Stereoselective Reactions of *N,N*-Dibenzyl Protected Synthons: Applications to Natural Product Synthesis

Karen S. Curley

Department of Chemistry
The University of Edinburgh
February 2002

Declaration

This thesis is submitted in part fulfilment of the requirements for the degree of Doctor of Philosophy at The University of Edinburgh. Unless otherwise stated the work described in this thesis is original and has not been submitted previously in whole or in part for any degree or other qualification at this, or any other university. In accordance with the regulations this thesis does not exceed 70,000 words in length.

Karen Sheena Curley

Acknowledgements

I would like to thank my supervisor, Dr. Alison Hulme, for her help, encouragement and advice throughout and for her thorough proofreading of this thesis.

I would also like to thank Dr. David Reed, John Millar and Wesley Kerr for running numerous NMR spectra for me. Thanks also go to Alan Taylor and Harry McKenzie for their mass spectrometry work and Dr. Simon Parsons and Andy Parkin for their X-ray diffraction work.

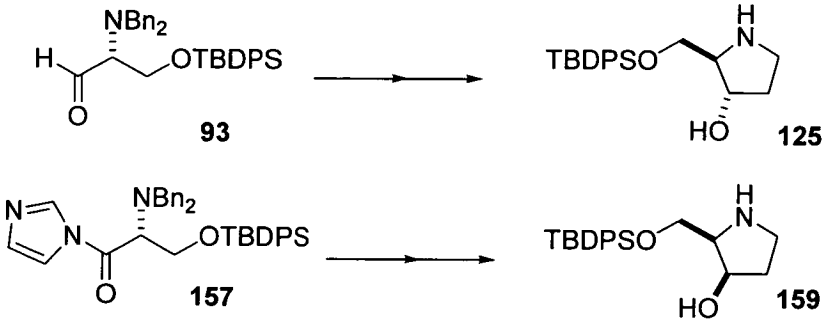
Thanks also to the past and present members of the group: Charlie Montgomery for helping me find my feet in the early years; Sarah Barron who always made time for 'just the one' at the union; Ed Rosser for his novel use of a cricket bat and for providing much amusement throughout the years, and to Jenny Aird for her help and advice.

Thanks also to Caroline Dick, Jenny Pringle and Clare Squires for some interesting lunchtimes and great nights out.

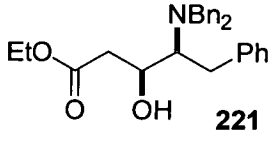
Thanks also to my parents for their continuous support and finally, to Neil for his love, encouragement, support and humour throughout, especially over the last few months.

Abstract

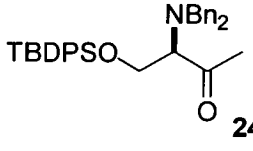
The first part of this thesis describes the synthesis of TBDPS protected CYB-3 **125** *via* a substrate controlled acetate aldol reaction of **93**. A Claisen condensation reaction of the imidazolide **157** followed by a highly diastereoselective reduction enabled a synthesis of the C(3) epimer of TBDPS protected CYB-3 **159**.



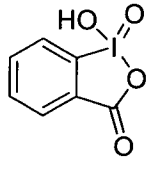
As a further demonstration of this methodology, the Claisen condensation reaction and reduction protocol was extended to the synthesis of β-hydroxy ester **221**.



The synthesis of methyl ketone **244** has been reported utilising the conditions optimised for the synthesis of **93**. Preliminary investigations of the aldol reaction of **244** with a range of achiral aldehydes have been conducted.



Finally studies into an interesting cyclisation using iodoxybenzoic acid (IBX) **262** are discussed.



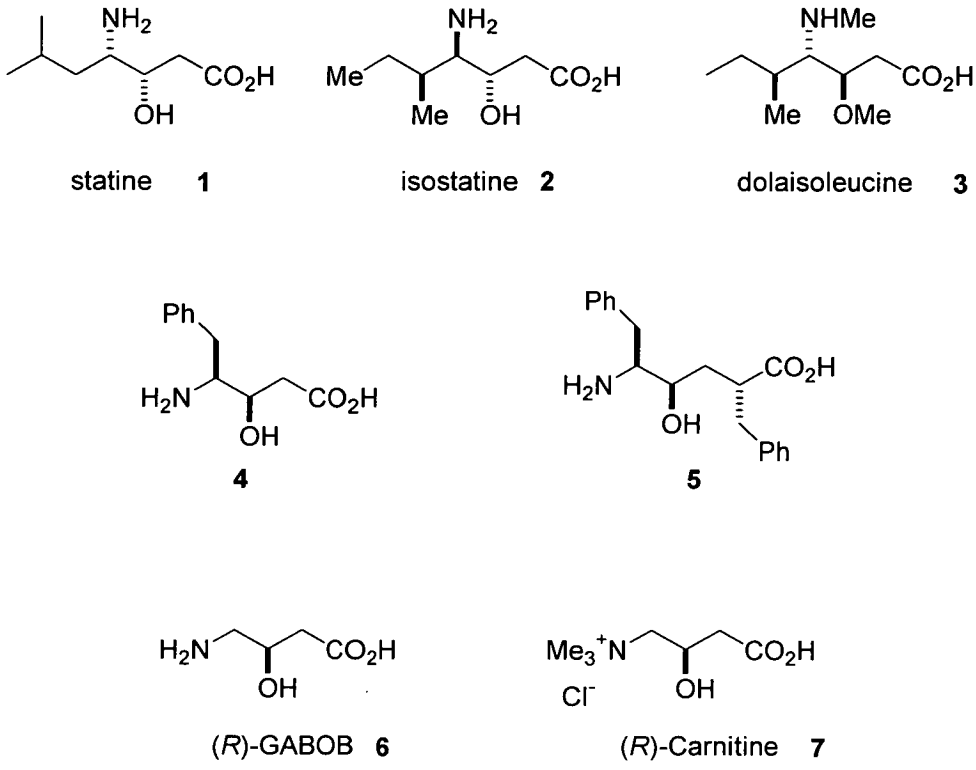
Contents

Chapter 1: Introduction

1.1 β-Hydroxy-γ-amino acids

The synthesis of nonproteogenic amino acids continues to provide a challenge for the organic chemist. Increasingly β-hydroxy-γ-amino acids have been attracting considerable attention as a result of their presence in biologically active compounds. Pertinent examples include statine **1**, the core constituent of the natural peptide pepstatin[1] and isostatine **2**, a component of the natural cytotoxic cyclodepsipeptides the didemnins A-C.[2] Structurally related to both statine and isostatine is dolaisoleucine **3**, a β-methoxy-γ-amino acid found in Dolastatin 10, a cytotoxic and antineoplastic peptide.[3] Hapalosin,[4] a multidrug reversing inhibitor contains the β-hydroxy-γ-amino acid **4**. SB-203386, a HIV protease inhibitor possesses the component **5**.[5] Even simple β-hydroxy-γ-amino acids such as γ-amino-3-hydroxybutanoic acid ((*R*)-GABOB)[6] **6**, a neuromodulator of the central nervous system and (*R*)-carnitine **7**,[7] an essential substance in mammalian fatty acid metabolism are of interest from a therapeutical aspect, **figure 1**.

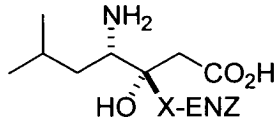
Figure 1



1.2 Statine

Pepstatin discovered by Umezawa in 1970[1] has been identified as a nonselective inhibitor of aspartic proteases such as renin, pepsin and cathepsin D. There has been tremendous interest in the synthesis of the amino acid statine which has been identified as an essential component of pepstatin. Statine is considered as a hydroxymethylene dipeptide isostere. Dipepetide isosteres are compounds in which the peptide bond is replaced by a functional group that mimics the peptide bond but is incapable of hydrolytic cleavage. Statine has consequently become the prototypical hydroxymethylene isostere of the tetrahedral transition state for peptide hydrolysis, **figure 2**. Statine's biological activities have been shown to be dependent on both the relative (*syn*) and absolute (3*S*,4*S*) configurations of its chiral centers.[8]

Figure 2

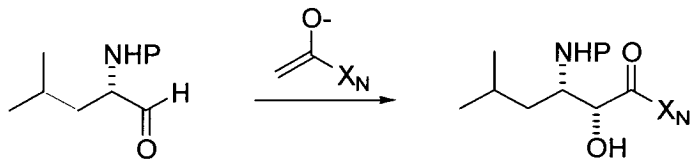


Numerous synthetic approaches have been developed for the synthesis of statine and other β-hydroxy-γ-amino acids. The low selectivity of pepstatin as a renin inhibitor has induced the development of more specific synthetic analogues. Typically the synthetic strategies can be summarised in the following manner: (i) aldol condensations of achiral and chiral enolates; (ii) acylation of ester enolates with activated α-amino acid derivatives followed by reduction of the resulting β-keto esters; (iii) stereoselective reduction of tetramic acids obtained from α-acylamino acid derivatives; and (iv) allylation or vinylation reactions of α-amino aldehydes followed by reductive transformation of the olefinic functionality. Some of these methodologies suffer from the following drawbacks: they are either not totally stereoselective thus leading to mixtures of diastereomers which can be extremely difficult to separate by chromatography and/or they are applicable only to the synthesis of *syn* or *anti* diastereomers. However, the literature is replete with highly diasteroselective routes to these types of compounds and a summary of some of the key synthetic strategies to statine will be illustrated showing that these limitations can be overcome.

1.3 Double asymmetric induction

A common approach to statine involves an aldol reaction between an *N*-protected α-amino aldehyde and either an achiral acetate enolate or a chiral enolate, **scheme 1**. In aldol reactions of an achiral aldehyde with a chiral enolate it is evidently the enolate which controls the stereochemical outcome of the reaction. However the interaction of a chiral aldehyde with a chiral enolate results in the stereoselectivity being controlled by both. This is an example of double asymmetric induction.[9] In examples where the diastereofacial selectivities of both favour the same product (i.e. a "matched" case) increased diastereoselectivities are apparent. Where the diastereofacial selectivities favour different products (i.e. a "mismatched" case) diminished diastereoselectivities occur.

Scheme 1

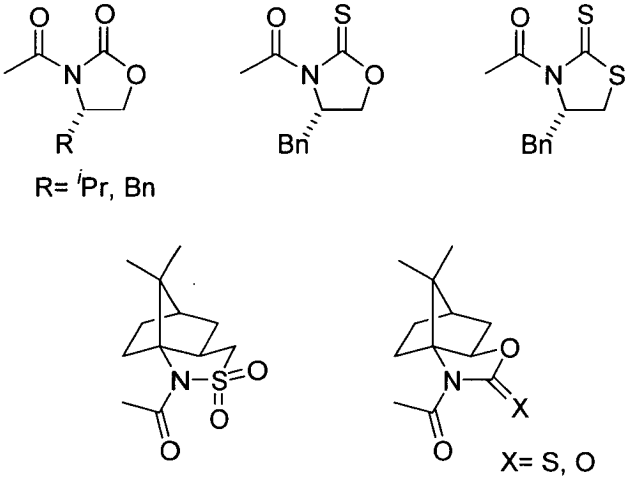


1.4 Stereoselective aldol reactions with α-unsubstituted chiral enolates

The introduction of α-substituted chiral enolates as initially developed by Evans in 1981,[10] has become a well accepted and useful method for the preparation of β-hydroxyacids and their derivatives. The stereochemical outcome of the reaction of aldehydes with these auxiliaries can be controlled with great efficiency to give excellent diastereoselectivities. However, in contrast the enolates derived from α-unsubstituted chiral enolates often lead to a mixture of diastereomers. A variety of auxiliaries have been developed more recently, each displaying varying degrees of stereocontrol, **figure 3**.[10,11] Both Seebach[12] and Thornton[13] have reported low

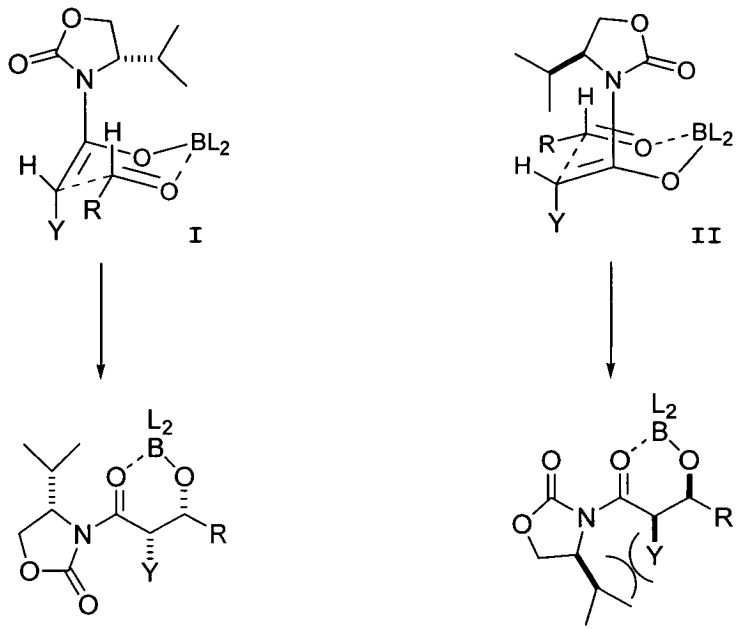
diastereoselectivities of Evans' oxazolidinone under a variety of enolization conditions with simple aldehydes.

Figure 3



The underlying causes of the low levels of selectivity are still not fully understood, however based on the Zimmerman-Traxler model[14] a plausible explanation for the failure of Evans' oxazolidinone has been proposed, **scheme 2**.[15] In this model the approach of the aldehyde to the enolate occurs from the side which faces away from the isopropyl residue of the oxazolidinone leading to two favourable transition states **I** and **II**. In the case of α-substitution steric repulsion occurs between the isopropyl group and the substituent Y, thus making transition state **I** more favourable. No appreciable steric hindrance will be present in the unsubstituted form (Y=H) hence each of the two transition states will be favoured thus leading to a mixture of products.

Scheme 2



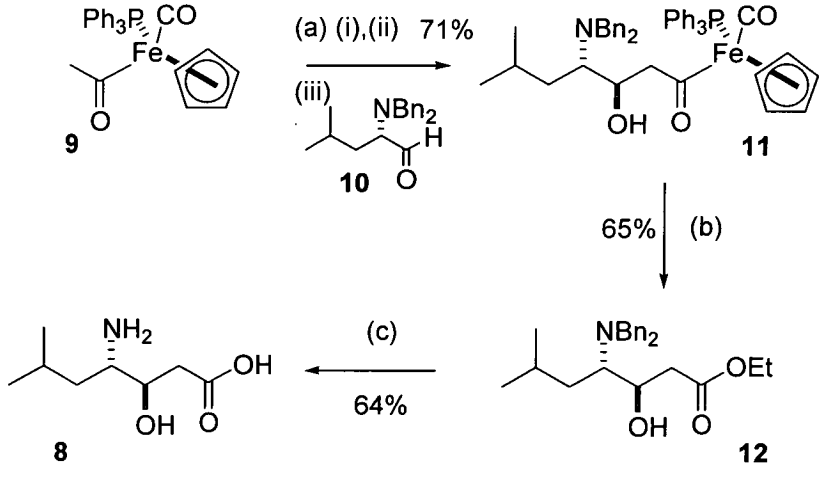
An alternative explanation for the low levels of selectivity observed in the reaction of α-unsubstituted enolates involves alternative transition state geometries. Hoffman[16] and Gennari[17] have shown that both boat **III** and twist shaped transition states **IV**, **figure 4**, can compete with the chair transition state. Since all three transition states have comparable activation energies by *ab initio* calculations it is conceivable that attack of the aldehyde will occur with no preference for either transition state, subsequently leading to a mixture of diastereomers.

Figure 4

1.5 Synthesis of (3*R*,4*S*)-statine *via* acetate aldol reaction

Davies'[18] however has developed a highly diastereoselective route to (3*R*,4*S*)-statine **8** by reacting the diethylaluminium enolate derived from the iron complex **9** with *N*,*N*-dibenzyl leucinal **10**, **scheme 3**. This generates the aldol adduct **11** in 71% yield and in 96% de in favour of the matched product. The lithium enolate of **9** was found to offer very little diastereoselectivity. Cleavage of the auxiliary was achieved with bromine to yield the auxiliary and the *β*-hydroxy ester **12**. One pot saponification with aqueous potassium hydroxide and deprotection afforded (3*R*,4*S*)-statine **8** in 30% yield from **9**. However the auxiliary cannot be recycled and is expensive to prepare.

Scheme 3



(a) (i) BuLi, THF; (ii) Et_2AlCl; (iii) **10** in PhMe; (b) Br_2, EtOH, DCM; (c) (i) KOH, H_2O, THF; (ii) $Pd(OH)_2/C$.

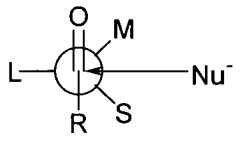
1.6 Models for chelation and non-chelation controlled additions to α-amino aldehydes

Davies choice of the nitrogen protecting group was important in his strategy towards this synthesis of (3*R*,4*S*)-statine. He observed that the Boc protected α-amino aldehyde was unsuitable for coupling to the iron complex due to competing deprotonation thus resulting in low yields. In comparison with the Boc protecting group the *N*,*N*-dibenzyl group developed by Reetz[19] confers greater diastereofacial selectivity and configurational stability. The propensity for *N*,*N*-dibenzyl protected α-amino aldehydes to undergo stereoselective non-chelation control with a range of nucleophiles can be explained by the Felkin-Anh model.

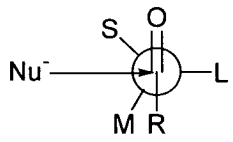
1.6.1 Felkin-Anh model

The Felkin-Anh model[20] was originally developed to account for the stereochemical outcome of α-chloro and α-alkoxy carbonyl compounds and is a refinement of the model proposed by Felkin. Felkin originally proposed that the most stable transition state was that where the separation between the incoming nucleophile and the electronegative group was the greatest. By assuming perpendicular attack transition state **A** is favoured, **scheme 4**.

Scheme 4



A

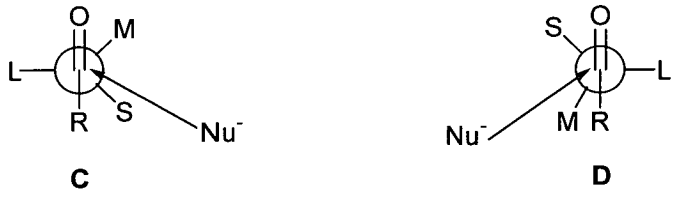


B

Anh however postulated that non-perpendicular attack by the nucleophile was occurring on the basis of molecular orbital calculations. During the reaction the

major interaction occurs between the nucleophiles HOMO and the substrates LUMO thus leading to transition states **C** and **D**, **scheme 4a**. The most reactive conformation is where the C2-L bond is parallel to the π-system of the carbonyl. Stabilisation of the LUMO is achieved by overlap of the π^*_{CO} orbital and the $\sigma^*_{C2\text{-}L}$ orbital. The most stable transition state is that where the nucleophile attacks *anti* to the L group. In consideration of the two conformers which would exist, the steric hindrance encountered by the nucleophile in conformer **D** would be much greater than in conformer **C**.

Scheme 4a

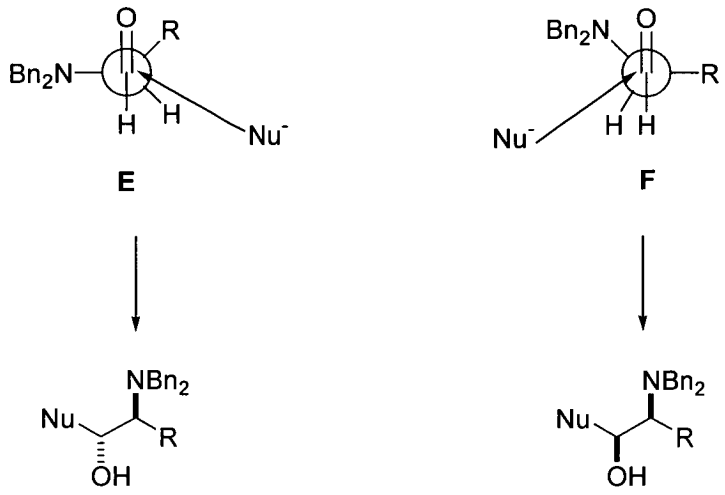


C **D**

In applying the Felkin-Anh model to the *N,N*-dibenzylamino aldehydes (L=NBn_2) conformers **C** and **D** need to be considered. The steric interaction between the incoming nucleophile and the R group is obviously minimised in **C.** This conformation predicts the *anti*-selectivity which is observed experimentally.

However where the R group is very bulky conformer **F** can compete with conformer **E** and can lead to diminished selectivity, **scheme 4b**. A variety of organometallic reagents are capable of forming the nonchelation controlled product when reacted with a *N,N*-dibenzylated aldehyde such as PhMgBr, MeLi, $MeTi(O^iPr)_3$ and Me_2CuLi.[21]

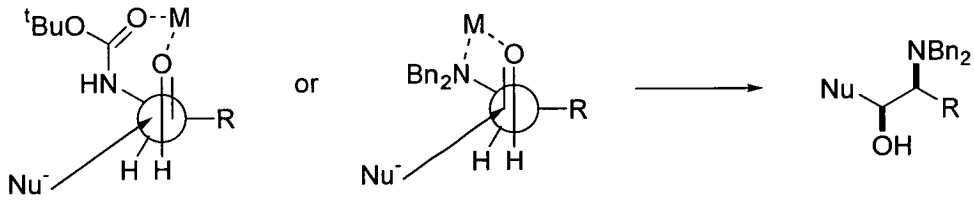
Scheme 4b



1.6.2 Cram Chelation model

The Cram chelation model[22] has provided a method of predicting the stereochemical outcome of chelation controlled additions to α-amino aldehydes. Complexation with the metal (M) occurs *via* the carbonyl oxygen and the nitrogen atom for the *N,N*-dibenzylated species and *via* the carbonyl oxygen and the carbonyl oxygen from the Boc group for the *N*-Boc protected species. Nucleophilic attack results in the *syn* adduct preferentially for both species, **scheme 5**. In contrast with *N*-Boc protected aldehydes, chelation control in the case of *N,N*-dibenzylamino aldehydes is much harder to attain. This can be explained by steric factors associated with the presence of the two *N*-benzyl groups. Addition of reagents such as $MeTiCl_3$, $SnCl_4$ and the combination of $TiCl_4/Me_2Zn$ to *N,N*-dibenzylamino aldehdyes have resulted in the chelation controlled product albeit with varying levels of diastereoselectivity.[21]

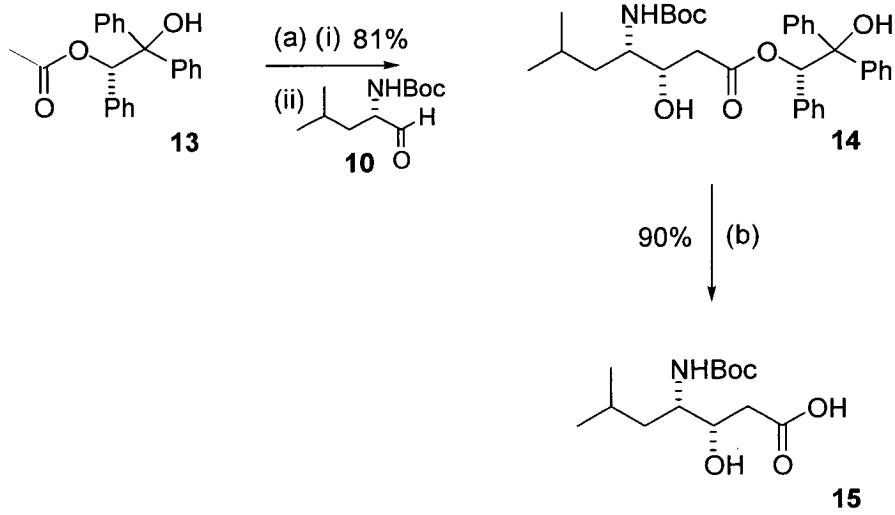
Scheme 5



1.7 Syntheses of (3*S*,4*S*) statine *via* acetate aldol reaction

Wuts[23] approach to statine utilises the lithium enolate of (*S*)-2-actetoxy-1,1,2-triphenylethanol **13**. Reacting this enolate with *N*-Boc leucinal **10** generated a mixture of diastereomers in favour of **14** in 89% de. Hydrolysis of the reaction mixture and crystallisation afforded *N*-Boc-statine **15** in 90% de, **scheme 6**.

Scheme 6

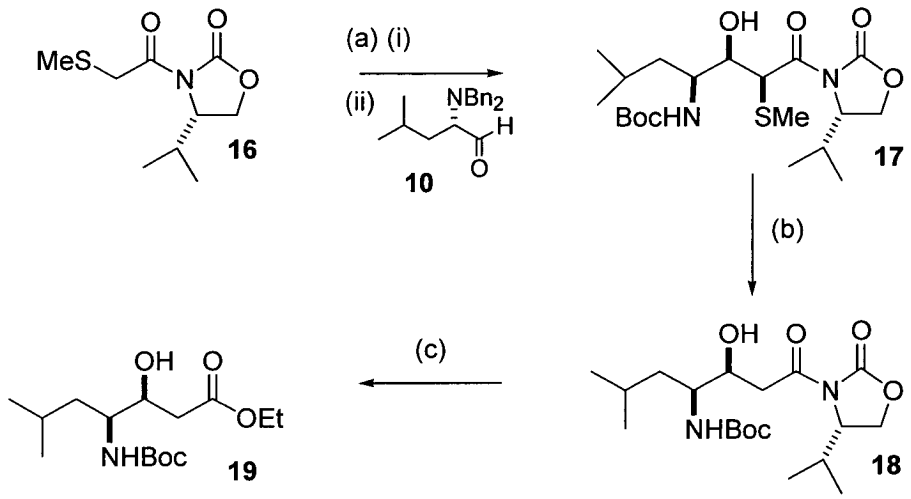


(a) (i) LDA, THF, -70 °C; (ii) **10** in Et_2O; (b) (i) KOH, H_2O; (ii) 10% HCl.

Another strategy that provides high levels of diastereoselectivity is the incorporation of an α-substituent onto the enolate. This strategy relies on the premise that the substituent can be removed after reacting the enolate with an α-amino

aldehyde. An example of this strategy has been demonstrated by Woo.[24] Enolisation of **16** under standard conditions ($^{n}Bu_2BOTf$, $^{i}Pr_2NEt$, 0 °C) followed by addition of aldehyde **10** generated the aldol adduct **17**. Desulphurisation and hydrolysis provided statine **19** in 24% yield from **10** in >99% de, **scheme 7**.

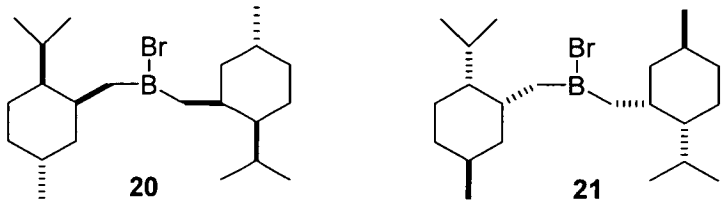
Scheme 7



(a) (i) $^{n}Bu_2BOTf$, $^{i}Pr_2NEt$, 0 °C; (ii) **10** in DCM; (b) Raney nickel, $(CH_3)_2CO$; (c) NaOEt, EtOH.

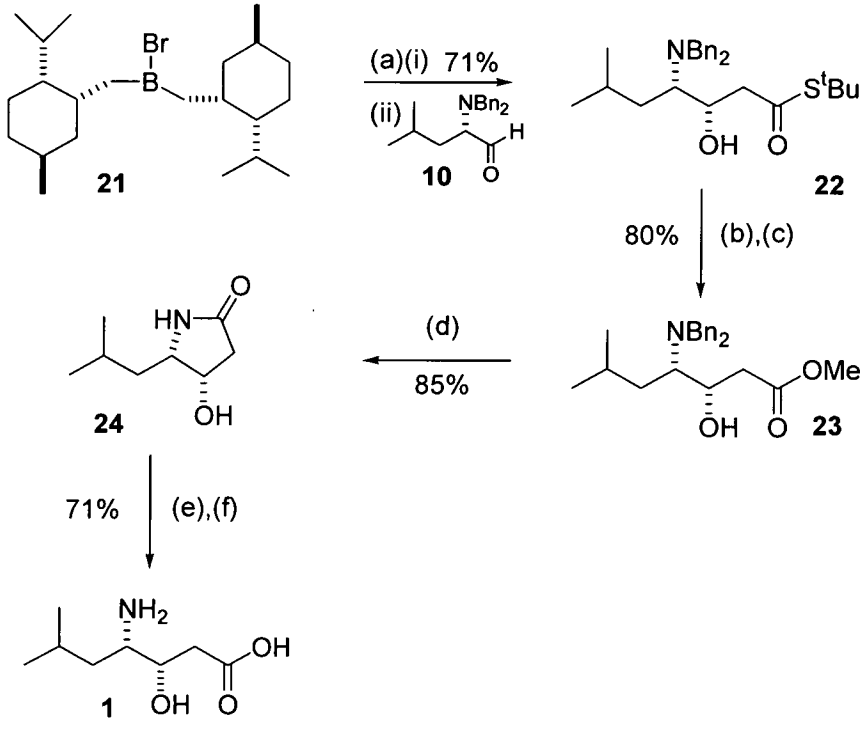
Gennari's[25] approach to statine utilised the boron enolates derived from (-)- and (+)- menthone, **20** and **21**, **figure 5**, which show a high degree of reagent control in reactions with chiral aldehydes. When the menthone derived boron bromide reagent **21** was used to generate the enolate of *tert*-butylthioacetate, the enolate was shown to be capable of overcoming the inherent preference of the substrate for the Felkin product. Both matched and mismatched cases provided the Felkin and *anti*-Felkin **22** products in excellent diastereoselectivity, >99.9 for the "matched case" and >97.5 for the "mismatched case".

Figure 5



Saponification of the aldol adduct **22** and esterification with diazomethane provided the methyl ester **23**. Debenzylation with concomitant cyclisation yielded lactam **24** which was subsequently ring opened with concentrated hydrochloric acid. Ion exchange furnished statine **1** in 34% overall yield, **scheme 8**.

Scheme 8

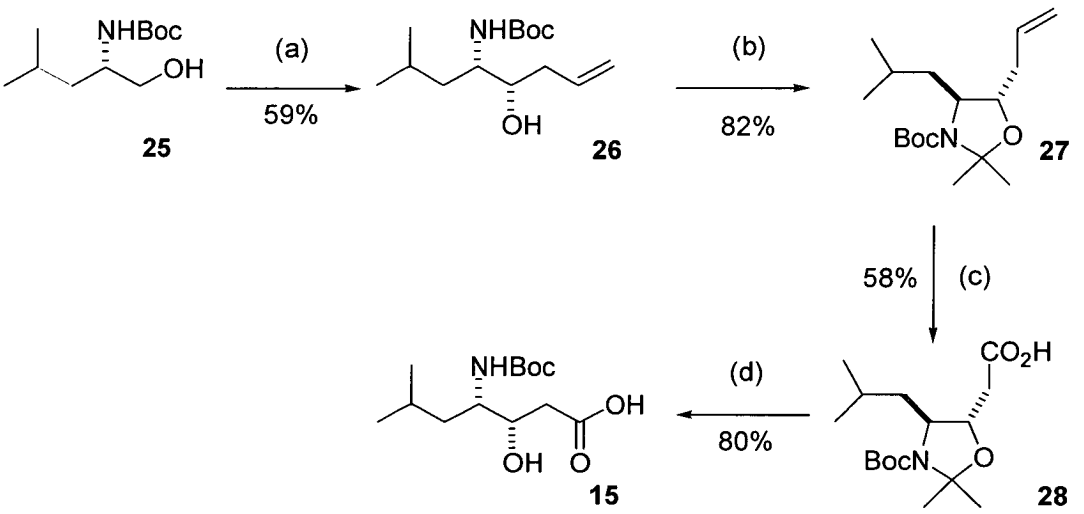


(a) (i) ^{t}BuSAc, Et_2O, DCM, Et_3N; (ii) **10** in DCM; (b) 1*M* NaOH, THF; (c) CH_2N_2, MeOH; (d) HCO_2NH_4, Pd/C, reflux; (e) conc. HCl, 80 °C; (f) DOWEX 50X8-100 (acid form).

1.8 Grignard addition to α-amino aldehyde as a route to statine

The addition of Grignard reagents to leucinal has been reported as a diastereoselective route to the *anti*-Felkin product **26**, **scheme 9**.[26] *N,O*-protection *via* an acetonide linkage followed by oxidation of the terminal olefin formed the corresponding carboxylic acid **28**. Deprotection afforded *N*-Boc protected statine **15** in 22% overall yield and 90% de.

Scheme 9

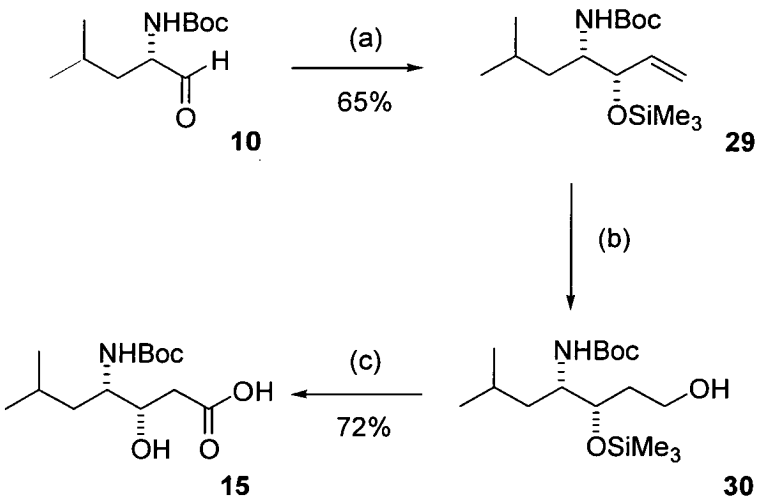


(a) (i) Swern, (ii) $H_2C{=}CHCH_2MgBr$; (b) $Me_2C(OMe)_2$, PPTS, PhMe; (c) $RuCl_3$, $NaIO_4$, aq. $NaHCO_3$, MeCN, CCl_4; (d) AcOH.

1.9 Vinylation of *N*-Boc leucinal as a route to statine

Condensation of *N*-Boc leucinal **10** with 2-trimethylsilylethylidentriphenylphosphorane furnished **29** as a single diastereomer in 65% yield *via* migration of the silyl group to the oxygen and subsequent elimination of triphenylphosphine. Oxidative hydroboration followed by further oxidation and desilylation provided *N*-Boc statine **15** in 47% overall yield, **scheme 10**.[27]

Scheme 10

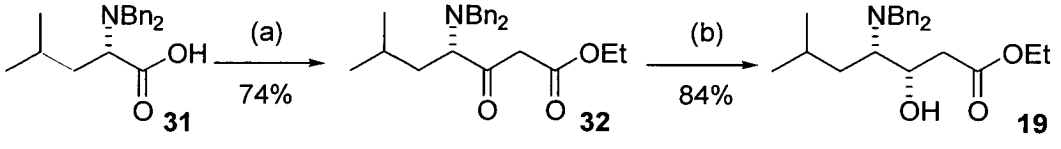


(a) (i) CH_3PPh_3Br, BuLi, THF; (ii) ICH_2SiMe_3, THF; (iii) BuLi; (iv) **10** in THF; (b) 9-BBN, NaOH, H_2O_2; (c) (i) PDC, DMF; (ii) TBAF, THF.

1.10 Claisen condensation reaction

The stereoselective reduction of *β*-keto esters is an additional route which has been investigated in the synthesis of statine. There are two main routes to the synthesis of *β*-keto esters, *via* the acylation of lithium ester enolates or *via* reaction of the magnesium enolates of malonic esters with acylamino acid derivatives. The *N,N*-dibenzylated leucine derived acid **31** developed by Reetz[28] was converted into its imidazolide and subsequently reacted with the magnesium enolate of malonic acid monoethyl ester thus affording the *β*-keto ester **32, scheme 11**. Reduction using $NaBH_4$ occurred stereoselectively under non-chelation control to give the *β*-hydroxy ester **33** preferentially (90% de) *via* the Felkin-Anh transition state. Hoffman and Tao[29] have also exploited this methodology in the synthesis of statine and related analogues.

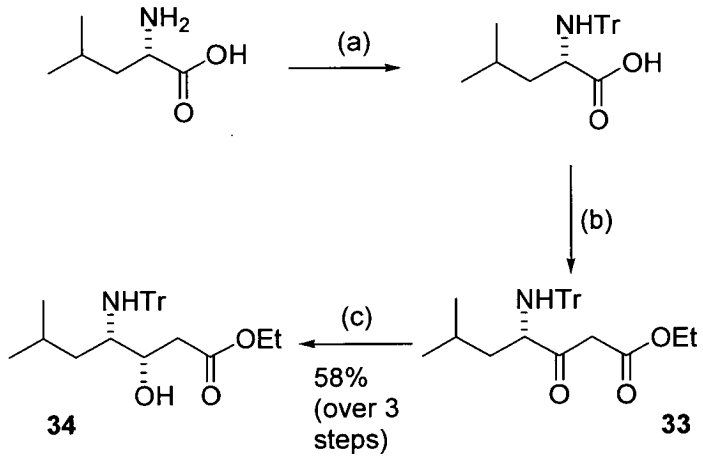
Scheme 11



(a) (i) CDI, THF; (ii) ^{i}PrMgCl, $CH_2(CO_2Et)CO_2H$; (b) $NaBH_4$, MeOH, -20 °C.

Further to Hoffman's[30] studies he reported the synthesis of statine in three steps utilising the bulkier trityl protecting group which can be easily added under basic conditions and readily removed by mild acid hydrolysis (HCl, acetone). An improved diastereoselectivity of 93% de was achieved for **34, scheme 12**.

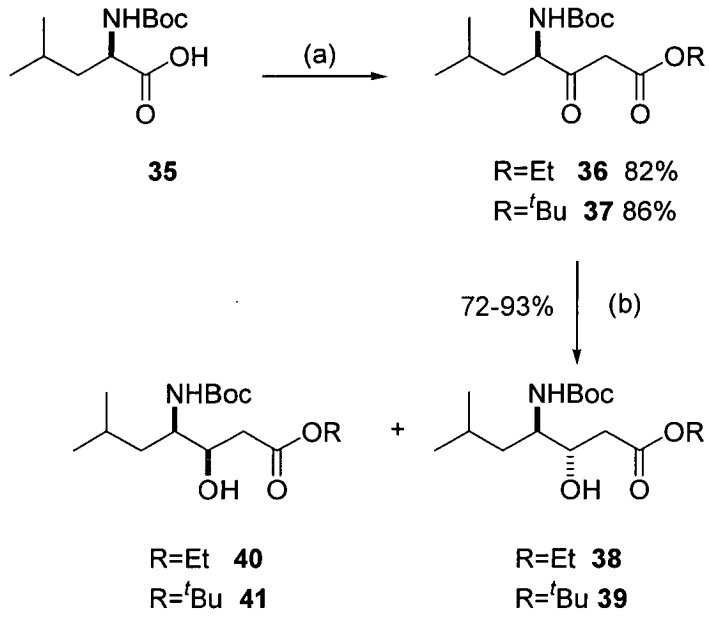
Scheme 12



(a) (i) TMSCl; (ii) TrCl, Et_3N; (iii) MeOH; (b) (i) CDI; (ii) $LiCH_2CO_2Et$; (c) $NaBH_4$, MeOH.

In Joullié's[31] approach to the synthesis of (3*S*,4*R*)-statine the Claisen condensation reaction of the imidazolide derived from *D*-leucine **35** with either ethyl or *tert*-butyl lithioacetate afforded the *β*-keto esters **36** and **37** in 86% and 82% respectively, **scheme 13**. Reduction of the *β*-keto esters with common borohydride reagents produced the corresponding *β*-hydroxy esters **38**, **39**, **40** and **41** with a de ranging from 63% to 88% in favour of the *anti* products **40** and **41**, **table 1**. A similar strategy has also been reported by Rich.[32]

Scheme 13



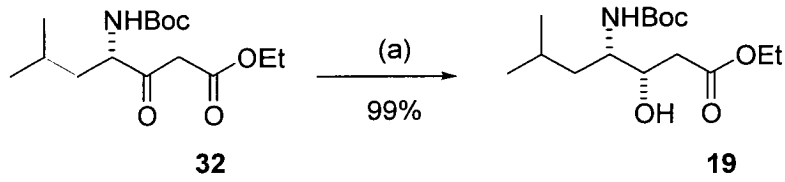
(a) (i) CDI, THF; (ii) $LiCH_2CO_2R$, THF, –78 °C; (b) $LiBH_4$, $NaBH_4$, KBH_4 or $Zn(BH_4)_2$.

Table 1

Reducing Agent	**Conditions**	**Yield % Diastereomeric ratio 40:38**	**Yield % Diastereomeric ratio 41:39**
$LiBH_4$	4eq, THF, 0.5h, -78 °C	87 63:37	93 63:37
$NaBH_4$	3.5eq, EtOH, 1h, 0 °C	83 75:25	84 75:25
KBH_4	3.5eq, EtOH, 1h, 0 °C	80 88:12	88 79:21
$Zn(BH_4)_2$	5eq, Et_2O, 0.5h, 0 °C	72 74:26	75 80:20

Noyori[33] has effectively carried out a highly diastereoselective hydrogenation of β-keto ester **32** catalysed by ruthenium BINAP to give *N*-Boc statine **19** in 99% yield and (>99% de), **scheme 14**.

Scheme 14

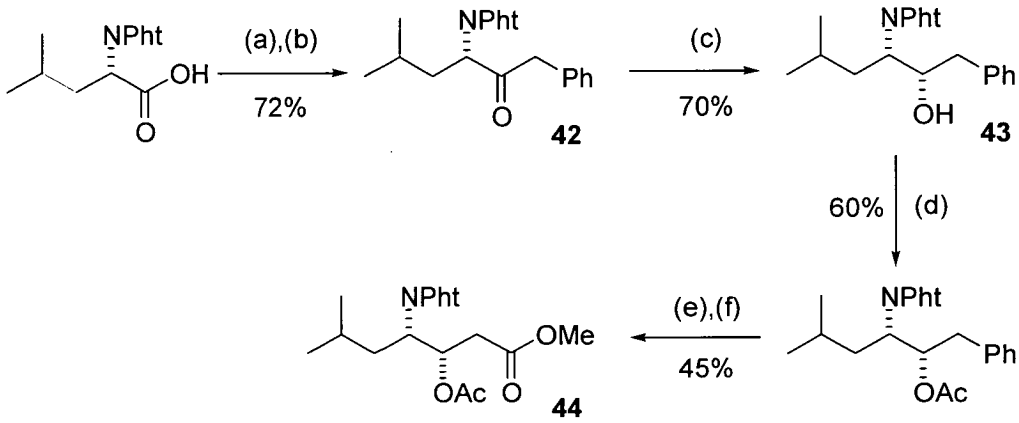


32 **19**

(a) $RuBr_2$[(*R*)]-binap], EtOH, H_2.

Both *N*-Fmoc[34] and *N*-phthaloyl protecting groups have also been employed in the synthesis of statine. Sengupta's[35] approach, **scheme 15**, utilises a highly diastereoselective *syn* reduction of **42** to furnish **43** in 90% de, employing LiAlH(O^{t}Bu) as the reducing agent. Sharpless oxidation of the phenyl ring to the carboxylic acid and subsequent esterification afforded the protected statine ester **44** in 14% overall yield.

Scheme 15

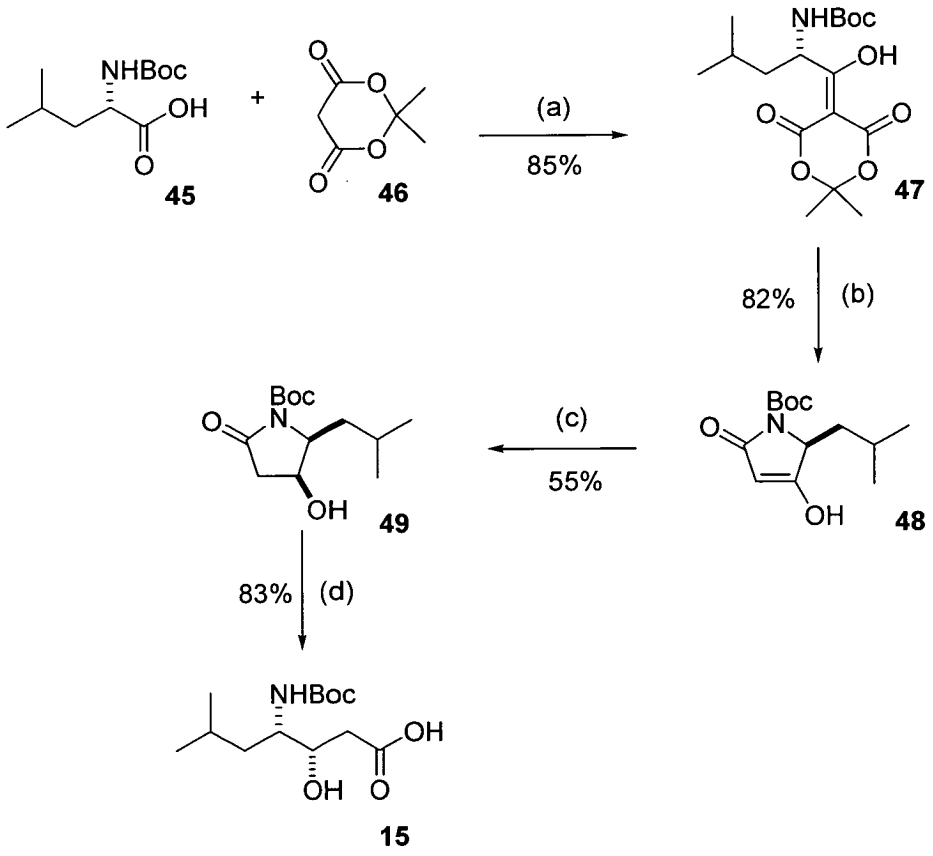


(a) $SOCl_2$, benzene; (b) $PhCH_2ZnBr$, 10% $Pd(PPh_3)_2Cl_2$, THF; (c) LiAlH(O^{t}Bu)$_3$, THF, -20 °C; (d) Ac_2O, Et_3N, DMAP, DCM; (e) cat. $RuCl_3$, $NaIO_4$, CH_3CN, CCl_4, H_2O; (f) CH_2N_2, Et_2O, 0 °C.

1.11 Synthesis of statine *via* tetramic acids

Stereoselective syntheses of statine and related analogues have been reported *via* stereocontrolled reduction of tetramic acids[36] In Jouin's[37] work the tetramic acid derivative **47** was formed from Meldrum's acid **46** and activated *N*-Boc protected leucinal **45** in the presence of DMAP, **scheme 16**. Refluxing **47** provided the tetramic acid **48** which was reduced with PtO_2. Hydrolysis of **49** provided *N*-Boc protected statine **15** in 41% overall yield.

Scheme 16

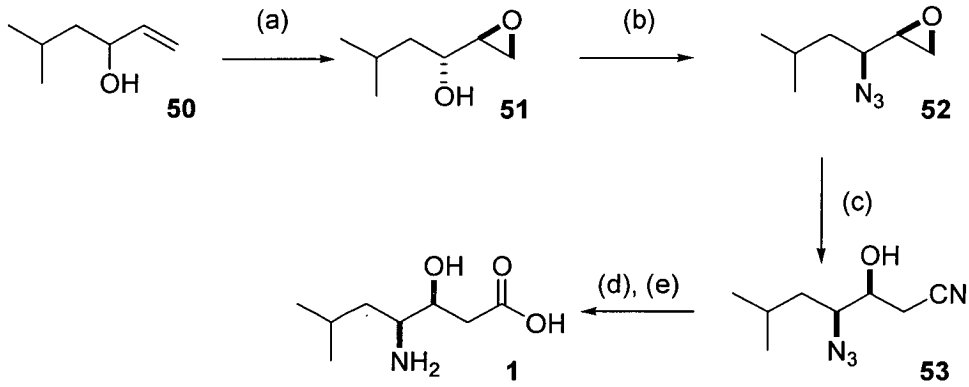


(a) Isoprenyl chloroformate, DMAP, DCM; (b) EtOAc, 40 °C; (c) PtO_2, EtOAc, H_2, 20 atm; (d) 1,4-Dioxane, 1M HCl.

1.12 Diastereoselective epoxidation as a route to statine

An alternative strategy to the nucleophilic addition to *N*-protected amino aldehyde is exemplified in Bessodes'[38] route, **scheme 17**. From racemic allylic alcohol **50** a Sharpless epoxidation followed by a Mitsunobu reaction generated the azide **52**. Ring opening of **52**, followed by hydrolysis and subsequent hydrogenation provided statine **1**.[ϕ]

Scheme 17

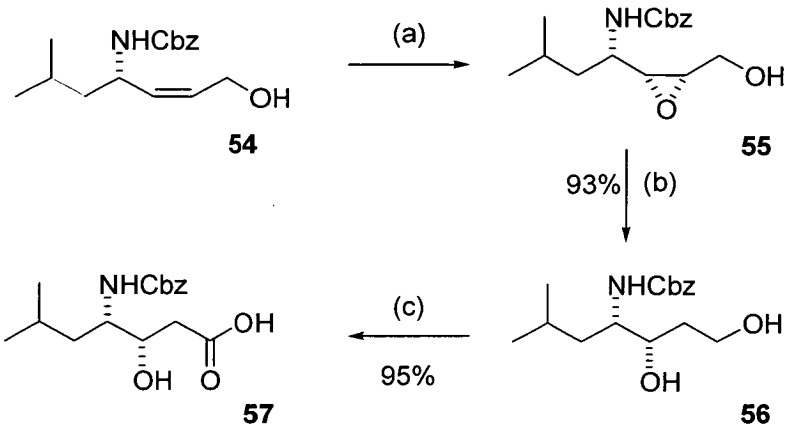


(a) Diisopropyl-*D*-tartrate, Ti(IV) isopropoxide, ^{t}BuOOH, DCM, -10 °C; (b) DEAD, Ph_3P, N_3H, DCM; (c) KCN, MeOH; (d) NaOH, H_2O_2; (e) H_2, Pd/C, MeOH.

A diastereoselective epoxidation of **54** using *m*-chloroperbenzoic acid yielded the *syn* epoxide **55** almost exclusively. Regioselective epoxide ring opening with sodium *bis* (2-methoxyethoxy)aluminium hydride (Red-Al) and selective oxidation of the primary alcohol yielded *N*-Cbz statine **57**, **scheme 18**.[39]

[ϕ] No yields were reported for this synthetic sequence to statine.

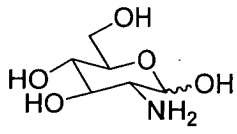
Scheme 18



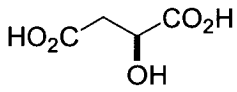
(a) MCPBA, DCM, -10 °C; (b) Red-Al, THF, 0 °C; (c) Pt, O_2, $NaHCO_3$, H_2O.

Additional reported examples to statine and related analogues utilise *D*-glucosamine **58**,[40] malic acid **59**,[41] butenediol **60**[42] and commercially available glycine templates **61**[43] as precursors, **figure 6**.

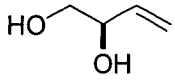
Figure 6



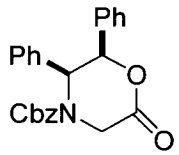
58



59



60



61

1.13 Isostatine

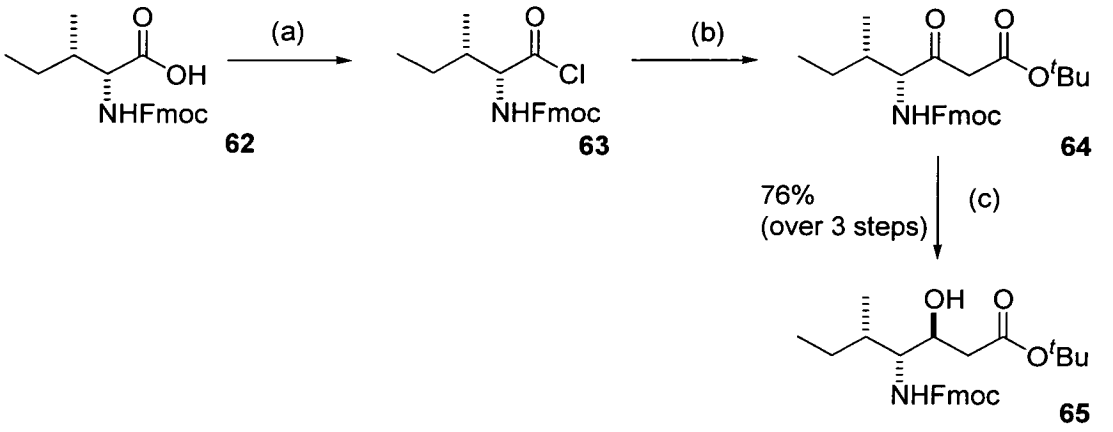
The cyclic depsipeptides didemnin A-C were isolated from the tunicate *Tridemnum solidum* in 1981 by Rinehart.[2] The didemnines share a common macrocycle and differ only in the side chain attachment. Didemnin B shows strong antitumour, antiviral as well as immunosuppressive activity. Isostatine **2** is a key unit in all three didemnins and has been recognised as essential for the biological activity of didemnin B.

Unlike the syntheses of statine *via* aldol or Claisen condensation reactions, the synthesis of isostatine requires the expensive *D*-alloisoleucine to be used as a precursor, thus syntheses of isostatine can be expensive or comparatively long due to the preparation of *D*-alloisoleucine.

1.14 Synthesis of isostatine from *D*-alloisoleucine

Fmoc-*D*-alloisoleucine **62** was employed as the starting material in Kessler's synthesis of isostatine.[34b] Conversion of **62** to its acid chloride and subsequent coupling with lithio *tert* butyl acetate provided the β-keto ester **64**, **scheme 19**. Without purification **64** was reduced with potassium borohydride (de 90%), subsequent recrystallisation furnished **65** as a single diastereomer and a single enantiomer.

