et al*. using periodic acid and chromium trioxide to oxidise **141** to acid **142** (**Scheme 4.26**).[97]



Scheme 4.26: Oxidation of **141** with H_5IO_4 and CrO_3

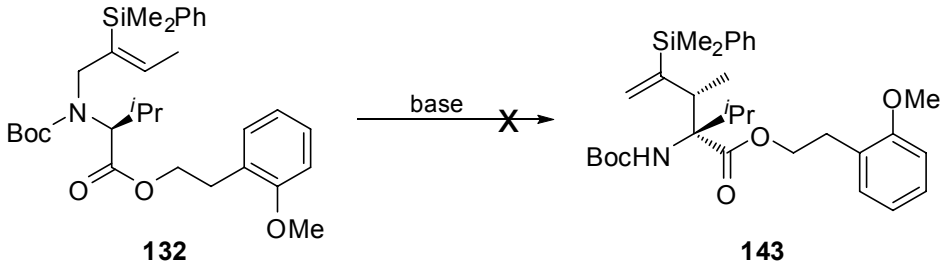
As this substrate contained similar functional groups to alcohol **137**, we were hopeful that these conditions would furnish acid **136**. Indeed, under these conditions, alcohol **137** was oxidised to acid **136** in 4 h in 87 % yield (**Scheme 4.27**). Esterification of acid **136** with 2-methoxyphenethyl alcohol proceeded well in 89 % yield (**Scheme 4.27**).



Scheme 4.27: Oxidation of **137** to acid **136** and esterification to **132**

4.2.6 Aza-[2,3]-Wittig rearrangement of 132

Precursor **132** was subjected to the rearrangement conditions established for the methoxyethyl ester analogue: KH (3 equiv.), THF, 0 °C to rt (**Scheme 4.28**). Disappointingly, none of the desired rearrangement product **143** was observed; only degradation products were isolated. The reaction was repeated in the presence of 18-crown-6; once more, only decomposition products were observed. The rearrangement was also attempted with other bases (KHMDS and LDA) with a similar result.

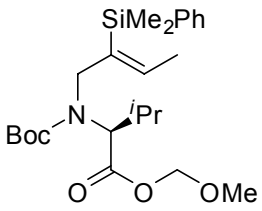


132 **143**

Scheme 4.28: Attempted rearrangement of **132**

4.2.7 Synthesis of precursor 144

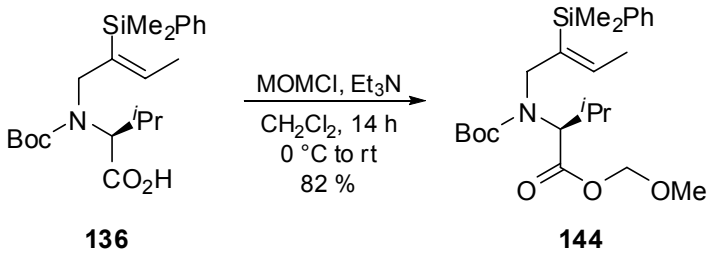
Due to the failure of **132** to undergo aza-[2,3]-Wittig rearrangement, attention turned to precursor **144** (**Figure 4.7**), in which the chain of the potential chelating group has one less carbon than that of **122**. Upon deprotonation, this would allow for the possible formation of a six-membered chelated ring, which may be more favourable than the seven-membered ring that would be required for **122**. The possibility of a geometrically more favoured intramolecular coordination may affect the reactivity of the resultant ester enolate.



144

Figure 4.7

Precursor **144** was prepared according to the procedure published by Oriyama *et al.*, which describes the esterification of acetic acid using chloromethyl methyl ether and triethylamine.[98] This method furnished precursor **144** in 82 % yield (**Scheme 4.29**).

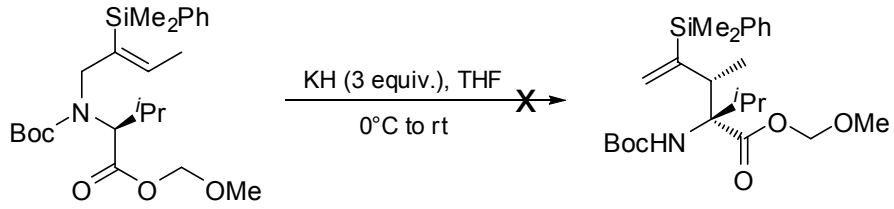


136 **144**

Scheme 4.29: Synthesis of precursor **144**

4.2.8 Aza-[2,3]-Wittig rearrangement of 144

Precursor **144** was treated with KH in THF at 0 °C warming to rt (**Scheme 4.30**). After 30 min, tlc analysis indicated that all of the precursor had been consumed. Upon work-up and separation by flash column chromatography, only degradation products were isolated. The reaction was repeated, maintaining the temperature at 0 °C with a similar result. The rearrangement of **144** was also attempted using KHMDS as base; however, only degradation products were observed.

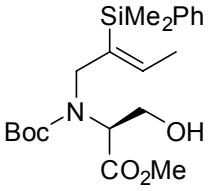


144 **145**

Scheme 4.30: Attempted aza-[2,3]-Wittig rearrangement of **144**

4.2.9 Synthesis of precursor 146

As the precursors with a pendant methoxy group had either failed to undergo rearrangement or yielded only racemic products, it was decided to investigate the aza-[2,3]-Wittig rearrangement of precursor **146** (**Figure 4.8**). Upon treatment with base, the free hydroxyl should be deprotonated. It was hoped that further deprotonation α to the ester would result in the formation of an enolate which may undergo rearrangement at lower temperatures.

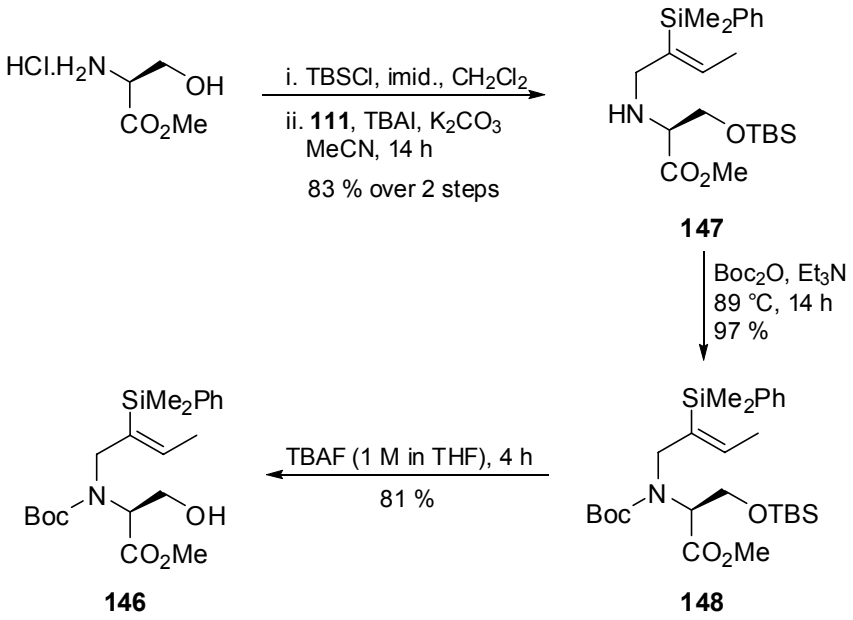


146

Figure 4.8

Serine methyl ester hydrochloride was treated with TBSCl and imidazole,[99] followed by alkylation with chloride **111** to yield amine **147** in 83 % yield

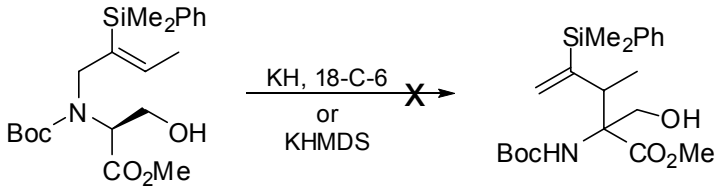
over two steps (**Scheme 4.31**). Boc protection, followed by TBS deprotection gave the desired precursor in 65 % overall yield (**Scheme 4.45**).



Scheme 4.31: Synthesis of precursor **146**

4.2.10 Aza-[2,3]-Wittig rearrangement of 146

Precursor **146** was treated with a solution of KHMDS (2.5 equiv. of 0.5 M solution in toluene) at 0 °C, warming to rt. After 2 days, no reaction was observed by tlc. Upon work-up, only starting material was recovered. Disappointingly, this was also the observed outcome when KH in the presence of 18-crown-6 was used to initiate rearrangement. The failure of **146** to undergo rearrangement may be due to the proximity of the deprotonated hydroxyl group to the required site of deprotonation.

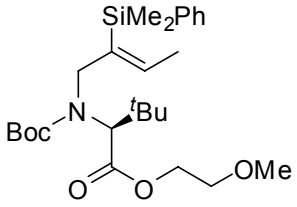


146 **149**

Scheme 4.32: Attempted aza-[2,3]-Wittig rearrangement of **146**

As no encouraging results had been obtained from the aza-[2,3]-Wittig rearrangement of precursors with potential chelating groups, this line of investigation not pursued any further.

4.3 Studies of *tert*-leucine-derived precursor 150



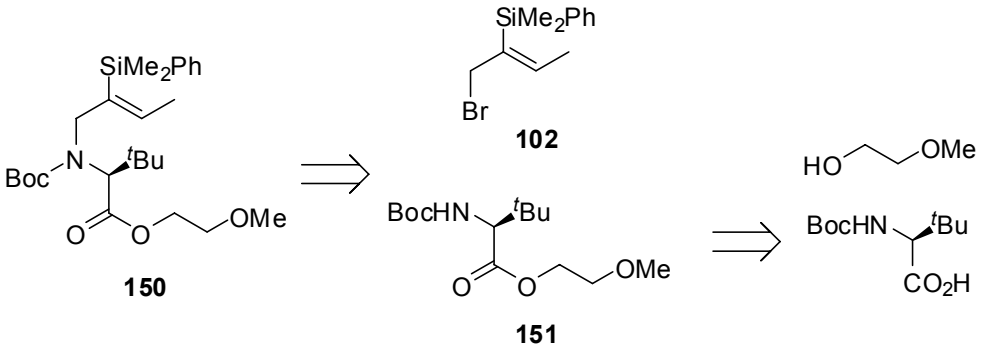
150

Figure 4.9

It was postulated that increasing the steric bulk at the site of deprotonation may hinder the bond rotation around the C_2-N bond and have a more pronounced effect on the possibility of generating a chiral axis. It seemed from the results so far obtained that an *iso*propyl group is not sufficiently sterically demanding. Previous work had shown that the precursor derived

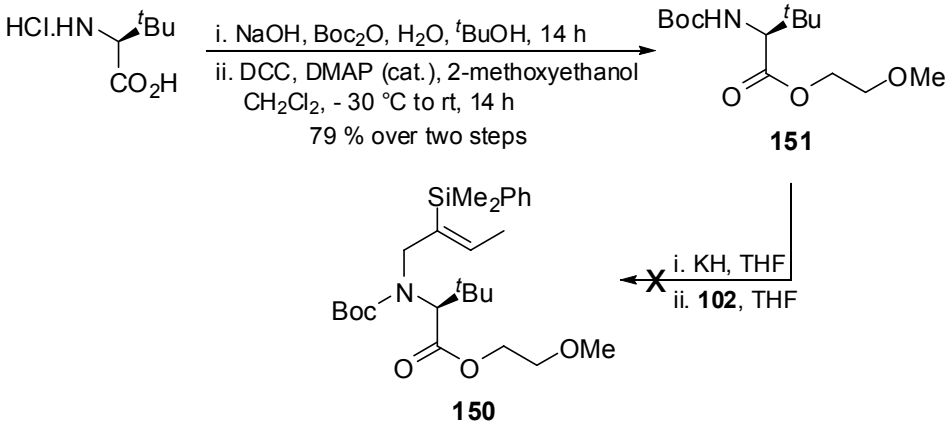
from phenylglycine does not undergo aza-[2,3]-Wittig rearrangement,[78] possibly due to over-stabilisation of the anion formed. Therefore, it was decided to investigate the synthesis and rearrangement of a precursor derived from *tert*-leucine. The site of deprotonation in this precursor is extremely hindered so it was thought that the most suitable base to initiate rearrangement would be the relatively small KH. As earlier results had shown that the methoxyethyl ester precursors readily underwent rearrangement with KH, it was decided that a desirable target would be **150** (**Figure 4.9**).

4.3.1 Synthesis of precursor 150



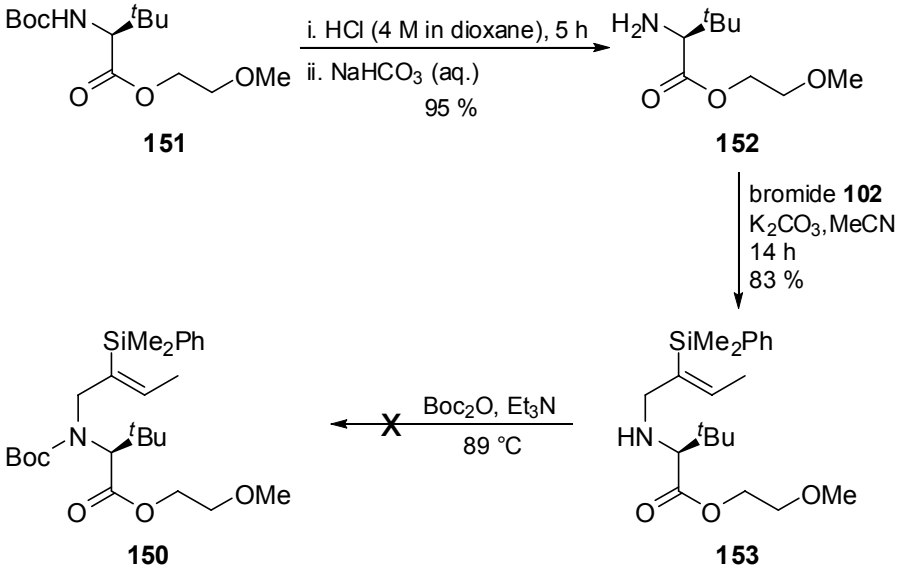
Scheme 4.33: Retrosynthetic analysis of **150**

It was thought that precursor **150** could be prepared by the same route as that proposed for the synthesis of **122**: esterification of Boc-(*L*)-*tert*-leucine with 2-methoxyethanol would furnish **151**, which would give precursor **150** upon alkylation with bromide **102** (**Scheme 4.33**).



Scheme 4.34: Attempted synthesis of **150**

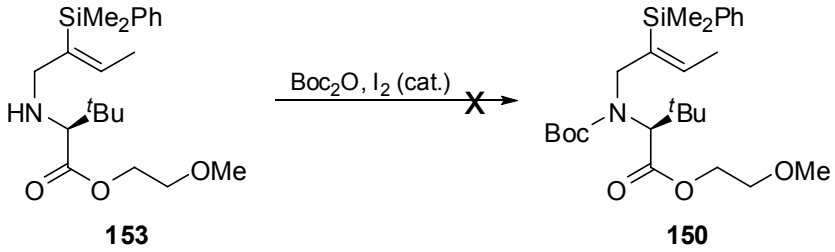
Boc-protection of *tert*-leucine hydrochloride followed by esterification provided **151** in 79 % over two steps (**Scheme 4.34**). The deprotonation/alkylation step was again unsuccessful; therefore, the Boc group was removed to give **152** in 95 % yield (**Scheme 4.35**). The primary amine then underwent alkylation with bromide **102** to furnish **153** in 83 % yield**.**



Scheme 4.35: Attempted synthesis of **150**

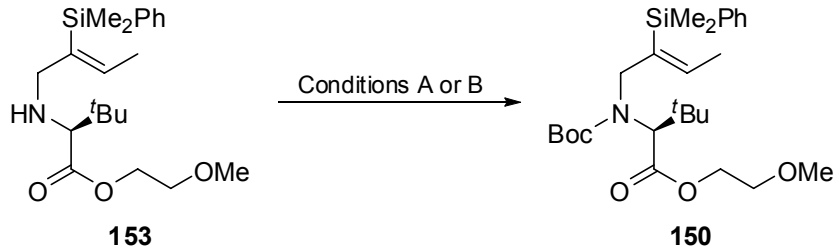
Under the conditions established for the Boc protection of the valine-derived precursors (Boc_2O, Et_3N, heat to reflux), secondary amine **153** did not undergo Boc protection, presumably due to the steric hindrance conferred by the neighbouring *tert*-butyl group.

Adapa *et al.* have reported the use of molecular iodine as a catalyst for the Boc protection of sterically hindered amines.[100] It is postulated that the iodine is able to co-ordinate to the carbonyl groups of the Boc anhydride, increasing its electrophilicity and, hence, its reactivity towards the amine. Amine **153** was subjected to these conditions; however, no desired product was obtained with only starting material **153** recovered from the reaction (94 %, **Scheme 4.36**). As no product had been observed, this approach was discarded.



Scheme 4.36: Attempted Boc protection of **153** with catalytic iodine

It was considered that, in order to introduce the Boc group at such a hindered position, the temperature of the reaction would have to be increased. The reaction was heated to reflux, replacing triethylamine with toluene as the reaction solvent (**Scheme 4.37**). Pleasingly, the Boc-protected product was isolated in a modest 45 % yield after 48 h. It was also found that the reaction could be carried out with no solvent, heating to 130 °C. This led to the formation of precursor **150** in 47 % yield after 16 h (**Scheme 4.37**).

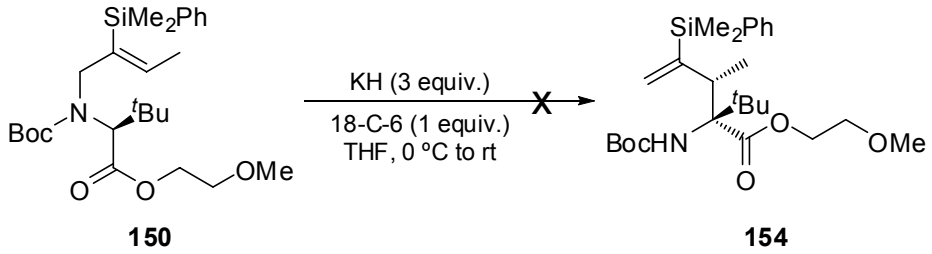


A: Boc_2O (2 equiv.), toluene, 110 °C, 48 h — 45 % yield
B: Boc_2O (2 equiv.), 130 °C, 16 h — 47 % yield

Scheme 4.37: Formation of precursor **150**

4.3.2 Aza-[2,3]-Wittig rearrangement of precursor 150

Precursor **150** was treated with KH and 18-crown-6 at 0 °C, warming to rt; under these conditions, only degradation products were observed (**Scheme 4.38**). The same result was obtained in the absence of 18-crown-6 at 0 °C, warming to rt.



150 **154**

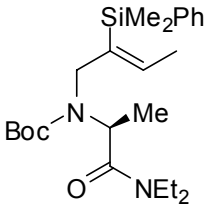
Scheme 4.38: Attempted rearrangement of **150**

When treated with KHMDS, precursor **150** did not react after 3 days and only starting material was recovered from the reaction (**Scheme 4.38**). The reaction was quenched with MeOD and the ^{1}H NMR of the starting material suggested that deuterium was not incorporated. The rearrangement was also attempted with LDA at - 40 °C. After 2 days, no reaction was observed by tlc and the temperature was increased to rt. After a further 2 days, the reaction was again quenched with MeOD. Only unreacted starting material (64 %, showing no deuterium incorporation) and degradation products were isolated. It was therefore presumed that the site of deprotonation is too hindered for the base to approach close enough to abstract the required

proton, resulting in either the recovery of unreacted starting material or access to degradation pathways. As increasing the steric bulk at the site of deprotonation hindered formation of the enolate required for rearrangement, we decided to concentrate on methods that would allow aza-[2,3]-Wittig rearrangement to be carried out at lower temperatures.

4.4 Studies of amide precursor 63

The ester-stabilised anions of precursors **66**, **122** and **127** do not undergo rearrangement at temperatures below around - 40 ºC. The racemic nature of the products obtained suggests that these temperatures are not low enough to prevent rotation around the C_2-N bond. Deuterium incorporation in precursor **66** at - 78 °C showed a degree of retention of chirality; therefore, we were keen to develop a system in which rearrangement could occur at lower temperatures.



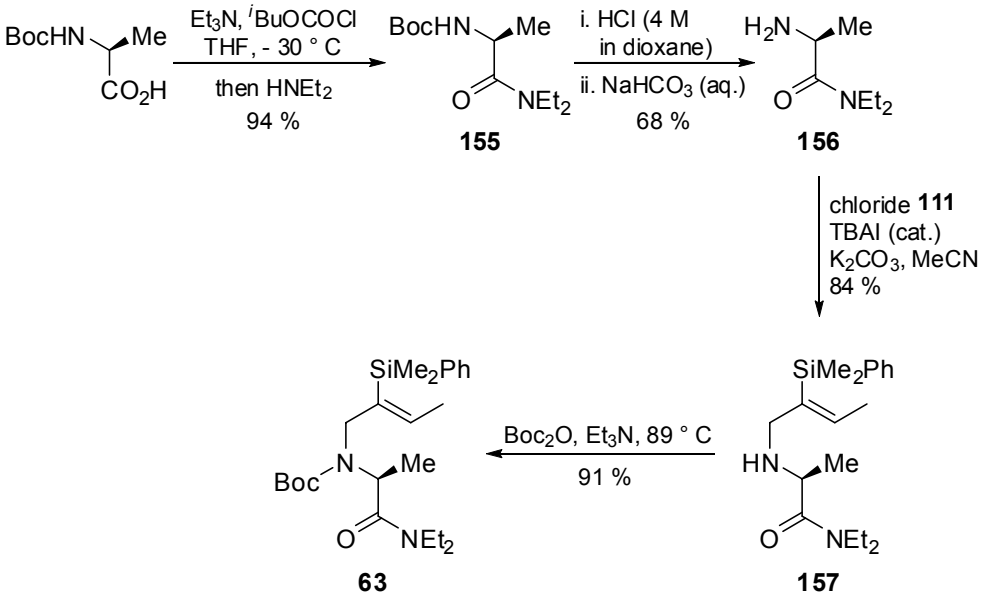
63

Figure 4.10

It was postulated that an amide may create a less stable enolate which could undergo aza-[2,3]-Wittig rearrangement at lower temperatures than the ester analogues. Therefore, it was decided to investigate the rearrangement of the previously studied amide precursor **63** (**Figure 4.10**).[78]

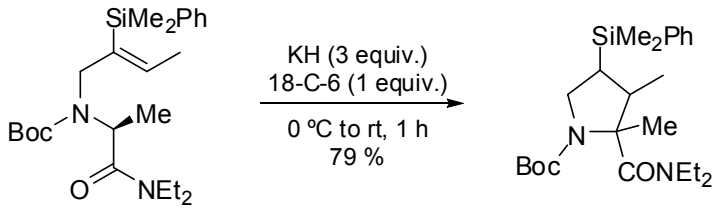
4.4.1 Synthesis of precursor 63

Precursor **63** was synthesised, according to the previously described route (**Scheme 4.39**).[78] Treatment of Boc-(*L*)-alanine with triethylamine and *iso*butyl chloroformate, followed by diethylamine gave amide **155** in 94 % yield. Removal of the Boc group under acidic conditions, alkylation of the resultant primary amine **156** with chloride **111**, then re-introduction of the Boc group furnished precursor **63** in 49 % overall yield.



Scheme 4.39: Synthesis of precursor **63**

4.4.2 Aza-[2,3]-Wittig rearrangement of precursor 63

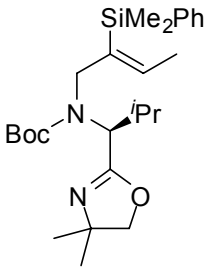


63 **158**

Scheme 4.40: Formation of pyrrolidine **158**

Precursor **63** was subjected to the rearrangement conditions previously used [KH (3 equiv.), 18-crown-6 (1 equiv.), THF, 0 ºC to rt]. Surprisingly, pyrrolidine **158** was isolated in 79 % yield after 1 h and none of the expected rearrangement product was observed (**Scheme 4.40**). The reaction was repeated, maintaining the temperature at 0 °C; only unreacted precursor **63** (91 %) was recovered after 4 days. The formation of pyrrolidine **158** will be discussed in further detail in **Section 5.6**.

4.5 Studies of precursor 159

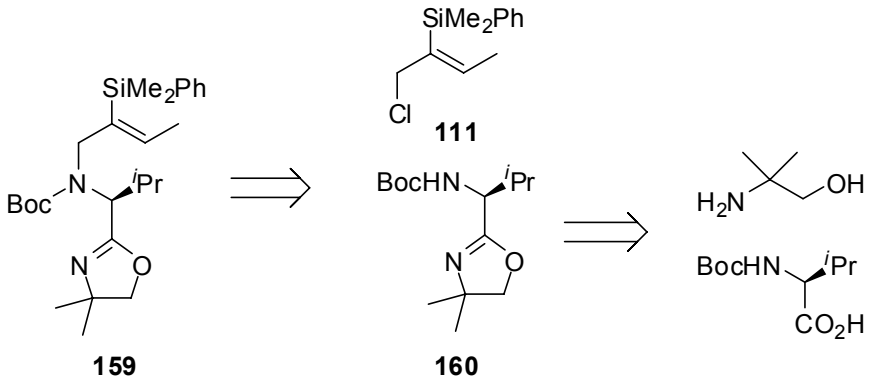


159

Figure 4.11

As precursor **63** had failed to yield the desired aza-[2,3]-Wittig rearrangement product, it was decided to investigate the rearrangement of oxazoline-based precursor **159** (**Figure 4.11**). Following the same principle as the amide precursor **63**, enolisation of **159** should result in an intermediate higher in energy than that of the ester analogues. Therefore, it was possible that the reaction could be carried out at a lower temperature.

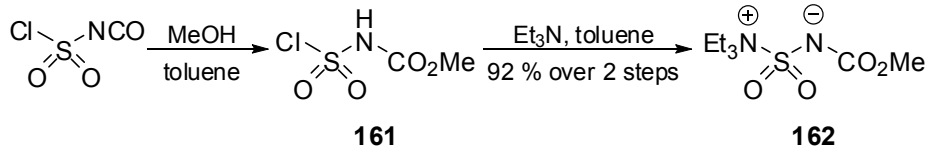
4.5.1 Synthesis of precursor 159



Scheme 4.41: Retrosynthetic analysis of **159**

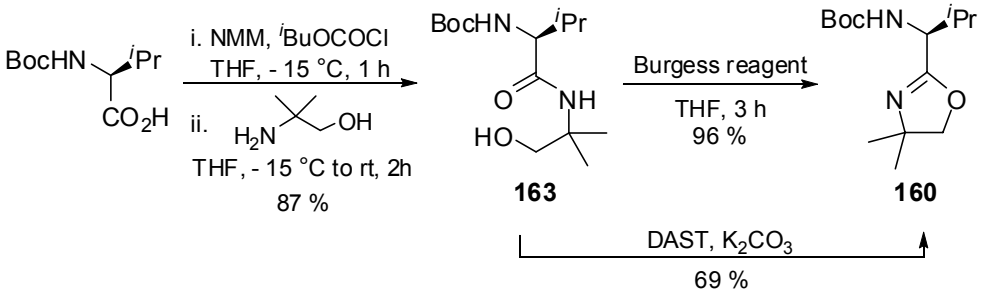
Retrosynthetically, precursor **159** could be accessed from chloride **111** and oxazoline **160**, which in turn could be synthesised from Boc-(*L*)-valine and 2-amino-2-methylpropan-1-ol (**Scheme 4.41**). Literature examples show that 2-oxazolines can be readily prepared from the corresponding hydroxyamides using Burgess reagent[101] or DAST.[102] Therefore, Burgess reagent **162** was synthesised by subjecting chlorosulfonyl isocyanate to

MeOH in toluene to give carbamate **161**, which was in turn treated with Et_3N in toluene to give **162** in 92 % yield over two steps (**Scheme 4.42**).[103]



Scheme 4.42: Synthesis of Burgess reagent **162**

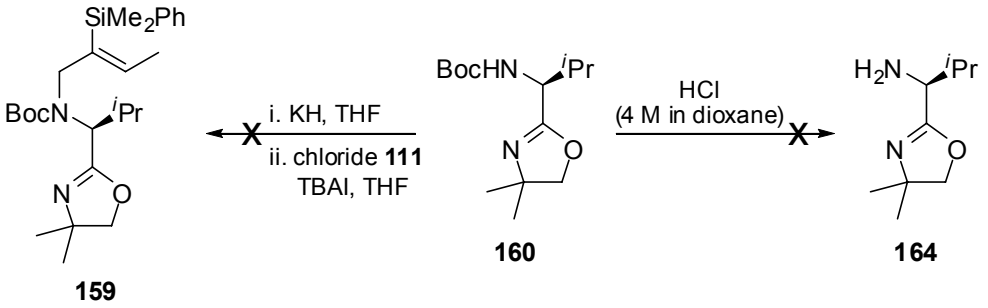
Hydroxyamide **163** was prepared in 87 % yield from Boc-(*L*)-valine and 2-amino-2-methylpropan-1-ol (**Scheme 4.43**). Both Burgess reagent and DAST were assessed in the cyclisation step; however, higher yields of oxazoline **160** were obtained with Burgess reagent (96 % yield compared to 69 % yield with DAST).



Scheme 4.43: Formation of oxazoline **160** using Burgess reagent or DAST

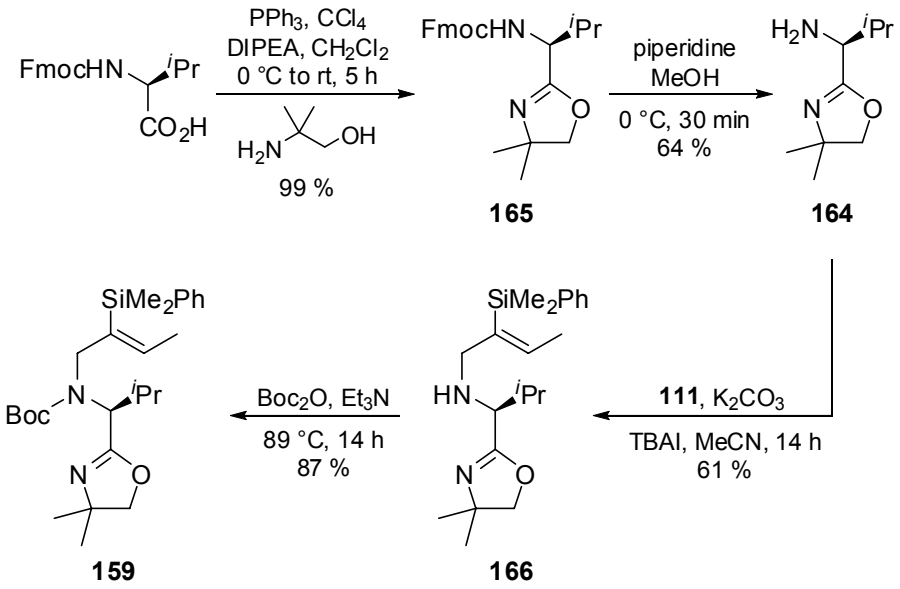
Oxazoline **160** was then treated with KH, followed by chloride **111** and TBAI (**Scheme 4.44**). No products were observed and the starting materials were recovered from the reaction mixture. Attempts to remove the Boc group in order to alkylate the primary amine **164** resulted only in

decomposition, presumably as the oxazoline is cleaved under acidic conditions (**Scheme 4.44**).



Scheme 4.44: Attempted alkylation and Boc deprotection of **160**

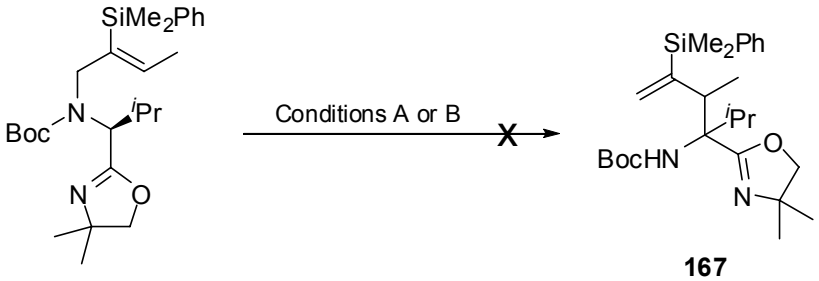
To overcome this problem, an alternative protecting group was investigated. A report by Sigman and Rajaram showed that oxazolines could be prepared in a one-pot procedure from their corresponding Fmoc-protected amino acids.[104] Consequently, Fmoc-(*L*)-valine was treated with triphenylphosphine, carbon tetrachloride, DIPEA and 2-amino-2-methylpropan-1-ol to furnish the Fmoc-protected oxazoline **165** in 99 % yield (**Scheme 4.45**). Deprotection of the Fmoc group proceeded smoothly upon treatment with piperidine to give the primary amine **164** in 64 % yield. Alkylation with chloride **111** and Boc protection gave the desired precursor in 53 % yield over the two steps (**Scheme 4.45**).



Scheme 4.45: Synthesis of precursor **159**

4.5.2 Aza-[2,3]-Wittig rearrangement of 159

Precursor **159** was subjected to KHMDS in an attempt to promote aza-[2,3]-Wittig rearrangement (**Scheme 4.46**). A solution of KHMDS (2.5 equiv. of 0.5 M in toluene) was added to a solution of **159** in THF/DMPU (4:1) at 0 °C. The reaction was warmed to rt and stirred for 3 days. As no reaction was observed by tlc, the reaction was quenched with MeOD. Upon work-up, the ^{1}H NMR of the unreacted starting material showed no deuterium incorporation. Conducting the reaction with KH and 18-crown-6 resulted in the same outcome (**Scheme 4.46**).



159 **167**

A: KHMDS (2.5 equiv.), THF/DMPU (4:1), 0 °C to rt
B: KH (3 equiv.), 18-C-6 (1 equiv.), THF, 0 °C to rt

Scheme 4.46: Attempted aza-[2,3]-Wittig rearrangement of **159**

It was speculated that the failure of precursor **159** to undergo aza-[2,3]-Wittig rearrangement was due to the sterically encumbered enolate that would form upon deprotonation at the α-centre (**Figure 4.12**). The $A^{1,3}$ strain experienced by the enolate may have been of sufficiently high energy as to prohibit deprotonation.

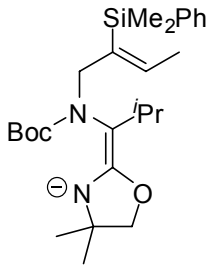


Figure 4.12

If this hypothesis is correct, decreasing the size of the substituent at the α-position, to a methyl group for example, may allow deprotonation and, hence, aza-[2,3]-Wittig rearrangement. Unfortunately, due to time

constraints, further investigation into the aza-[2,3]-Wittig rearrangement of an alanine-derived oxazoline was not possible.

4.6 Summary

The aza-[2,3]-Wittig rearrangement of precursor **66** has been re-examined. A short survey of bases has shown that the use of KHMDS furnishes pyrrolidine **119** as the major product. The aza-[2,3]-Wittig rearrangements of precursors **122** and **127** with a pendant methoxyethyl group have been achieved using KH. An investigation into the effect of lowering the reaction temperature in order to promote the formation of an axially chiral enolate in the rearrangements of **66**, **122** and **127** has been conducted. The results suggest that, below temperatures of around - 40 °C, the precursors did not possess enough energy to undergo rearrangement; however, the temperature was not low enough to suppress bond rotation around the C_2-N bond, resulting in the formation of racemic products. This is supported by deuterium quench studies on **66**, performed at - 78 °C, which showed 90 % D incorporation with significant retention of stereochemistry based on $[\alpha]_D$. Precursors **132** and **144** failed to undergo aza-[2,3]-Wittig rearrangement when treated with KH, KHMDS and LDA. Precursor **146** was synthesised from (*L*)-serine methyl ester hydrochloride. Neither KH in the presence of

18-crown-6 nor KHMDS were successful in initiating aza-[2,3]-Wittig rearrangement of **146**.

Precursor **150**, derived from *tert*-leucine, was synthesised and subjected to rearrangement conditions, using KH, KHMDS and LDA. No rearrangement product was isolated; recovered precursor that had not been deprotonated and degradation products were observed.

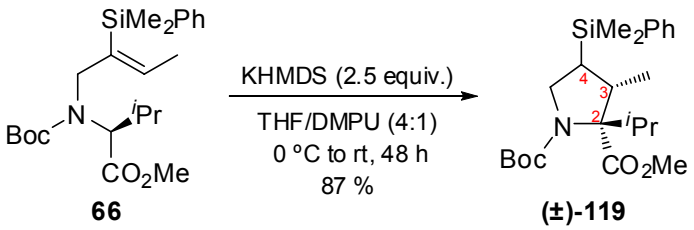
Precursor **63** was treated with KH and 18-crown-6; only pyrrolidine **158** was isolated. Oxazoline **159** was synthesised from Fmoc-(*L*)-valine and subjected to rearrangement conditions; however, deuterium quench studies indicated that no deprotonation had occurred, possibly due to the sterically encumbered nature of the resultant enolate.

At this point, this line of research was discontinued and concentration was focused on the cyclisation products that were obtained in the rearrangements of **66** and **63**.

5 Cyclisation studies

5.1 Investigations into the formation of 119

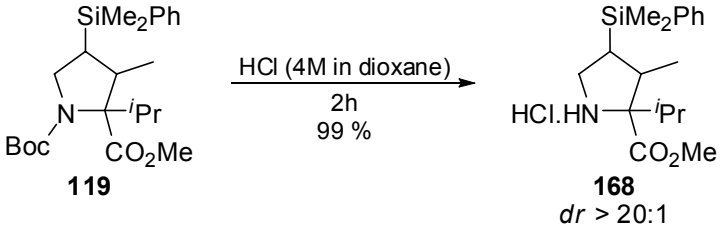
As shown in **Section 4.1** (**Scheme 4.11**), reaction of precursor **66** with KHMDS yielded two products, the major one being characterised as pyrrolidine **119**. The reaction was monitored by tlc by comparison with a sample of isolated rearrangement product **99**. It showed that the spot corresponding to the rearrangement product **99** appeared and then gradually became smaller as the reaction progressed, conceding to the emergent spot corresponding to the pyrrolidine **119**. This would suggest that the cyclisation occurs after rearrangement. This supposition is supported by the fact that a longer reaction time of 48 h yields only the pyrrolidine **119** in 87 % yield (**Scheme 5.1**). Again, monitoring the reaction by tlc confirmed that a spot corresponding to the rearrangement product appeared and then faded during the course of the reaction.



66 **(±)-119**

Scheme 5.1: Formation of pyrrolidine **119** from **66**

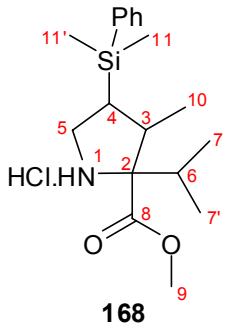
The ^{1}H NMR in $CDCl_3$ of **119** indicated two different isomers of this product were present in a 2:1 ratio. It was originally thought that these may be diastereoisomers. If the rearrangement occurs before the cyclisation, the relative stereochemistry of C_2 and C_3 would already be established as shown (**Scheme 5.1**). However, the relative stereochemistry of C_4 was unknown and it was possible that a mixture of diastereoisomers were formed upon protonation. Attempts to separate them by column chromatography were unsuccessful and it was thought that removal of the Boc group may allow easier separation. Therefore, pyrrolidine **119** was treated with 4 M HCl (**Scheme 5.2**). The hydrochloride salt **168** was obtained in 99 % yield as a single diastereoisomer with no need for further purification. From this we deduce that the 2:1 ratio of products seen in the ^{1}H NMR of **119** was caused by a rotameric mixture around the N-Boc bond. Measurement of the $[\alpha]_D$ of **168** indicated that it was racemic.



Scheme 5.2: Boc deprotection of **119**

The next step was to determine the relative stereochemistry of pyrrolidine **168**. Attempts to crystallise **168** resulted in the formation of very fine, needle-like crystals which were unsuitable for X-ray crystallography.

Therefore, a number of nOe experiments were carried out. For this purpose, the following numbering system was used (**Figure 5.1**).



168

Figure 5.1

5.1.1 NMR interpretation of 168

Before carrying out the nOe experiments, it was vital to ensure that the ^{1}H NMR data (**Figure 5.2**) had been correctly interpreted. This was accomplished with the aid of COSY and ^{13}C-^{1}H correlation experiments.

The signals at δ 1.12 (3H, d, J = 6.9 Hz) and δ 1.21 (3H, d, J = 6.8 Hz) are both coupled to a signal at δ 2.32 (1H, septet, J = 6.8 Hz) as shown by the COSY spectrum. These three signals are therefore assigned to Me_7, $Me_{7'}$ and H_6 respectively. The signal at δ 0.96 (3H, d, J = 7.3 Hz) is shown by the COSY to couple to a single proton resonance at δ 2.69 (1H, app. quintet, J = 6.8 Hz); these are assigned as Me_{10} and H_3 respectively, despite the slight discrepancy in J values, which we attributed to some broadening of the

signal at δ 2.69. A correlation in the COSY spectrum between the single proton resonance at δ 1.99 (1H, ddd, J = 13.7, 8.4, 6.4 Hz) and the signal corresponding to H_3 suggests that the former relates to H_4. This signal at δ 1.99 is also coupled to a signal at δ 3.88 (1H, dd, J = 11.4, 8.5 Hz); this is assigned as H_5. Taking into account the multiplicity and electronic effects of the substituents, the signals at δ 3.73 (1H, app. t, J = 12.5 Hz) and δ 3.79 (3H, s) are assigned as $H_{5'}$ and Me_9 respectively. The peaks in the ^{1}H NMR spectrum at δ 0.38 (3H, s), δ 0.44 (3H, s) and δ 7.36 - 7.51 (5H, m) are assigned as Me_{11}, $Me_{11'}$ and the Ph group respectively.

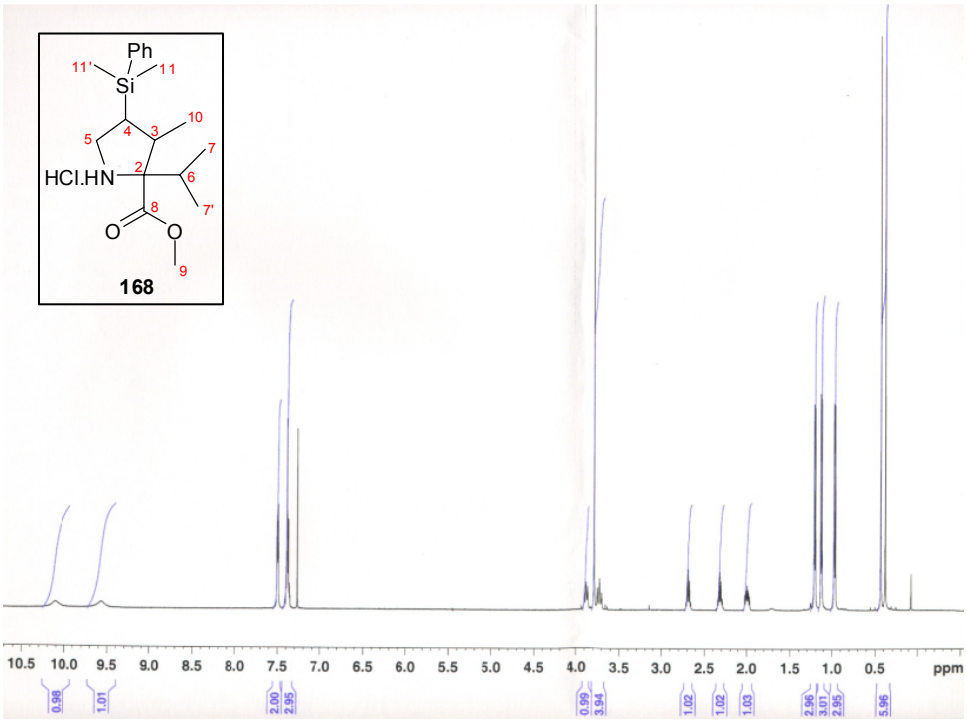


Figure 5.2

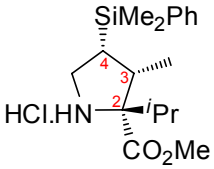
5.1.2 ^{1}H NMR nOe data of 168

Irradiated	Enhanced (%)
H_3	Me_{10} (4.2), Me_7 (4.8), H_4 (4.5), H_6 (0.7)
H_4	H_6 (5.9), H_3 (6.4), H_5 (3.5)
H_6	Me_7 (5.3), $Me_{7'}$ (6.0), H_4 (6.2), H_3 (2.0), H_5 (1.5)
Me_{10}	Me_{11} (0.9), $Me_{11'}$ (1.3), H_3 (3.0), $H_{5'}$ (0.7), Me_9 (0.6)

Table 5.1: nOe data for **168**

Once the ^{1}H NMR had been successfully analysed, we were able to obtain nOe data from selective irradiation of H_3, H_4, H_6 and Me_{10} (**Table 5.1**). Irradiation of the signal at δ 2.69, assigned as H_3, induced an enhancement of 4.8 % at δ 1.12 (Me_7) and 0.7 % at δ 2.32 (H_6). This suggests that H_3 is on the same face as the *iso*propyl group. This would be expected if cyclisation occurs after rearrangement as the relative stereochemistry of these two centres would already be established as (2*R**,3*R**). There was also an induced enhancement of 4.5 % at δ 1.99 (H_4), which implies that H_4 is also on the same face of the pyrrolidine ring as H_3. This was supported by the enhancements of 5.9 % shown at δ 2.32 (H_6) and 6.4 % at δ 2.69 (H_3) upon irradiation of the signal at δ 1.99 (H_4). Irradiation of the signal at δ 0.96 (Me_{10}) generated enhancements of 0.9 % and 1.3 % at δ 0.38 (Me_{11}) and δ 0.44 ($Me_{11'}$) respectively. An enhancement of 0.6 % at δ 3.79 (Me_9) was also seen. Although these enhancements are relatively small, they support the proposal that the *iso*propyl group, H_3 and H_4 are on the same

face of the molecule. Taking all of the data into account, we propose that the relative stereochemistry of pyrrolidine **168** is 2*R**,3*R**,4*R** (**Figure 5.3**).



(±)-168

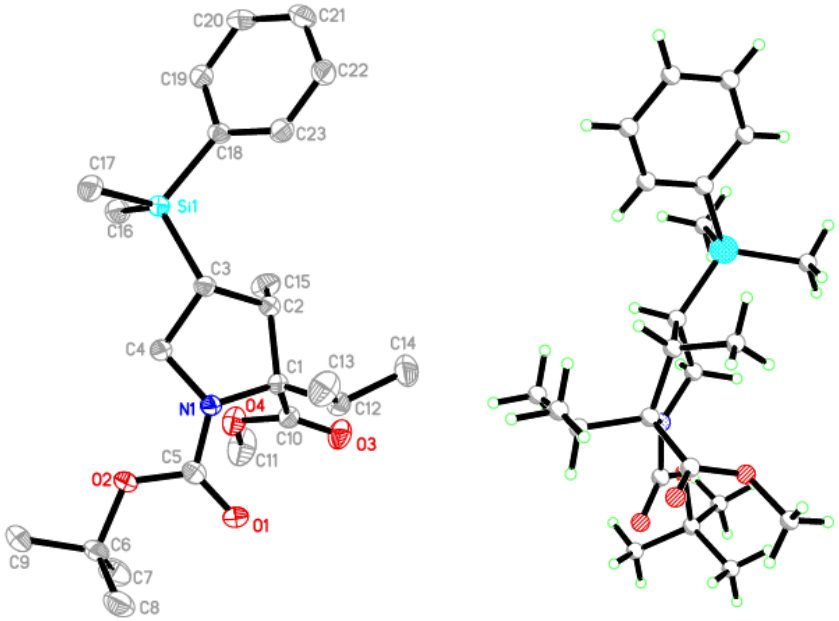
Figure 5.3

5.1.3 X-ray structure of 119

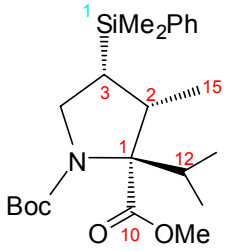
We were later able to obtain an X-ray crystal structure of the Boc-protected pyrrolidine **119** (**Figure 5.4**). The two structures **A** and **B** are the same crystal structure viewed from different angles. The calculated torsion angles (**Table 5.2**) show that the silyl, C_{15} and the methyl ester group are on the same face of the molecule, confirming our analysis of the nOe data.

Torsion angles (°)	
C_{10}-C_1-C_2-C_{15}	7.29 (19)
C_{12}-C_1-C_2-C_{15}	129.95 (15)
C_{15}-C_2-C_3-Si_1	- 34.50 (18)

Table 5.2: Selected torsion angles for crystal structure **119**



A **B**



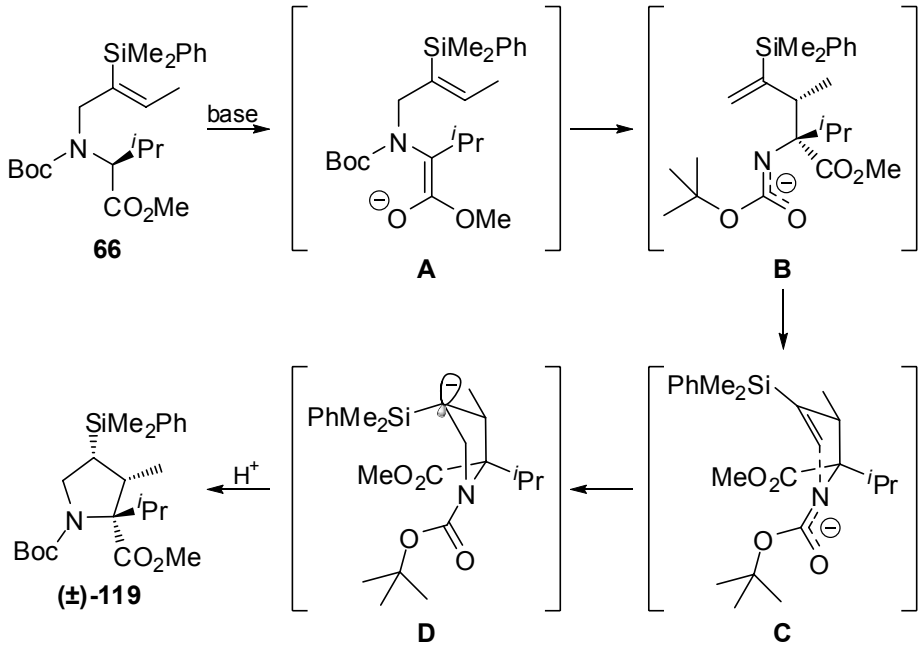
(±)-119

Figure 5.4

5.1.4 Mechanism of formation of 119

As previously discussed, there is evidence to suggest that the cyclisation occurs after rearrangement of **66**. We therefore propose a mechanism

whereby the negative charge associated with the carbamate upon rearrangement attacks the double bond (**Scheme 5.3**). This would occur *via* a transition state **C** similar in structure to that of the rearrangement. The silyl group would then adopt the least sterically hindered position. The high diastereoselectivity observed suggests that the 1,3 interaction between the silyl group and the *iso*propyl group is more important than the 1,2 interaction between the silyl group and the methyl substituent. This results in the formation of intermediate **D**, which, upon protonation, gives pyrrolidine **119**.

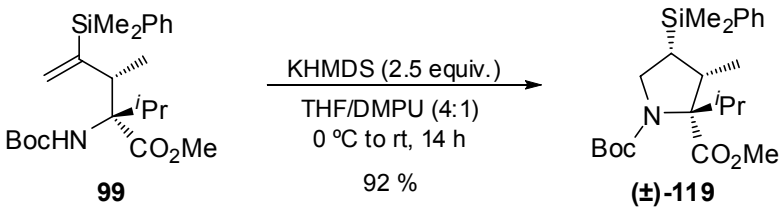


Scheme 5.3: Postulated mechanism for the formation of **119**

Regarding this proposed mechanism, it is conceivable that the transformation **C** to **D** is reversible; indeed, it is likely that **C** would be

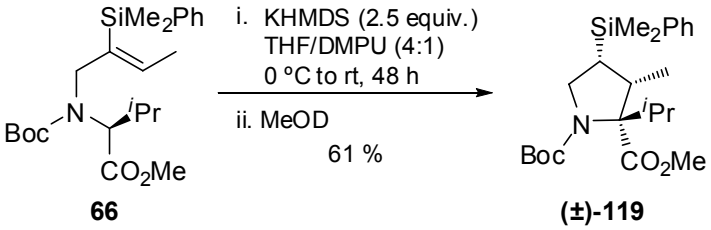
lower in energy than **D**. However, experimental evidence shows that a longer reaction time leads to a greater yield of the cyclised product **119**. It is therefore possible that the bis(trimethylsilyl)amine formed upon deprotonation of the precursor **66** provides the proton source. In an attempt to provide some support for our postulated mechanism, further experiments were performed.

Firstly, the rearrangement product **99** was resubjected to the reaction conditions (**Scheme 5.4**). Pyrrolidine **119** was isolated in 92 % yield. This would be expected if intermediate **B** is generated**,** which could then undergo cyclisation to form **D**, yielding **119** upon protonation.



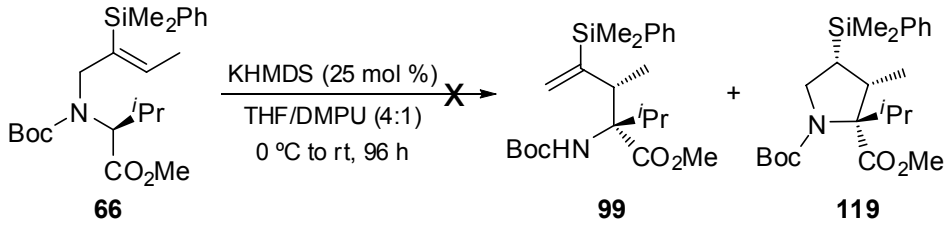
Scheme 5.4: Formation of **119** from **99**

To probe the process of protonation, the cyclisation of **66** was quenched after 48 h with MeOD (**Scheme 5.5**). This resulted only in the formation of pyrrolidine **119** in 61 % with no deuterium incorporation, implying that protonation had already occurred.



Scheme 5.5: Formation of **119** with deuterium quench

If the α-silyl anion is protonated by the bis(trimethylsilyl)amine, the cyclisation reaction could occur with sub-stoichiometric amounts of base. Precursor **66** was subjected to the rearrangement/cyclisation conditions using 25 mol % of KHMDS (**Scheme 5.6**). Unfortunately, no reaction occurred at all (90 % recovered starting material); it would appear that at least a stoichiometric amount of base is needed to complete rearrangement.



Scheme 5.6: Subjection of **66** to 25 mol % KHMDS

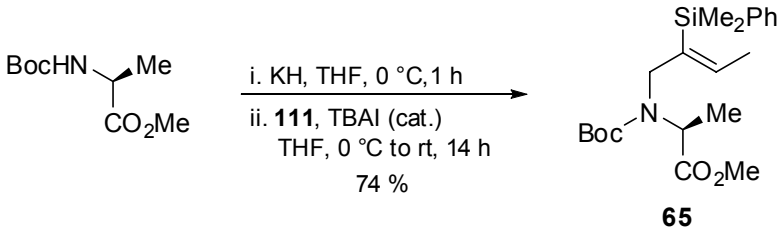
Although this latter experiment was inconclusive, the other reactions shown above (**Scheme 5.4** and **Scheme 5.5**) provide continuing support for the postulated mechanism. At this point, we were interested to see whether other amino acid-derived precursors would undergo this cyclisation and to establish the scope of the cyclisation pathway. We decided to investigate the

cyclisation of alanine-, phenylalanine- and glycine-derived precursors, a terminal alkene precursor and the amide precursor **63**. These will be discussed in turn in the following Sections.

5.2 Investigations into the cyclisation of 65

5.2.1 Synthesis of precursor 65

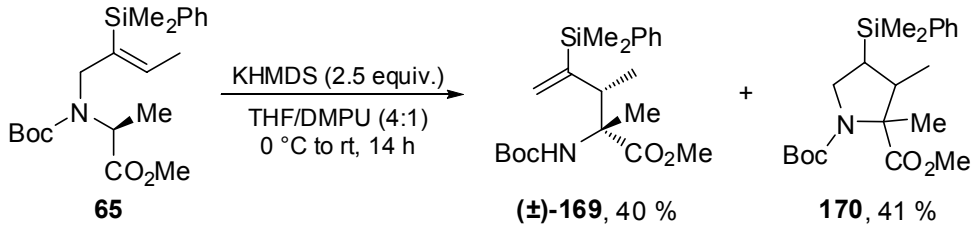
Precursor **65** was prepared in 74 % yield *via* an analogous route to that used in previous studies.[78] Boc-(*L*)-alanine methyl ester was deprotonated with KH and the resulting potassium salt was reacted with chloride **111** in the presence of catalytic TBAI (**Scheme 5.7**). As with the *iso*propyl analogue, this precursor was obtained in 74 % as a single isomer, with none of the (*E*)-isomer detected.



Scheme 5.7: Synthesis of precursor **65**

5.2.2 Cyclisation of 65

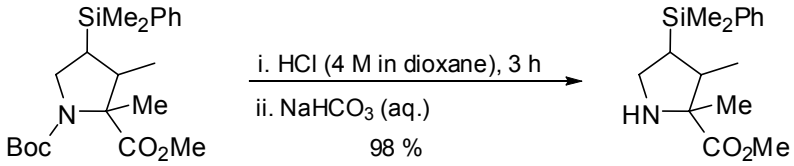
Previously, KH and 18-crown-6 had been used to initiate aza-[2,3]-Wittig rearrangement of **65** in 77 % yield and 7:1 *dr* in favour of the *syn* product (**Scheme 2.30**).[78] In an attempt to promote cyclisation, **65** was treated with KHMDS (2.5 equiv. of 0.5 M solution in toluene) in THF and DMPU (**Scheme 5.8**). The reaction was quenched after 14 h and two products were isolated: the rearrangement product **169** in 40 % yield and pyrrolidine **170** in 41 % yield. The reaction was monitored by tlc, which showed that the spot corresponding to the rearrangement product **169** appeared and then became smaller as the reaction progressed. The spot corresponding to the pyrrolidine **170** gradually increased, suggesting that the cyclisation occurs after rearrangement.



Scheme 5.8: Treatment of **65** with KHMDS

It was very interesting to note that the rearrangement product **169** was formed in a diminished *dr* of 3:1 in favour of the *syn* isomer (as shown in **Scheme 5.8**) as determined by comparison with literature data.[78] We were unable to ascertain the *dr* of the cyclisation product as the NMR data for

pyrrolidine **170** was ambiguous. Multiple peaks shown for certain signals indicated the presence of either diastereomers or rotamers as previously observed for the valine analogue. To determine whether rotamers were the cause of the duplicate signals, VT NMR experiments were carried out. Although some of the signals did merge upon heating to 80 °C in DMSO, the broadening of other signals meant that an accurate measurement of the *dr* was not possible. It was therefore decided to completely eliminate the possibility of rotamers by removing the Boc group under acidic conditions to furnish **171** in 98 % yield after a basic work-up, with no further purification necessary (**Scheme 5.9**). Pleasingly, the ^{1}H NMR of **171** showed that only one diastereomer was present. Measurement of the $[\alpha]_D$ of **171** indicated no chirality transfer had occurred.



170 **171**

Scheme 5.9: Removal of Boc group of **170**

As pyrrolidine **171** was formed as a single diastereomer and the *dr* of rearrangement product **169** was only 3:1, it seemed that only the major diastereomer formed upon rearrangement underwent cyclisation to yield **170**. A possible reason for the failure of the minor rearrangement product to undergo cyclisation could be the steric repulsion experienced between the α-

methyl group and both the silyl group and the vicinal methyl in the transition state **B** (**Figure 5.5**). In contrast, the major isomer can access transition state **A** which experiences less steric interactions than **B**.

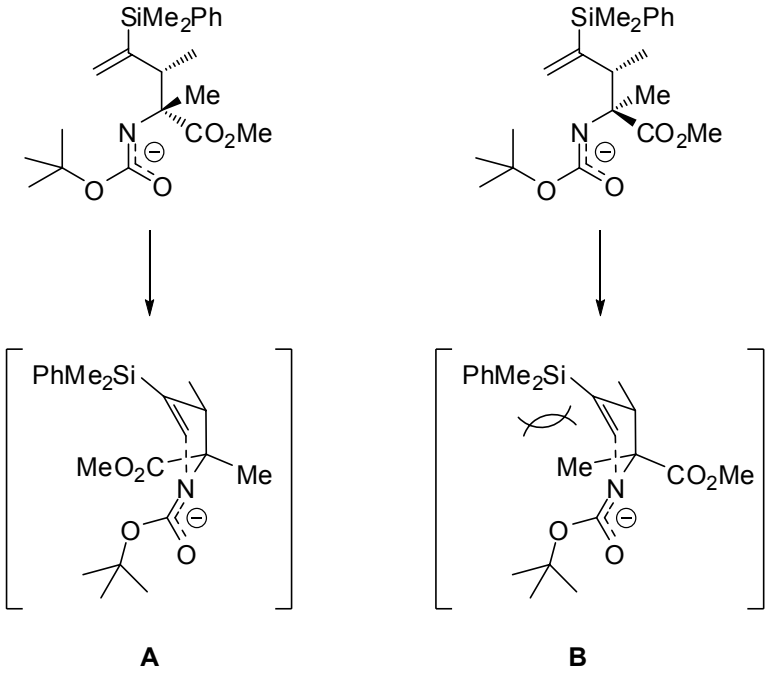


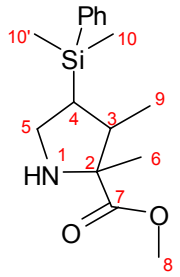
Figure 5.5: Transition states for cyclisation of **65**

For valine methyl ester precursor **66**, it was shown that longer reaction times led to a higher yield of the cyclisation product **119**. It was postulated that allowing a longer reaction time for the alanine analogue would result in a higher yield of **170** as well as a further decline in the *dr* of rearrangement product **169** with respect to the *syn* isomer. Therefore, the reaction was repeated, allowing to stir for 48 h. The yields of **169** and **170** were 11 % and 68 % respectively. Analysis of the ^{1}H NMR of **169** showed that the *dr* was

now 9.6:1 in favour of the *anti* product, confirming our speculation that only the major isomer formed upon rearrangement underwent cyclisation. Again, the Boc group was removed from **170** to yield **171** in 97 % yield as a single diastereomer. The next step was to determine the sense of diastereoselectivity of the cyclisation.

5.2.3 Determination of relative stereochemistry of 171

Attempts were made to recrystallise **170** and **171** from a number of solvents, and samples were cooled in an effort to induce crystallisation, all to no avail. As suitable crystals could not be obtained for X-ray studies, nOe experiments were carried out on **171**. The following numbering scheme was used (**Figure 5.6**).



171

Figure 5.6

Again, it was necessary to ensure that the ^{1}H NMR data had been correctly interpreted. This was accomplished with the aid of COSY experiments. The signal at δ 0.99 (3H, d, J = 7.3 Hz) is coupled to a signal at δ 2.81 (1H, app. quintet, J = 7.0 Hz) as shown in the COSY spectrum. These signals are therefore assigned as Me_9 and H_3 respectively. The signal at δ 2.81 is also coupled to a single proton resonance at δ 1.80 (1H, ddd, J = 11.2, 9.4, 6.4 Hz), which is assigned as H_4. A correlation in the COSY spectrum between the signals at δ 3.18 (1H, app. t, J = 10.5 Hz) and 3.28 (1H, app. t, J = 9.6 Hz) and the signal corresponding to H_4 suggests that the former signals relate to H_5 and $H_{5'}$. Taking into account the electronic effects of the substituents, the signals at δ 3.39 (3H, s) and δ 1.37 (3H, s) are assigned as Me_8 and Me_6 respectively. The peaks in the ^{1}H NMR spectrum at δ 0.35 (3H, s), δ 0.42 (3H, s) and δ 7.29 - 7.52 (5H, m) are assigned as Me_{10}, $Me_{10'}$ and the Ph group respectively.

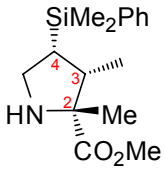
Irradiated	Enhanced (%)
H_3	H_4 (2.2)
H_4	H_3 (1.9), $H_{5'}$ (1.7)
Me_9	H_3 (1.5), H_5 (0.6), $H_{5'}$ (0.4)

Table 5.3: nOe data for **171**

We were able to obtain nOe data from selective irradiation of H_3, H_4 and Me_9 (**Table 5.3**). Irradiation of the signal at δ 2.81, assigned as H_3, induced an enhancement of 2.2 % at δ 1.80 (H_4). An enhancements of 1.9 % was

shown at δ 2.81 (H_3) upon irradiation of the signal at δ 1.80 (H_4). Irradiation of the signal at δ 0.99 (Me_9) generated enhancements of 1.5 % at δ 2.81 (H_3).

These results suggest that H_3 is on the same face of the pyrrolidine ring as H_4. If only the major isomer of the rearrangement product underwent cyclisation, the relative stereochemistry at C_2 and C_3 would already be established as 2*R**,3*R**. Taking into account the results of the nOe experiments of **171** and the precedence set by the valine analogue, we propose that the relative stereochemistry of **171** is 2*R**,3*R**,4*R** (**Figure 5.7**).



(±)-171

Figure 5.7

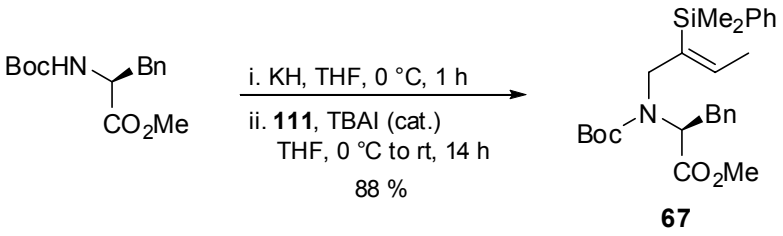
5.3 Investigations into the cyclisation of 67

It was also chosen to subject phenylalanine methyl ester derivative **67** to the cyclisation conditions as this precursor had previously undergone aza-[2,3]-

Wittig rearrangement upon treatment with KH and 18-crown-6 in a surprising *dr* of 1:1.[78]

5.3.1 Synthesis of precursor 67

The precursor was synthesised in a similar manner to **65**, by deprotonating Boc-(*L*)-phenylalanine methyl ester with KH and then reacting the resulting anion with chloride **111** in the presence of catalytic TBAI (**Scheme 5.10**). The desired precursor was formed in 88 % yield, as a single isomer.

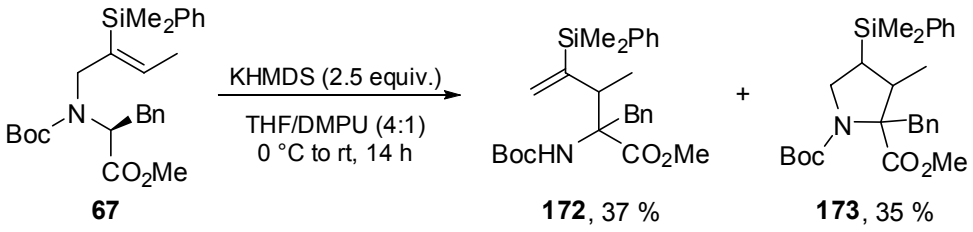


Scheme 5.10: Synthesis of precursor **67**

5.3.2 Cyclisation of 67

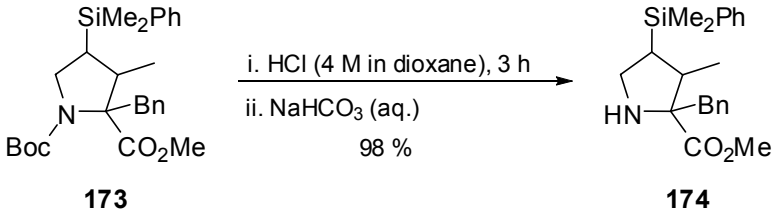
Subjection of **67** to the cyclisation conditions resulted in the formation of rearrangement product **172** in 37 % yield and pyrrolidine **173** in 35 % yield after 14 h (**Scheme 5.11**). It was highly interesting to discover that **172** was formed as a single diastereomer, suggesting that only one of the

diastereomers formed upon rearrangement underwent cyclisation, as observed for the alanine derivative. From following the reaction by tlc, it was observed that two spots formed, presumably corresponding to the two diastereomers of the rearrangement product. During the course of the reaction, one of these spots disappeared and the spot relating to the pyrrolidine **173** appeared.



Scheme 5.11: Treatment of **67** with KHMDS

Again, interpretation of the ^{1}H NMR data of **173** was ambiguous for determination of the *dr* of cyclisation. As with the previous pyrrolidines, multiple peaks were observed for some signals. In an attempt to rule out different diastereomers as the cause, VT NMR experiments were carried out with no conclusive results. Therefore the Boc group was removed to give pyrrolidine **174** in 98 % yield, with no need for further purification (**Scheme 5.12**). Gratifyingly, the ^{1}H NMR showed only one diastereomer was present.

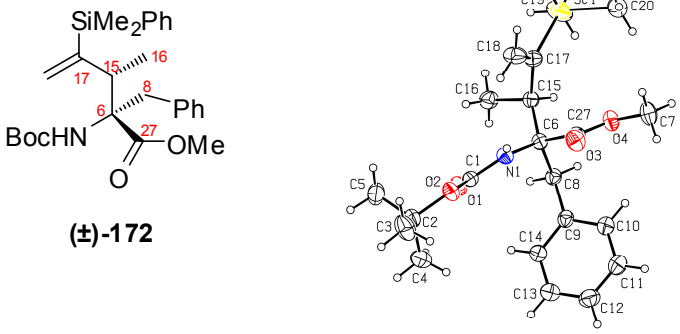


173 **174**

Scheme 5.12: Removal of Boc group of **173**

Measurement of the $[\alpha]_D$ of **174** showed that the product was racemic. In order to contemplate the reasons behind the observed diastereoselectivities, it was necessary to determine the relative stereochemistry of both **172** and **173**.

5.3.3 Determination of relative stereochemistry of 172



(±)-172

Figure 5.8: Crystal structure of **172**

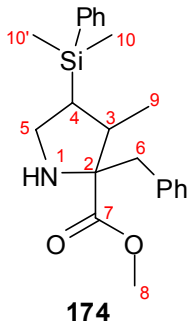
After a few days of standing in the freezer, rearrangement product **172** crystallised and X-ray data was obtained (**Figure 5.8**). The calculated torsion angles show that the benzyl group is *syn* to Me_{16} (**Table 5.4**).

Torsion angles (°)	
N_1-C_6-C_{15}-C_{16}	- 51.5(2)
C_{27}-C_6-C_{15}-C_{16}	- 167.01(18)
C_8-C_6-C_{15}-C_{16}	75.2(2)
N_1-C_6-C_{15}-C_{17}	75.0(2)
C_{27}-C_6-C_{15}-C_{17}	- 40.4(2)
C_8-C_6-C_{15}-C_{17}	- 158.18(18)

Table 5.4: Selected torsion angles for **172**

5.3.4 Determination of relative stereochemistry of 174

Unfortunately, pyrrolidines **173** and **174** did not crystallise and so nOe experiments were carried out on **174**. The following numbering scheme was used (**Figure 5.9**).



174

Figure 5.9

The ^{1}H NMR data for **174** was interpreted with the aid of COSY and ^{13}C-^{1}H correlation experiments. The signals at δ 1.16 (3H, d, *J* = 7.2 Hz) and δ 1.55 (1H, ddd, *J* = 11.2, 9.9, 6.2 Hz) are both coupled to a signal at δ 2.77 (1H, app. quintet, *J* = 6.7 Hz) as shown by the COSY spectrum. These three signals are therefore assigned as Me_9, H_4 and H_3 respectively. A correlation in the COSY spectrum between the signals at δ 3.20 (1H, dd, *J* = 11.2, 10.2 Hz) and δ 3.27 (1H, app. t, *J* = 9.8 Hz) and the signal corresponding to H_4 suggests that the former signals relates to H_5 and $H_{5'}$. Taking into account the multiplicity and electronic effects of the substituents, the signals at δ 3.12 (1H, d, *J* = 12.8 Hz), δ 2.84 (1H, d, *J* = 12.8 Hz) and δ 3.63 (3H, s) are assigned as H_6, $H_{6'}$ and Me_8 respectively. The peaks in the ^{1}H NMR spectrum at δ 0.38 (3H, s), δ 0.44 (3H, s) and δ 7.19 - 7.57 (10H, m) are assigned to Me_{10}, $Me_{10'}$ and the Ph groups respectively.