Scheme 19

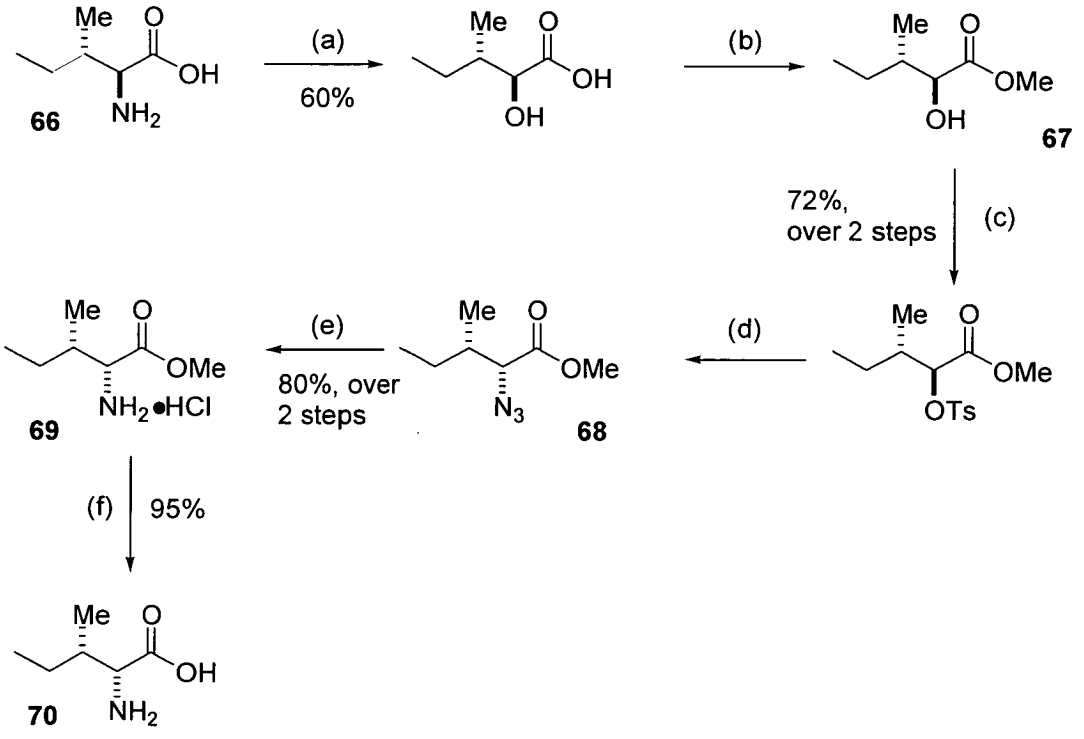


(a) $SOCl_2$, DCM; (b) $LiCH_2CO_2{}^tBu$, THF, -85 °C; (c) (i) KBH_4, EtOH, 0 °C; (ii) EtOAc, 2-methylpentane.

N-Boc-*D*-alloisoleucine was employed as the precursor in Joullié's synthesis of isostatine. A Claisen condensation reaction followed by a stereoselective reduction furnished protected isostatine in 89% overall yield and 90% de.[31b]

A six step synthesis of *D*-allosioleucine from *L*-isoleucine **66** by Giralt[44] commenced with diazotisation and subsequent hydrolysis of the amino group, **scheme 20**. Esterification with diazomethane yielded hydroxy ester **67** which was tosylated under standard conditions. Nucleophilic substitution with azide ion gave azide **68** which was reduced to the hydrochloride **69** by catalytic hydrogenation. Saponification furnished *D*-Allosioleucine **70** in 33% overall yield. The synthetic sequence to isostatine was similar to that discussed in **scheme 19.**

Scheme 20



(a) $NaNO_2$, H_2SO_4; (b) CH_2N_2, 0 °C; (c) TsCl, pyridine; (d) NaN_3, DMF, 50 °C; (e) H_2, Pd; (f) 1*M* NaOH.

1.15 Summary of chapter 1

This chapter illustrates some of the key routes used in the synthesis of statine and isostatine. The majority of these syntheses have been shown to be highly diastereoselective and high yielding. The strategies undertaken have led to the development of new chiral auxiliaries capable of providing high diastereoselectivities in the acetate aldol reaction. The Claisen condensation reaction has also been depicted as an important route to these substrates.

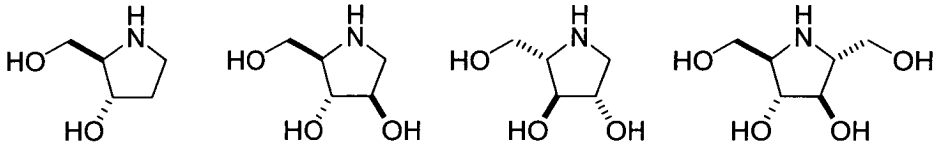
Chapter 2: Results and Discussion Part 1

2.0 Synthesis of silyl protected CYB-3

2.1.1 Introduction

(2*R*,3*S*)-2-hydroxymethyl-3-hydroxypyrrolidine (CYB-3), **71** was isolated from *Castanospermum australe* in 1987 by Nash and Bell.[45] This tree is also the source of the α- and β-glucosidase inhibitor (+)-castanospermine, a polyhydroxylated indolizidine alkaloid.[46] CYB-3's biological activity was compared with other pyrrolidine alkaloids such as DMDP **74**, DAB-1 **72** and LAB-1 **73**, **figure 7** and it was observed to be either a poor inhibitor or inactive against known targets of these enzymes, **table 2**.

Figure 7



CYB-3	DAB-1	LAB-1	DMDP
71	**72**	**73**	**74**

In a study of these pyrrolidine derivatives as inhibitors of mammalian digestive disaccharides, CYB-3 was observed to exhibit only modest inhibitory activity against several of the glycosidase targets.[47] These findings were also comparable with a study involving insect glycosidase targets.[48] Despite CYB-3's inactivity it has been proposed as both a chemical[49] and biosynthetic[50] precursor for a number of more active indolizidine alkaloids and has also been used in the synthesis of modified oligonucleotides.[51]

Table 2

Concentration of Inhibitor (M) resulting in 50% inhibition of Hydrolysis

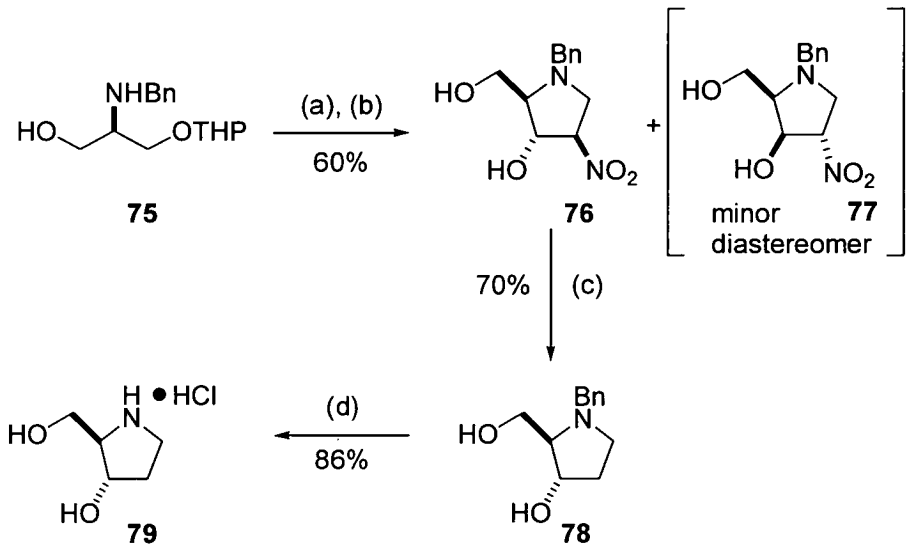
Inhibitor / Substrate	CYB-3	DAB-1	LAB-1	DMDP
α-glucoside	NI[a]	4.7×10^{-5}	2.0×10^{-6}	3.0×10^{-4}
Maltose	NI	3.5×10^{-5}	2.5×10^{-6}	2.0×10^{-4}
Trehalose	NI	2.2×10^{-5}	2.6×10^{-4}	3.2×10^{-4}
Sucrose	1 × 10-4	2.3×10^{-5}	2.2×10^{-6}	4.2×10^{-5}
Isomaltose	1.7×10^{-4}	4.0×10^{-6}	6.6×10^{-8}	2.3×10^{-5}
Turanose	2.3×10^{-4}	2.8×10^{-5}	2.0×10^{-6}	7.1×10^{-5}
β-glucoside	NI	NI	NI	1.0×10^{-5}
Gentiobiose	2.7×10^{-4}	1×10^{-4}	3.0×10^{-4}	2.2×10^{-6}
β-galactoside	NI	2.1×10^{-4}	NI	2.0×10^{-6}
Lactose	2.6×10^{-4}	NI	NI	2.1×10^{-6}

a NI=less than 50% inhibition at 3.3×10^{-4} M

2.1.2 Previous syntheses of CYB-3

Several chemical syntheses of CYB-3 have been reported utilising the amino acid serine, a number of different strategies have been used to achieve the required two-carbon homologation.[52] Barco's[53] approach relies on a tandem Michael-Henry reaction to generate the pyrrolidine structure, **scheme 21**. Intermediate **75** was obtained in 5 steps from *L*-serine; reductive amination of *L*-serine with benzaldehyde followed by TBS protection gave the *N,O* protected serine ester. Lithium aluminium hydride reduction, transformation to the tetrahydropyranyl ether and TBS deprotection provided the required intermediate **75**. Treating this with 2-benzoyloxy-1-nitroethane (precursor to nitroethylene) resulted in the expected Michael adduct. Subsequent Swern oxidation of this adduct gave a 3:1 mixture of the pyrrolidine derivatives **76** and **77**. Denitration of **76** by Ono's procedure to **78** and hydrogenolysis in the presence of acid furnished the pyrrolidine salt **79** in 25% overall yield.

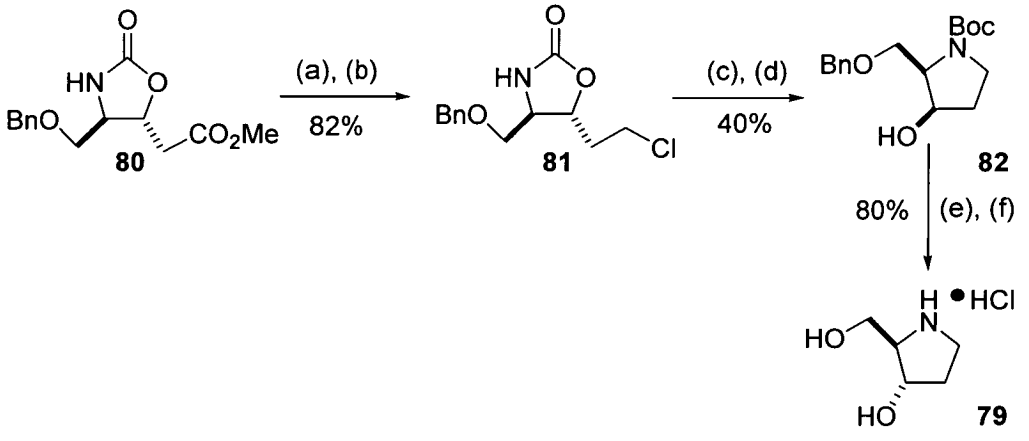
Scheme 21



(a) (i) $BzOCH_2CH_2NO_2$; (ii) $(COCl)_2$, DMSO, DCM, NEt_3; (b) H_3O^+; (c) $(^tBu)_3SnH$, AIBN, MeC_6H_5; (d) H_2, Pd/C, MeOH, HCl.

A second approach by Dell'Uomo from *L*-serine derived oxazolidinone **80** involves ester reduction and alkyl chloride formation to give **81**, **scheme 22**.[49] Cleavage of the cyclic carbamate was achieved by refluxing with sodium hydroxide in methanol/water and subsequent Boc protection furnished **82**. The inversion of the alcohol configuration was achieved *via* a Mitsunobu reaction. The hydrochloride salt of CYB-3 **79** was obtained in 38% overall yield using this 11 step procedure.

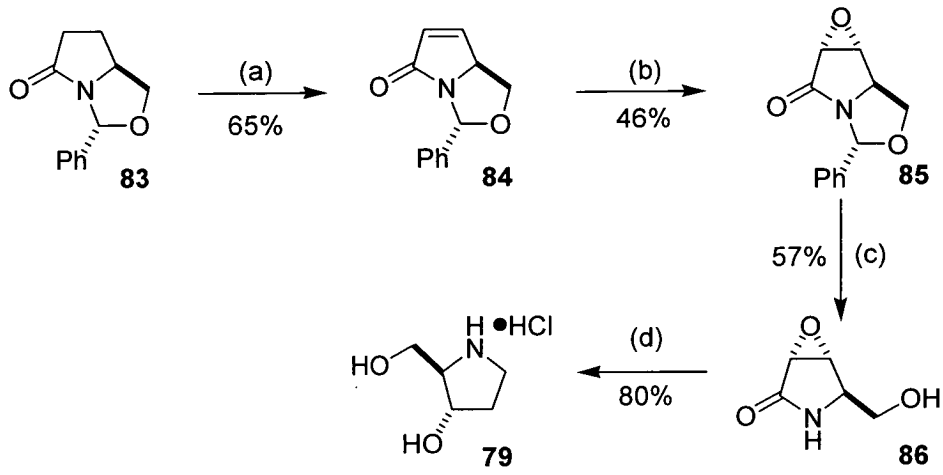
Scheme 22



(a) $NaBH_4$, THF, MeOH; (b) Ph_3P, CCl_4; (c) NaOH, MeOH, H_2O, 80 °C; (d) Boc_2O, NEt_3, DCM; (e) *p*-$NO_2C_6H_4COOH$, DEAD, Ph_3P, Benzene; (f) 10% Pd/C, 3M HCl, EtOAc.

A further key building block that has been employed in CYB3 synthesis is pyroglutamic acid.[54] The approach used by the Langlois'[55] group involves deprotonation of pyrrolidine **83**, followed by phenylselenation and selenoxide elimination, **scheme 23**. This enabled introduction of the conjugated double bond in **84**. Epoxidation with lithium *tert*-butylhydroperoxide gave a 87:13 mixture of diastereomers in 46% yield. Trifluoroacetic hydrolysis allowed deprotection without opening of the epoxide ring in **85**. Finally lithium aluminium hydride reduction gave the desired pyrrolidine salt **79** in 21% overall yield.

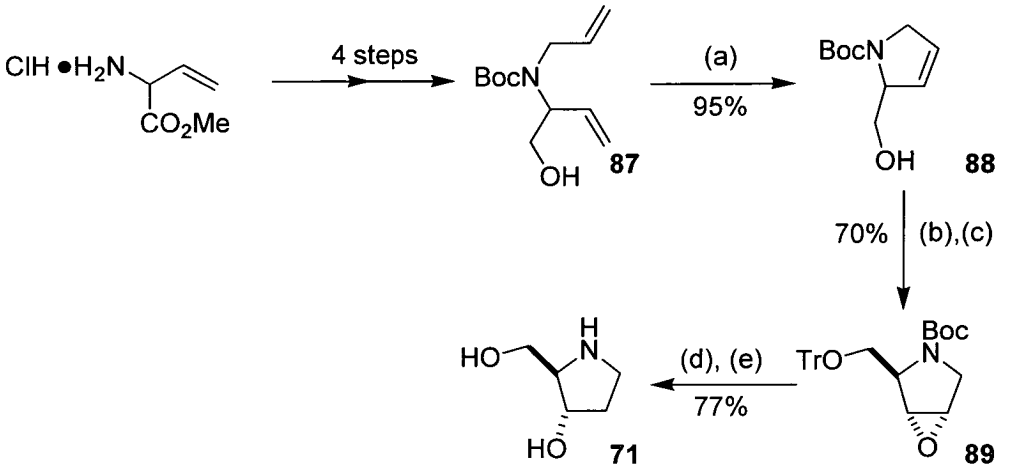
Scheme 23



(a) LiHMDS, PhSeCl; (ii) H_2O_2; (b) Li-^{t}BuOOH; (c) TFA; (d) $LiAlH_4$.

A novel racemic route from vinyl glycine methyl ester relies on olefin metathesis as the key step.[56] Using 4 mol% of Grubbs catalyst the *N*-Boc protected dehydroprolinol **87** was prepared in 95% yield. The protected trans-3,4-epoxy-prolinol **88** was obtained by tritylation of the free hydroxyl group and diastereoselective epoxidation. Regioselective ring opening and acidic deprotection provided CYB-3 **71** in 14% overall yield, **scheme 24**.

Scheme 24



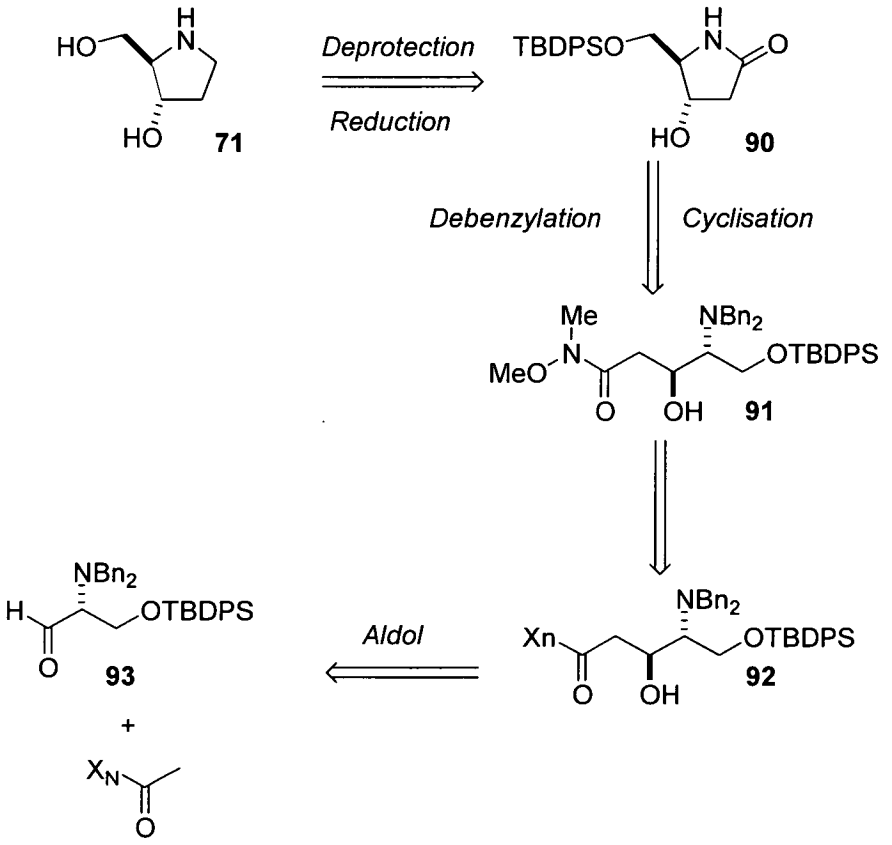
(a) $Cl_2(PCY_3)_2Ru{=}CH\text{-}CH{=}Ph_2$ (4 mol %), PhH; (b) Ph_3CCl, DMAP, NEt_3, DCM; (c) MCPBA, Et_2O; (d) $LiBH_4$, MeOH, diglyme; (e) HCl, MeOH.

As illustrated from the above examples there have been several synthesis of CYB-3 undertaken relying upon readily available chiral pool starting materials.

2.1.3 Retrosynthesis of CYB-3

Our retrosynthetic analysis of CYB-3 is shown in **scheme 25**. The important step was an acetate aldol reaction with serine-derived aldehyde **93** with Felkin-Anh control, which would generate the required C(3)-C(4) stereochemistry in **92**. Conversion to the Weinreb amide **91**, followed by debenzylation with concomitant cyclisation to would yield the pyrrolidinone **90**. Reduction and deprotection would give the target molecule.

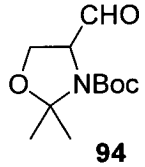
Scheme 25



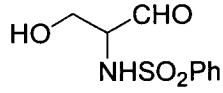
2.1.4 Use of serine derived aldehydes in syntheses

The key building block in our synthesis was *N*-protected serinal. There have been a variety of protecting groups employed for all three of serines functional groups. Examples of protected serinal derivatives include Garner's cyclic oxazolidinone aldehyde **94**, Rapaport's acyclic *N*-(phenylsulfonyl)-protected serine **95** and a *N*-(9-phenylfluoren-9-yl) cyclic carbamate **96**,[57] **figure 8**.

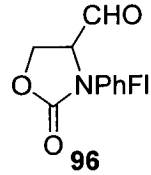
Figure 8



94



95

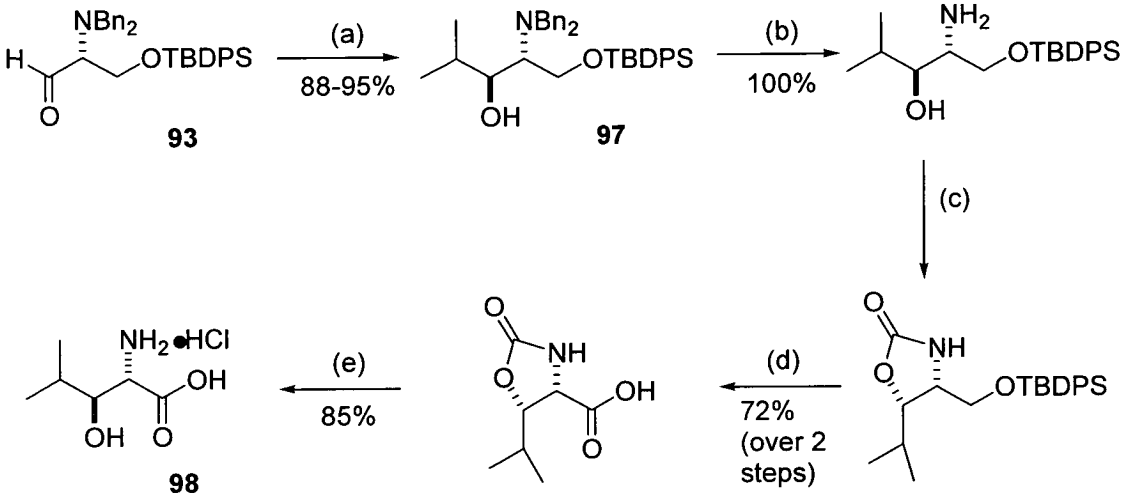


96

Garner's aldehyde is probably the most important synthon and has been used as the starting material of a wide range of bioactive compounds.[58] Though moderate to good selectivities are obtained, the facial selectivity of the addition of Grignard reagents or other organometallic reagents to this aldehyde has been shown to be moderate to poor and to be reagent dependent. Chelated and non-chelated processes (section 1.6) have been reported to occur concomitantly which has led to diminished diastereoselectivity or even a reversal in selectivity. This obviously has made the stereochemical outcome in some cases difficult to predict.[59]

In continuation with the work developed within the group[60] our attention was turned to the *N,N*-dibenzylamino aldehydes introduced by Reetz and his concept of protective group tuning as a means of achieving high levels of asymmetric control in organometallic reactions involving *N,N*-dibenzylamino aldehydes.[19,61] Despite this development the use of this serine-derived aldehyde has been very limited.[60,62] Zhu[62b] has reported the nucleophilic addition of a Grignard reagent to *N,N*-dibenzyl serine as the key step in the synthesis of (2*S*,3*S*)-*β*-hydroxyleucine **98**, **scheme 26**. Treatment of the crude amino aldehyde **93** with two equivalents of isopropylmagnesium chloride furnished **97** in >95% de.

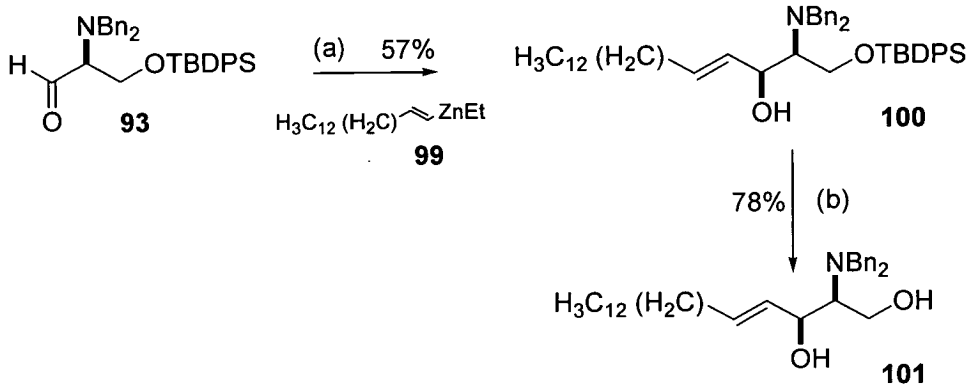
Scheme 26



(a) ^{i}PrMgCl, Et_2O; (b) $Pd(OH)_2$, H_2, MeOH; (c) CDI, THF, DMAP (cat.); (d) (i) KF, (ii) Jones oxidation; (e) conc. HCl.

Pedrosa[62c] has developed a synthetic route to all four stereoisomeric *N,N*-dibenzyl sphingosines from aldehyde **93** in two steps. The synthetic strategy is dependent on the choice of starting amino aldehyde (*D* or *L*) and the alkylating agent. The synthesis of *N*-protected *L-threo*-sphingosine was achieved by *syn* addition of pentadec-1-enyl(ethyl)zinc **99** to serine-derived aldehyde **93** to afford **100** in 80% de. Subsequent silyl deprotection provided **101** in 44% overall yield, **scheme 27**.

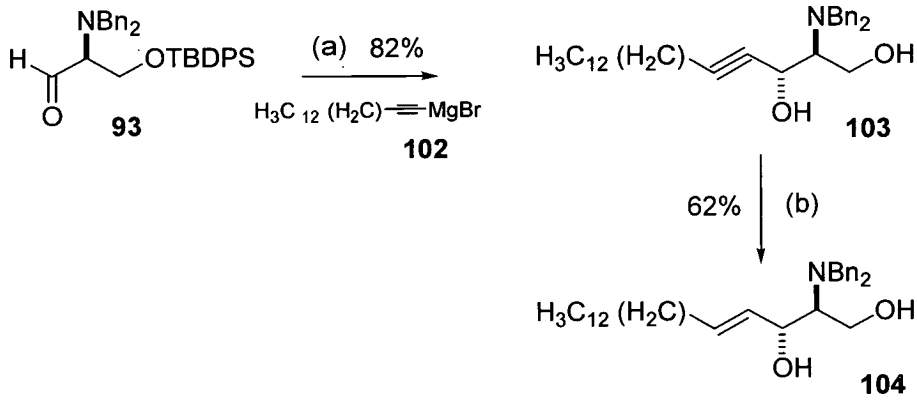
Scheme 27



(a) Toluene, Heptane, **99**, 0 °C; (b) TBAF, THF, 0 °C.

D-ethyro-spingosine **104** was achieved by addition of pentadecynyl magnesium bromide **102** to **93** affording **103** as a single diastereomer. Refluxing a mixture of **103** and $LiAlH_4$ resulted in concomitant silyl deprotection and reduction of the triple bond to give **104** in 51% overall yield. **scheme 28**.

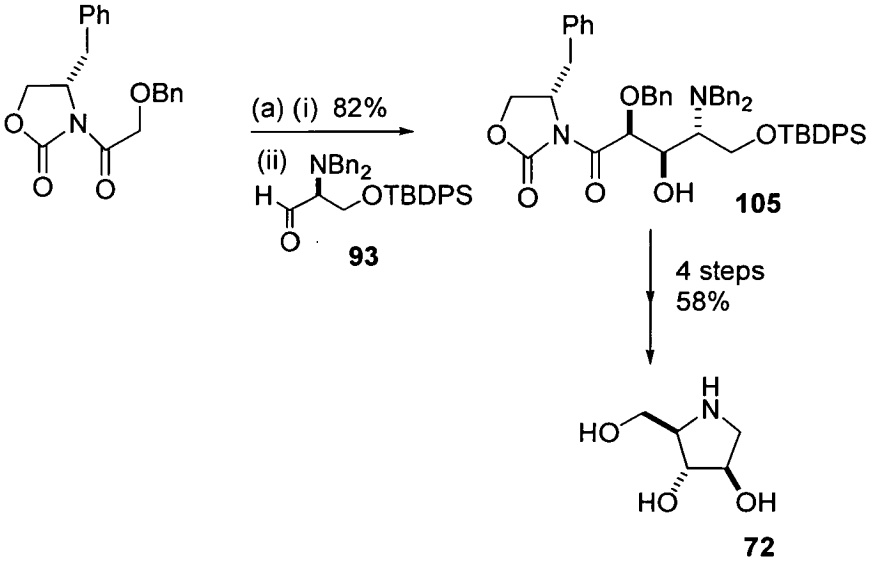
Scheme 28



(a) Et_2O, **102**, 0 °C; (b) $LiAlH_4$, THF, 90 °C.

Finally the Hulme group[60] has reported a synthesis of DAB-1 using an asymmetric boron mediated *syn* aldol as the key step affording **105** as a single diastereomer, **scheme 29**.

Scheme 29

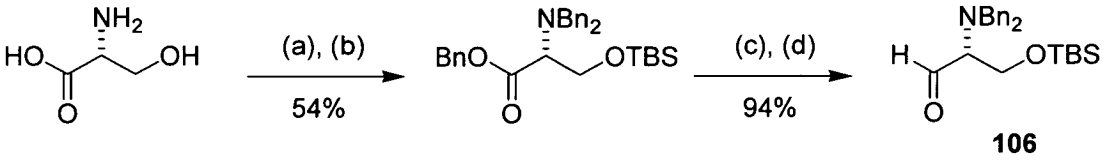


(a) Bu_2BOTf, Et_3N, DCM, -78 °C→0 °C, 1.25h, recooled to –78 °C; **93** in DCM.

2.1.5 Synthesis of serine derived aldehyde 93

Reetz's[21] reported synthesis of the aldehyde **106** was achieved in 51% overall yield and >98% ee, **scheme 30**. The one pot benzylation of serine was found to be the lowest yielding step in the synthesis. Hence, we decided to pursue an alternative strategy for the nitrogen protection and ester formation.

Scheme 30

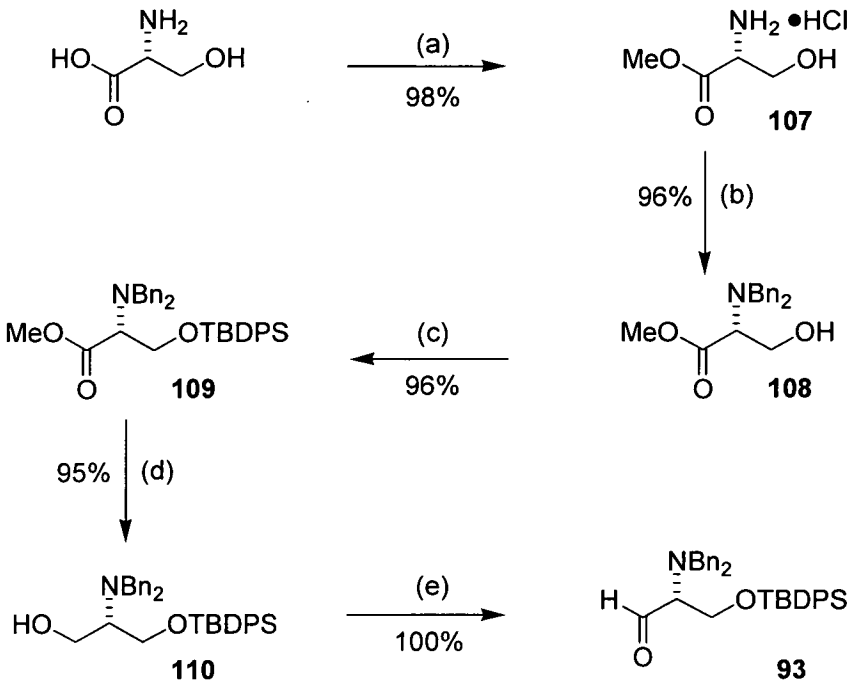


(a) BnBr, K_2CO_3, H_2O; (b) TBSCl, Imidazole, DMF; (c) $LiAlH_4$, (d) Swern.

Our 5-step synthesis of the differentially protected aldehyde **93** commences with the conversion of *D*-serine to its methyl ester hydrochloride salt in 98% yield, scheme **31**. This salt was subsequently *N,N*-dibenzyl protected under non-aqueous conditions to give **107** in 96% yield. The free hydroxyl group was protected as its *tert*-butyldiphenylsilylether in good yield. The TBDPS group was chosen as a suitable orthogonal protecting group due to its stability in subsequent manipulations. Reduction of methyl ester **109** was achieved with $LiBH_4$ and finally the aldehyde **93** was afforded cleanly *via* a Swern oxidation. The aldehyde was used in subsequent reactions in its crude form, since chromatographic purification can lead to racemisation.[21,58] Our optimised route provided the aldehyde in 86% overall yield (>98% ee).[Ψ]

[Ψ] The enantiomeric excess was determined by C. Montgomery

Scheme 31

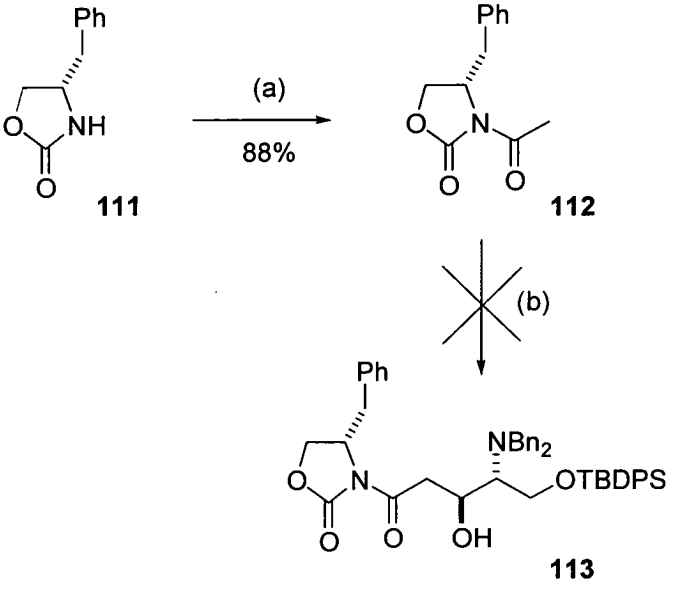


(a) CH_3COCl, MeOH, 80 °C; (b) K_2CO_3, BnBr, CH_3CN; (c) TBDPSCl, imidazole, DMF; (d) $LiBH_4$, Et_2O, MeOH; (e) $(COCl)_2$, DMSO, NEt_3, DCM.

2.1.6 Boron mediated acetate aldol

The oxazolidinone **111** was prepared by C. Montgomery *via* condensation of diethyl carbonate and *S*-phenylalaninol. This oxazolidinone was *N* acylated with butyl lithium and acetyl chloride to afford **112**. However, attempts at the boron mediated aldol using this chiral auxiliary proved unsuccessful with no product **113** being isolated under a variety of conditions, **scheme 32**.

Scheme 32

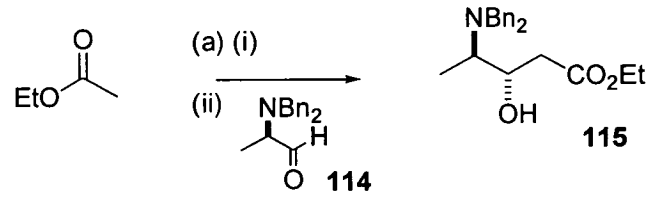


(a) (i) BuLi, THF, -78 °C; (ii) CH_3COCl; (b) (i) $^nBu_2BOTf$, Et_3N, DCM, -78 °C→0 °C, 30 mins, recooled to –78 °C; (ii) **93** in DCM at -78 °C.

2.1.7 Lithium mediated acetate aldol

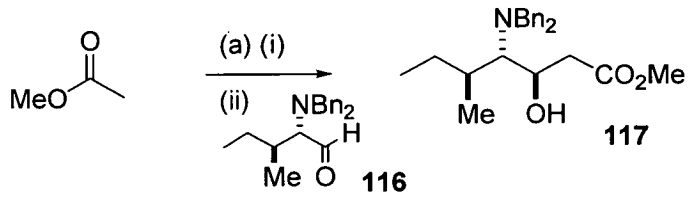
As an alternative to the boron mediated aldol we turned our attention to a lithium mediated aldol. Reetz has shown that the reactive lithium enolate derived from ethyl acetate preferentially reacts with the aldehyde derived from alanine **114** to give the aldol adduct **115** as the major diastereomer in >93% yield with no reports of racemisation, **scheme 33**.[21] He also reported that the aldol reaction of the more sterically demanding aldehyde isoleucinal **116** afforded the aldol adduct **117** in 82% yield and >98% de, **scheme 34**.[63]

Scheme 33



(a) LiHMDS, -78 °C; (ii) THF, -78 °C.

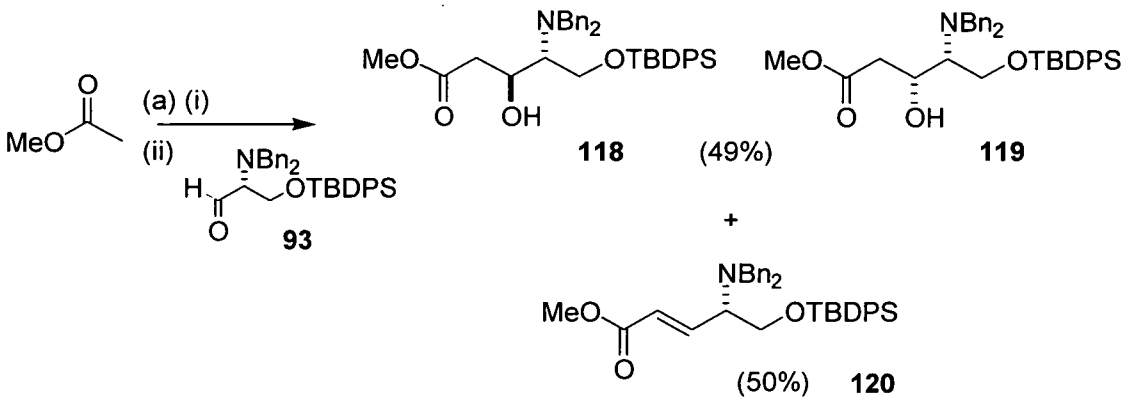
Scheme 34



(a) LiHMDS, -78 °C; (ii) THF, -78 °C.

Our initial studies into the aldol reaction using lithio methyl acetate and the differentially protected aldehyde **93** gave a mixture of the aldol adducts **118** and **119** (diastereomeric ratio not determined) in 49%. A major by-product from this reaction (50%) was observed to be the α,β-unsaturated ester **120** resulting from dehydration of these aldol adducts, **scheme 35**.

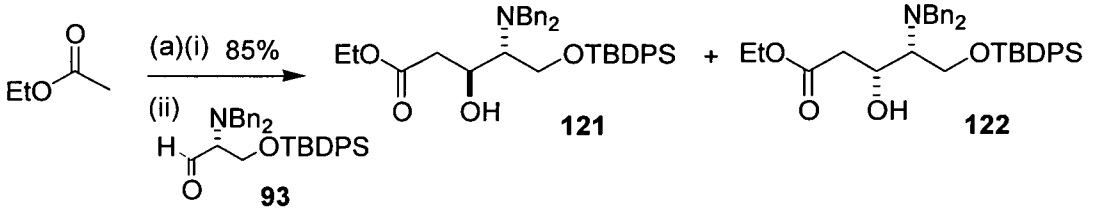
Scheme 35



(a) (i) LiHMDS, -78 °C; (ii) THF, -78 °C→0 °C.

Proceeding to the slightly bulkier lithio ethyl acetate produced solely a mixture of the aldol adducts **121** and **122**; none of the elimination product was observed, **scheme 36**.

Scheme 36



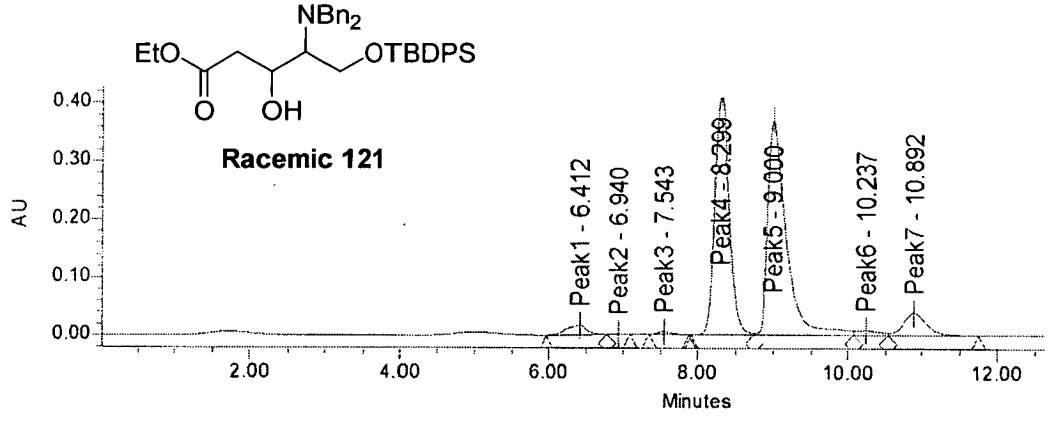
(a) (i) LiHMDS, -78 °C; (ii) THF, -78 °C→0 °C.

Rather disappointingly only a 6:1 mixture of diastereomers was obtained which was in sharp contrast to the 10:1 selectivities being observed by Reetz. The diastereoselectivity was calculated by measurement of the integrals from the crude ^{1}H NMR corresponding to the protons at C(2). In the major aldol adduct these were apparent as two sets of doublet of doublets at 2.31 and 2.98 ppm. In the minor aldol adduct the peaks appeared at 2.45 and 2.30 ppm. [The minor peaks were consistent with those obtained *via* reduction of the Claisen product, section 2.2.]

Chiral HPLC (5% IPA in Hexane) further confirmed the selectivity by comparison of the major peak at R_t=8.3 (corresponding to the enantiomer of *β*-hydroxy ester **121**) and the minor peak R_t=10.9 (corresponding to the enantiomer of *β*-hydroxy ester **122**), **figure 9**.

The enantiomeric purity of the aldol adduct was determined by chiral HPLC by a comparison with the racemic adduct synthesised in the same manner. The adduct was observed to have undergone considerable racemisation (90% ee, major enantiomer R_t 9.0, minor enantiomer R_t 8.3). Lengthier reaction times as a direct result of the presence of the bulky TBDPS group may have been one contributing factor to racemisation of the aldol adduct.

Figure 9

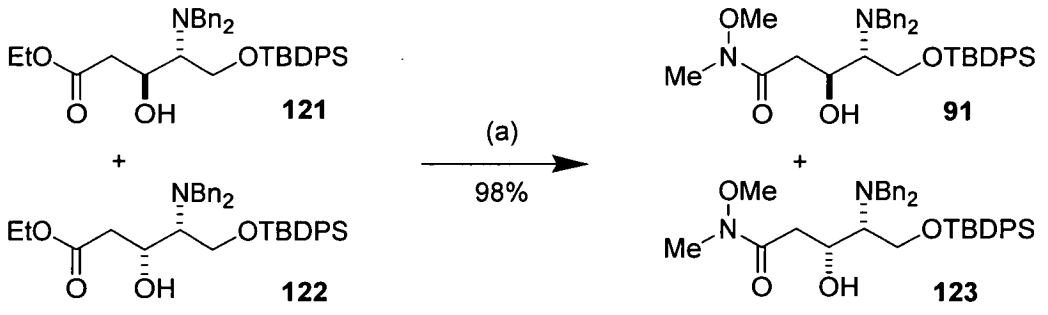


2.1.8 Formation of pyrrolidine 125

The separation of the aldol adducts **121** and **122** proved unattainable by flash chromatography or by HPLC. Hence, they were converted as a mixture to their Weinreb amides[64] using *N,O*-dimethylhydroxylamine•hydrochloride and trimethylaluminium, **scheme 37**. The hygroscopic nature of the hydroxylamine salt did have deleterious effects on the reaction but this was overcome by driving the

water off under vacuum immediately prior to the reaction. This provided the amides **91** and **123** in near quantitative yield.

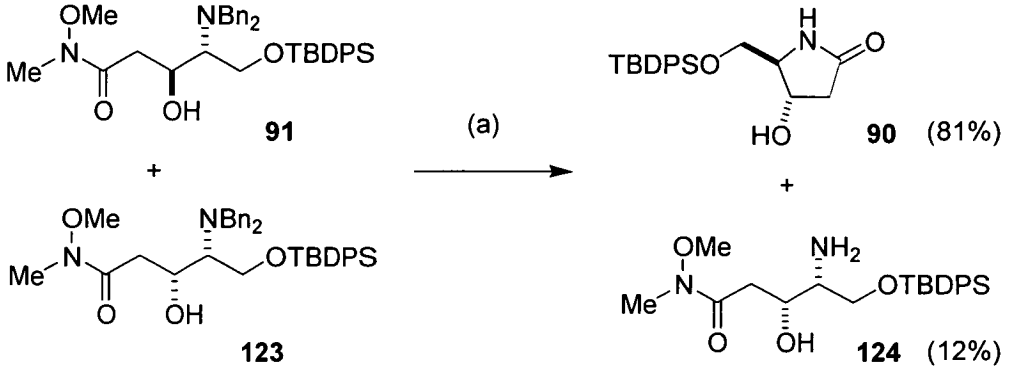
Scheme 37



(a) (MeO)NHMe•HCl, Me_3Al, THF, 0 °C→35 °C.

The synthesis of lactam **90** occurred uneventfully *via* debenzylation using Pearlman's catalyst ($Pd(OH)_2/C$)[65] with concomitant cyclisation as reported in the synthesis of DAB-1[60] and (+)-castanospermine.[66] The separation of the diastereomers was now possible due to conformational constraints associated with the minor diastereomer which resulted in the isolation of the acyclic amino amide **124** and not its associated lactam, **scheme 38**.

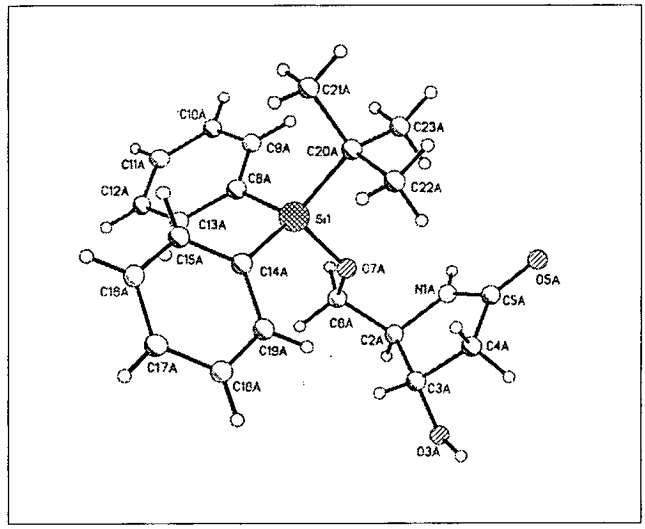
Scheme 38



(a) $Pd(OH)_2/C$, MeOH, H_2.

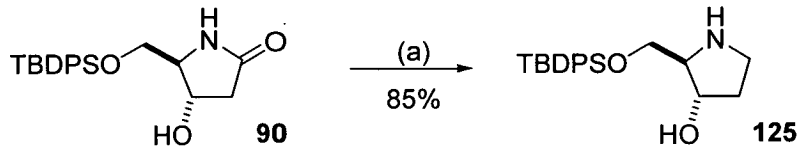
Compound **90** was isolated as a crystalline solid and its structure was unequivocally determined by X-ray diffraction, **figure 10**. This therefore confirmed the stereochemistry which we had predicted for the aldol reaction of the serine derived aldehyde **93**.

Figure 10



The lactam **90** was successfully reduced with BH_3•THF complex to give the protected pyrrolidine **125**.

Scheme 39



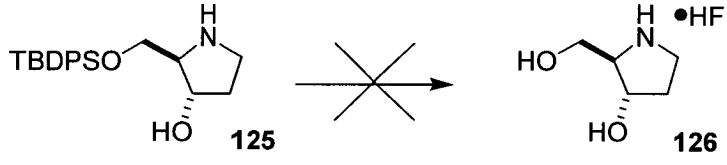
(a) BH_3•THF, THF, 0 °C→80 °C.

2.1.9 Attempted deprotection of silyl protecting group

The remaining step in the sequence the removal of the TBDPS protecting group proved unattainable *via* a variety of routes. The TBDPS group was chosen as it offered greater stability than the TBS protecting group to the reducing conditions employed in our synthesis of aldehyde **93**. (The TBS group was cleaved when DIBAL-H and $LiAlH_4$ were employed as the reducing agents).

The TBDPS group is stable to reagents typically used to cleave the TBS group such as 80% acetic acid. Longer reaction times are generally employed for the removal of the TBDPS with a variety of options available for cleavage such as *tert*-butylammoniumfluoride (TBAF), HF/Acetonitrile and HF/Pyridine.

Scheme 40



The deprotection was initially attempted using TBAF, which is far less toxic than hydrofluoric acid. Purification of the hydroxylated pyrrolidine from tetrabutylammonium salts by chromatography proved difficult. We expected that deprotection following the HF protocol would provide a cleaner reaction mixture. Surprisingly after stirring for 48 hours starting material was still apparent by t.l.c.. The mixture was warmed gently to 40 °C and the mixture stirred for a further 6 hours. Upon workup large quantities of salts were present, purification by silica gel chromatography provided a mixture of starting material and TBDPS alcohol by elution with ethyl acetate. Elution with a 5:3:1 mixture of chloroform:methanol:ammonia (28%) gave a colourless solid, which was subjected to final purification by ion exchange chromatography (Dowex 1X2 (OH^- form)). However none of the desired product was obtained.

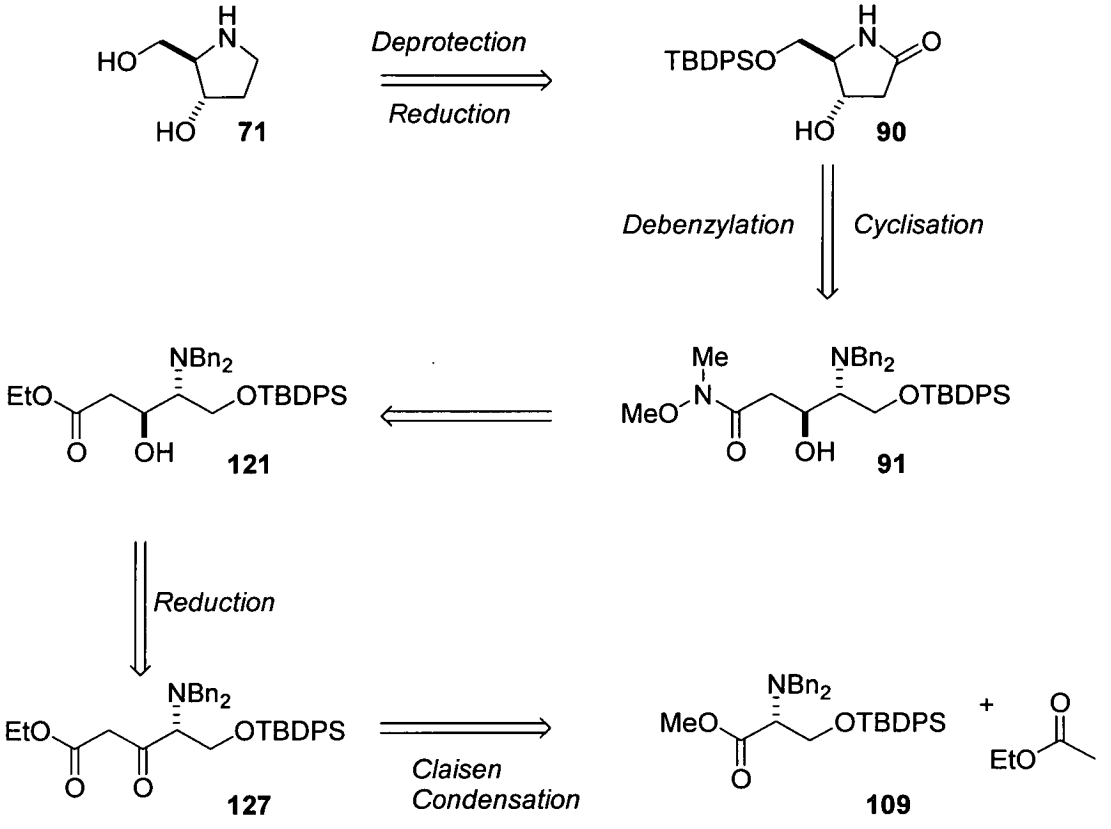
Hannessian[67] has reported the deprotection of the TBDPS group to occur using a 3% methanolic hydrochloric acid solution. This protocol was also attempted but again none of the pyrrolidine was acquired. T.l.c. of the reaction mixture showed that extensive decomposition had occurred.