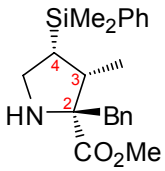
Irradiated	Enhanced (%)
H_3	H_4 (5.5), H_6 (1.2)
H_4	H_3 (3.9), $H_{5'}$ (3.7)
Me_9	H_3 (2.7), $H_{6'}$ (2.4), H_6 (0.6), H_5 (0.6)

Table 5.5: nOe data for **174**

Once the ^{1}H NMR had been successfully analysed, we were able to obtain nOe data from selective irradiation of H_3, H_4, Me_9 (**Table 5.5**). Irradiation of the signal at δ 2.77, assigned as H_3, induced an enhancement of 5.5 % at δ 1.55 (H_4) and 1.2 % at δ 3.12 (H_6). An enhancement of 3.9 % was shown at

δ 2.77 (H_3) upon irradiation of the signal at δ 1.55 (H_4). Irradiation of the signal at δ 1.16 (Me_9) generated enhancements of 2.7 % and 2.4 % at δ 2.77 (H_3) and δ 2.84 ($H_{6'}$) respectively. An enhancement of 0.6 % at δ 3.12 (H_6) was also seen.

As with the valine and alanine analogues, the nOe data for **174** suggests that H_3 and H_4 are on the same face of the pyrrolidine ring. Less clear from this data is the relationship between the benzyl group and the vicinal Me_9, as enhancements were seen at the benzylic position upon irradiation of both H_3 and Me_9. However, the X-ray data for **172** shows that the relative stereochemistry at these positions is 2*S**,3*R** and, therefore, it is the *syn* rearrangement product that must have undergone cyclisation. This outcome would be in agreement with the previous cyclisations of the alanine and valine methyl esters. Taking all of the data into account, we propose that the relative stereochemistry of pyrrolidine **174** is 2*R**,3*R**,4*R** (**Figure 5.10**).

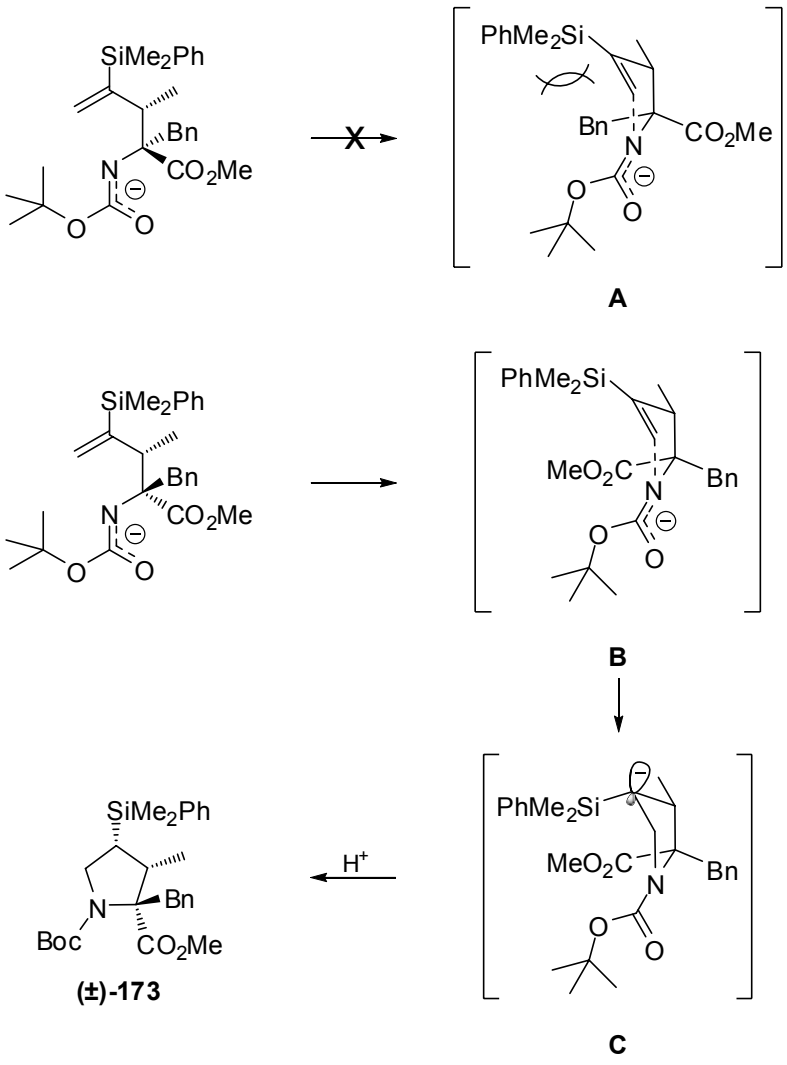


(±)-174

Figure 5.10

This result is in accord with the steric argument put forward for the previous cyclisations. The benzyl group is larger than the methyl ester (*A* values of

1.68 and 1.27 kcal mol^{-1} respectively) and, therefore, transition state **A** experiences a prohibitive steric interaction between the benzyl group and the silyl group. Cyclisation occurs only through transition state **B**, in which both $A^{1,3}$ and $A^{1,2}$ strain are minimised (**Scheme 5.13**). The silyl group then adopts the least sterically hindered position (transition state **C**), with respect to the benzyl group, resulting in the observed relative stereochemistry.



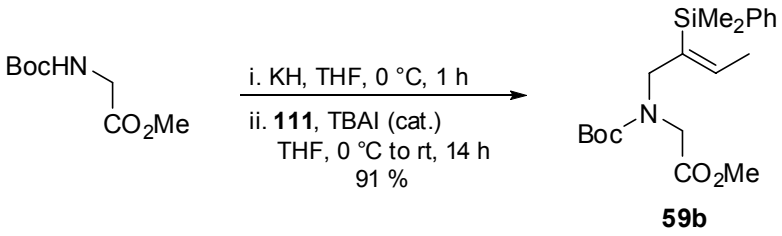
Scheme 5.13: Suggested mechanism of formation of **173**

5.4 Investigations into the cyclisation of 59b

We were interested to determine the importance of the α-substituent on the cyclisation process and, hence, precursor **59b** was synthesised. This glycine derivative had previously undergone aza-[2,3]-Wittig rearrangement upon treatment with LDA in THF/HMPA at - 78 °C to - 40 °C.[75]

5.4.1 Synthesis of precursor 59b

The precursor was synthesised in 91 % yield by treatment of Boc-glycine methyl ester with KH, followed by chloride **111** with catalytic TBAI (**Scheme 5.14**).

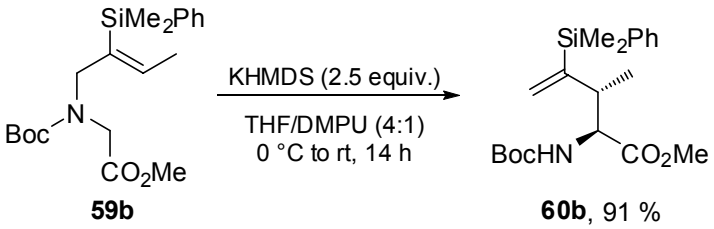


Scheme 5.14: Synthesis of precursor **59b**

5.4.2 Attempted cyclisation of 59b

Upon treatment with KHMDS in THF/DMPU, precursor **59b** underwent aza-[2,3]-Wittig rearrangement to yield **60b** in 91 % yield and *dr* > 20:1

(**Scheme 5.15**). No cyclisation product was observed, suggesting that the presence of a quaternary centre is necessary in order for cyclisation to occur. This is in accordance with the Thorpe-Ingold effect which is the accelerated rate of cyclisation observed for a compound bearing a *gem*-dialkyl moiety.



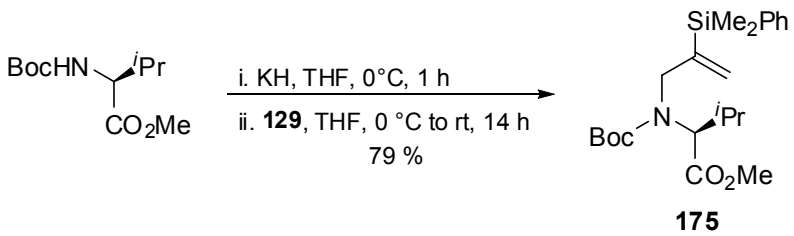
59b **60b**, 91 %

Scheme 5.15: Treatment of **59b** with KHMDS

5.5 Investigations into the cyclisation of 175

5.5.1 Synthesis of precursor 175

To assess the importance of the alkene substituent, precursor **175** was synthesised. Deprotonation of Boc-(*L*)-valine methyl ester with KH, followed by treatment with bromide **129** resulted in the formation of the desired precursor in 79 % yield (**Scheme 5.16**).

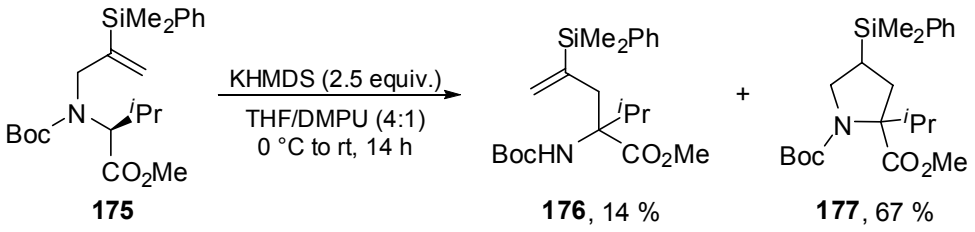


175

Scheme 5.16: Formation of precursor **175**

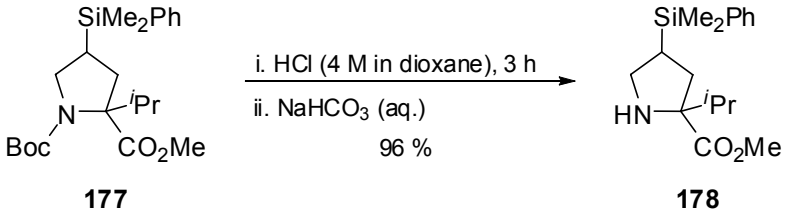
5.5.2 Cyclisation of 175

Upon treatment with KHMDS in THF/DMPU, **175** reacted to give rearrangement product **176** in 14 % yield and pyrrolidine **177** in 67 % yield (**Scheme 5.17**). Rearrangement product **176** was found to be racemic by measurement of $[\alpha]_D$. The yields of **176** and **177** in this reaction are comparable to those observed upon subjecting precursor **66** to these conditions (**Scheme 4.11**). Therefore, it appears that the methyl substituent on the alkene is not important in the cyclisation pathway.



Scheme 5.17: Treatment of **175** with KHMDS

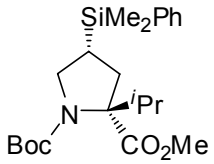
As with all the pyrrolidine analogues thus far, it was necessary to remove the Boc group in order to determine the *dr* of the cyclisation product. Treatment of **177** with HCl (4 M in dioxane), followed by a basic work-up furnished pyrrolidine **178** in 96 % yield as a single isomer with no need for further purification (**Scheme 5.18**). Analysis of ^{1}H NMR showed that only one diastereomer was present. Measurement of the $[\alpha]_D$ suggested the product was racemic.



177 **178**

Scheme 5.18: Boc deprotection of **177**

Disappointingly, pyrrolidines **177** and **178** did not crystallise and nOe studies were not possible on either due to overlapping signals in the ^{1}H NMR. Therefore, it has not been possible to determine the relative stereochemistry of **177**. We tentatively suggest that, following the pattern of the previous cyclisations, the larger *iso*propyl group is on the opposite face of the ring to the silyl moiety (**Figure 5.11**).



(±)-177

Figure 5.11

5.6 Investigations into the cyclisation of 63

As discussed in **Section 4.4.2**, amide precursor **63** underwent cyclisation upon treatment with KH and 18-crown-6 in THF in 1 h to yield pyrrolidine **158** in 75 % yield as the only isolated product (**Scheme 4.38**). This result was

interesting as the reaction was carried out following the experimental procedure used previously in the group, which resulted in the formation of rearrangement product **98** in 77 % yield. In an attempt to explain this discrepancy in results, the reaction was repeated with slight variations - using a new supply of KH; using the precursor without drying by azeotrope from toluene; leaving the reaction to stir for 14 h - to no avail; pyrrolidine **158** was the only product obtained in yields ranging from 60 to 74 %. Although it was unsatisfying that this cyclisation had to be attributed to a subtle difference that we could not identify, we were nevertheless intrigued by the result and wanted to further investigate.

5.6.1 Mechanism of cyclisation of 63

By monitoring the cyclisation of **63** by tlc, it became apparent that there was a significant difference between the cyclisation of this amide precursor and that of the methyl ester analogues. Upon addition of the precursor and 18-crown-6 to a stirred suspension of KH in THF, the spot corresponding to the precursor disappeared within 1 h and only one spot appeared, that corresponding to the pyrrolidine **158**. An intermediate spot corresponding to the rearrangement product **98** was not seen. It is therefore surmised that pyrrolidine **158** could be formed from an incomplete rearrangement pathway. It is also possible that the rearrangement product is formed but the increased steric requirements of an amide (compared to an ester) increase

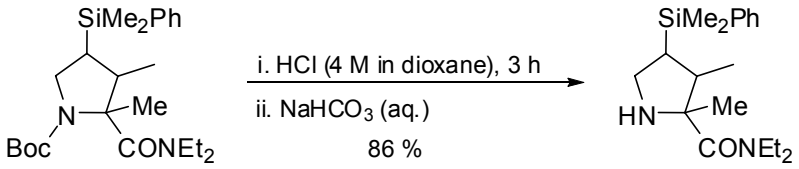
the Thorpe-Ingold effect. This would increase the rate of cyclisation, possibly to such an extent that cyclisation occurred instantly upon rearrangement.

In an attempt to shed some light on the mechanism of formation of pyrrolidine **158**, the reaction was repeated and quenched with MeOD. Upon work-up and column chromatography, the ^{1}H NMR showed that there was no deuterium incorporation, indicating that protonation had already occurred before the reaction was quenched. As KH was the base used in this case, the proton source was not immediately obvious. It was possible that the intermediate α-silyl anion could be protonated by the solvent; the reaction was therefore repeated in d_8-THF. Again, the ^{1}H NMR of the purified pyrrolidine showed that there was no deuterium present.

5.6.2 Determination of relative stereochemistry of 158

Attempts to recrystallise **158** from a variety of solvents were unsuccessful. Therefore, the relative stereochemistry of **158** had to be determined by a number of nOe experiments. As seen with the methyl ester analogues, the NMR data of Boc-protected **158** showed a number of peaks, which could be accounted for either by the presence of diastereomers, rotamers or impurities. It was therefore necessary to remove the Boc group in order to simplify the NMR data. This was done using HCl (4 M in dioxane),

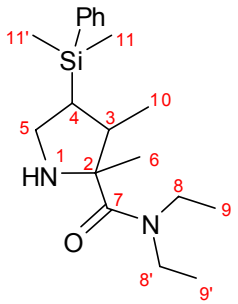
followed by a basic work-up (**Scheme 5.19**). The ^{1}H NMR of the resulting pyrrolidine **179** showed that one diastereomer was present as the major compound. However, the spectrum still showed some impurities; therefore, the material was run through a column of SCX powder (eluting with 2 % methanolic ammonia) to give pure **179** as a single diastereoisomer in 86 % yield.



158 **179**

Scheme 5.19: Boc deprotection of **158**

In order to determine the relative stereochemistry of **179**, a number of nOe experiments were carried out. It was necessary to ensure that the NMR was correctly interpreted and the following numbering scheme was used (**Figure 5.12**).



179

Figure 5.12

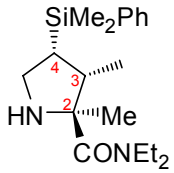
The signals at δ 0.93 (3H, d, J = 7.2 Hz) and δ 1.46 (1H, ddd, J = 11.8, 9.0, 5.9 Hz) are both coupled to a signal at δ 2.53 (1H, app. quintet, J = 6.6 Hz) as shown by the COSY spectrum. These three signals are therefore assigned as Me_{10}, H_4 and H_3 respectively. The resonances at δ 2.99 (1H, app. t, J = 11.1 Hz) and δ 3.13 (1H, app. t, J = 9.6 Hz) both show a correlation in the COSY spectrum with the signal corresponding to H_4, suggesting that the former relate to H_5 and $H_{5'}$. The signal at δ 3.25 - 3.50 (4H, br m) is coupled to a resonance at δ 1.11 (6H, t, J = 7.0 Hz); these are assigned as H_8 and Me_9 respectively. Taking into account the electronic effects of the substituents, the peaks in the ^{1}H NMR spectrum at δ 0.27 (3H, s), δ 0.35 (3H, s), δ 1.27 (3H, s) and δ 7.33 - 7.49 (5H, m) are assigned as Me_{11}, $Me_{11'}$, Me_6 and the Ph group respectively.

Irradiated	Enhanced (%)
H_3	H_4 (6.7), Me_9 (1.2), Me_{10} (2.7), $Me_{11'}$ (1.1)
H_4	H_3 (7.0), Ph (3.1)
Me_{10}	Me_{11} (0.9), $Me_{11'}$ (0.9), H_3 (0.6), H_5 (- 0.8), $H_{5'}$ (- 1.3), Me_6 (1.8)

Table 5.6: nOe data for **179**

With the NMR correctly interpreted, it was possible to obtain nOe data from selective irradiation of H_3, H_4 and Me_{10} (**Table 5.6**). Irradiation of the signal at δ 2.53, assigned as H_3, induced an enhancement of 6.7 % at δ 1.46 (H_4). This implies that H_4 is on the same face of the pyrrolidine ring as H_3. This was supported by an enhancement of 7.0 % shown at δ 2.53 (H_3) upon

irradiation of the signal at δ 1.46 (H_4). Unfortunately, the other nOe enhancements are relatively small and, therefore, somewhat inconclusive. An enhancement of 1.2 % at δ 1.11 (Me_9) was observed upon irradiation at δ 2.53 (H_3), suggesting H_3 is on the same face of the ring as the diethylamide group. This is also supported by the enhancement of 1.8 % at δ 1.27 (Me_6) upon irradiation at δ 0.93 (Me_{10}). Previous studies had determined that only the 2*S**,3*R**-diastereomer of **98** was formed upon rearrangement of **63**, and it therefore seemed probable that this relative stereochemistry was also exhibited in pyrrolidine **179**. Taking all of the data into account, we propose that the relative stereochemistry of pyrrolidine **179** is 2*S**,3*R**,4*R** (**Figure 5.13**).



(±)-179

Figure 5.13

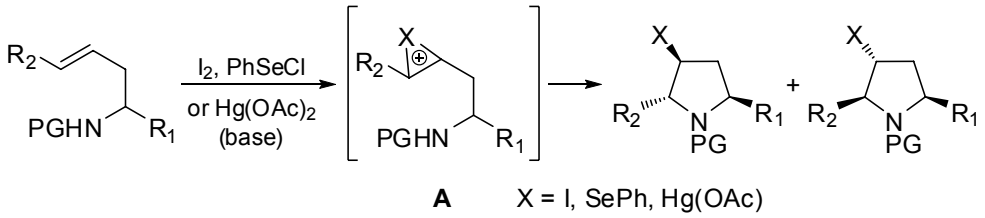
This stereochemistry may provide further evidence that the mechanism of this cyclisation is one of incomplete rearrangement. As discussed in **Section 5.2.2**, the minor rearrangement product of alanine methyl ester **65** does not cyclise, presumably due to a combination of the $A^{1,3}$ strain between the silyl group and Me_6 and the steric interaction between the vicinal methyl groups Me_6 and Me_9 (**Figure 5.5**). As the methyl group is smaller than the

diethylamide group, in order for **63** to cyclise after rearrangement, the molecule would have to adopt a transition state which would experience these same steric interactions. It is therefore possible that the pyrrolidine is formed by an incomplete aza-[2,3]-Wittig rearrangement pathway. Alternatively, the increased sterics of the amide group overrides the $A^{1,3}$ strain to give rapid cyclisation after rearrangement.

5.7 Significance of cyclisation

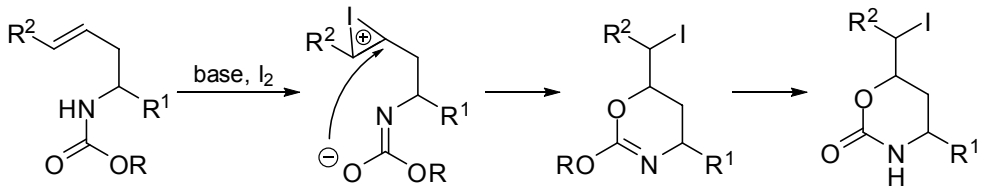
Assuming that the mechanism of cyclisation of the methyl ester precursors discussed in the preceding Sections is correct, the cyclisation of precursors **66**, **65**, **67** and **175** constitutes a 5-*endo-trig* process, a geometrically disfavoured ring closure according to Baldwin's rules.[105] However, there have been numerous accounts of the employment of 5-*endo-trig* cyclisations in the synthesis of five-membered rings, suggesting that the process may be more useful than previously considered. Of particular interest to our work is the formation of nitrogen heterocycles *via* a 5-*endo-trig* cyclisation. This transformation allows for the convenient preparation of the prolific pyrrolidine motif and can be divided into three classes: radical-initiated[106] electrophile-driven and nucleophile-driven. Electrophile-driven 5-*endo-trig* cyclisation involves the addition of an electrophile to a homoallylic amine, which forms a cationic species **A** (**Scheme 5.20**). This encourages attack

from the nearby nitrogen and may occur in the absence of base. Electrophiles that have been shown to promote 5-*endo-trig* cyclisation include iodine,[107] phenylselenyl chloride[108] and mercury (II) acetate.[109] Careful selection of the conditions allows for the preparation of either *cis* or *trans* pyrrolidines in high selectivity; for example, Knight *et al.* showed that under protic conditions, iodocyclisations occurred with complete 2,5-*cis* selectivity, whereas addition of K_2CO_3 resulted in formation of the 2,5-*trans* isomer only.[107]



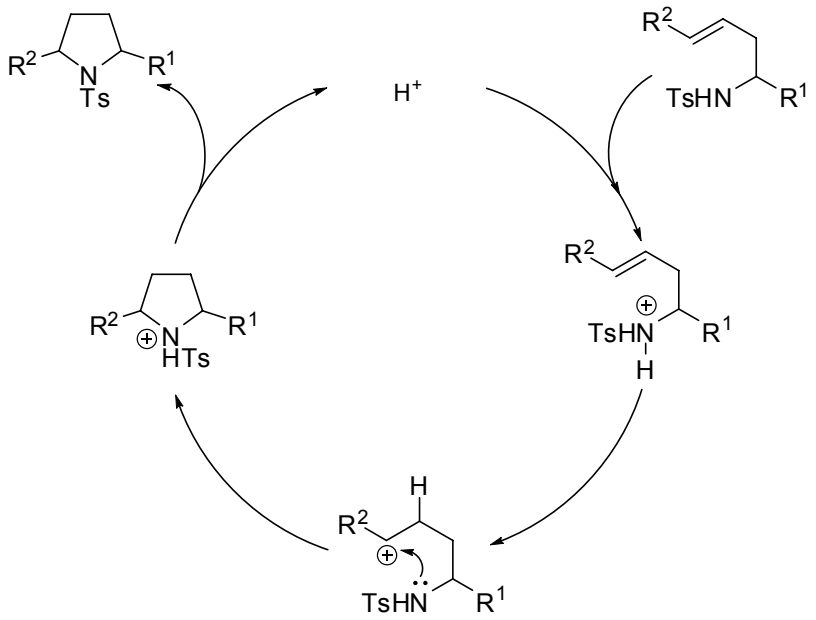
Scheme 5.20: Pyrrolidine synthesis *via* electrophile-driven 5-*endo-trig* cyclisation

The protecting group of choice in these cyclisations was the tosyl group; interestingly, a carbamate protecting group has been shown to encourage the cyclisation to occur *via* a 6-*exo-trig* pathway, involving the carbamate oxygen (**Scheme 5.21**).[107]



Scheme 5.21: 6-*Exo-trig* cyclisation of an *N*-carbamate homoallylic amine

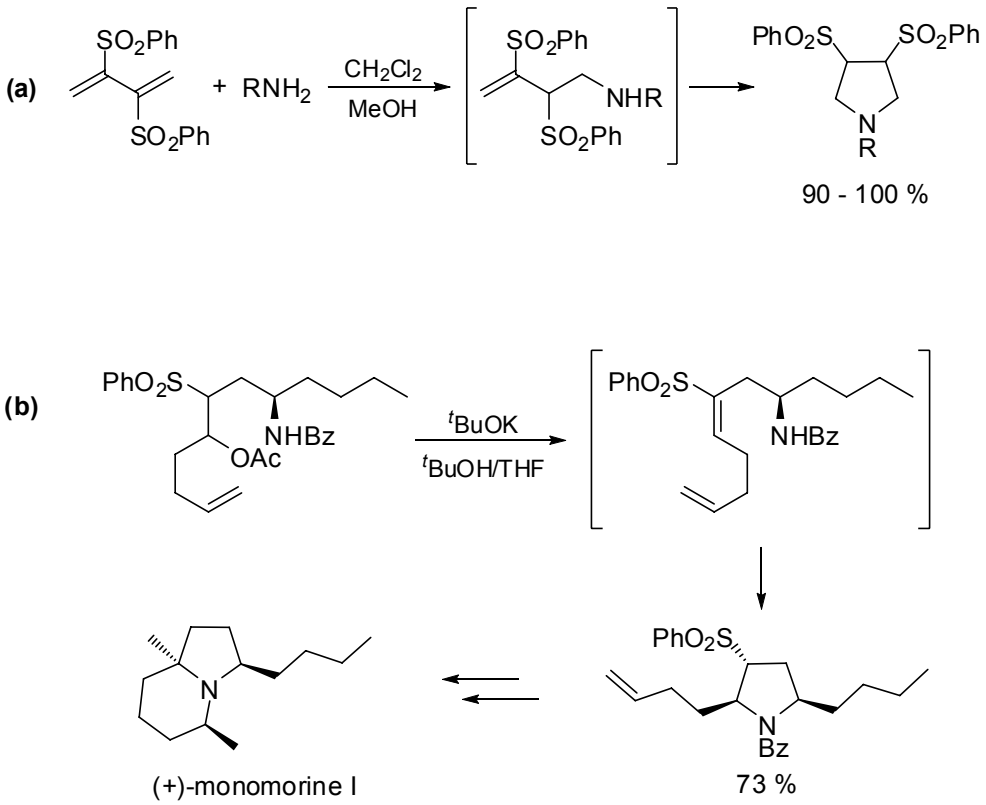
The 5-*endo-trig* cyclisation can also be promoted by catalytic Brønsted acid (**Scheme 5.22**).[110] The authors propose that the tosylamide is protonated at either oxygen or nitrogen. A proton is then transferred intramolecularly to the double bond. Trapping of the cation by the sulfonamide and transfer of the proton from the product to another reactant completes the catalytic cycle.



Scheme 5.22: Proposed catalytic cycle for Brønsted acid-catalysed 5-*endo-trig* cyclisation of homoallylic amines

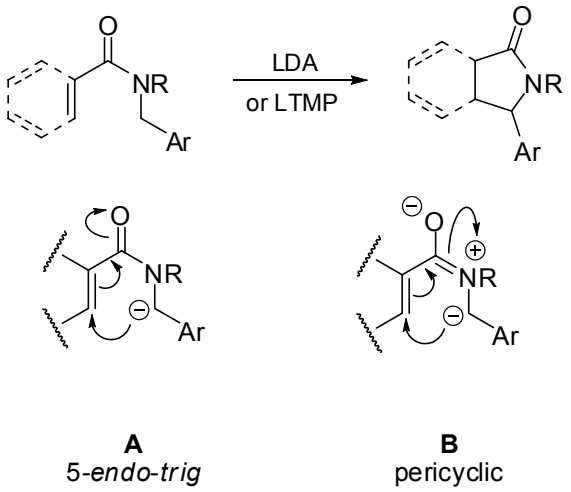
The nucleophile-driven, anionic 5-*endo-trig* cyclisation of homoallylic amines is less common than its cationic counterpart and usually necessitates the presence of an electron-withdrawing group or a conjugated group in the central vinylic position. For example, Padwa *et al*. have shown that 5-*endo-trig* cyclisation of vinylsulfones occurs in high yields [**Scheme 5.23, (a)**].[111]

Craig *et al*. have also made use of the 5-*endo-trig* cyclisation of vinylsulfones in their total synthesis of (+)-monomorine I [**Scheme 5.23, (b)**].[112]



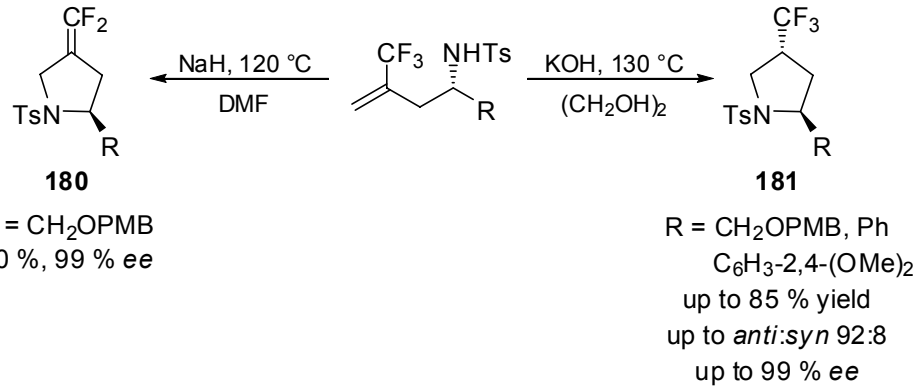
Scheme 5.23: 5-*Endo-trig* cyclisation of vinylsulfones

Clayden *et al.* have reported the cyclisation of tertiary amides upon treatment with base (**Scheme 5.24**);[113] however, it is unclear whether the reaction occurs *via* a 5-*endo-trig* cyclisation (**A**) or a six-electron disrotatory ring closure (**B**).



Scheme 5.24: Cyclisation of tertiary amides

Pyrrolidine formation *via* nucleophilic 5-*endo-trig* cyclisation has also been realised with the use of a trifluoromethyl group (**Scheme 5.25**).[114] Altering the conditions allowed either the S_N2'-type product **180** or the addition product **181** to be isolated. The cyclisation was attributed to the highly electrophilic nature of the double bond and the stabilised α-CF_3 carbanion intermediate, both of which are caused by the strong electron-withdrawing ability of the CF_3 group. Further work by this group showed that the trifluoromethyl group could be substituted for other electron-withdrawing groups such as an ester or nitrile [115]



Scheme 5.25: 5-*Endo-trig* cyclisation of 2-trifluoromethyl-1-alkenes

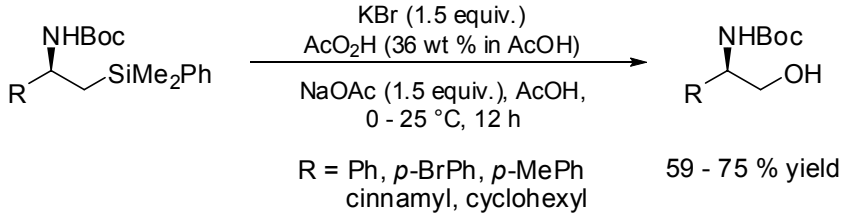
This latter example using the trifluoromethyl group particularly interested us as it demonstrates the nucleophilic 5-*endo-trig* cyclisation of an amine onto a non-conjugated alkene. Although the dimethylphenylsilyl group is not electron-withdrawing, its ability to stabilise α-negative charge must be the factor that allows the cyclisation of precursors **66**, **65**, **67** and **175** to proceed and, therefore, these cyclisations can also be described as a nucleophilic 5-*endo-trig* cyclisation of an amine onto a non-conjugated alkene. To the best of our knowledge, these cyclisations represent the first example of this type of reaction involving a carbamate nitrogen protecting group. We also believe that this is the first example of any type of 5-*endo-trig* cyclisation onto a vinylsilane.

We were also interested in demonstrating the value of our cyclisation by further manipulation of the pyrrolidines. These were carried out on the valine-derivative **119** and are discussed in the following Sections.

5.7.1 Fleming oxidation of 119

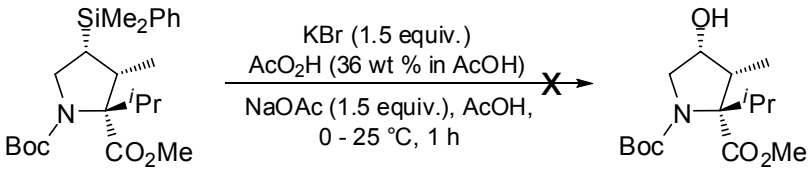
Oxidation of the dimethylphenylsilyl group to a hydroxyl group is a well-documented transformation. The original work published by Fleming showed that it was possible to displace the phenyl group on silicon using HBF_4 and oxidise the intermediate with peroxide. Upon work-up, this yielded the corresponding alcohol with retention of stereochemistry.[116a] In a following publication, it was shown that this two-step procedure could be accomplished in one pot, by using Hg^{2+} or Br^{+}.[116b] Since these initial results, a myriad of reviews and examples have been reported for this transformation, which often constitutes a key step in retrosynthetic pathways, as a chemically reactive hydroxyl group can be masked as a relatively inert silyl group.

Several procedures have been established for this oxidation of the dimethylphenylsilyl group. A common method is the use of KBr and peracetic acid with NaOAc, as shown by Kim *et al.* for the formation of Boc-protected amino alcohols (**Scheme 5.26**).[117]



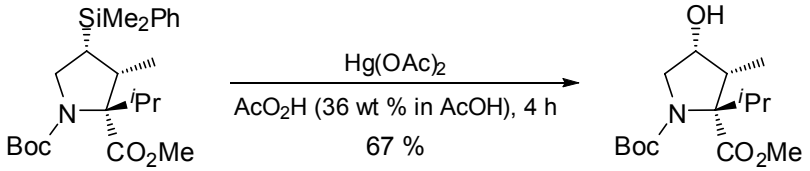
Scheme 5.26: Fleming oxidation of Boc-protected amines

Following this procedure, Boc-protected pyrrolidine **119** was treated with KBr, NaOAc and peracetic acid in acetic acid (**Scheme 5.27**). After stirring for 1 h at rt, all of the precursor had been consumed and tlc analysis showed that several products had formed. Upon work-up and attempted purification by column chromatography, it was not possible to characterise these degradation products and none of the desired alcohol **182** was isolated.



Scheme 5.27: Attempted Fleming oxidation of **119**

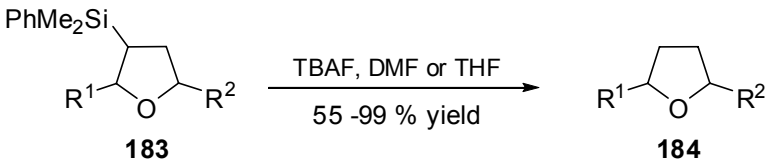
Another common procedure for the Fleming oxidation of the dimethylphenylsilyl group involves the use of bromine and peracetic acid.[118] Once again, when pyrrolidine **119** was subjected to these reaction conditions, only degradation was observed. The oxidation was also attempted using mercury (II) acetate, with peracetic acid as the oxidant (**Scheme 5.28**). Pleasingly, under these conditions, alcohol **182** was isolated in an unoptimised yield of 67 %.



Scheme 5.28: Fleming oxidation of **119** using $Hg(OAc)_2$ and AcO_2H

5.7.2 Protiodesilylation of 119

Aside from its potential as a masked hydroxyl group, the dimethylphenylsilyl group does not have much synthetic value. It played a crucial role in our cyclisation of the methyl ester series, firstly by directing the stereochemical course of the aza-[2,3]-Wittig rearrangement step, and also by providing the probable driving force for the cyclisation by stabilising the α-negative charge. However, we considered that it would be useful to be able to remove the silyl group, thus establishing a method of forming 2,2,3-trisubstituted proline derivatives in a diastereoselective manner.

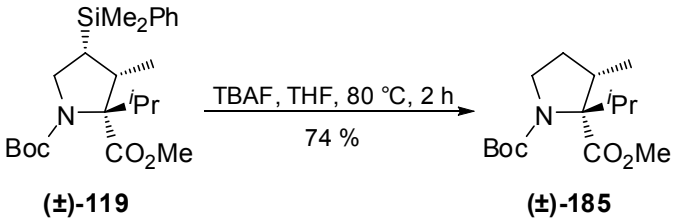


183 **184**

Scheme 5.29: Protiodesilylation of **183**

Until recently, the established procedure for protiodesilylation of unactivated $C(sp^3)$-$SiMe_2R$ bonds involved extended basic hydrolysis ($DMSO/H_2O$, 5 - 10 % KO^{t}Bu, 18-crown-6, 95 °C, 2 - 7 days).[119] However, in 2005, Roush *et al*. published an efficient and relatively mild alternative for this transformation.[120] They showed that protiodesilylation of tetrahydrofuran **183** occurred upon treatment with TBAF in wet THF or

DMF (**Scheme 5.29**). Pleasingly, under the same conditions, **119** underwent protiodesilylation to give **185** in 74 % yield (**Scheme 5.30**).



(±)-119 **(±)-185**

Scheme 5.30: Protiodesilylation of **119**

5.8 Summary

Investigations into the cyclisation of methyl ester precursors **65**, **66**, **67** and **175** have shown that this process delivers highly substituted proline-derivatives in good yields and excellent diastereoselectivities. It is believed that the first step in the synthesis of these pyrrolidines is aza-[2,3]-Wittig rearrangement, followed by a nucleophilic 5-*endo*-*trig* cyclisation. The relative stereochemistry of the pyrrolidines has been determined by ^{1}H NMR nOe experiments. The precursor **59b** derived from glycine methyl ester did not cyclise which leads us to believe that the presence of a quaternary centre in the rearranged intermediate is necessary in order for cyclisation to occur.

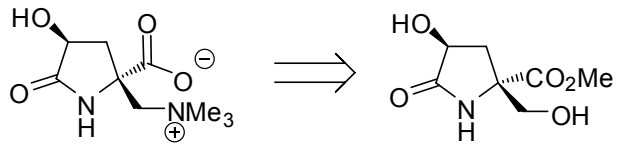
Pyrrolidine **158** was isolated upon treating diethylamide precursor **63** with KH and 18-crown-6. It is unknown whether this is the product of an incomplete rearrangement, or a rapid rearrangement-cyclisation sequence.

The utility of this cyclisation has been shown by further derivatisation of **119**. It was shown that the dimethylphenylsilyl group can be oxidised to a hydroxyl group or removed by treatment with TBAF.

6 Future Work and Conclusions

6.1 Future Work

As we have developed a method for the diastereoselective synthesis of pyrrolidines, we are interested in applying this methodology to the synthesis of a natural product. From our investigations we have shown that a quaternary centre at C_2 is necessary in order for cyclisation to occur. We have also demonstrated that the dimethylphenylsilyl group can be removed or oxidised to a hydroxyl group. A survey of the literature revealed the natural product dysibetaine, which possesses a quaternary centre at C_2 and a hydroxyl group at C_4 (**Figure 6.1**).

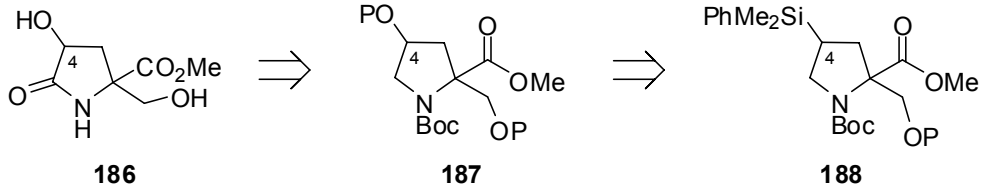


(2*S*,4*S*)-Dysibetaine **186**

Figure 6.1

Since its isolation from the marine sponge *Dysidea herbacea* in 1999,[121] there have been three total syntheses reported.[122] The total synthesis of Langlois and Le Nguyen proceeds *via* intermediate **186**,[122c] which we

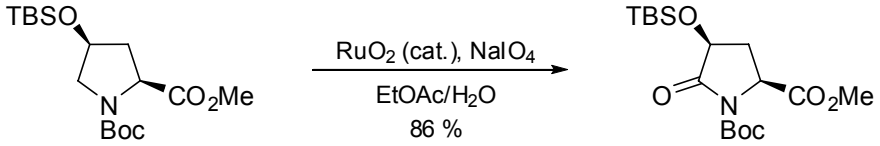
consider to be an attractive target for a formal synthesis of this natural product using our cyclisation procedure.



186 **187** **188**

Scheme 6.1: Possible retrosynthetic pathway for the synthesis of **165**

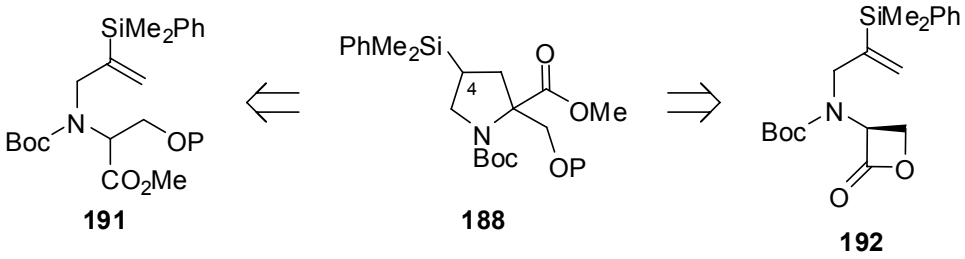
Retrosynthetically, this intermediate could be accessed from pyrrolidine **187**. Oxidation at C_5 of the pyrrolidine ring may be achieved using catalytic ruthenium oxide and sodium periodate, as demonstrated by Honda *et al*. in the formation of pyrrolidinone **190**, an intermediate in their total synthesis of (+)-febrifugine (**Scheme 6.2**).[123] Using this protocol, pyrrolidine **187** could undergo oxidation, followed by removal of the protecting groups to furnish the desired intermediate **186**. Pyrrolidine **187** could be obtained from the Fleming oxidation of **188** and subsequent protection of the alcohol.



189 **190**

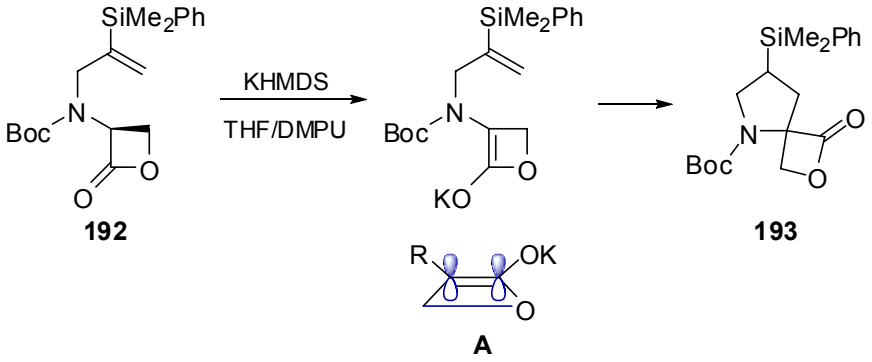
Scheme 6.2: Oxidation of **189** to form pyrrolidinone **190**

In order to synthesise **188** from our cyclisation procedure, it would be necessary for precursor **191** to undergo aza-[2,3]-Wittig rearrangement followed by cyclisation (**Scheme 6.3**). However, upon deprotonation of **191**, it is likely that β-elimination of the protected alcohol would occur, leading to undesired products. This issue could be overcome by the use of β-lactone **192** (**Scheme 6.3**).



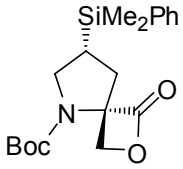
Scheme 6.3: Retrosynthetic analysis of **188**

Upon deprotonation, β-elimination would not be possible as the p orbitals of the enolate are orthogonal to the C-O bond, prohibiting the interaction required for elimination (**A**, **Scheme 6.4**). Hopefully, this enolate will undergo aza-[2,3]-Wittig rearrangement to form **193**. Opening of the β-lactone with methoxide and protection of the resulting alcohol would yield **188**.



Scheme 6.4: Formation of **193**

The cyclisations presented in **Section 5** have shown the silyl group adopts a position *anti* to the largest group at C_2. However, as these substituents at C_2 would be tethered in the rearranged product of **192**, the steric effects may not be as important. It is therefore difficult to predict whether the cyclisation of **192** would be diastereoselective. The methylene group is larger in size than the ester (for example, the *A* values of -CH_2OH and CO_2H are 1.76 and 1.35 kcal mol^{-1}, respectively) and, therefore, we suggest that the relative stereochemistry of the cyclised product would be 2*S**, 4*R** (**Figure 6.2**).



2*S, 4*R**-193**

Figure 6.2

6.2 Conclusions

The aims of this project were to establish a procedure for the enantioselective aza-[2,3]-Wittig rearrangement. Unfortunately, this was not achieved. Investigations into the effect of temperature on the rearrangement of methyl ester **66** and methoxy esters **122** and **127** resulted only in the formation of racemic products. Deuterium quench studies, performed on precursor **66** at - 78 °C, showed 90 % D incorporation with significant retention of stereochemistry based on $[\alpha]_D$. This suggests that atropisomerism does exist at this temperature; however, rearrangement was not observed below temperatures of around - 40 °C.

Whilst our attempts to obtain enantioenriched rearrangement products were unsuccessful, we have isolated highly substituted proline derivatives in good yields and excellent diastereoselectivities. It is thought that these pyrrolidines are the result of an aza-[2,3]-Wittig rearrangement-5-*endo*-*trig* cyclisation sequence; however, in the case of the alanine diethylamide derivative, it may be the result of an incomplete rearrangement. The dimethylphenylsilyl group has proven to be a useful synthetic handle; it can be oxidised to a hydroxyl group or removed by treatment with TBAF. We are hopeful that this cyclisation can be exploited in the formal synthesis of dysibetaine and other related natural products.

7 Experimental

7.1 General experimental details

All non-aqueous reactions were carried out under an oxygen-free atmosphere of nitrogen in flame-dried glassware with rigorous exclusion of moisture. Low temperature conditions were achieved using an ice bath (0 ºC) or a CO_2/acetone bath (< 0 ºC). All reactions were monitored by thin layer chromatography using Merck 5554 $60F_{254}$ silica gel coated plates. Visualisation was achieved using ultraviolet light and then either potassium permanganate or anisaldehyde. Flash column chromatography was performed using Merck silica gel 60 as the stationary phase and Fisher, certified or specified grade solvents. Vacuum was provided either by water pump or by a Vacubrand Teflon pump fitted with CVC-2 vacuum regulators.

Characterisation

Melting points are uncorrected and were determined using a Kofler hot-stage micro melting point apparatus. Specific rotations were determined on a Jasco DIP-370 digital polarimeter, and unless otherwise stated were

carried out at 25 ºC. $[\alpha]_D$ values are reported in 10^{-1}deg cm^2 g^{-1} and concentration (*c*) in g per 100 mL. Infrared spectra are recorded on a Perkin-Elmer 157G and all values are given in cm^{-1}. Nuclear magnetic resonance spectra were recorded at either 500 MHz on a Brucker DRX-500, 400 MHz on a Brucker AV-400 or 270 MHz on a Jeol EX-270. All chemical shifts (δ) are quoted in ppm relative to residual solvent for ^{1}H NMR and relative to internal resonance for ^{13}C NMR. Coupling constants (*J*) are given in Hz and are quoted twice, each being recorded as observed in the spectrum without averaging. The multiplicity of the signal is designated by the following abbreviations: m = multiplet, s = singlet, d = doublet, t = triplet, q = quartet. The abbreviation br refers to a broad signal and app refers to apparent. The subscript $_{rot}$ is used to denote signals caused by a rotameric mixture. The NMR spectra were obtained at room temperature unless otherwise stated. Those run at high temperature were recorded on the Jeol EX-270 in either deuterated DMSO (80 °C) or deuterated benzene (70 °C). Mass spectra were acquired on a VG micromass 70E, VG Autospec or Micromass LCTOF, using electron impact electrospray (ES^+) techniques.

7.2 Purification of solvents and reagents

Solvents and reagents were either used as supplied or, when necessary, purified in accordance with standard procedures as described below.

Acetonitrile (bp. 82 ºC), HMPA (bp. 70 ºC at 1 mmHg), DMPU (bp. 146 °C at 44 mmHg) and triethylamine (bp. 89 ºC) were distilled from calcium hydride and stored over 4 Å molecular sieves. Anhydrous grade dichloromethane (bp. 39 ºC) was distilled from calcium hydride immediately prior to use. Anhydrous grade tetrahydrofuran (bp. 66 ºC) was freshly distilled from sodium/benzophenone ketyl immediately prior to use. 18-crown-6 was recrystallised from acetonitrile. For work-up purposes, standard laboratory grade solvents were used as supplied.

7.3 General Procedures

General Procedure A - cyclisation of precursors using KHMDS

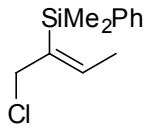
To a stirred solution of precursor (dried by azeotrope from toluene) in THF/DMPU (4:1, 3 mL/mmol) at 0 °C was added KMHDS (2.5 equiv. of 0.5 M solution in toluene) dropwise. The reaction was stirred for 14 h, allowing to warm to rt. The reaction was then quenched with saturated aq. NH_4Cl (3 mL/mmol) and Et_2O (3 mL/mmol) added. The layers were separated and the aqueous layer was re-extracted with Et_2O (2 x 3 mL/mmol). The combined organic layers were washed with brine (2 x 10 mL/mmol), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by column chromatography.

General Procedure B - Boc-deprotection of pyrrolidines using HCl

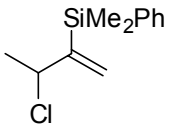
To Boc-protected pyrrolidine was added, with stirring, HCl (3 equiv. of 4 M solution in dioxane). The reaction was stirred for 3 h, after which time the solvent was removed *in vacuo*. The residue was taken up in CH_2Cl_2 (5 mL/mmol) and saturated aq. $NaHCO_3$ (5 mL/mmol) added. The layers were separated and the aqueous layer was re-extracted with CH_2Cl_2 (5 mL/mmol). The combined organic layers were washed with brine (2 x 10 mL/mmol), dried ($MgSO_4$) and the solvent removed *in vacuo* to yield the pyrrolidine with no need for further purification.

7.4 Preparation of novel compounds

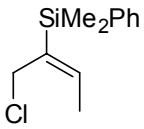
((*Z*)-1-Chloromethylpropenyl)dimethylphenylsilane 111, (2-chloro-1-methylenepropyl)dimethylphenylsilane 113 and ((*E*)-1-chloromethyl-propenyl)dimethylphenylsilane 112



111



113

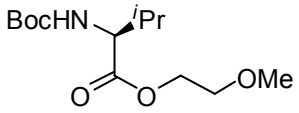


112

To a stirred solution of alcohol **110** (85 mg, 0.41 mmol) in Et_2O (2 mL) was added dropwise *via* cannula a solution of thionyl chloride (59 mg, 0.50

mmol) in Et_2O (1 mL + 0.5 mL wash). The reaction was stirred for 20 h, after which time the crude material was adsorbed onto silica. Gel filtration (eluting with pet. ether) furnished chlorides **111**, **113** and **112** (91 mg, 98 %) as an inseparable mixture in a ratio of 20 : 3 : 1; R_f = 0.51 (100 % pet. ether); IR ν_{max} (film) 3070 - 2914 (C-H), 1613, 1427, 1251, 1131, 1116 1068 cm^{-1}; ^{1}H NMR **111** (400 MHz, $CDCl_3$) δ 0.52 (6H, s, Si(CH_3)$_2$), 1.68 (3H, d, *J* = 7.1, C=CHCH_3), 4.22 (2H, s, CH_2Cl), 6.57 (1H, q, *J* = 7.0, C=C*H*CH$_3$), 7.38 - 7.41 (3H, m, Ar*H*), 7.56 - 7.62 (2H, m, Ar*H*); ^{1}H NMR **113** (400 MHz, $CDCl_3$) δ 0.43 (3H, s, Si(CH_3)$_2$), 0.52 (3H, s, Si(CH_3)$_2$), 1.56 (3H, d, *J* = 6.7, CHCH_3), 4.74 (1H, q, *J* = 6.7, C*H*CH$_3$), 5.59 (1H, s, C=CH_2), 6.12 (1H, s, C=CH_2), 7.38 - 7.41 (3H, m, Ar*H*), 7.56 - 7.62 (2H, m, Ar*H*); ^{1}H NMR **112** (400 MHz, $CDCl_3$) δ 0.52 (6H, s, Si(CH_3)$_2$), 1.87 (3H, d, *J* = 6.8, C=CHCH_3), 4.19 (2H, s, CH_2Cl), 6.19 (1H, q, *J* = 6.7, C=C*H*CH$_3$), 7.38 - 7.41 (3H, m, Ar*H*), 7.56 - 7.62 (2H, m, Ar*H*); ^{13}C NMR **111** (400 MHz, $CDCl_3$) δ - 1.7 (Si(*C*H$_3$)$_2$), 18.2 (C=CH*C*H$_3$), 52.3 (*C*H$_2$Cl), 127.9 (*C*H), 129.7 (*C*H), 134.1 (*C*H), 137.6 (*C*), 138.5 (*C*), 144.7 (*C*H); Anal. calcd. for $C_{12}H_{17}ClSi$: C 64.11, H 7.62, found: C 63.97, H 7.58 %.

(*S*)-2-*tert*-Butoxycarbonylamino-3-methylbutyric acid 2-methoxyethyl ester 123

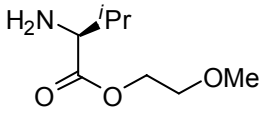


123

A stirring solution of Boc-(*L*)-valine (5.72 g, 26.3 mmol) in CH_2Cl_2 (80 mL) was cooled to - 30 ºC and treated with DMAP (322 mg, 2.63 mmol) and DCC (5.43 g, 26.3 mmol). After stirring for 15 min at - 30 ºC, 2-methoxyethanol (4.00 g, 26.3 mmol) was added to the reaction mixture. The solution was allowed to warm to rt over 1 h, after which the solvent was removed *in vacuo*. The white precipitate was taken up in EtOAc (50 mL), filtered through a plug of Celite and concentrated *in vacuo*. Purification by flash-column chromatography (20 % Et_2O/pet. ether) yielded ester **123** (8.12 g, 89 %) as a colourless oil; R_f = 0.38 (30 % Et_2O/pet. ether); $[\alpha]_D$ + 8.2 (c = 2.4, $CHCl_3$); IR ν_{max} (film) 3361 (N-H), 2969 - 2933 (C-H), 1716 (C=O), 1503, 1367, 1160 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (3H, d, *J* = 6.9, $CH(CH_3)_2$), 0.95 (3H, d, *J* = 6.9, $CH(CH_3)_2$), 1.43 (9H, s, $C(CH_3)_3$), 2.14 (1H, app. br octet, *J* = 6.1, $CH(CH_3)_2$), 3.36 (3H, s, OCH_3), 3.58 (2H, t, *J* = 4.8, CH_2OCH_3), 4.21 - 4.33 (3H, m, NCH, CO_2CH_2), 5.03 (1H, br d, *J* = 8.8, NH); ^{13}C NMR (400 MHz, $CDCl_3$) δ 17.4 ($CH(CH_3)_2$), 18.9 ($CH(CH_3)_2$), 28.3 ($C(CH_3)_3$), 31.3 ($CH(CH_3)_2$), 58.5 (OCH_3), 58.8 (NCH), 63.9

(CH_2OCH_3), 70.3 (CO_2CH_2), 79.6 ($C(CH_3)_3$), 155.6 (*C*=O), 172.3 (*C*=O); m/z (ES^+) 298 (64 %, MNa^+), 176 (100 %, MH^+ - Boc); HRMS $C_{13}H_{25}NNaO_5$ calcd. 298.1625, found 298.1620; Anal. calcd. for $C_{13}H_{25}NO_5$: C 56.71, H 9.15, N 5.09, found: C 56.46, H 9.21, N 5.04 %.

(*S*)-2-Amino-3-methylbutyric acid 2-methoxyethyl ester 124

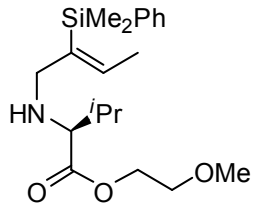


124

Anhydrous HCl (18.6 mL of 4 M solution in dioxane, 74.4 mmol) was added dropwise to **123** (6.82 g, 24.8 mmol) with stirring. The reaction was stirred at rt for 3 h then the solvent was removed *in vacuo*. The oil was partitioned between Et_2O (20 mL) and saturated aq. $NaHCO_3$ (20 mL). The layers were separated and the aqueous layer re-extracted with Et_2O (20 mL). The combined organic layers were washed with water (20 mL) then brine (20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The resulting oil was filtered through Celite to yield **124** (4.30 g, 99 %) as a colourless oil; R_f = 0.11 (70 % Et_2O/pet. ether); $[\alpha]_D$ + 15.3 (c = 0.9, $CHCl_3$); IR ν_{max} (film) 3666, 3398 (N-H), 2964 - 2894 (C-H), 1731 (C=O), 1127, 1054 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.91 (3H, d, *J* = 6.8, $CH(CH_3)_2$), 0.99 (3H, d, *J* = 6.8, $CH(CH_3)_2$), 1.42 (2H, br s, NH_2), 2.05 (1H, d septet, *J* = 6.9, 4.9,

C*H*(CH_3)$_2$), 3.34 (1H, d, *J* = 4.9, NC*H*), 3.39 (3H, s, OC*H*$_3$), 3.61 (2H, t, *J* = 4.7, C*H*$_2$OCH$_3$), 4.27 (1H, dt, *J* = 11.5, 4.7, CO_2CH_2), 4.31 (1H, dt, *J* = 11.5, 4.7, CO_2CH_2); ^{13}C NMR (500 MHz, $CDCl_3$) δ 17.1 (CH(*C*H$_3$)$_2$), 19.2 (CH(*C*H$_3$)$_2$), 32.1 (*C*H(CH$_3$)$_2$), 58.8 (O*C*H$_3$), 59.8 (N*C*H), 63.5 (*C*H$_2$OCH$_3$), 70.4 (CO_2CH_2), 175.6 (*C*=O); m/z (ES^+) 176 (100 %, MH^+); HRMS $C_8H_{18}NO_3$ calcd. 176.1281, found 176.1291.

(*S*)-2-[(*Z*)-2-(Dimethylphenylsilanyl)but-2-enylamino]-3-methylbutyric acid 2-methoxyethyl ester 125

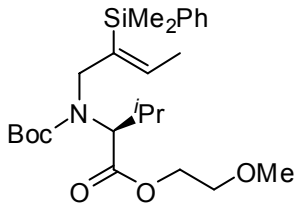


125

To a stirred solution of amine **124** (1.30 g, 7.43 mmol) in MeCN (20 mL) was added bromide **102** (2.00 g, 7.43 mmol) in MeCN (10 mL + 1 mL wash). Potassium carbonate (1.23 g, 8.91 mmol) was added and the reaction mixture was stirred for 14 h. The reaction was quenched with water (20 mL) and diluted with Et_2O (20 mL). The layers were separated and the aqueous layer re-extracted with Et_2O (20 mL). The combined organic layers were washed with water (20 mL) then brine (20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash-column chromatography (20

% Et_2O/pet. ether) yielded **125** (2.10 g, 78 %) as a colourless oil; R_f = 0.27 (25 % Et_2O/pet. ether); $[\alpha]_D$ - 12.0 (c = 1.5, $CHCl_3$); IR ν_{max} (film) 3334 (N-H), 2960 - 2896 (C-H), 1726 (C=O), 1456, 1371, 1126, 1109 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.42 (3H, s, $Si(CH_3)_2$), 0.43 (3H, s, $Si(CH_3)_2$), 0.92 (3H, d, *J* = 6.8, $CH(CH_3)_2$), 0.93 (3H, d, *J* = 6.8, $CH(CH_3)_2$), 1.27 (1H, br s, N*H*), 1.59 (3H, d, *J* = 7.0, C=CHCH_3), 1.86 (1H, app. octet, *J* = 6.7, C*H*$(CH_3)_2$), 2.97 (1H, d, *J* = 6.4, NC*H*), 3.06 (1H, d, *J* = 11.6, NCH_2), 3.26 (1H, d, *J* = 11.7, NCH_2), 3.39 (3H, s, OCH_3), 3.61 (2H, t, *J* = 4.7, CH_2OCH_3), 4.29 (1H, dt, *J* = 12.0, 4.4, CO_2CH_2), 4.32 (1H, dt, *J* = 12.0, 4.4, CO_2CH_2), 6.26 (1H, q, *J* = 6.9, C=C*H*CH_3), 7.32 - 7.35 (3H, m, Ar*H*), 7.56 - 7.59 (2H, m, Ar*H*); ^{13}C NMR (500 MHz, $CDCl_3$) δ -1.3 ($Si(CH_3)_2$), 18.0 (CH_3), 18.8 (CH_3), 19.6 (CH_3), 31.8 ($CH(CH_3)_2$), 56.6 (CH_2), 59.0 (OCH_3), 63.1 (CH_2), 66.8 (NCH), 70.7 (CH_2), 127.7 (CH), 128.6 (CH), 133.9 (CH), 136.7 (*C*), 140.0 (*C*), 140.7 (CH), 175.6 (*C*=O); m/z (ES^+) 364 (100 %, MH^+); HRMS $C_{20}H_{34}NO_3Si$ calcd. 364.2302, found 364.2299.

(*S*)-2-{*tert*-Butoxycarbonyl-[(*Z*)-2-(dimethylphenylsilanyl)but-2-enyl]amino}-3-methylbutyric acid 2-methoxyethyl ester 122

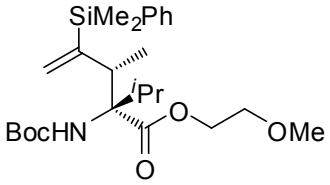


122

To a stirred solution of **125** (1.45 g, 3.99 mmol) in Et_3N (15 mL) was added di-*tert*-butyldicarbonate (2.62 g, 12.0 mmol) in Et_3N (10 mL + 2 mL wash). The reaction mixture was heated to reflux for 48 h after which the reaction was allowed to cool to rt and all volatile material was removed *in vacuo*. Purification by flash-column chromatography (20 % Et_2O/pet. ether) yielded **122** (1.43 g, 77 %) as a colourless oil; R_f = 0.31 (20 % Et_2O/pet. ether); $[\alpha]_D$ - 51.2 (c = 2.9, $CHCl_3$); IR ν_{max} (film) 2967 - 2931 (C-H), 1736 (C=O), 1662 (C=O), 1367, 1130, 1110 cm^{-1}; ^1H NMR (500 MHz, d_6-DMSO) δ 0.37 (3H, s, Si(CH_3)$_2$), 0.38 (3H, s, Si(CH_3)$_2$), 0.83 (3H, d, *J* = 6.7, CH(CH_3)$_2$), 0.91 (3H, br d, *J* = 4.8, CH(CH_3)$_2$), 1.37 (9H, s, C(CH_3)$_3$), 1.58 (3H, d, *J* = 7.0, C=CHCH_3), 2.16 (1H, br s, C*H*(CH_3)$_2$), 3.25 (3H, s, OCH_3), 3.50 (2H, t, *J* = 4.7, CH_2OCH_3), 3.81 - 4.15 (5H, m, CO_2CH_2, NCH_2, NC*H*), 6.05 (1H, br m, C=C*H*CH_3), 7.36 - 7.38 (3H, m, Ar*H*), 7.52 - 7.54 (2H, m, Ar*H*); ^{13}C NMR (270 MHz, d_6-DMSO) δ - 1.1, - 1.0, 28.4, 79.5, 128.3, 129.4, 134.0; ^{13}C NMR (270 MHz, d_6-DMSO, 80 °C) δ - 1.2 (Si(*C*H_3)$_2$), - 1.1 (Si(*C*H_3)$_2$),

17.7, 19.3, 20.4, 28.5, 28.7, 50.7, 58.6, 63.9, 64.3, 70.2, 79.8, 128.3, 129.4, 132.9, 134.0, 136.3, 139.2, 155.5 (*C*=O), 170.7 (*C*=O); m/z (ES^+) 486 (100 %, MNa^+), 430 (16 %, MNa^+ - C_4H_8), 364 (27 %, MH^+ - Boc), 330 (28 %); HRMS $C_{25}H_{41}NNaO_5Si$ calcd. 486.2646, found 486.2645.

(2*R,3*R**)-2-*tert*-Butoxycarbonylamino-4-(dimethylphenylsilanyl)-2-*iso*propyl-3-methylpent-4-enoic acid 2-methoxyethyl ester 126**

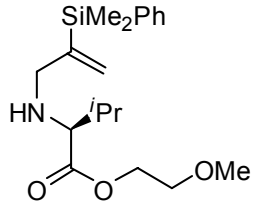


(±)-126

To a stirred suspension of KH (23 mg, 0.57 mmol) in THF (1 mL) at 0 ºC was added **122** (88 mg, 0.19 mmol) in THF (0.5 mL + 0.5 mL wash). The reaction was stirred for 14 h, allowing to warm to rt then quenched with saturated aq. NH_4Cl (1 mL). The layers were separated and the aqueous layer re-extracted with Et_2O (3 mL). The combined organic layers were washed with water (3 mL) then brine (3 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash-column chromatography (20 % Et_2O/pet. ether) yielded **126** (70 mg, 79 %) as a colourless oil; R_f = 0.54 (20 % Et_2O/pet. ether); IR ν_{max} ($CHCl_3$) cm^{-1} 3423 (N-H), 2973 (C-H), 1731 (C=O), 1496, 1251, 1166 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.39 (3H, s,

Si(CH_3)$_2$), 0.49 (3H, s, Si(CH_3)$_2$), 0.71 (6H, app. t, J = 5.5, CH(CH_3)$_2$), 1.18 (3H, d, J = 7.1, CHCH_3), 1.46 (9H, s, C(CH_3)$_3$), 2.05 - 2.10 (1H, m, CH(CH$_3$)$_2$), 3.32 (3H, s, OCH_3), 3.46 - 3.53 (1H, m, CHCH$_3$), 3.57 (2H, t, J = 4.9, CH_2OCH$_3$), 4.16 - 4.23 (1H, m, CO$_2$CH_2), 4.26 - 4.31 (1H, m, CO$_2$CH_2), 4.87 (1H, br s, NH), 5.61 (1H, s, C=CH_2), 5.90 (1H, s, C=CH_2), 7.32 - 7.36 (3H, m, ArH), 7.55 - 7.59 (2H, m, ArH); ^{13}C NMR (500 MHz, CDCl$_3$) δ - 0.9 (Si(*C*H$_3$)$_2$), - 1.8 (Si(*C*H$_3$)$_2$), 17.4 (*C*H$_3$), 17.9 (*C*H$_3$), 18.7 (*C*H), 28.3 (*C*H$_3$), 33.6 (*C*H), 58.7 (O*C*H$_3$), 63.6 (*C*H$_2$OCH$_3$), 67.9 (*C*), 70.3 (CO$_2$*C*H$_2$), 78.8 (*C*), 127.8 (*C*H), 129.0 (*C*H), 129.8 (C=*C*H$_2$), 134.2 (*C*H), 139.0 (*C*), 152.1 (*C*), 154.5 (*C*=O), 171.8 (*C*=O); m/z (ES$^+$) 486 (100%, MNa$^+$); HRMS C$_{25}$H$_{41}$NNaO$_5$Si calcd. 486.2646, found 486.2649.

(*S*)-2-[2-(Dimethylphenylsilanyl)allylamino]-3-methylbutyric acid 2-methoxyethyl ester 130

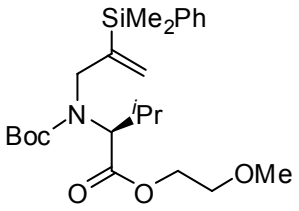


130

To a stirred solution of amine **124** (1.00 g, 5.71 mmol) in MeCN (15 mL) was added bromide **129** (1.32 g, 5.19 mmol) in MeCN (10 mL + 5 mL wash). Potassium carbonate (861 mg, 6.23 mmol) was added and the

reaction stirred for 14 h. The reaction was then quenched with water (15 mL), diluted with CH_2Cl_2 (20 mL) and the layers were separated. The aqueous layer was re-extracted with CH_2Cl_2 (2 x 15 mL) and the combined organic layers were washed with water (20 mL) then brine (2 x 15 mL), dried (MgSO4) and concentrated *in vacuo*. Purification by flash-column chromatography (20 % Et_2O/pet. ether) yielded **130** (1.43 g, 79 %) as a colourless oil; R_f = 0.33 (20 % Et_2O/pet. ether); $[\alpha]_D$ - 14.6 (c = 1.2, $CHCl_3$); IR ν_{max} (solution in $CHCl_3$) 3330 (N-H), 2960 - 2822 (C-H), 1729 (C=O), 1454, 1372, 1111 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.40 (3H, s, Si(CH_3)$_2$), 0.41 (3H, s, Si(CH_3)$_2$), 0.89 (3H, d, *J* = 6.9, CH(CH_3)$_2$), 0.91 (3H, d, *J* = 7.0, CH(CH_3)$_2$), 1.42 (1H, br s, N*H*), 1.87 (1H , app. octet, *J* = 6.7, C*H*(CH$_3$)$_2$), 2.97 (1H, d, *J* = 6.1, NC*H*), 3.10 (1H, d, *J* = 13.5, NCH_2), 3.35 (1H, d, *J* = 13.5, NCH_2), 3.37 (3H, s, OCH_3), 3.58 (2H, t, *J* = 4.8, CH_2OCH$_3$), 4.22 - 4.31 (2H, m, CO_2CH_2), 5.44 (1H, s, C=CH_2), 5.85 (1H, s, C=CH_2), 7.32 - 7.35 (3H, m, Ar*H*), 7.53 - 7.55 (2H, m, Ar*H*); ^{13}C NMR (500 MHz, $CDCl_3$) δ - 2.8 (Si(*C*H$_3$)$_2$), - 2.7 (Si(*C*H$_3$)$_2$), 18.7 (CH(*C*H$_3$)$_2$), 19.4 (CH(*C*H$_3$)$_2$), 31.7 (*C*H(CH$_3$)$_2$), 54.3 (*C*H$_2$), 58.9 (O*C*H$_3$), 63.1 (*C*H$_2$), 67.0 (N*C*H), 70.6 (*C*H$_2$), 126.9 (C=*C*H$_2$), 127.7 (Ar*C*H), 128.9 (Ar*C*H), 134.0 (Ar*C*H), 138.5 (*C*), 148.7 (*C*), 175.3 (*C*=O); m/z (ES^+) 350 (100 %, MH^+); HRMS $C_{19}H_{32}NO_3Si$ calcd. 350.2146, found 350.2148; Anal. calcd. for $C_{19}H_{31}NO_3Si$: C 65.29, H 8.94, N 4.01, found: C 65.26, H 9.01, N 3.91 %.

(*S*)-2-{*tert*-Butoxycarbonyl-[2-(dimethylphenylsilanyl)allyl]amino}-3-methylbutyric acid 2-methoxyethyl ester 127

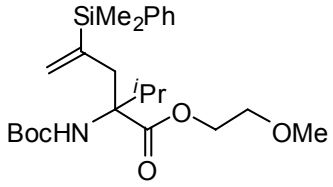


127

To a stirred solution of **130** (134 mg, 0.384 mmol) in Et_3N (2 mL) was added a solution of di-*tert*-butyldicarbonate (251 mg, 1.15 mmol) in Et_3N (2 mL). The reaction mixture was heated to reflux for 48 h after which the solvent was removed *in vacuo*. Purification by flash-column chromatography (20 % Et_2O/pet. ether) yielded **127** (152 mg, 88 %); R_f = 0.22 (20 % Et_2O/pet. ether); $[\alpha]_D$ - 56.8 (c = 1.2, $CHCl_3$); IR ν_{max} (solution in $CHCl_3$) 2965 - 2932 (C-H), 1735 (C=O), 1684 (C=O), 1454, 1368, 1131, 1110 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.40 (6H, s, $Si(CH_3)_2$), 0.87 (3H, d, *J* = 6.8, $CH(CH_3)_2$), 0.91 (3H, d, *J* = 6.4, $CH(CH_3)_2$), 1.39 - 1.46 (9H, m, $C(CH_3)_3$), 2.14 (1H, br m, $CH(CH_3)_2$), 3.36 (3H, s, OCH_3), 3.52 - 3.59 (2H, m, CH_2OCH_3), 3.75 - 4.50 (5H, m, CO_2CH_2, NCH_2, NCH), 5.40 (1H, s, $C=CH_2$), 5.62 - 5.70 (1H, m, $C=CH_2$), 7.35 - 7.37 (3H, m, ArH), 7.52 - 7.53 (2H, m, ArH); ^{13}C NMR (270 MHz, d_6-DMSO) δ - 2.9, - 2.8, 28.3, 58.6, 64.0, 70.1, 128.4, 129.8, 134.2, 170.6; ^{13}C NMR (270 MHz, d_6-DMSO, 80 °C) δ - 2.8 ($Si(CH_3)_2$), - 2.7 ($Si(CH_3)_2$), 19.3, 20.1, 28.4, 28.5, 49.1, 58.6,

63.9, 64.8, 70.2, 79.9, 123.9, 128.3, 129.7, 134.2, 137.8, 145.7, 155.7 (*C*=O), 170.6 (*C*=O); m/z (ES^+) 472 (71 %, MNa^+), 416 (100 %, MNa^+ - C_4H_8), 372 (58 %, MNa^+ - Boc); HRMS $C_{24}H_{39}NNaO_5Si$ calcd. 472.2490, found 472.2511.