2.2 Synthesis of C(3) epimer of CYB-3

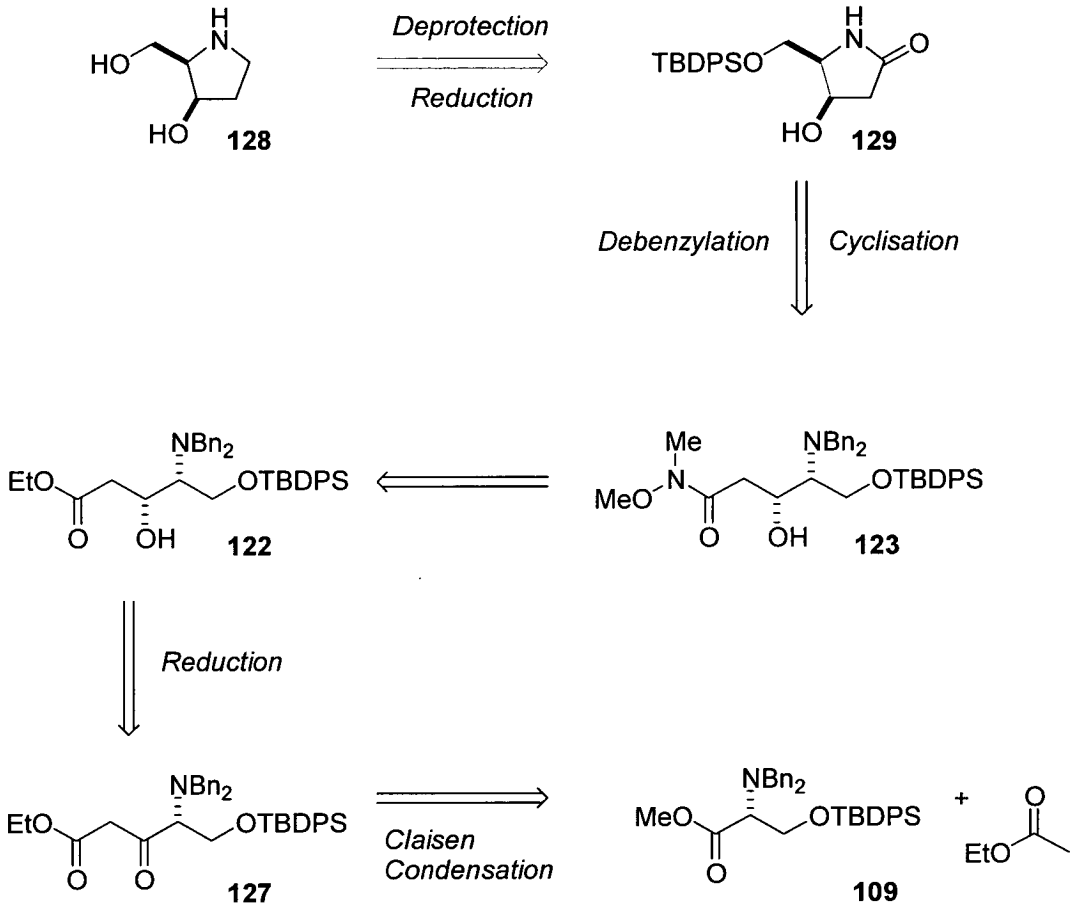
2.2.1 Retrosynthesis of CYB-3 and C(3) epimer

In view of the moderate enantiomeric purity of the aldol adduct **121** (90% ee) and the reduced diastereoselectivity (6:1) an alternative strategy for the synthesis of CYB-3 was considered. The literature is replete with examples of the synthesis of β-hydroxy-γ-amino acids *via* the stereoselective reduction of the corresponding β-keto ester. We envisaged that a Claisen condensation between the serine derived ester **109** and lithio ethyl acetate to give β-keto ester **127** followed by a stereoselective reduction would yield **121**. By judicious choice of the reducing agent it would be possible to synthesise CYB-3 **71**, **scheme 41** and it's C(3) epimer **128**, **scheme 42**.

Scheme 41


HO
HO
71
Deprotection
Reduction
TBDPSO
HO
90
Debenzylation
Cyclisation
NBn2
EtO
OTBDPS
O
OH
121
Me
MeO
N
NBn2
OTBDPS
O
OH
91
Reduction
NBn2
EtO
OTBDPS
O
O
127
Claisen
Condensation
NBn2
MeO
OTBDPS
O
109
+
O
EtO

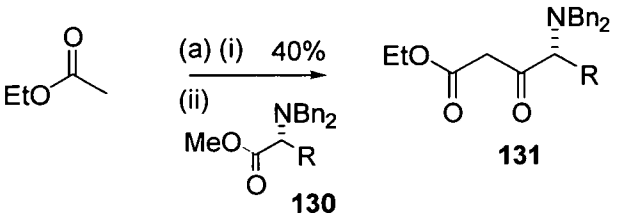
Scheme 42


HO
H
N
HO
128
Deprotection
Reduction
TBDPSO
H
N
O
HO
129
Debenzylation
Cyclisation
EtO
NBn2
OTBDPS
O
OH
122
Me
N
MeO
NBn2
OTBDPS
O
OH
123
Reduction
EtO
NBn2
OTBDPS
O
O
127
Claisen
Condensation
MeO
NBn2
OTBDPS
O
109
+
O
EtO

2.2.2 Formation of β-hydroxy esters 119 and 122

Reetz[28] has previously reported that β-keto esters **131** were accessible *via* the reaction of *N*-benzyl esters **130** with lithio ethyl acetate albeit in low yields (40 %), **scheme 43**.

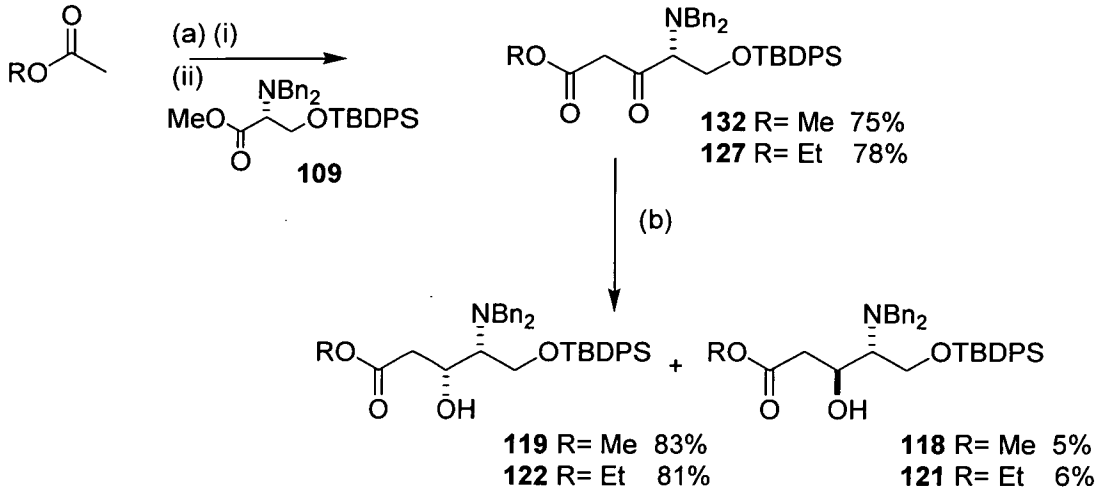
Scheme 43



(a) (i) LiHMDS, THF –78 °C; (ii) THF, **130**, -78 °C; R=^{i}PrCH$_2$, cyclohexyl-CH$_2$, PhCH$_2$.

We carried out the Claisen reaction of ester **109** using both lithio methyl acetate and lithio ethyl acetate with both routes yielding comparable amounts of product **132** (75%) and **127** (78%) respectively. However, concerns were raised with regards to the enantiomeric purity of the β-keto esters. In order to confirm this by chiral HPLC, the β-keto esters were selectively reduced to give the *syn* **119**, **122** and *anti* **118**, **121** β-hydroxy ester, **scheme 44**.

Scheme 44



(a) (i) LiHMDS, -78 °C; (ii) THF, **109**, -78 °C→0 °C; (c) $NaBH_4$, $LiBH_4$ or $NaCNBH_3$.

Reetz reported excellent diastereoselectivities (>90% de) for the reduction of β-keto esters **131** using $NaBH_4$/MeOH at –20 °C to give the non-chelation controlled product selectively, **table 3**.

Table 3

R	Diastereoselectivity %
$^{i}PrCH_2$	90
Cyclohexyl-CH_2	93
$PhCH_2$	94

Reduction of β-keto esters **132** and **127** using this methodology did not produce the yields or diastereoselectivities which we expected in favour of the *anti*-Felkin product **119** and **122**. The results for the reduction of the methyl keto ester **132** and the ethyl keto ester **127** are summarised in **tables 4** and **5** respectively.

Due to the hindered nature of β-keto esters **132** and **127** the reaction was found to be extremely sluggish at low temperatures (0 °C) and heating at higher temperatures (r.t.) was required to drive the reaction to go to completion. When using $NaBH_4$ and $LiBH_4$ as the reducing agents, reduction of the ester moiety occurred concurrently with reduction of the carbonyl group resulting in very low yields of the desired β-hydroxy ester. The reduction with $NaCNBH_3$ required longer reaction times and a greater excess of the borohydride to be used, however the problem of ester reduction was eliminated, with yields of >80% β-hydroxy ester generated. The diastereoselectivities were also consistently much higher with de's of >90% being produced. Separation of the diastereomeric β-hydroxy esters was attainable by flash chromatography.

The diastereoselectivity for the ethyl hydroxy ester **122** was calculated from the crude ^1H NMR by comparison of the C(2) protons for both the major and minor adducts. The diastereoselectivity for the methyl hydroxy ester **119** was also calculated by measurement of the integrals from the crude ^1H NMR corresponding to the protons at C(2). In the major β-hydroxy ester **122** these were apparent as two sets of doublet of doublets at 2.31 and 2.47 ppm. In the minor β-hydroxy ester **119** the peaks appeared at 2.13 and 2.85 ppm.

Table 4

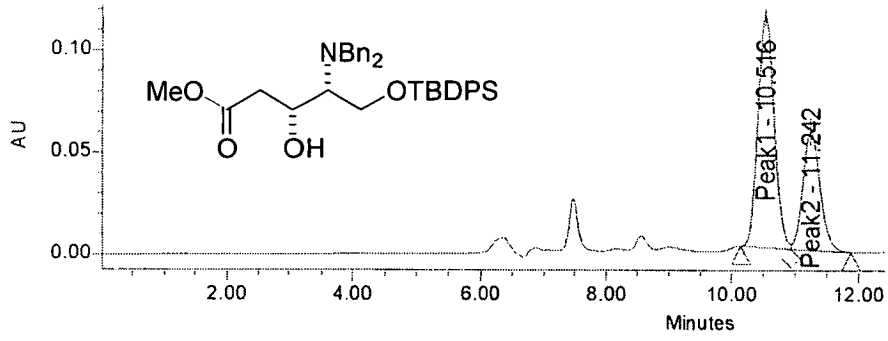
Conditions	% Yield	Diastereomeric ratio 119:118	Ester reduction
1.0 eq $NaBH_4$, 2 h, R.T.	32	89:11	Yes
2.5 eq $NaBH_4$, 1 h, R.T.	53	88:12	Yes
5.0 eq $NaBH_4$, 1 h, R.T.	52	87:13	Yes
2.0 eq $LiBH_4$, 0.5 h, R.T.	40	83:17	Yes
3.0 eq $LiBH_4$, 0.5 h, R.T.	20	83:17	Yes
8.0 eq $NaCNBH_3$, 7 h, R.T.	83	>90:10	No

Table 5

Conditions	% Yield	Diastereomeric ratio 122:121	Ester reduction
2.5 eq $NaBH_4$, 1 h, R.T.	50	88:12	Yes
8.0 eq $NaCNBH_3$, 7 h, R.T.	81	>90:10	No

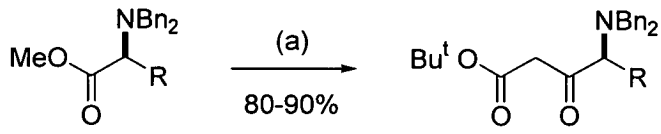
The enantiomeric purity of the *β*-hydroxy esters **119**, **121** were determined by chiral HPLC (5% IPA in Hexane) with a sample of the racemate prepared *via* the same route. The results showed that extensive racemisation had occurred with ee's of 43 and 50% for the methyl and ethyl *β*-keto esters respectively, **figure 11**.

Figure 11



These findings were consistent with those reported by Hoffman[29] who observed ee's of between 78 and 90% for the *β*-keto esters **134** formed *via* the reaction of *α*-amino esters **133** with lithio *tert*-butyl acetate, **scheme 45**. To circumvent these problems a more reactive acylating agent was required.

Scheme 45



133 **134**

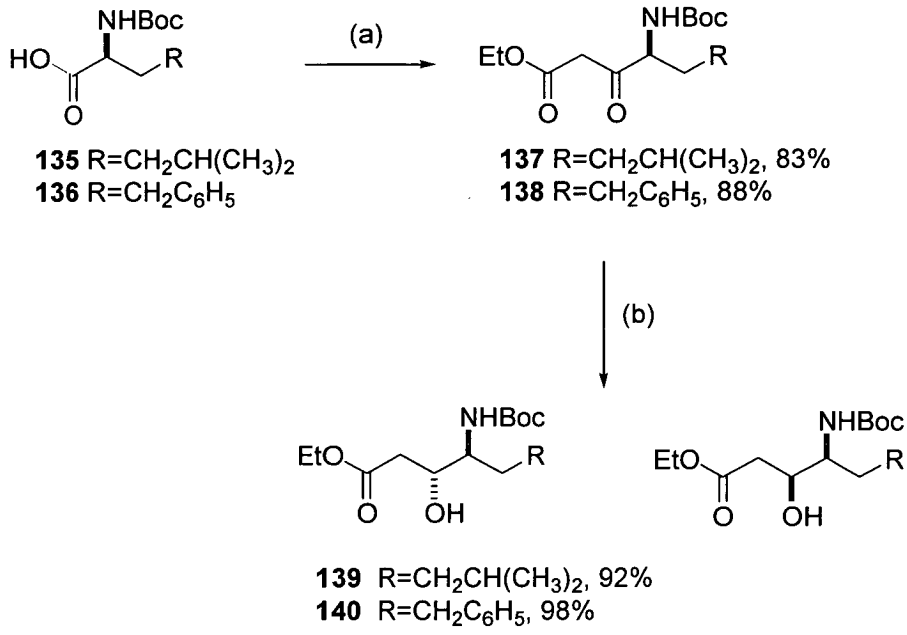
(a) $LiCH_2(CH_2)O^tBu$, THF.

2.2.3 *N,N*-Carbonyldiimidazole Coupling

By converting the ester functionality to the acylimidazole the reactivity of the moiety is substantially increased, since the reactivity of the acylimidazoles is similar to that of acid chlorides. The imidazolides are generally crystalline and easy to handle, isolation is simple but not necessary. The imidazolides are formed by reacting the carboxylic acid with *N,N*-carbonyldiimidazole (CDI) at room temperature resulting in the formation of the imidazolide and the evolution of carbon dioxide.[68] A consideration of the pK_a values also explains why it is harder to remove the proton and cause racemisation. The pK_a value of an ester is 25 whereas that of an amide is 17, the difference largely being attributed to the extent of *N*-lone pair delocalisation into the amide carbonyl. In the imidazolide this will obviously be somewhat reduced due to the lone pair involvement in the imidazolide aromaticity.

In Richs' synthesis of statine[32] from *N*-Boc-protected *L*-amino acids **135** and **136** by *N,N*-carbonyldiimidazole activation and subsequent treatment with the magnesium enolate of hydrogen ethyl malonate, **scheme 46**, he noted that considerable racemisation had occurred, 92% ee for **139** and 58% ee for **140** formed *via* the $NaBH_4$ reduction of **137** and **138**, respectively.

Scheme 46



135 R=$CH_2CH(CH_3)_2$
136 R=$CH_2C_6H_5$

137 R=$CH_2CH(CH_3)_2$, 83%
138 R=$CH_2C_6H_5$, 88%

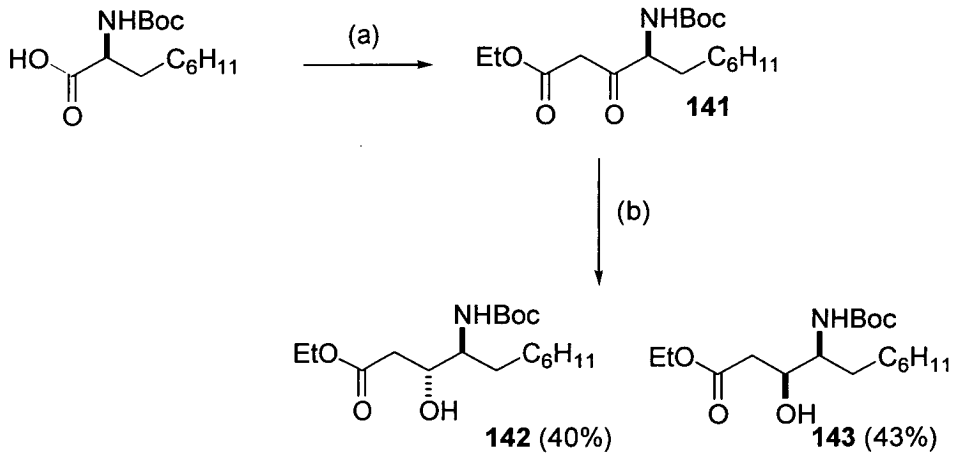
139 R=$CH_2CH(CH_3)_2$, 92%
140 R=$CH_2C_6H_5$, 98%

(a) (i) CDI, THF; (ii) NEt_3, $MgCl_2$, $EtOOCCH_2COOH$; (b) $NaBH_4$, THF, -78 °C.

It had previously been reported in the 1960's[69] that CDI caused as much as 5% racemisation of protected amino acids under certain conditions during peptide synthesis. By decreasing the reaction time and the temperature for formation of the imidazolide from 12 hours at r.t. to 1 hour at 0 °C followed by 3 hours at r.t. gave ee's of 97% and 98% for **139** and **140**.

Schudas'[70] preparation of the cyclohexylmethyl derived β-hydroxy esters **142** and **143** led to 15% racemisation when Raney nickel was used as the reducing agent but ee's were improved to 92.4% when sodium cyanoborohydride was employed in the reduction of **141**, **scheme 47**.

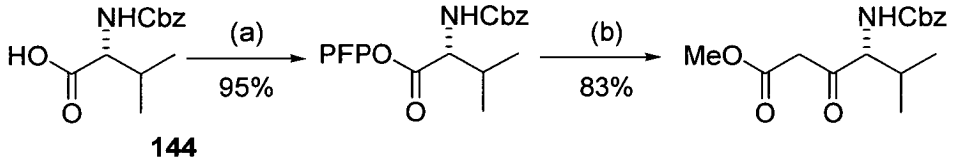
Scheme 47



(a) (i) CDI, THF; (ii) NEt_3, $MgCl_2$, $EtOOCCH_2COOH$; (b) $NaCNBH_3$, THF, AcOH.

Joullié [71] recently reported a synthesis of tamandarin B where activation of the carboxylic functionality in **144** was achieved using pentafluorophenol, **scheme 48**.

Scheme 48



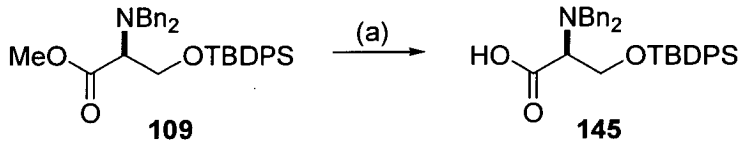
(a) C_6F_5OH, EDCI•HCl, DMAP, DCM; (b) $LiCH_2CO_2Me$, THF.

Other routes to the *β*-keto esters *via* acylation of Meldrum's acid[72] and acylation of (TMS) ethyl malonate with acyl imidazoles[73] have been reported.
At present, little research has been conducted into the coupling reactions of *N,N*-dibenzylamino acids with CDI.

2.2.4 Acid hydrolysis of 109

In order to proceed *via* this route, saponification of the *N,N*-dibenzylamino ester **109** was required, **scheme 49**.

Scheme 49

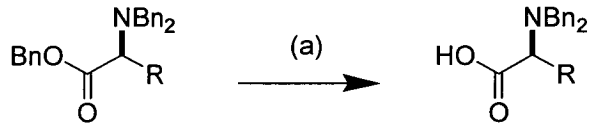


109 **145**

(a) See table 6.

Reetz reported the saponification of benzyl esters **130** to occur with KOH in aqueous dioxane thus yielding the corresponding acids **146** for a range of substrates, **scheme 50**. However no experimental details were reported.[28]

Scheme 50

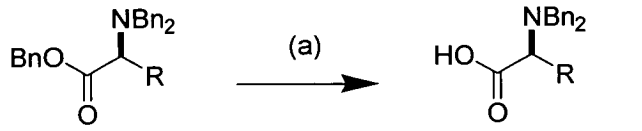


130 **146**

(a) KOH, H_2O, Dioxane, R= R=^{i}PrCH_2, cyclohexyl-CH_2, PhCH_2.

We found that hydrolysis of the *N,N*-dibenzylamino ester **109** using these reagents did not produce any of the desired acid **145** under a range of conditions. This was consistent with that reported by Hoffman who found that refluxing benzyl ester **147** with KOH in aqueous dioxane for 6 days produced less than 10% of the corresponding acid **149**, (90% ee). The *β*-branched compound **148** showed no detectable hydrolysis after 7 days under the same conditions.

Scheme 51



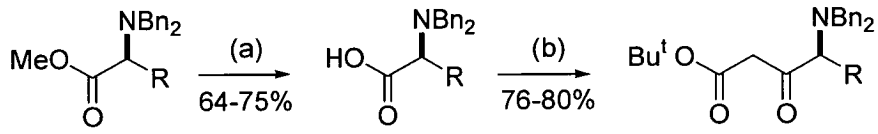
147 R= ^{i}Bu
148 R= ^{sec}Bu

149 R= ^{i}Bu
150 R= ^{sec}Bu

(a) KOH, H_2O, Dioxane, 100 °C.

Hoffman reported an iodide-based hydrolysis as an alternative to standard methods with yields of between 64 and 75% being reported by refluxing the methyl esters **151-153** with a mixture of lithium iodide and sodium cyanide. The amino acids were converted to the *β*-keto esters **154-155** *via* the CDI coupling with lithio *tert* butyl acetate. Their optical purity was determined by a chiral lanthanide induced shift study using a Europium shift reagent which showed compounds **154** and **155** to have ≥97% ee, however compound **156** was observed to have an ee of 70%, **scheme 52**.

Scheme 52



151 R= ^{i}Bu
152 R= $PhCH_2$
153 R= Me

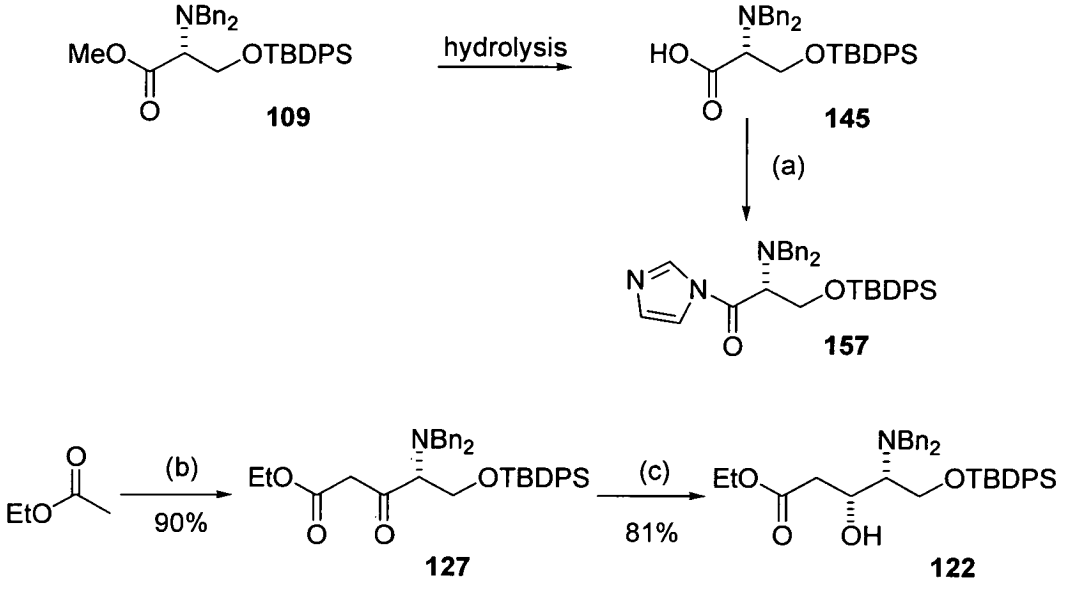
154 R= ^{i}Bu
155 R= $PhCH_2$
156 R= Me

(a) LiI, NaCN, Pyridine; (b) CDI, $LiCH_2CO_2{}^{t}Bu$, THF.

2.2.5 Analysis of hydrolysis routes

The methyl ester **109** was hydrolysed under a range of conditions. The acid **145** was converted to the imidazolide **157** which without isolation was coupled with lithioethyl acetate. The *β*-keto ester **127** was selectively reduced to give the *β*-hydroxy alcohol **122**, **scheme 53**. Chiral HPLC analysis was carried out on the *β*-hydroxy alcohol **122** and the results are summarised in **table 6**.

Scheme 53



(a) CDI, THF, R. T.; (b) (i) LiHMDS, -78 °C; (ii) **157**, -78 °C 1.5 h then 0 °C; (c) $NaCNBH_3$, Et_2O, MeOH, AcOH.

Table 6

Conditions	Yield %	ee %
LiOH, THF/H_2O, R.T., 72 hours	0	nd$^{\phi}$
LiOH, THF/H_2O, reflux 6 hours	60	70
LiOH, THF/H_2O, reflux 24 hours	90$^{\varphi}$	nd
LiI, Pyridine, reflux 24 hours	72	60
LiI/NaCN, Pyridine, reflux 24 hours	78	66
$Ba(OH)_2$, MeOH, R.T., 48 hours	32	70
NaOH, 1,4-Dioxane, R.T., 72 hours	0	nd
KOH, MeOH, R.T., 72 hours	0	nd
2M HCl, R.T., 72 hours	0	nd

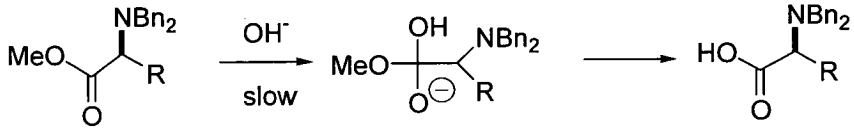
$^{\varphi}$ Yield refers to TBDPS deprotected acid
$^{\phi}$ not determined

2.2.6 Mechanism of acid and base hydrolysis

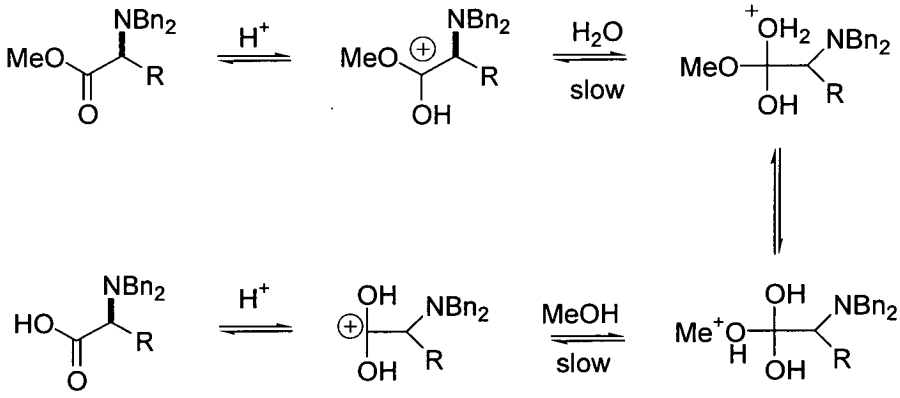
In general hydrolysis of the ester functionality in compound **109** with a variety of reagents showed the extraordinary inertness of the ester group towards nucleophilic addition resulting in longer reaction times and higher temperatures being required. There are eight possible mechanisms for the acid and base hydrolysis of esters with the most common routes being the $A_{AC}2$ and $B_{AC}2$ respectively, **scheme 54**. Both of these go *via* a tetrahedral transition state. The tetrahedral mechanism for substitution at the carbonyl carbon is slowed or blocked completely by α or β branching.[74] The combination of the bulky *N*,*N*-dibenzylamino and the TBDPS groups appear to have a deleterious effect on the hydrolysis of **109**.

Scheme 54

$B_{AC}2$ Mechanism



$A_{AC}2$ Mechanism



Hoffman reported that upon increasing the steric bulk of the R group the reaction time increases and the yield decreases. He also noted that where β-branching exists no hydrolysis occurs under base catalysis.

The best results we obtained were refluxing **109** with lithium hydroxide for 6 hours, upon increasing the reaction time the TBDPS group was cleaved. Sodium and potassium hydroxide led to the recovery of starting material as did acid hydrolysis. The iodide-based hydrolysis which proceeds *via* a different mechanism gave disappointedly low ee's. The reaction occurs with displacement of the carboxylate by S_N2 dealkylation but again the reaction appears to be sterically hindered as would be expected for a S_N2 reaction.[75] Upon scaling the lithium hydroxide saponification of **109** to >500 mg, the reaction was observed to proceed sluggishly with very little

product recovered, hence several small 500 mg reactions were carried out in order to continue with the synthesis.

2.2.7 Consideration of other factors leading to racemisation

We considered that the extensive racemisation in compound **122** was due to the CDI coupling reaction of the *N,N*-dibenzylamino acid **145**. However with the high ee's (>92%) obtained for the synthesis of the phenylalanine derived *β*-hydroxy ester *via* the same route (chapter 3), it was evidently the hydrolysis step that was resulting in the racemisation and not the proceeding steps in the synthesis.

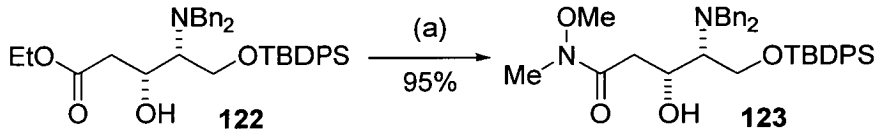
The quality of the LiHMDS used to generate the enolate in the Claisen condensation was considered as another factor and this was either freshly prepared[76] or fresh supplies from Lancaster were used. Long storage of the base led to the formation of lithium hydroxide which would be detrimental to the reaction. The advantage of preparing the base from hexamethyldisilazane and butyl lithium was that the concentration of the butyllithium could be determined by simple titration[φ] and hence the concentration of LiHMDS known exactly.

[φ] LiHMDS (1.0 *M* in THF) was prepared as follows: To a stirred solution of hexamethyldisilazane (10.55 cm^3) at -23 °C was added dropwise ^{n}BuLi (20.0 cm^3, 2.5 *M*) and the resultant solution allowed to warm to R.T. and diluted to 50 cm^3 with THF.

2.2.8 Formation of silyl protected pyrrolidine 159

The Weinreb amide **123** was synthesised by treating ethyl ester **122** with *N,O*-dimethylhydroxylamine•HCl and trimethylaluminium in excellent yield.

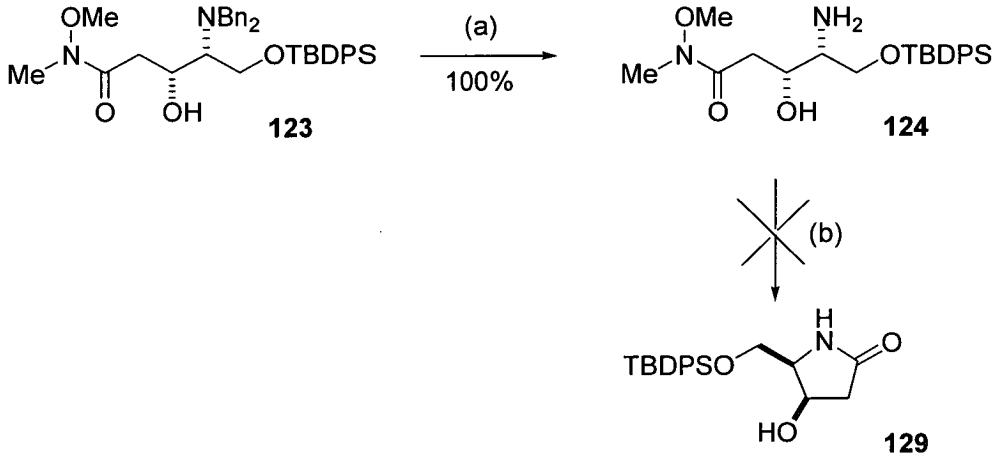
Scheme 55



(a) (MeO)NMe•HCl, Me_3Al, THF, 0 °C- 35 °C.

Treating the amide **123** with Pearlman's catalyst under an atmosphere of hydrogen removed the dibenzyl protecting groups but did not yield the lactam **129** as expected rather the acyclic amino amide **124** was isolated in quantitative yield.

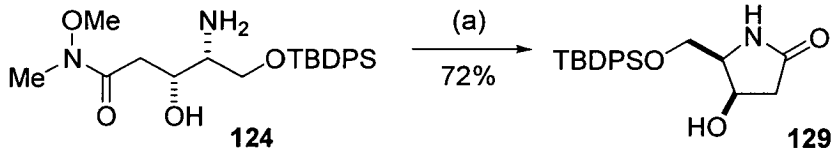
Scheme 56



(a) $Pd(OH)_2/C$, H_2, MeOH; (b) $Pd(OH)_2/C$, H_2, MeOH.

The lactam **129** could however be prepared from the amino amide **124** by filtering **124** through a small column of silica and the residue refluxed in methanol for 24 hours to give lactam **129** in 72% yield.

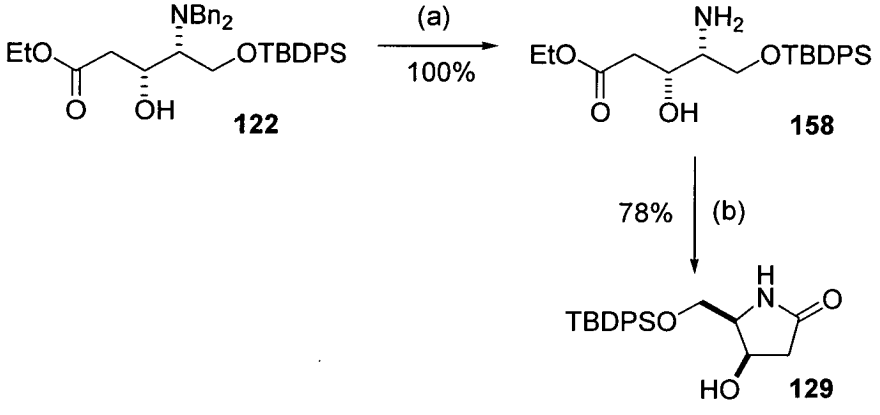
Scheme 57



(a) MeOH, 80 °C.

Debenzylation of ester **122** with Pearlmans' catalyst occurred in quantitative yield to give the amino ester **158** which was subsequently filtered through a short path of silica and refluxed in methanol for 24 hours to give the lactam **129**, **scheme 58**. Hence we therefore no longer needed to convert the *β*-hydroxy ester **122** to the Weinreb amide **123**.

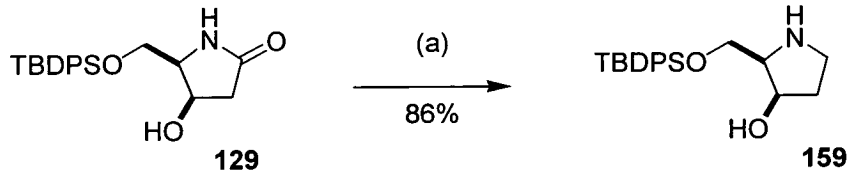
Scheme 58



(a) $Pd(OH)_2/C$, H_2, MeOH; (b) MeOH, 80 °C.

The lactam **129** was successfully reduced with BH_3•THF complex to give the protected pyrrolidine **159** in 4 steps and 29% overall yield from the serine derived methyl ester **109**.

Scheme 59



129 **159**

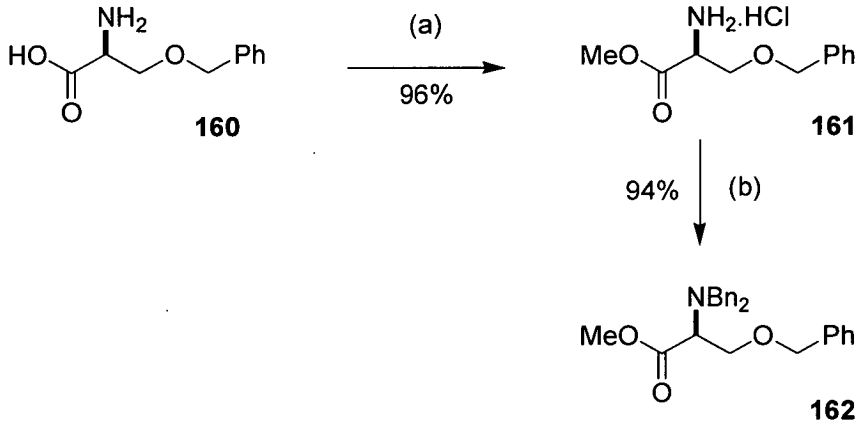
(a) BH_3•THF, THF, 0 °C- 80 °C.

2.3 Alternative to silyl protecting group

2.3.1 Formation of β-hydroxy ester 166

A potential solution to the problems associated with *N,N*-dibenzyl-*O*-TBDPS protected serine methyl ester **109** was to select an alternative protecting group for the hydroxyl group. In view of the high ee's obtained with the phenylalanine derived *β*-hydroxy ester (chapter 3) we felt that an *O*-benzyl protecting group might offer comparable results. The *N,N*-dibenzylated methyl ester **162** was prepared using the conditions optimised for the serine derived methyl ester **109**, from the commercially available *O*-Benzylserine **160** in 90% overall yield, **scheme 60**.

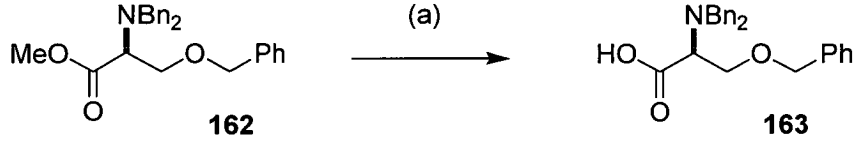
Scheme 60



(a) CH_3COCl, MeOH, 80 °C; (b) BnBr, K_2CO_3, MeCN.

Saponification of the methyl ester **162** to the acid **163** was carried out under a range of conditions, **scheme 61**. In most cases the reaction times were shorter and the yields almost quantitative in comparison with the saponification of the TBDPS protected serine, **table 7**.

Scheme 61



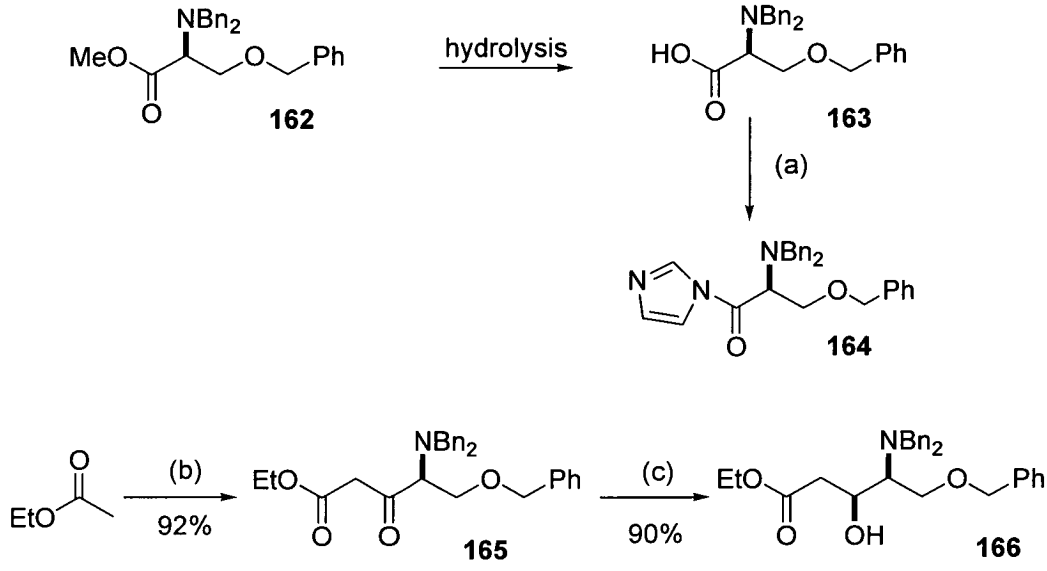
(a) See table 7.

Table 7

	OBn serine		**OTBDPS serine**	
Conditions	**Reaction time h**	**Yield %**	**Reaction time h**	**Yield %**
$LiOH•H_2O$,THF/H_2O, R.T.	24	0	72	0
$LiOH•H_2O$,THF/H_2O, Reflux	4	100	6	60
LiI/NaCN, Pyridine, Reflux	20	89	24	78
$Ba(OH)_2$, MeOH, R.T.	24	17	48	32
$Ba(OH)_2$, MeOH, Reflux	3	97	-	-
KOH THF/H_2O, R.T.	24	10	0	0
NaOH, 1,4-dioxane, R.T.	24	5	0	0

The acid **163** was converted to the corresponding *β*-keto ester **165** *via* the CDI mediated coupling with lithio ethyl acetate in excellent yield. Conversion to the *β*-hydroxy ester **166** was achieved with $NaCNBH_3$ in excellent diastereoselectivity, **scheme 62**.

Scheme 62



(a) CDI, THF, R. T.; (b) (i) LiHMDS, -78 °C; (ii) **164**, -78 °C 1.5 h then 0 °C; (c) $NaCNBH_3$, Et_2O, MeOH, AcOH.

2.3.2 Determination of diastereoselectivity and enantioselectivity of 166

The diastereoselectivity was calculated from the crude ^1H NMR of **166**. The integrals for the protons at C(2) were compared for the minor and major diastereomers. The major peaks were at peaks are at 2.50 and 2.34 ppm and the minor peaks at 2.81 and 2.90 ppm. A ratio of >10:1 was determined. The enantiomeric purity of the *β*-hydroxy ester **166** was determined by chiral HPLC (5% IPA in Hexane) by a direct comparison with the racemic *β*-hydroxy ester, **figure 12**. The results are summarised in **table 8**.

Figure 12

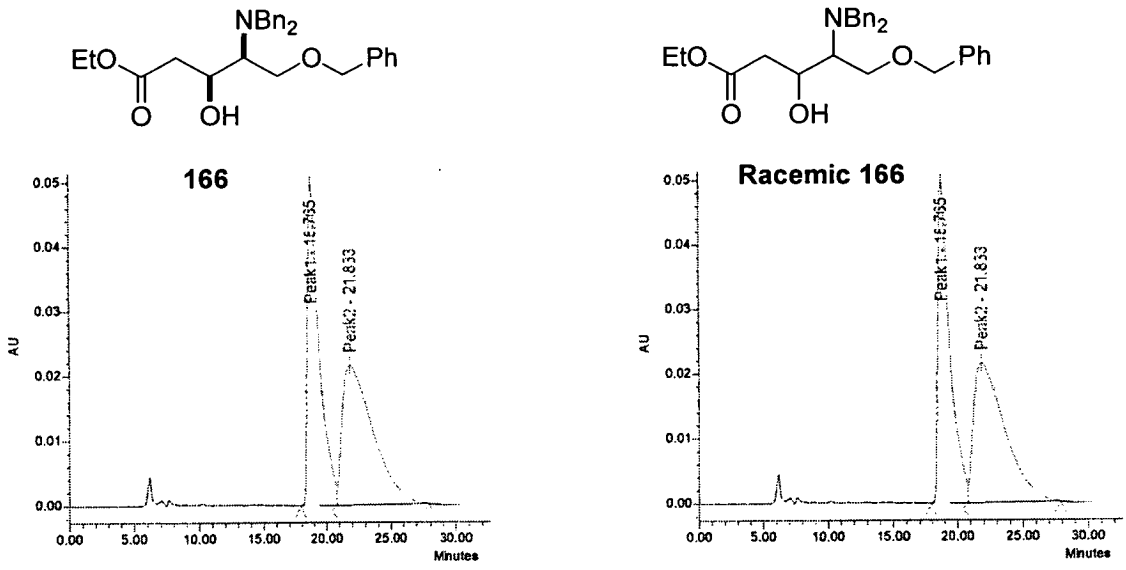


Table 8

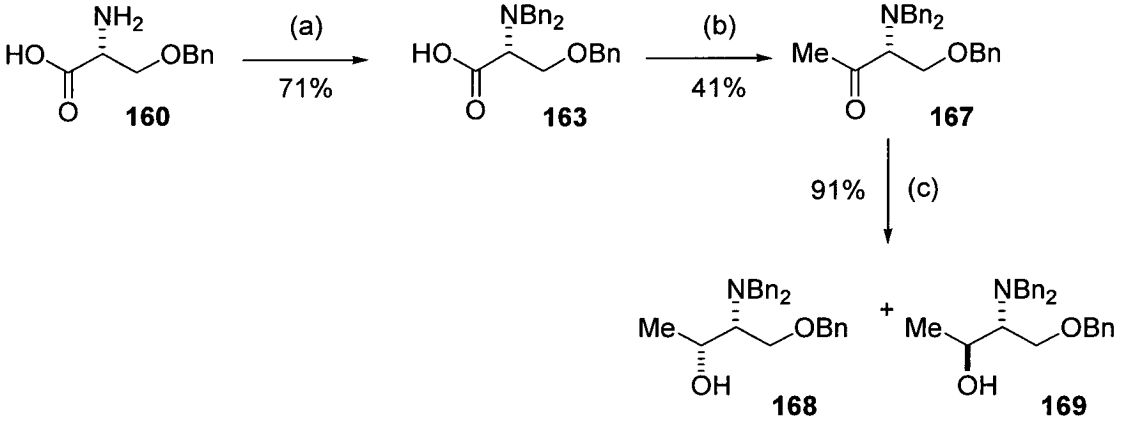
Conditions	%ee
6eq $LiOH•H_2O$, THF/H_2O, Reflux	0
LiI/NaCN, Pyridine, Reflux	0
5eq $Ba(OH)_2$, MeOH, R.T.	0

These results were contrary to what we had expected with all cases resulting in complete racemisation. One possible reason for this observation is due to the presence of the *O*-methylene moiety which is aiding in the removal of steric congestion (i.e. the phenyl ring) from the ester site and the chiral centre. Consequently the decrease of the steric bulk at the chiral centre substantially increased racemisation.

2.4 Alternative to methyl ester

Reetz[77] has shown that the serine derived *N,N*-dibenzylated alcohol **168** can be prepared in >99% ee. Treating *O*-Benzylserine **160** with benzyl bromide furnished the benzyl ester which was subsequently hydrolysed with KOH to give **163** in 71% over the two steps (detailed experimental conditions were not reported), **scheme 63**. Conversion to the Weinreb amide, Grignard addition and reduction with $NaBH_4$ furnished **168** in 94% de.

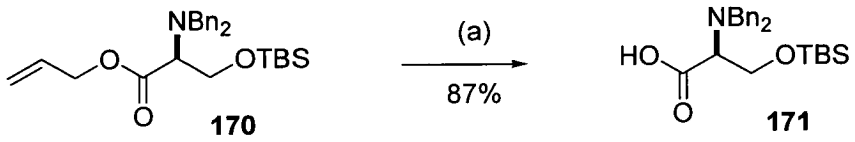
Scheme 63



(a) (i) BnBr, K_2CO_3, MeCN; (ii) KOH, MeOH, Dioxane; (b) (i) (MeO)NMe•HCl, Me_3Al, PhMe; (ii) MeLi, THF, -40 °C; (c) $NaBH_4$, MeOH, -20 °C.

Chandrasekhar[78] has reported cleavage of the allyl group from allyl ester **170** using polymethylhydrosiloxane (PMHS), $ZnCl_2$ and $Pd(PPh_3)_4$ to occur in high yield providing the corresponding acid **171** in 87% yield, **scheme 64**.

Scheme 64



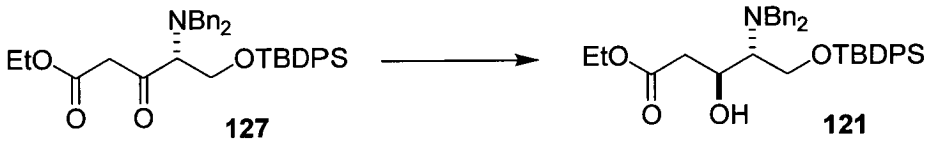
(a) PMHS, $ZnCl_2$, $Pd(PPh_3)_4$, THF.

Although no ee was reported, an $[\alpha]_D$ of –50.85° (*c* 0.35, $CHCl_3$) was determined for **171**. As this is the first example of this serine-derived acid, the determination of the optical rotation is not conclusive proof for the optical purity of this compound, chiral analysis would be required to confirm this.

2.5 Introduction to CBS reagent

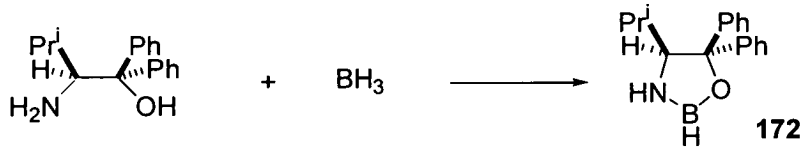
One of the main objectives was to synthesise *β*-hydroxy ester **121** *via* a chiral reduction of the *β*-keto ester **127** with higher diastereoselectivity than that obtained for the aldol reaction discussed in section 2.1.7.

Scheme 65



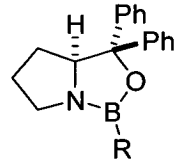
The combination of chiral oxazaborolidines and borane to mediate the asymmetric reduction of prochiral ketones has received considerable attention since its discovery by Itsuno.[79] He reported an enantioselective ketone reduction using an aminoalcohol-borane complex **172** as a catalyst, which forms a five membered ring which reduces ketones in high enantiomeric excess, **scheme 66**. The catalyst was noted to be more efficient when used in combination with a borane e.g. borane-methyl suphide complex.

Scheme 66



Corey, Bakshi and Shibata subsequently developed the CBS oxazaborolidines **173** and **174**, **figure 12**.[80] The enantioselective reduction occurs with borane or catecholborane as a stoichiometric reductant. The B-Me complex **174** is a stable and storable white crystalline solid whereas the B-H complex **173** is both air and moisture sensitive. Slightly higher ee's are also obtained with the B-Me complex making it a superior complex.

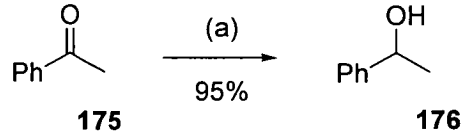
Figure 13



173 R= H
174 R= Me

For example the reduction of acetophenone **175** to give *R*-phenylethanol **176** occurred in 97% ee with the B-Me complex compared with 94.7% ee for the B-H complex, **scheme 67**.[81]

Scheme 67

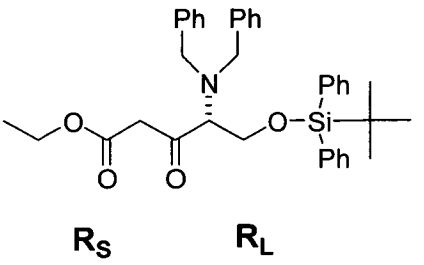


175 **176**

(a) **174**, BH_3•THF, THF.

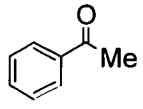
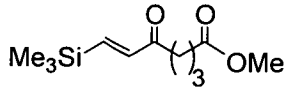
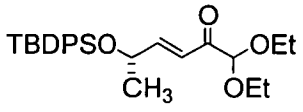
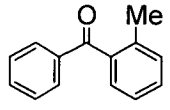
A variety of modified analogues of the CBS oxazaborolidine have been developed in an attempt to overcome the main limitation associated with the catalyst which is the requirement that the appendages R_S and R_L must differ appreciably in the ketone. Enantioselectivity should occur when there is a preference for the larger of the two ketone appendages to adopt an orientation *anti* to the bulky area of the catalyst thus inducing intramolecular delivery of a hydride to one enantiotopic face of the ketone. In our substrate **127**, R_S and R_L, **figure 14**, appeared sufficiently different to allow the formation of one diastereomer preferentially.

Figure 14



Examples of compounds enantioselectively reduced by the CBS oxazolidinone are shown in **table 9**.[81]

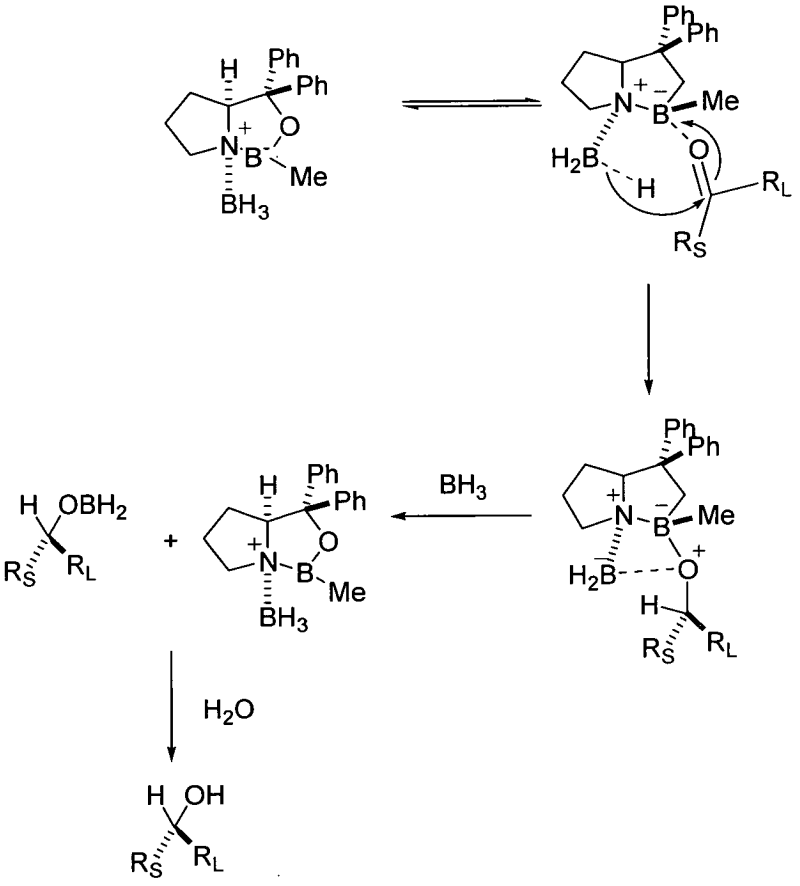
Table 9

Ketone	%ee
	99
	94
	95
	93

2.5.1 Mechanism of reduction by CBS reagent

The complex binds the substrate by coordination of the electrophilic boron and the carbonyl oxygen. The binding minimises any unfavourable steric interactions between the oxazaborolidine and the ketone. Hydride transfer occurs from the NBH_3^- unit to the activated carbonyl *via* a six membered ring transition state. Ligand exchange occurs to form the alkoxyborane followed by displacement to regenerate the catalyst and give the desired product, **scheme 68**.[82]

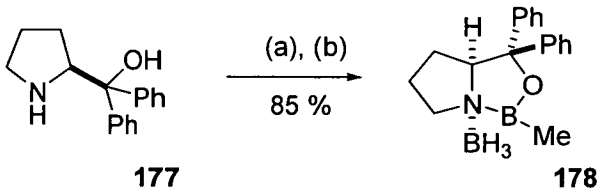
Scheme 68



2.5.2 Formation of CBS reagent 178

The oxazaborolidine **178** was prepared from (*s*)-(+)-α,α-diphenyl-2-pyrrolidinemethanol **177**, **scheme 69**. Azeotroping with toluene enabled the removal of any unreacted amino alcohol, trimethylboroxine and water which could decrease enantioselection. [83] Addition of dimethylsulfide-borane complex generated a white crystalline solid after 12 hours which was subsequently dried under vacuum to remove excess dimethylsulfide and give **178** in 85% yield.