2-*tert*-butoxycarbonylamino-4-(dimethylphenylsilanyl)-2-*iso*propylpent-4-enoic acid 2-methoxyethyl ester 131

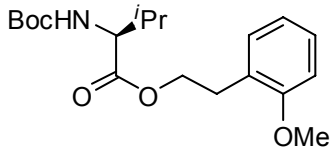


131

To a stirred suspension of KH (56 mg, 1.4 mmol) in THF (1 mL) at 0 ºC was added **127** (210 mg, 0.467 mmol) in THF (0.5 mL + 0.5 mL wash). The reaction was stirred for 2 h, allowing to warm to rt then it was quenched with saturated aq. NH_4Cl (1 mL). The mixture was then diluted with Et_2O (2 mL) and the layers separated. The aqueous layer was further extracted with Et_2O (1 mL) and the combined organic layers were washed with water (4 mL) and brine (4 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash column chromatography (25 % Et_2O/pet.ether) yielded **131** (151 mg, 72 %) as a colourless oil; R_f = 0.36 (30 % Et_2O/pet. ether); IR ν_{max} (solution in $CHCl_3$) 3443 (N-H), 2971 - 2934 (C-H), 1714 (C=O), 1503,

1456, 1393, 1369, 1353, 1160 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.35 (3H, s, Si(CH_3)$_3$), 0.37 (3H, s, Si(CH_3)$_3$), 0.85 (3H, d, *J* = 6.9, CH(CH_3)$_2$), 0.91 (3H, d, *J* = 6.9, CH(CH_3)$_2$), 1.42 (9H, s, C(CH_3)$_3$), 2.44 (1H, septet, *J* = 6.9, C*H*(CH$_3$)$_2$), 2.78 (1H, d, *J* = 16.3, H_2C=C(SiMe$_2$Ph)CH_2), 3.32 (3H, s, OCH_3), 3.39 (1H, d, *J* = 16.3, H_2C=C(SiMe$_2$Ph)CH_2), 3.48 (1H, dt, *J* = 11.5, 4.1, CH_2OCH$_3$), 3.52 (1H, dt, *J* = 11.2, 3.8, CH_2OCH$_3$), 4.07 (1H, dt, *J* = 12.3, 4.6, CO_2CH_2), 4.24 (1H, ddd, *J* = 10.2, 5.9, 3.9, CO_2CH_2), 5.46 (1H, s, C=CH_2), 5.52 (1H, s, N*H*), 5.75 (1H, s, C=CH_2), 7.32 - 7.35 (3H, m, Ar*H*), 7.50 - 7.52 (2H, m, Ar*H*); ^{13}C NMR (500 MHz, $CDCl_3$) δ - 3.0 (Si(*C*H$_3$)$_2$), - 2.4 (Si(*C*H$_3$)$_2$), 17.5 (CH(*C*H$_3$)$_2$), 17.6 (CH(*C*H$_3$)$_2$), 28.5 (C(*C*H$_3$)$_3$), 34.6 (*C*H(CH$_3$)$_2$), 36.5 (H_2C=C(SiMe$_2$Ph)*C*H$_2$), 58.8 (O*C*H$_3$), 64.2 (*C*H$_2$OCH$_3$), 66.1 (*C*), 70.1 (CO_2*C*H$_2$), 78.8 (*C*), 127.7 (Ar*C*H), 128.0 (H_2*C*=C), 128.9 (Ar*C*H), 134.1 (Ar*C*H), 138.4 (*C*), 145.9 (*C*), 153.8 (*C*=O), 173.1 (*C*=O); m/z (ES^+) 472 (100 %, MNa^+), 450 (12 %, MH^+), 394 (95 %, MH^+ - C_4H_8), 350 (21 %, MH^+ - Boc), 333 (13 %), 316 (31 %), 280 (16 %); HRMS $C_{24}H_{39}NNaO_5Si$ calcd. 472.2490, found 472.2491; Anal. calcd. for $C_{24}H_{39}NO_5Si$: C 64.11, H 8.74, N 3.11, found: C 64.13, H 8.80, N 3.05 %.

(*S*)-2-*tert*-Butoxycarbonylamino-3-methylbutyric acid 2-(2-methoxy-phenyl)ethyl ester 133

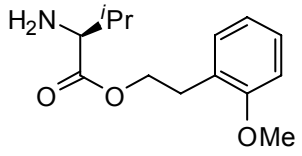


133

To a stirred solution of Boc-(*L*)-valine (1.50 g, 6.90 mmol) in CH_2Cl_2 (50 mL) at - 30 ºC was added DCC (1.42 g, 6.90 mmol) and DMAP (84 mg, 0.69 mmol). The reaction was stirred at - 30 ºC for 10 min then 2-methoxyphenethyl alcohol (1.05 g, 6.90 mmol) in CH_2Cl_2 (10 mL + 2 mL wash) was added. The reaction was allowed to warm to rt and stirred for 14 h. The solvent was then removed *in vacuo* and the residue was taken up in EtOAc (50 mL) and filtered through a plug of Celite. The solvent was then removed *in vacuo*. Purification by flash-column chromatography (30 % Et_2O/pet. ether) yielded **133** (2.07 g, 85 %) as a colourless oil; R_f = 0.38 (30 % Et_2O/pet. ether); $[\alpha]_D$ + 2.4 (c = 1.0, $CHCl_3$); IR ν_{max} (film) 3440 (N-H), 2967 - 2838 (C-H), 1713 (C=O), 1493, 1392, 1367, 1156 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.81 (3H, d, *J* = 6.9, $CH(CH_3)_2$), 0.91 (3H, d, *J* = 6.9, $CH(CH_3)_2$), 1.45 (9H, s, $C(CH_3)_3$), 2.09 (1H, app. br sextet, *J* = 5.7, $CH(CH_3)_2$), 2.98 (2H, t, *J* = 7.0, CH_2Ar), 3.84 (3H, s, OCH_3), 4.20 (1H, br dd, *J* = 8.8, 4.5, NC*H*), 4.31 (1H, dt, *J* = 10.5, 6.9, CO_2CH_2), 4.37 (1H, dt, *J* = 10.5, 7.2, CO_2CH_2), 5.02 (1H, br d, *J* = 8.3, N*H*), 6.85 [1H, d, *J* = 8.2,

Ar*H* (*o*-OMe)], 6.89 [1H, dt, *J* = 7.4, 1.0, Ar*H* (*p*-OMe)], 7.14 [1H, dd, *J* = 7.4, 1.6, Ar*H* (*o*-CH_2)], 7.22 [1H, dt, *J* = 7.6, 1.7, Ar*H* (*m*-OMe)]; ^{13}C NMR (500 MHz, $CDCl_3$) δ 17.5 (CH(*C*H_3)$_2$), 19.0 (CH(*C*H_3)$_2$), 28.4 (C(*C*H_3)$_3$), 30.0 (*C*H_2Ar), 31.4 (*C*H(CH$_3$)$_2$), 55.3 (O*C*H$_3$), 58.6 (N*C*H), 64.5 (CO_2*C*H_2), 79.7 (*C*(CH$_3$)$_3$), 110.3 (Ar*C*H), 120.5 (Ar*C*H), 125.7 (Ar*C*), 128.1 (Ar*C*H), 130.8 (Ar*C*H), 155.7 (Ar*C*), 157.7 (*C*=O), 172.4 (*C*=O); m/z (ES^+) 374 (100 %, MNa^+), 252 (38 %, MH^+ - Boc), 135 (82 %, $(CH_2)_2C_6H_4OMe^+$); HRMS $C_{19}H_{29}NNaO_5$ calcd. 374.1938, found 374.1933.

(*S*)-2-amino-3-methylbutyric acid 2-(2-methoxyphenyl)ethyl ester 134

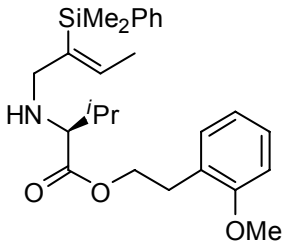


134

Anhydrous HCl (4.42 mL of 4 M solution in dioxane, 17.7 mmol) was added dropwise to **133** (2.07 g, 5.90 mmol) with stirring. The reaction was stirred for 2 h then the solvent was removed *in vacuo*. The residue was taken up in CH_2Cl_2 (20 mL) and saturated aq. $NaHCO_3$ (15 mL) was added. The layers were separated and the aqueous layer was re-extracted with CH_2Cl_2 (15 mL). The combined organic layers were washed with water (20 mL) and brine (2 x 15 mL), dried ($MgSO_4$) and concentrated *in vacuo* to yield **134** (1.24 g, 84 %) as a colourless oil with no need for further purification;

$[\alpha]_D$ + 8.8 (c = 3.1, $CHCl_3$); IR ν_{max} (film) 3393 (N-H), 2959 - 2838 (C-H), 1730 (C=O), 1602, 1462, 1123, 1048 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.84 (3H, d, *J* = 6.8, $CH(CH_3)_2$), 0.93 (3H, d, *J* = 6.9, $CH(CH_3)_2$), 1.40 (2H, br s, NH_2), 1.98 (1H, app. d sextet, *J* = 6.8, 1.7, $CH(CH_3)_2$), 2.97 (2H, t, *J* = 7.0, CH_2Ar), 3.24 (1H, br d, *J* = 5.0, NC*H*), 3.81 (3H, s, OCH_3), 4.30 (1H, dt, *J* = 10.7, 7.0, CO_2CH_2), 4.35 (1H, dt, *J* = 10.4, 7.1, CO_2CH_2), 6.84 [1H, d, *J* = 8.2, Ar*H*, (*o*-OMe)], 6.88 [1H, dt, *J* = 7.4, 0.9, Ar*H*, (*p*-OMe)], 7.14 [1H, d, *J* = 7.4, Ar*H*, (*o*-CH_2)], 7.21 [1H, dt, *J* = 8.2, 2.5, Ar*H*, (*m*-OMe)]; ^{13}C NMR (500 MHz, $CDCl_3$) δ 17.1 ($CH(CH_3)_2$), 19.4 ($CH(CH_3)_2$), 30.1 (CH_2Ar), 32.0 ($CH(CH_3)_2$), 55.2 (OCH_3), 60.0 (NCH), 64.0 (CO_2CH_2), 110.3 (ArCH), 120.4 (ArCH), 125.9 (ArC), 128.0 (ArCH), 130.7 (ArCH), 157.7 (ArC), 175.6 (C=O); m/z (ES^+) 274 (12 %, MNa^+), 252 (100 %, MH^+), 135 (68 %, $(CH_2)_2C_6H_4OMe^+$); HRMS $C_{14}H_{22}NO_3$ calcd. 252.1594, found 252.1594; Anal. calcd. for $C_{14}H_{21}NO_3$: C 66.91, H 8.42, N 5.57, found: C 66.51, H 8.38, N 5.45 %.

(*S*)-2-[(*Z*)-2-(Dimethylphenylsilanyl)but-2-enylamino]-3-methylbutyric acid 2-(2-methoxyphenyl)ethyl ester 135

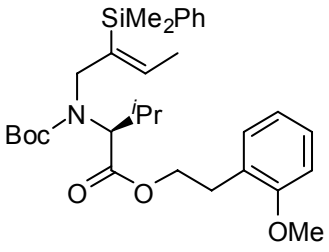


135

To a stirred solution of amine **134** (957 mg, 3.81 mmol) in MeCN (10 mL) was added *via* cannula bromide **102** (1.23 g, 4.58 mmol) in MeCN (5 mL + 2 mL wash). Potassium carbonate (1.05 g, 7.63 mmol) was added and the reaction was stirred for 14 h. The reaction was quenched with water (15 mL) and Et_2O (20 mL) was added. The layers were separated and the aqueous layer was re-extracted with Et_2O (20 mL). The combined organic layers were washed with brine (2 x 20 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash-column chromatography (10 % Et_2O/pet. ether) yielded **135** (1.35 g, 81 %) as a colourless oil; R_f = 0.24 (10 % Et_2O/pet. ether); $[\alpha]_D$ - 9.6 (c = 1.0, $CHCl_3$); IR ν_{max} (film) 3423 (N-H), 2965 - 2878 (C-H), 1714 (C=O), 1504, 1253, 1157 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.43 (3H, s, Si(CH_3)$_2$), 0.44 (3H, s, Si(CH_3)$_2$), 0.90 (6H, d, *J* = 6.8, CH(CH_3)$_2$), 1.28 (1H, br s, N*H*), 1.59 (3H, d, *J* = 6.9, C=CHCH_3), 1.82 (1H, app. octet, *J* = 6.7, C*H*(CH_3)$_2$), 2.89 (1H, d, *J* = 6.4, NC*H*), 3.00 (2H, t, *J* = 7.1, CH_2Ar), 3.03 (1H, d, *J* = 12.5, NCH_2), 3.22 (1H, d, *J* = 11.7,

NCH_2), 3.84 (3H, s, OCH_3), 4.36 (2H, t, J = 7.1, CO_2CH_2), 6.21 (1H, q, J = 6.9, C=CHCH$_3$), 6.87 [1H, d, J = 8.2, ArH, (*o*-OMe)], 6.90 [1H, dt, J = 7.4, 1.0, ArH, (*p*-OMe)], 7.17 [1H, dd, J = 7.4, 1.6, ArH, (*o*-CH_2)], 7.23 [1H, dt, J = 7.8, 1.7, ArH, (*m*-OMe)], 7.34 - 7.36 (3H, m, ArH), 7.56 - 7.59 (2H, m, ArH); ^{13}C NMR (500 MHz, $CDCl_3$) δ - 1.3 (Si(CH_3)$_2$), 18.0 (CH_3), 18.9 (CH_3), 19.7 (CH_3), 30.2 (CH_2Ar), 31.7 (CH(CH$_3$)$_2$), 55.3 (OCH_3), 56.7 (CH_2), 63.6 (CH_2), 66.9 (NCH), 110.3 (CH), 120.4 (CH), 125.9 (C), 127.7 (CH), 128.0 (CH), 128.6 (CH), 130.7 (CH), 133.9 (CH), 136.7 (C), 140.1 (C), 140.6 (CH), 157.7 (C), 175.6 (C=O); m/z (ES$^+$) 440 (100 %, MH$^+$); HRMS $C_{26}H_{38}NO_3Si$ calcd. 440.2615, found 440.2634.

(*S*)-2-{*tert*-Butoxycarbonyl[(*Z*)-2-(dimethylphenylsilanyl)but-2-enyl]amino}-3-methylbutyric acid 2-(2-methoxyphenyl)ethyl ester 132

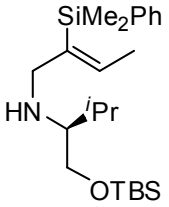


132

To a solution of **135** (621 mg, 1.41 mmol) in Et_3N (5 mL) was added di-*tert*-butyldicarbonate (370 mg, 1.70 mmol) in Et_3N (3 mL + 1 mL wash). The reaction was heated to reflux for 5 h then allowed to cool to rt. The solvent was then removed *in vacuo*. Purification by flash-column chromatography

(20 % Et_2O/pet. ether) yielded **132** (528 mg, 69 %) as a colourless oil; R_f = 0.69 (20 % Et_2O/pet. ether); $[\alpha]_D$ - 52.6 (c = 1.0, $CHCl_3$); IR ν_{max} (solution in $CHCl_3$) 2932 - 2873 (C-H), 1731 (C=O), 1682 (C=O), 1456, 1367, 1124, 1110 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.41 (6H, s, $Si(CH_3)_2$), 0.88 (3H, d, *J* = 6.8, $CH(CH_3)_2$), 0.90 (3H, d, *J* = 6.1, $CH(CH_3)_2$), 1.42 (9H, s, $C(CH_3)_3$), 1.58 (3H, br s, $C=CHCH_3$), 2.17 - 2.31 (1H, br m, $CH(CH_3)_2$), 2.95 (2H, t, *J* = 7.3, CH_2Ar), 3.80 (3H, s, OCH_3), 3.93 - 4.49 (5H, m, NCH, NCH_2, CO_2CH_2), 5.95 - 6.18 (1H, br m, $C=CHCH_3$), 6.85 [1H, d, *J* = 8.2, ArH, (*o*-OMe)], 6.89 [1H, dt, *J* = 7.4, 0.9, ArH, (*p*-OMe)], 7.14 [1H, d, *J* = 7.3, ArH, (*o*-CH_2)], 7.22 [1H, dt, *J* = 8.2, 1.5, ArH, (*m*-OMe)], 7.33 - 7.36 (3H, m, ArH), 7.52 - 7.55 (2H, m, ArH); ^{13}C NMR (270 MHz, d_6-DMSO, 80 °C) δ - 2.1 ($Si(CH_3)_2$), 17.7, 19.3, 25.0, 25.7, 28.5, 28.6, 47.5, 50.6, 56.0, 64.2, 64.3, 79.8, 111.7, 120.9, 126.1, 128.2, 128.3, 128.4, 129.4, 130.7, 133.0, 134.0, 134.1, 138.8, 157.9 (C=O), 170.6 (C=O); ^{13}C NMR (400 MHz, $CDCl_3$) - 0.1 ($Si(CH_3)_2$), 29.8 ($CH(CH_3)_2$), 31.4 (CH_2Ar), 56.7 (OCH_3), 65.6 (CH_2), 111.7 (CH), 122.0 (CH), 127.3 (C), 129.3 (CH), 129.5 (CH), 130.4 (CH), 132.3 (CH), 133.3 (CH), 140.6 (C), 159.1 (C=O), 172.4 (C=O); m/z (ES^+) 562 (100 %, MNa^+), 506 (48 %, MNa^+ - C_4H_8), 462 (30 %, MNa^+ - Boc); HRMS $C_{31}H_{46}NO_5Si$ calcd. 540.3140, found 540.3109.

[(*S*)-1-(*tert*-Butyldimethylsilanyloxymethyl)-2-methylpropyl][(*Z*)-2-(dimethylphenylsilanyl)but-2-enyl]amine 139

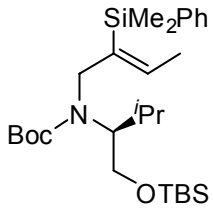


139

To a stirred solution of *O*-TBS-(*L*)-valinol (3.46 g, 15.9 mmol) in MeCN (50 mL) was added *via* cannula bromide **102** (4.72 g, 17.5 mmol) in MeCN (20 mL + 5 mL wash). Potassium carbonate (2.64 g, 19.1 mmol) was added and the reaction was stirred for 14 h. The reaction was then diluted with Et_2O (50 mL) and water (50 mL) added. The layers were separated and the aqueous re-extracted with Et_2O (30 mL). The combined organic layers were washed with brine (50 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash-column chromatography (20 % Et_2O/pet. ether) yielded **139** (4.42 g, 69 %) as a colourless oil; R_f = 0.49 (20 % Et_2O/pet. ether); $[\alpha]_D$ + 20.9 (c = 0.9, $CHCl_3$); IR ν_{max} (film) 3322 (N-H), 2954 - 2857 (C-H), 1462, 1386, 1362, 1109 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.07 (6H, s, Si(CH_3)$_2$), 0.44 (3H, s, Si(CH_3)$_2$), 0.45 (3H, s, Si(CH_3)$_2$), 0.89 - 0.95 (15H, m, SiC(CH_3)$_3$, CH(CH_3)$_2$), 1.03 (1H, br s, N*H*), 1.62 (3H, d, *J* = 6.9, C=CHCH_3), 1.84 (1H, d septet, *J* = 6.9, 1.9, C*H*(CH_3)$_2$), 2.36 (1H, app. q, *J* = 5.1, NC*H*), 3.26 (2H, s, NCH_2), 3.53 (1H, dd, *J* = 10.0, 5.8, OCH_2), 3.63 (1H, dd, *J* = 10.1, 4.8, OCH_2), 6.32 (1H, q, *J* = 6.9, C=C*H*CH_3), 7.33 - 7.35

(3H, m, Ar*H*), 7.57 - 7.60 (2H, m, Ar*H*); ^{13}C NMR (500 MHz, $CDCl_3$) δ -1.1 (Si(*C*H_3)$_2$), 18.2 (*C*H_3), 18.4 (*C*(CH_3)$_3$), 18.9 (*C*H_3), 19.0 (*C*H_3), 26.1 (*C*H_3), 28.9 (*C*H(CH_3)$_2$), 56.2 (*C*H_2), 62.2 (*C*H_2), 64.3 (N*C*H), 127.8 (*C*H), 128.7 (*C*H), 134.0 (*C*H), 137.6 (*C*), 139.9 (*C*H), 140.2 (*C*); m/z (ES^+) 406 (100 %, MH^+); HRMS $C_{23}H_{44}NOSi_2$ calcd. 406.2956, found 406.2945; Anal. calcd. for $C_{23}H_{43}NOSi_2$ C 68.08, H 10.68, N 3.45, found C 68.13, H 10.78, N 3.47 %.

[(*S*)-1-(*tert*-Butyldimethylsilanyloxymethyl)-2-methylpropyl][(*Z*)-2-(dimethylphenylsilanyl)but-2-enyl]carbamic acid *tert*-butyl ester 138

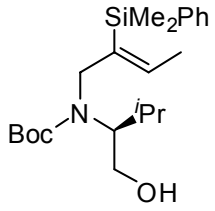


138

To a stirred solution of **139** (4.42 g, 10.9 mmol) in Et_3N (30 mL) was added di-*tert*-butyldicarbonate (4.76 g, 21.8 mmol) in Et_3N (20 mL + 5 mL wash). The reaction mixture was heated to reflux for 14 h after which the reaction was allowed to cool to rt and the solvent was removed *in vacuo*. Purification by flash-column chromatography (10 % Et_2O/pet. ether) yielded **138** (3.91 g, 71 %) as a white solid (mp 53.9 - 54.7 °C); R_f = 0.27 (10 % Et_2O/pet. ether); $[\alpha]_D$ + 9.8 (c = 1.9, $CHCl_3$); IR ν_{max} (solution in $CHCl_3$) 2956 - 2857 (C-H), 1679 (C=O), 1456, 1309, 1366, 1110, 1076 cm^{-1}; ^{1}H NMR (500

MHz, $CDCl_3$) δ 0.03 (3H, s, Si(C*H*$_3$)$_2$), 0.04 (3H, s, Si(C*H*$_3$)$_2$), 0.41 (3H, s, Si(C*H*$_3$)$_2$), 0.42 (3H, s, Si(C*H*$_3$)$_2$), 0.88 - 0.90 (12H, m, SiC(C*H*$_3$)$_3$, CH(C*H*$_3$)$_2$), 0.96 (3H, d, *J* = 6.5, CH(C*H*$_3$)$_2$), 1.40 - 1.50 (9H, m, OC(C*H*$_3$)$_3$), 1.65 - 1.71 (3H, m, C=CHC*H*$_3$), 1.80 - 1.92 (1H, br m, C*H*(CH$_3$)$_2$), 3.60 - 3.95 (5H, m, NC*H*$_2$, NC*H*, OC*H*$_2$), 6.28 (1H, br q, *J* = 6.0, C=C*H*CH$_3$), 7.34 - 7.35 (3H, m, Ar*H*), 7.55 - 7.56 (2H, m, Ar*H*); ^{13}C NMR (270 MHz, d_6-DMSO) δ - 9.8, - 5.6, - 1.4, 18.1, 29.3, 28.8, 128.3, 129.5, 134.0; ^{13}C NMR (270 MHz, d_6-DMSO, 80 °C) δ - 2.2 (Si(*C*H$_3$)$_2$), - 1.0 (Si(*C*H$_3$)$_2$), - 0.9 (Si(*C*H$_3$)$_2$), 20.6, 20.7, 24.3, 26.3, 27.6, 28.6, 31.8. 50.6, 63.2, 67.6, 78.2, 111.2, 124.8, 128.2, 129.4, 132.9, 134.0, 155.9 (*C*=O); m/z (ES$^+$) 528 (71 %, MNa$^+$), 450 (38 %, MH$^+$ - C_4H_8), 406 (100 %, MH$^+$ - Boc), 372 (24 %); HRMS $C_{28}H_{51}NNaO_3Si_2$ calcd. 528.3300, found 528.3314.

[(*Z*)-2-(dimethylphenylsilanyl)but-2-enyl]((*S*)-1-hydroxymethyl-2-methylpropyl)carbamic acid *tert*-butyl ester 137

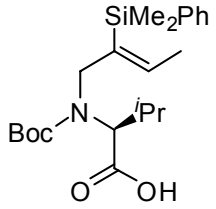


137

A stirred solution of **138** (1.23 g, 2.44 mmol) in THF (10 mL) was treated with TBAF (6.1 mL of 1 M solution in THF, 6.1 mmol). The reaction was

stirred at rt for 3 h, then diluted with Et_2O (10 mL). Water (10 mL) was added and the layers were separated. The aqueous layer was re-extracted with Et_2O (10 mL). The combined organic layers were washed with brine (15 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash-column chromatography (30 % Et_2O/pet. ether) yielded **137** (740 mg, 78 %) as a colourless oil; R_f = 0.17 (30 % Et_2O/pet. ether); $[\alpha]_D$ - 11.3 (c = 2.0, $CHCl_3$); IR ν_{max} (solution in $CHCl_3$) 3355 (O-H), 2966 (C-H), 1666 (C=O), 1455, 1390, 1367, 1350, 1110 cm^{-1}; ^1H NMR (500 MHz, d_6-DMSO) δ 0.37 (6H, s, Si(C*H*$_3$)$_2$), 0.79 (3H, d, *J* = 6.6, CH(C*H*$_3$)$_2$), 0.91 (3H, d, *J* = 6.6, CH(C*H*$_3$)$_2$), 1.36 (9H, s, C(C*H*$_3$)$_3$), 1.59 (3H, d, *J* = 6.9, C=CHC*H*$_3$), 1.82 (1H, app. br sextet, *J* = 7.1, C*H*(CH$_3$)$_2$), 3.49 - 3.80 (5H, m, NC*H*$_2$, O*H*, OC*H*$_2$), 4.47 (1H, app. t, *J* = 4.8, NC*H*), 6.17 (1H, q, *J* = 6.9, C=C*H*CH$_3$), 7.35 - 7.37 (3H, m, Ar*H*), 7.52 - 7.54 (2H, m, Ar*H*); ^{13}C NMR (270 MHz, d_6-DMSO, 80 °C) δ - 1.0 (Si(*C*H$_3$)$_2$), - 0.9 (Si(*C*H$_3$)$_2$), 17.8, 20.6, 20.8, 28.7, 29.0, 51.0, 62.1, 65.1, 78.7, 128.3, 129.3, 133.5, 134.0, 136.0, 139.4, 156.0 (*C*=O); m/z (ES^+) 414 (100 %, MNa^+); HRMS $C_{22}H_{37}NNaO_3Si$ calcd. 414.2435, found 414.2425.

(*S*)-2-{*tert*-Butoxycarbonyl[(*Z*)-2-(dimethylphenylsilanyl)but-2-enyl]amino}-3-methylbutyric acid 136

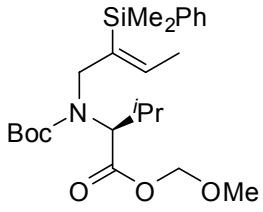


136

A solution of periodic acid (146 mg, 0.639 mmol) and chromium trioxide (1 mg, 0.01 mmol) in wet MeCN (1.6 mL) was added dropwise to a stirring solution of **137** (100 mg, 0.256 mmol) in MeCN (1 mL). The reaction was stirred for 4 h, then quenched with pH 7 phosphate buffer (2 mL). Toluene (2 mL) was added and the layers separated. The organic layer was washed with water (2 mL), 0.4 M aq. $NaHSO_3$ (2 mL) and brine (2 mL), then dried ($MgSO_4$). The solvent was removed *in vacuo* to furnish **136** (90 mg, 87 %) as a colourless oil, which was used with no further purification; $[\alpha]_D$ - 55.2 (c = 1.0, $CHCl_3$); IR ν_{max} (film) 3069 - 2875 (C-H), 1739 (C=O), 1688 (C=O), 1613, 1427, 1280, 1251, 1182, 1154 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.39 (3H, s, Si(CH_3)$_2$), 0.43 (3H, s, Si(CH_3)$_2$), 0.91 (3H, d, *J* = 6.6, CH(CH_3)$_2$), 1.00 (3H, d, *J* = 6.6, CH(CH_3)$_2$), 1.46 (9H, s, C(CH_3)$_3$), 1.68 (3H, d, *J* = 6.7, C=CHCH_3), 2.60 (1H, br s, C*H*(CH$_3$)$_2$), 3.41 - 3.45 (2H, br m, NCH_2), 4.42 (1H, br d, *J* = 14.3, NC*H*) 6.13 - 6.21 (1H, br m, C=C*H*CH$_3$), 7.36 (3H, br s, Ar*H*), 7.51 (2H, br s, Ar*H*); ^{13}C NMR (270 MHz, d_6-DMSO) δ - 2.9 (Si(*C*H$_3$)$_2$), -2.8 (Si(*C*H$_3$)$_2$), 18.9, 19.8, 28.3, 48.9,

58.6, 63.4, 64.0 (*C*H_2), 70.0 (*C*H_2), 79.8, 122.1, 128.4 (*C*H), 129.8 (*C*H), 134.2 (*C*H), 137.2, 145.3, 170.6 (*C*=O) ^{13}C NMR (270 MHz, d_6-DMSO, 80 °C) δ - 1.1 (Si(*C*H_3)$_2$), - 1.0 (Si(*C*H_3)$_2$), 17.8, 19.5, 20.7, 22.9, 28.5, 28.7, 50.9, 64.5, 79.6, 128.3, 129.3, 132.9, 134.0, 136.5, 139.3, 155.7 (*C*=O), 172.1 (*C*=O); m/z (ES$^+$) 428 (100 %, MNa^+), 372 (50 %, MNa^+ - C_4H_8), 328 (50 %, MH^+ - Boc), 272 (44 %); HRMS $C_{22}H_{35}NNaO_4Si$ calcd. 428.2228, found 428.2230.

(*S*)-2-{*tert*-Butoxycarbonyl-[(*Z*)-2-(dimethylphenylsilanyl)but-2-enyl]amino}-3-methylbutyric acid methoxymethyl ester 144

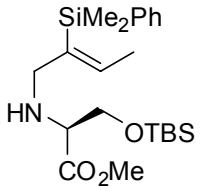


144

To a stirred solution of **136** (23 mg, 57 μmol) in CH_2Cl_2 (1 mL) at 0 °C was added Et_3N (7.9 μL, 57 μmol), followed by chloromethyl methyl ether (4.6 μL, 57 μmol). The reaction was allowed to warm to rt and stirred for 14 h. The reaction mixture was then diluted with $CHCl_3$ (1 mL) and washed with 0.1 M aq. HCl (1 mL). The organic layer was dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash-column chromatography (30 % Et_2O/pet. ether) gave **144** (21 mg, 82 %) as a colourless oil; R_f = 0.39 (30 % Et_2O/pet. ether); $[\alpha]_D$ - 27.6 (c = 2.0, $CHCl_3$); IR ν_{max} (solution in $CHCl_3$)

2960 - 2874 (C-H), 1744 (C=O), 1682 (C=O), 1456, 1367, 1110, 1089 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.41 (6H, s, Si(CH_3)$_2$), 0.90 (3H, d, *J* = 6.8, CH(CH_3)$_2$), 0.98 (3H, d, *J* = 6.5, CH(CH_3)$_2$), 1.42 - 1.45 (9H, m, C(CH_3)$_3$), 1.63 (3H, d, *J* = 7.0, C=CHCH_3), 2.25 (1H, br s, C*H*(CH_3)$_2$), 3.45 (3H, s, OCH_3), 3.72 - 4.41 (3H, m, NCH_2, N*CH*), 5.10 (1H, d, *J* = 5.8, CH_2OCH_3), 5.22 (1H, d, *J* = 5.7, CH_2OCH_3), 6.04 - 6.15 (1H, br m, C=C*H*CH_3), 7.34 - 7.35 (3H, m, Ar*H*), 7.51 - 7.55 (2H, m, Ar*H*); ^{13}C NMR (500 MHz, $CDCl_3$) δ - 1.6 (Si(CH_3)$_2$), - 1.5 (Si(CH_3)$_2$), 28.3, 57.8, 90.9, 127.8, 128.9, 133.8, 134.1, 170.6 (*C*=O); ^{13}C NMR (270 MHz, d_6-DMSO, 80 °C) δ - 1.2 (Si(CH_3)$_2$), - 1.1 (Si(CH_3)$_2$), 17.7, 19.4, 20.5, 28.5, 28.7, 51.2, 57.6, 64.6, 80.0, 91.1, 128.3, 129.4, 133.0, 134.0, 136.5, 139.2, 155.5 (*C*=O), 170.3 (*C*=O); m/z (ES^+) 472 (100 %, MNa^+); HRMS $C_{24}H_{39}NNaO_5Si$ calcd. 472.2490, found 472.2483.

(*S*)-3-(*tert*-Butyldimethylsilanyloxy)-2-[(*Z*)-2-(dimethylphenylsilanyl)-but-2-enylamino]propionic acid methyl ester 147

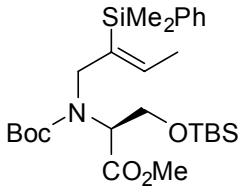


147

To a stirred solution of *O*-TBS-(*L*)-serine methyl ester (1.44 g, 6.18 mmol) in MeCN (20 mL) was added a solution of chloride **111** (1.53 g, 6.80 mmol)

in MeCN (10mL + 1 mL wash). Potassium carbonate (1.02 g, 7.42 mmol) and TBAI (228 mg, 0.618 mmol) were added and the reaction mixture was stirred for 14 h. The reaction was diluted with Et_2O (15 mL) and water (20 mL) added. The layers were separated and the aqueous layer was re-extracted with Et_2O (20 mL). The combined organic layers were washed with brine (2 x 30 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash-column chromatography (25 % Et_2O/pet. ether) yielded **147** (2.29 g, 88 %) as a colourless oil; R_f = 0.58 (25 % Et_2O/pet. ether); $[\alpha]_D$ - 13.7 (c = 1.2, $CHCl_3$); IR ν_{max} (solution in $CHCl_3$) 3334 (N-H), 2953 - 2857 (C-H), 1739 (C=O), 1462, 1110 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.04 (3H, s, Si(C*H*$_3$)$_2$), 0.05 (3H, s, Si(C*H*$_3$)$_2$), 0.44 (3H, s, Si(C*H*$_3$)$_2$), 0.45 (3H, s, Si(C*H*$_3$)$_2$), 0.88 (9H, s, SiC(C*H*$_3$)$_3$), 1.64 (3H, d, *J* = 6.9, C=CHC*H*$_3$), 1.73 (1H, br s, N*H*), 3.12 (1H, d, *J* = 12.3, NC*H*$_2$), 3.31 (1H, t, *J* = 5.0, NC*H*), 3.41 (1H, d, *J* = 12.3, NC*H*$_2$), 3.70 (1H, dd, *J* = 9.6, 5.4, C*H*$_2$O), 3.72 (3H, s, OC*H*$_3$), 3.81 (1H, dd, *J* = 9.6, 4.7, C*H*$_2$O), 6.29 (1H, q, *J* = 6.9, C=C*H*CH$_3$), 7.33 - 7.35 (3H, m, Ar*H*), 7.57 - 7.58 (2H, m, Ar*H*); ^{13}C NMR (500 MHz, $CDCl_3$) δ - 1.4 (Si(*C*H$_3$)$_2$), - 1.1 (Si(*C*H$_3$)$_2$), 18.0 (*C*H$_3$), 18.3 (*C*(CH$_3$)$_3$), 25.9 (C(*C*H$_3$)$_3$), 51.6 (OCH$_3$), 55.9 (*C*H$_2$), 62.1 (NCH), 64.8 (*C*H$_2$), 127.7 (*C*H), 128.7 (*C*H), 133.9 (*C*H), 136.6 (*C*), 139.8 (*C*), 140.5 (*C*H), 174.3 (*C*=O); m/z (ES^+) 444 (36 %, MNa^+), 422 (100 %, MH^+), 316 (53 %); HRMS $C_{22}H_{40}NO_3Si_2$ calcd. 422.2541, found 422.2546; Anal. calcd. for $C_{22}H_{39}NO_3Si_2$ C 62.66, H 9.32, N 3.32, found C 62.36, H 9.20, N 3.28 %.

(*S*)-2-{*tert*-Butoxycarbonyl-[(*Z*)-2-(dimethylphenylsilanyl)but-2-enyl]amino}-3-(*tert*-butyldimethylsilanyloxy)propionic acid methyl ester 148

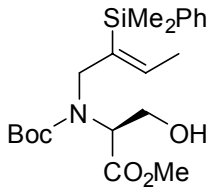


148

To a stirred solution of **147** (993 mg, 2.36 mmol) in Et_3N (5 mL) was added di-*tert*-butyldicarbonate (617 mg, 2.83 mmol) in Et_3N (5 mL + 0.5 mL wash). The reaction mixture was heated to reflux for 14 h after which the reaction was allowed to cool to rt and the solvent was removed *in vacuo*. Purification by flash-column chromatography (15 % Et_2O/pet. ether) furnished **148** (1.19 mg, 97 %) as a colourless oil; R_f = 0.34 (10 % Et_2O/pet. ether); $[\alpha]_D$ - 48.6 (c = 1.0, CH_2Cl_2); IR ν_{max} (solution in CH_2Cl_2) 2928 - 2857 (C-H), 1738 (C=O), 1693 (C=O), 1367, 1109, 1075 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.06 (6H, s, Si(CH_3)$_2$), 0.41 (3H, s, Si(CH_3)$_2$), 0.43 (3H, s, Si(CH_3)$_2$), 0.90 (9H, s, SiC(CH_3)$_3$), 1.42 - 1.47 (9H, m, OC(CH_3)$_3$), 1.66 (3H, d, *J* = 7.0, C=CHCH_3), 3.55 - 4.65 (8H, m, NCH_2, NC*H*, CH_2O, OCH_3), 6.41 (1H, br s, C=C*H*CH$_3$), 7.34 - 7.35 (3H, m, Ar*H*), 7.52 - 7.56 (2H, m, Ar*H*); ^{13}C NMR (270 MHz, d_6-DMSO) δ - 1.3 (Si(*C*H$_3$)$_2$), - 1.1 (Si(*C*H$_3$)$_2$), 18.4, 26.2, 28.4, 52.0, 128.3, 134.0; ^{13}C NMR (270 MHz, d_6-DMSO, 80 °C) δ - 5.1 (Si(*C*H$_3$)$_2$), - 5.0 (Si(*C*H$_3$)$_2$), - 1.2 (Si(*C*H$_3$)$_2$), - 1.1

($Si(CH_3)_2$), 18.0, 18.3, 26.2, 28.5, 51.9, 53.8, 60.7, 62.6, 79.9, 128.3, 129.3, 133.7, 134.0, 139.3, 154.8 (*C*=O), 170.4 (*C*=O), 1 peak missing; m/z (ES^+) 544 (100 %, MNa^+), 488 (98 %, MNa^+ - C_4H_8), 444 (63 %, MNa^+ - Boc), 388 (17 %), 334 (22 %); HRMS $C_{27}H_{47}NNaO_5Si_2$ calcd. 544.2885, found 544.2910; Anal. calcd. for $C_{27}H_{47}NO_5Si_2$ C 62.14, H 9.08, N 2.68, found C 61.89, H 9.07, N 2.66 %.

(*S*)-2-{*tert*-Butoxycarbonyl-[(*Z*)-2-(dimethylphenylsilanyl)but-2-enyl]amino}-3-hydroxypropionic acid methyl ester 146

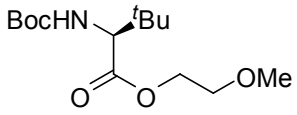


146

A stirred solution of **148** (1.00 g, 1.92 mmol) in THF (4 mL) was treated with TBAF (2.3 mL of 1 M solution in THF, 2.3 mmol). The reaction was stirred at rt for 4 h. Water (5 mL) was added and the layers were separated. The aqueous layer was re-extracted with Et_2O (5 mL). The combined organic layers were washed with brine (2 x 5 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash-column chromatography (30 % Et_2O/pet. ether) yielded **146** (633 mg, 81 %) as a colourless oil; R_f = 0.19 (25 % Et_2O/pet. ether); $[\alpha]_D$ - 22.3 (c = 2.0, $CHCl_3$); IR ν_{max} (solution in $CHCl_3$) 3566 (O-H), 2954 (C-H), 1730 (C=O), 1698 (C=O), 1455, 1368,

1110, 1044 cm^{-1}; ^1H NMR (500 MHz, d_6-DMSO) δ 0.36 (3H, s, Si(CH_3)$_2$), 0.38 (3H, s, Si(CH_3)$_2$), 1.34 (9H, s, C(CH_3)$_3$), 1.59 (3H, d, *J* = 7.0, C=CHCH_3), 3.57 (3H, s, OCH_3), 3.67 - 4.35 (5H, m, NCH_2, NC*H*, CH_2OH), 4.85 - 4.90 (1H, br m, O*H*), 6.19 - 6.39 (1H, br m, C=C*H*CH$_3$), 7.35 - 7.37 (3H, m, Ar*H*), 7.51 - 7.53 (2H, m, Ar*H*); ^{13}C NMR (270 MHz, d_6-DMSO, 80 °C) δ - 2.8 (Si(*C*H$_3$)$_2$), 18.3, 26.2, 52.0, 61.7, 62.2, 79.7, 80.0, 125.4, 128.3, 129.6, 134.1, 138.0, 146.0, 155.1 (*C*=O), 170.3 (*C*=O); m/z (ES^+) 430 (100 %, MNa^+), 374 (26 %, MNa^+ - C_4H_8); HRMS $C_{21}H_{33}NNaO_5Si$ calcd. 430.2020, found 430.2004.

(*S*)-2-*tert*-Butoxycarbonylamino-3,3-dimethylbutyric acid 2-methoxyethyl ester 151

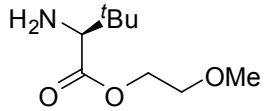


151

A stirring solution of Boc-(*L*)-*tert*-leucine (2.26 g, 9.78 mmol) in CH_2Cl_2 (20 mL) was cooled to - 30 ºC and treated with DMAP (120 mg, 0.978 mmol) and DCC (2.02 g, 9.78 mmol). After stirring for 10 min at - 30 ºC, 2-methoxyethanol (0.77 mL, 9.8 mmol) was added. The solution was stirred for 14 h, allowing to warm to rt, after which the solvent was removed *in vacuo*. The white precipitate was taken up in EtOAc (30 mL), filtered

through a plug of Celite and concentrated *in vacuo*. Purification by flash-column chromatography (10 % Et_2O/pet. ether) yielded ester **151** (2.71 g, 96 %) as a colourless oil; R_f = 0.09 (10 % Et_2O/pet. ether); $[\alpha]_D$ + 9.0 (c = 1.0, $CHCl_3$); IR ν_{max} (film) 3444 (N-H), 2967 - 2934 (C-H), 1713 (C=O), 1392, 1369, 1339, 1129, 1064 cm^{-1}; ^1H NMR (500 MHz, $(CD_3)_2CO$) δ 1.00 (9H, s, $CHC(CH_3)_3$), 1.40 (9H, s, $OC(CH_3)_3$), 3.31 (3H, s, OCH_3), 3.58 (2H, t, *J* = 4.8, CH_2OCH_3), 4.04 (1H, br d, *J* = 9.5, NC*H*), 4.19 (1H, br dt, *J* = 11.8, 4.6, CO_2CH_2), 4.29 (1H, ddd, *J* = 12.0, 5.5, 4.2, CO_2CH_2), 5.99 (1H, br d, *J* = 8.5, N*H*); ^{13}C NMR (500 MHz, $(CD_3)_2CO$) δ 25.9 ($C(CH_3)_3$), 27.3 ($C(CH_3)_3$), 34.1 ($CHC(CH_3)_3$), 57.8 (OCH_3), 62.1 (NCH), 63.3 (CH_2OCH_3), 70.0 (CO_2CH_2), 78.4 ($OC(CH_3)_3$), 155.5 (*C*=O), 171.4 (*C*=O); m/z (ES^+) 312 (84 %, MNa^+), 190 (100 %, MH^+ - Boc); HRMS $C_{14}H_{27}NNaO_5$ calcd. 312.1787, found 312.1772.

(*S*)-2-Amino-3,3-dimethylbutyric acid 2-methoxyethyl ester 152

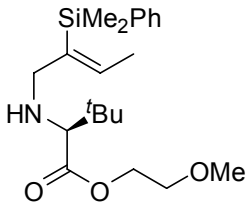


152

Anhydrous HCl (2.27 mL of 4 M solution in dioxane, 9.09 mmol) was added dropwise to **151** (876 mg, 3.03 mmol) with stirring. The reaction was stirred at rt for 5 h then the solvent was removed *in vacuo*. The oil was

partitioned between CH_2Cl_2 (10 mL) and saturated aq. $NaHCO_3$ (10 mL). The layers were separated and the aqueous layer re-extracted with CH_2Cl_2 (10 mL). The combined organic layers were washed with water (15 mL) then brine (15 mL) and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield **152** (544 mg, 95 %) as a colourless oil with no need for further purification; $[\alpha]_D$ + 44.9 (c = 1.3, CH_2Cl_2); IR ν_{max} (film) 3406 (N-H), 2873 - 2818 (C-H), 1731 (C=O), 1126, 1098, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (9H, s, $C(CH_3)_3$), 1.58 (2H, br s, NH_2), 3.17 (1H, s, NC*H*), 3.34 (3H, s, OCH_3), 3.56 (2H, t, *J* = 4.7, CH_2OCH_3), 4.18 - 4.27 (2H, m, CO_2CH_2); ^{13}C NMR (400 MHz, $CDCl_3$) δ 26.4 ($C(CH_3)_3$), 34.4 ($C(CH_3)_3$), 58.8 (OCH_3), 63.2 (CH_2OCH_3), 63.3 (NCH), 70.4 (CO_2CH_2), 175.0 (C=O); m/z (ES^+) 190 (100 %, MH^+); HRMS $C_9H_{20}NO_3$ calcd. 190.1438, found 190.1433.

(*S*)-2-[(*Z*)-2-(Dimethylphenylsilanyl)but-2-enylamino]-3,3-dimethyl-butyric acid 2-methoxyethyl ester 153

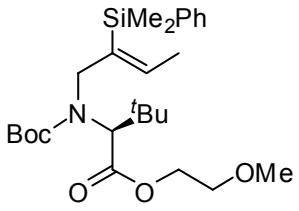


153

To a stirred solution of amine **152** (681 mg, 3.60 mmol) in MeCN (10 mL) was added bromide **102** (1.16 g, 4.32 mmol) in MeCN (10 mL + 1 mL

wash). Potassium carbonate (598 mg, 4.32 mmol) was added and the reaction mixture was stirred for 14 h. The reaction was quenched with water (15 mL) and diluted with Et_2O (15 mL). The layers were separated and the aqueous re-extracted with Et_2O (10 mL). The combined organic layers were washed with brine (20 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash-column chromatography (15 % Et_2O/pet. ether) yielded **153** (1.13 g, 83 %) as a colourless oil; R_f = 0.36 (20 % Et_2O/pet. ether); $[\alpha]_D$ + 7.2 (c = 1.0, $CHCl_3$); IR ν_{max} (film) 3682 (N-H), 2957 (C-H), 1723 (C=O), 1369, 1126, 1110 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.40 (3H, s, $Si(CH_3)_2$), 0.43 (3H, s, $Si(CH_3)_2$), 0.95 (9H, s, $C(CH_3)_3$), 1.32 (1H, br s, N*H*), 1.59 (3H, d, *J* = 6.9, C=CHCH_3), 2.93 (1H, s, NC*H*), 3.07 (1H, d, *J* = 11.4, NCH_2), 3.18 (1H, d, *J* = 11.4, NCH_2), 3.39 (3H, s, OCH_3), 3.61 (2H, t, *J* = 4.8, CH_2OCH_3), 4.28 (1H, dt, *J* = 12.2, 3.7, CO_2CH_2), 4.32 (1H, dt, *J* = 12.2, 4.9, CO_2CH_2), 6.26 (1H, q, *J* = 6.9, C=C*H*CH_3), 7.33 - 7.34 (3H, m, Ar*H*), 7.56 - 7.59 (2H, m, Ar*H*); ^{13}C NMR (500 MHz, $CDCl_3$) δ -1.3 ($Si(CH_3)_2$), - 1.2 ($Si(CH_3)_2$), 18.1 (CH_3), 27.0 (CH_3), 34.0 ($C(CH_3)_3$), 57.1 (CH_2), 59.0 (OCH_3), 62.9 (CH_2), 70.1 (NCH), 70.7 (CH_2), 127.8 (CH), 128.7 (CH), 134.0 (CH), 136.8 (*C*), 140.2 (*C*), 141.0 (CH), 175.3 (*C*=O); m/z (ES^+) 378 (100 %, MH^+); HRMS $C_{21}H_{36}NO_3Si$ calcd. 378.2464, found 378.2458; Anal. calcd. for $C_{21}H_{35}NO_3Si$: C 66.80, H 9.34, N 3.71, found: C 66.46, H 9.37, N 4.00 %.

(*S*)-2-{*tert*-Butoxycarbonyl-[(*Z*)-2-(dimethylphenylsilanyl)but-2-enyl]-amino}-3,3-dimethylbutyric acid 2-methoxyethyl ester 150

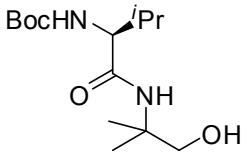


150

To **153** (298 mg, 0.790 mmol) was added di-*tert*-butyldicarbonate (190 mg, 0.869 mmol) with stirring. The reaction was heated to 130°C for 16 h then allowed to cool to rt. Purification by flash-column chromatography (20 % Et_2O/pet. ether) yielded **150** (172 mg, 47 %) as a colourless oil; R_f = 0.32 (20 % Et_2O/pet. ether); $[\alpha]_D$ - 23.9 (c = 2.9, $CHCl_3$); IR ν_{max} (solution in $CHCl_3$) 2958 (C-H), 1738 (C=O), 1682 (C=O), 1455, 1368, 1110, 1046 cm^{-1}; ^1H NMR (270 MHz, d_6-DMSO) δ 0.30 (6H, s, $Si(CH_3)_2$), 0.94 (9H, s, $C(CH_3)_3$), 1.35 (9H, s, $C(CH_3)_3$), 1.54 (3H, d, *J* = 7.0, C=CHCH_3), 3.23 (3H, s, OCH_3), 3.48 (2H, t, *J* = 4.7, CH_2OCH_3), 3.85 - 4.65 (5H, m, CO_2CH_2, NCH_2, NCH), 5.82 (1H, br s, C=CHCH$_3$), 7.31 - 7.40 (3H, m, ArH), 7.48 - 7.59 (2H, m, ArH); ^{13}C NMR (270 MHz, d_6-DMSO) δ - 2.4, - 2.3, 16.7, 26.4, 27.2, 35.5, 50.1, 57.6, 62.7, 69.0, 78.5, 127.3, 128.5, 131.7, 133.0, 137.8, 168.6; ^{13}C NMR (270 MHz, d_6-DMSO, 80 °C) δ - 2.1 ($Si(CH_3)_2$), 16.7, 26.7, 27.6, 35.6, 50.7, 57.8, 62.8, 64.5, 69.4, 78.9, 127.4, 128.6, 132.3, 132.8, 133.2, 138.2, 155.3 (C=O), 168.9 (C=O); m/z (ES^+) 500 (94 %,

MNa^+), 444 (100 %, MNa^+ - C_4H_8), 400 (45 %, MNa^+ - Boc); HRMS $C_{26}H_{43}NNaO_5Si$ calcd. 500.2803, found 500.2832; Anal. calcd. for $C_{26}H_{43}NO_5Si$: C 65.37, H 9.07, N 2.93, found: C 65.18, H 8.78, N 3.21 %.

[(*S*)-1-(2-Hydroxy-1,1-dimethylethylcarbamoyl)-2-methylpropyl]-carbamic acid *tert*-butyl ester 163

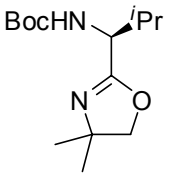


163

A stirring solution of Boc-(*L*)-valine (13.1 g, 60.5 mmol) in THF (100 mL) was cooled to - 15 ºC and treated with *N*-methyl morpholine (8.00 mL, 72.6 mmol) and *iso*butyl orthochloroformate (9.42 mL, 72.6 mmol). After stirring for 1 h at - 15 ºC, 2-amino-2-methyl-1-propanol (5.39 g, 60.5 mmol) in THF (50 mL) was added. The solution was stirred for 2 h, allowing to warm to rt. The reaction mixture was then filtered through a plug of Celite and concentrated *in vacuo*. Purification by flash-column chromatography (100 % Et_2O) yielded amide **163** (15.2 g, 87 %) as a white solid (mp 153.8 - 154.2 °C); R_f = 0.28 (100 % Et_2O); $[\alpha]_D$ - 17.0 (c = 1.0, $CHCl_3$); IR ν_{max} (solution in $CHCl_3$) 3430 (N-H), 3008 - 2876 (C-H), 1704 (C=O), 1497, 1392, 1369, 1241, 1162 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.94 (3H, d, *J*

= 6.8, CH(CH_3)$_2$), 0.97 (3H, d, *J* = 6.8, CH(CH_3)$_2$), 1.28 (3H, s, NHC(CH_3)$_2$), 1.31 (3H, s, NHC(CH_3)$_2$) 1.45 (9H, s, OC(CH_3)$_3$), 2.00 - 2.09 (1H, br m, C*H*(CH$_3$)$_2$), 3.55 (1H, dd, *J* = 11.0, 6.0, CH_2OH), 3.63 (1H, dd, *J* = 11.6, 5.9, CH_2OH), 3.74 (1H, app. t, *J* = 7.4, NC*H*), 4.52 (1H, br s, O*H*), 5.05 (1H, br s, N*H*), 6.15 (1H, br s, N*H*); ^{13}C NMR (400 MHz, $CDCl_3$) δ 18.2 (CH(*C*H$_3$)$_2$), 19.2 (CH(*C*H$_3$)$_2$), 24.2 (NHC(*C*H$_3$)$_2$), 24.7 (NHC(*C*H$_3$)$_2$), 28.2 (C(*C*H$_3$)$_3$), 30.7 (*C*H(CH$_3$)$_2$), 56.1 (NH*C*(CH$_3$)$_2$), 60.8 (N*C*H), 69.8 (*C*H$_2$OH), 80.1 (O*C*(CH$_3$)$_3$), 156.2 (*C*=O), 175.5 (*C*=O); m/z (ES$^+$) 311 (100 %, MNa$^+$); HRMS $C_{14}H_{28}N_2NaO_4$ calcd. 311.1941, found 311.1941; Anal. calcd. for $C_{14}H_{28}N_2O_4$: C 58.31, H 9.79, N 9.71, found: C 58.20, H 9.96, N 9.56 %.

[(*S*)-1-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-2-methylpropyl]carbamic acid *tert*-butyl ester 160

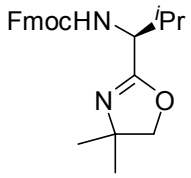


160

To a stirred solution of **163** (534 mg, 1.85 mmol) in THF (10 mL) was added Burgess reagent **162** (530 mg, 2.23 mmol). The reaction was stirred at rt for 3 h then the solvent was removed *in vacuo*. Purification by flash-column chromatography (50 % Et_2O/pet. ether) furnished **160** (480 mg, 96

%) as a colourless oil; R_f = 0.61 (50 % Et_2O/pet. ether); $[\alpha]_D$ - 12.0 (c = 1.0, $CHCl_3$); IR ν_{max} (solution in $CHCl_3$) 3445 (N-H), 3011 - 2933 (C-H), 1712 (C=O), 1666 (C=N), 1503, 1392, 1368, 1169 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.74 (3H, d, *J* = 6.9, $CH(CH_3)_2$), 0.78 (3H, d, *J* = 6.8, $CH(CH_3)_2$), 1.07 (6H, s, $NHC(CH_3)_2$), 1.26 (9H, s, $C(CH_3)_3$), 1.90 (1H, app. br sextet, *J* = 6.3, $CH(CH_3)_2$), 3.76 (1H, d, *J* = 8.1, CH_2O), 3.79 (1H, d, *J* = 8.1, CH_2O), 4.06 (1H, dd, *J* = 8.8, 5.0, NC*H*), 5.04 (1H, br d, *J* = 8.8, N*H*); ^{13}C NMR (400 MHz, $CDCl_3$) δ 17.6 ($CH(CH_3)_2$), 18.7 ($CH(CH_3)_2$), 28.3 ($C(CH_3)_3$), 28.7 ($C(CH_3)_3$), 31.7 ($CH(CH_3)_2$), 53.7 (NCH), 67.0 ($C(CH_3)_2$), 79.3 (CH_2O), 79.4 ($C(CH_3)_3$), 155.5 (*C*), 165.0 (*C*); m/z (ES^+) 293 (100 %, MNa^+); HRMS $C_{14}H_{26}N_2NaO_3$ calcd. 293.1836, found 293.1838; Anal. calcd. for $C_{14}H_{26}N_2O_3$: C 62.19, H 9.69, N 10.36, found: C 61.98, H 9.90, N 10.06 %.

[(*S*)-1-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-2-methylpropyl]carbamic acid 9*H*-fluoren-9-ylmethyl ester 165

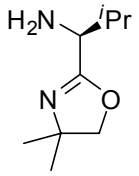


165

To a stirred solution of Fmoc-(*L*)-valine (4.35 g, 12.8 mmol) in CH_2Cl_2 (250 mL) was added 2-amino-2-methyl-1-propanol (1.14 g, 12.8 mmol),

triphenylphosphine (10.1 g, 38.5 mmol) and DIPEA (6.70 mL, 38.5 mmol). The reaction mixture was cooled to 0 °C and carbon tetrachloride (6.18 mL, 64.1 mmol) was added over 4 h using a syringe pump. During this time, the reaction was allowed to warm to rt. The reaction was stirred for 1 h and then adsorbed onto silica. The solvent was removed *in vacuo* and gel filtration (40 % EtOAc/pet. ether) followed by removal of the solvent *in vacuo* furnished **165** (4.98 g, 99 %) as a white solid (mp 59.5 - 60.4 °C); R_f = 0.29 (40 % EtOAc/pet. ether); $[\alpha]_D$ - 14.4 (c = 1.7, $CHCl_3$); IR ν_{max} (solution in $CHCl_3$) 3437 (N-H), 2965 - 2875 (C-H), 1722 (C=O), 1666 (C=N), 1367, 1313, 1094 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.95 (3H, d, *J* = 6.8, $CH(CH_3)_2$), 0.98 (3H, d, *J* = 6.9, $CH(CH_3)_2$), 1.30 (6H, s, $NHC(CH_3)_2$), 2.13 (1H, app. br octet, *J* = 6.3, $CH(CH_3)_2$), 3.99 (2H, s, $CH_2C(CH_3)_2$), 4.25 (1H, t, *J* = 7.1, OCH_2CH), 4.32 - 4.47 (3H, m, OCH_2CH, NCH), 5.41 (1H, br d, *J* = 8.9, NH), 7.32 (2H, app. t, *J* = 7.4, ArH), 7.41 (2H, app. t, *J* = 7.5, ArH), 7.63 (2H, app. t, *J* = 8.0, ArH), 7.77 (2H, d, *J* = 7.5, ArH); ^{13}C NMR (500 MHz, $CDCl_3$) δ 17.7 ($CH(CH_3)_2$), 18.9 ($CH(CH_3)_2$), 28.4 ($C(CH_3)_2$), 28.6 ($C(CH_3)_2$), 31.8 ($CH(CH_3)_2$), 47.4 ($CHCH_2O$), 54.4 (NCH), 67.0 ($C(CH_3)_2$), 67.3 (CO_2CH_2), 79.6 ($CH_2C(CH_3)_2$), 120.1 (ArCH), 125.3 (ArCH), 127.2 (ArCH), 127.8 (ArCH), 141.4 (*C*), 144.2 (*C*), 156.3 (*C*), 164.8 (*C*); m/z (ES^+) 415 (53 %, MNa^+), 393 (100 %, MH^+); HRMS $C_{24}H_{29}N_2O_3$ calcd. 393.2173, found 393.2190.

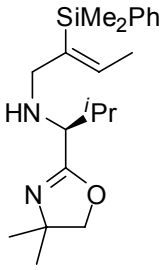
(*S*)-1-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-2-methylpropylamine 164



164

To a stirred solution of **165** (1.10 g, 2.81 mmol) in MeOH (28 mL) at 0 °C was added *via* cannula piperidine (28 mL, 10 mL/mmol). The reaction was stirred for 30 min after which time the solvent was removed *in vacuo* to yield **164** (306 mg, 64 %) as a colourless oil, which was used with no further purification; $[\alpha]_D$ - 1.5 (c = 1.9, $CHCl_3$); IR ν_{max} (solution in $CHCl_3$) 3390 (N-H), 2931 - 2872 (C-H), 1661 (C=N), 1462, 1367, 1292, 1131 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.74 (3H, d, *J* = 6.8, $CH(CH_3)_2$), 0.77 (3H, d, *J* = 6.8, $CH(CH_3)_2$), 1.07 (3H, s, $C(CH_3)_2$), 1.08 (3H, s, $C(CH_3)_2$), 1.45 (2H, br s, NH_2), 1.75 (1H, app. octet, *J* = 6.6, $CH(CH_3)_2$), 3.09 (1H, d, *J* = 5.7, NCH), 3.75 (2H, s, CH_2O); ^{13}C NMR (500 MHz, $CDCl_3$) δ 17.5 (CH_3), 19.3 (CH_3), 28.4 (CH_3), 32.1 ($CH(CH_3)_2$), 55.4 (NCH), 66.7 ($C(CH_3)_2$), 79.2 (CH_2O), 168.1 (C=N); m/z (ES^+) 171 (100 %, MH^+); HRMS $C_9H_{19}N_2O$ calcd. 171.1492, found 171.1494.

[(*S*)-1-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-2-methylpropyl][(*Z*)-2-(dimethylphenylsilanyl)but-2-enyl]amine 166

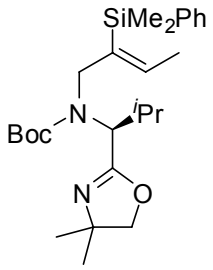


166

To a stirred solution of amine **164** (260 mg, 1.53 mmol) in MeCN (5 mL) was added a solution of chloride **111** (378 mg, 1.68 mmol) in MeCN (5 mL + 1 mL wash). Potassium carbonate (253 mg, 1.84 mmol) and TBAI (56 mg, 0.15 mmol) were added and the reaction mixture was stirred for 14 h. The reaction was diluted with Et_2O (10 mL) and water (10 mL) added. The layers were separated and the aqueous layer was re-extracted with Et_2O (10 mL). The combined organic layers were washed with brine (2 x 10 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. Purification by flash-column chromatography (50 % Et_2O/pet. ether) yielded **166** (334 mg, 61 %) as a colourless oil; R_f = 0.48 (50 % EtOAc/pet. ether); $[\alpha]_D$ - 12.2 (c = 1.0, CH_2Cl_2); IR ν_{max} (solution in CH_2Cl_2) 3321 (N-H), 2894 - 2812 (C-H), 1660 (C=N), 1365, 1110 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.42 (3H, s, $Si(CH_3)_2$), 0.44 (3H, s, $Si(CH_3)_2$), 0.92 (3H, d, *J* = 6.7, $CH(CH_3)_2$), 0.98 (3H, d, *J* = 6.7, $CH(CH_3)_2$), 1.29 (3H, s, $C(CH_3)_2$), 1.31 (3H, s, $C(CH_3)_2$), 1.59 (3H, d, *J* = 6.9, $C{=}CHCH_3$), 1.79 (1H, app. octet, *J* = 6.9, $CH(CH_3)_2$),

2.96 (1H, d, *J* = 7.6, NC*H*), 3.10 (1H, d, *J* = 12.0, NCH_2), 3.30 (1H, d, *J* = 12.0, NCH_2), 3.91 (1H, d, *J* = 8.1, OCH_2), 3.95 (1H, d, *J* = 8.1, OCH_2), 6.26 (1H, q, *J* = 6.9, C=C*H*CH_3), 7.31 - 7.33 (3H, m, Ar*H*), 7.55 - 7.57 (2H, m, Ar*H*); ^{13}C NMR (500 MHz, $CDCl_3$) δ - 1.4 (Si(*C*H_3)$_2$), - 1.3 (Si(*C*H_3)$_2$), 18.0, 19.6, 28.6, 28.8, 31.8, 55.9, 61.8, 67.0, 78.8, 127.7, 128.6, 133.8, 136.6, 140.0, 140.3, 166.5 (*C*=N); m/z (ES^+) 359 (100 %, MH^+); HRMS $C_{21}H_{35}N_2OSi$ calcd. 359.2513, found 359.2505.

[(*S*)-1-(4,4-Dimethyl-4,5-dihydrooxazol-2-yl)-2-methylpropyl]-[(*Z*)-2-(dimethylphenylsilanyl)but-2-enyl]carbamic acid *tert*-butyl ester 159

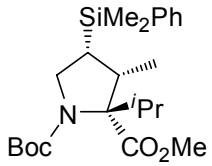


159

To a stirred solution of **166** (129 mg, 0.360 mmol) in Et_3N (2 mL) was added di-*tert*-butyldicarbonate (118 mg, 0.541 mmol) in Et_3N (1 mL + 0.5 mL wash). The reaction mixture was heated to reflux for 14 h after which the reaction was allowed to cool to rt and the solvent was removed *in vacuo*. Purification by flash-column chromatography (40 % Et_2O/pet. ether) yielded **159** (143 mg, 87 %) as a colourless oil; R_f = 0.12 (30 % Et_2O/pet. ether); $[\alpha]_D$ + 14.8 (c = 1.3, $CHCl_3$); IR ν_{max} (solution in $CHCl_3$) 2964 - 2929 (C-H),

1682, 1455, 1367, 1110 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.43 (3H, s, Si(CH_3)$_2$), 0.47 (3H, s, Si(CH_3)$_2$), 0.94 (3H, d, *J* = 6.7, CH(CH_3)$_2$), 1.04 (3H, br d, *J* = 3.9, CH(CH_3)$_2$), 1.29 (3H, s, NC(CH_3)$_2$), 1.30 (3H, s, NC(CH_3)$_2$), 1.46 - 1.54 (9H, m, C(CH_3)$_3$), 1.66 (3H, d, *J* = 7.0, C=CHCH_3), 2.23 (1H, d septet, *J* = 11.2, 6.6, C*H*(CH$_3$)$_2$), 3.70 - 4.71 (5H, m, NC*H*, NCH_2, OCH_2), 6.02 - 6.08 (1H, br m, C=C*H*CH$_3$), 7.32 - 7.39 (3H, m, Ar*H*), 7.58 - 7.59 (2H, m, Ar*H*); ^{13}C NMR (500 MHz, $CDCl_3$) δ - 1.4 (Si(*C*H$_3$)$_2$), 28.1, 28.4, 28.8, 127.8, 133.8; ^{13}C NMR (270 MHz, d_6-DMSO, 80 °C) δ - 1.2 (Si(*C*H$_3$)$_2$), - 1.0 (Si(*C*H$_3$)$_2$), 17.6, 19.2, 20.1, 28.3, 28.5, 28.6, 29.1, 48.5, 58.7, 67.2, 78.7, 79.5, 128.3, 128.4, 129.4, 133.2, 134.0, 139.0, 155.9 (*C*=O), 162.8 (*C*=O); m/z (ES^+) 459 (100 %, MH^+), 403 (68 %, MH^+ - C_4H_8); HRMS $C_{26}H_{43}N_2O_3Si$ calcd. 459.3037, found 459.3020.

(2*R,3*R**,4*R**)-4-(Dimethylphenylsilanyl)-2-*iso*propyl-3-methyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester 119**

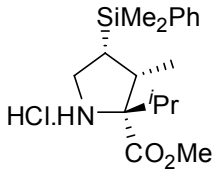


(±)-119

Precursor **66** (1.68 g, 4.01 mmol) was converted to pyrrolidine **119** *via* general procedure A. The crude material was purified by flash-column chromatography (20 % Et_2O/pet. ether) to yield **119** (1.09 g, 65 %) as a

colourless solid (mp 72.1 - 73.3 °C); R_f = 0.21 (20 % Et_2O/pet. ether); IR ν_{max} (solution in $CHCl_3$) 2967 - 2878 (C-H), 1733 (C=O), 1682 (C=O), 1392, 1367, 1350, 1113 cm^{-1}; ^1H NMR (400 MHz, d_6-DMSO) δ $0.30_{rot.}$, $0.32_{rot.}$, $0.37_{rot.}$ (6H, s, $Si(CH_3)_2$), 0.79 (3H, d, *J* = 7.3, $CH(CH_3)_2$), $0.82_{rot.}$, $0.84_{rot.}$ (3H, d, *J* = 6.8, $CH(CH_3)_2$), 1.12 (3H, app. t, *J* = 6.7, $CHCH_3$), $1.37_{rot.}$, $1.46_{rot.}$ (9H, s, $C(CH_3)_3$), 1.70 - 1.84 (1H, m, $CHSiMe_2Ph$), 2.63 (1H, app. sextet, *J* = 6.7, $CH(CH_3)_2$), 2.74 (1H, app. septet, *J* = 6.9, $CHCH_3$), 3.34 - 3.58 (5H, m, NCH_2, OCH_3), 7.38 - 7.40 (3H, m, Ar*H*), 7.52 - 7.54 (2H, m, Ar*H*); ^{13}C NMR (270 MHz, d_6-DMSO) δ - 2.3 ($Si(CH_3)_2$), - 2.1 ($Si(CH_3)_2$), - 1.8 ($Si(CH_3)_2$), 17.4 (CH_3), 17.5 (CH_3), 19.8 (CH_3), 20.3 (CH_3), 28.3 (CH_3), 28.5 (CH_3), 30.5 (*C*H), 31.4 (*C*H), 31.9 (*C*H), 32.9 (*C*H), 38.8 (*C*H), 49.9 (CH_2), 50.1 (CH_2), 51.3 (CH_3), 51.5 (CH_3), 75.9 (*C*), 76.4 (*C*), 79.2 (*C*), 79.3 (*C*), 128.4 (Ar*C*H), 129.6 (Ar*C*H), 133.9 (Ar*C*H), 138.4 (Ar*C*), 153.5 (*C*=O), 154.1 (*C*=O), 173.7 (*C*=O), 174.0 (*C*=O); ^{13}C NMR (270 MHz, d_6-DMSO, 80 °C) δ - 2.4 ($Si(CH_3)_2$), - 1.8 ($Si(CH_3)_2$), 17.4, 19.8, 20.0, 28.6, 30.8, 32.6, 50.3, 51.2, 76.6, 79.4, 128.5, 129.6, 133.9, 138.7, 153.7 (*C*=O), 173.7 (*C*=O); m/z (ES^+) 442 (40 %, MNa^+), 320 (100 %, MH^+ - Boc); HRMS $C_{23}H_{37}NNaO_4Si$ calcd. 422.2384, found 442.2387; Anal. calcd. for $C_{23}H_{37}NO_4Si$ C 65.83, H 8.89, N 3.34, found C 65.57, H 8.90, N 3.29 %.