Scheme 69



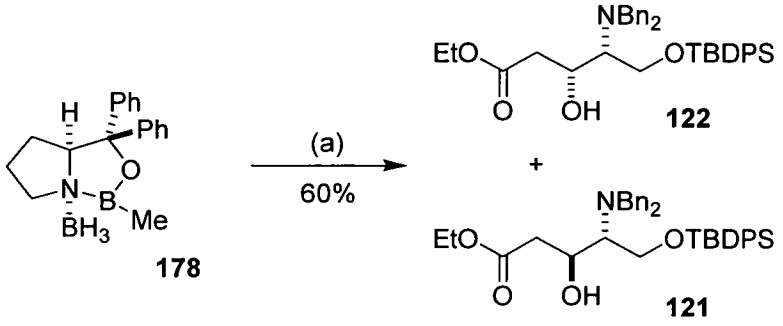
177 **178**

(a) $CH_3B(OH)_2$, Toluene; (b) $BH_3 \bullet SMe_2$.

2.5.3 Chiral reduction of β-keto ester 125

A variety of reaction conditions were employed for the chiral reduction of β-keto ester **127**, it was found that heating the mixture at 40 °C for 24 hours gave the maximum yield of products. However the reaction was never observed to go to completion with a maximum yield of 60% being obtained. From analysis of NMR and t.l.c. it was apparent that no selectivity had occurred for the Felkin-Anh adduct **121**. This result was unexpected considering the differences in the small and large appendages. To ensure that the lack of enantioselection was not due to the catalyst, acetophenone was reduced and it was found to be optically pure by a comparison of the optical rotation with an authentic sample, (found $[\alpha]_D - 40.2°$ (neat), lit (Aldrich) $[\alpha]_D -41.3°$ (neat)).

Scheme 70



178 **122** **121**

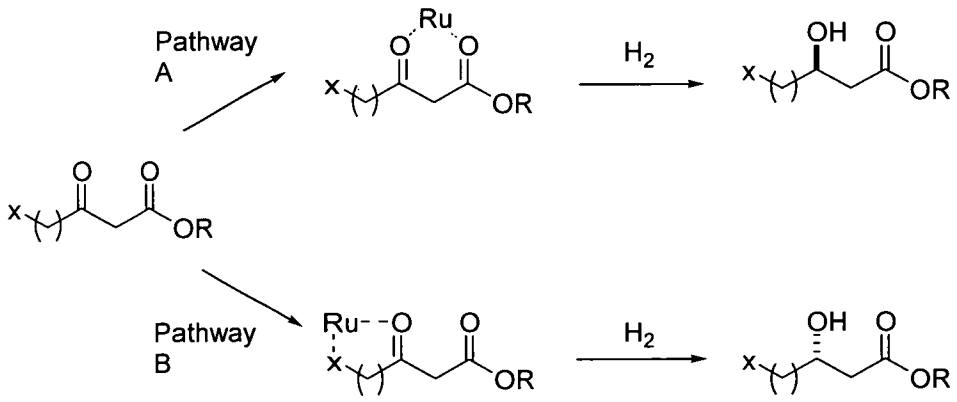
(a) (i) BMS, DCM, 0 °C; (ii) **127**, 40 °C.

The reasons for the lack of enantioselection remain unclear for the more complex β-keto ester **127**, unfavourable steric interactions between the *N,N*-dibenzyl and the phenyl groups may be one cause of this. Coordination of the nitrogen to the oxazaborolidine catalyst may also occur which could account for the low yield of the β-hydroxy esters obtained. Research in this area has generally focussed on the oxazaborolidine rather than the substrate. Based on our research on the *N,N*-dibenzylated compounds discussed in this section and chapter 3 it is possible that these compounds are not viable substrates for this chiral reduction.

2.6 Introduction to Ru[BINAP] catalyst

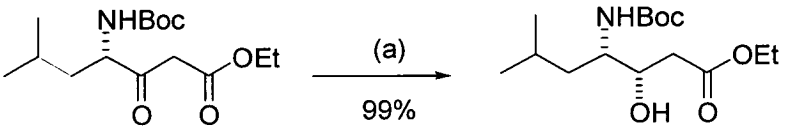
Ru[BINAP] catalysts can hydrogenate β-keto esters that contain a wide variety of functionality including amides and esters with high stereoselectivities.[84] Esters whose functionality is at the γ-position are capable of affecting the stereocontrol due to competing pathways.[85] Instead of the hydrogenation proceeding *via* pathway A, chelation of the ruthenium between the carbonyl group and group x is now possible yielding the enantiomeric product, **scheme 71**.

Scheme 71



In our case the presence of the *N,N* dibenzylamino group should show the effects of double asymmetric induction and hence generate the diastereomer with high selectivity as observed in Noyori's synthesis of statine.[33] Noyori reported a facile and highly diastereoselective route (>99% de) to **19** *via* the hydrogenation of **32, scheme 72**.

Scheme 72



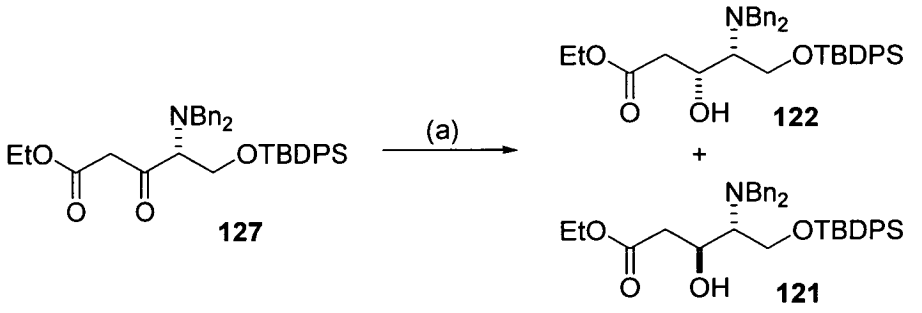
32 **19**

(a) $RuBr_2$[(*R*)]-binap], EtOH, H_2.

2.6.1 Ru[BINAP] reduction of *β*-keto ester 127

Catalytic hydrogenation was carried out on *β*-keto ester **127** under 1 atm of hydrogen at 40 °C for 5 days. All solvents were degassed by three freeze-thaw cycles. The initial results were encouraging at such a low pressure, by t.l.c. and NMR it appeared that there was diastereoselectivity for the Felkin-Anh adduct **121** was ca. 80%. Based on recovered starting material the yield of products was 60%, **scheme 73**.

Scheme 73



127

(a) H_2, $RuCl_2$[(*S*)-BINAP], MeOH, DCM, 40 °C.

A Parr hydrogenator provided us with pressures of 50 psi and temperatures of 50 °C. The limitation of this apparatus was the size of the reaction vessel which resulted in large volumes of solvent being required.[ϕ] Schmidt[86] reported in the synthesis of biphenomycin A that high diastereoselectivities are only achieved when the solutions of the catalyst and the substrate contain very little methanol. By t.l.c. and NMR large quantities of starting material were apparent, undoubtedly due to the increased volume of solvent. No product was isolated from this reaction.

Finally hydrogenations were carried out using an autoclave which eliminated the requirement of large volumes of solvent. A pressure of 120 psi and a temperature of 18 °C was employed. King[87] has observed that the addition of trace amounts of strong acid can reduce the reaction time from days to hours.

Hence, hydrogenations were carried out on our substrate **125** with and without acid for 72 hours. T.l.c. showed that no product had formed for either case. Consequently, it would appear that for successful reduction of this substrate in quantitative yield and with high diastereoselectivities to occur both high temperatures and high pressures are required in low concentrations of solvent.

2.7 Summary of chapter 2

We have further explored the chemistry of the *N,N*-dibenzylated serine aldehyde **93** and ester **106** and have shown the limitations associated with these substrates. The optimisation of the Claisen chemistry has enabled studies in the synthesis of hapalosin (chapter 3) and the synthesis of anisomycin analogues to be investigated (Hulme group). Initial work in catalytic hydrogenations of the *β*-keto ester has proved encouraging and ongoing work in this area will undoubtedly lead to a complementary route to the major diastereomer observed in the aldol route with higher ee's.

[ϕ] 0.86 mmol of the ester was dissolved in methanol (25 cm^3) and DCM (25 cm^3)

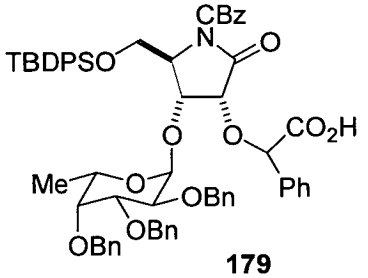
2.8 Future work

Future work in this area will focus on the synthesis of di- and tri-saccharides from the pyrrolidinones (**90** and **129**) and pyrrolidines (**125** and **128**) thus allowing an investigation into their biological role.

The expanding interest in the development of carbohydrate mimetics has led to the synthesis of a wide variety of novel structures particularly belonging to the family of iminosugars.

Furthermore, the biosynthesis of polysaccharides and glycoconjugates mediated by glycosyltransferases has attracted increasing interest partly due to the limited information regarding their 3D structure. It is therefore likely that a greater understanding on the glycosyl transfer will be derived from studies using substrate analogues.[88] For example increased effort has been expended towards the synthesis of simplified analogues of sialyl Lewis X mimics.[89] Several analogues have been prepared where a sugar residue has been replaced with a pyrrolidine ring as illustrated in **figure 15**. Silyl deprotection of **179** in the presence of the sugar was achieved in 90% using TBAF and acetic acid.[90]

Figure 15



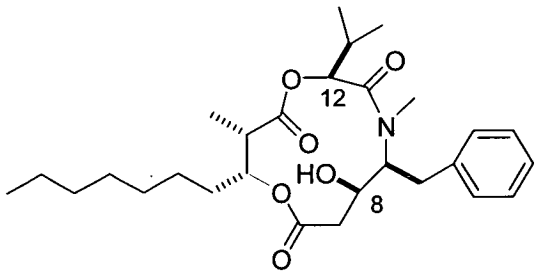
179

Chapter 3: Results and Discussion Part 2

3.1 Hapalosin

Hapalosin **180** was isolated in 1994 by Moore and co-workers[91] from the blue-green alga *Hapalosin welwitschii* W. and S. West (Stignonemataceae), in 0.12% yield based on dry weight of alga. It is a twelve membered cyclic depsipeptide and exists as an inseparable mixture of two conformers ca. 3:1 around the amide function. The major isomer possesses the *s-cis* stereochemistry. Structure elucidation was determined by ^{1}H NMR, ^{13}C NMR and two dimensional ^{1}H-^{1}H and ^{1}H-^{13}C NMR experiments along with mass spectral analysis.

Figure 16

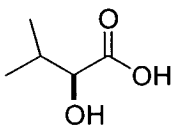


Hapalosin

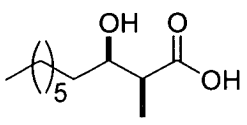
180

Structurally, hapalosin consists of three subunits; an α-hydroxyacid **181**, a β-hydroxy acid **182**, and a γ-amino-β-hydroxy acid **183**, **figure 17**.

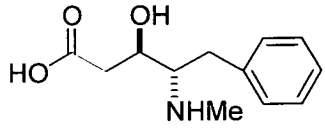
Figure 17



181



182

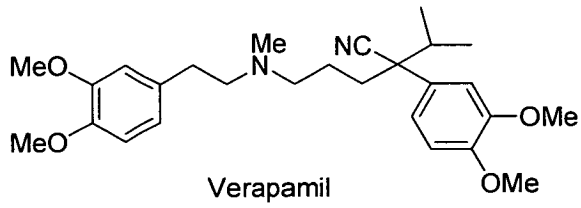


183

3.1.1 MDR reversing activity

Hapalosin was found to reverse multidrug resistance (MDR) in tumour cells.[91] Multiple drug resistance is a phenomenon found in cancer therapy where there is cellular resistance to a wide range of structurally unrelated cytotoxic drugs. The reduced accumulation of the drug inside the tumour cells has been identified as one of the main causes of this phenomenon. A possible mechanism for this multidrug resistance is the overexpression of a P-glycoprotein (P-gp), which is a transmembrane protein acting as an ATP-dependent drug efflux pump. Antagonists of P-gp activity may be useful in combination therapy with cytotoxic drugs. In comparison with verapamil **184** which is the standard among MDR modulators hapalosin was observed to have better MDR reversing activity.

Figure 18



Verapamil

184

3.1.2 Structure-activity relationship studies

To elucidate the structure-activity relationship a variety of analogues have been synthesised. In general the majority of the analogues prepared proved to have comparable or lower biological activities than hapalosin,[92] although there are exceptions.[93]

The conclusions which can be established are that the *s-cis* conformer is vital for MDR reversing activity. The presence of the hydroxyl group at C(8) is also necessary due to internal hydrogen bonding, A non-bulky substituent (methyl or isopropyl) at the C(12) position is also a requirement due to a hydrophobic interaction with the receptor site. Both the long heptyl chain and the methylated

nitrogen are a prerequisite for activity. In addition examples where *D*-glucose mimetics [94] have been prepared have resulted in reduced activity, thus suggesting that the ring flexibility in hapalosin is a further requirement for the biological activity. Evidently it is the combination of all these factors that make hapalosin the only depsipeptide to be reported with this MDR reversing activity.

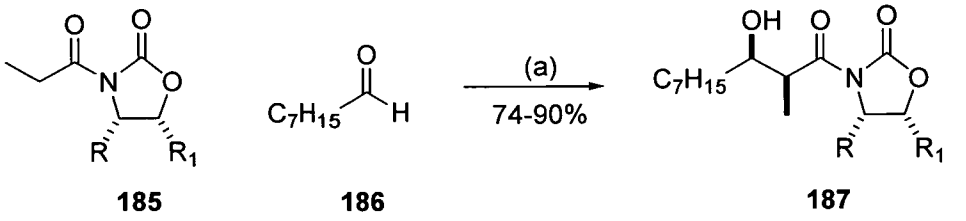
3.1.3 Previous syntheses of hapalosin

Since the discovery of hapalosin there have been several total and partial syntheses undertaken. These have been based on the stepwise construction of each of the three constituent fragments by linking and cyclisation. Typically coupling of the acid **182** with γ-amino-β-hydroxy acid **183** (or the corresponding ester) occurs under Yamaguchi's conditions (2,4,6-trichlorobenzoyl chloride and triethylamine). The commercially available α-hydroxyacid **181** can also be coupled under these conditions and finally diphenylphosphoryl azide (DPPA) mediated macrolactamization leads to the natural product hapalosin.

3.1.4 Syntheses of β-hydroxy acid 182

Several approaches have been reported in the synthesis of fragment **182**, a key route utilises an Evans aldol reaction as the important step.[92,95] Oxazolidinone **185** was coupled with octanal **186** in the presence of dibutylborontriflate and triethylamine to give **187** in good yield (74-90%) and essentially as one diastereomer, **scheme 74**. The free hydroxyl group can be protected as a silyl ether[92c,d] or as a tetrahydropyranyl ether[92f] prior to removal of the auxiliary. Cleavage of the auxiliary has been undertaken using lithium hydroxide to give the acid and LiOBn (prepared from BuLi and BnOH) to give the benzyl ester.

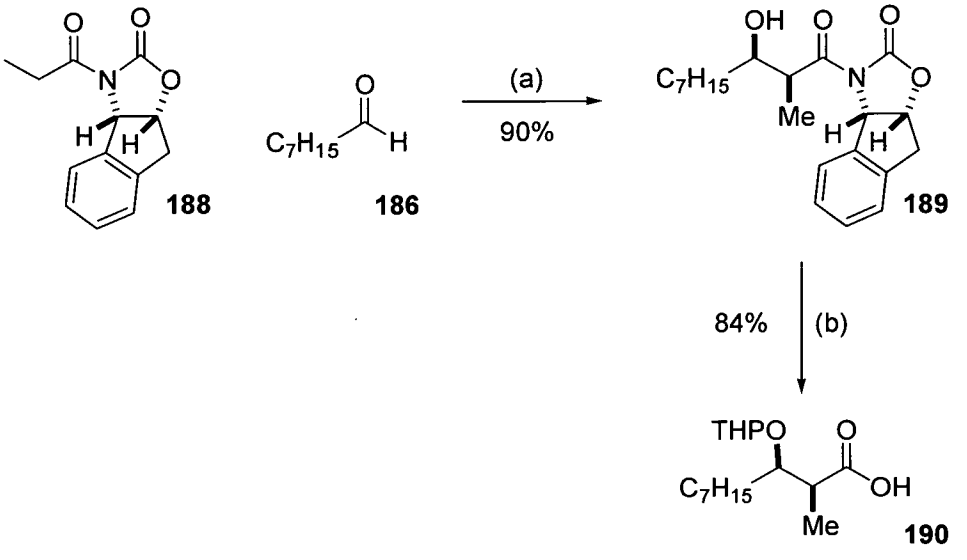
Scheme 74



(a) $^{n}Bu_2BOTf$, Et_3N, DCM, -78 °C→0 °C; R=Ph or Bn, R_1=H or Me.

In Ghosh's[96] approach the acid **190** was prepared *via* an asymmetric aldol using an aminoindan-2-ol derived chiral auxiliary. Reacting this auxiliary **188** with octanal **186** generates aldol adduct **189** in 90% yield, **scheme 75**. Hydroxyl protection as the tetrahydropyranyl ether and subsequent cleavage of the auxiliary afforded acid **190** in 84% yield.

Scheme 75

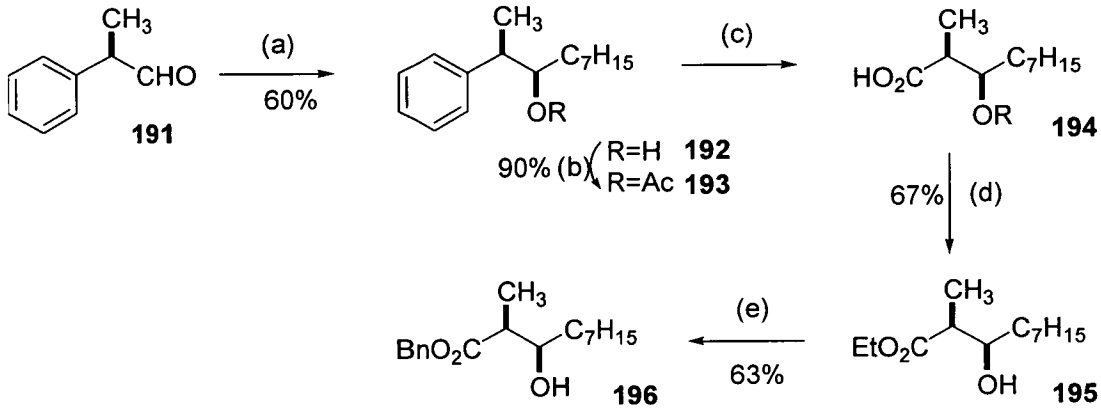


(a) $^{n}Bu_2BOTf$, Et_3N, DCM, -78 °C; (b) (i) Dihydropyran, *p*TsOH, DCM; (ii) LiOOH.

Haddad[97] has reported that upon reacting aldehyde **191** with *n*-heptyllithium in the presence of a crown ether the aldol adduct **192** is formed almost exclusively

(de 90%). Oxidation with sodium periodate in the presence of a catalytic amount of ruthenium trichloride generated acid **194**, subsequent esterification with hydrobromic acid in ethanol afforded ester **195**. Transesterification with benzyl alcohol in the presence of titanium isopropoxide provided the more usable benzyl ester **196** in 63% yield, **scheme 76**.

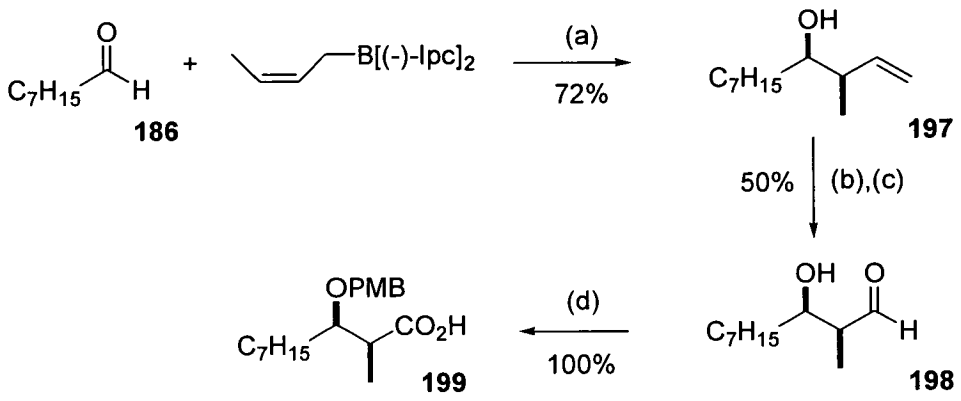
Scheme 76



(a) $C_7H_{15}Li$, 15-crown-5 ether, -78 °C; (b) Ac_2O, Et_3N, DMAP, DCM; (c) $NaIO_4$, $RuCl_3$ (2%), CCl_4-CH_3CN-H_2O (2/2/3); (d) 30% HBr in acetic acid, EtOH, 60 °C; (e) BnOH, $Ti(Oi\text{-}Pr)_4$, 120 °C.

The route by Armstrong[93a] utilised a Brown allyboration of octanal **186** thus generating homoallylic alcohol **197**, **scheme 77**. The hydroxyl group was protected as a PMB group and the olefin was ozonized to give aldehyde **198**. Oxidation with sodium chlorite provided acid **199** in 36% overall yield.

Scheme 77



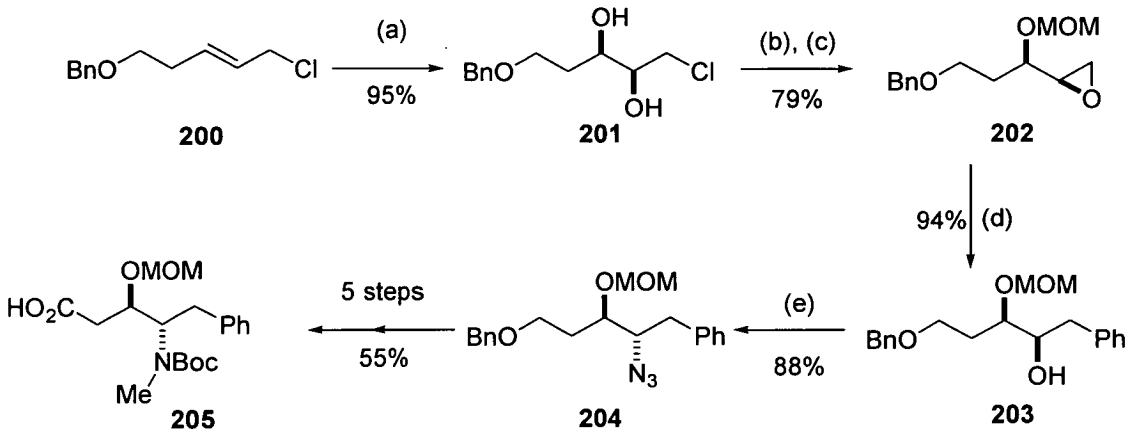
(a) $BF_3.OEt_2$, THF, -78 °C→R.T.; (b) Trichloroacetimidate, TfOH, THF; (c) O_3, PPh_3, DCM; (d) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, ^tBuOH, H_2O.

3.1.5 Synthesis of *N*-methyl-4-amino-3-hydroxy-5-phenyl pentanoic acid (*N*-Me-AHPPA)

A variety of routes to this synthon have been employed primarily from phenylalanine, however alternative strategies have also been employed.

Maier[98] has reported two synthetic routes to *N*-Me-AHPPA which have enabled analogues of hapalosin to be developed. One route utilises an asymmetric dihydroxylation reaction of the allylic chloride **200** under standard conditions using $(DHQD)_2PHAL$ as the chiral ligand to generate diol **201** in 96% ee. Epoxide formation, protection of the secondary hydroxy group, followed by ring opening of the oxirane furnished **203**. The required stereochemistry was acquired *via* a Mitsunobu reaction thus generating azide **204**, subsequent manipulations furnished acid **205** in 32% overall yield (11 steps), **scheme 78**.

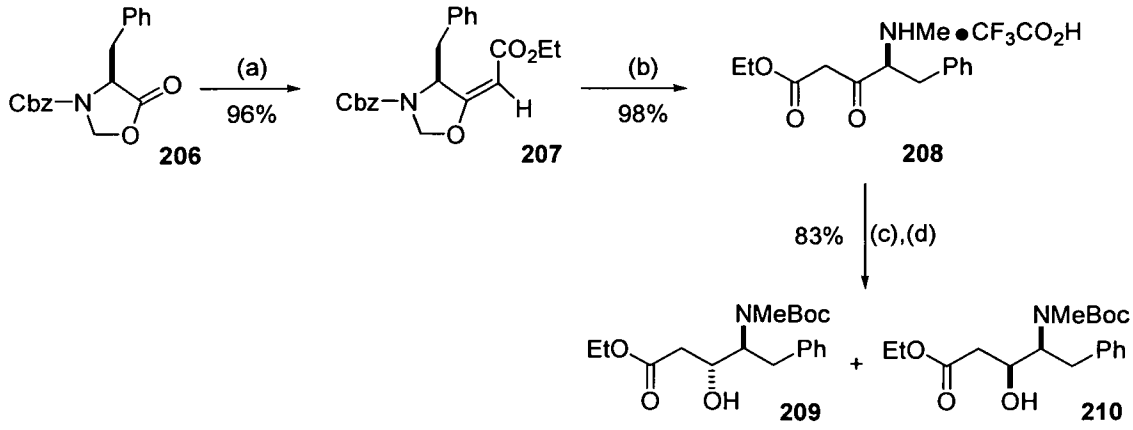
Scheme 78



(a) $K_2OsO_2(OH)_4$, ^tBuOH, H_2O, $(DHQD)_2PHAL$, $K_3Fe(CN)_6$, 0 °C; (b) NaOH, Et_2O, 0 °C; (c) MOMCl, DIPEA, DCM; (d) PhLi, CuCN, THF; (e) $(PhO)_2P(O)N_3$, PPh_3, DEAD, THF.

An example by Iyengar[99] utilises a Wittig reaction of oxazolidinone **206** followed by reduction as a key step to *N*-Me-APPHA. *N*-Cbz oxazolidinone **206** was subjected to a Wittig reaction to give α,β-unsaturated ester **207**. Pd/C hydrogenolysis of **207** generated β-keto ester **208** which was subsequently reduced to yield a mixture of diastereomers. The mixture was *N*-Boc protected to give the required synthon **209**, in 80% de, 78% overall yield, **scheme 79**.

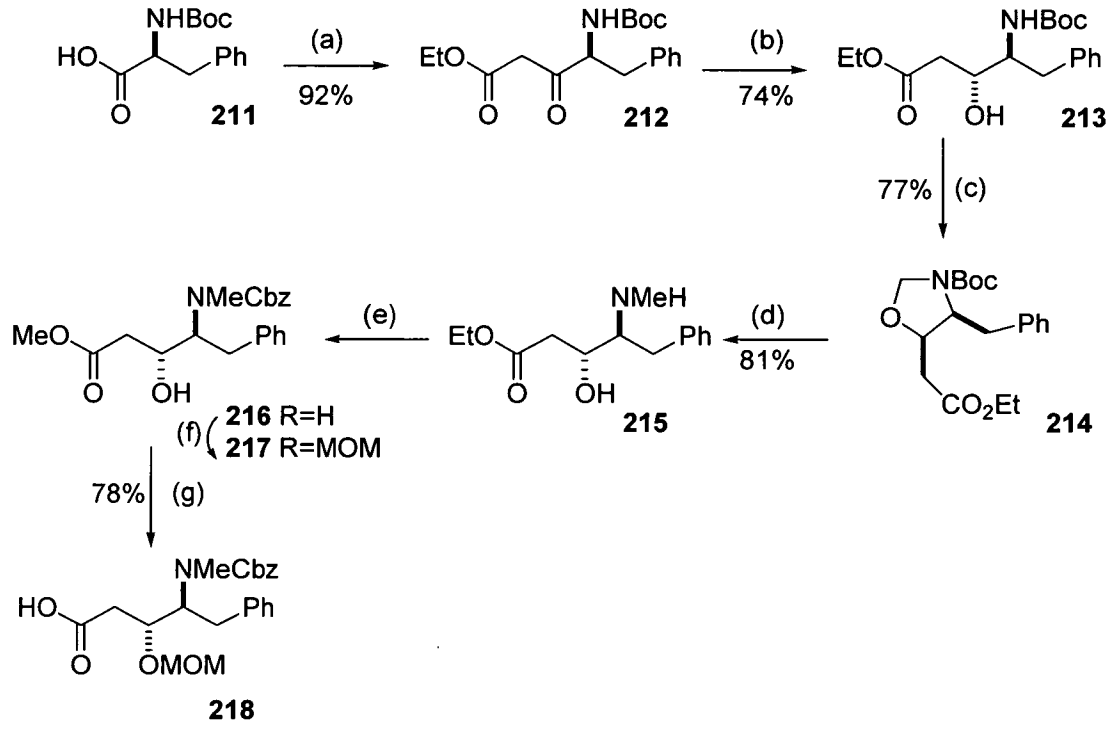
Scheme 79



(a) $Ph_3P{=}CHCO_2Et$, $PhCH_3$; (b) 10% Pd/C, H_2, MeOH, 0 °C→R.T.; (c) $NaBH_4$, NEt_3, MeOH, -10 °C; (d) Boc_2O, DMAP, $CHCl_3$.

An approach utilised by several groups is the CDI coupling of a phenylalanine derived acid to give the corresponding *β*-keto ester.[92a-e,95] Both Boc and Cbz protecting groups have been utilised In an example by Zhu, *N*-Boc phenylalanine **211** was treated with CDI, then directly reacted with lithioethyl acetate to give *β*-keto ester **212** in 92% yield. Reduction of **212** with $NaBH_4$ at –78 °C provided amino alcohol **213** in 74% yield (>90% de), **scheme 80**. Conversion to the oxazolidine **214** followed by reduction furnished *N*-methylated ester **215** which was subsequently *N*-acylated to give **216**. The free hydroxyl group in **216** was protected as a MOM ether and subsequent ester hydrolysis provided the fully protected acid **218** in 33% overall yield.

Scheme 80



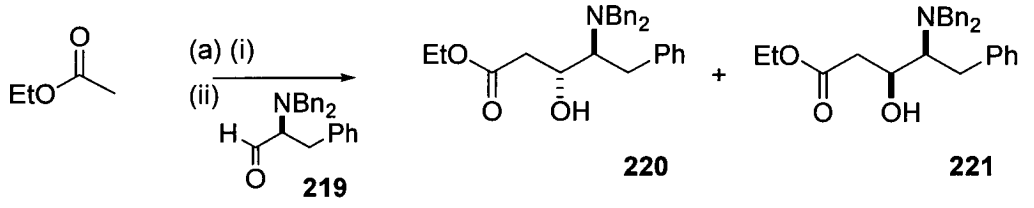
(a) (i) CDI, THF; (ii) $LiCH_2CO_2H$, THF –78 °C; (b) $NaBH_4$, EtOH, -78 °C; (c) HCHO, *p*TsOH, PhMe, Dean-Stark; (d) $NaBH_3CN$, DCM, TFA; (e) CbzOSu, $NaHCO_3$, Acetone, H_2O; (f) MOMBr, $^iPr_2NEt$; (g) K_2CO_3, MeOH.

In summary the synthetic strategies to *N*-Me-AHPPA which do not rely upon phenylalanine as a precursor typically generate single diastereomers thus eliminating the problem of diastereomer separation. However these syntheses can be laborious. Comparable with our approach are those syntheses that proceed *via* a CDI coupling reaction of a phenylalanine derived synthon. Varying levels of selectivity have been reported for this strategy. We therefore felt that our synthetic approach based on this CDI coupling of a *N,N*-dibenzylamino substrate would offer an alternative approach to *N*-Me-AHPPA and its unnatural diastereomer.

3.2 Aldol based approach to *N*-Me-AHPPA

Preliminary studies carried out within the group by O'Dowd[100] involved an aldol based approach to the synthesis of *β*-hydroxy-*γ*-amino acid **220**. The aldehyde **219** was prepared in three steps from phenylalanine in 60% overall yield. An acetate aldol reaction with phenylalanine-derived aldehyde **219** furnished an inseparable mixture of **220** and **221** in 71%. The diastereoselectivity was determined to be approximately 80% in favour of the *anti* diastereomer.

Scheme 81



(a) (i) LDA, THF; (ii) **219** in THF.

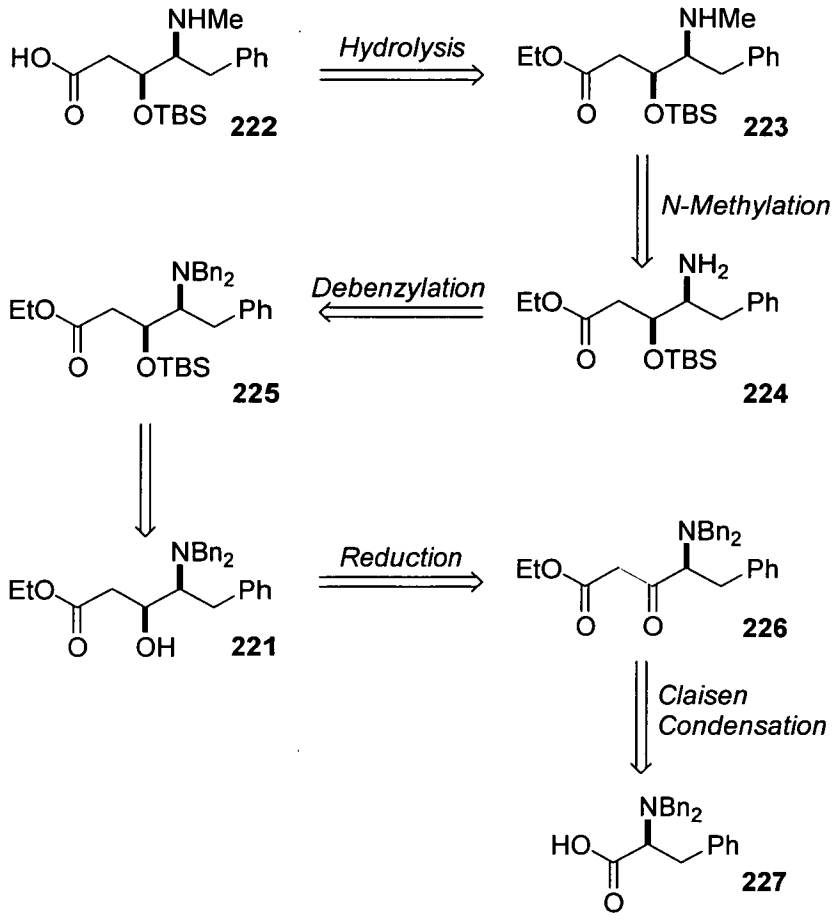
3.3 Claisen based approach of the unnatural diastereomer of *N*-Me-AHPPA

We felt that the aldol approach to *N*-Me-AHPPA under these conditions may have resulted in a reduced enantiomeric excess of **220** based on our previous results, section 2.1.7. In addition we were keen to improve upon the moderate diastereoselectivity of the aldol reaction. Furthermore we were anxious to demonstrate that the cause of the racemisation in the Claisen approach to TBDPS protected CYB-3 was solely due to saponification of the serine derived methyl ester. Therefore our initial aim was to synthesise the unnatural diastereomer of *N*-Me-AHPPA in high enantiomeric excess and adapt this methodology to the synthesis of the natural diastereomer.

3.3.1 Retrosynthesis of the unnatural diastereomer of *N*-Me-AHPPA

The retrosynthetic analysis of **221** is shown in **scheme 82**. We envisaged that a Claisen condensation between the phenylalanine derived acid **227** and lithio ethyl acetate to give *β*-keto ester **226** followed by a stereoselective reduction would yield the *β*-hydroxy alcohol **221**. It was hoped that the reduced steric bulk of the side-chain would allow a racemisation-free synthesis of acid **227**. Hence the Claisen condensation route might represent a high yielding approach to the synthesis of **222**. Furthermore reagent derived stereocontrol might override the inherent substrate selectivity of *β*-keto ester **226** and allow an alternative synthesis of the natural diastereomer.

Scheme 82


NHMe
HO
Ph
O
OTBS
222
Hydrolysis
NHMe
EtO
Ph
O
OTBS
223
N-Methylation
NBn2
EtO
Ph
O
OTBS
225
Debenzylation
NH2
EtO
Ph
O
OTBS
224
NBn2
EtO
Ph
O
OH
221
Reduction
NBn2
EtO
Ph
O
O
226
Claisen
Condensation
NBn2
HO
Ph
O
227

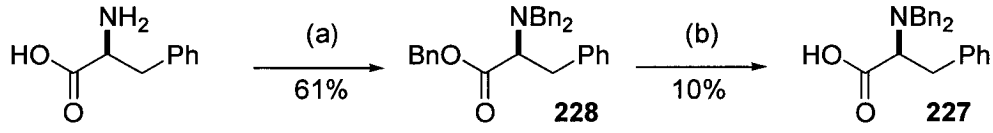
3.3.2 Formation of phenylalanine derived acid 227

In view of the racemisation problems associated with hydrolysis of the serine derived ester (chapter 2) we initially looked at alternative routes to the synthesis of the phenylalanine acid derivative **227**.

Reacting phenylalanine with three equivalents of benzyl bromide generated the *N,N*-dibenzylamino benzyl ester **228** in moderate yield.[21] Purification of ester **228** was difficult due to the large excess of benzyl bromide required.

It has previously been reported that removal of an *O*-benzyl protecting group may be achieved using potassium carbonate under aqueous conditions.[101] This was attempted on substrate **228**, however none of the required acid **227** was formed. Chemoselective debenzylation using 10% Pd/C (10 mol%) under an atmosphere of hydrogen produced 10% of the acid **227** after eight hours. The reaction was extremely slow and concern was raised over the stability of the dibenzyl protecting groups to these conditions.

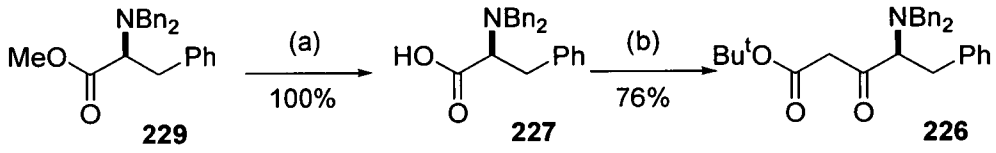
Scheme 83



(a) BnBr, K_2CO_3, NaOH, BnBr; (b) 10% Pd/C, MeOH, H_2.

Hoffman[29] reported that the ester hydrolysis of the phenylalanine derivative **229** using a mixture of lithium iodide and sodium cyanide gave the corresponding acid **227** in quantitative yield, conversion to the corresponding *β*-keto ester **226** enabled the optical purity to be determined. This derivative was found to have an ee of >97%, **scheme 84**. The subsequent reduction of **226** with $NaBH_4$ furnished a fully protected statine analogue. We therefore felt that the use of our methodology discussed in chapter 2 would allow the extension of this work to a novel synthesis of the unnatural diastereomer of *N*-Me-AHPPA.

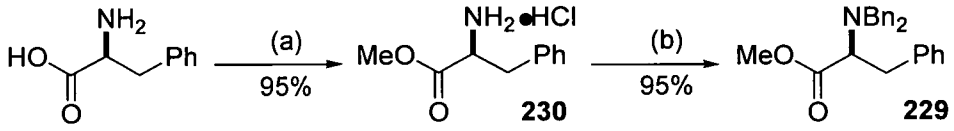
Scheme 84



(a) LiI, NaCN, Py, 115 °C; (b) (i) CDI, THF; (ii) $LiCH_2CO_2{}^tBu$.

We were encouraged by this result and decided to pursue the synthesis of acid **227** in this manner. The phenylalanine derived methyl ester **229** was prepared in two steps from phenylalanine. Phenylalanine was converted to the hydrochloride salt **230** in 95% yield and subsequent treatment with benzyl bromide provided the methyl ester in 95% yield, **scheme 85.**

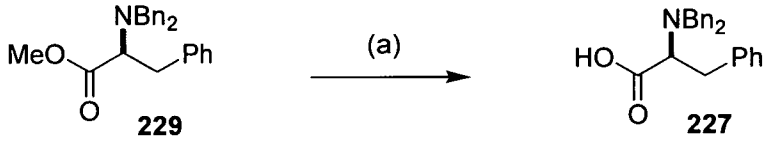
Scheme 85



(a) CH_3COCl, MeOH, 80 °C; (b) K_2CO_3, BnBr, CH_3CN.

Hydrolysis of ester **229** to give acid **227** was carried out under a variety of conditions, the results are summarised in **table 10**.

Scheme 86



(a) Refer to table 10.

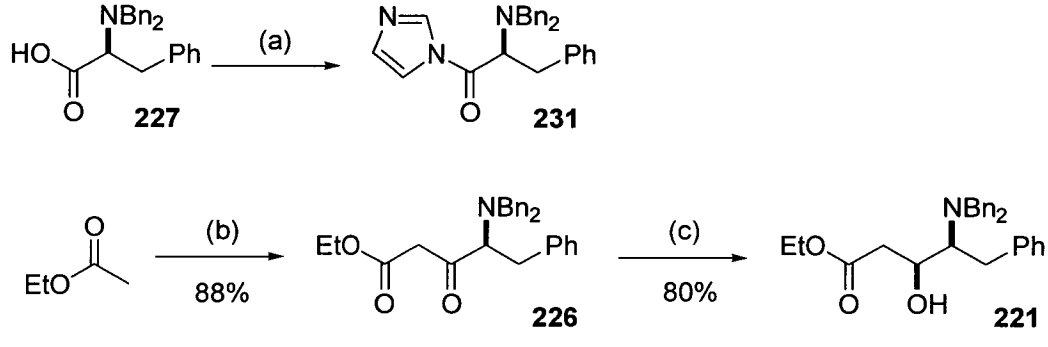
Table 10

Hydrolysis Conditions	Yield %
LiI/NaCN, Py, Reflux, 24h	78
5 eq $LiOH•H_2O$, THF/H_2O, Reflux, 24h	100
5 eq $LiOH•H_2O$, THF/H_2O, Reflux 6h	85
3 eq KOH, MeOH, R.T., 17h	0
3 eq NaOH, 1,4-Dioxane, R.T., 24h	0

3.3.3 Determination of enantiomeric excess of 221

To confirm that no racemisation had occurred the enantiomeric purity of the corresponding *β*-hydroxy alcohol **221** was determined. Conversion of acid **227** to the imidazolide **231** with CDI and subsequent treatment with lithio ethyl acetate provided the *β*-keto ester **226** in 88% yield. Reduction of this *β*-keto ester using sodium cyanoborohydride provided a diastereoselectivity of >90%, in favour of the *syn* diastereomer **221**, **scheme 87**.

Scheme 87



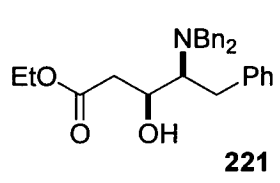
(a) CDI, THF, R.T.; (b) (i) LiHMDS, THF, -78 °C; (ii) **231**, -78 °C, 30 mins then 0 °C; (b) $NaCNBH_3$, Et_2O, MeOH, AcOH.

The enantiomeric purity was compared with a racemic sample prepared in an analogous manner and analysed using chiral HPLC (5% IPA in Hexane). In all cases the ee's were greater than 90% with refluxing with LiOH for 6 hours generating the highest ee, **table 11**.

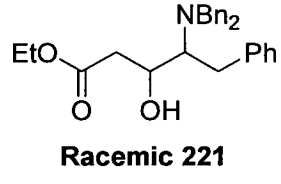
Table 11

Conditions	ee%
LiI/NaCN, Py, Reflux, 24h	92
5 eq LiOH•H_2O, THF/H_2O, Reflux 6h	99.2
5 eq LiOH•H_2O, THF/H_2O, Reflux, 24h	94

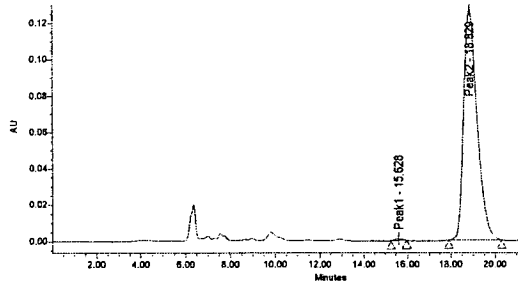
Figure 19

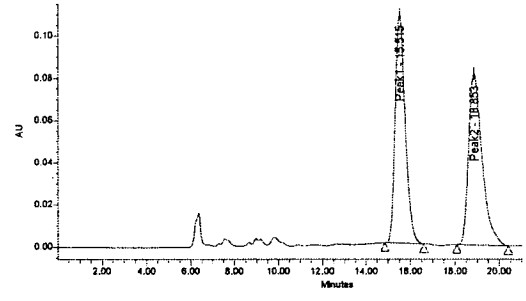


221



Racemic 221





3.3.4 Determination of diastereomeric ratio of 221

The crude ^{1}H NMR spectra obtained from the reduction of β-keto ester **226** and from the aldol reaction of the phenylalanine derived α-amino aldehyde **219** enabled the diastereoselectivity of the cyanoborohydride reduction to be determined. The ratio was calculated by measurement of the integrals from the ^{1}H NMR corresponding to the protons at C(2) protons which appeared as two sets of doublet of doublets. The integrals corresponding to the *N* benzyl protons were also used in the calculation of the ratio. **Table 12** summarises the peaks used in this calculation.

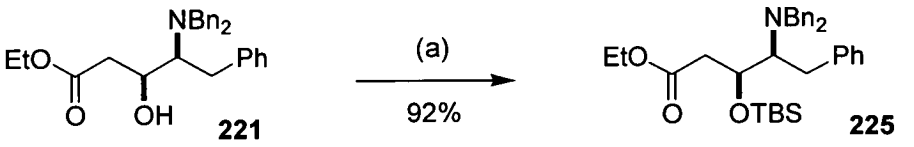
Table 12

Claisen Major Peaks	**Aldol Minor Peaks**
2.1 and 2.4 ($C_2H_AH_B$)	2.15 and 2.4 ($C_2H_AH_B$)
3.4 and 4.1 ($NCH_XH_Y \times 2$)	3.4 and 4.0-4.2 ($NCH_XH_Y \times 2$)
Claisen Minor Peaks	**Aldol Major Peaks**
2.3 and 2.7 ($C_2H_AH_B$)	2.3 and 2.7 ($C_2H_AH_B$)
3.6 and 3.8 ($NCH_XH_Y \times 2$)	3.6 and 3.8 ($NCH_XH_Y \times 2$)

3.3.5 Formation of *N*-methylated pyrrolidinone 235

With the synthesis of the optically pure β-hydroxy alcohol **221** in hand the remaining steps of the synthetic sequence were attempted. The free hydroxyl group was protected as a *tert*-butyldimethylsilylether under standard conditions[102], **scheme 88**.

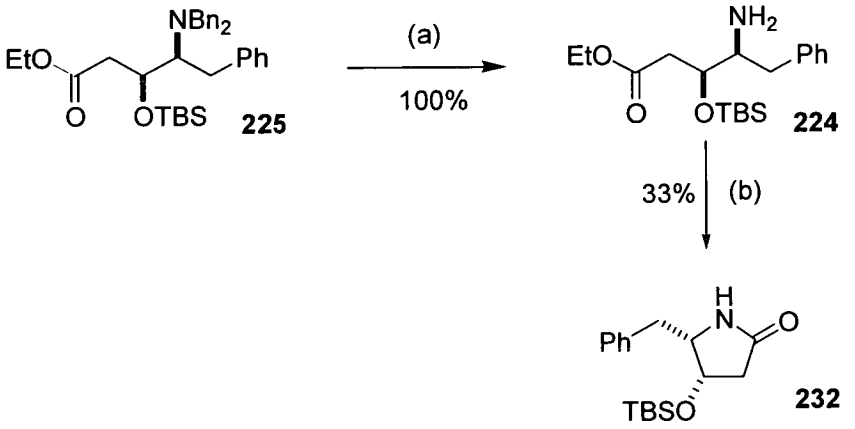
Scheme 88



(a) TBSOTf, 2,6-lutidine, DCM.

Debenzylation using Pearlman's catalyst provided the acyclic amino ester **224** in quantitative yield. From our retrosynthetic analysis the subsequent step was *N*-methylation of the nitrogen. Evidently *N*-methylation of a primary amine under standard conditions would be virtually impossible to control and dimethylation would undoubtedly occur. Similarly reductive amination might be expected to favour dimethylation unless conducted on a two-step protocol. However, we decided to proceed *via* the formation of pyrrolidinone **232** which was considered to be a suitable precursor for the *N*-methylation step thus providing the required synthon with greater control. Filtering **224** through a short path of silica and refluxing the residue in methanol for 24 hours furnished pyrrolidinone **232** in a disappointing 33% yield, **scheme 89**. The remainder of the mass recovered was starting material.

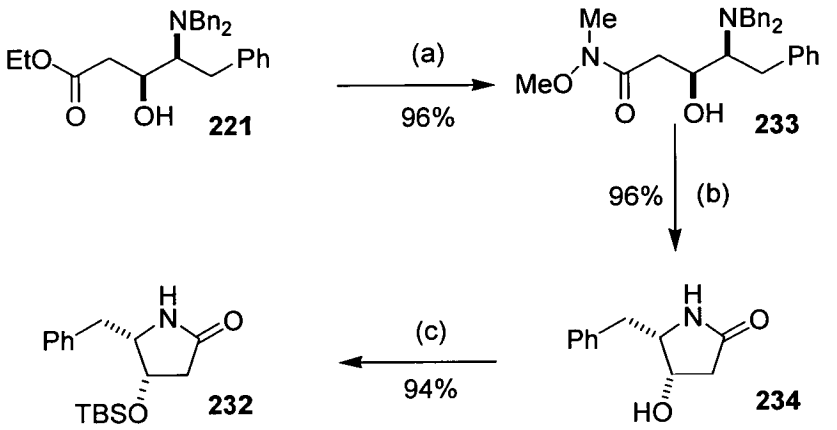
Scheme 89



(a) $Pd(OH_2)/C$, H_2, MeOH; (b) MeOH, 80 °C.

The low yield of pyrrolidinone **232** was improved by converting ester **221** into the corresponding Weinreb amide **233** under standard conditions. Debenzylation of the amide **233** provided the pyrrolidinone in 96% yield. The TBS protected pyrrolidinone **232** was obtained uneventfully in 94% yield, **scheme 90**.

Scheme 90



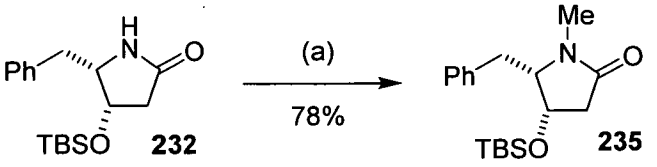
(a) (MeO)NMe•HCl, Me_3Al, THF, 0 °C-35 °C; (b) $Pd(OH_2)/C$, H_2, MeOH; (c) TBSOTf, 2,6-lutidine, DCM.

The penultimate step was the *N*-methylation of **232**. Maier[98a] has reported that *N*-methylation using methyl iodide and sodium hydride could result in cleavage of a neighbouring silicon protecting group. However Nishiyama successfully managed to *N*-methylate under these conditions in the presence of a TBS group in 77% yield. Zhu [92c,d] and others[103] reported difficulties in the selective *N*-methylation of Boc protected *β*-hydroxy esters possibly due to competitive *β*-elimination.

The TBS protected pyrrolidinone **232** was *N*-methylated with methyl iodide[φ] and sodium hydride to give the *N*-methylated pyrrolidinone **235** in 78% yield, **scheme 91**.

[φ] Methyl iodide was filtered through a plug of alumina to remove hydrogen iodide.

Scheme 91

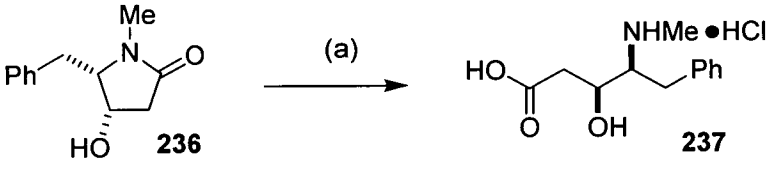


(a) MeI, NaH, THF.

3.3.6 Attempted hydrolysis of *N*-methyl pyrrolidinone 235

The remaining step in the synthetic sequence was the hydrolysis of the pyrrolidinone. Two groups[104] have reported the hydrolysis of 1-methyl-pyrrolidin-2-one using either barium hydroxide or concentrated hydrochloric acid. Directly comparable with our work was that reported by Huang[105] in their synthesis of *N*-Me-AHPPA where the pyrrolidinone **236** was refluxed in the presence of 6N HCl to afford the acid **237**. However it would be expected that under these acidic conditions the labile TBS protecting would have been cleaved in our substrate.