(2*R,3*R**,4*R**)-4-(Dimethyphenylsilanyl)-2-*iso*propyl-2-methoxy-carbonyl-3-methylpyrrolidium chloride 168**

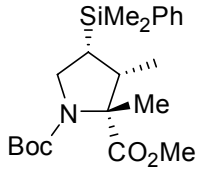


(±)-168

To Boc-protected pyrrolidine **119** (156 mg, 0.372 mmol) was added, with stirring, HCl (0.28 mL of 4 M solution in dioxane, 1.1 mmol). The reaction was stirred for 2 h, at which time the solvent was removed *in vacuo* to yield **168** (131 mg, 99 %) as a colourless solid (mp 80.4 - 81.5 °C), which was deemed > 95 % pure by ^{1}H NMR; IR ν_{max} (solution in $CHCl_3$) 2926 - 2854 (C-H), 1746 (C=O), 1459, 1380, 1266, 1113 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.38 (3H, s, Si(CH_3)$_2$), 0.44 (3H, s, Si(CH_3)$_2$), 0.96 (3H, d, *J* = 7.3, CHCH_3), 1.12 (3H, d, *J* = 6.9, CH(CH_3)$_2$), 1.21 (3H, d, *J* = 6.8, CH(CH_3)$_2$), 1.99 (1H, ddd, *J* = 13.7, 8.4, 6.4, C*H*SiMe$_2$Ph), 2.32 (1H, septet, *J* = 6.8, C*H*(CH$_3$)$_2$), 2.69 (1H, app. quintet, *J* = 6.8, C*H*CH$_3$), 3.73 (1H, app. t, *J* = 12.5, NCH_2), 3.79 (3H, s, OCH_3), 3.88 (1H, dd, *J* = 11.4, 8.5, NCH_2), 7.36 - 7.40 (3H, m, Ar*H*), 7.49 - 7.51 (2H, m, Ar*H*), 9.55 (1H, br s, N*H*), 10.10 (1H, br s, N*H*); ^{13}C NMR (270 MHz, d$_6$-DMSO) δ - 3.1 (Si(*C*H$_3$)$_2$), - 2.3 (Si(*C*H$_3$)$_2$), 15.2 (CH*C*H$_3$), 17.8 (CH(*C*H$_3$)$_2$), 18.4 (CH(*C*H$_3$)$_2$), 29.8 (*C*HSiMe$_2$Ph), 32.8 (*C*H(CH$_3$)$_2$), 41.6 (*C*HCH$_3$), 47.1 (N*C*H$_2$), 52.7 (O*C*H$_3$), 81.6 (N*C*), 128.4 (Ar*C*H), 129.8 (Ar*C*H), 133.6 (Ar*C*H), 136.6 (Ar*C*), 169.2

(*C*=O); m/z (ES^+) 320 (100 %, MH^+ - HCl); HRMS $C_{18}H_{30}NO_2Si$ calcd. 320.2046, found 320.2036.

(2*R,3*R**,4*R**)-4-(Dimethylphenylsilanyl)-2,3-dimethylpyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester 170**

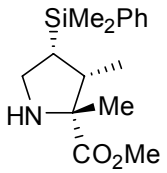


(±)-170

Precursor **65** (616 mg, 1.58 mmol) was converted *via* general procedure A to pyrrolidine **170**. The crude products were purified by flash-column chromatography (25 % Et_2O/pet. ether) to furnish **170** (253 mg, 41 %) as a colourless oil; R_f = 0.22 (25 % Et_2O/pet. ether); IR ν_{max} (solution in $CHCl_3$) 2954 - 2879 (C-H), 1732 (C=O), 1683 (C=O), 1392, 1368, 1118 cm^{-1}; ^1H NMR (500 MHz, d_6-DMSO) δ 0.30 - 0.35 (6H, m, Si(CH_3)$_2$), 0.89$_{rot.}$, 0.91$_{rot.}$ (3H, d, *J* = 7.3, CHCH_3), 1.30 - 1.43 (12H, m, C(CH_3)$_3$, CCH_3), 1.77 (1H, ddd, *J* = 12.5, 8.1, 6.2, C*H*SiMe$_2$Ph), 2.27$_{rot.}$, 2.36$_{rot.}$ (1H, app. quintet, *J* = 6.7, C*H*CH$_3$), 3.29 - 3.41 (1H, m, NCH_2), 3.55 - 3.66 (4H, m, NCH_2, OCH_3), 7.38 - 7.41 (3H, m, Ar*H*), 7.49 - 7.54 (2H, m, Ar*H*); ^{13}C NMR (500 MHz, d_6-DMSO) δ - 2.4 (Si(*C*H$_3$)$_2$), - 2.2 (Si(*C*H$_3$)$_2$), 13.9 (*C*H$_3$), 14.1 (*C*H$_3$), 19.7 (*C*H$_3$), 20.7 (*C*H$_3$), 28.3 (*C*H), 28.5 (*C*H), 28.6 (*C*H), 44.7 (*C*H),

45.9 (*C*H), 48.5 (*C*H_2), 48.7 (*C*H_2), 52.6 (*C*H_3), 52.7 (*C*H_3), 69.1 (*C*), 69.5 (*C*), 79.1 (*C*), 79.3 (*C*), 128.4 (*C*H), 128.5 (*C*H), 129.7 (*C*H), 133.9 (*C*H), 134.1 (*C*H), 138.1 (*C*), 138.2 (*C*), 154.0 (*C*=O), 175.1 (*C*=O), 175.4 (*C*=O); ^{13}C NMR (270 MHz, d_6-DMSO, 80 °C) δ - 2.6 (Si(*C*H_3)$_2$), - 2.1 (Si(*C*H_3)$_2$), 14.0, 28.7, 28.9, 48.8, 52.5, 69.2, 79.1, 128.4, 129.7, 133.9, 138.4, 153.5 (*C*=O), 3 peaks missing; m/z (ES^+) 414 (100 %, MNa^+), 358 (73 %, MNa^+ - C_4H_8), 314 (93 %, MNa^+ - Boc); HRMS $C_{21}H_{33}NNaO_4Si$ calcd. 414.2071, found 414.2075.

(2*R,3*R**,4*R**)-4-(Dimethylphenylsilanyl)-2,3-dimethylpyrrolidine-2-carboxylic acid methyl ester 171**

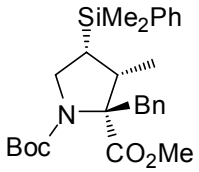


(±)-171

Boc-deprotection of **170** (100 mg, 0.256 mmol) occured *via* general procedure B to yield **171** (72 mg, 98 %) as a colourless oil; IR ν_{max} (solution in $CHCl_3$) 3168 (N-H), 2958 (C-H), 1710 (C=O), 1454, 1372, 1039 cm^{-1}; ^{1}H NMR (500 MHz, C_6D_6) δ 0.35 (3H, s, Si(C*H*$_3$)$_2$), 0.42 (3H, s, Si(C*H*$_3$)$_2$), 0.99 (3H, d, *J* = 7.3, CHC*H*$_3$), 1.37 (3H, s, CC*H*$_3$), 1.80 (1H, ddd, *J* = 11.2, 9.4, 6.4, C*H*SiMe$_2$Ph), 2.12 (1H, br s, N*H*), 2.81 (1H, app. quintet, *J* = 7.0, C*H*CH$_3$), 3.18 (1H, app. t, *J* = 10.5, NC*H*$_2$), 3.28 (1H, app. t, *J* = 9.6,

NCH_2), 3.39 (3H, s, OCH_3), 7.29 - 7.32 (3H, m, Ar*H*), 7.51 - 7.52 (2H, m, Ar*H*); ^{13}C NMR (400 MHz, $CDCl_3$) δ - 0.7 (Si(*C*H_3)$_2$), 0.0 (Si(*C*H_3)$_2$), 16.1 (*C*H_3), 23.8 (*C*H_3), 34.3 (*C*H), 44.5 (*C*H), 48.6 (N*C*H_2), 73.0 (NH*C*), 130.3 (Ar*C*H), 131.6 (Ar*C*H), 136.2 (Ar*C*H), 141.1 (Ar*C*), 181.5 (*C*=O); m/z (ES$^+$) 292 (100 %, MH$^+$); HRMS $C_{16}H_{26}NO_2Si$ calcd. 292.1727, found 292.1730.

(2*R,3*R**,4*R**)-2-Benzyl-4-(dimethylphenylsilanyl)-3-methyl-pyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester 173**

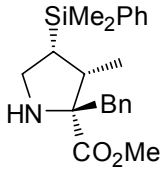


(±)-173

Cyclisation of **67** (103 mg, 0.221 mmol) was achieved *via* general procedure A. Purification by flash-column chromatography (25 % Et_2O/pet. ether) gave **173** (36 mg, 35 %) as a colourless oil; R_f = 0.19 (25 % Et_2O/pet. ether); IR ν_{max} (solution in $CHCl_3$) 2978 (C-H), 1732, (C=O), 1683 (C=O), 1393, 1367, 1114 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.05 - 0.32 (6H, m, Si(CH_3)$_2$), 0.73 - 0.85 (3H, m, CHCH_3), 1.13$_{rot.}$, 1.42$_{rot.}$, 1.46$_{rot.}$ (9H, s, C(CH_3)$_3$), 1.82 - 1.98 (1H, m, C*H*SiMe$_2$Ph), 2.56$_{rot.}$, 2.71$_{rot.}$ (1H, app. quintet, *J* = 8.4, C*H*CH$_3$), 2.97 - 3.85 (7H, m, NCH_2, OCH_3, CH_2Ph), 7.13 - 7.23 (5H, m, Ar*H*), 7.35 - 7.38 (3H, m, Ar*H*), 7.51 - 7.53 (2H, m, Ar*H*); ^{13}C

NMR (500 MHz, d_6-DMSO) δ - 2.6 (Si(*C*H_3)$_2$), - 2.1 (Si(*C*H_3)$_2$), 16.0 (*C*H_3), 28.0 (*C*H), 28.6 (*C*H), 28.8 (*C*H), 29.1 (*C*H), 36.6 (*C*H_2), 37.2 (*C*H_2), 45.1 (*C*H), 47.3 (*C*H), 48.8 (*C*H_2), 52.6 (*C*H_3), 72.0 (*C*), 73.0 (*C*), 79.5 (*C*), 79.6 (*C*), 126.3 (*C*H), 127.2 (*C*H), 128.3 (*C*H), 128.4 (*C*H), 128.7 (*C*H), 129.7 (*C*H), 130.4 (*C*H), 130.6 (*C*H), 130.7 (*C*H), 133.6 (*C*H), 133.9 (*C*H), 134.0 (*C*H), 138.2 (*C*), 138.7 (*C*), 138.8 (*C*), 153.4 (*C*=O), 174.3 (*C*=O); ^{13}C NMR (270 MHz, d_6-DMSO, 80 °C) δ - 2.5 (Si(*C*H_3)$_2$), - 2.0 (Si(*C*H_3)$_2$), 15.8, 28.5, 29.3, 37.1, 46.2, 49.0, 52.2, 72.7, 79.6, 126.3, 128.3, 128.5, 129.7, 130.5, 130.8, 133.7, 134.0, 138.4, 138.9, 153.9 (*C*=O), 174.4 (*C*=O); m/z (ES$^+$) 490 (100 %, MNa$^+$), 434 (74 %, MNa$^+$ - C_4H_8), 390 (61 %, MNa$^+$ - Boc); HRMS $C_{27}H_{37}NNaO_4Si$ calcd. 490.2384, found 490.2407.

(2*R,3*R**,4*R**)-2-Benzyl-4-(dimethylphenylsilanyl)-3-methyl-pyrrolidine-2-carboxylic acid methyl ester 174**

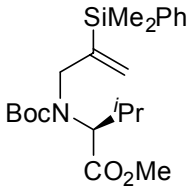


(±)-174

Boc-deprotection of **173** (48 mg, 0.10 mmol) was achieved *via* general procedure B to yield **174** (37 mg, 98 %) as a colourless oil; IR ν_{max} (solution in $CHCl_3$) 3341 (N-H), 2952 - 2873 (C-H), 1727 (C=O), 1455, 1375, 1110, 1049 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.38 (3H, s, Si(CH_3)$_2$), 0.44 (3H,

s, Si(CH_3)$_2$), 1.16 (3H, d, J = 7.2, CHCH_3), 1.55 (1H, ddd, J = 11.2, 9.9, 6.2, CHSiMe$_2$Ph), 2.45 (1H, br s, NH), 2.77 (1H, app. quintet, J = 6.7, CHCH$_3$), 2.84 (1H, d, J = 12.8, CH_2Ph), 3.12 (1H, d, J = 12.8, CH_2Ph), 3.20 (1H, dd, J = 11.2, 10.2, NCH_2), 3.27 (1H, app. t, J = 9.8, NCH_2), 3.63 (3H, s, OCH_3), 7.19 - 7.20 (2H, m, ArH), 7.24 - 7.32 (3H, m, ArH), 7.41 - 7.44 (3H, m, ArH), 7.54 - 7.57 (2H, m, ArH); ^{13}C NMR (500 MHz, $CDCl_3$) δ - 3.0 (Si(CH$_3$)$_2$), - 2.6 (Si(CH$_3$)$_2$), 14.0 (CHCH$_3$), 31.3 (CHSiMe$_2$Ph), 41.8 (CH$_2$Ph), 43.1 (CHCH$_3$), 45.8 (NCH$_2$), 52.1 (OCH$_3$), 75.6 (NHC), 126.6 (ArCH), 127.9 (ArCH), 128.3 (ArCH), 129.1 (ArCH), 129.5 (ArCH), 133.8 (ArCH), 138.0 (ArC), 138.7 (ArC), 177.5 (C=O); m/z (ES$^+$) 390 (94 %, MNa$^+$), 368 (47 %, MH$^+$), 308 (48 %); HRMS $C_{22}H_{29}NNaO_2Si$ calcd. 390.1860, found 390.1845.

(*S*)-2-{*tert*-Butoxycarbonyl-[2-(dimethylphenylsilanyl)allyl]amino}-3-methylbutyric acid methyl ester 175



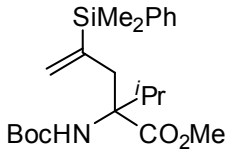
175

To a stirred suspension of KH (44 mg, 1.1 mmol) in THF (3 mL) at 0 °C was added a solution of Boc-(*L*)-valine methyl ester (231 mg, 1.00 mmol) in

THF (3 mL). The reaction was stirred for 1 h at 0 °C, then bromide **129** (306 mg, 1.20 mmol) in THF (2 mL) was added. The reaction was stirred for a further 14 h, then quenched with saturated aq. NH_4Cl (5 mL). Et_2O (4 mL) was added and the layers separated. The aqueous layer was re-extracted with Et_2O (5 mL) and the combined organic layers were washed with water (10 mL), brine (10 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash-column chromatography (25 % Et_2O/pet.ether) yielded **175** (320 mg, 79 %) as a colourless oil; R_f = 0.37 (25 % Et_2O/pet. ether); $[\alpha]_D$ - 26.5 (c = 2.1, $CHCl_3$); IR ν_{max} (solution in $CHCl_3$) 2965 - 2876 (C-H), 1737 (C=O), 1683 (C=O), 1455, 1391, 1368, 1329, 1138, 1110 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.39 (3H, s, $Si(CH_3)_2$), 0.40 (3H, s, $Si(CH_3)_2$), 0.86 (3H, d, *J* = 6.8, $CH(CH_3)_2$), 0.90 (3H, d, *J* = 6.5, $CH(CH_3)_2$), 1.40 - 1.48 (9H, m, $C(CH_3)_3$), 2.08 - 2.22 (1H, br m, $CH(CH_3)_2$), 3.59 (3H, s, OCH_3), 3.71 - 4.04 (3H, m, NCH_2, NCH), 5.35 - 5.42 (1H, br m, $C=CH_2$), 5.55 - 5.65 (1H, br m, $C=CH_2$), 7.34 - 7.37 (3H, m, ArH), 7.52 - 7.54 (2H, m, ArH); ^{13}C NMR (270 MHz, d_6-DMSO) δ - 3.1 ($Si(CH_3)_2$), 18.4, 18.9, 19.5, 20.3, 28.0, 47.2 (CH_2), 49.0 (CH_2), 51.8 (CH), 62.9, 64.4, 79.4, 79.7, 121.8 (CH_2), 124.8 (CH_2), 128.0 (CH), 129.1 (CH), 133.5 (CH), 137.1 (C), 145.3 (C), 155.4 (C=O), 170.6 (C=O); ^{13}C NMR (270 MHz, d_6-DMSO, 80 °C) δ - 3.9 ($Si(CH_3)_2$), - 3.8 ($Si(CH_3)_2$), 18.1, 19.1, 27.4, 47.8, 50.7, 63.3, 78.8, 122.7, 127.2, 128.6, 133.1, 136.7, 144.7, 154.5 (C=O), 170.0 (C=O); m/z (ES^+) 428 (100 %, MNa^+), 372 (27 %, MNa^+ - C_4H_8), 306 (16 %, MH^+ - Boc); HRMS $C_{22}H_{35}NNaO_4Si$ calcd. 428.2228, found 428.2222; Anal.

calcd. for $C_{22}H_{35}NO_4Si$ C 65.15, H 8.70, N 3.45, found C 65.12, H 8.78, N 3.21 %.

2-*tert*-Butoxycarbonylamino-4-(dimethylphenylsilanyl)-2-*iso*propylpent-4-enoic acid methyl ester 176

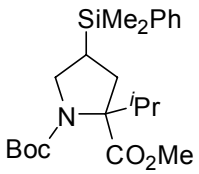


176

To a stirred solution of **175** (254 mg, 0.627 mmol, dried by azeotrope from toluene) in THF/DMPU (4:1, 2 mL) at 0 °C was added KMHDS (3.14 mL of 0.5 M solution in toluene, 1.57 mmol) dropwise. The reaction was stirred for 14 h, allowing to warm to rt. The reaction was then quenched with saturated aq. NH_4Cl (2 mL) and Et_2O (2 mL) added. The layers were separated and the aqueous layer was re-extracted with Et_2O (2 x 2 mL). The combined organic layers were washed with brine (2 x 5 mL), dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was purified by column chromatography (20 % Et_2O/pet. ether) to yield **176** (36 mg, 14 %) as a colourless oil; R_f = 0.45 (25 % Et_2O/pet. ether); IR ν_{max} (solution in $CHCl_3$) 3421 (N-H), 2954 (C-H), 1715 (C=O), 1456, 1391, 1367, 1110, 1069 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 0.35 (3H, s, Si(CH_3)$_3$), 0.38 (3H, s, Si(CH_3)$_3$), 0.84 (3H, d, J = 6.9, CH(CH_3)$_2$), 0.88 (3H, d, J = 6.9,

CH(CH_3)$_2$), 1.43 (9H, s, C(CH_3)$_3$), 2.44 (1H, septet, J = 6.9, CH(CH$_3$)$_2$), 2.74 (1H, d, J = 16.1, CH_2), 3.40 (1H, d, J = 16.1, CH_2), 3.58 (3H, s, OCH_3), 5.47 (1H, s, C=CH_2 or NH), 5.55 (1H, s, C=CH_2 or NH), 5.75 (1H, s, C=CH_2 or NH), 7.35 - 7.36 (3H, m, ArH), 7.50 - 7.52 (2H, m, ArH); ^{13}C NMR (500 MHz, $CDCl_3$) δ - 2.9 (Si(*C*H$_3$)$_2$), - 2.4 (Si(*C*H$_3$)$_2$), 17.7 (CH(*C*H$_3$)$_2$), 17.8 (CH(*C*H$_3$)$_2$), 28.5 (C(*C*H$_3$)$_3$), 34.8 (*C*H(CH$_3$)$_2$), 36.3 (*C*H$_2$), 52.1 (O*C*H$_3$), 66.3 (*C*), 78.9 (*C*), 127.7 (Ar*C*H), 128.2 (H$_2$*C*=C), 128.9 (Ar*C*H), 134.1 (Ar*C*H), 138.4 (*C*), 146.0 (*C*), 153.8 (*C*=O), 173.5 (*C*=O); m/z (ES$^+$) 428 (68 %, MNa$^+$), 372 (92 %, MNa$^+$ - C_4H_8), 328 (100 %, MNa$^+$ - Boc); HRMS $C_{22}H_{35}NNaO_4Si$ calcd. 428.2228, found 428.2222.

4-(Dimethylphenylsilanyl)-2-*iso*propylpyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester 177

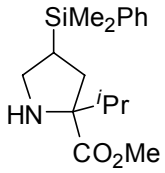


177

Precursor **175** (254 mg, 0.627 mmol) was converted *via* general procedure A to pyrrolidine **177**. The crude products were purified by flash-column chromatography (20 % Et_2O/pet. ether) to furnish **177** (170 mg, 67 %) as a colourless oil; R_f = 0.28 (25 % Et_2O/pet. ether); IR ν_{max} (solution in $CHCl_3$) 2968 (C-H), 1710 (C=O), 1494, 1392, 1367, 1110 cm^{-1}; ^{1}H NMR (500

MHz, $CDCl_3$) δ 0.30 (6H, s, Si(CH_3)$_2$), 0.90 (3H, d, *J* = 6.3, CH(CH_3)$_2$), 1.11 (3H, d, *J* = 6.6, CH(CH_3)$_2$), 1.40$_{rot.}$, 1.43$_{rot.}$ (9H, s, C(CH_3)$_3$), 1.57 - 1.65 (1H, m, C*H*SiMe$_2$Ph), 1.92 (1H, app. t, *J* = 13.3, CCH_2), 2.19$_{rot.}$, 2.26$_{rot.}$ (1H, dd, *J* = 12.8, 7.8, CCH_2), 2.68$_{rot.}$, 2.78$_{rot.}$ (1H, septet, *J* = 6.8 C*H*(CH_3)$_2$), 3.35$_{rot.}$, 3.45$_{rot.}$ (1H, app. t, *J* = 11.7, NCH_2), 3.60 (3H, s, OCH_3), 3.67$_{rot.}$, 3.75$_{rot.}$ (1H, app t, *J* = 9.5, NCH_2), 7.36 - 7.37 (3H, m, Ar*H*), 7.49 - 7.50 (2H, m, Ar*H*); ^{13}C NMR (500 MHz, $CDCl_3$) δ - 5.0 (Si(*C*H_3)$_2$), - 1.7 (Si(*C*H_3)$_2$), 19.2 (*C*H_3), 19.6 (*C*H_3), 24.0 (*C*H), 24.9 (*C*H), 28.1 (*C*H_3), 28.3 (*C*H_3), 30.9 (*C*H), 31.4 (*C*H), 34.2 (*C*H_2), 35.2 (*C*H_2), 51.1 (*C*H_2), 51.4 (*C*H_2), 51.5 (*C*H_3), 52.1 (*C*H_3), 71.5 (*C*), 72.0 (*C*), 79.3 (*C*), 80.0 (*C*), 127.8 (Ar*C*H), 129.2 (Ar*C*H), 133.6 (Ar*C*H), 136.7 (Ar*C*), 153.9 (*C*=O), 175.0 (*C*=O); m/z (ES$^+$) 428 (100 %, MNa$^+$); HRMS $C_{22}H_{35}NNaO_4Si$ calcd. 428.2228, found 428.2225.

4-(Dimethylphenylsilanyl)-2-*iso*propylpyrrolidine-2-carboxylic acid methyl ester 178

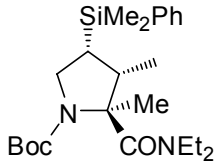


178

Boc-deprotection of **177** (99 mg, 0.24 mmol) was achieved *via* general procedure B to yield **178** (73 mg, 96 %) as a colourless oil; IR ν_{max} (solution

in CH_2Cl_2) 3020 (N-H), 2925 (C-H), 1722 (C=O), 1216, 845 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.30 (6H, s, $Si(CH_3)_2$), 0.87 (3H, d, J = 6.7, $CH(CH_3)_2$), 0.94 (3H, d, J = 6.8, $CH(CH_3)_2$), 1.52 - 1.69 (2H, m, $CHSiMe_2Ph$, N*H*), 1.90 - 2.03 (3H, m, CCH_2, $CH(CH_3)_2$), 2.69 (1H, dd, J = 12.5, 9.3, NCH_2), 3.07 (1H, dd, J = 9.2, 6.9, NCH_2), 3.71 (3H, s, OCH_3), 7.32 - 7.42 (3H, m, Ar*H*), 7.53 - 7.54 (2H, m, Ar*H*); ^{13}C NMR (500 MHz, $CDCl_3$) δ - 2.8 ($SiCH_3)_2$), - 2.5 ($Si(CH_3)_2$), 18.0 (CH_3), 25.7 (*C*H), 31.2 (*C*H), 35.5 (CH_2), 53.2 (CH_2), 62.1 (CH_3), 71.4 (*C*), 127.7 (Ar*C*H), 128.7 (Ar*C*H), 133.9 (Ar*C*H), 138.2 (Ar*C*), 173.9 (*C*=O); m/z (ES^+) 306 (100 %, MH^+); HRMS $C_{17}H_{28}NO_2Si$ calcd. 306.1884, found 306.1885.

(2*S,3*R**,4*R**)-2-Diethylcarbamoyl-4-(dimethylphenylsilanyl)-2,3-dimethylpyrrolidine-1-carboxylic acid *tert*-butyl ester 158**

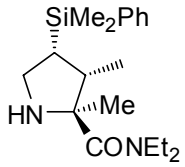


(±)-158

To a stirred suspension of KH (223 mg, 30 % suspension in mineral oil, washed twice with pet. ether, 5.56 mmol) in THF (16 mL) at 0 °C was added **63** (801 mg, 1.85 mmol) and 18-crown-6 (490 mg, 1.85 mmol) in THF (5 mL + 1 mL wash). The reaction was stirred for 1 h, then quenched with saturated aq. NH_4Cl (10 mL). Et_2O (10 mL) was added and the layers

were separated. The aqueous layer was re-extracted with Et_2O (10 mL) and the combined organic layers were washed with water (15 mL) then brine (15 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Purification by flash-column chromatography (50 % Et_2O/pet. ether) yielded **158** (602 mg, 75 %) as a colourless oil; R_f = 0.32 (50 % Et_2O/pet. ether); IR ν_{max} (solution in $CHCl_3$) 2975 (C-H), 1681 (C=O), 1629 (C=O), 1455, 1374, 1114 cm^{-1}; ^1H NMR (500 MHz, d_6-DMSO) δ 0.26 - 0.47 (6H, m, $Si(CH_3)_2$), $0.88_{rot.}$, $0.92_{rot.}$ (3H, d, *J* = 6.8, $CHCH_3$), 0.98 - 1.05 (6H, m, $N(CH_2CH_3)_2$), $1.32_{rot.}$, $1.38_{rot.}$ (9H, s, $C(CH_3)_3$), 1.50 - 1.53 (4H, m, CCH_3, $CHSiMe_2Ph$), $2.29_{rot.}$, $2.38_{rot.}$ (1H, br quintet, *J* = 6.6, $CHCH_3$), 3.00 - 3.55 (6H, m, NCH_2, $N(CH_2CH_3)_2$), 7.37 - 7.40 (3H, m, Ar*H*), 7.47 - 7.48 (2H, m, Ar*H*); ^{13}C NMR (500 MHz, d_6-DMSO) δ - 2.0 ($Si(CH_3)_2$), 13.3 (CH_3), 13.6 (CH_3), 21.1 (CH_3), 22.4 (CH_3), 27.3 (CH_3), 27.6 (CH_3), 28.5 (*C*H), 28.8 (*C*H), 42.9 (*C*H), 43.9 (*C*H), 48.1 (CH_2), 48.6 (CH_2), 71.5 (*C*), 71.7 (*C*), 78.3 (*C*), 78.6 (*C*), 128.4 (Ar*C*H), 129.7 (Ar*C*H), 133.7 (Ar*C*H), 138.3 (Ar*C*), 155.7 (*C*=O), 171.4 (*C*=O), 171.9 (*C*=O); ^{13}C NMR (270 MHz, d_6-DMSO, 80 °C) δ - 2.8 ($Si(CH_3)_2$), - 2.1 ($Si(CH_3)_2$), 13.5, 13.6, 21.5, 27.8, 28.8, 43.5, 48.6, 71.9, 78.7, 128.4, 129.6, 133.9, 138.5, 172.1 (*C*=O), 2 peaks missing; m/z (ES^+) 455 (100 %, MNa^+), 333 (60 %, MH^+); HRMS $C_{24}H_{40}N_2NaO_3Si$ calcd. 455.2700, found 455.2681.

(2*S,3*R**,4*R**)-4-(Dimethylphenylsilanyl)-2,3-dimethylpyrrolidine-2-carboxylic acid diethylamide 179**

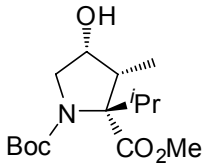


(±)-179

Boc-deprotection of **158** (200 mg, 0.463 mmol) was achieved *via* general procedure B. The crude pyrrolidine was purified by column chromatography using SCX powder. Before loading the product, the column was flushed with AcOH (5 % in MeOH), then MeOH. The crude material was loaded in CH_2Cl_2 and the column was once again flushed with MeOH. Methanolic ammonia (2 %) was then used as the eluent to furnish **179** (132 mg, 86 %) as a colourless oil; IR ν_{max} (solution in CH_2Cl_2) 3019 (N-H), 2873 (C-H), 1615 (C=O), 1360, 1215, 1109, 1064 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 0.27 (3H, s, Si(CH_3)$_2$), 0.35 (3H, s, Si(CH_3)$_2$), 0.93 (3H, d, *J* = 7.2, CHCH_3), 1.11 (6H, t, *J* = 7.0, N(CH_2CH_3)$_2$), 1.27 (3H, s, CCH_3), 1.46 (1H, ddd, *J* = 11.8, 9.0, 5.9, C*H*SiMe$_2$Ph), 2.53 (1H, app. quintet, *J* = 6.6, C*H*CH_3), 2.99 (1H, app. t, *J* = 11.1, NCH_2), 3.13 (1H, app. t, *J* = 9.6, NCH_2), 3.25 - 3.50 (4H, br m, N(CH_2CH_3)$_2$), 7.33 - 7.34 (3H, m, Ar*H*), 7.48 - 7.49 (2H, m, Ar*H*); ^{13}C NMR (500 MHz, $CDCl_3$) δ - 3.0 (Si(CH_3)$_2$), - 2.3 (Si(CH_3)$_2$), 12.6 (CH_3), 13.6 (CH_3), 13.9 (CH_3), 21.9 (CH_3), 32.3 (*C*H), 41.1 (CH_2), 41.3 (*C*H), 42.7 (CH_2), 45.7 (CH_2), 70.5 (*C*), 127.8 (Ar*C*H), 129.0 (Ar*C*H),

133.8 (Ar*C*H), 138.8 (Ar*C*), 176.3 (*C*=O); m/z (ES^+) 333 (100 %, MH^+); HRMS $C_{19}H_{33}N_2OSi$ calcd. 333.2357, found 333.2357.

(2*R,3*R**,4*R**)-4-Hydroxy-2-*iso*propyl-3-methylpyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester 182**

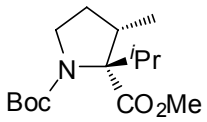


(±)-182

To a stirred solution of **119** (52 mg, 0.12 mmol) in peracetic acid solution (0.13 mL of 36 - 40 wt. % solution in AcOH, 0.62 mmol) was added mercury (II) acetate (47 mg, 0.15 mmol). The reaction was stirred for 4 h then Et_2O (1 mL) was added. The solution was washed with saturated aq. sodium thiosulfate (1 mL), water (1 mL), saturated aq. $NaHCO_3$ (1 mL) and brine (1 mL). The organic layer was then dried ($MgSO_4$) and concentrated *in vacuo*. The crude product was purified by flash-column chromatography (40 % Et_2O/pet. ether) to yield **182** (25 mg, 67 %) as a colourless oil; R_f = 0.38 (40 % Et_2O/pet. ether); IR ν_{max} (solution in CH_2Cl_2) 3445 (O-H), 2876 (C-H), 1752 (C=O), 1690 (C=O), 1398, 1368, 1139, 1110, 1076 cm^{-1}; ^1H NMR (270 MHz, d_6-DMSO) δ $0.73_{rot.}$, $0.74_{rot.}$ (3H, d, *J* = 7.0, CH(CH_3)$_2$), 0.91 (3H, d, *J* = 7.2, CHCH_3), $1.09_{rot.}$, $1.10_{rot.}$ (3H, d, *J* = 7.0, CH(CH_3)$_2$), $1.33_{rot.}$, $1.39_{rot.}$ (9H, s, C(CH_3)$_3$), 2.35 - 2.47 (1H, m, C*H*CH$_3$), $2.72_{rot.}$,

$2.79_{rot.}$ (1H, septet, J = 6.9, C*H*(CH_3)$_2$), $3.22_{rot.}$, $3.30_{rot.}$ (1H, dd, J = 11.8, 4.0, NC*H*$_2$), 3.55 - 3.65 (4H, m, OC*H*$_3$, NC*H*$_2$), 3.95 (1H, app. dt, J = 8.4, 4.5, C*H*OH), $4.23_{rot.}$, $4.27_{rot.}$ (1H, d, J = 7.9, CHO*H*); ^{13}C NMR (400 MHz, C_6D_6) δ 11.8 (*C*H_3), 11.9 (*C*H_3), 16.9 (*C*H_3), 17.2 (*C*H_3), 18.9 (*C*H_3), 19.0 (*C*H_3), 28.3 (*C*H_3), 28.4 (*C*H_3), 30.8 (*C*H), 32.6 (*C*H), 41.1 (*C*H), 42.3 (*C*H), 51.5 (*C*H_3), 52.1 (*C*H_3), 57.1 (*C*H_2), 57.7 (*C*H_2), 72.8 (*C*), 72.9 (*C*H), 73.4 (*C*), 73.7 (*C*H), 79.6 (*C*), 79.7 (*C*), 153.1 (*C*=O), 154.1 (*C*=O), 174.5 (*C*=O), 175.5 (*C*=O); m/z (ES^+) 324 (100 %, MNa^+); HRMS $C_{15}H_{27}NNaO_5$ calcd.324.1781, found 324.1773.

(2*R,3*S**)-2-*Iso*propyl-3-methylpyrrolidine-1,2-dicarboxylic acid 1-*tert*-butyl ester 2-methyl ester 185**



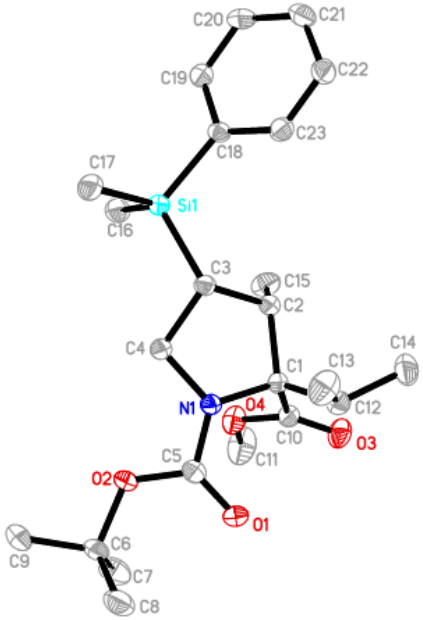
(±)-185

To a stirred solution of **119** (26 mg, 62 μmol) in DMF (0.5 mL) was added TBAF (0.31 mL of 1 M solution in THF, 0.31 mmol). The reaction was heated to 80 °C and stirred for 2 h. The reaction was then allowed to cool to rt and diluted with EtOAc (1 mL) and pet. ether (1 mL). The solution was washed sequentially with 1 M aq. HCl (1 mL), saturated aq. $KHCO_3$ (1 mL) and brine (1 mL). The organic layer was then dried ($MgSO_4$) and

concentrated *in vacuo*. Purification by flash-column chromatography (50 % Et_2O/pet. ether) gave **185** (13 mg, 74 %) as a colourless oil; R_f = 0.44 (50 % Et_2O/pet. ether); IR ν_{max} (solution in CH_2Cl_2) 2876 (C-H), 1740 (C=O), 1686 (C=O), 1398, 1367, 1216, 1118 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ $0.79_{rot.}$, $0.81_{rot.}$ (3H, d, *J* = 6.8, $CH(CH_3)_2$), $0.98_{rot.}$, $0.99_{rot.}$ (3H, d, *J* = 6.5, $CHCH_3$), 1.14 (3H, d, *J* = 7.0, $CH(CH_3)_2$), $1.39_{rot.}$, $1.42_{rot.}$ (9H, s, $C(CH_3)_3$), 1.65 - 1.86 (2H, m, NCH_2CH_2), 2.30 - 2.41 (1H, m, $CHCH_3$), $2.81_{rot.}$, $2.95_{rot.}$ (1H, septet, *J* = 6.9, $CH(CH_3)_2$), 3.08 (1H, ddd, *J* = 11.9, 10.8, 5.8, NCH_2), 3.66 (3H, s, OCH_3), $3.73_{rot.}$, $3.85_{rot.}$ (1H, app. dd, *J* = 10.8, 8.3, NCH_2); ^{13}C NMR (270 MHz, d_6-DMSO) δ 17.0 (CH_3), 17.1 (CH_3), 17.2 (CH_3), 17.4 (CH_3), 18.9 (CH_3), 19.1 (CH_3), 28.3 (CH_3), 28.5 (CH_3), 31.0 (CH), 32.1 (CH_2), 32.3 (CH_2), 32.7 (CH_2), 37.1 (CH), 38.2 (CH), 47.5 (CH_2), 51.3 (CH_3), 72.6 (C), 72.8 (C), 79.3 (C), 79.9 (C), 153.4 (C=O), 153.6 (C=O), 173.5 (C=O), 173.6 (C=O); ^{13}C NMR (270 MHz, d_6-DMSO, 80 °C) δ 17.3, 17.5, 19.3, 28.6, 32.2, 32.4, 37.0, 38.0, 47.5, 51.4, 73.0, 79.3, 152.8 (C=O), 173.3 (C=O); m/z (ES^+) 308 (100 %, MNa^+); HRMS $C_{15}H_{27}NNaO_4$ calcd. 308.1832, found 308.1833.

7.5 Crystallographic data

7.5.1 X-ray crystallographic data for 119



119

Table 1. Crystal data and structure refinement for sipyro

Identification code	sipyro
Empirical formula	C23 H37 N O4 Si
Formula weight	419.63
Temperature	150(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic

Space group	P 21 21 21	
Unit cell dimensions	a = 10.4558(7) Å	α = 90°
	b = 10.8496(7) Å	β = 90°
	c = 21.3975(15) Å	γ = 90°
Volume	2427.4(3) Å3	
Z	4	
Density (calculated)	1.148 Mg/m3	
Absorption coefficient	0.123 mm-1	
F(000)	912	
Crystal size	0.48 x 0.39 x 0.36 mm3	
Theta range for data collection	2.17 to 27.62°.	
Index ranges	-13<=h<=11, -10<=k<=14, -27<=l<=26	
Reflections collected	13706	
Independent reflections	5495 [R(int) = 0.026]	
Completeness to theta = 27.50°	99.7 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F2	
Data / restraints / parameters	5495 / 0 / 263	
Goodness-of-fit on F2	0.993	
Final R indices [I>2sigma(I)]	R1 = 0.0351, wR2 = 0.0842	
R indices (all data)	R1 = 0.0394, wR2 = 0.0858	
Absolute structure parameter	0.13(10)	
Largest diff. peak and hole	0.268 and -0.163 e.Å^{-3}	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 10^3) for sipyro

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor

	x	y	z	U(eq)
N(1)	6949(1)	3906(1)	919(1)	19(1)
Si(1)	5977(1)	6386(1)	-445(1)	19(1)
O(1)	7449(1)	2767(1)	1775(1)	27(1)
O(2)	8934(1)	4011(1)	1306(1)	25(1)
O(3)	4360(1)	3558(1)	1971(1)	31(1)
O(4)	5833(1)	5042(1)	1868(1)	28(1)
C(1)	5561(1)	3697(1)	994(1)	19(1)
C(2)	4950(2)	4601(1)	497(1)	22(1)
C(3)	6079(2)	4956(1)	60(1)	18(1)
C(4)	7238(1)	4930(1)	496(1)	20(1)
C(5)	7760(2)	3500(2)	1373(1)	21(1)
C(6)	9926(2)	3766(2)	1783(1)	25(1)
C(7)	9465(2)	4195(2)	2418(1)	38(1)
C(8)	10305(2)	2422(2)	1777(1)	34(1)
C(9)	11044(2)	4554(2)	1557(1)	39(1)
C(10)	5175(2)	4057(1)	1666(1)	22(1)
C(11)	5487(2)	5471(2)	2489(1)	45(1)
C(12)	5191(2)	2319(2)	880(1)	24(1)
C(13)	5854(2)	1770(2)	309(1)	36(1)
C(14)	3748(2)	2103(2)	828(1)	36(1)

C(15)	4259(2)	5717(2)	774(1)	33(1)
C(16)	6091(2)	7870(1)	-1(1)	28(1)
C(17)	7349(2)	6315(2)	-1005(1)	29(1)
C(18)	4452(1)	6366(2)	-908(1)	19(1)
C(19)	3998(2)	7461(1)	-1176(1)	22(1)
C(20)	2939(2)	7469(2)	-1567(1)	25(1)
C(21)	2291(2)	6390(2)	-1696(1)	27(1)
C(22)	2711(2)	5294(2)	-1430(1)	27(1)
C(23)	3774(2)	5291(2)	-1043(1)	23(1)

Table 3. Bond lengths [Å] and angles [°] for sipyro

N(1)-C(5)	1.363(2)	C(1)-C(2)	1.581(2)
N(1)-C(4)	1.4647(19)	C2)-C(15)	1.529(2)
N(1)-C(1)	1.4776(19)	C(2)-C(3)	1.555(2)
Si(1)-C(17)	1.8710(17)	C(3)-C(4)	1.530(2)
Si(1)-C(16)	1.8725(16)	C(6)-C(8)	1.511(2)
Si(1)-C(18)	1.8779(15)	C(6)-C(7)	1.516(3)
Si(1)-C(3)	1.8932(15)	C(6)-C(9)	1.526(2)
O(1)-C(5)	1.2156(19)	C(12)-C(13)	1.526(2)
O(2)-C(5)	1.3545(19)	C(12)-C(14)	1.530(2)
O(2)-C(6)	1.4799(18)	C(18)-C(23)	1.396(2)
O(3)-C(10)	1.2010(19)	C(18)-C(19)	1.402(2)
O(4)-C(10)	1.3430(19)	C(19)-C(20)	1.388(2)
O(4)-C(11)	1.453(2)	C(20)-C(21)	1.381(2)

C(1)-C(10)	1.545(2)	C(21)-C(22)	1.389(2)
C(1)-C(12)	1.563(2)	C(22)-C(23)	1.386(2)
C(5)-N(1)-C(4)	123.91(13)	C(10)-C(1)-C(12)	108.79(12)
C(5)-N(1)-C(1)	118.96(12)	N(1)-C(1)-C(2)	103.24(11)
C(4)-N(1)-C(1)	112.69(12)	C(10)-C(1)-C(2)	111.30(13)
C(17)-Si(1)-C(16)	108.18(9)	C(12)-C(1)-C(2)	112.87(12)
C(17)-Si(1)-C(18)	108.16(7)	C(15)-C(2)-C(3)	113.31(13)
C(16)-Si(1)-C(18)	109.41(8)	C(15)-C(2)-C(1)	114.99(13)
C(17)-Si(1)-C(3)	106.74(8)	C(3)-C(2)-C(1)	104.53(12)
C(16)-Si(1)-C(3)	114.31(7)	C(4)-C(3)-C(2)	103.29(12)
C(18)-Si(1)-C(3)	109.84(7)	C(4)-C(3)-Si(1)	114.04(10)
C(5)-O(2)-C(6)	119.22(12)	C(2)-C(3)-Si(1)	120.21(11)
C(10)-O(4)-C(11)	114.92(13)	N(1)-C(4)-C(3)	103.15(12)
N(1)-C(1)-C(10)	108.57(12)	O(1)-C(5)-O(2)	125.83(14)
N(1)-C(1)-C(12)	111.94(13)	C(13)-C(12)-C(14)	109.32(15)
O(1)-C(5)-N(1)	123.36(14)	C(13)-C(12)-C(1)	112.67(13)
O(2)-C(5)-N(1)	110.80(13)	C(14)-C(12)-C(1)	113.68(14)
O(2)-C(6)-C(8)	110.61(13)	C(23)-C(18)-C(19)	116.85(14)
O(2)-C(6)-C(7)	109.88(13)	C(23)-C(18)-Si(1)	123.43(12)
C(8)-C(6)-C(7)	112.78(15)	C(19)-C(18)-Si(1)	119.56(12)
O(2)-C(6)-C(9)	102.59(13)	C(20)-C(19)-C(18)	121.46(15)
C(8)-C(6)-C(9)	109.69(15)	C(21)-C(20)-C(19)	120.44(15)
C(7)-C(6)-C(9)	110.83(16)	C(20)-C(21)-C(22)	119.26(15)
O(3)-C(10)-O(4)	123.19(15)	C(23)-C(22)-C(21)	120.02(15)
O(3)-C(10)-C(1)	125.22(15)	C(22)-C(23)-C(18)	121.95(15)
O(4)-C(10)-C(1)	111.55(13)		

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for sipyro

The anisotropic displacement factor exponent takes the form:

$-2\pi^2[\ h^2\ a^{*2}U11 + ...\ + 2\ h\ k\ a^*\ b^*\ U12\ ]$

	U11	U22	U33	U23	U13	U12
N(1)	17(1)	23(1)	18(1)	4(1)	0(1)	0(1)
Si(1)	18(1)	20(1)	20(1)	3(1)	-2(1)	-1(1)
O(1)	27(1)	29(1)	25(1)	10(1)	-6(1)	-2(1)
O(2)	20(1)	32(1)	25(1)	8(1)	-7(1)	-3(1)
O(3)	32(1)	35(1)	27(1)	2(1)	9(1)	-8(1)
O(4)	33(1)	29(1)	22(1)	-6(1)	6(1)	-7(1)
C(1)	16(1)	21(1)	20(1)	3(1)	0(1)	-1(1)
C(2)	17(1)	25(1)	22(1)	5(1)	-2(1)	-1(1)
C(3)	18(1)	19(1)	18(1)	1(1)	-1(1)	1(1)
C(4)	18(1)	22(1)	19(1)	3(1)	0(1)	0(1)
C(5)	20(1)	22(1)	20(1)	-3(1)	-1(1)	2(1)
C(6)	22(1)	29(1)	25(1)	2(1)	-9(1)	0(1)
C(7)	36(1)	46(1)	31(1)	-6(1)	-11(1)	3(1)
C(8)	27(1)	32(1)	44(1)	1(1)	-11(1)	6(1)
C(9)	24(1)	43(1)	50(1)	12(1)	-14(1)	-6(1)
C(10)	20(1)	22(1)	24(1)	3(1)	0(1)	0(1)
C(11)	60(1)	47(1)	29(1)	-15(1)	16(1)	-16(1)
C(12)	26(1)	22(1)	23(1)	2(1)	-3(1)	-3(1)
C(13)	47(1)	26(1)	35(1)	-6(1)	6(1)	-3(1)
C(14)	30(1)	31(1)	46(1)	-1(1)	-5(1)	-9(1)

C(15)	27(1)	37(1)	34(1)	12(1)	8(1)	11(1)
C(16)	33(1)	24(1)	28(1)	0(1)	-7(1)	-4(1)
C(17)	24(1)	34(1)	29(1)	8(1)	3(1)	0(1)
C(18)	18(1)	23(1)	15(1)	-1(1)	1(1)	2(1)
C(19)	24(1)	21(1)	21(1)	-1(1)	1(1)	-1(1)
C(20)	28(1)	28(1)	20(1)	3(1)	-1(1)	9(1)
C(21)	23(1)	38(1)	21(1)	-1(1)	-4(1)	2(1)
C(22)	30(1)	29(1)	23(1)	-2(1)	-2(1)	-7(1)
C(23)	26(1)	22(1)	22(1)	2(1)	0(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for sipyro

	x	**y**	**z**	**U(eq)**
H(2A)	4316	4122	245	26
H(3A)	6191	4248	-234	22
H(4A)	8037	4776	260	24
H(4B)	7321	5715	728	24
H(7A)	9235	5070	2397	56
H(7B)	10147	4080	2727	56
H(7C)	8713	3713	2542	56
H(8A)	10599	2194	1358	51
H(8B)	9566	1914	1891	51
H(8C)	10997	2286	2079	51
H(9A)	11331	4257	1148	58

H(9B)	11750	4495	1857	58
H(9C)	10769	5414	1522	58
H(11A)	6015	6183	2600	68
H(11B)	5628	4808	2793	68
H(11C)	4583	5709	2494	68
H(12A)	5495	1843	1251	29
H(13A)	5595	908	259	54
H(13B)	6783	1814	365	54
H(13C)	5610	2237	-65	54
H(14A)	3583	1224	763	53
H(14B)	3408	2575	475	53
H(14C)	3330	2373	1215	53
H(15A)	3909	6223	435	49
H(15B)	4864	6208	1019	49
H(15C)	3561	5435	1044	49
H(16A)	6033	8564	-292	43
H(16B)	6910	7903	221	43
H(16C)	5389	7918	302	43
H(17A)	7334	7043	-1275	43
H(17B)	7276	5570	-1261	43
H(17C)	8155	6294	-771	43
H(19A)	4425	8214	-1088	27
H(20A)	2658	8222	-1747	30
H(21A)	1566	6396	-1964	33
H(22A)	2269	4546	-1514	33
H(23A)	4048	4534	-865	28

Table 6. Torsion angles [°] for sipyro

C(5)-N(1)-C(1)-C(10)	46.20(18)	C(5)-O(2)-C(6)-C(8)	66.27(18)
C(4)-N(1)-C(1)-C(10)	-111.09(13)	C(5)-O(2)-C(6)-C(7)	-58.88(18)
C(5)-N(1)-C(1)-C(12)	-73.91(17)	C(5)-O(2)-C(6)-C(9)	-176.80(14)
C(4)-N(1)-C(1)-C(12)	128.80(13)	C(11)-O(4)-C(10)-O(3)	0.0(2)
C(5)-N(1)-C(1)-C(2)	164.41(13)	C(11)-O(4)-C(10)-C(1)	177.59(15)
C(4)-N(1)-C(1)-C(2)	7.12(16)	N(1)-C(1)-C(10)-O(3)	-145.83(16)
N(1)-C(1)-C(2)-C(15)	-109.00(15)	C(12)-C(1)-C(10)-O(3)	-23.8(2)
C(10)-C(1)-C(2)-C(15)	7.29(19)	C(2)-C(1)-C(10)-O(3)	101.19(18)
C(12)-C(1)-C(2)-C(15)	129.95(15)	N(1)-C(1)-C(10)-O(4)	36.62(17)
N(1)-C(1)-C(2)-C(3)	15.87(15)	C(12)-C(1)-C(10)-O(4)	158.66(13)
C(10)-C(1)-C(2)-C(3)	132.16(13)	C(2)-C(1)-C(10)-O(4)	-76.36(16)
C(12)-C(1)-C(2)-C(3)	-105.18(14)	N(1)-C(1)-C(12)-C(13)	-43.90(18)
C(15)-C(2)-C(3)-C(4)	93.94(15)	C(10)-C(1)-C(12)-C(13)	-163.88(14)
C(1)-C(2)-C(3)-C(4)	-31.99(15)	C(2)-C(1)-C(12)-C(13)	72.07(17)
C(15)-C(2)-C(3)-Si(1)	-34.50(18)	N(1)-C(1)-C(12)-C(14)	-168.97(14)
C(1)-C(2)-C(3)-Si(1)	-160.44(10)	C(10)-C(1)-C(12)-C(14)	71.05(17)
C(17)-Si(1)-C(3)-C(4)	67.52(12)	C(2)-C(1)-C(12)-C(14)	-53.00(19)
C(16)-Si(1)-C(3)-C(4)	-52.04(13)	C(17)-Si(1)-C(18)-C(23)	93.68(14)
C(18)-Si(1)-C(3)-C(4)	-175.45(10)	C(16)-Si(1)-C(18)-C(23)	-148.70(13)
C(17)-Si(1)-C(3)-C(2)	-169.05(12)	C(3)-Si(1)-C(18)-C(23)	-22.46(15)
C(16)-Si(1)-C(3)-C(2)	71.39(14)	C(17)-Si(1)-C(18)-C(19)	-81.58(13)
C(18)-Si(1)-C(3)-C(2)	-52.02(13)	C(16)-Si(1)-C(18)-C(19)	36.04(14)
C(5)-N(1)-C(4)-C(3)	176.54(13)	C(3)-Si(1)-C(18)-C(19)	162.28(12)
C(1)-N(1)-C(4)-C(3)	-27.47(16)	C(23)-C(18)-C(19)-C(20)	-1.3(2)
C(2)-C(3)-C(4)-N(1)	35.83(14)	Si(1)-C(18)-C(19)-C(20)	174.31(12)

Si(1)-C(3)-C(4)-N(1)	168.00(10)	C(18)-C(19)-C(20)-C(21)	0.8(2)
C(6)-O(2)-C(5)-O(1)	-5.6(2)	C(19)-C(20)-C(21)-C(22)	0.0(2)
C(6)-O(2)-C(5)-N(1)	175.13(13)	C(20)-C(21)-C(22)-C(23)	-0.4(2)
C(4)-N(1)-C(5)-O(1)	169.60(15)	C(21)-C(22)-C(23)-C(18)	-0.1(2)
C(1)-N(1)-C(5)-O(1)	15.0(2)	C(19)-C(18)-C(23)-C(22)	0.9(2)
C(4)-N(1)-C(5)-O(2)	-11.1(2)	Si(1)-C(18)-C(23)-C(22)	-174.50(12)
C(1)-N(1)-C(5)-O(2)	-165.65(13)		

Symmetry transformations used to generate equivalent atoms:

7.5.2 X-ray crystallographic data for 172

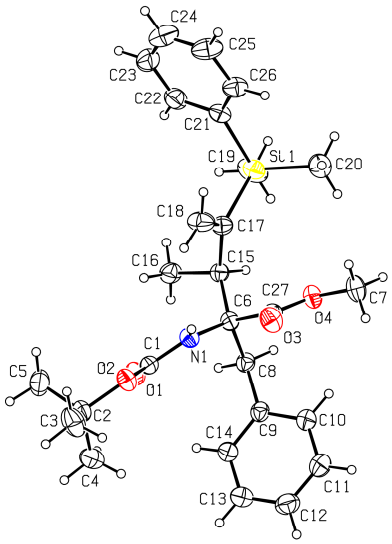


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Table 1. Crystal data and structure refinement for SICOAM at 296(2) K

Empirical formula	C27 H37 N O4 Si	
Formula weight	467.67	
Crystal description	colourless column	
Crystal size	0.37 x 0.21 x 0.20 mm	
Crystal system	Triclinic	
Space group	P -1	
Unit cell dimensions	a = 9.5243(14) Å	α = 86.164(2) °
	b = 10.640(2) Å	β = 71.849(2) °
	c = 14.072(2) Å	γ = 88.368(2) °
Volume	1352.0(6) $Å^3$	
Reflections for cell refinement	2268	
Range in theta	2.25 to 22.85 °	
Z	2	
Density (calculated)	1.149 Mg/m^3	
Absorption coefficient	0.117 mm^{-1}	
F(000)	504	
Diffractometer type	Bruker SMART1000 CCD area detector	
Wavelength	0.71073 Å	
Scan type	omega	
Reflections collected	10624	
Theta range for data collection	1.92 to 26.37 °	
Index ranges	-11<=h<=11, -13<=k<=13, -17<=l<=17	
Independent reflections	5329 [R(int) = 0.105]	
Observed reflections	3315 [I>2sigma(I)]	
Absorption correction	None	

Decay correction	None
Structure solution by	direct methods
Hydrogen atom location	placed geometrically
Hydrogen atom treatment	riding model
Data / restraints / parameters	5329/0/298 (least-squares on F^2)
Final R indices [I>2sigma(I)]	R1 = 0.0544, wR2 = 0.141
Final R indices (all data)	R1 = 0.0889, wR2 = 0.160
Goodness-of-fit on F^2	1.05
Final maximum delta/sigma	0.001
Weighting scheme	w=1/[\s^2^(Fo^2^)+(0.063P)^2^+0.056P] where P=(Fo^2^+2Fc^2^)/3
Largest diff. peak and hole	0.25 and -0.24 e.Å^{-3}

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^2 x 10^3) for SICOAM

U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Si(1)	6379 (1)	5130(1)	1761(1)	54(1)
O(1)	11846(2)	7078(2)	2993(1)	56(1)
N(1)	9506(2)	7855(2)	3205(1)	45(1)
C(1)	10738(2)	7610(2)	3479(2)	44(1)
O(2)	10509(2)	8033(2)	4394(1)	54(1)
C(2)	11667(3)	7927(2)	4894(2)	55(1)

O(3)	7357(2)	9263(2)	2928(1)	66(1)
C(3)	10967(4)	8625(3)	5831(2)	86(1)
O(4)	7696(2)	8653(2)	1377(1)	59(1)
C(4)	13071(3)	8574(3)	4241(2)	84(1)
C(5)	11945(4)	6568(3)	5142(2)	77(1)
C(6)	9331(2)	7769(2)	2213(2)	43(1)
C(7)	6484(3)	9484(3)	1308(2)	79(1)
C(8)	10709(2)	8285(2)	1356(2)	46(1)
C(9)	11170(2)	9614(2)	1429(2)	47(1)
C(10)	10464(3)	10651(2)	1128(2)	61(1)
C(11)	10924(3)	11861(3)	1154(2)	72(1)
C(12)	12113(3)	12062(3)	1485(2)	72(1)
C(13)	12821(3)	11057(3)	1782(2)	71(1)
C(14)	12365(3)	9843(3)	1753(2)	60(1)
C(15)	8959(2)	6423(2)	1979(2)	44(1)
C(16)	10024(3)	5405(2)	2168(2)	59(1)
C(17)	7374(2)	5974(2)	2496(2)	48(1)
C(18)	6698(3)	6115(3)	3463(2)	70(1)
C(19)	7709(3)	4328(4)	698(2)	86(1)
C(20)	5234(3)	6232(3)	1223(2)	80(1)
C(21)	5173(2)	3920(2)	2644(2)	80(1)
C(22)	5749(3)	2772(3)	2899(2)	67(1)
C(23)	4894(4)	1902(3)	3610(2)	77(1)
C(24)	3448(4)	2175(3)	4089(2)	84(1)
C(25)	2837(3)	3285(3)	3856(2)	81(1)
C(26)	3687(3)	4149(3)	3136(2)	64(1)
C(27)	8016(2)	8648(2)	2236(2)	48(1)

Table 3. Bond lengths [Å], angles and torsions [°]

for SICOAM

Si1-C20	1.860(3)	C10-C11	1.378(4)
Si1-C19	1.870(3)	C10-H10	0.93
Si1-C21	1.872(3)	C11-C12	1.379(4)
Si1-C17	1.886(2)	C11-H11	0.93
O1-C1	1.212(3)	C12-C13	1.360(4)
N1-C1	1.358(3)	C12-H12	0.93
N1-C6	1.466(3)	C13-C14	1.382(4)
N1-H1N	0.86	C13-H13	0.93
C1-O2	1.344(3)	C14-H14	0.93
O2-C2	1.480(3)	C15-C16	1.530(3)
C2-C5	1.501(4)	C15-C17	1.532(3)
C2-C3	1.513(4)	C15-H15	0.98
C2-C4	1.520(4)	C16-H16A	0.96
O3-C27	1.204(3)	C16-H16B	0.96
C3-H3A	0.96	C16-H16C	0.96
C3-H3B	0.96	C17-C18	1.329(3)
C3-H3C	0.96	C18-H18A	0.93
O4-C27	1.336(3)	C18-H18B	0.93
O4-C7	1.457(3)	C19-H19A	0.96
C4-H4A	0.96	C19-H19B	0.96
C4-H4B	0.96	C19-H19C	0.96
C4-H4C	0.96	C20-H20A	0.96
C5-H5A	0.96	C20-H20B	0.96
C5-H5B	0.96	C20-H20C	0.96

C5-H5C	0.96	C21-C26	1.391(3)
C6-C27	1.534(3)	C21-C22	1.396(4)
C6-C8	1.563(3)	C22-C23	1.390(4)
C6-C15	1.565(3)	C22-H22	0.93
C7-H7A	0.96	C23-C24	1.364(4)
C7-H7B	0.96	C23-H23	0.93
C7-H7C	0.96	C24-C25	1.367(5)
C8-C9	1.511(3)	C24-H24	0.93
C8-H8A	0.97	C25-C26	1.391(4)
C8-H8B	0.97	C25-H25	0.93
C9-C14	1.385(3)	C26-H26	0.93
C9-C10	1.386(3)		
C20-Si1-C19	107.50(15)	C10-C11-H11	120
C20-Si1-C21	109.89(12)	C12-C11-H11	120
C19-Si1-C21	109.13(14)	C13-C12-C11	119.3(3)
C20-Si1-C17	111.73(13)	C13-C12-H12	120.3
C19-Si1-C17	111.41(12)	C11-C12-H12	120.3
C21-Si1-C17	107.16(10)	C12-C13-C14	120.8(3)
C1-N1-C6	127.79(17)	C12-C13-H13	119.6
C1-N1-H1N	116.1	C14-C13-H13	119.6
C6-N1-H1N	116.1	C13-C14-C9	121.1(3)
O1-C1-O2	125.5(2)	C13-C14-H14	119.4
O1-C1-N1	126.1(2)	C9-C14-H14	119.4
O2-C1-N1	108.31(18)	C16-C15-C17	108.51(19)
C1-O2-C2	121.42(18)	C16-C15-C6	113.12(18)
O2-C2-C5	110.0(2)	C17-C15-C6	116.29(17)
O2-C2-C3	102.0(2)	C16-C15-H15	106.1

C5-C2-C3	111.5(2)	C17-C15-H15	106.1
O2-C2-C4	110.4(2)	C6-C15-H15	106.1
C5-C2-C4	111.6(3)	C15-C16-H16A	109.5
C3-C2-C4	111.0(2)	C15-C16-H16B	109.5
C2-C3-H3A	109.5	H16A-C16-H16B	109.5
C2-C3-H3B	109.5	C15-C16-H16C	109.5
H3A-C3-H3B	109.5	H16A-C16-H16C	109.5
C2-C3-H3C	109.5	H16B-C16-H16C	109.5
H3A-C3-H3C	109.5	C18-C17-C15	121.7(2)
3B-C3-H3C	109.5	C18-C17-Si1	118.79(18)
C27-O4-C7	115.6(2)	C15-C17-Si1	119.43(15)
C2-C4-H4A	109.5	C17-C18-H18A	120
C2-C4-H4B	109.5	C17-C18-H18B	120
H4A-C4-H4B	109.5	H18A-C18-H18B	120
C2-C4-H4C	109.5	Si1-C19-H19A	109.5
H4A-C4-H4C	109.5	Si1-C19-H19B	109.5
H4B-C4-H4C	109.5	H19A-C19-H19B	109.5
C2-C5-H5A	109.5	Si1-C19-H19C	109.5
C2-C5-H5B	109.5	H19A-C19-H19C	109.5
H5A-C5-H5B	109.5	H19B-C19-H19C	109.5
C2-C5-H5C	109.5	Si1-C20-H20A	109.5
H5A-C5-H5C	109.5	Si1-C20-H20B	109.5
H5B-C5-H5C	109.5	H20A-C20-H20B	109.5
N1-C6-C27	103.65(17)	Si1-C20-H20C	109.5
N1-C6-C8	111.92(17)	H20A-C20-H20C	109.5
C27-C6-C8	108.09(18)	H20B-C20-H20C	109.5
N1-C6-C15	114.85(17)	C26-C21-C22	116.4(2)

C27-C6-C15	108.57(17)	C26-C21-Si1	122.0(2)
C8-C6-C15	109.38(17)	C22-C21-Si1	121.39(19)
O4-C7-H7A	109.5	C23-C22-C21	122.2(3)
O4-C7-H7B	109.5	C23-C22-H22	118.9
H7A-C7-H7B	109.5	C21-C22-H22	118.9
O4-C7-H7C	109.5	C24-C23-C22	119.5(3)
H7A-C7-H7C	109.5	C24-C23-H23	120.2
H7B-C7-H7C	109.5	C22-C23-H23	120.2
C9-C8-C6	116.55(18)	C23-C24-C25	120.2(3)
C9-C8-H8A	108.2	C23-C24-H24	119.9
C6-C8-H8A	108.2	C25-C24-H24	119.9
C9-C8-H8B	108.2	C24-C25-C26	120.3(3)
C6-C8-H8B	108.2	C24-C25-H25	119.8
H8A-C8-H8B	107.3	C26-C25-H25	119.8
C14-C9-C10	117.2(2)	C25-C26-C21	121.4(3)
C14-C9-C8	121.2(2)	C25-C26-H26	119.3
C10-C9-C8	121.6(2)	C21-C26-H26	119.3
C11-C10-C9	121.6(2)	O3-C27-O4	123.9(2)
C11-C10-H10	119.2	O3-C27-C6	125.2(2)
C9-C10-H10	119.2	O4-C27-C6	110.91(19)
C10-C11-C12	120.0(3)		
C6-N1-C1-O1	-13.0(4)	C16-C15-C17-Si1	-93.7(2)
C6-N1-C1-O2	168.36(18)	C6-C15-C17-Si1	137.42(17)
O1-C1-O2-C2	2.6(3)	C20-Si1-C17-C18	88.6(2)
N1-C1-O2-C2	-178.74(19)	C19-Si1-C17-C18	-151.2(2)
C1-O2-C2-C5	-66.7(3)	C21-Si1-C17-C18	-31.9(3)
C1-O2-C2-C3	174.9(2)	C20-Si1-C17-C15	-94.3(2)

C1-O2-C2-C4	56.9(3)	C19-Si1-C17-C15	26.0(2)
C1-N1-C6-C27	-157.0(2)	C21-Si1-C17-C15	145.30(18)
C1-N1-C6-C8	-40.8(3)	C20-Si1-C21-C26	-25.7(2)
C1-N1-C6-C15	84.7(3)	C19-Si1-C21-C26	-143.4(2)
N1-C6-C8-C9	-55.1(3)	C17-Si1-C21-C26	95.9(2)
C27-C6-C8-C9	58.4(2)	C20-Si1-C21-C22	159.2(2)
C15-C6-C8-C9	176.45(19)	C19-Si1-C21-C22	41.5(2)
C6-C8-C9-C14	102.6(2)	C17-Si1-C21-C22	-79.3(2)
C6-C8-C9-C10	-80.6(3)	C26-C21-C22-C23	-0.3(4)
C14-C9-C10-C11	-0.2(4)	Si1-C21-C22-C23	175.1(2)
C8-C9-C10-C11	-177.2(2)	C21-C22-C23-C24	-0.9(4)
C9-C10-C11-C12	-0.1(4)	C22-C23-C24-C25	1.4(5)
C10-C11-C12-C13	0.1(4)	C23-C24-C25-C26	-0.5(5)
C11-C12-C13-C14	0.2(4)	C24-C25-C26-C21	-0.8(5)
C12-C13-C14-C9	-0.6(4)	C22-C21-C26-C25	1.2(4)
C10-C9-C14-C13	0.6(4)	Si1-C21-C26-C25	-174.2(2)
C8-C9-C14-C13	177.5(2)	C7-O4-C27-O3	1.1(3)
N1-C6-C15-C16	-51.5(2)	C7-O4-C27-C6	-178.5(2)
C27-C6-C15-C16	-167.01(18)	N1-C6-C27-O3	1.6(3)
C8-C6-C15-C16	75.2(2)	C8-C6-C27-O3	-117.3(3)
N1-C6-C15-C17	75.0(2)	C15-C6-C27-O3	124.1(2)
C27-C6-C15-C17	-40.4(2)	N1-C6-C27-O4	-178.78(17)
C8-C6-C15-C17	-158.18(18)	C8-C6-C27-O4	62.3(2)
C16-C15-C17-C18	83.3(3)	C15-C6-C27-O4	-56.3(2)
C6-C15-C17-C18	-45.5(3)		

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for SICOAM

The anisotropic displacement factor exponent takes the form:

$-2\pi^2[h^2 a^{*2}U11 + ... + 2 h k a^* b^* U12]$

	U11	**U22**	**U33**	**U23**	**U13**	**U12**
Si1	46(1)	64(1)	52(1)	-8(1)	-14(1)	-6(1)
O1	49(1)	66(1)	55(1)	-7(1)	-18(1)	11(1)
N1	39(1)	54(1)	41(1)	-5(1)	-10(1)	0(1)
C1	47(1)	42(1)	44(1)	0(1)	-16(1)	-4(1)
O2	55(1)	64(1)	50(1)	-11(1)	-25(1)	6(1)
C2	62(2)	57(2)	55(1)	-2(1)	-31(1)	-1(1)
O3	60(1)	70(1)	71(1)	-20(1)	-24(1)	21(1)
C3	100(2)	102(3)	75(2)	-32(2)	-50(2)	19(2)
O4	54(1)	65(1)	60(1)	0(1)	-25(1)	10(1)
C4	80(2)	96(2)	86(2)	11(2)	-41(2)	-31(2)
C5	101(2)	66(2)	74(2)	6(2)	-44(2)	7(2)
C6	41(1)	47(1)	41(1)	-3(1)	-12(1)	0(1)
C7	67(2)	82(2)	97(2)	4(2)	-44(2)	20(2)
C8	43(1)	48(1)	43(1)	2(1)	-10(1)	0(1)
C9	47(1)	50(1)	42(1)	2(1)	-11(1)	0(1)
C10	67(2)	53(2)	70(2)	4(1)	-32(1)	-3(1)
C11	82(2)	51(2)	87(2)	3(1)	-35(2)	4(1)
C12	82(2)	60(2)	75(2)	-1(2)	-25(2)	-15(2)
C13	67(2)	73(2)	77(2)	6(2)	-32(2)	-18(2)
C14	50(1)	62(2)	68(2)	11(1)	-24(1)	-8(1)

C15	45(1)	45(1)	42(1)	-3(1)	-12(1)	-1(1)
C16	57(1)	46(1)	74(2)	-7(1)	-20(1)	3(1)
C17	47(1)	49(1)	48(1)	-6(1)	-11(1)	-4(1)
C18	66(2)	83(2)	56(2)	-11(1)	-8(1)	-26(2)
C19	65(2)	119(3)	73(2)	-34(2)	-14(1)	-9(2)
C20	78(2)	93(2)	76(2)	10(2)	-34(2)	-12(2)
C21	48(1)	55(2)	58(1)	-12(1)	-20(1)	-5(1)
C22	57(2)	69(2)	81(2)	-8(2)	-30(1)	0(1)
C23	100(2)	57(2)	84(2)	-1(2)	-43(2)	-9(2)
C24	100(2)	65(2)	75(2)	-7(2)	-8(2)	-26(2)
C25	64(2)	74(2)	89(2)	-19(2)	6(2)	-15(2)
C26	54(2)	58(2)	75(2)	-12(1)	-10(1)	-2(1)
C27	44(1)	46(1)	55(1)	-4(1)	-16(1)	0(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for SICOAM

	x	**y**	**z**	**U(eq)**
H1N	8736	8090	3670	54
H3A	10088	8196	6234	130
H3B	10717	9467	5649	130
H3C	11651	8654	6206	130
H4A	13502	8109	3656	126
H4B	13759	8607	4612	126

H4C	12839	9415	4041	126
H5A	12394	6153	4533	116
H5B	11025	6169	5503	116
H5C	12593	6511	5546	116
H7A	6339	9424	667	118
H7B	6718	10336	1381	118
H7C	5597	9238	1829	118
H8A	11538	7726	1337	55
H8B	10509	8244	724	55
H10	9660	10527	904	73
H11	10433	12542	948	86
H12	12427	12876	1504	86
H13	13621	11188	2008	85
H14	12870	9168	1954	72
H15	9096	6458	1258	53
H16A	9749	4603	2010	88
H16B	9983	5372	2860	88
H16C	11012	5600	1753	88
H18A	7187	6495	3845	84
H18B	5735	5834	3759	84
H19A	8314	3747	954	129
H19B	8324	4945	240	129
H19C	7171	3878	356	129
H20A	4541	6662	1752	121
H20B	4709	5767	882	121
H20C	5862	6837	757	121
H22	6737	2583	2584	80

H23	5305	1139	3757	93
H24	2876	1605	4576	100
H25	1848	3464	4181	98
H26	3253	4895	2979	77

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