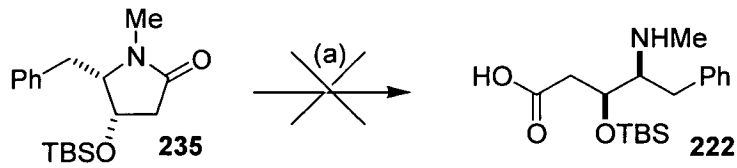
Scheme 92



(a) 6N HCl, 100 °C.

Under basic conditions hydrolysis of 1-methyl-pyrrolidin-2-one to give the acid occurred in 58% yield and in three hours. Refluxing our bulkier substrate **235** for 24 hours under these conditions provided only starting material, **scheme 93**. The quantity of base was doubled from three to six equivalents but again none of the acid was obtained. Unfortunately time did not permit further investigations into this hydrolysis reaction.

Scheme 93

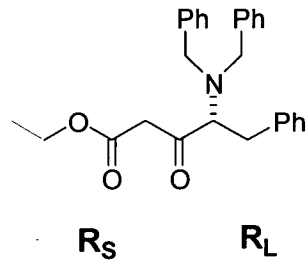


(a) $Ba(OH)_8 \bullet H_2O$, H_2O, 110 °C.

3.4 Reduction of 226 using CBS reagent and Ru[BINAP] catalyst

An alternative synthesis of the natural diastereomer **220** *via* the chiral reduction of *β*-keto ester **226** using the CBS reagent **178** was pursued. This route would therefore provide a complementary method to the aldol strategy investigated by O'Dowd.[100] As discussed in chapter 2, for a highly enantioselective reduction to occur the appendages R_S and R_L must differ appreciably in the ketone. We felt that **220** was a suitable substrate for this chiral reduction.

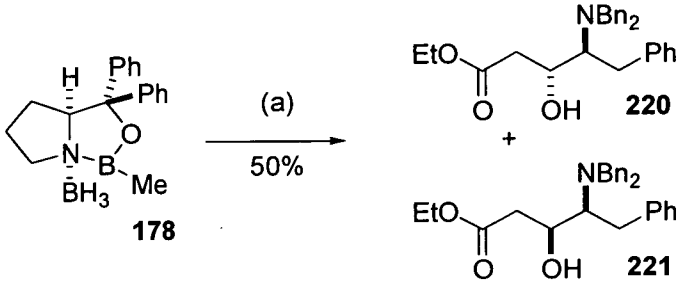
Figure 20



The oxazaborolidine **178** was prepared from (S)-(+)-*α*,*α*-diphenyl-2-pyrrolidinemethanol and dimethylsulfide-borane.[83] Reduction of **226** using the conditions optimised previously provided a 1:1 mixture of **220** and **221** in a modest yield of 50%.

This was consistent with our earlier findings from the chiral reduction of the serine derived β-keto ester.

Scheme 94



(a) (i) BMS, DCM, 0 °C; (ii) **226** in DCM, 40 °C.

Finally we attempted the hydrogenation of the β-keto ester **226** using a ruthenium BINAP catalyst under an atmosphere of 120 psi at room temperature. Disappointingly this route resulted in the recovery of starting material. As discussed in chapter 2 it appeared that both high temperatures and pressures were required for the successful hydrogenation of these substrates.

3.5 Summary of chapter 3

In conclusion we have shown that the Claisen condensation reaction followed by a diastereoselective reduction affords β-hydroxy alcohol **221** in excellent diastereoselectivity and enantioselectivity (>99%) for our phenylalanine derived substrate. From studies carried out subsequently in the group for a tyrosine derived substrate, the β-hydroxy alcohol has been determined to have an ee of >99%. Therefore the problems of racemisation using this route appear to be confined to the serine derivatives.

In contrast to Hoffman's work we have shown that the phenylalanine derived methyl ester **229** does undergo hydrolysis in the presence of lithium hydroxide. The corresponding β-hydroxy ester **221** was furnished in higher ee and higher overall

yield than the lithium iodide/sodium cyanide procedure. Although Hoffman reported that debenzylation of the *β*-hydroxy esters could be achieved *via* catalytic hydrogenation, no further work was reported for these fully protected statine analogues. We have therefore extended this work for the phenylalanine derivative to the synthesis of the fully protected lactam form of the unnatural *N*-Me-AHPPA **235** *via* four steps from the *β*-hydroxy ester **221**. Furthermore pyrrolidinone **234** would also serve as a viable substrate for the synthesis of disaccharides.

Chapter 4: Results and Discussion Part 3

4.1 Introduction

In parallel with the work discussed in chapter 2, we have synthesised a new threonine-derived *N,N*-dibenzylamino α-amino ketone. Our initial aims were to construct the α-amino ketone **244** in high ee and subsequently investigate the diastereoselectivity of the aldol reaction of **244** with a series of achiral aldehyde substrates. The bulky *N,N*-dibenzylamino group should effectively direct π-face selectivity in the addition reaction.

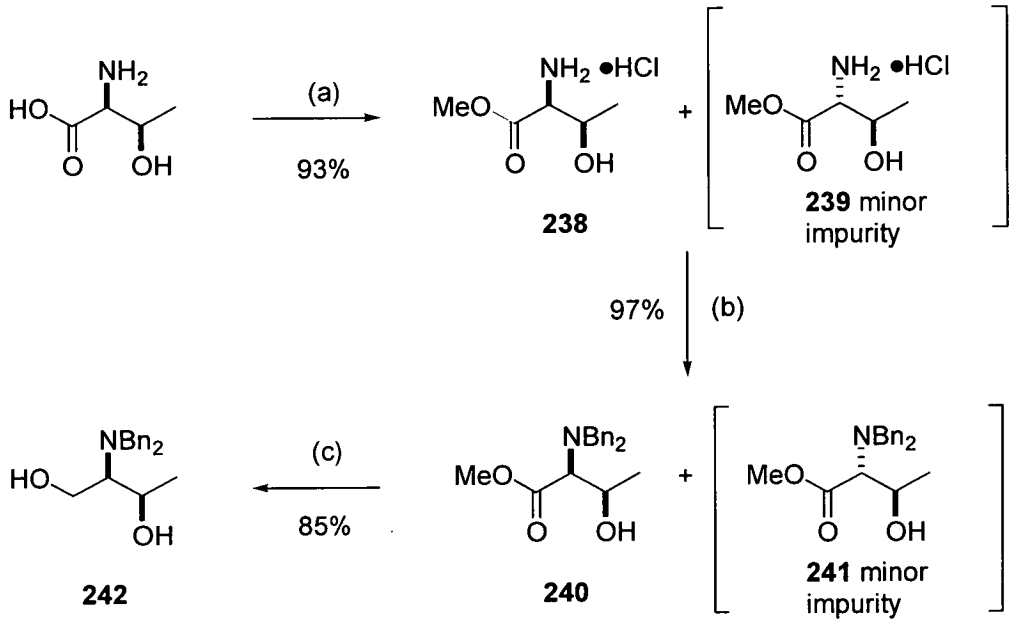
4.2 Synthesis of *N,N*-dibenzyl protected threonine derivative 244

Our five step synthesis of this novel threonine methyl ketone **244** was carried out using the conditions developed for the synthesis of the serine derived aldehyde (chapter 2). Methyl ester **238** was formed in 93% yield from *L*-threonine under standard conditions, **scheme 95**. Surprisingly, the methyl ester was an oil and not a solid as expected. The ^{1}H NMR also showed the presence of a minor impurity. We continued with the *N,N*-dibenzylation step which proceeded in excellent yield. However the ^{1}H NMR still clearly showed the presence of the impurity which had not been removed by flash chromatography. Fortunately purification of the amino diol **242** furnished a pure sample due to its crystalline nature. The impurity was identified as the *anti* diastereomer although the absolute stereochemistry was not determined.

The ^{1}H NMR spectrum of **238** showed a doublet at 3.75 ppm with a coupling constant of 3.8 Hz corresponding to the proton at C(2) in the impurity **239**. This was consistent with that for the major diastereomer where a doublet at 4.01 ppm with a coupling constant of 3.8 Hz was determined as being the proton at C(2) in **238**. The ^{1}H NMR spectrum of **240** showed sidebands off the major peaks corresponding to the minor diastereomers benzyl protons at 4.10 and 3.50 ppm (coupling constants

could not determined). At 3.15 ppm a doublet with a coupling constant of 9.6 Hz was visible, again corresponding to the proton at C(2) in **241**. The ^{13}C NMR further confirmed the presence of the minor diastereomer. For the spectrum of **238** two sets of peaks were apparent with almost identical chemical shifts corresponding to **238** and **239**. The distinctive ^{13}C NMR chemical shifts for **241** were visible to a lesser extent in the spectrum of **240**. The source of this contamination could possibly be from racemisation of the α-stereocentre in the initial methylation step but it was more likely that it was present in the starting material supplied by Aldrich.

Scheme 95

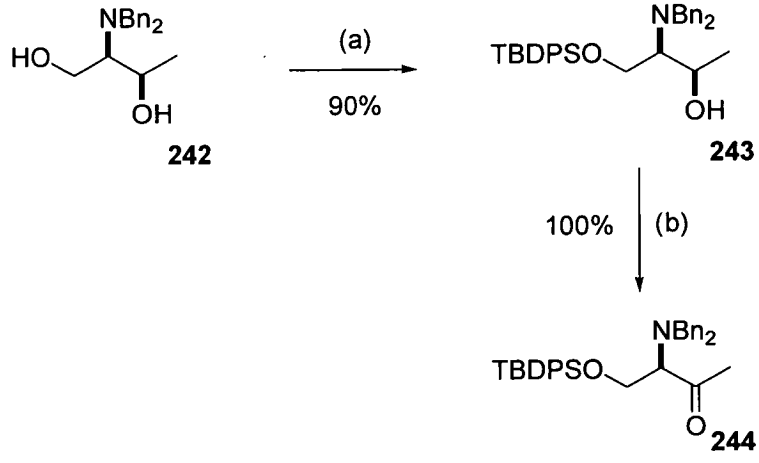


(a) CH_3COCl, MeOH, 80 °C; (b) K_2CO_3, BnBr, CH_3CN; (c) $LiBH_4$, Et_2O, MeOH.

Selective TBDPS protection of the primary alcohol in **242** was achieved in the presence of TBDPSCl and imidazole, however it proved extremely difficult to separate TBDPS protected alcohol **243** from TBDPSOH by flash chromatography. Further purification by HPLC (15 % EtOAc in hexane) provided **243** in 90% yield. Finally Swern oxidation furnished methyl ketone **244** in quantitative yield. The

ketone was used without purification and was prepared when required to eliminate any possibility of racemisation, **scheme 96**.

Scheme 96

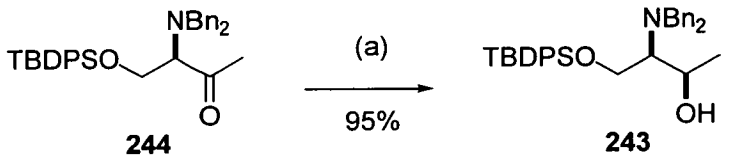


(a) TBDPSCl, imidazole, DMF; (b) $(COCl)_2$, DMSO, NEt_3, DCM.

4.2.1 Determination of the enantiomeric excess of methyl ketone 244

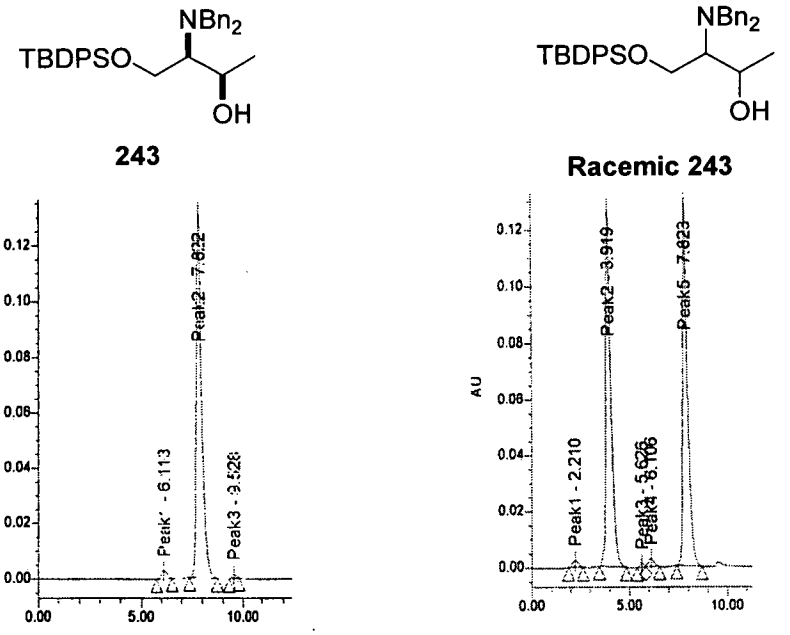
Due to the potential instability of ketone **244** upon contact with silica gel, the enantiomeric excess was measured indirectly *via* alcohol **243**. Freshly prepared ketone **244** was reduced with DIBAL-H to provide a sample of the alcohol **scheme 97**. A racemic synthesis of the alcohol was carried out as shown in **schemes 95** and **96**. Both chiral and racemic alcohols were analysed by chiral HPLC (5% IPA in Hexane). The optical purity of the alcohol was measured at >99% ee.

Scheme 97



(a) DIBAL-H, toluene, -78 °C.

Figure 21



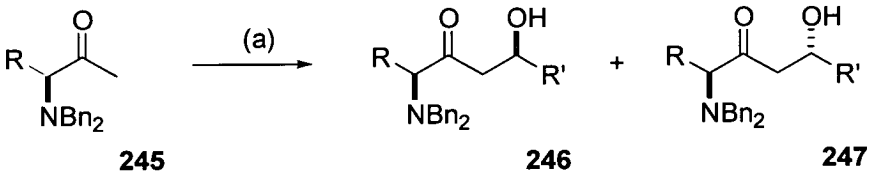
4.3 Asymmetric aldol reactions of α-amino ketones

Diastereoselective aldol reactions have emerged as one of the most efficient methods available for the construction of a wide range of optically active compounds. Very high diastereoselectivities have been reported for aldol reactions involving chiral enolates derived from ethyl or higher alkyl substituted ketone derivatives.[106] This approach however is much less successful with enolates derived from methyl ketones. Relatively few examples of highly diastereoselective aldol

reactions of chiral methyl ketones[107] or aldol reactions of methyl ketones with chiral reagents have been reported.[108]

Liotta[109] has reported that the aldol reactions of lithium enolates of *α-N,N*-dibenzylamino methyl ketones **245** proceeded with high diastereoselectivity (80:20->98:2) and in excellent yield (64-91%) in favour of **246**. The results are summarised in **table 13**.

Scheme 98



245 **246** **247**

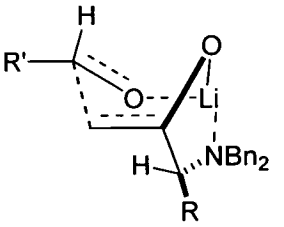
(a) (i) LDA, THF, -78 °C; (ii) R'CHO, THF.

Table 13

Ketone **R**	**Aldehyde** **R'**	**Yield** **%**	**Diastereoselectivity** **246:247**
Me	Ph	84	80:20
Me	$(CH_3)_3C$	81	89:11
Bn	$(CH_3)_2CH$	78	90:10
Bn	$(CH_3)_3C$	76	92:7
^iPr	Ph	90	>98:2
^iPr	$(CH_3)_3C$	88	>98:2

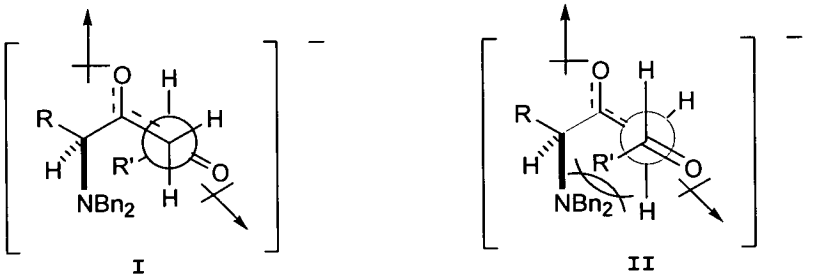
This exceptionally high diastereoselectivity has been rationalised by Liotta by a twist boat transition state which involves internal chelation of the dibenzylamino group, **figure 22**. [109]

Figure 22



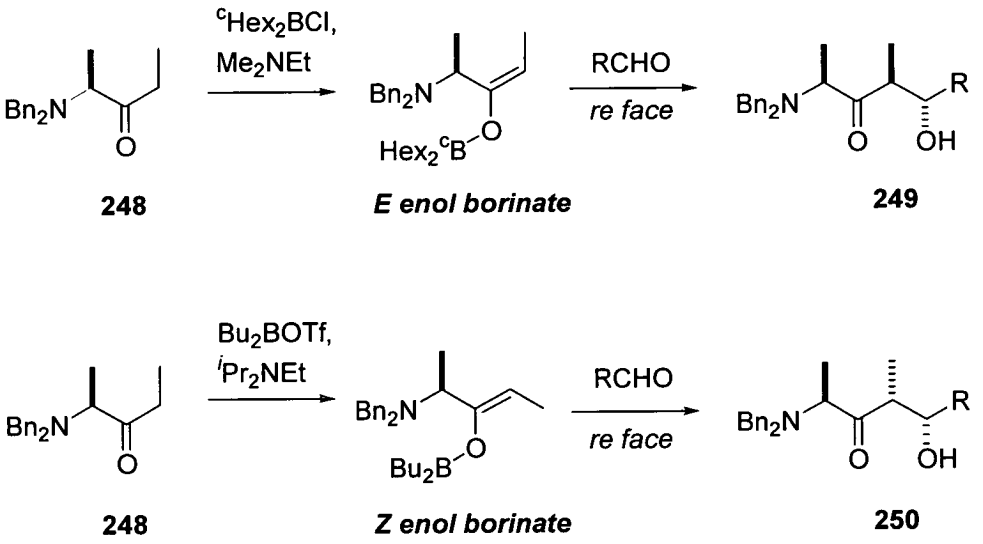
An extension to Liotta's[110] work showed that higher diastereoselectivities could be obtained for sodium enolates compared with lithium enolates, typically >98:2 for a range of aldehydes. An alternative model to account for the observed selectivities was proposed based on the premise that sodium, which has strong tendency to form ionic bonds with oxygen, would disrupt the internal chelation present in a twist boat transition state. Furthermore the diastereoselectivities observed for the aldol reactions of *N,N*-dibenzylamino ethyl ketones using LDA or NaHMDS as base can only be rationalised by this open transition state model, **figure 23.**[111] In model **I** the aldehyde approaches in a manner whereby the two oxygen atoms are orientated such that the dipoles are opposed. The aldehyde will therefore attack from the less hindered *si* face to produce the *syn* adducts **246.** Attack of the aldehyde from the *re* face would be less likely to occur due to unfavourable steric interactions between the *N,N*-dibenzyl group and the R' group as shown in model **II.**

Figure 23



Recently Paterson[112] has reported his findings for the boron mediated aldol reaction of ethyl *α-N,N*-dibenzylamino ketones **248**. By appropriate choice of boron reagent and base the *syn* **249** or *anti* **250** adducts can be formed preferentially, **scheme 99**. For a range of aldehydes diastereoselectivities in the range of 84:16-89:11 were obtained for the *anti* adduct in yields of 64-95%. Comparable results were obtained for the synthesis of the *syn* adducts using $Bu_2BOTf/^iPr_2NEt$.

Scheme 99

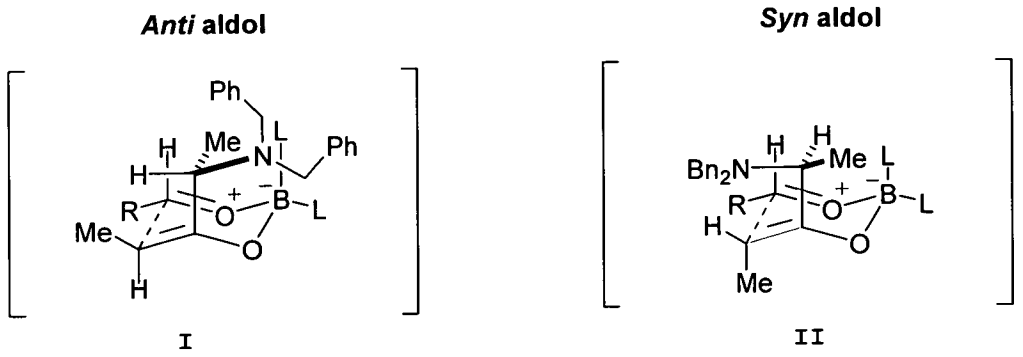


248 ***E enol borinate*** **249**

248 ***Z enol borinate*** **250**

The products formed can be rationalised by the corresponding transition structures which are determined by steric and electronic factors, **figure 24**. In the case of the *anti* aldol adducts addition of the *E*-enolate to the aldehyde occurs *via* transition state ***I***. The bulky dibenzylamino group is directed outside the transition state and the methyl group is orientated inwards. The formation of the *syn* adducts can be rationalised by transition state ***II***, where the enolate C-O and C-N dipoles are opposed and the methyl group is orientated outwards.

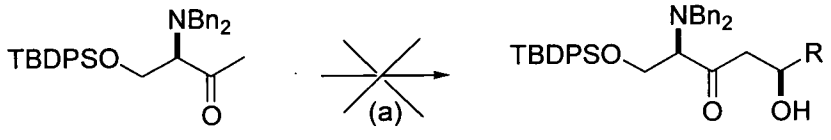
Figure 24



4.4 Boron mediated aldol reaction of 244

At the time the research was conducted the only examples of aldol reactions involving *α-N,N*-dibenzylamino ketones were those reported by Liotta[109,110] using LDA as the base. Although no reports of racemisation were reported for the aldol adducts we were concerned in light of the racemisation that had occurred for our serine derived aldehyde under similar enolisation conditions (chapter 2), thus we attempted the boron mediated aldol reaction of **244** with a range of aldehydes. Initial attempts using Bu_2BOTf/NEt_3 for enolisation produced only starting materials under a range of conditions, **scheme 100**. Examples of some of the conditions employed are summarised in **table 14**.

Scheme 100



244 **251**

(a) (i) Bu_2BOTf, NEt_3, DCM; or $^c(Hex)_2BCl$, NEt_3, Et_2O; (ii) RCHO, (R=^{i}Pr, $CH_2{}^i$Pr, Ph).

Table 14

Bu_2BOTf eq.	NEt_3 eq.	RCHO eq.	Enolisation Conditions	Reaction Conditions
1.5	2.0	3.0 ^{i}PrCHO	-78 °C (3.5 h) then 0 °C (20 mins) then recooled to –78 °C	-78 °C (1 h) then 0 °C (3 h)
2.5	3.2	3.3 PhCHO	-78 °C (2 h) then 0 °C (30 mins) then recooled to –78 °C	-78 °C (1 h) then 0 °C (2.5 h)
2.5	2.8	3.0 ^{i}PrCHO	-78 °C (45 mins)	-78 °C (1 h) then 0 °C (4 h)
2.0	2.25	2.8 PhCHO	-78 °C (40 mins)	-78 °C (30 mins) then -30 °C (16 h)

The bulky reagent (^{c}Hex)$_2$BCl, which could be freshly prepared from cyclohexene and monochloroborane-methylsulphide complex, was also used.[113] A variety of enolisation conditions were employed but again the reaction failed to produce any of the desired aldol adduct **251**. **Table 15** summarises the conditions for the reaction.

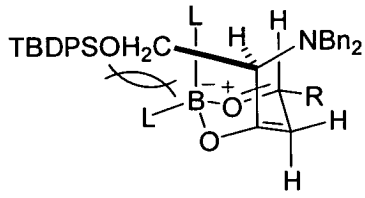
Table 15

(^{c}Hex)$_2$BCl eq.	NEt_3 eq.	PhCHO eq.	Enolisation Conditions	Reaction Conditions
3.0	3.4	4.0	-78 °C (3h)	-78 °C (2 h) then 0 °C (3 h)
3.0	3.4	4.0	-78 °C (2h)	-78 °C (2 h) then – 10 °C (16 h)
3	3.4	4.0	-78 °C (1h) then 0 °C (30 mins), recooled to – 78 °C	-78 °C (2 h) then 0 °C (20 h)

In consideration of Paterson's[112] recent report regarding the boron aldol reaction of ethyl *α-N,N*-dibenzylamino ketones it could be reasoned that the presence of the bulky TBDPS group was one cause of the lack of reactivity under these

conditions. Increased steric congestion between the ligand on boron and the TBDPS group are apparent in **figure 25** for our ketone **244** thus making this reaction unfavourable. A further investigation into the effect of other protecting groups was not explored due to time constraints. Instead we explored the lithium mediated aldol reaction of ketone **244** in the hope that an open transition state such as that proposed by Liotta might provide more favourable results.

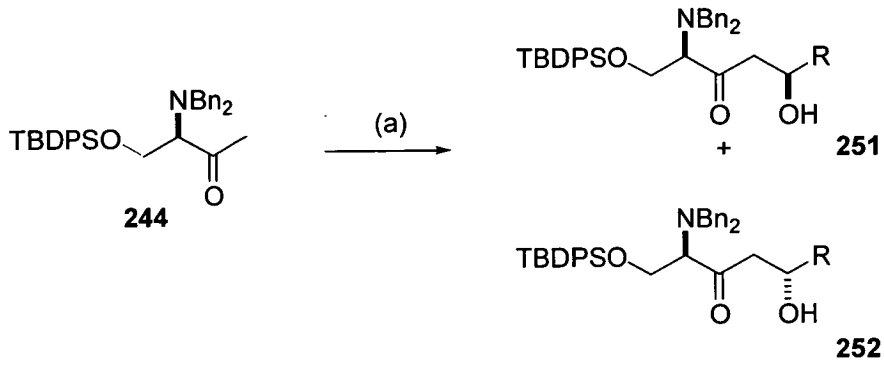
Figure 25



4.5 Lithium mediated aldol reaction of 244

Enolisation of ketone **244** was carried out at –78 °C in the presence of LiHMDS for one hour followed by addition of the aldehdye. After ten minutes t.l.c. showed that all of the starting material had been consumed hence the reaction was quenched. Chromatography provided a mixture of inseparable diastereomers **251** and **252**. The yields for the reaction for a range of aldehydes are summarised in **table 16**.

Scheme 101



(a) (i) LiHMDS, THF; (ii) RCHO.

Table 16

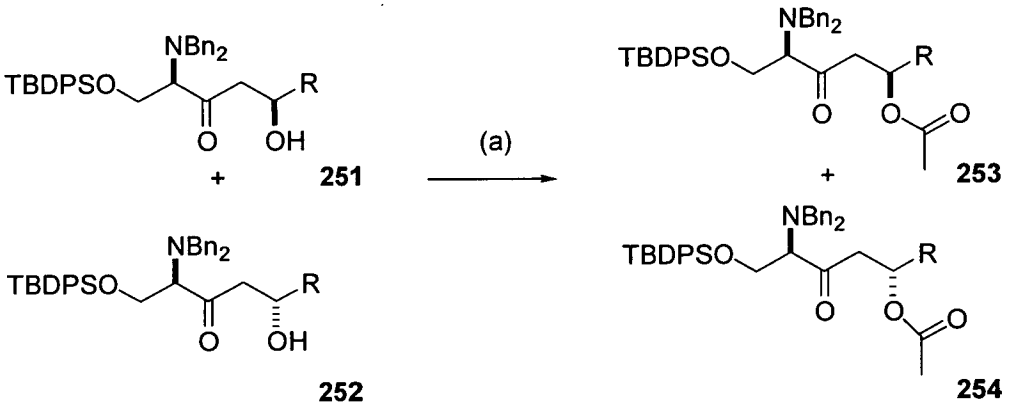
Aldehyde **R**	**Yield** **%**
$CH_2{}^iPr$	88
Ph	82
PhCl	89
PhOMe	86

The reactions proceeded in good yield, however it was found to be difficult to ascertain the selectivity of the reaction from the ^1H NMR as there were no obvious diagnostic signals characteristic for either diastereomer. It was therefore thought that formation of the corresponding acetate derivatives would allow the selectivity to be determined.

4.6 Formation of acetate derivatives

The mixture of aldol adducts **251** and **252** were converted to their acetate derivatives **253** and **254** under standard conditions in excellent yield.

Scheme 102



(a) DMAP (cat.), Et_3N, acetic anhydride, DCM.

The selectivity for each reaction was determined by integration of the methyl peaks which were readily distinguishable for each diastereomer. The results are summarised in **table 17**, and are supported by ratios determined from the ^1H NMR spectra of the aldol adduct (integration of ^tBu signal from silyl protecting group) where these could subsequently be ascertained.

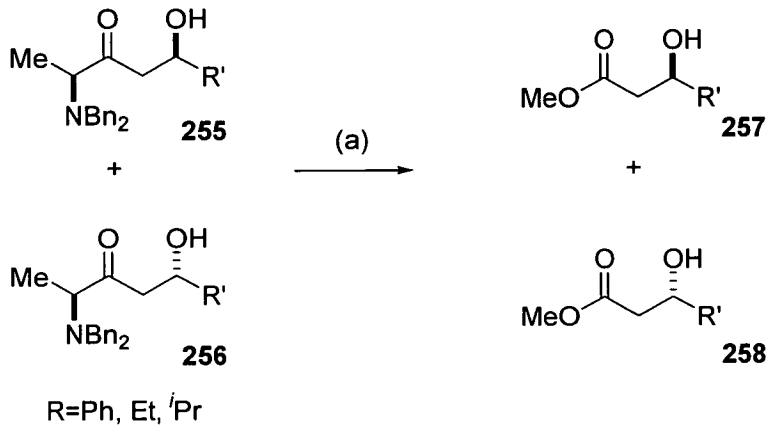
Table 17

Aldehyde R	**Diastereoselectivity from acetate 253:254**	**Diastereoselectivity from aldol 251:252**
$CH_2{}^iPr$	72:28	70:30
Ph	71:29	70:30
PhCl	60:40	60:40
PhOMe	55:45	55:45

In summary the diastereoselectivities were very poor from 55:45 to a modest 70:30. Although Liotta had shown that the use of sodium enolates rather than lithium enolates gave rise to an increased diastereoselection in the case of simple *N,N*-dibenzylamino ketones time did not permit a more lengthy investigation of the enolisation conditions or the role of the TBDPS protecting group.

Our tentative assignment of the stereochemistry of **251** was based on Liotta's[109,110] precedent which established the configuration of the new stereogenic center by converting the crude aldol adducts **255** and **256** into the corresponding 3-hydroxy methyl esters **257** and **258, scheme 103**. Lanthanide induced ^{1}H NMR shifts of the methoxy groups of the two enantiomers was significantly different the confirmation of absolute configuration by comparison with literature values.

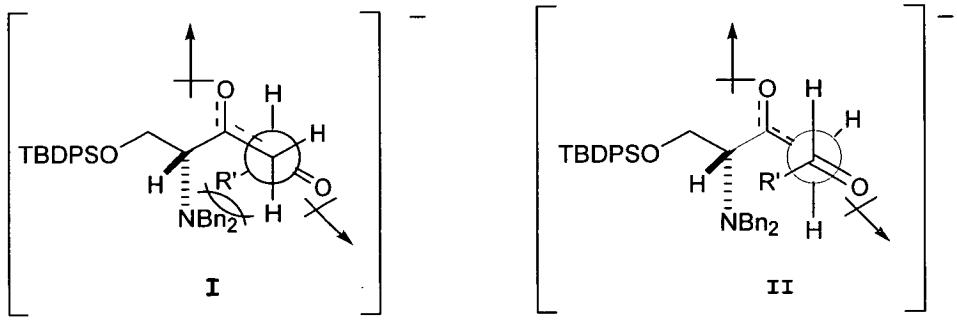
Scheme 103



(a) (i) CH_3CO_3H, (ii) CH_2N_2.

By considering the transition state for the reaction of threonine methyl ketone **244** with a range of aldehydes we can see that model **II** is favoured thus generating the *syn* adducts preferentially, **figure 26**. Therefore on the basis of Liotta's results we have assigned the major diastereomer as the *syn* adduct.

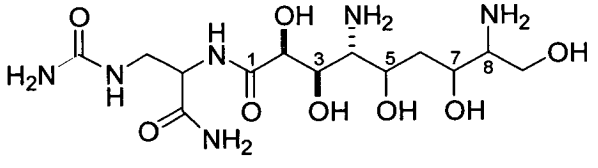
Figure 26



4.7 Future work

From this preliminary work conducted, an investigation into the synthesis of complex polyhydroxylated *δ*-amino acids such as that found in the antibiotic Zwittermicin A may be possible. Zwittermicin A **259**, a novel linear aminopolyol was isolated by Clardy *et al.* from *Bacillus cereus* UW85 in 1993.[114] Zwittermicin A inhibits the growth of the plant pathogen *Phytophthora medicaginis* at low concentrations. Although the structure of the carbon backbone has been determined, the relative stereochemistry of the complex amino polyol fragment at C(5), C(7) and C(8) remains unknown.

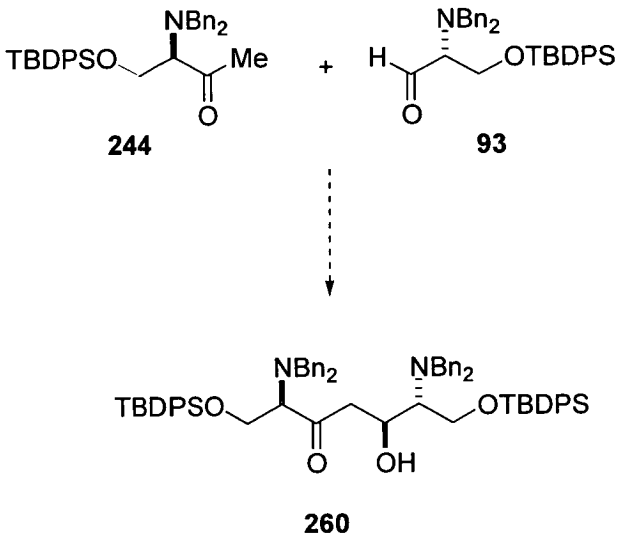
Figure 27



259

Future studies in this area will therefore look at combining the substrate-derived selectivity of this novel ketone **244** and aldehyde **93** to give the complex fragment **260**, **scheme 104**. Ketone reduction and elaboration using a glycolate aldol at one of the termini will allow synthesis of Zwittermicin A.

Scheme 104

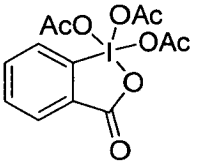

NBn2
TBDPSO
Me
O
244
+
NBn2
H
OTBDPS
O
93
NBn2
NBn2
TBDPSO
OTBDPS
O
OH
260

Chapter 5: Results and Discussion Part 4

5.1 Introduction

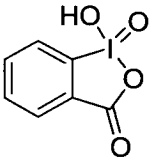
In the last twenty years hypervalent iodine reagents have enjoyed an increasing popularity in organic synthesis. They have attracted attention because of their mild, selective and environmentally friendly properties as oxidizing agents. The Dess-Martin periodinane (DMP) **261**[115] has received considerable interest due to its ease of oxidation of alcohols to carbonyl compounds. Iodoxybenzoic acid (IBX) **262** was first synthesised in 1893[116] however until recently very little was known about its chemical properties in part due to its insolubility in most organic solvents. Santagostino[117] reported that IBX can be readily dissolved in DMSO and has shown that IBX functions as a valuable oxidant toward a variety of alcohols. Unlike DMP IBX is not moisture or air sensitive.

Figure 28



DMP

261

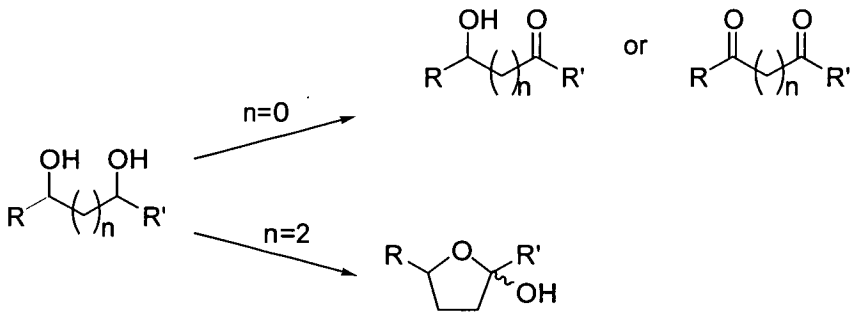


IBX

262

Interestingly the chemoselective oxidation of alcohols by IBX in the presence of thioethers and amines has been reported to occur in excellent yield (>89%).[118] However, for a clean reaction of the primary and secondary amine substrates to occur the amino functionalities must be protected as their TFA salts. It has also been observed that 1,2-diols can be oxidised to 1,2-ketol or 1,2-diketo derivatives without oxidative cleavage of the glycol C-C bond which occurs with DMP.[118] Corey[119] reported a novel route to the synthesis of γ-lactols *via* the IBX oxidation of 1,4-diols. DMSO not only serves as a solvent but as a catalytic base in this example, **scheme 105**.

Scheme 105

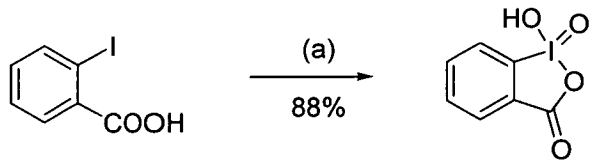


R, R'=H, Alkyl, Aryl, Hetereoaryl

Alcohols can also be converted to α,β-unsaturated carbonyl compounds directly by using an excess of IBX.[120] Recently the oxidative properties of polymer supported IBX have been reported producing carbonyl derivatives in high yield (>80%).[121]

IBX was prepared by Jenny Aird according to the procedure of Dess and Martin[115b] from *o*-Iodoxybenzoic acid, **scheme 106**.

Scheme 106



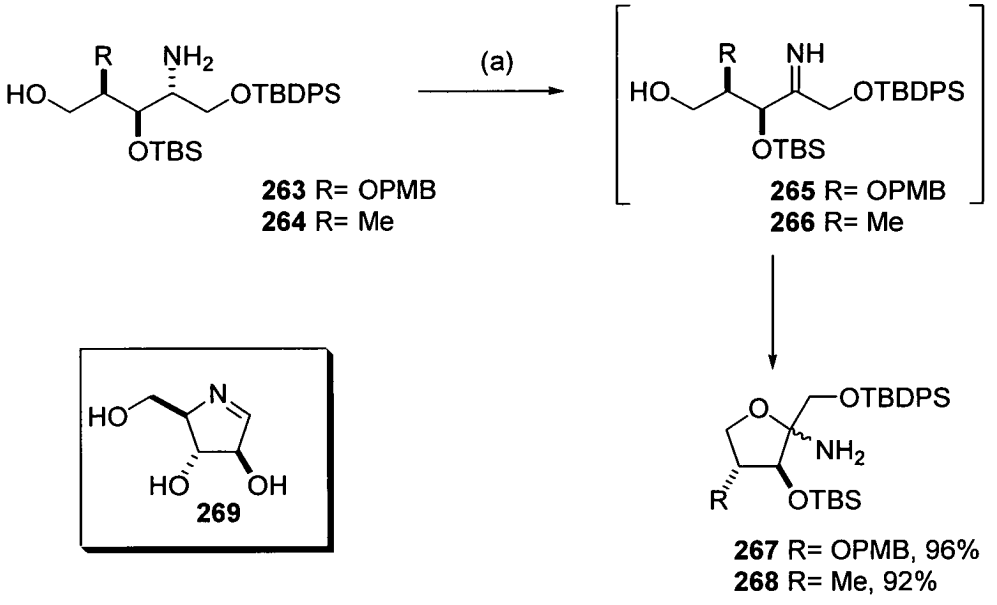
262

(a) $KBrO_3$, H_2SO_4 (0.7 *M*), 70 °C, 3.5 hours.

In the course of research pursued by Charlie Montgomery[122] towards the synthesis of the glycosidase inhibitor nectrisine **269**, an interesting cyclisation reaction was observed under IBX oxidation of amino alcohols **263** and **264**. Rather

than oxidation of the primary hydroxyl occurring, oxidation of the amine occurred to afford the cyclic sugars **267** and **268** as a 3:2 mixture of anomers, **scheme 107**.

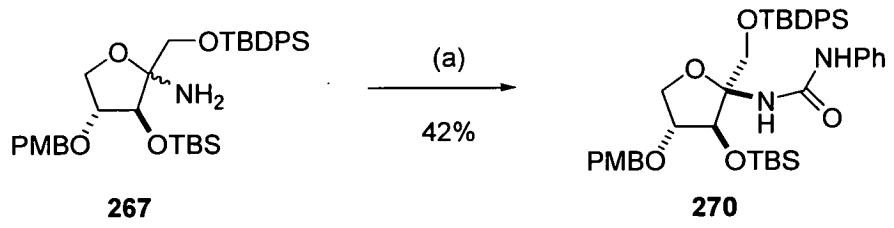
Scheme 107



(a) IBX, DMSO, THF.

Confirmation of the proposed structure **267** was determined by reacting the amine **267** with phenyl isocyanate, **scheme 108**.[123] A single urea **270** was isolated in pure form. Signals for the urea N*H* protons were visible in the ^{1}H NMR spectrum (at 7.71 and 5.17 ppm). Further evidence for the formation of urea **270** was obtained from HRMS ($C_{42}H_{57}N_2O_6Si_2$ requires 741.3755, found 741.3758). The stereochemical relationship at the anomeric position was assigned on the basis of NOE experiments.

Scheme 108



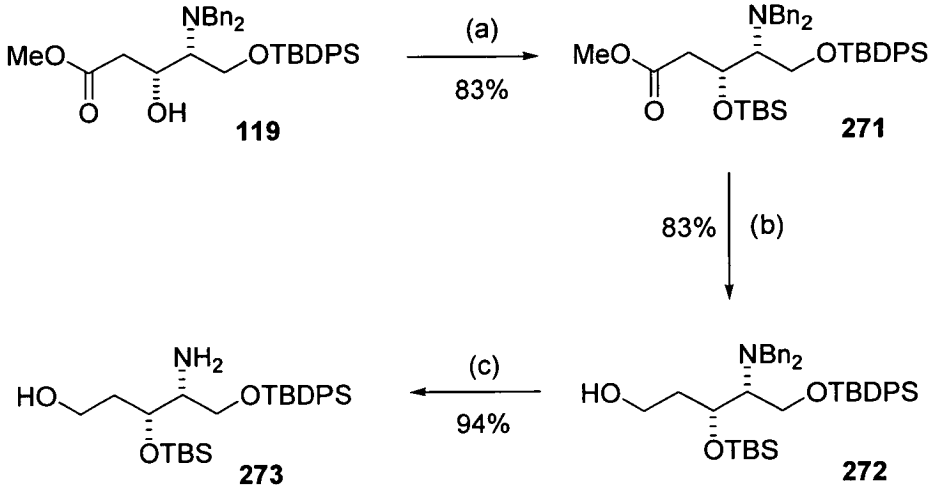
267 **270**

(a) PhNCO, THF.

5.2 IBX oxidation of amino alcohol 273

Further studies into this amine to imine oxidation were investigated in the related amino alcohol **273**. This was prepared in three steps from *β*-keto alcohol **119**. TBS protection, ester reduction and debenzylation afforded the amino alcohol in 65% overall yield.

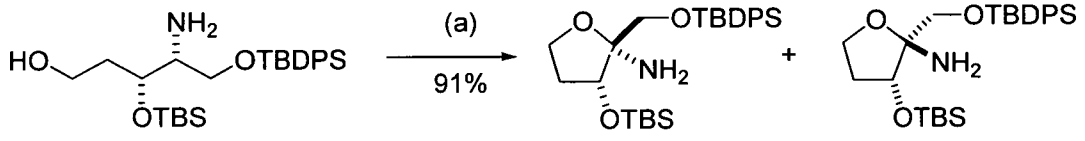
Scheme 109



(a)TBSOTF, 2,6-lutidine, DCM; (b) DIBAL-H, PhMe, -78 °C; (c) $Pd(OH)_2/C$, H_2, MeOH.

To a clear solution of one equivalent of IBX in DMSO was added a solution of **273** in THF. Work up after 15 minutes and chromatography suggested again the formation of **274** and **275** as a mixture of anomers, **scheme 110**.

Scheme 110

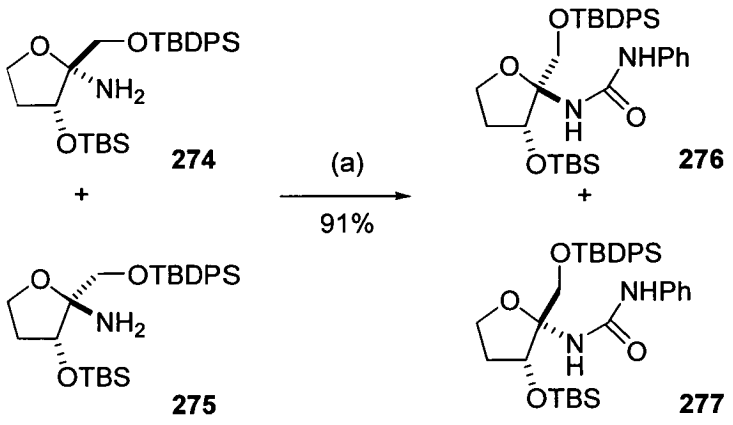


273 **274** **275**

(a) IBX, DMSO, THF.

The mixture of amines **274** and **275** was reacted with phenyl isocyanate to give a mixture of ureas **276** and **277**, **scheme 111**. For the mixture of diastereomers HRMS confirmed the formation of the urea and furthermore signals for the urea N*H* protons were visible in the ^{1}H NMR spectrum (at 7.93, 5.50, 5.00 ppm (4th signal under aromatic region)). For this less substituted tetrahydrofuran derivative, it appears that both isomers had reacted equally rapidly with the isocyanate. It is not clear whether steric hindrance due to additional ring substitution , or simply failure to identify the second urea (suggested by the 42% yield) gave rise to the isolation of a single diastereomer in the "nectrisine" system.

Scheme 111



(a) PhNCO, THF.

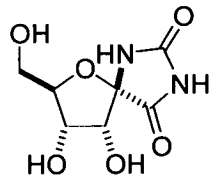
This novel cyclisation was of great interest to us as we felt that it would provide a route to the synthesis of analogues of hydantocidin **278** as well as a new route to the synthesis of amino sugars.

5.3 Hydantocidin

Hydantocidin **278** was isolated from the fermentation broth of *Streptomyces hygroscopias*[124] and exhibits potent herbicidal and plant growth regulatory activities. The mode of action is as a proherbicide of a metabolite that inhibits purine biosynthesis.[125] Its unique structure provides the first example of a nucleoside with a spirohydantoin nucleus attached at the anomeric position of *D*-ribofuranose. Due to its unusual structure and potent biological activity considerable synthetic work has been invested on the synthesis of hydantocidin and on various deoxyhydantocidins. Approaches to the synthesis of hydantocidin and its stereoisomers have been achieved utilising an aldol approach,[126] dihydroxylation[127] and stereoselective bromination[128] as the key steps. *D*-fructose[129] and *D*-ribose[130] have also been employed as precursors to hydantocidin and analogues. The synthesis of deoxyhydantocidin derivatives has also been undertaken.[131] Examples of analogues

of hydantocidin where the furanose ring has been replaced with a pyranose ring have also been reported.[132]

Figure 29



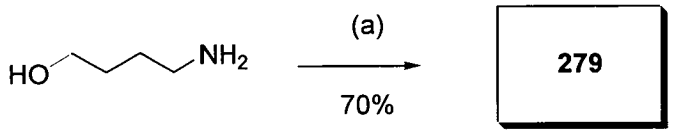
278

However although this compound was of synthetic interest to us we required additional evidence of this novel cyclisation. We believed that by studying the IBX oxidation of simpler systems the spectroscopic data would enable us to determine unambiguously the structure of the product.

5.4 IBX oxidation of 5-amino-pentanol

In combination with work carried out by H. M^{c}Elroy[133] the IBX oxidation of simple amino alcohols was investigated. 5-Amino-pentanol in THF was added to a clear solution of 1 equivalent of IBX in DMSO. After 20 minutes t.l.c. showed that the starting material had been consumed and a new spot had appeared, **scheme 112**.

Scheme 112



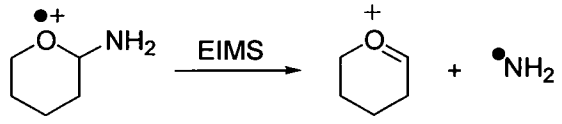
(a) IBX, DMSO, THF.

In an attempt to determine the structure of the product unequivocally the following spectroscopic techniques were used: ^{1}H NMR, ^{13}C DEPT, ^{1}H-^{13}C correlation NMR, ^{1}H-^{1}H-Cosy NMR, NOESY NOE difference experiments and EIMS.

5.4.1 Analysis of spectroscopic data

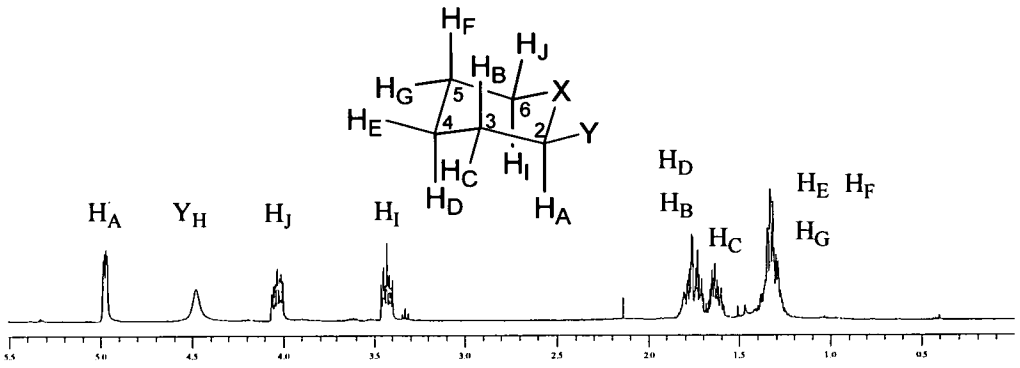
Low resolution EIMS shows the presence of M^{+} at 101 mass units (30%) which corresponds to the mass of **280** or **281**. However a peak at 85 mass units is apparent with an intensity of 28% which would correspond to the loss of the amino group, thus providing evidence for structure **280**, **scheme 113**.

Scheme 113



280 **283**

The data extracted from the 1D and 2D NMR for compound **279** is summarised in **table 18**. The combination of COSY and NOESY spectra enabled the ring protons to be assigned definitely. The 1D NOE experiments confirmed the couplings observed in the NOESY. Interestingly the expected NOE between H_I and H_D is missing. Only one of the expected exchangeable protons was apparent at 4.50 ppm. Irridiation of the signal at 4.98 ppm results in an enhancement of the signal at 9.20 ppm. This signal is characteristic of either an imine-like proton or an aldehyde proton. From the NMR data the only real conclusion which can be established is that a six membered ring has formed. The NMR data does not allow the unequivocal assignment of either of the two structures **280** or **281**, in fact the absence of the other exchangeable proton is suggestive of an alternative product having formed. In order to determine the structure of **279** further experiments were conducted.



6-ring in C_6D_6: 0-5.5ppm

Table 18

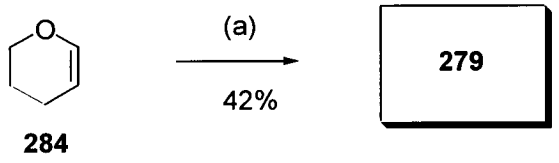
Proton/Carbon	Proton (360 MHz, C_6D_6) ppm	Carbon (90.6 MHz, $CDCl_3$) ppm	COSY (360 MHz, C_6D_6) ppm	NOESY (360 MHz, C_6D_6) ppm
H_A C(2)	**4.98**	**95**	**1.60** H_C **1.75** H_B **4.50** YH	**1.60** H_C **1.75** H_D **3.40** H_I **9.20**[a]
Exchangeable Proton (YH) C(2)	**4.50**	**95**	**4.98** H_A	
H_B C(3)	**1.75**	**32**	**1.60** H_C **4.98** H_A	**1.30** H_F **1.60** H_C
H_C C(3)	**1.60**	**32**	**1.75** H_B **4.98** H_A	**1.30** H_E **4.98** H_A
H_D C(4)	**1.75**	**20**	**1.30** H_E	**4.98** H_A
H_E C(4)	**1.30**	**20**	**1.30** H_D **1.60** H_C **1.75** H_B	**1.60** H_C
H_F C(5)	**1.30**	**25**	**3.40** H_I **4.00** H_J	**1.30** H_G **1.75** H_B **4.00** H_J
H_G C(5)	**1.30**	**25**	**3.40** H_I **4.00** H_J	**1.30** H_F
H_I C(6)	**3.40**	**65**	**1.30** H_G **1.30** H_F **4.00** H_J	**1.30** H_G **4.00** H_J **4.98** H_A
H_J C(6)	**4.00**	**65**	**1.30** H_F **3.40** H_I	**1.30** H_G **3.40** H_I

[a] NOE observed in 1D experiment

5.5 Formation of 2-aminotetrahydropyran *via* alternative strategy

Attempts to form a crystalline derivative of **279** such as the synthesis of acetyl, benzoyl and formyl derivatives proved unsuccessful. The synthesis of 2-aminotetrahydropyran **280** *via* an alternative route was envisaged as a method of determining the product from the IBX oxidation. Kabalka[134] has reported that organoboranes react with ammonium hydroxide in the presence of sodium hypochlorite to generate amines. The one pot procedure involves the formation of the organoborane *via* hydroboration, thus to a solution of dihydropyran **284** in THF was added BH_3•THF and the solution stirred at 0 °C for 2 hours, **scheme 114**. Aqueous ammonium hydroxide was added followed by sodium hypochlorite resulting in the *in situ* formation of chloramines[135] which reacted with the intermediate organoborane. T.l.c. showed the presence of several impurities but only one compound could be isolated (42% yield) and characterised.

Scheme 114



284

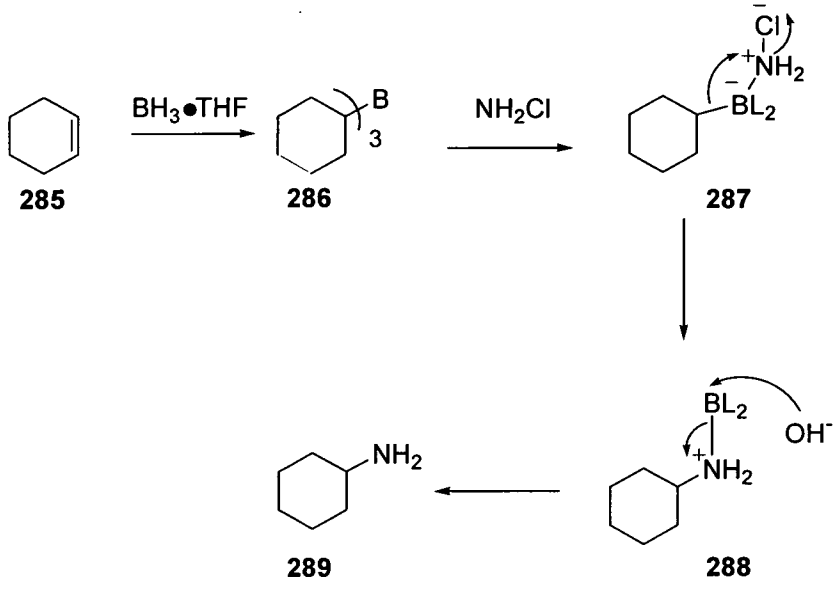
(a) (i) THF, BH_3•THF, 0 °C; (ii) NH_4OH, NaOCl, 0 °C →R.T..

5.5.1 Mechanism for hydroboration-amination reaction

Kabalka has proposed the following mechanism for the hydroboration-amination reaction as exemplified by the reaction of cyclohexene.[134,136] Hydroboration of cyclohexene **285** yields the intermediate trialkylborane **286**, **scheme 115**. The *in situ* formation of chloramine and attack on the trialkylborane gives intermediate **287**. Migration of the carbon boron bond to nitrogen with

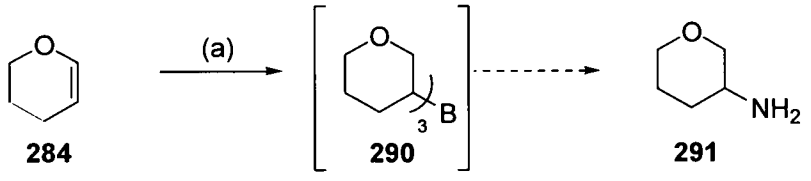
concomitant displacement of chloride yields **288**. Base hydrolysis results in cleavage of the nitrogen boron bond and formation of aminocyclohexane **289**.

Scheme 115



However, it is known that hydroboration of dihydropyran occurs to give the 3-substituted borane **290**[137], when the reaction mixture is stirred at r.t. for 4 hours. Thus it would be expected that reacting **284** with chloroamine would give the 3-aminotetrahydropyran **291**, **scheme 116**.

Scheme 116



(a) (i) BH_3•THF, THF; (ii) NH_2Cl, (iii) OH^-.

Comparison of the ^1H NMR and the ^{13}C DEPT with that for the product obtained from the IBX oxidation **279** showed the spectra to be identical, **table 19**. It

was therefore apparent that the two products were in fact the same and that an alternative product had formed from the two reactions.

Table 19

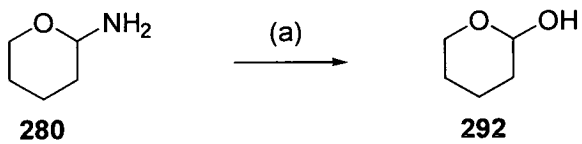
IBX oxidation product ^{13}C DEPT (62.9 MHz, $CDCl_3$) ppm	**Hydroboration product ^{13}C DEPT (62.9 MHz, $CDCl_3$) ppm**
94.9 (CH)	94.3 (CH)
64.2 (CH_2)	63.7 (CH_2)
32.3 (CH_2)	31.8 (CH_2)
25.7 (CH_2)	25.1 (CH_2)
20.8 (CH_2)	20.1 (CH_2)

5.6 Formation of tetrahydropyranol 292

The 2-aminotetrahydropyran might be expected to be significantly less stable towards conditions of acidic hydrolysis than the more complex tetrahydrofuran derivatives discussed earlier in this chapter, due to the lack of an oxygen functionality at the 3-position. This is known to stabilise 2-amino derivatives, such as those found in amino sugars, through internal hydrogen bonding.

It is likely that hydrolysis of the product from the IBX oxidation occurred on contact with silica gel generating tetrahydropyranol **292**.

Scheme 117



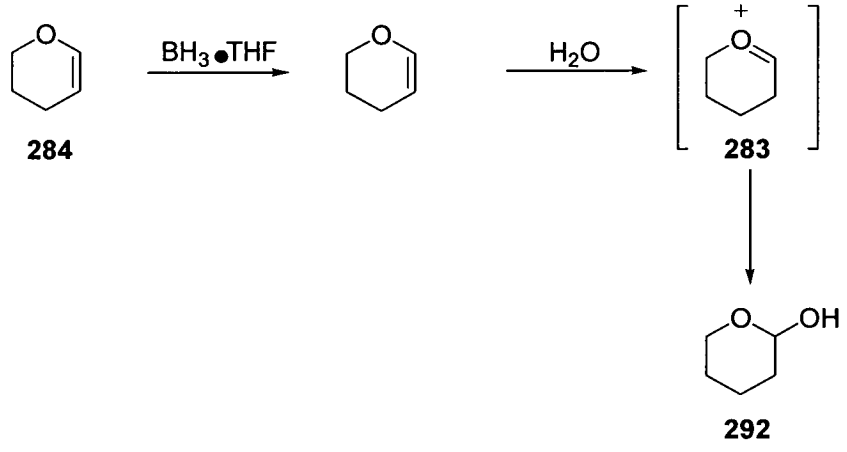
280 **292**

(a) SiO_2, H_2O.

The NMR data analysed also fits well for this product. From the NOESY data we observed only one exchangeable proton and not two as expected. EIMS data also contains a peak at 102 corresponding to the mass of **292**. Furthermore loss of the OH radical from the pyranol could also account for the peak observed at 85.

In the hydroboration reaction which was conducted at r.t. it is feasible that hydrolysis of the dihydropyran **284** occurred to give the tetrahydropyranol **292**. Instead of the desired hydroboration reaction the borane may have acted as a Lewis acid catalyst allowing the formation of oxonium intermediate **283** which would then react with water, **scheme 118**.

Scheme 118



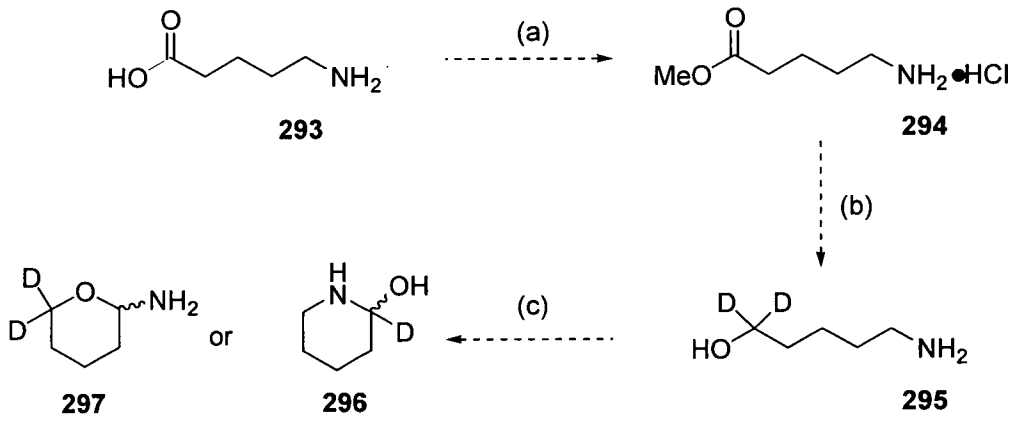
Further studies into the hydroboration-amination reaction are being pursued within the group.

5.7 Conclusion and future work

Although oxidation of 5-aminopentanol has most likely furnished the tetrahydropyranol, it does suggest that oxidation of the amine to imine has probably occurred followed by hydrolysis under storage/work-up conditions. In order to

confirm the product from the IBX oxidation the reaction could be followed by NMR or alternatively, a different method of purification of the product could be used. Further reactions using alternative substrates would also possibly confirm the mechanism of the IBX oxidation. The synthesis of a deuterium labelled structure would be one such route. Methylation of commercially available 5-amino valeric acid would yield the hydrochloride salt **294**. The salt could be freed up under basic conditions and subsequent treatment with lithium aluminium deuteride[138] would afford the amino alcohol **295**. Oxidation of **295** with IBX would furnish either **296** or **297**, **scheme 119**. ^{1}H NMR analysis and MS should be able to differentiate between the two structures or their hydrolysis products.

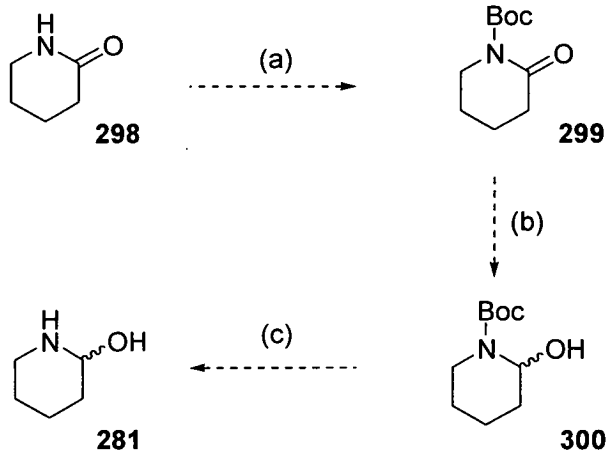
Scheme 119



(a) MeOH, AcCl, 80 °C; (b) (i) $NaHCO_3$; (ii) $LiAlHD_4$, Et_2O; (c) IBX, DMSO, THF.

An alternative strategy would be to synthesise **281** from *δ*-Valerolactone *via* a three-step synthesis. *N*-Boc protection followed by superhydride reduction according to Dieter's[139] protocol would afford the known compound **300**, **scheme 120**. Boc deprotection would furnish **281** and therefore enable a comparison of ^{1}H NMR's and thus provide more evidence for the presence of the structure.

Scheme 120



(a) Boc_2O, Et_2O, DMAP, DCM; (b) $LiEt_3BH$, THF, -78 °C; (c) 3M HCl, EtOAc.

In summary in order to realise the full potential of this reaction, which would offer a new route to the synthesis of amino sugars and a possible route to the synthesis of analogues of hydantocidin, further study is required.

Chapter 6: Experimental

6.1 General experimental

^{1}H nuclear magnetic resonance (NMR) spectra were recorded using an internal deuterium lock for the indicated reference at ambient probe temperatures on Varian Gemini 200 (200 MHz) and a Bruker AM260 (260 MHz) Fourier transform instruments. The data is presented as follows: chemical shift (in ppm on the δ scale relative to δ_{TMS} =0), integration, multiplicity (s= singlet, d= doublet, t= triplet, q= quartet, qn= quintet, m= multiplet, br= broad), coupling constant and the interpretation. ^{13}C NMR spectra were recorded using an internal deuterium lock for the indicated reference at ambient probe temperatures on Varian Gemini 200 (50.3 MHz) and Bruker AM260 (62.9 MHz) Fourier transform instruments and are reported in ppm on the δ scale.

Infra-red spectra were recorded on a Perkin Elmer Paragon 1000 FT-IR instrument using 5 mm sodium chloride plates or 0.1 mm sodium chloride solution cells. The wavelengths of maximum absorbance (ν_{max}) are quoted in cm^{-1}.

Fast atom bombardment (FAB) mass spectra were performed on a Kratos MS50TC mass spectrometer. Electron impact (EI) mass spectra were performed on a Finnigan 4500 mass spectrometer. The parent ion or relevant fragment are quoted, followed by significant fragments and their relative intensities.

Optical rotations were measured on an AA-1000 polarimeter with a path length of 1.0 dm at the sodium D line (589 nm) and are reported as follows:$[\alpha]_D$, concentration (c in g/100 cm^3), and solvent. All optical rotations were measured at a temperature of 23°C.

Elemental analysis was carried out on a Perkin Elmer 2400 CHN Elemental analyser.

T.L.C. was performed on Merck 60F_{254} (0.25mm) glass backed silica plates and visualised by ultraviolet (UV) light and/or ammonium molybdate or potassium permanganate stain.[ϕ] Flash column chromatography was carried out on Merck

[ϕ] Ammonium molybdate dip prepared as follows: to water (950 cm^3) was added concentrated sulphuric acid (50 cm^3) followed by ammonium molybdate (50 g) and ceric sulfate (3 g). The mixture was stirred until all solid material had disappeared and a bright yellow solution remained.

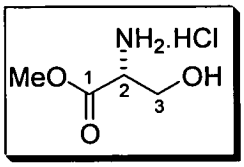
Kieselgel 60 (Merck 9385) under positive pressure by means of a hand pump or air flow. Eluent compositions are quoted as v/v ratios. High performance liquid chromatography (HPLC) was carried out on a Gilson instrument using a Spherisorb column (internal diamaeter:20 mm) and equipped with a Gilson refractive index detector. A standard flow of 7 cm^3/min was used. Chiral HPLC was carried out on a Waters 786 instrument with a Chiralcel OD column (internal diameter 4.6mm) equipped with a UV detector. A standard flow of 0.5 cm^3/min was used. All HPLC samples were filtered through 45 μm nylon syringe filters prior to analysis. All solvents used for HPLC analysis were vacuum filtered and degassed prior to use.

Reagents were purified by standard means. Dichloromethane (DCM), dimethylformamide (DMF), triethylamine, pyridine and 2,6-lutidine were distilled from calcium hydride and stored over calcium hydride under an argon atmosphere. Methyl and ethyl acetate was distilled over potassium carbonate and stored over 4Å sieves. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl and stored under an argon atmosphere. All other reagents were used as supplied.

All experiments were performed in an inert atmosphere of argon under anhydrous conditions using oven dried apparatus cooled in a desiccator prior to use. Standard techniques for the handling of air-sensitive techniques were employed.

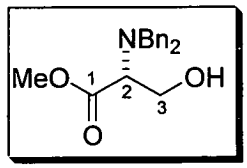
Potassim permanagante dip prepared as follows: to water (1000 cm^3) was added potassium permanganate (10 g), potassium carbonate (50 g) and sodium hydroxide pellets (40). The mixture was stirred until all solid material disappeared and a purple solution remained.

Methyl (2*R*)-2-amino-3-hydroxypropanoate•hydrochloride 107



Acetyl chloride (56.1 g, 50.8 cm^3, 0.710 mol) was added dropwise to methanol (300 cm^3) at 0 °C. The mixture was stirred for 15 mins and *D*-serine (25.0 g, 0.236 mol) was then added portionwise to the solution. The resulting mixture was heated to reflux and held at reflux for 3 hours. Concentration under reduced pressure provided the title compound (36.3 g, 98%) as a solid. Recrystallisation from methanol provided an analytical sample, mp 163-165 °C; $[\alpha]_D$ –9.0 (*c* 0.66, MeOH) [lit., (Aldrich) mp 163-166 °C, $[\alpha]_D$ –4.0 (*c* 4.0, EtOH)]; ν_{max} (solution cell, $CHCl_3$)/cm^{-1} 3345, 2921, 1747, 1593, 1513, 1471; δ_H (250 MHz, D_2O) 4.13 (1H, t, *J* 4.0, C_2H), 3.94 (1H, dd, *J* 12.3, 4.0, $C_3H_AH_B$), 3.87 (1H, dd, *J* 12.3, 3.6, $C_3H_AH_B$) 3.70 (3H, s, O*Me*); δ_C (62.9 MHz) 173.9 (C), 58.8 (CH_3), 54.3 (CH_2), 53.3 (CH); m/z (FAB) 120 ($[M+H]^+$, 100%), 60 (55), 45 (27); HRMS (FAB) $C_4H_9NO_3$•HCl $[M+H]^+$ requires 120.0661, found 120.0661; Found: C, 30.42; H, 6.33; N, 8.87. $C_4H_9NO_3$•HCl requires C, 30.87; H, 6.43; N, 9.00%.

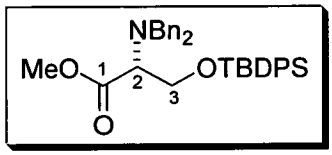
Methyl (2*R*)-2-*N*,*N*-dibenzylamino-3-hydroxyproponoate 108



To a solution of the *D*-serine methyl ester•hydrochloride **107** (6.80 g, 43.7 mmol) in anhydrous acetonitrile (190 cm^3) was anhydrous potassium carbonate (29.0 g, 210 mmol) followed by benzyl bromide (13.5 cm^3, 110 mmol). The mixture was stirred at room temperature for 24 hours. Water (200 cm^3) was added and the aqueous phase was extracted with EtOAc (3 × 125 cm^3). The combined organic phases were washed

with brine (100 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (4:1)] to give the title compound (12.5 g, 96%) as an oil. R_f [hexane:EtOAc (4:1)] 0.35; $[\alpha]_D$ +174.6 (*c* 0.8, $CHCl_3$)]; ν_{max} (neat)/cm^{-1} 3455, 3061, 3028, 2950, 2844, 1731, 1491, 1453; δ_H (250 MHz, $CDCl_3$) 7.39-7.21 (10H, m, Ar*H*), 3.92 (2H, d, *J* 13.4, $NCH_XH_YPh \times 2$), 3.80 (3H, s, O*Me*), 3.80-3.69 (2H, m, C_2H + $C_3H_AH_BOH$), 3.69 (2H, d, *J* 13.4, $NCH_XH_YPh \times 2$), 3.59 (1H, dd, *J* 15.0, 7.5, $C_3H_AH_BOH$), 2.58 (1H, br s, O*H*); δ_C (62.9 MHz) 171.1 (C), 138.6 (2C), 128.9 (4 × CH), 128.4 (4 × CH), 127.3 (2 × CH), 61.6 (CH_3), 59.2 (CH_2) 54.6 (2 × CH_2), 51.2 (CH); m/z (FAB) 299 ($[M]^+$, 59%), 268 (100), 240 (96), 181 (41), 92 (41); HRMS (FAB) $C_{18}H_{21}NO_3$ $[M]^+$ requires 299.1571, found 299.1576.

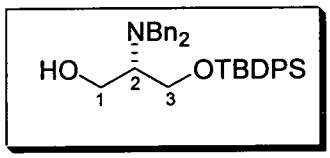
Methyl (2*R*)-3-*tert*-butyldiphenylsilyloxy-2-*N*,*N*-dibenzylaminoproponoate 109



To a solution of ester **108** (9.25 g, 30.1 mmol) in anhydrous DMF (50 cm^3) was added *tert*-butyldiphenylsilylchloride (16.4 cm^3, 60.3 mmol) followed by imidazole (8.20 g, 121 mmol). The mixture was stirred at room temperature for 24 hours. Brine (200 cm^3) was added and the aqueous phase was extracted with EtOAc (3 × 150 cm^3). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (15:1)] to give the title compound (15.0 g, 96%) as an oil. R_f [hexane:EtOAc (4:1)] 0.64; $[\alpha]_D$ +29.0 (*c* 0.9, $CDCl_3$); ν_{max} (neat)/cm^{-1} 3069, 3027, 2856, 1736, 1588, 1428; δ_H (250 MHz, $CDCl_3$) 7.62-7.22 (20H, m, Ar*H*), 4.06 (1H, dd, *J* 10.2, 6.2, $C_3H_AH_BOTBDPS$), 4.03 (2H, d, *J* 14.3, $NCH_XH_YPh \times 2$), 4.00 (1H, dd, *J* 10.2, 6.2, $C_3H_AH_BOTBDPS$), 3.77 (2H, d, *J* 14.3, $NCH_XH_YPh \times 2$), 3.76 (3H, s, O*Me*), 3.70 (1H, t, *J* 6.2, C_2H), 1.05 (9H, s, ^tBu); δ_C (62.9 MHz) 171.8 (C) 139.6

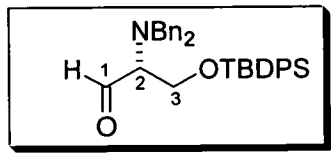
(2C), 135.4 (4 × CH), 132.9 (2C), 129.5 (2 × CH), 128.5 (4 × CH), 128.0 (4 × CH), 127.5 (4 × CH), 126.8 (2 × CH), 63.2 (CH_2), 62.8 (CH), 55.3 (2 × CH_2), 51.0 (CH_3) 26.5 (3 × CH_3), 18.9 (C); m/z (FAB) 538 ($[M+H]^+$, 14%), 478 (13), 268 (18), 135 (26), 91 (100); HRMS (FAB) $C_{34}H_{40}NO_3Si$ $[M+H]^+$ requires 538.2777, found 538.2773.

(2*S*)-3-*tert*-Butyldiphenylsilyloxy-2-*N*,*N*-dibenzylaminopropan-1-ol 110



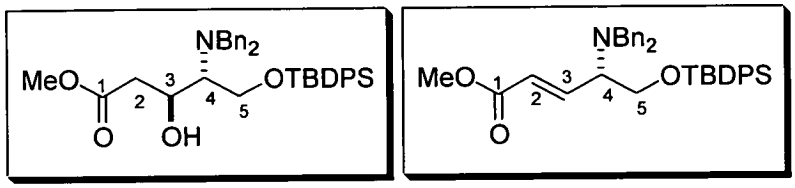
To a solution of ester **109** (4.20 g, 7.82 mmol), in anhydrous ether (60 cm^3) at 0 °C was added lithium borohydride (0.99 g, 49.9 mmol) followed by anhydrous methanol (1 cm^3). The mixture was stirred at 0 °C until effervescence ceased and then heated to reflux and held at reflux for 4 hours. Saturated aqueous NH_4Cl (140 cm^3) was added cautiously and the aqueous phase was extracted with DCM (3 × 100 cm^3). The combined organic phases were washed with brine (200 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (5:1)] to give the title compound (3.80 g, 95%) as an oil. R_f [(hexane:EtOAc (4:1)] 0.55; $[\alpha]_D$ –58.4 (*c* 1.15, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3449, 3069, 3027, 2930, 2857, 1589; δ_H (250 MHz, $CDCl_3$) 7.72-7.22 (20H, m, Ar*H*), 3.90 (1H, dd, *J* 10.7, 6.0, $C_3H_AH_BOTBDPS$), 3.88 (2H, d, *J* 13.4, NCH_XH_YPh × 2), 3.75 (1H, dd, *J* 10.7, 6.0, $C_3H_AH_BOTBDPS$), 3.61 (2H, d, *J* 13.4, NCH_XH_YPh × 2), 3.58 (2H, d, *J* 7.4, C_1H_2), 3.10 (1H, ddd, *J* 7.4, 6.0, 6.0, C_2H), 2.92 (1H, brs, O*H*), 1.10 (9H, s, ^tBu); δ_C (62.9 MHz) 139.9 (2C), 136.1 (CH), 136.0 (CH), 133.5 (CH), 133.4 (CH), 130.5 (C), 130.3 (C), 130.2 (2 × CH), 129.4 (4 × CH), 128.9 (4 × CH), 128.3 (4 × CH), 127.6 (2 × CH), 61.8 (CH_2), 60.5 (CH), 60.0 (CH_2), 54.5 (2 × CH_2), 27.3 (3 × CH_3), 19.6 (C); m/z (FAB) 510 ($[M+H]^+$, 61%), 420 (37), 217 (43), 199 (28), 91 (100); HRMS (FAB) $C_{33}H_{40}NO_2Si$ $[M+H]^+$ requires 510.2828, found 510.2828.

(2*R*)-3-*tert*-Butyldiphenylsilyloxy-2-*N*,*N*-dibenzylaminopropanal 93



To a solution of oxalyl chloride (0.25 cm^3, 4.13 mmol) in DCM (10 cm^3) at –78 °C was added DMSO (0.51 cm^3, 4.13 mmol). The mixture was stirred for ca. 5 minutes whereupon it became cloudy. A solution of the alcohol **110** (1.50 g, 2.94 mmol) in DCM (5 cm^3) was added *via* cannula. The resulting clear solution was stirred at –78 °C for 1 hour. Triethylamine (1.72 cm^3, 11.8 mmol) was added and the cloudy solution was allowed to warm to room temperature over ca. 15 minutes. Water (25 cm^3) was added and the aqueous phase was extracted with DCM (3 × 25 cm^3). The combined organic phases were washed sequentially with 1% HCl (30 cm^3), water (30 cm^3), saturated aqueous $NaHCO_3$ (30 cm^3) and brine (30 cm^3), then dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound (1.49 g, 100%) as a very pale yellow oil which was used in subsequent stages without further purification. R_f [hexane:EtOAc (4:1)] 0.56; ν_{max} (neat)/cm^{-1} 3068, 3028, 2930, 2856, 2711, 1731, 1427; δ_H (200 MHz, $CDCl_3$) 9.80 (1H, s, CO*H*), 7.76-7.26 (20H, m, Ar*H*), 4.16 (1H, dd, *J* 11.0, 5.7, $C_3H_AH_B$OTBDPS), 4.09 (1H, dd, *J* 11.0, 5.7, $C_3H_AH_B$OTBDPS), 3.98 (2H, d, *J* 13.9, NCH_XH_YPh × 2), 3.90 (2H, d, *J* 13.9, NCH_XH_YPh × 2), 3.52 (1H, t, *J* 5.7, C_2H), δ_C (50.3 MHz) 202.8 (C), 139.3 (2C), 135.6 (2 × CH), 135.5 (2 × CH), 132.8 (CH), 132.7 (CH), 129.8 (2 × CH), 128.6 (4 × CH), 128.3 (4 × CH), 127.7 (4 × CH), 127.1 (2C), 67.8 (CH_2), 60.5 (CH), 55.6 (2 × CH_2), 26.7 (3 × CH_3), 19.9 (C).

Methyl (3*S*,4*R*)-5-*tert*-butyldiphenylsilyloxy-4-*N*,*N*-dibenzylamino-3-hydroxypentanoate 118 and Methyl (2*E*,4*S*)-5-*tert*-butyldiphenylsilyloxy-4-*N*,*N*-dibenzylamino-2-pentenoate 120

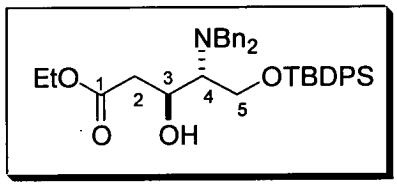


To a solution of LiHMDS (1.77 cm^3, 1.06 *M* in THF, 1.88 mmol) at –78 °C was added methyl acetate (0.150 cm^3, 1.77 mmol). The solution was stirred at –78 °C for 20 minutes. A solution of the aldehyde **93** (300 mg, 0.589 mmol) in THF (2 cm^3) was added dropwise *via* cannula. The reaction mixture was stirred at –78 °C for 30 minutes then allowed to warm to 0 °C over a period of 2 hours then stirred at 0 °C for 20 minutes. Saturated aqueous NH_4Cl (25 cm^3) was added and the aqueous phase extracted with DCM (3 × 15 cm^3). The combined organic phases were washed with brine (30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:Et_2O (5:1) to give **118** (160 mg, 47%) and **120** (170 mg, 51%).

Data for compound **118**: R_f [hexane:Et_2O (1:1)] 0.52; $[\alpha]_D$ –36.4 (*c* 0.85, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3460, 2930, 1738, 1427; δ_H (250 MHz, $CDCl_3$) 7.79-7.22 (20H, m, Ar*H*), 4.22 (1H, m, C_3HOH), 4.02 (1H, dd, *J* 11.2, 5.5, $CH_AH_BOTBDPS$), 3.93 (1H, dd, *J* 11.2, 5.2, $CH_AH_BOTBDPS$), 3.82 (2H, d, *J* 13.5, NCH_XH_YPh × 2), 3.60 (2H, d, *J* 13.5, NCH_XH_YPh × 2), 3.59 (3H, s, O*Me*), 3.20 (1H, br s, O*H*), 2.85 (1H, dd, *J* 16.1, 2.2, $C_2H_CH_D$), 2.61 (1H, m, C_4H), 2.13 (1H, dd, *J* 16.1, 9.5, $C_2H_CH_D$), 1.02 (9H, s, *^{t}Bu*); δ_C (62.9 MHz) 172.2 (C), 138.8 (2C), 135.6 (CH), 135.5 (CH), 132.7 (C), 132.6 (C), 129.9 (2 × CH), 129.8 (2 × CH), 128.9 (4 × CH), 128.3 (4 × CH), 127.7 (4 × CH), 127.1 (2 × CH), 65.2 (CH_3), 62.7 (CH), 60.0 (CH_2), 54.3 (2 × CH_2), 51.5 (CH), 39.3 (CH_2), 26.8 (3 × CH_3), 19.0 (C); m/z (FAB) 582 ($[M+H]^+$, 7%), 564 (17), 217 (43), 199 (10), 135 (16), 109 (21), 91 (100); HRMS (FAB) $C_{36}H_{44}NO_4Si$ $[M+H^+]$ requires 582.3040, found 582.3043.

Data for **120**: R_f [hexane:Et_2O (1:1)] 0.70; $[\alpha]_D$ +50.1 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1724, 1652, 1600, 1566, 1492; δ_H (250 MHz, $CDCl_3$) 7.78-7.22 (20H, m, Ar*H*), 7.13 (1H, dd, *J* 15.8, 7.0, C_2H), 6.10 (1H, dd, *J* 15.8, 1.3, C_3H), 4.00 (1H, dd, *J* 10.4, 6.3, $C_5H_AH_B$OTBDPS), 3.89 (1H, dd, *J* 10.4, 7.0, $C_5H_AH_B$OTBDPS), 3.87 (2H, d, *J* 13.3, $NCH_XH_YPh \times 2$), 3.80 (3H, s, O*Me*), 3.61 (2H, d, *J* 13.3, $NCH_XH_YPh \times 2$), 3.56 (1H, m, C_4H), 1.08 (9H, s, *t-Bu*); δ_C (62.9 MHz) 166.6 (C), 146.0 (CH), 139.5 (2C), 135.5 (4 × CH), 134.7 (CH), 133.0 (C), 132.9 (C), 129.6 (2 × CH), 129.5 (CH), 128.3 (2 × CH), 128.2 (4 × CH), 127.6 (4 × CH), 126.8 (2 × CH), 123.4 (CH), 63.7 (CH_2), 60.3 (CH), 54.4 (2 × CH_2), 26.7 (3 × CH_3), 26.4 (CH_3), 19.0 (C); m/z (FAB) 564 ($[M+H]^+$, 91%), 474 (23), 294 (40), 217 (12), 204 (12), 199 (35), 183 (12), 135 (60), 91 (100); HRMS (FAB) $C_{36}H_{42}NO_3Si$ $[M+H]^+$ requires 564.2929, found 564.2934.

Ethyl (3*S*,4*R*)-5-*tert*-butyldiphenylsilyloxy-4 *N*,*N*-dibenzylamino-3 hydroxypentanoate 121



To a solution of LiHMDS (8.84 cm^3, 1.06 *M* in THF, 9.37 mmol) at –78 °C was added ethyl acetate (0.871 cm^3, 8.84 mmol). The solution was stirred at –78 °C for 20 minutes. A solution of the aldehyde **93** (1.49 g, 2.94 mmol) in THF (6 cm^3) was added dropwise *via* cannula. The reaction mixture was stirred at –78 °C for 30 minutes then allowed to warm to 0 °C over a period of 2 hours, then stirred at 0 °C for 20 minutes. Saturated aqueous NH_4Cl (50 cm^3) was added and the aqueous phase extracted with DCM (3 × 60 cm^3). The combined organic phases were washed with brine (60 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:Et_2O (6:1) to give the title compound (1.48 g, 85%) as a 6:1 mixture of diastereomers. $[\alpha]_D$ –26.9 (*c* 0.52,

$CHCl_3$); ν_{max} (neat)/cm^{-1} 3469, 2930, 1736, 1720, 1427; m/z (FAB) 538 ($[M+H]^+$, 14%), 478 (13), 268 (18), 135 (26), 91 (100); HRMS (FAB) $C_{37}H_{46}NO_4Si$ $[M+H]^+$ requires 596.3196, found 596.3192.

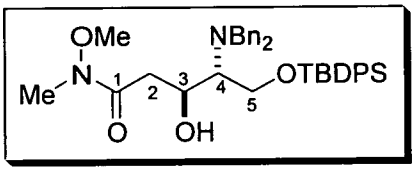
Major diastereomer:

R_f [hexane:Et_2O (1:1)] 0.40; δ_H (250 MHz, $CDCl_3$) 7.76-7.19 (20H, m, Ar*H*), 4.39 (1H, m, C_3*H*OH), 4.25 (2H, q, *J* 7.2, OC*H*$_2$CH$_3$), 4.23-4.17 (1H, m, $C_5H_AH_B$OTBDPS), 4.07 (1H, dd, *J* 10.6, 5.3, $C_5H_AH_B$OTBDPS), 3.89 (2H, d, *J* 13.6, NCH_XH_YPh × 2), 3.58 (2H, d, *J* 13.6, NCH_XH_YPh × 2), 3.45 (1H, br s, O*H*), 2.98 (1H, dd, *J* 16.3, 2.7, $C_2H_CH_D$), 2.78 (1H, br ddd, *J* 10.6, 8.7, 5.3, C_4*H*), 2.31 (1H, dd, *J* 16.3, 8.7, $C_2H_CH_D$), 1.28 (3H, t, *J* 7.2, OCH$_2$C*H*$_3$), 1.09 (9H, s, ^{t}*Bu*); δ_C (62.9 MHz) 173.0 (C), 139.6 (2C), 135.6 (4 × CH), 132.8 (C), 132.7 (C), 128.9 (2 × CH), 128.7 (4 × CH), 128.2 (4 × CH), 127.7 (4 × CH), 126.9 (2 × CH), 68.1 (CH), 61.2 (CH), 60.9 (CH_2), 60.4 (CH_2), 55.1 (CH_2), 50.0 (CH_2), 39.5 (CH_2), 26.8 (CH_3), 19.0 (C), 14.1 (3 × CH_3); HPLC (5% propan-2-ol in hexane) **121** R_t=9.0 min, ***ent*-121** R_t=8.3 min, 90% ee.

Minor diastereomer:

R_f [hexane:Et_2O (1:1)] 0.38; δ_H (250 MHz, $CDCl_3$) in good agreement with that reported for **122**.

(3*S*,4*R*)-5-*tert*-butyldiphenylsilyoxy-4-*N*,*N*-dibenzylamino-3-hydroxypentanoic acid methoxy methyl amide 91



To a slurry of *N*,*O*-dimethylhydroxylamine•hydrochloride (494 mg, 5.04 mmol) in THF (3 cm^3) at 0 °C was added trimethylaluminium (2.52 cm^3, 2.0 *M* in toluene, 5.04

mmol). The solution was stirred at 0 °C for 5 minutes then allowed to warm to room temperature over ca. 15 minutes, after which time a clear solution remained. The 6:1 mixture of aldol adducts **121** (500 mg, 0.839 mmol) in THF (4 cm^3) was added dropwise *via* cannula. The mixture was warmed to 35 °C and stirred for 3 hours. The reaction mixture was cooled and then cannulated rapidly into a mixture of DCM (30 cm^3) and saturated aqueous potassium sodium tartrate (30 cm^3) and stirred vigorously for 5 hours whereupon two distinct phases were apparent. The aqueous phase was extracted with DCM (3 × 30 cm^3). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:EtOAc (4:1) to give the title compound (506 mg, 98%) as a 6:1 mixture of diastreomers $[\alpha]_D$ –13.0 (*c* 0.10, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3457, 3069, 2937, 2856, 1643, 1427; m/z (FAB) 611 ($[M+H]^+$, 27%), 478 (36), 210 (11) 197 (20) 135 (41), 91 (100); HRMS (FAB) $C_{37}H_{47}N_2O_4Si$ $[M+H]^+$ requires 611.3305, found 611.3290.

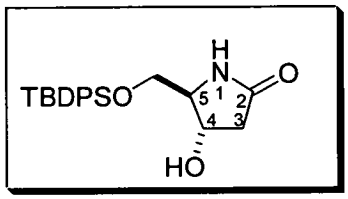
Major diastereomer:

R_f [hexane:EtOAc (4:1)] 0.35; δ_H (360 MHz, $CDCl_3$) 7.83-7.24 (20H, m, Ar*H*), 4.39-4.32 (1H, m, C_3HOH), 4.27 (1H, dd, *J* 10.9, 4.0, $C_5H_AH_B$OTBDPS), 4.14 (1H, dd *J* 10.9, 6.4, $C_5H_AH_B$OTBDPS), 3.99 (2H, d, *J* 13.7, NCH_XH_YPh × 2), 3.80 (2H, d, *J* 13.7, NCH_XH_YPh × 2), 3.66 (3H, s, O*Me*), 3.21 (3H, s, *Me*), 2.89 (1H, m, C_4H), 2.80 (1H, br m, $C_2H_AH_B$), 2.32 (1H, br m, $C_2H_AH_B$), 1.18 (9H, s, *^{t}Bu*); δ_C (62.9 MHz) 174.8 (C), 140.7 (2C), 136.3 (2 × CH), 136.2 (2 × CH), 133.8 (C), 133.6 (C), 130.2 (2 × CH), 129.6 (2 × CH), 129.4 (4 × CH), 128.6 (4 × CH), 128.3 (2 × CH), 128.2 (CH), 127.3 (CH), 67.6 (CH), 66.6 (CH_3), 62.2 (CH), 61.7 (CH_2), 55.7 (2 × CH_2), 37.1 (CH_2), 32.3 (CH_3), 27.4 (3 × CH_3), 19.6 (C).

Minor diasteromer:

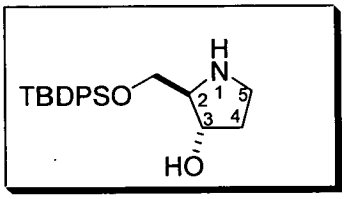
R_f [hexane:EtOAc (4:1)] 0.34; δ_H (360 MHz, $CDCl_3$) in good agreement with that reported for **123**.

(4*S*,5*R*)-5-*tert*-Butyldiphenylsilyloxymethyl-4-hydroxypyrrolidin-2-one 90



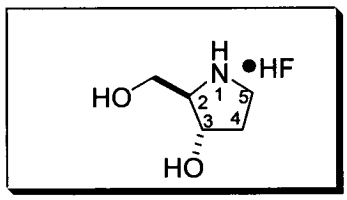
To a solution of the 6:1 mixture of Weinreb amides **91** (450 mg, 0.74 mmol) in methanol was added 20% $Pd(OH)_2/C$ (450 mg), the flask was flushed with argon before being stirred under an atmosphere of hydrogen for 12 hours. The reaction mixture was filtered through a layer of celite and concentrated under reduced pressure. The residue was chromatographed on silica gel [DCM:MeOH (50:1) to give the title compound (206 mg, 81%) as a white solid. mp 117-118 °C; R_f [DCM:MeOH (10:1)] 0.32; $[\alpha]_D$ +17.2 (*c* 0.36, $CHCl_3$); ν_{max} (solution cell)/cm^{-1} 3200, 2910, 1678, 1426; δ_H (250 MHz, $CDCl_3$) 7.64-7.59 (4H, m, Ar*H*), 7.43-7.32 (6H, m, Ar*H*), 6.40 (1H, s, N*H*), 4.30-4.28 (1H, m, C_4HOH), 3.63-3.60 (4H, m, C_3H_2 + C_5H + O*H*), 2.74 (1H, dd, *J* 17.2, 6.8, $C_5H_AH_B$OTBDPS), 2.30 (1H, dd, *J* 17.2, 2.9, $C_5H_AH_B$OTBDPS), 1.00 (9H, s, ^tBu); δ_C (62.9 MHz) 176.4 (C), 135.4 (2 × CH), 135.3 (2 × CH), 132.6 (C), 132.4 (C), 129.8 (2 × CH), 127.7 (4 × CH), 69.5 (CH), 64.7 (CH_2), 64.5 (CH), 40.0 (CH_2), 26.6 (3 × CH_3), 18.9 (C); m/z (FAB) 370 ($[M+H]^+$, 68%), 312 (15), 292 (53), 234 (27), 214 (61), 135 (100); HRMS (FAB) $C_{21}H_{28}NO_3Si$ $[M+H]^+$ requires 370.1838, found 370.1830.

(2*R*,3*S*)-2-*tert*-Butyldiphenylsilyloxymethyl-3-hydroxypyrrolidine 125



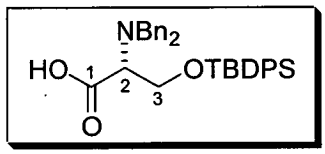
To a solution of pyrrolidinone **90** (120 mg, 0.332 mmol) in THF (5 cm^3) at 0 °C was added BH_3•THF complex (4.95 cm^3, 1.0 *M* in THF, 4.95 mmol). The solution was stirred at 0 °C until effervescence ceased and then stirred at reflux for 24 hours. Methanol was added cautiously to the cooled (0 °C) reaction mixture. The resulting mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel [DCM:MeOH (50:1)] to give the title compound (100 mg, 85%) as a white solid. mp 105-106 °C; R_f [DCM: MeOH (10:1)] 0.27; $[\alpha]_D$ +33.3 (*c* 0.09, $CHCl_3$); (90% ee); δ_H (250 MHz, $CDCl_3$) 7.65-7.61 (4H, m, Ar*H*), 7.50-7.37 (6H, m, Ar*H*), 4.35 (1H, ddd, *J* 11.0, 7.4, 4.3 C_3HOH), 4.19 (1H, dd, *J* 11.1, 3.0 $CH_AH_BOTBDPS$), 3.80 (1H, dd, *J* 11.1, 2.4 $CH_AH_BOTBDPS$), 3.37 (1H, ddd, *J* 11.7, 8.0, 7.4, $C_5H_EH_F$), 3.21 (1H, ddd, *J* 11.7, 9.4, 4.3, $C_5H_EH_F$) 2.94 (1H, ddd, *J* 11.0, 3.0, 2.4 C_2H), 2.14 (1H, ddt, *J* 16.2, 9.4, 7.4, $C_4H_CH_D$), 1.99 (1H, ddt, *J* 16.2, 8.0, 4.3, $C_4H_CH_D$), 1.74 (1H, br s, O*H*), 1.06 (9H, s, ^tBu) ; δ_C (62.9 MHz) 135.4 (4 × CH), 132.2 (CH), 131.8 (C), 130.1 (2 × CH), 127.9 (4 × CH), 74.0 (CH), 73.1 (CH), 59.5 (CH_2), 53.0 (CH_2), 34.1 (CH_2), 26.8 (3 × CH_3), 19.2 (C); m/z (FAB) 356 ($[M+H]^+$, 65%), 278 (26), 197 (53), 183 (22), 135 (100); HRMS (FAB) $C_{21}H_{30}NO_2Si$ $[M+H]^+$ requires 356.2046, found 356.2046.

Attempted Synthesis of (2*R*,3*S*)-3-hydroxy-2-hydroxymethylpyrrolidine 126



To a solution of the silyl protected compound **125** (38 mg, 0.11 mmol) in acetonitrile (0.10 cm^3) was added hydrofluoric acid (0.31 cm^3, 48% solution in water, ca. 5eq). The mixture was stirred for 48 hours. Methoxytrimethylsilane (3.0 cm^3) was added cautiously and the mixture concentrated under reduced pressure. The remaining residue was again treated with methoxytrimethylsilane (3.0 cm^3) and concentrated. This procedure was repeated once more. The remaining residue was chromatographed on silica gel [$CHCl_3$:MeOH:NH_3 (28% aqueous)] but no product was recovered.

(2*R*)-3-*tert*-butyldiphenylsilyloxy-2-*N*,*N*-dibenzylaminopropanoic acid 145



To a solution of methyl ester **109** (500 mg, 0.931 mmol) in THF (15 cm^3) was added dropwise a slurry of LiOH•H_2O (195 mg, 4.65 mmol) in H_2O (3.75 cm^3). The solution was heated to reflux and held at reflux for 6 hours. The solution was cooled to r.t. and H_2O (15 cm^3) was added. The aqueous phase was extracted with EtOAc (2 × 25 cm^3) then the mixture was acidified to pH 3 with 1N HCl and the aqueous phase was extracted with Et_2O (3 × 20 cm^3). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound (280 mg, 58%) as a tacky solid. R_f [hexane:EtOAc (4:1)] 0.20; $[\alpha]_D$ –15.45 (*c* 0.22, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3200, 3069, 2930, 2856, 1709, 1428; δ_H (250 MHz, $CDCl_3$)

7.79-7.29 (20H, m, Ar*H*), 4.21-4.12 (2H, m, C_3H_2), 4.09 (2H, d, *J* 13.5, $NCH_XH_YPh \times 2$), 4.03 (2H, d, *J* 13.5, $NCH_XH_YPh \times 2$), 3.09 (1H, dd, *J* 8.5, 5.1, C_2H), 1.16 (9H, s, *t*Bu); δ_C (62.9 MHz) 172.3 (C), 137.2 (2C), 136.1 (2 × CH), 135.9 (2 × CH), 133.0 (C), 132.9 (C), 130.5 (CH), 129.5 (4 × CH), 129.3 (4 × CH), 128.5 (CH), 128.4 (4 × CH), 128.1 (2 × CH), 63.5 (CH), 62.3 (CH_2), 55.6 (2 × CH_2), 27.4 (3 × CH_3), 19.6 (C); m/z (FAB) 524 ($[M+H]^+$, 56%), 154 (44), 136 (37), 107 (16), 91 (100); HRMS (FAB) $C_{33}H_{38}NO_3Si$ $[M+H]^+$requires 524.2621, found 524.2622.

Lithium Iodide/Sodium Cyanide Procedure:[φ]

To a solution of methyl ester **109** (200 mg, 0.372 mmol) in pyridine (5 cm^3) was added lithium iodide (280 mg, 1.86 mmol) followed by sodium cyanide (100 mg, 1.86 mmol). The mixture was heated to 115 °C for 24 hours then cooled to r.t. and EtOAc (30 cm^3) was added. The organic phase was washed sequentially with saturated aqueous NH_4Cl (30 cm^3), water (30 cm^3) and brine (30 cm^3). The organic phase was concentrated under reduced pressure and the residue was extracted with pentane (2 × 15 cm^3) and the combined organic phases dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound (150 mg, 78%).

Lithium Iodide Procedure:

To a solution of methyl ester **109** (455 mg, 0.847 mmol) in pyridine (8 cm^3) was added lithium iodide (1.28 g, 8.50 mmol). The mixture was heated to 115 °C for 24 hours then cooled to r.t. and EtOAc (30 cm^3) was added. The organic phase was washed sequentially with saturated aqueous NH_4Cl (30 cm^3), water (30 cm^3) and brine (30 cm^3). The organic phase was concentrated under reduced pressure and the residue was extracted with pentane (2 × 15 cm^3) and the combined organic phases

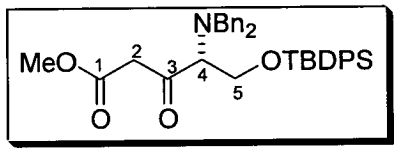
[φ] R. V. Hoffman and J. Tao, *J. Org. Chem.*, **1997**, *62*, 2292

dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound (300 mg, 72%).

Barium Hydroxide Procedure:

To a solution of methyl ester **109** (100 mg, 0.186 mmol) in MeOH (4 cm^3) was added activated barium hydroxide (318 mg, 186 mmol) and the mixture stirred at r.t. for 12 hours. Water (15 cm^3) was added and the aqueous phase was extracted with EtOAc (2 × 15 cm^3) then the mixture was acidified to pH 3 with 1N HCl. The aqueous phase was extracted with Et_2O (3 × 15 cm^3). The combined organic phases were washed with brine (25 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound (65 mg, 65%).

Methyl (4*R*)-5-*tert*-butyldiphenylsilyloxy-4-*N*,*N*-dibenzylamino-3-oxo-pentanoate 132



From methyl ester 109:

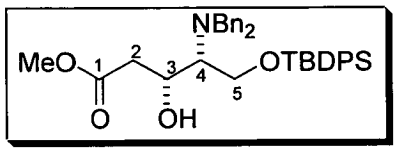
To a solution of LiHMDS (1.21 cm^3, 1.06 *M* in THF, 1.28 mmol) at –78 °C was added methyl acetate (0.100 cm^3, 1.21 mmol) and the solution stirred at –78 °C for 30 mins. The methyl ester **109** (118 mg, 0.220 mmol) in THF (2 cm^3) was added *via* cannula and the resultant solution stirred at –78 °C for 3 hours then warmed to 0 °C and stirred at 0 °C for 1 hour. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 cm^3) and the aqueous phase was extracted with DCM (3 × 10 cm^3). The combined organic phases were washed with brine (20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was

chromatographed on silica gel [hexane:Et_2O (10:1)] to give the title compound as a pale yellow oil (95 mg, 75%). R_f [hexane:Et_2O (1:1)] 0.58; $[\alpha]_D$ +25.1 (*c* 0.92, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3069, 2930, 2856, 1748, 1718, 1427; δ_H (250 MHz, $CDCl_3$) 7.71-7.23 (20H, m, Ar*H*), 4.13 (1H, dd, *J* 10.8, 6.1, $C_5H_AH_B$OTBDPS), 4.05 (1H, dd, *J* 10.8, 6.1, $C_5H_AH_B$OTBDPS), 3.80 (2H, d, *J* 12.8, $NCH_XH_YPh \times 2$), 3.70 (2H, d, *J* 12.8, $NCH_XH_YPh \times 2$), 3.63 (3H, s, O*Me*), 3.62-3.56 (1H, m, C_4H), 3.59 (1H, d, *J* 16.0, $C_2H_CH_D$), 3.47 (1H, d, *J* 16.0, $C_2H_CH_D$), 1.09 (9H, s, ^tBu); δ_C (62.9 MHz) 202.6 (C), 167.6 (C), 139.6 (C), 139.0 (2C), 135.5 (CH), 135.4 (CH), 132.9 (C), 129.7 (2 × CH), 129.6 (2 × CH), 128.8 (4 × CH), 128.5 (2 × CH), 128.3 (4 × CH), 128.1 (CH), 127.7 (2 × CH), 127.1 (CH), 67.1 (CH), 60.1 (CH_2), 55.0 (2 × CH_2), 52.0 (CH_3), 46.7 (CH_2), 26.7 (3 × CH_3), 19.0 (C); (m/z (FAB) 580 ($[M+H]^+$, 85%), 525 (12), 450 (10), 239 (10), 199 (48), 137 (26) 105 (10), 91 (100); HRMS (FAB) $C_{36}H_{42}NO_4Si$ $[M+H]^+$ requires 580.2888, found 580.2890.

From acid 145:

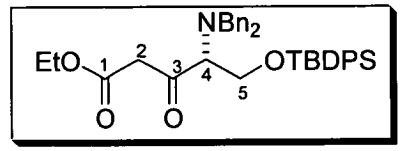
To a solution of acid **145** (300 mg, 0.569 mmol) in THF (6 cm^3) was added *N,N*-carbonyldiimidazole (324 mg, 2.00 mmol). The solution was stirred at room temperature for 2 hours. Meanwhile to a solution of LiHMDS (1.71 cm^3, 1.0 *M* in THF, 1.71 mmol) at –78 °C was added methyl acetate (0.140 cm^3, 1.71 mmol) and the resultant solution was stirred for 20 mins at –78 °C. The imidazolide (300 mg, 0.569 mmol) in THF (6 cm^3) was added *via* cannula. The reaction mixture was stirred at –78 °C for 20 mins and allowed to warm to 0 °C over 30 mins and stirred for a further 1 hour at 0 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl (15 cm^3) and the aqueous phase was extracted with DCM (3 × 15 cm^3). The combined organic phases were washed with brine (30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:Et_2O (10:1)] to give the title compound as a pale yellow oil (300 mg, 91%); $[\alpha]_D$ +30.2 (c 1.0, $CHCl_3$); *all other spectroscopic data was identical to the compound from methyl ester* ***109***.

Methyl (4*R*)-5-*tert*-butyldiphenylsilyloxy-4-*N*,*N*-dibenzylamino-3-hydroxy-pentanoate 119



To a solution of *β*-keto ester **132** (150 mg, 0.259 mmol) in Et_2O (4 cm^3) and MeOH (1.5 cm^3) was added acetic acid (ca. 0.5 cm^3) until the solution was pH 4. The solution was cooled to 0 °C and sodium cyanoborohydride (161 mg, 2.60 mmol) was added. Once effervescence had ceased the resulting solution was stirred at r.t. for 7 hours. The reaction was quenched by the addition of saturated aqueous NH_4Cl (20 cm^3) and the aqueous phase was extracted with DCM (3 × 20 cm^3). The combined organic phases were washed with brine (30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:Et_2O (7:1)] to give the title compound (125 mg, 83%) as a colourless oil. R_f [hexane:Et_2O (1:1)] 0.48; $[\alpha]_D$ –22.0 (*c* 1.3, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3445, 2928, 2865, 1730, 1428; δ_H (250 MHz, $CDCl_3$) 7.79-7.22 (20H, m, Ar*H*), 4.22 (1H, ddd, *J* 11.0, 8.9, 3.0, C_3HOH), 4.02 (2H, d, *J* 13.3, NCH_XH_YPh × 2), 3.98-3.90 (2H, m, C_5H_2), 3.65 (3H, s, O*Me*), 3.60 (2H, d, *J* 13.3, NCH_XH_YPh × 2), 2.76 (1H, ddd, *J* 11.0, 8.9, 5.1, C_4H), 2.47 (1H, dd, *J* 15.1, 3.0, $C_2H_CH_D$), 2.31 (1H, dd, *J* 15.1, 8.9, $C_2H_CH_D$), 1.13 (9H, s, ^tBu); δ_C (62.9 MHz) 172.2 (C), 138.8 (2C), 135.6 (CH), 135.5 (CH), 132.7 (C), 132.6 (C), 129.9 (2 × CH), 129.8 (2 × CH), 128.9 (4 × CH), 128.3 (4 × CH), 127.7 (4 × CH), 127.1 (2 × CH), 65.2 (CH_3), 62.7 (CH), 60.0 (CH_2), 54.3 (2 × CH_2), 51.5 (CH), 39.3 (CH_2), 26.8 (3 × CH_3), 19.0 (C); m/z (FAB) 582 ($[M+H]^+$,77%), 564 (17), 217 (44), 199 (16), 135 (16), 91 (100); HRMS (FAB) $C_{36}H_{44}NO_4Si$ $[M+H]^+$, requires 582.3039, found 582.3030; HPLC (5% propan-2-ol in hexane) **119** R_t=10.5 min, ***ent*-119** R_t=11.2 min, 43% ee.

Ethyl (4*R*)-5-*tert*-butyldiphenylsilyloxy-4-*N*,*N*-dibenzylamino-3-oxo-pentanoate 127



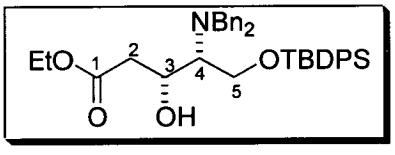
From methyl ester 109:

To a solution of LiHMDS (2.79 cm^3, 1.06 *M* in THF, 2.79 mmol) at –78 °C was added ethyl acetate (0.270 cm^3, 1.21 mmol) and the solution stirred at –78 °C for 25 mins. The methyl ester **109** (300 mg, 0.560 mmol) in THF (4 cm^3) was added *via* cannula and the resultant solution stirred at –78 °C for 3 hours then warmed to 0 °C and stirred at 0 °C for 1 hour. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 cm^3) and the aqueous phase was extracted with DCM (3 × 10 cm^3). The combined organic phases were washed with brine (20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:Et_2O (10:1)] to give the title compound as a pale yellow oil (260 mg, 78%). R_f [hexane:EtOAc (4:1)] 0.62; $[\alpha]_D$ +29.9 (*c* 0.80, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3069, 2930, 2856, 1745, 1716, 1427; δ_H (250 MHz, $CDCl_3$) 7.80-7.21 (20H, m, Ar*H*), 4.18 (2H, q, *J* 7.2, OCH_2CH_3), 4.17-4.09 (2H, m, C_5H_2), 3.92 (2H, d, *J* 13.6, NCH_XH_YPh × 2), 3.81 (2H, d, *J* 13.6 NCH_XH_YPh × 2), 3.76-3.72 (1H, m, C_4H), 3.69 (1H, d, *J* 16.0, $C_2H_CH_D$), 3.58 (1H, d, *J* 16.0, $C_2H_CH_D$), 1.27 (3H, t, *J* 7.2, OCH_2CH_3), 1.14 (9H, s, *'Bu*); δ_C (62.9 MHz) 203.3 (C), 167.8 (C), 139.6 (2C), 136.1 (2 × CH), 136.0 (CH), 135.7 (C), 135.2 (C), 130.3 (2 × CH), 129.4 (4 × CH), 128.9 (4 × CH), 128.7 (2 × CH), 128.2 (3 × CH), 128.1 (CH), 127.2 (CH), 67.6 (CH), 61.6 (CH_2), 60.7 (CH_2), 55.6 (2 × CH_2), 47.5 (CH_2), 27.3 (3 × CH_3), 19.6 (C), 14.5 (CH_3); m/z (FAB) 594 ($[M+H]^+$,12%), 478 (204), 199 (12), 181 (7), 135 (33), 91 (100); HRMS (FAB) $C_{37}H_{44}NO4_3Si$ $[M+H]^+$, requires 594.3040, found 594.3039.

From acid 145:

To a solution of acid **145** (500 mg, 0.958 mmol) in THF (10 cm^3) was added *N,N*-carbonyldiimidazole (542 mg, 3.35 mmol). The solution was stirred at room temperature for 2 hours. Meanwhile to a solution of LiHMDS (2.88 cm^3, 1.0 *M* in THF, 2.88 mmol) at –78 °C was added ethyl acetate (0.280 cm^3, 2.88 mmol) and the resultant solution was stirred for 20 mins at –78°C. The imidazolide **157** (500 mg, 0.958 mmol) in THF (10 cm^3) was added *via* cannula. The reaction mixture was stirred at –78 °C for 20 mins and allowed to warm to 0 °C over 30 mins and stirred for a further 1 hour at 0 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl (15 cm^3) and the aqueous phase was extracted with DCM (3 × 15 cm^3). The combined organic phases were washed with brine (30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:EtOAc (10:1)] to give the title compound as a pale yellow oil (510 mg, 90%); $[\alpha]_D$ +33.6 (*c* 0.27, $CHCl_3$); *all other spectroscopic data was identical to the compound from methyl ester* ***109***.

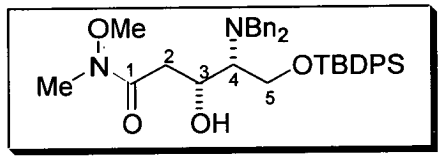
Ethyl (3*R*,4*R*)-5-*tert*-butyldiphenylsilyloxy-4-*N*,*N*-dibenzylamino-3-hydroxy-pentanoate 122



To a solution of *β*-keto ester **127** (360 mg, 0.621 mmol) in Et_2O (8 cm^3) and MeOH (3 cm^3) was added acetic acid (ca. 1 cm^3) until the solution was pH 4. The solution was cooled to 0 °C and sodium cyanoborohydride (385 mg, 6.22 mmol) was added. Once effervescence had ceased the resulting solution was stirred at r.t. for 7 hours. The reaction was quenched by the addition of a saturated solution of NH_4Cl (30 cm^3) and the aqueous phase was extracted with DCM (3 × 30 cm^3). The combined organic phases were washed with brine (40 cm^3), dried ($MgSO_4$) and concentrated under

reduced pressure. The residue was chromatographed on silica gel [hexane:Et_2O (7:1)] to give the title compound (290 mg, 81%) as a colourless oil. R_f [hexane:Et_2O (1:1)] 0.38; $[\alpha]_D$ –18.75 (*c* 1.6, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3456, 3070, 2931, 2858, 1732, 1428; δ_H (250 MHz, $CDCl_3$) 7.76-7.24 (20H, m, Ar*H*), 4.24-4.20 (1H, m, C_3HOH), 4.19 (2H, q, *J* 7.1, OCH_2CH_3), 4.18-4.06 (2H, m, C_5H_2), 4.05 (2H, d, *J* 13.3, $NCH_XH_YPh \times 2$), 3.60 (2H, d, *J* 13.3, $NCH_XH_YPh \times 2$), 2.77-2.72 (1H, m, C_4H), 2.45 (1H, dd, *J* 15.2, 3.0, $C_2H_CH_D$), 2.30 (1H, dd, *J* 15.2, 9.0, $C_2H_CH_D$), 1.28 (3H, t, *J* 7.1, OCH_2CH_3), 1.15 (9H, s, *'Bu*); δ_C (62.9 MHz) 172.4 (C), 139.5 (2C), 136.2 (2 × CH), 136.1 (2 × CH), 133.3 (C), 133.2 (C), 130.5 (CH), 130.4 (CH), 129.5 (4 × CH), 128.9 (4 × CH), 128.3 (4 × CH), 127.7 (2 × CH), 65.8 (CH), 63.4 (CH), 60.9 (CH_2), 60.6 (CH_2), 54.9 (2 × CH_2), 40.1 (CH_2), 27.4 (3 × CH_3), 19.6 (C), 14.6 (CH_3); m/z (FAB) 596 ($[M+H]^+$, 40%), 478 (51), 326 (12), 197 (12), 135 (26), 91 (100); HRMS (FAB) $C_{37}H_{46}NO_4Si$ $[M+H]^+$ requires 596.3196, found 596.3197; HPLC (5% propan-2-ol in hexane) **122** R_t=9.1 min, ***ent*-121** R_t=10.8 min, 70% ee.

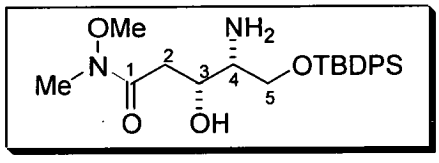
(3*R*,4*R*)-5-*tert*-butyldiphenylsilyloxy-4-*N*,*N*-dibenzylamino-3-hydroxypentanoic acid methoxy methyl amide 123



To a slurry of *N*,*O*-dimethylhydroxylamine•hydrochloride (371 mg, 3.82 mmol) in THF (4 cm^3) at 0 °C was added trimethylaluminium (3.82 cm^3, 2.0 *M* in toluene, 7.64 mmol). The solution was stirred at 0 °C for 5 minutes then allowed to warm to room temperature over ca. 15 minutes, after which time a clear solution remained. **122** (380 mg, 0.637 mmol) in THF (4 cm^3) was added dropwise *via* cannula. The mixture was warmed to 35 °C and stirred for 3 hours. The reaction mixture was cooled and then cannulated rapidly into a mixture of DCM (30 cm^3) and saturated aqueous potassium sodium tartrate (30 cm^3) and stirred vigorously for 5 hours whereupon two distinct phases were apparent. The aqueous phase was extracted with DCM (3 × 30

cm^3). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:EtOAc (4:1) to give the title compound (370 mg, 95%) as a colourless oil. R_f [hexane:EtOAc (4:1)] 0.34; $[\alpha]_D$ –4.74 (*c* 0.45, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3460, 3075, 2925, 2826, 1644, 1428; δ_H (360 MHz, $CDCl_3$) 7.82-7.24 (20H, m, Ar*H*), 4.28-4.20 (1H, m, C_3HOH), 4.10 (1H, dd, *J* 10.9, 8.0, $C_5H_AH_B$OTBDPS), 4.04 (2H, d, *J* 13.4, $NCH_XH_YPh \times 2$), 4.00 (1H, dd, *J* 10.9, 5.4, $C_5H_AH_B$OTBDPS), 3.91 (2H, d, *J* 13.4, $NCH_XH_YPh \times 2$), 3.60 (3H, s, O*Me*), 3.20 (3H, s, *Me*), 2.80-2.73 (1H, m, C_4H), 2.69-2.58 (1H, br m, $C_2H_CH_D$), 2.30-2.19 (1H, br m, $C_2H_CH_D$), 1.12 (9H, s, ^tBu); δ_C (90.6 MHz) 173.6 (C), 140.2 (2C), 136.2 (2 × CH), 136.1 (2 × CH), 133.6 (C), 133.5 (C), 130.4 (CH), 130.3 (CH), 129.6 (4 × CH), 128.7 (4 × CH), 128.3 (4 × CH), 127.4 (2 × CH), 66.7 (CH), 63.6 (CH_3), 61.5 (CH), 61.4 (CH_2), 55.4 (2 × CH_2), 37.2 (CH_2), 32.4 (CH_3), 27.4 (3 × CH_3), 19.6 (C); m/z (FAB) 416 ($[M+H]^+$,72%), 478 (81), 341 (17), 197 (43), 181 (16), 135 (70), 105 (34), 91 (100); HRMS (FAB) $C_{37}H_{46}N_2O_4Si$ $[M+H]^+$ requires 611.3305, found 611.3305.

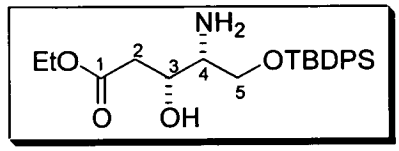
(3*R*,4*R*)-5-*tert*-butyldiphenylsilyloxy-4-amino-3-hydroxypentanoic acid methoxy methyl amide 124



To a solution of **123** (300 mg, 0.492 mmol) in methanol (5 cm^3) was added 20% $Pd(OH)_2/C$ (300 mg), the flask was flushed with argon before being stirred under an atmosphere of hydrogen for 12 hours. The reaction mixture was filtered through a layer of celite and concentrated under reduced pressure. The residue was chromatographed on silica gel [DCM:MeOH (50:1) to give the title compound (210 mg, 100%) as an oil. R_f [DCM:MeOH (10:1)] 0.12; δ_H (250 MHz, $CDCl_3$) 8.14-8.12 (2H, br s, NH_2), 7.60-7.32 (10H, m, Ar*H*), 4.25-4.20 (1H, br m, C_3HOH), 4.01-3.85

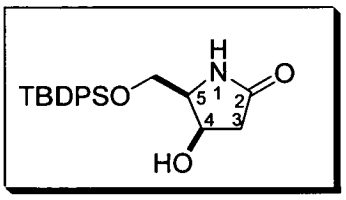
(2H, m, C_5H_2), 3.50 (3H, s, O*Me*), 2.97 (3H, s, *Me*), 2.90-2.82 (2H, br m, $C_2H_CH_D$ + C_4H), 2.39-2.30 (1H, br m, $C_2H_CH_D$), 1.08 (9H, s, ^{t}Bu).

Ethyl (3*R*,4*R*)-5-*tert*-butyldiphenylsilyloxy-4-amino-3-hydroxy-pentanoate 158



To a solution of *β*-hydroxy ester **122** (270 mg, 0.451 mmol) in methanol (5 cm^3) was added 20% $Pd(OH)_2/C$ (270 mg), the flask was flushed with argon before being stirred under an atmosphere of hydrogen for 12 hours. The reaction mixture was filtered through a layer of celite and concentrated under reduced pressure. The residue was chromatographed on silica gel [DCM:MeOH (50:1) to give the title compound (186 mg, 100%) as an oil. R_f [DCM:MeOH (10:1)] 0.20; $[\alpha]_D$ −11.1 (*c* 1.2, $CHCl_3$; ν_{max} (neat)/cm^{-1} 3363, 2932, 2888, 1724, 1426; δ_H (250 MHz, $CDCl_3$) 7.76-7.06 (10H, m, Ar*H*), 4.22 (2H, q, *J* 7.0, OCH_2CH_3), 3.78-3.47 (5H, br m, C_3HOH + C_5H_2, NH_2), 3.10-3.00 (1H, m, C_4H), 2.65 (1H, dd, *J* 15.0, 3.2, $C_2H_CH_D$), 2.30 (1H, dd, *J* 15.0, 8.9, $C_2H_CH_D$), 1.31 (3H, t, *J* 7.0, OCH_2CH_3), 1.13 (9H, s, ^{t}*Bu*); δ_C (50.3 MHz) 169.9 (C), 134.7 (2 × CH), 132.2 (CH), 131.3 (C), 129.9 (C), 128.9 (CH), 128.0 (4 × CH), 126.9 (2 × CH), 64.7 (CH), 61.5 (CH), 60.1 (CH_2), 59.9 (CH_2), 45.6 (CH_2), 25.5 (3 × CH_3), 18.2 (C), 14.9 (CH_3); m/z (FAB) 416 ($[M+H]^+$,100%), 199 (20), 142 (7), 135 (38), 105 (12), 95 (11); HRMS (FAB) $C_{23}H_{34}NO_4Si$ $[M+H]^+$ requires 416.2257, found 416.2252.

(4*R*,5*R*)-5-*tert*-Butyldiphenylsilyloxymethyl-4-hydroxypyrrolidin-2-one 129



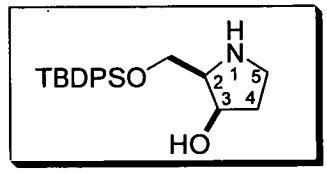
From amino ester 124:

A solution of amino alcohol **124** (186 mg, 0.448 mmol) in MeOH (4 cm^3) was heated to reflux and held at reflux for 24 hours. The solution was cooled and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel gel [DCM:MeOH (50:1) to give the title compound (130 mg, 78%) as a white solid. R_f [DCM:MeOH (10:1)] 0.30; mp 110-112°C; $[\alpha]_D$ +11.30 (*c* 0.2, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3385, 2931, 1682, 1427; δ_H (250 MHz, $CDCl_3$) 7.66-7.25 (10H, m, Ar*H*), 6.20 (1H, br s, N*H*), 4.61 (1H, ddd, *J* 10.4, 7.0, 4.2, C_4HOH), 3.95 (1H, dd, *J* 10.5, 5.8, $CH_4H_BOTBDPS$), 3.81 (1H, dd, *J* 10.5, 4.8, $CH_AH_BOTBDPS$), 3.78 (1H, dt, *J* 10.4, 5.5, C_5H), 3.29 (1H, br s, O*H*), 2.68 (1H, dd, *J* 17.3, 7.0, $C_3H_CH_D$), 2.41 (1H, dd, *J* 17.3, 4.2, $C_3H_CH_D$), 1.05 (9H, s, ^tBu); δ_C (62.9 MHz) 176.0 (C), 135.4 (2 × CH), 135.3 (2 × CH), 132.4 (C), 132.2 (C), 130.0 (2 × CH), 128.0 (4 × CH), 68.2 (CH), 63.0 (CH_2), 59.2 (CH), 40.3 (CH_2), 26.7 (3 × CH_3), 19.0 (C); m/z (FAB) 370 ($[M+H]^+$, 59%), 292 (34), 234 (37), 214 (66), 199 (80), 135 (94), 105 (46); HRMS (FAB) $C_{21}H_{28}NO_3Si$ $[M+H]^+$requires 370.1838, found 370.1838.

From amino methyl methoxy amide 158:

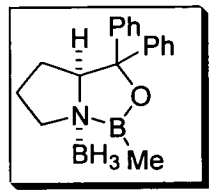
A solution of **158** (100 mg, 0.234 mmol) in MeOH (3 cm^3) was heated to reflux and held at reflux for 24 hours. The solution was cooled and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel gel [DCM:MeOH (50:1) to give the title compound (62 mg, 72%) as a white solid; *spectroscopic data was identical to the compound from amino ester **124**.*

(4*R*,5*R*)-2-*tert*-Butyldiphenylsilyloxymethyl-3-hydroxypyrrolidine 159



To a solution of pyrrolidinone **129** (120 mg, 0.330 mmol) in THF (5 cm^3) at 0 °C was added BH_3•THF complex (4.95 cm^3, 1.0 *M* in THF, 4.95 mmol). The solution was stirred at 0 °C until effervescence ceased and then stirred at reflux for 24 hours. Methanol (ca. 5 cm^3) was added cautiously to the cooled (0 °C) reaction mixture. The resulting mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel DCM: MeOH (50:1) to give the title compound (105 mg, 86%) as a white solid. mp 100-101 °C; R_f[DCM: MeOH (10:1)] 0.25; $[\alpha]_D$ +8.5 (*c* 0.5, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 7.69-7.60 (4H, m, Ar*H*), 7.52-7.25 (6H, m, Ar*H*), 6.20 (1H, s, N*H*), 4.56 (1H, ddd, *J* 11.4, 6.3, 4.6, C_3*H*OH), 4.52-4.51 (1H, br s, O*H*), 4.23 (1H, dd, *J* 11.2, 4.8, C$H_A$$H_B$OTBDPS), 4.20 (1H, dd, *J* 11.2, 8.0, C$H_A$$H_B$OTBDPS) 3.59 (1H, ddd, *J* 11.4, 8.0, 4.8, C_2*H*), 3.06 (1H, ddd, *J* 12.7, 7.6, 6.0, $C_5H_EH_F$), 2.97 (1H, ddd, *J* 12.7, 6.5, 4.5, $C_5H_EH_F$), 2.19 (1H, ddt, *J* 16.1, 6.0, 4.5, $C_4H_CH_D$), 1.94 (1H, ddt, *J* 16.1, 7.6, 6.5, $C_4H_CH_D$), 1.08 (9H, s, ^tBu) ; δ_C (62.9 MHz) 135.5 (2 × CH), 135.3 (2 × CH), 131.6 (C), 131.2 (C), 130.3 (2 × CH), 128.0 (4 × CH), 73.8 (CH), 69.0 (CH), 60.3 (CH_2), 52.8 (CH_2), 32.5 (CH_2), 26.8 (3 × CH_3), 19.0 (C); m/z (FAB) 356 (MH^+, 65%), 278 (26), 197 (53), 183 (22), 135 (100); HRMS (FAB) $C_{21}H_{30}NO_2Si$ (MH^+) requires 356.2046, found 356.2043.

Tetrahydro-1-methyl-3,3-diphenyl-1*H*,3*H*-pyrrolo[1,2-c][1,3,2]-oxazaborole-borane (CBS•BH_3 complex) 178



To a solution of (+)-α, α-diphenyl-2-pyrrolidinemethanol (400 mg, 1.58 mmol) in toluene was added methylboronic acid (63.0 mg, 1.06 mmol). The mixture was stirred at r.t. for 2 hours. The solution was then heated to reflux and subsequently concentrated under vacuum. This was followed by three successive toluene flushes (3 × 3 cm^3), each followed by vacuum distillation to remove any water and unreacted methylboronic acid. The flask was subsequently cooled to r.t. and dimethylsulfide-borane was added (1.25 cm^3, 12.6 mmol). The mixture was stirred for 12 hours during which time a white crystalline solid formed. This was dried under vacuum for 10 hours thus removing any excess dimethylsulfide to yield the title compound (375 mg, 85%), mp 125-126 °C; m/z (FAB) 292 ($[M+H]^+$,45%), 278 (20), 254 (100), 136 (72); HRMS (FAB) $C_{18}H_{24}B_2NO$ $[M+H]^+$ requires 292.2047, found 292.2046.

Ethyl (3*S*,4*R*)-5-*tert*-butyldiphenylsilyloxy-4-*N*,*N*-dibenzylamino-3-hydroxy-pentanoate 121 and Ethyl (3*R*,4*R*)-5-*tert*-butyldiphenylsilyloxy-4-*N*,*N*-dibenzylamino-3-hydroxy-pentanoate 122

To a solution of the CBS•BH_3 complex **178** (23 mg, 0.085 mmol) in THF (2 cm^3) was added BH_3•SMe_2 complex (0.16 cm^3, 0.17 mmol). The solution was stirred for 10 mins. The *β*-keto ester **127** (100 mg, 0.173 mol) in THF (2 cm^3) was added *via*

cannula. The solution was stirred at 45 °C for 24 hours. The reaction was cooled to r.t. and quenched by the addition of MeOH and allowed to stir for 1 hour before being concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:Et_2O (10:1)] to give the title compounds (60 mg, 60%) as a 1:1 mixture of diastereomers. R_f [hexane:Et_2O (1:1)] 0.37; *^1H NMR data in agreement with compounds **121** and **122**.*

Methyl (3*S*,4*R*)-5-*tert*-butyldiphenylsilyloxy-4-*N*,*N*-dibenzylamino-3-hydroxy-pentanoate 118 and Methyl (3*R*,4*R*)-5-*tert*-butyldiphenylsilyloxy-4-*N*,*N*-dibenzylamino-3-hydroxy-pentanoate 119

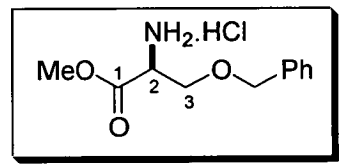
Low Pressure, High Temperature Hydrogenation

The methyl ester **132** (113 mg, 0.195 mmol) was dissolved in MeOH:DCM (1.5 cm^3: 1.5 cm^3). Three freeze and thaw cycles were carried out and the solution was cannulated into a flask containing $[RuCl_2(S\text{-BINAP})]_n$ (1 mol%) (Note: all manipulations involving $[RuCl_2(S\text{-BINAP})]_n$ were carried out in a glove bag under an atmosphere of argon). The solution was stirred at 50 °C under an atmosphere of hydrogen (1 atm) for 5 days. The solution was flushed with argon before being concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:Et_2O (10:1)] to give the title compounds (62 mg, 58%) as a 4:1 mixture of diastereomers based on recovered starting material. R_f [hexane:Et_2O (1:1)] 0.38; *^1H NMR data in agreement with compounds **118** and **119**.*

High Pressure, Low Temperature Hydrogenation

The methyl ester **132** (110 mg, 0.201 mmol) was dissolved in MeOH:DCM (1.0 cm^3: 1.0 cm^3). Three freeze and thaw cycles were carried out and the solution was cannulated into a flask containing $[RuCl_2(S\text{-BINAP})]_n$ (1 mol%) (Note: all manipulations involving $[RuCl_2(S\text{-BINAP})]_n$ were carried out in a glove bag under an atmosphere of argon). The flask was transferred to a high pressure autoclave. The autoclave was flushed with nitrogen (3×), then flushed with hydrogen (3×) before being stirred at r.t. under an atmosphere of hydrogen (8 atm) for 4.5 days. The hydrogen was evacuated and the autoclave flushed with nitrogen (3 ×) before removal of the flask. The solution was concentrated under reduced pressure to give unreacted starting material.

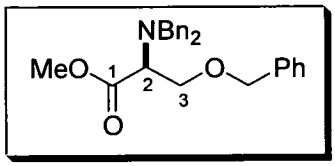
Methyl (2*S*)-2-amino-3-*O*-benzylpropanoate•hydrochloride 161



Acetyl chloride (2.20 cm^3, 30.8 mmol) was added dropwise to methanol (24 cm^3) at 0 °C. The mixture was stirred for 15 mins and l-*O*-benzylserine (2.00 g, 10.3 mmol) was then added portionwise to the solution. The resulting mixture was heated to reflux and held at reflux for 3 hours. Concentration under reduced pressure provided the title compound (2.25 g, 96%) as a solid. Recrystallisation from methanol provided an analytical sample, mp 162-164 °C; $[\alpha]_D$ +15.2 (*c* 1.4, MeOH); δ_H (250 MHz, D_2O) 7.37-7.26 (5H, m, Ar*H*), 4.57 (1H, d, *J* 12.0, OCH_EH_FPh), 4.47 (1H, d, *J* 12.0, OCH_EH_FPh), 4.28 (1H, t, *J* 3.7 C_2H), 3.93 (1H, dd, *J* 11.0, 4.2, $C_3H_AH_B$,), 3.83 (1H, dd, *J* 11.0, 3.0, $C_3H_AH_B$), 3.71 (3H, s, O*Me*); δ_C (62.9 MHz) 169.0 (C), 137.1 (C), 129.1 (2 × CH), 128.9 (CH), 128.8 (2 × CH), 73.5 (CH_2), 66.7 (CH_2), 54.1 (CH_3), 53.5 (CH); m/z (FAB) 210 $[M+H]^+$, 95%), 196 (8), 150 (5), 120 (10), 102

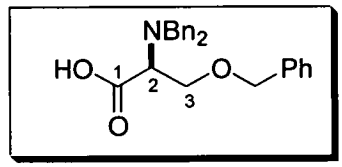
(10), 91 (100); HRMS (FAB) $C_{11}H_{16}NO_3$ $[M+H]^+$,requires 210.1130, found 210.1133.

Methyl (2*S*)-3-*O*-benzyl-2-*N*,*N*-dibenzylaminopropanoate 162



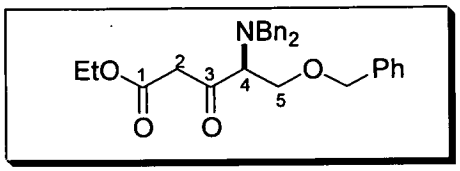
To a solution of ester **161** (2.00 g, 8.71 mmol) in anhydrous acetonitrile (30 cm^3) was added anhydrous potassium carbonate (5.55 g, 43.6 mmol) followed by benzyl bromide (2.38 cm^3, 21.8 mmol). The mixture was stirred at room temperature for 24 hours. H_2O (50 cm^3) was added and the aqueous phase was extracted with EtOAc (3 × 30 cm^3). The combined organic phases were washed with brine (100 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (10:1)] to give the title compound (3.20 g, 94%) as a colourless oil. R_f [hexane:EtOAc (4:1)] 0.60; $[\alpha]_D$ –48.5 (*c* 1.07, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3062, 3028, 2948, 2855, 1735, 1602, 1494, 1453; δ_H (250 MHz, $CDCl_3$) 7.41-7.21 (15H, m, Ar*H*), 4.52-4.30 (2H, m, OCH_2Ph), 3.96 (2H, d, *J* 13.9, NCH_XH$_Y$Ph × 2), 3.89 (1H, t, *J* 2.8, C_2H), 3.85-3.59 (1H, m, $C_3H_AH_B$), 3.78 (3H, s, O*Me*), 3.75-3.68 (1H, m, $C_3H_AH_B$), 3.72 (2H, d, *J* 13.9, NCH$_X$H$_Y$Ph × 2); δ_C (62.9 MHz) 171.8 (C), 139.5 (2C), 137.9 (C), 128.6 (4 × CH), 128.2 (2 × CH), 128.1 (4 × CH), 127.4 (3 × CH), 126.9 (2 × CH), 73.0 (CH_2), 69.4 (CH_2), 60.8 (CH), 55.2 (2 × CH_2), 51.2 (CH_3); m/z (FAB) 390 ($[M+H]^+$, 15%), 330 (32), 282 (8), 268 (41), 181 (9), 91 (100); HRMS (FAB) $C_{25}H_{28}NO_3$ $[M+H]^+$,requires 390.2069, found 390.2070.

(2*S*)-3-*O*-benzyl-2-*N*,*N*-dibenzylaminopropanoic acid 163



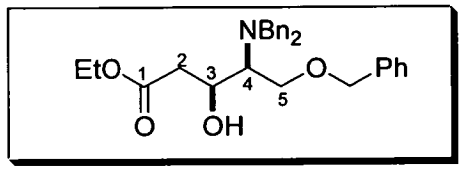
To a solution of the ester **162** (300 mg, 0.771 mmol) in THF (8 cm^3) was added a slurry of $LiOH{\bullet}H_2O$ (194 mg, 4.63 mmol) in H_2O (2 cm^3). The mixture was heated to reflux and held at reflux for 4 hours. The solution was cooled to r.t., water (15 cm^3) was added and the mixture was acidified to pH 3 with 1 N HCl. The aqueous phase was extracted with Et_2O (3 × 15 cm^3). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound (288 mg, 100%). R_f [hexane:EtOAc (4:1)] 0.13; ν_{max} (neat)/cm^{-1} 4059, 3067, 3028, 2923, 2854, 1715, 1495; δ_H (250 MHz, $CDCl_3$) 7.67-7.03 (15H, m, Ar*H*), 4.63 (1H, d, *J* 11.9, OC$H_E$$H_F$Ph), 4.55 (1H, d, *J* 11.9, OC$H_E$$H_F$Ph), 4.17 (1H, dd, *J* 10.3, 4.6, $C_3H_4H_B$), 4.06 (2H, d, *J* 13.3, NC$H_X$$H_Y$Ph × 2), 4.01-3.67 (2H, m, $C_3H_AH_B$+C_2H), 3.94 (2H, d, *J* 13.3, NC$H_X$$H_Y$Ph × 2); δ_C (62.9 MHz) 171.1 (C), 137.5 (C), 135.8 (2C), 129.2 (4 × CH), 128.7 (4 × CH), 128.4 (2 × CH), 128.1 (2 × CH), 127.8 (CH), 127.2 (2 × CH), 73.4 (CH_2), 67.5 (CH_2), 61.5 (CH), 55.1 (2 × CH_2); m/z (FAB) 376 (MH^+, 100%), 330 (16), 286 (31), 240 (12) 181 (20), 91 (91); HRMS (FAB) $C_{24}H_{26}NO_3$ (MH^+) requires 376.1913, found 376.1914.

Ethyl (4*S*)-5-*O*-benzyl-4-*N*,*N*-dibenzylamino-3-oxo-pentanoate 165



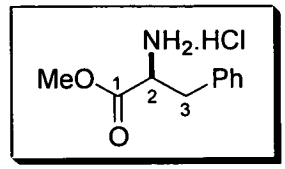
To a solution of acid **163** (300 mg, 0.825 mmol) in THF (8 cm^3) was added *N*,*N*-carbonyldiimidazole (404 mg, 2.49 mmol). The solution was stirred at r.t. for 2 hours. Meanwhile to a solution of LiHMDS (2.49 cm^3, 1.0 *M* in THF, 2.49 mmol) at –78 °C was added ethyl acetate (0.240 cm^3, 2.49 mmol) and the solution stirred for 20 mins. The imidazolide **164** (300 mg, 0.83 mmol) in THF (8 cm^3) was added *via* cannula and the solution stirred at –78 °C for 30 mins then warmed to 0 °C over a period of 1 hour. The mixture was stirred at 0 °C for 1 hour before being quenched with saturated aqueous NH_4Cl (20 cm^3). The aqueous phase was extracted with DCM (3 × 20 cm^3). The combined organic phases were washed with brine (30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:EtOAc(10:1)] to give the title compound (340 mg, 92%) as a pale yellow oil. R_f [hexane:EtOAc (4:1)] 0.53; ν_{max} (neat)/cm^{-1} 3062, 3029, 2081, 2926, 2860, 1744, 1716, 1494, 1453; δ_H (250 MHz, $CDCl_3$) 7.43-7.22 (15H, m, Ar*H*), 4.62 (1H, d, *J* 12.0, OCH_EH_FPh), 4.55 (1H, d, *J* 12.0, OCH_EH_FPh), 4.14 (2H, q, *J* 7.2, OCH_2CH_3), 4.01 (1H, dd, *J* 9.2, 6.5, $C_5H_AH_B$), 3.94 (1H, dd, *J* 9.2, 4.0, $C_5H_AH_B$), 3.85 (2H, d, *J* 13.1, NCH_XH_YPh × 2), 3.75-3.65 (1H, m, C_4H), 3.73 (1H, d, *J* 16.0, $C_2H_CH_D$), 3.70 (2H, d, *J* 13.1, NCH_XH_YPh × 2), 3.54 (1H, d, *J* 16.0, $C_2H_CH_D$), 1.23 (3H, t, *J* 7.2, OCH_2CH_3); δ_C (62.9 MHz) 202.7 (C), 167.3 (C), 138.9 (2C), 137.9 (C), 128.9 (4 × CH), 128.5 (2 × CH), 128.3 (4 × CH), 127.5 (2 × CH), 127.1 (2 × CH), 126.8 (CH), 73.4 (CH_2), 66.1 (CH), 65.4 (CH_2), 61.0 (CH_2), 55.0 (2 × CH_2), 46.5 (CH_2), 13.9 (CH_3); m/z (FAB) 446 ($[M+H]^+$,100%), 356 (39), 330 (53), 240 (22), 196 (17), 132 (9), 106 (37), 91 (97); HRMS (FAB) $C_{28}H_{32}NO_4$ $[M+H]^+$ requires 446.2331, found 446.2332.

Ethyl (3*S*,4*S*)-5-*O*-benzyl-4-*N*,*N*-dibenzylamino-3-hydroxy-pentanoate 166



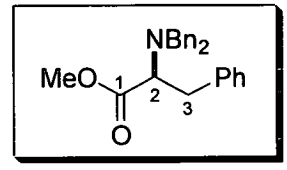
To a solution of ester **165** (80 mg, 0.18 mmol) in Et_2O (4 cm^3), MeOH (2 cm^3) was added acetic acid (ca. 0.5 cm^3) until the solution was pH 4. The solution was cooled to 0 °C and sodium cyanoborohydride (60 mg, 1.4 mmol) was added. Once effervescence ceased the solution was warmed to r.t. and stirred for 8 hours. The solution was quenched by the addition of a saturated solution of NH_4Cl (15 cm^3) and the aqueous phase was extracted with DCM (3 × 15 cm^3). The combined organic phases were washed with brine (20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:EtOAc(6:1)] to give the title compound (72 mg, 90%) as an oil. R_f [hexane:EtOAc (4:1)] 0.38; ν_{max} (neat)/cm^{-1} 3371, 2936, 1726, 1452; δ_H (250 MHz, $CDCl_3$) 7.43-7.19 (15H, m, Ar*H*), 4.59 (1H, d, *J* 12.0, OCH_EH_FPh), 4.52 (1H, d, *J* 12.0, OCH_EH_FPh), 4.19 (1H, ddd, *J* 11.2, 8.5, 3.6, C_3HOH), 4.14 (2H, q, *J* 7.2, OCH_2CH_3), 4.05 (2H, d, *J* 13.2, NCH_XH_YPh × 2), 3.80 (1H, dd, *J* 10.2, 5.5, $C_5H_AH_B$), 3.69 (1H, dd, J 10.2, 4.8, $C_5H_AH_B$), 3.53 (2H, d, *J* 13.2, NCH_XH_YPh × 2), 3.47 (1H, s, O*H*), 2.80-2.72 (1H, m, C_4H), 2.50 (1H, dd, *J* 15.4, 3.6, $C_2H_CH_D$), 2.37 (1H, dd, *J* 15.4, 8.5, $C_2H_CH_D$), 1.23 (3H, t, *J* 7.1, OCH_2CH_3); δ_C (62.9 MHz) 172.0 (C), 138.8 (2C), 137.8 (C), 129.0 (4 × CH), 128.4 (6 × CH), 127.7 (CH), 127.5 (2 × CH), 127.1 (2 × CH), 73.2 (CH_2), 66.3 (CH_2), 65.7 (CH_2), 61.3 (CH), 60.4 (CH), 54.3 (2 × CH_2), 39.45 (CH_2), 14.0 (CH_3); m/z (FAB) 448 ($[M+H]^+$, 20%), 330 (19), 326 (5), 210 (2), 181 (4), 91 (100); HRMS (FAB) $C_{28}H_{34}NO_4$ $[M+H]^+$ requires 448.2488, found 448.2489; HPLC (5% propan-2-ol in hexane) R_t=18.7 min, R_t=21.8 min, 0% ee.

Methyl (2*S*)-2-amino-3-phenylpropanoate•hydrochloride 230



Acetyl chloride (17.2 cm^3, 240 mmol) was added dropwise to methanol (150 cm^3) at 0 °C. The mixture was stirred for 15 mins and *L*-phenylalanine (13.0 g, 78.7 mmol) was then added portionwise to the solution. The resulting mixture was heated to reflux and held at reflux for 3 hours. Concentration under reduced pressure provided the title compound (16.2 g, 95%) as a solid. Recrystallisation from methanol provided an analytical sample, mp 158-160 °C; $[\alpha]_D$ +30.9 (*c* 1.8, EtOH) [lit., (Aldrich) mp 158-162 °C; $[\alpha]_D$ +32.4 (*c* 2.0, EtOH)]; δ_H (250 MHz, $CDCl_3$) 7.45-7.24 (5H, m, Ar*H*), 4.37 (1H, dd, *J* 7.5, 5.9, C_2H), 3.81 (3H, s, O*Me*), 3.30 (1H, dd, *J* 12.6, 5.9, $C_3H_AH_B$), 3.19 (1H, dd, *J* 12.6, 7.5, $C_3H_AH_B$); δ_C (62.9 MHz) 170.1 (C), 133.7 (C), 129.3 (2 × CH), 129.2 (2 × CH), 128.1 (C), 54.1 (CH_3), 53.5 (CH), 35.6 (CH_2); m/z (FAB) 180 ($[M+H]^+$, 100%), 154 (78), 135 (68), 91 (90); HRMS (FAB) $C_{10}H_{14}NO_2$ $[M+H]^+$ requires 180.1024, found 180.1024; Found: C, 55.68; H, 6.50; N, 6.50. $C_{10}H_{14}NO_2$ requires C, 55.60; H, 6.52; N, 6.37%.

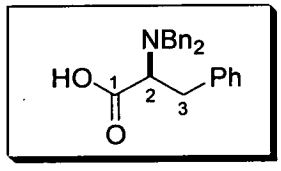
Methyl (2*S*)-2-*N*,*N*-dibenzylamino-3-phenylpropanoate 229



To a solution of methyl ester **230** (10.0 g, 46.7 mmol) in anhydrous acetonitrile (150 cm^3) was added anhydrous potassium carbonate (34.7 g, 250 mmol) followed by benzyl bromide (14.2 cm^3, 120 mmol). The mixture was stirred at room temperature for 24 hours. Water (150 cm^3) was added and the aqueous phase was extracted with EtOAc (3 × 125 cm^3). The combined organic phases were washed with brine (100

cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (8:1)] to give the title compound (16.2 g, 95%) as a colourless oil. R_f [hexane:EtOAc (4:1)] 0.76; $[\alpha]_D$ – 86.1 (*c* 0.38, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3027, 2948, 2847, 1731, 1453; δ_H (250 MHz, $CDCl_3$) 7.38-7.15 (15H, m, Ar*H*), 3.92 (2H, d, *J* 14.0, NCH_XH$_Y$Ph × 2), 3.73 (3H, s, O*Me*), 3.67 (1H, dd, *J* 8.3, 7.1, C_2H), 3.51 (2H, d, *J* 14.0, NCH$_X$$H_Y$Ph × 2), 3.08 (1H, dd, *J* 13.9, 7.1, $C_3H_AH_B$), 2.94 (1H, dd, *J* 13.9) δ_C (60.9 MHz) 173.2 (C), 139.7 (2C), 138.6 (C), 129.9 (2 × CH), 129.1 (4 × CH), 128.6 (6 × CH), 127.4 (2 × CH), 126.7 (CH), 62.8 (CH_3), 54.9 (2 × CH_2), 51.6 (CH), 36.2 (CH_2); m/z (FAB) 360 ($[M+H]^+$, 36%), 358 (40), 300 (66), 268 (84), 91 (100); HRMS (FAB) $C_{24}H_{26}NO_2$ $[M+H]^+$ requires 360.1963, found 360.1957.

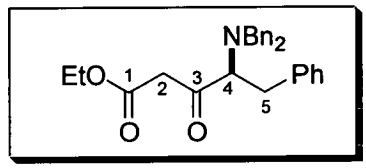
(2*S*)-2-*N*,*N*-dibenzylamino-3-phenylpropanoic acid 227



To a solution of methyl ester **229** (4.20 g, 11.7 mmol) in THF (40 cm^3) was added dropwise a slurry of LiOH•H_2O (2.95 g, 70.2 mmol) in water (10 cm^3). The solution was heated to reflux and held at reflux for 6 hours. The solution was cooled to r.t.. Water (40 cm^3) was added and the aqueous phase was extracted with EtOAc (3 × 20 cm^3). The mixture was acidified to pH 3 with 1N HCl and the aqueous phase was extracted with Et_2O (3 × 50 cm^3). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound (3.00 g, 75%) as a white solid. R_f [hexane:EtOAc (4:1)] 0.30; mp 115-117 °C; $[\alpha]_D$ –65.7 (*c* 0.54, $CHCl_3$); ν_{max}/ (solution cell, $CHCl_3$) cm^{-1} 3402, 3027, 1704, 1453; δ_H (250 MHz, $CDCl_3$) 7.43-7.16 (15H, m, Ar*H*), 3.91 (2H, d, *J* 13.8, NCH_XH$_Y$Ph × 2), 3.85 (1H, m, C_2H), 3.82 (2H, d, *J* 13.8, NCH$_X$$H_Y$Ph × 2), 3.40 (1H, dd, *J* 14.4, 6.2, $C_3H_AH_B$), 3.15 (1H, dd, *J* 14.4, 8.7, $C_3H_AH_B$); δ_C (62.9 MHz) 176.6 (C), 138.6 (2C), 138.4 (C), 129.9

(2 × CH), 129.3 (4 × CH), 128.9 (6 × CH), 127.9 (2 × CH), 127.0 (CH), 63.0 (CH), 54.9 (2 × CH_2), 34.7 (CH_2); m/z (FAB) 346 ($[M+H]^+$, 74%), 300 (62), 254 (26), 210 (19), 181 (11), 91 (100); HRMS (FAB) $C_{23}H_{24}NO_2$ $[M+H]^+$ requires 346.1807, found 346.1807.

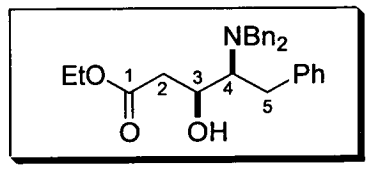
Ethyl (4*S*)-4-*N*,*N*-Dibenzylamino-3-oxo-5-phenylpentanoate 226



To a solution of acid **227** (1.99 g, 5.77 mmol) in THF (27 cm^3) was added *N*,*N*-carbonyldiimidazole (2.80, 17.3 mmol). The solution was stirred at room temperature for 2 hours. Meanwhile to a solution of LiHMDS (19.4 cm^3, 1.0 *M* in THF, 19.4 mmol) at –78 °C was added ethyl acetate (1.89 cm^3, 19.4 mmol) and the resultant solution was stirred for 20 mins at –78 °C. The imidazolide **231** (1.99g, 4.84 mmol) in THF (27 cm^3) was introduced *via* cannula. The reaction mixture was stirred at –78 °C for 20 mins and allowed to warm to 0 °C over 30 mins and stirred for a further 1 hour at 0 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl (50 cm^3) and the aqueous phase was extracted with DCM (3 × 50 cm^3). The combined organic phases were washed with brine (75 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:EtOAc (10:1)] to give the title compound (1.75 g, 88%) as a pale yellow oil. R_f [hexane:EtOAc (4:1)] 0.85; $[\alpha]_D$ –32.29 (*c* 2.66, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3085, 3027, 2841, 1745, 1716, 1495, 1454; δ_H (250 MHz, $CDCl_3$) 7.42-7.08 (15H, m, Ar*H*), 4.09-3.94 (2H, m, OCH_2CH_3), 3.91 (2H, d, *J* 13.4, NCH_XH_YPh × 2), 3.75 (1H, d, *J* 15.9, $C_2H_CH_D$), 3.72 (1H, dd, *J* 9.1, 3.8 C_4H), 3.61 (2H, d, *J* 13.4, NCH_XH_YPh × 2), 3.45 (1H, d, *J* 15.9 $C_2H_CH_D$), 3.30 (1H, dd, *J* 13.5, 9.1, $C_5H_AH_B$), 3.03 (1H, dd, *J* 13.5, 3.8, $C_5H_AH_B$), 1.15 (3H, t, *J* 7.0, OCH_2CH_3); δ_C (62.9 MHz) 202.5 (C), 167.7 (C), 139.6 (C), 139.2 (2C), 129.9 (2 × CH), 129.5 (4 × CH), 128.9 (4 × CH), 128.8 (2

× CH), 128.6 (CH), 127.9 (2 × CH), 68.8 (CH), 61.5 (CH_2), 55.0 (2 × CH_2), 47.1 (CH_2), 28.8 (CH_2), 14.3 (CH_3); m/z (FAB) 416 $[M+H]^+$, 13%), 324 (15), 300 (55), 208 (10), 181 (12), 91 (100); HRMS (FAB) $C_{27}H_{30}NO_3$ $[M+H]^+$ requires 416.2226, found 416.2226.

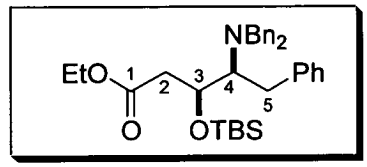
Ethyl (3*S*,4*S*)-4-*N*,*N*-Dibenzylamino-3-hydroxy-5-phenylpentanoate 221



To a solution of *β*-keto ester **226** (1.00 g, 2.40 mmol) in Et_2O (30 cm^3) and MeOH (5 cm^3) was added acetic acid (ca. 2 cm^3) until the solution was pH 4. The solution was cooled to 0 °C and sodium cyanoborohydride (908 mg, 14.4 mmol) was added. Once effervescence had ceased the resulting solution was stirred at r.t. for 7 hours. The reaction was quenched by the addition of a saturated solution of NH_4Cl (40 cm^3) and the aqueous phase was extracted with DCM (3 × 50 cm^3). The combined organic phases were washed with brine (80 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:EtOAc(8:1)] to give the title compound (800 mg, 80%) as a colourless oil. R_f [hexane:EtOAc (4:1)] 0.60; $[\alpha]_D$ +16.50 (*c* 0.52, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3516, 3026, 2808, 1727, 1495, 1454; δ_H (250 MHz, $CDCl_3$) 7.42-7.23 (15H, m, Ar*H*), 4.26 (2H, q, *J* 7.1, OCH_2CH_3), 4.15 (2H, d, *J* 13.6, NCH_XH_YPh × 2), 4.06-4.00 (2H, m, C_3HOH + O*H*), 3.50 (2H, d, *J* 13.6, NCH_XH_YPh × 2), 3.25 (1H, dd, *J* 11.1, 8.6, $C_5H_AH_B$), 2.93 (2H, m, $C_5H_AH_B$ + C_4H), 2.51 (1H, dd, *J* 15.8, 9.8, $C_2H_CH_D$), 2.19 (1H, dd, *J* 15.8, 2.6, $C_2H_CH_D$), 1.27 (3H, t, *J* 7.2, OCH_2CH_3) ; δ_C (62.9 MHz) 173.3 (C), 140.5 (2C), 139.7 (C), 129.7 (2 × CH), 129.4 (4 × CH), 129.1 (2 × CH), 128.9 (4 × CH), 127.6 (2 × CH), 126.7 (CH), 68.4 (CH), 63.5 (CH), 61.0 (CH_2), 54.9 (2 × CH_2), 40.2 (CH_2), 31.3 (CH_2), 14.3 (CH_3); m/z (FAB) 418 ($[M+H]^+$, 80%), 326 (18), 300 (59), 154 (22), 136 (17), 91 (100); HRMS (FAB) $C_{27}H_{32}NO_3$ $[M+H]^+$ requires

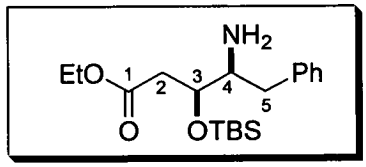
418.2382, found 418.2384; HPLC (5% propan-2-ol in hexane) **221** R_t=18.9 min, ***ent*-121** R_t=15.5 min, >99% ee.

Ethyl (3*S*,4*S*)-4-*N*,*N*-Dibenzylamino-3-*tert*-butyldimethylsilyloxy-5-phenylpentanoate 225



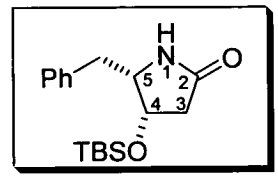
To a solution of ester **221** (300 mg, 0.719 mmol) in DCM (5 cm^3) was added 2,6-lutidine (0.20 cm^3, 1.59 mmol) followed by *tert*-butyldimethylsilyltrifluoromethanesulfonoate (0.990 cm^3, 4.32 mmol). The mixture was stirred at r.t. for 6 hours. DCM (30 cm^3) was added and the organic phase was washed sequentially with saturated aqueous sodium bicarbonate (30 cm^3), brine (30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc(10:1)] to give the title compound (360 mg, 92%) as an oil. R_f [hexane:EtOAc (4:1)] 0.74; $[\alpha]_D$ +6.92 (*c* 0.67, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3062, 2854, 2928, 1733, 1602, 1494; δ_H (250 MHz, $CDCl_3$) 7.41-7.07 (15H, m, Ar*H*), 4.29-4.18 (1H, m, C_3*H*OTBS), 4.23 (2H, d, *J* 13.3, NCH_XH$_Y$Ph × 2), 3.93-3.81 (2H, m, OCH_2CH$_3$), 3.49 (2H, d, *J* 13.6, NCH$_X$$H_Y$Ph × 2), 3.26 (1H, dd, J 14.5, 4.5, C_2H_AH$_B$), 3.19-3.97 (1H, m, C_4*H*), 3.13 (1H, dd, *J* 9.9, 5.6, C_5H_CH$_D$Ph), 3.04 (1H, dd, *J* 9.9, 6.2, C_5H$_C$$H_D$Ph), 2.58 (1H, dd, *J* 14.5, 5.3, C_2H$_A$$H_B$), 1.18 (3H, t, *J* 7.2, OCH$_2$CH_3), 0.90 (9H, s, ^{t}*Bu*), 0.04 (6H, s, *Me* × 2) ; δ_C (62.9 MHz) 171.9 (C), 141.0 (C), 139.9 (2C), 129.8 (2 × CH), 129.6 (4 × CH), 128.8 (2× CH), 128.6 (4 × CH), 127.2 (2 × CH), 126.4 (CH), 61.6 (CH), 60.5 (CH), 56.3 (2 × CH_2), 54.1 (CH_2), 39.9 (CH_2), 31.5 (CH_2), 26.4 (3 × CH_3), 18.5 (C), 14.4 (CH_3), -3.9 (CH_3), -4.3 (CH_3); m/z (FAB) 532 ($[M+H]^+$, 84%), 442 (30), 217 (47), 210 (18), 109 (36), 91 (100); HRMS (FAB) $C_{33}H_{46}NO_3Si$ $[M+H]^+$ requires 532.3247, found 532.3259.

Ethyl (3*S*,4*S*)-4-Amino-3-*tert*-butyldimethylsilyloxy-5-phenylpentanoate 224



To a solution of **225** (150 mg, 0.282 mmol) in methanol (3 cm^3) was added 20% $Pd(OH)_2/C$ (400 mg), the flask was flushed with argon before being stirred under an atmosphere of hydrogen for 8 hours. The reaction mixture was filtered through a layer of celite and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:EtOAc (6:1)] to give the title compound (100 mg, 100%) as an oil. R_f [hexane:EtOAc (1:1)] 0.23; $[\alpha]_D$ –33.2 (*c* 0.60, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2954, 2928, 2856, 1692, 1497; δ_H (250 MHz, $CDCl_3$) 7.26-7.13 (5H, m, Ar*H*), 4.13-4.07 (1H, m, C_3H), 4.07 (2H, q, *J* 7.1, OCH_2CH_3), 3.62-3.60 (2H, br s, NH_2), 3.17-3.15 (1H, br m, C_4H), 2.95-2.84 (1H, br m, $C_5H_AH_B$), 2.84 (1H, dd, *J* 15.8, 6.0, $C_2H_CH_D$), 2.66 (1H, dd, *J* 13.7, 9.3, $C_5H_AH_B$), 2.49 (1H, dd, *J* 15.8, 6.3, $C_2H_CH_D$), 1.19 (3H, t, *J* 7.1, OCH_2CH_3), 0.85 (9H, s, ^tBu), 0.00 (6H, s, *Me* × 2); δ_C (62.9 MHz) 171.5 (C), 138.3 (C), 129.1 (2 × CH), 128.5 (2 × CH), 126.4 (CH), 70.4 (CH), 60.5 (CH_2), 56.6 (CH), 39.1 (CH_2), 38.6 (CH_2), 25.7 (3 × CH_3), 17.9 (C), 14.0 (CH_3), -4.7 (CH_3), -5.1 (CH_3); m/z (FAB) 352 ($[M+H]^+$, 100%), 306 (14), 338 (10),174 (5), 91 (14), 73 (35); HRMS (FAB) $C_{19}H_{34}NO_3Si$ $[M+H]^+$ requires 352.2307, found 352.2300.

(4*S*,5*S*)-4-*tert*-Butyldimethylsilyloxy-5-benzylpyrrolidin-2-one 232



From ester 224:

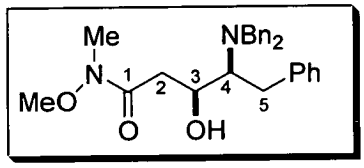
A solution of amino ester **224** (60 mg, 0.17 mmol) in MeOH (3 cm^3) was heated to reflux and held at reflux for 24 hours. The solution was cooled and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel gel [DCM:MeOH (100:1)] to give the title compound (17 mg, 33%) as a colourless oil. R_f [DCM:MeOH (10:1)] 0.63; $[\alpha]_D$ –63.3 (*c* 0.35, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2954, 2928, 2856, 1697; δ_H (250 MHz, $CDCl_3$) 7.34-7.16 (5H, m, Ar*H*), 5.63 (1H, s, N*H*), 4.57 (1H, td, *J* 6.2, 4.7, C_4H), 3.87 (1H, ddd, *J* 10.3, 6.2, 3.8, C_5H), 2.95 (1H, dd, *J* 13.9, 3.8, CH_AH_BPh), 2.77 (1H, dd, *J* 13.9, 10.3, CH_AH_BPh), 2.58 (1H, dd, *J* 16.7, 6.2, $C_3H_CH_D$), 2.35 (1H, dd, *J* 16.7, 4.7, $C_3H_CH_D$), 0.92 (9H, s, ^tBu), -0.05 (3H ,s, *Me*), -0.04 (3H, s, *Me*); δ_C (62.9 MHz) 174.8 (C), 138.0 (C), 129.0 (2 × CH), 128.7 (2 × CH), 126.6 (CH), 69.2 (CH), 60.5 (CH), 40.2 (CH_2), 36.0 (CH_2), 25.6 (3 × CH_3), 25.5 (C), -3.1 (CH_3), -4.7 (CH_3); m/z (FAB) 306 ($[M+H]^+$, 100%), 290 (20), 248 (16), 206 (8), 174 (17), 157 (6), 115 (10), 73 (85); HRMS (FAB) $C_{17}H_{28}NO_2Si$ $[M+H]^+$ requires 306.1893, found 306.1893.

From Pyrrolidinone 234:

To a solution of pyrrolidinone **234** (90 mg, 0.47 mmol), in DCM (5 cm^3) was added 2,6-lutidine (0.13 cm^3, 1.0 mmol) followed by *tert*-butyldimethylsilyltrifluoromethanesulphonate (0.65 cm^3, 2.8 mmol). The mixture was stirred at room temperature 5 hours then diluted with DCM (25 cm^3) and washed with a saturated aqueous solution of sodium bicarbonate (20 cm^3) and brine (20 cm^3).

The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [DCM:MeOH (100:1)] to give the title compound (130 mg, 94%) as a colourless oil. *all spectroscopic data was identical to the compound from ester* ***224****.*

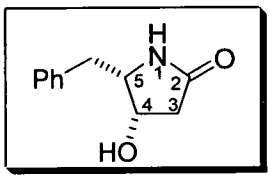
(3*S*,4*S*)-4-*N*,*N*-Dibenzylamino-3-hydroxy-5-phenylpentanoic acid methoxy-methyl-amide 233



To a slurry of N,O-dimethylhydroxylamine•hydrochloride (698 mg, 7.20 mmol) in THF (4 cm^3) at 0 °C was added trimethylaluminium (3.60 cm^3, 2.0 *M* in toluene, 7.20 mmol). The solution was stirred at 0 °C for 5 minutes then allowed to warm to room temperature over ca. 15 minutes, after which time a clear solution remained. The *β*-hydroxy ketone **221** (500 mg, 1.20 mmol) in THF (4 cm^3) was added dropwise *via* cannula. The mixture was warmed to 35 °C and stirred for 3 hours. The reaction mixture was cooled and then cannulated rapidly into a mixture of DCM (30 cm^3) and saturated aqueous potassium sodium tartrate (30 cm^3) and stirred vigorously for 5 hours whereupon two distinct phases were apparent. The aqueous phase was extracted with DCM (3 × 30 cm^3). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:EtOAc (5:1) to give the title compound. R_f [hexane:EtOAc (5:1)] 0.52; $[\alpha]_D$ +10.5 (*c* 0.61, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3384, 2933, 2559, 1658, 1415; δ_H (250 MHz, $CDCl_3$) 7.38-7.16 (15H, m, Ar*H*), 4.21 (2H, d, *J* 13.3, NCH_XH_YPh × 2), 4.16 (1H, br s, O*H*), 4.02 (1H, ddd, *J* 7.3, 5.0, 2.1, C_3HOH), 3.53 (3H, s, O*Me*), 3.49 (2H, d, *J* 13.3, NCH_XH_YPh × 2), 3.18 (1H, m, $C_5H_AH_B$), 3.11 (3H, s, *Me*), 3.05 (1H, dd, *J* 13.3, 9.3, $C_5H_AH_B$), 2.89-2.73 (2H, m, $C_2H_CH_D$ + C_4H), 2.71 (1H, dd, *J* 9.3, 5.0, $C_2H_CH_D$); δ_C (62.9 MHz) 174.1 (C), 140.3 (C), 139.9 (2C),

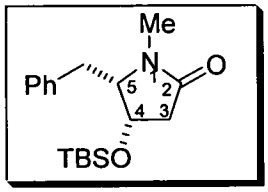
129.3 (2 × CH), 128.9 (4 × CH), 128.3 (2 × CH), 128.1 (4 × CH), 126.8 (2 × CH), 125.8 (CH), 67.8 (CH_3), 63.1 (CH_3), 60.9 (CH), 54.8 (2 × CH_2), 36.6 (CH_2), 31.7 (CH), 30.3 (CH_2); m/z (FAB) 433 ($[M+H]^+$, 76%), 341 (27), 300 (65), 210 (16), 181 (13), 131 (10), 105 (23), 91 (100); HRMS (FAB) $C_{27}H_{33}N_2O_2$ $[M+H]^+$ requires 433.2494, found 433.2494.

4*S*,5*S*)-5-Benzyl-4-hydroxypyrrolidin-2-one 234



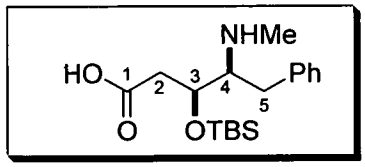
To a solution of Weinreb amide **233** (400 mg, 0.962 mmol) in methanol (5 cm^3) was added 20% $Pd(OH)_2/C$ (400 mg), the flask was flushed with argon before being stirred under an atmosphere of hydrogen for 8 hours. The reaction mixture was filtered through a layer of celite and concentrated under reduced pressure. The residue was chromatographed on silica gel [DCM:MeOH (50:1) to give the title compound (175 mg, 96%) as a white solid. R_f[DCM:MeOH (10:1)] 0.50; $[\alpha]_D$ –78.8 (*c* 0.41, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3356, 2923, 1679, 1496; δ_H (250 MHz, $CDCl_3$) 7.31-7.16 (5H, m, Ar*H*), 6.28 (1H, s, N*H*), 4.38-4.35 (1H, m, C_4*H*OH), 3.87 (1H, ddd, *J* 10.8, 8.5, 6.0, C_5*H*), 3.55 (1H, d, *J* 8.8, O*H*), 3.07 (1H, dd, *J* 13.7, 6.2, C$H_A$$H_B$Ph), 2.86 (1H, dd, *J* 13.7, 8.5, C$H_A$$H_B$Ph), 2.64 (1H, dd, *J* 17.2, 6.0, $C_3H_C$$H_D$), 2.42 (1H, dd, *J* 17.2, 1.7, $C_3H_C$$H_D$); δ_C (62.9 MHz) 176.4 (C), 137.7 (C), 128.9 (2 × CH), 128.6 (2 × CH), 126.6 (CH), 68.2 (CH), 61.0 (CH), 40.9 (CH_2), 34.9 (CH_2); m/z (FAB) 192 $[M+H]^+$, 100%), 174 (8), 120 (8), 109 (13), 105 (10), 81 (13), 73 (22), 69 (18); HRMS (FAB) $C_{11}H_{14}NO_2$ $[M+H]^+$ requires 192.1025, found 192.1026.

(4*S*,5*S*)-4-*tert*-Butyldimethylsilyloxy-5-benzyl-*N*-methylpyrrolidin-2-one 235



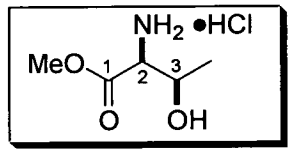
To a solution of hydroxyl protected pyrrolidinone **232** (140 mg, 0.438 mmol) in THF (4 cm^3) at 0 °C was added NaH (52.3 mg, 60% dispersion in oil, 1.05 mmol). The suspension was stirred for 20 mins before the addition of MeI (0.156 cm^3, 2.53 mmol). The mixture was stirred for 24 hours at r.t.. Water (10 cm^3) was added and the aqueous layer was extracted with DCM (3 × 10 cm^3). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel[DCM:MeOH (50:1)] to give the title compound (117 mg, 78%) as a white solid. R_f [DCM:MeOH (10:1)] 0.75; δ_H (250 MHz, $CDCl_3$) 7.26-7.21 (5H, m, Ar*H*), 4.52 (1H, ddd, *J* 10.3, 7.4, 7.0, C_4HOTBS), 3.83-3.74 (1H, m, C_5H), 3.14 (2H, dd, *J* 14.6, 5.1, CH_XH_YPh), 2.84 (1H, dd, *J* 14.6, 7.4, CH_XH_YPh), 2.57 (3H, s, *Me*), 2.47 (1H, dd, *J* 15.8, 7.4, $C_3H_AH_B$), 2.30 (1H, *J* 15.8, 7.0, $C_3H_AH_B$), 0.90 (9H, s, ^tBu), 0.00 (3H, s, *Me*), -0.01 (3H, s, *Me*). m/z (FAB) 320 $[M+H]^+$, 95%), 262 (17), 228 (24), 217 (11), 188 (22), 135 (14), 109 (13), 73 (100); HRMS (FAB) $C_{18}H_{30}NO_2Si$ $[M+H]^+$ requires 320.2046, found 320.2046.

Attempted synthesis of (3*S*,4*S*)-3-*tert*-Butyldimethylsilyloxy-4-*N*-methyl-phenylpentanoic acid 222



To a suspension of lactam **235** (20 mg, 0.06 mmol) in water was added activated barium hydroxide (44 mg, 0.14 mmol). The mixture was heated to reflux and heated at reflux for 24 hours. H_2O (8 cm^3) was added and the aqueous layer was extracted with EtOAc (3 × 5 cm^3). The aqueous layer was then acidified with 1N HCl to pH 3 and the aqueous layer was extracted with Et_2O (3 × 5 cm^3). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. No material was recovered.

Methyl (2*S*,3*R*)-2-amino-3-hydroxybutanoate•hydrochloride 238



Acetyl chloride (19.5 cm^3, 2.52 mol) was added dropwise to methanol (90 cm^3) at 0 °C. The mixture was stirred for 15 mins and *L*-threonine (10.0 g, 0.841 mol) was then added portionwise to the solution. The resulting mixture was heated to reflux and held at reflux for 3 hours. Concentration under reduced pressure provided the title compound (13.0 g, 93%) as a yellow oil; $[\alpha]_D$ –4.78 (*c* 3.37, MeOH); ν_{max} (solution cell, $CHCl_3$)/cm^{-1} 3391, 2980, 1715, 1613, 1514, 1443; m/z (FAB) 134 $[M+H]^+$, 100%), 116 (32), 84 (21), 74 (84), 56 (73); HRMS (FAB) $C_5H_{12}NO_3$ $[M+H]^+$, requires 134.0817, found 134.0813.

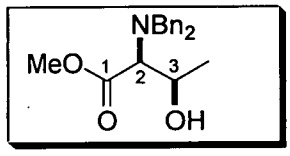
Major Diastereomer:

δ_H (250 MHz, D_2O) 4.34-4.30 (1H, m, C_3HOH), 4.01 (1H, d, *J* 3.8, C_2H), 3.75 (3H, s, O*Me*), 1.24 (3H, d, *J* 6.6, *Me*); δ_C (62.9 MHz) 169.5 (C), 65.5 (CH_3), 58.7 (CH), 54.0 (CH), 19.1 (CH_3).

Minor Diasteromer (Diagnostic signals) 239:

δ_H (250 MHz, D_2O) 3.87 (1H, d, *J* 3.8, C_2H), 3.23 (3H, s, O*Me*), 1.23 (3H, d, *J* 6.6, *Me*); δ_C (62.9 MHz) 171.1 (C), 65.6 (CH_3), 58.9 (CH), 49.2 (CH), 19.3 (CH_3).

Methyl (2*S*,3*R*)-2-*N*,*N*-Dibenzylamino-3-hydroxybutanoate 240



To a solution of ester **238** (10.5 g, 61.9 mmol) in anhydrous acetonitrile (250 cm^3) was added anhydrous potassium carbonate (42.3 g, 297 mmol) followed by benzylbromide (18.2 cm^3, 14.8 mmol). The resultant mixture was stirred for 24 hours at r.t.. Water (150 cm^3) was added and the aqueous layer was extracted with EtOAc (3 × 100 cm^3). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane then hexane:EtOAc(4:1)] to give the title compound (18.9 g, 97 %) as an oil. R_f [Hexane:EtOAc (4:1)] 0.48; $[\alpha]_D$ −166.7 (*c* 1.64, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3432, 3029, 2949, 2848, 1731, 1435; m/z (FAB) 314 ($[M+H]^+$, 51%), 268 (55), 254 (56), 236 (18), 181 (20), 91 (100); HRMS (FAB) $C_{19}H_{24}NO_3$ $[M+H]^+$ requires 314.1756, found 314.1753.

Major Diastereomer:

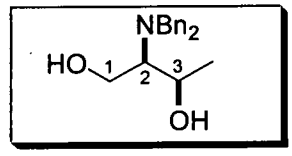
δ_H (250 MHz, $CDCl_3$) 7.51-7.25 (10H, m, Ar*H*), 4.11 (2H, d, *J* 13.1, NCH_XH_YPh × 2), 4.08-4.03 (1H, m, C_3HOH), 3.86 (3H, s, O*Me*), 3.48 (2H, d, *J* 13.1, NCH_XH_YPh × 2), 3.13 (1H, d, *J* 9.6, C_2H), 1.13 (3H, d, *J* 6.0, *Me*); δ_C (62.9 MHz) 171.2 (C), 138.5

(2C), 129.6 (4 × CH), 129.1 (4 × CH), 128.0 (2 × CH), 67.8 (CH), 63.6 (CH), 55.3 (2 × CH_2), 51.9 (CH_3), 19.6 (CH_3).

Minor Diasteromer (Diagnostic signals) 241:

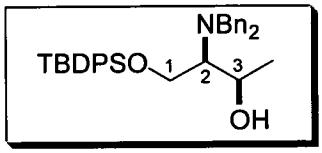
δ_H (250 MHz, $CDCl_3$) 4.10-4.00 (2H, m, NCH_XH_YPh × 2), 3.50-3.40 (2H, m, NCH_XH_YPh × 2), 3.15 (1H, d, *J* 9.6, C_2H), 1.11 (3H, d, *J* 6.0, *Me*); δ_C (62.9 MHz) 170.6 (C), 66.8 (CH).

(2*R*,3*R*)-2-*N*,*N*-Dibenzylamino-1,3-dihydroxybutane 242



To a solution of **240** (10.0 g, 32.0 mmol) in ether (100 cm^3) at 0 °C was added lithium borohydride (4.03 g, 192 mmol) followed by methanol (10 cm^3). The mixture was stirred at 0 °C until effervescence ceased and then heated to reflux and held at reflux for 4 hours. The reaction was quenched by the cautious addition of saturated aqueous NH_4Cl (100 cm^3) and the aqueous phase was extracted with EtOAc (3 × 100 cm^3). The combined organic phases were washed with brine (100 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [DCM:MeOH(30:1)] to give the title compound (7.80 g, 85 %) as a white solid. R_f [DCM:MeOH (10:1)] 0.54; mp 84-85 °C; $[\alpha]_D$ –57.5 (*c* 0.88, $CHCl_3$); ν_{max} (solution cell, $CHCl_3$)/cm^{-1} 3361, 3023, 1493; δ_H (250 MHz, $CDCl_3$) 7.35-7.21 (10H, m, Ar*H*), 3.94 (2H, d, *J* 13.2, NCH_XH$_Y$Ph × 2), 3.86 (1H, dq, *J* 9.3, 5.8, C_3HOH), 3.82-3.70 (2H, m, C_1H_2),3.68 (2H, d, *J* 13.2, NCH$_X$$H_Y$Ph × 2), 2.55 (1H, dt, *J* 9.3, 5.5, C_2H), 1.12 (3H, d, *J* 6.1, *Me*); δ_C (62.9 MHz) 139.0 (2C), 129.0 (4 × CH), 128.4 (4 × CH), 127.1 (2C), 65.1 (CH), 64.5 (CH), 59.0 (CH_2), 54.3 (2 × CH_2), 20.1 (CH_3); m/z (FAB) 286 ($[M+H]^+$, 52%), 240 (35), 91 (100); HRMS (FAB) $C_{18}H_{24}NO_2$ $[M+H]^+$ requires 286.1807, found 286.1801; Found : C, 75.79; H, 7.92; N, 4.89. $C_{18}H_{23}NO_2$ requires C, 75.78; H, 8.07; N, 4.91 %.

(2*R*,3*R*)-1-*tert*-Butyldiphenylsilyloxy-2-*N*,*N*-dibenzylamino-3-hydroxybutane 243



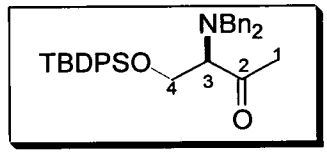
From diol 242:

To a solution of **242** (5.00 g, 17.5 mmol) in anhydrous DMF (60 cm^3) was added *tert*-butyldiphenylsilylchloride (5.40 cm^3, 21.0 mmol) followed by imidazole (4.26 g, 61.3 mmol). The resultant mixture was stirred for 22 hours at room temperature. Brine (80 cm^3) was added and the aqueous phase was extracted with EtOAc (3 × 50 cm^3). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:EtOAc (4:1)] to give an impure mixture. Further purification by HPLC (15 % EtOAc in hexane) gave the title compound (8.20 g, 90 %) as a white solid. R_t=11.2 min; R_f [hexane:EtOAc (4:1)] 0.57; $[\alpha]_D$ –66.2 (*c* 1.14, $CHCl_3$); ν_{max} (solution cell, $CHCl_3$)/cm^{-1} 3376, 2930, 2856, 1427; δ_H (250 MHz, $CDCl_3$) 7.78-7.22 (20H, m, Ar*H*), 4.21 (1H, br s, O*H*), 4.04 (2H, d, *J* 13.3, NCH_XH$_Y$Ph × 2), 3.98 (1H, dd, *J* 11.5, 4.0, C$_1H_A$H$_B$OTBDPS), 3.89 (1H, dd, *J* 11.5, 5.6, C$_1$H$_A$$H_B$OTBDPS), 3.83 (1H, dq, *J* 9.5, 5.9, C$_3$*H*OH), 3.67 (2H, d, *J* 13.3, NCH$_X$$H_Y$Ph × 2), 2.64 (1H, ddd, *J* 9.5, 5.6, 4.0, C$_4$*H*), 1.16 (9H, s, ^{t}*Bu*), 1.02 (3H, d, *J* 6.0, *Me*); δ_C (62.9 MHz) 139.2 (2C), 135.6 (CH), 13.5 (CH), 132.9 (C), 132.8 (C), 129.9 (2 × CH), 129.8 (2 × CH), 129.0 (4 × CH), 18.3 (4 × CH), 127.7 (4 × CH), 127.1 (2 × CH), 65.6 (CH), 63.2 (CH), 60.2 (CH_2), 54.5 (2 × CH_2), 26.8 (3 × CH_3), 19.6 (CH_3), 19.0 (C); m/z (FAB) 524 ($[M+H]^+$, 56%), 434 (50), 199 (46), 105 (51), 91 (83), 45 (100); HRMS (FAB) $C_{34}H_{42}NO_2Si$ $[M+H]^+$ requires 524.2984, found 524.2985; HPLC (5% propan-2-ol in hexane) **243** R_t=7.8 min, ***ent*-243** R_t=3.9 min, >99% ee.

From reduction of ketone 244:

To a solution of ketone **244** (104 mg, 0.200 mmol) in toluene at –78 °C was added DIBAL-H (0.810 cm^3, 0.81 mmol). The solution was stirred at –78 °C for 1 hour. The reaction was quenched by the cautious addition of methanol (ca. 5 cm^3). The mixture was allowed to warm to r.t. before being diluted with DCM (20 cm^3). The mixture was poured onto saturated aqueous potassium sodium tartrate (30 cm^3) and the mixture stirred vigorously for 5 hours when two distinct phases were apparent. The organic layer was separated and the aqueous layer was extracted with DCM (2 × 20 cm^3). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound (95 mg, 90%). $[\alpha]_D$ –66.0 (*c* 1.0, $CHCl_3$); *all spectroscopic data was identical to the compound from diol* ***242****.*

(3*R*)-4-*tert*-Butyldiphenylsilyloxy-3-*N*,*N*-dibenzylaminobutan-2-one 244



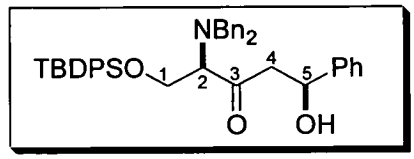
To a solution of oxalyl chloride (0.050 cm^3, 0.54 mmol) in DCM (2 cm^3) at –78 °C was added DMSO (0.060 cm^3, 0.82 mmol). The mixture was stirred for ca. 5 minutes when it became cloudy. A solution of alcohol **243** (0.20 mg, 0.39 mmol) in DCM (2 cm^3) was added *via* cannula. The resulting clear solution was stirred at –78 °C for 1 hour. Triethylamine (0.22 cm^3, 1.6 mmol) was added and the cloudy solution was allowed to warm to room temperature over ca. 15 minutes. Water (15 cm^3) was added and the aqueous phase was extracted with DCM (3 × 15 cm^3). The combined organic phases were washed sequentially with 1% HCl (15 cm^3), water (15 cm^3), saturated aqueous $NaHCO_3$ (15 cm^3) and brine (15 cm^3), then dried ($MgSO_4$) and concentrated under reduced pressure to give the title compound (200 mg, 100%) as a very pale yellow oil which was used in subsequent stages without further purification. R_f [hexane:EtOAc (4:1)] 0.70; ν_{max} (neat)/cm^{-1} 2930, 2857, 1717, 1427;

δ_H (250 MHz, $CDCl_3$) 7.71-7.23 (20H, m, Ar*H*), 4.15 (1H, dd, *J* 10.7, 4.5, $C_4H_AH_B$OTBDPS), 4.09 (1H, dd, *J* 10.7, 6.7, $C_4H_AH_B$OTBDPS), 3.88 (2H, d, *J* 13.8, $NCH_XH_YPh \times 2$), 3.79 (2H, d, *J* 13.8, $NCH_XH_YPh \times 2$), 3.58 (1H, br t, *J* 5.9, C_3H), 2.16 (3H, s, *Me*), 1.08 (9H, s, ^tBu); δ_C (60.9 MHz) 208.8 (C), 139.5 (2C), 135.5 (4 × CH), 133.0 (C), 129.7 (CH), 129.6 (CH), 128.9 (C), 128.7 (4 × CH), 128.1 (4 × CH), 128.0 (CH), 128.0 (CH), 127.6 (2 × CH), 129.7 (2 × CH), 67.6 (CH), 60.7 (CH_2), 55.1 (2 × CH_2), 28.9 (CH_3), 26.7 (3 × CH_3), 19.0 (C).

Preparation of Dicyclohexylchloroborane $(C_6H_{11})_2BCl$

To a freshly distilled solution of cyclohexene (10.6 cm^3, 105 mmol) in ether (45 cm^3) at r.t. was added monochloroborane-methylsulphide complex (5.20 cm^3, 50.2 mmol). The solution was stirred at r.t. for 2 hours. The solvent was removed in *vacuo* (r.t., *ca.*10 mm Hg, vacuum line) to give the chloroborane-methyl sulphide complex as a white solid. Distillation under reduced pressure gave dicyclohexylchloroborane as a colourless oil (8.11 g, 76%; estimated density=0.98). The complex was stored in the freezer; bp 98-104°C (10 mm Hg).

Attempted synthesis of (2*R*,5*S*)-1-*tert*-Butyldiphenylsilyloxy-2-*N*,*N*-dibenzylamino-5-hydroxy-5-phenyl-pentan-3-one 251B



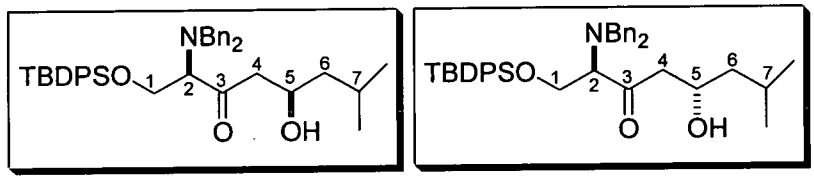
To a solution of dicyclohexylchloroborane (0.260 cm^3, 1.22 mmol) in Et_2O (1 cm^3) at –78 °C was added triethylamine (0.195 cm^3, 1.39 mmol) followed by ketone **244** (210 mg, 0.410 mmol) in Et_2O (3.5 cm^3) *via* cannula. The mixture was stirred at –78 °C for 10 mins before being stirred at 0 °C for 2 hours. The mixture was cooled to –78 °C and freshly distilled benzaldehyde (0.159 cm^3, 1.64 mmol) was added. The mixture was stirred at –78 °C for 1 hour, warmed to 0 °C over a period of 1 hour and stirred at 0 °C for 3 hours. The reaction was quenched by the addition of methanol (1 cm^3) and pH 7 phosphate buffer (2 cm^3). Hydrogen peroxide (2 cm^3) in methanol (2 cm^3) was added cautiously and the resultant cloudy solution was stirred at 0 °C for 1 hour. The solution was diluted by addition of DCM (20 cm^3). The organic phase was separated and the aqueous phase was extracted with DCM (2 × 20 cm^3). The combined organic phases were washed with saturated aqueous sodium bicarbonate (30 cm^3), brine (30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (15:1)] to give the unreacted starting materials.

General Procedure A:

To a solution of LiHMDS (1.0 *M* in THF, 0.62 mmol) at –78 °C was added the ketone **244** (250 mg, 0.48 mmol) in THF (4 cm^3) *via* cannula. The solution was stirred at –78 °C for 1 hour. The aldehyde (0.72 mmol) was added and the solution stirred for 10 mins. The reaction was quenched by the addition of saturated aqueous NH_4Cl (20 cm^3) and the aqueous phase was extracted with DCM (3 × 15 cm^3). The

combined organic phases were washed with brine (20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (15:1)] to give the title compounds.

(2*R*,5*R*)-*tert*-Butyldiphenylsilyloxy-2-*N*,*N*-dibenzylamino-5-hydroxy-7-methyl-octan-3-one 251A and (2*R*,5*S*)-*tert*-Butyldiphenylsilyloxy-2-*N*,*N*-dibenzylamino-5-hydroxy-7-methyl-octan-3-one 251B



General procedure **A** was followed with ketone **244** (250 mg, 0.480 mmol), LiHMDS (0.620 cm^3, 1.0 *M* in THF, 0.620 mmol) and isovalderaldehyde (0.080 cm^3, 0.720 mmol) thus providing the title compounds (230 mg, 88%) as an inseparable mixture after chromatography. R_f [hexane:EtOAc (4:1)] 0.48; ν_{max} (neat)/cm^{-1} 3429, 3069, 2959, 2857, 1706; m/z (FAB) 608 ($[M+H]^+$, 28%), 478 (35), 197 (30), 181 (10), 165 (6), 135 (55), 105 (20), 91 (100); HRMS (FAB) $C_{39}H_{50}NO_3Si$ $[M+H]^+$ requires 608.3555, found 608.3555.

Major diastereomer 251A:

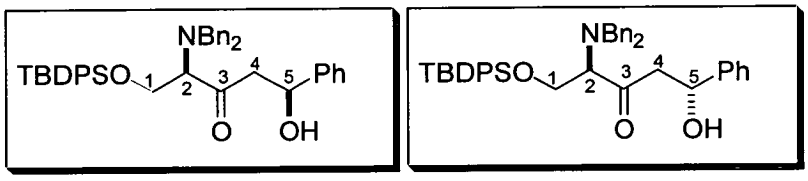
δ_H (250 MHz, $CDCl_3$) 7.76-7.23 (20H, m, Ar*H*), 4.18 (1H, dd, *J* 10.5, 6.4, $C_1H_AH_B$OTBDPS), 4.07 (1H, dd, *J* 10.5, 5.8, $C_1H_AH_B$OTBDPS), 3.88 (2H, d, *J* 13.7, $NCH_XH_YPh \times 2$), 3.78 (2H, d, *J* 13.7, $NCH_XH_YPh \times 2$), 3.60 (1H, br t, *J* 6.0, C_2H), 2.63 (1H, dd, *J* 17.4, 8.5, $C_4H_CH_D$), 2.43 (1H, dd, *J* 17.4, 2.8, $C_4H_CH_D$), 1.83-1.69 (1H, m, C_5HOH), 1.52-1.41 (1H, m, C_7H), 1.17-1.00 (2H, m, C_6H_2), 1.08 (9H, s, ^tBu) 0.93 (3H, d, *J* 6.6, *Me*), 0.92 (3H, d, *J* 6.6, *Me*); δ_C (60.9 MHz) 211.9 (C), 139.2 (2C), 135.5 (4 × CH), 132.8 (C), 132.7 (C), 129.7 (CH), 128.7 (4 × CH), 128.2 (4 × CH), 127.7 (4 × CH), 127.1 (CH), 127.0 (2 × CH), 67.0 (CH), 65.5 (CH), 60.5 (CH_2), 55.1

(2 × CH_2), 48.6 (CH_2), 45.4 (CH_2), 26.7 (3 × CH_3), 24.2 (CH), 23.2 (CH_3), 21.9 (CH_3), 18.9 (C).

Minor diastereomer (diagnostic signals) 252A:

δ_H (250 MHz, $CDCl_3$) 3.76 (2H, d, *J* 13.7 NCH_XH_Y × 2), 2.81 (1H, dd, *J* 17.4, 2.8, $C_4H_CH_D$), 2.43 (1H, dd, *J* 17.4, 8.5, $C_4H_CH_D$), 1.09 (9H, s, ^{t}Bu), 0.94 (3H, d, *J* 6.6 *Me*), 0.93 (3H, d, *J* 6.6, *Me*); δ_C (60.9 MHz) 211.8 (C), 67.3 (CH), 65.9 (CH), 59.9 (CH_2), 48.6 (2 × CH_2), 47.9 (CH_2), 26.4 (3 × CH_3), 23.1 (CH_3), 22.0 (CH_3).

(2*R*,5*S*)-1-*tert*-Butyldiphenylsilyloxy-2-*N*,*N*-dibenzylamino-5-hydroxy-5-phenyl-pentan-3-one 251B and (2*R*,5*R*)-*tert*-Butyldiphenylsilyloxy-2-*N*,*N*-dibenzylamino-5-hydroxy-5-phenyl-pentan-3-one 252B



General procedure **A** was followed with ketone **244** (250 mg, 0.480 mmol), LiHMDS (0.62 cm^3, 1.0 *M* in THF, 0.620 mmol) and benzaldehyde (0.070 cm^3, 0.720 mmol) thus providing the title compounds (240 mg, 82%) as an inseparable mixture after chromatography. R_f [hexane:EtOAc (4:1)] 0.55; ν_{max} (neat)/cm^{-1} 3446, 3061, 2930, 2857, 1708; m/z (FAB) 628 ($[M+H]^+$, 56%), 478 (20), 217 (20), 197 (20), 181 (9), 135 (32), 109 (18), 91 (100); HRMS (FAB) $C_{41}H_{46}NO_3Si$ $[M+H]^+$ requires 628.3247, found 628.3253.

Major diastereomer 251B:

δ_H (250 MHz, $CDCl_3$) 7.72-7.15 (25H, m Ar*H*), 5.07 (1H, dd, *J* 9.2, 3.3, C_5HOH), 4.17 (1H, dd, *J* 10.5, 6.3, $C_1H_AH_BOTBDPS$), 4.08 (1H, dd, *J* 10.5, 5.7, $C_1H_AH_BOTBDPS$), 3.88 (2H, d, *J* 13.6, NCH_XH_YPh × 2), 3.77 (2H, d, *J* 13.6, NCH_XH_YPh × 2), 3.60 (1H, br t, *J* 6.0, C_2H), 3.40-3.30 (1H, br s, O*H*), 2.99 (1H, dd,

J 17.3, 9.2, $C_4H_CH_D$), 2.83 (1H, dd, *J* 17.3, 3.3, $C_4H_CH_D$), 1.07 (9H, s, ^tBu); δ_C (60.9 MHz) 210.8 (C), 142.8 (C), 139.1 (2C), 135.5 (4 × CH), 132.8 (C), 132.7 (C), 129.8 (CH), 129.7 (CH), 128.9 (2 × CH), 128.8 (2 × CH), 128.3 (4 × CH), 128.1 (CH), 127.7 (4 × CH), 127.4 (2 × CH), 127.1 (2 × CH), 125.6 (2 × CH), 69.8 (CH), 67.1 (CH), 60.5 (CH_2), 55.1 (2 × CH_2), 50.0 (CH_2), 26.7 (3 × CH_3), 18.9 (C).

Minor diastereomer (diagnostic signals) 252B:

δ_H (250 MHz, $CDCl_3$) 4.16 (1H, dd, *J* 10.5, 6.4, $C_1H_AH_BOTBDPS$), 3.87 (2H, d, *J* 13.7, NCH_XH_YPh × 2), 3.01 (1H, dd, *J* 17.3, 3.3, $C_4H_CH_D$), 1.08 (9H, s, ^tBu); δ_C (60.9 MHz) 211.0 (C), 70.0 (CH), 67.5 (CH), 60.2 (CH_2), 55.2 (2 × CH_2), 49.4 (CH_2), 19.0 (C).

(2*R*,5*S*)-1-*tert*-Butyldiphenylsilyloxy-2-*N*,*N*-dibenzylamino-5-hydroxy-5-(*p*-chlorophenyl)-pentan-3-one 251C and (2*R*,5*R*)-*tert*-Butyldiphenylsilyloxy-2-*N*,*N*-dibenzylamino-5-hydroxy-5-(*p*-chlorophenyl)-pentan-3-one 252C

General procedure **A** was followed with ketone **244** (250 mg, 0.480 mmol), LiHMDS (0.620 cm^3, 1.0 *M* in THF, 0.620 mmol) and chlorobenzaldehyde (100 mg, 0.720 mmol) thus providing the title compounds (275 mg, 89%) as an inseparable mixture after chromatography. R_f [hexane:EtOAc (4:1)] 0.40; ν_{max} (neat)/cm^{-1} 3424, 3969, 2930, 2857, 1708; m/z (FAB) 662 ($[M+H]^+$, 19%), 478 (14), 217 (17), 197 (17), 135 (15), 91 (100); HRMS (FAB) $C_{41}H_{46}NO_3SiCl$ $[M+H]^+$ requires 662.2845, found 662.2840.

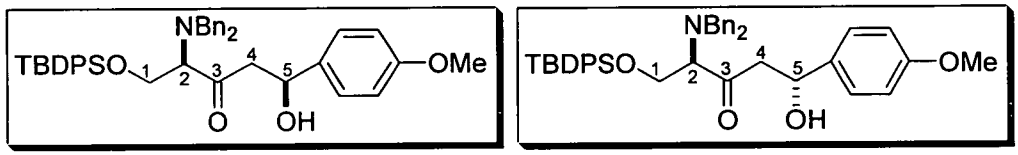
Major diastereomer 251C:

δ_H (250 MHz, $CDCl_3$) 7.77-7.23 (24H, m, Ar*H*), 5.09 (1H, dd, *J* 8.4, 3.2, C_5HOH), 4.24 (1H, dd, *J* 10.5, 6.3, $C_1H_AH_BOTBDPS$), 4.15 (1H, dd, *J* 10.5, 5.9, $C_1H_AH_BOTBDPS$), 3.94 (2H, d, *J* 13.7, $NCH_XH_YPh \times 2$), 3.82 (2H, d, *J* 13.7, $NCH_XH_YPh \times 2$), 3.64 (1H, t, *J* 5.9, C_2H), 3.52-3.46 (1H, br s, O*H*), 3.06 (1H, d, *J* 17.1, 3.2, $C_4H_CH_D$), 2.87 (1H, d, *J* 17.1, 8.4, $C_4H_CH_D$), 1.13 (9H, s, ^tBu); δ_C (60.9 MHz) 210.6 (C), 141.3 (C), 139.1 (2C), 135.5 (4 × CH), 133.0 (C), 132.8 (C), 132.7 (C), 129.8 (2 × CH), 129.7 (2 × CH), 128.8 (2 × CH), 128.7 (2 × CH), 128.4 (4 × CH), 127.7 (4 × CH), 127.2 (2 × CH), 127.0 (2 × CH), 69.2 (CH), 67.2 (CH), 60.4 (CH_2), 55.1 (2 × CH_2), 49.8 (CH_2), 26.1 (3 × CH_3), 19.0 (C).

Minor diastereomer (diagnostic signals) 252C:

δ_H (250 MHz, $CDCl_3$) 3.00 (1H, dd, *J* 17.2, 8.4, $C_4H_CH_D$), 2.85 (1H, dd, *J* 17.2, 3.2, $C_4H_CH_D$), 1.14 (9H, s, ^{t}Bu); δ_C (60.9 MHz) 210.8 (C), 69.4 (CH), 67.5 (CH), 60.0 (CH_2), 55.2 (2 × CH_2), 49.1 (CH_2).

(2*R*,5*S*)-1-*tert*-Butyldiphenylsilyloxy-2-*N*,*N*-dibenzylamino-5-hydroxy-5-(*p*-methoxyphenyl)pentan-3-one 251D and (2*R*,5*R*)-*tert*-Butyldiphenylsilyloxy-2-*N*,*N*-dibenzylamino-5-hydroxy-5-(*p*-methoxyphenyl)-pentan-3-one 252D



General procedure **A** was followed with ketone **244** (250 mg, 0.480 mmol), LiHMDS (0.620 cm^3, 1.0 *M* in THF, 0.620 mmol) and anisaldehyde (0.090 cm^3, 0.720 mmol) thus providing the title compounds (262 mg, 86%) as an inseparable mixture after chromatography. R_f [hexane:EtOAc (4:1)] 0.45; ν_{max} (neat)/cm^{-1} 3450, 2930, 2857, 1706; m/z (FAB) 658 ($[M+H]^+$, 14%), 478 (37), 197 (20), 135 (37), 121 (10), 91 (100); HRMS (FAB) $C_{42}H_{48}NO_4Si$ $[M+H]^+$ requires 658.3352, found 658.3353.

Major diastereomer 251D:

δ_H (250 MHz, $CDCl_3$) 7.75-7.15 (22H, m, Ar*H*), 6.89 (1H, d, *J* 6.4, Ar*H*OMe), 6.85 (1H, d, *J* 6.4, Ar*H*OMe), 5.02 (1H, dd, *J* 8.9, 3.5, C_5HOH), 4.16 (1H, dd, *J* 10.5, 6.2, $C_1H_AH_B$OTBDPS), 4.08-4.01 (1H, m, $C_1H_AH_B$OTBDPS), 3.86 (2H, d, *J* 13.2, $NCH_XH_YPh \times 2$), 3.82 (3H, s, O*Me*), 3.77 (2H, d, *J* 13.2, $NCH_XH_YPh \times 2$), 3.60 (1H, dd, *J* 6.2, 4.2, C_2H), 2.98 (1H, d, *J* 17.2, 8.9, $C_4H_CH_D$), 2.83 (1H, dd, *J* 17.2, 3.5, $C_4H_CH_D$), 1.06 (9H, s, ^tBu); δ_C (60.9 MHz) 210.8 (C), 158.9 (C), 139.2 (2C), 135.5 (4 × CH), 135.0 (2C), 134.7 (C), 132.8 (CH), 129.7 (CH), 128.8 (2 × CH), 128.2 (4 × CH), 128.0 (2 × CH), 127.7 (4 × CH), 127.1 (2 × CH), 126.9 (2 × CH), 113.7 (2 × CH), 69.5 (CH), 67.1 (CH), 60.4 (CH_2), 55.2 (CH_3), 55.1 (2 × CH_2), 49.9 (CH_2), 26.7 (3 × CH_3), 19.0 (C).

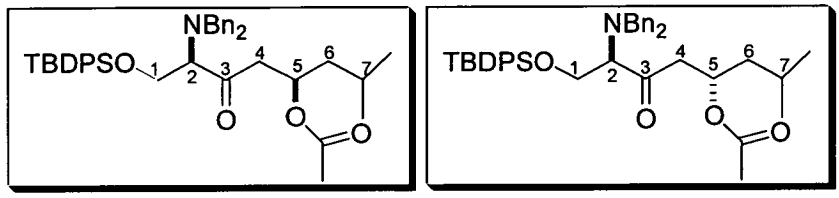
Minor diastereomer (diagnostic signals) 252D:

δ_H (250 MHz, $CDCl_3$) 6.92 (1H, d, *J* 2.3 Ar*H*OMe), 6.88 (1H, d, *J* 2.3, Ar*H*OMe), 3.89 (2H, d, *J* 13.3, $NCH_XH_YPh \times 2$), 3.82 (3H, s, O*Me*), 3.76 (2H, d, *J* 13.3, $NCH_XH_YPh \times 2$), 3.55 (1H, dd, *J* 6.2, 4.2, C_2H), 2.80 (1H, dd, *J* 17.2, 3.5, $C_4H_CH_D$), 1.08 (9H, s, ^tBu); δ_C (60.9 MHz) 210.9 (C), 69.6 (CH), 67.4 (CH), 60.1 (CH_2), 49.4 (CH_2).

General Procedure B:

To a solution of the aldol adducts **251** and **252** (100 mg, 0.170 mmol) in DCM (4 cm^3) at 0 °C was added DMAP (cat.), triethylamine (0.450 cm^3, 0.340 mmol) followed by acetic anhydride (0.320 cm^3, 0.340 mmol). The reagents were stirred at r.t. for 4 hours. The reaction was quenched by the addition of a saturated solution of hydrogen carbonate (20 cm^3). The aqueous layer was extracted with DCM (3 × 20 cm^3). The combined organic phases were washed with 1N HCl (20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure The remaining residue was chromatographed on silica gel [hexane:EtOAc (15:1)] to give the title compounds.

(2*R*,5*R*)-1-*tert*-Butyldiphenylsilyloxy-2-*N*,*N*-dibenzylamino-5-ethanoyloxy-7-methyl-octan-3-one 253A and (2*R*,5*S*)-*tert*-Butyldiphenylsilyloxy-2-*N*,*N*-dibenzylamino-5-ethanoyloxy-7-methyl-octan-3-one 254A



General procedure **B** was followed with aldol adducts **251A** and **252A** (20 mg, 0.030 mmol) DMAP (cat.), triethylamine (0.080 cm^3, 0.060 mmol) and acetic anhydride (0.060 cm^3, 0.06 mmol). This provided the title compounds (17 mg, 86%) as a 72:28 inseparable mixture of diastereomers after chromatography. R_f [hexane:EtOAc (4:1)] 0.65; ν_{max} (neat)/cm^{-1} 3406, 3701, 2929, 2857, 1686, 1679, 1599, 1546; m/z (FAB) 662 ($[M+H]^+$, 19%), 478 (14), 217 (17), 197 (17), 135 (15), 91 (100); HRMS (FAB) $C_{41}H_{46}NO_3SiCl$ $[M+H]^+$ requires 662.2845, found 662.2840.

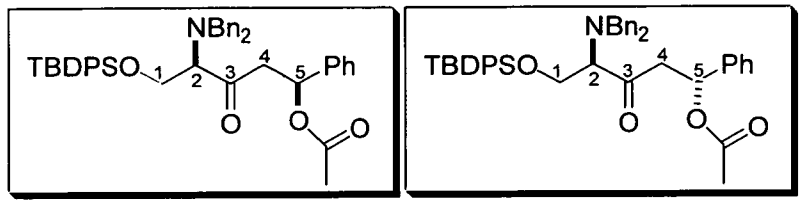
Major diastereomer 253A:

δ_H (200 MHz, $CDCl_3$) 7.77-7.14 (20H, m, Ar*H*), 4.22 (1H, dd, *J* 10.5, 6.3, $C_1H_AH_BOTBDPS$), 4.14 (1H, dd, *J* 10.5, 6.3, $C_1H_AH_BOTBDPS$), 3.91 (2H, d, *J* 13.5, $NCH_XH_YPh \times 2$), 3.80 (2H, d, *J* 13.5, $NCH_XH_YPh \times 2$), 3.65 (1H, t, *J* 6.3, C_2H), 2.93 (1H, dd, *J* 16.8, 7.0, $C_4H_CH_D$), 2.69 (1H, dd, *J* 16.8, 5.1, $C_4H_CH_D$), 1.96 (3H, s, *Me*), 1.60-1.47 (1H, m, C_5HOH), 1.44-1.18 (3H, m, $C_6H_2 + C_7H$), 1.13 (9H, s, ^tBu), 0.98 (3H, d, *J* 6.5, *Me*), 0.96 (3H, d, *J* 6.5, *Me*).

Minor diastereomer (diagnostic signals) 254A:

δ_H (200 MHz, $CDCl_3$) 1.98 (3H, s, *Me*), 1.14 (9H, s, ^{t}Bu), 1.00 (3H, d, *J* 6.5 *Me*), 0.99 (3H, d, *J* 6.5, *Me*).

(2*R*,5*S*)-1-*tert*-Butyldiphenylsilyloxy-2-*N*,*N*-dibenzylamino-5-ethanoyloxy-5-phenyl-pentan-3-one 253B and (2*R*,5*R*)-*tert*-Butyldiphenylsilyloxy-2-*N*,*N*-dibenzylamino-5-ethanoyloxy-5-phenyl-pentan-3-one 254B



General procedure **B** was followed with aldol adducts **251B** and **252B** (60 mg, 0.10 mmol) DMAP (cat.), triethylamine (0.27 cm^3, 0.20 mmol) and acetic anhydride (0.20 cm^3, 0.20 mmol). This provided the title compounds (50 mg, 90%) as a 71:29 inseparable mixture of diastereomers after chromatography. R_f [hexane:EtOAc (4:1)] 0.37; ν_{max} (neat)/cm^{-1} 3029, 2930, 2856, 1744, 1652; m/z (FAB) 670 ($[M+H]^+$, 10%), 478 (20), 240 (10), 198 (24), 135 (33), 91 (100); HRMS (FAB) $C_{43}H_{48}NO_4Si$ $[M+H]^+$ requires 670.3352, found 670.3358.

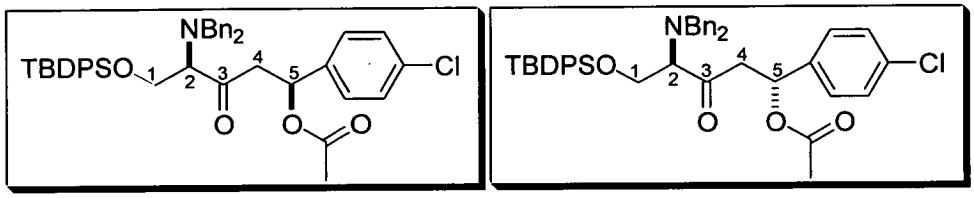
Major diastereomer 253B:

δ_H (250 MHz, $CDCl_3$) 7.67-7.16 (25H, m, Ar*H*), 6.12 (1H, dd, *J* 8.7, 5.1, C_5H), 4.10-3.98 (2H, m, C_1H_2), 3.83 (2H, d, *J* 13.6, $NCH_XH_YPh \times 2$), 3.71 (2H, d, *J* 13.6, $NCH_XH_YPh \times 2$), 3.50 (1H, dd, *J* 6.9, 5.9, C_2H), 3.33 (1H, dd, *J* 17.0, 8.7, $C_4H_CH_D$), 3.06 (1H, dd, *J* 17.0, 5.1, $C_4H_CH_D$), 1.90 (3H, s, *Me*), 1.00 (9H, s, ^tBu); δ_C (60.9 MHz) 206.0 (C), 169.6 (C), 139.7 (C), 139.3 (2C), 139.2 (C), 135.5 (4 × CH), 132.9 (C), 129.8 (CH), 129.7 (CH), 128.8 (4 × CH), 128.4 (2 × CH), 128.3 (4 × CH), 128.0 (CH), 127.6 (4 × CH), 127.1 (2 × CH), 126.4 (2 × CH), 71.3 (CH), 66.6 (CH), 60.1 (CH_2), 54.9 (2 × CH_2), 46.6 (CH_2), 26.7 (3 × CH_3), 20.9 (CH_3), 18.9 (C).

Minor diastereomer (diagnostic signals) 254B:

δ_H (250 MHz, $CDCl_3$) 3.12 (1H, dd, *J* 17.0, 8.7, $C_4H_CH_D$), 2.90 (1H, dd, *J* 17.0, 5.1, $C_4H_CH_D$), 1.89 (3H, s, *Me*), 1.04 (9H, s, ^tBu); δ_C (60.9 MHz) 206.4 (C), 169.9 (C), 71.7 (CH_2), 67.2 (CH), 60.2 (CH_2), 47.1 (CH_2).

(2*R*,5*S*)-1-*tert*-Butyldiphenylsilyloxy-2-*N*,*N*-dibenzylamino-5-ethanoyloxy-5-(*p*-chlorophenyl)-pentan-3-one 253C and (2*R*,5*R*)-*tert*-Butyldiphenylsilyloxy-2-*N*,*N*-dibenzylamino-5- ethanoyloxy -5-(*p*-chlorophenyl)-pentan-3-one 253C



General procedure **B** was followed with aldol adducts **251C** and **252C** (20 mg, 0.030 mmol) DMAP (cat.), triethylamine (0.080 cm^3, 0.060 mmol) and acetic anhydride (0.060 cm^3, 0.060 mmol). This provided the title compounds (17 mg, 89%) as a 60:40 inseparable mixture of diastereomers after chromatography. (R_f [hexane:EtOAc (4:1)] 0.35; m/z (FAB) 704 ($[M+H]^+$, 74%), 478 (84), 217 (47), 199 (47), 181 (14), 135 (32), 91 (100); HRMS (FAB) $C_{43}H_{48}NO_4SiCl$ $[M+H]^+$ requires 704.2963, found 704.2962.

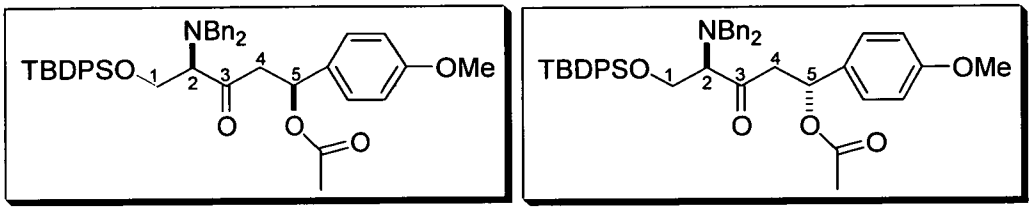
Major diastereomer 253C:

δ_H (200 MHz, $CDCl_3$) 7.82-7.18 (24H, m, Ar*H*), 4.17-3.92 (2H, m, $C_1H_AH_B$OTBDPS), 3.92 (2H, d, *J* 13.7, $NCH_XH_YPh \times 2$), 3.75-3.68 (1H, m, C_2H), 3.74 (2H, d, *J* 13.7, $NCH_XH_YPh \times 2$), 3.38 (1H, dd, *J* 17.0, 8.7, $C_4H_CH_D$), 2.82 (1H, dd, *J* 17.0, 5.1, $C_4H_CH_D$), 1.99 (3H, s, *Me*), 1.10 (9H, s, *^{t}Bu*).

Minor diastereomer (diagnostic signals) 254C:

δ_H (200 MHz, $CDCl_3$) 3.17 (2H, d, *J* 17.0, 8.7, $C_4H_CH_D$), 3.00 (2H, d, *J* 17.0, 5.1, $C_4H_CH_D$), 2.00 (3H, s, *Me*), 1.13 (9H, s, ^{t}Bu).

(2*R*,5*S*)-1-*tert*-Butyldiphenylsilyloxy-2-*N*,*N*-dibenzylamino-5-ethanoyloxy-5-(*p*-methoxyphenyl)pentan-3-one 253D and (2*R*,5*R*)-*tert*-Butyldiphenylsilyloxy-2-*N*,*N*-dibenzylamino-5-ethanoyloxy-5-(*p*-methoxyphenyl)-pentan-3-one 254D



General procedure B was followed with aldol adducts **253D** and **254D** (20 mg, 0.030 mmol) DMAP (cat.), triethylamine (0.080 cm^3, 0.060 mmol) and acetic anhydride (0.060 cm^3, 0.060 mmol). This provided the title compounds (17 mg, 89%) as a 55:45 mixture of inseparable diastereomers after chromatography. R_f [hexane:EtOAc (4:1)] 0.33.

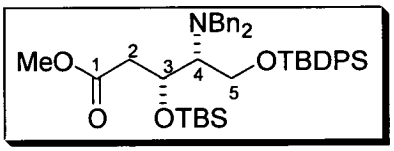
Major diastereomer 253D:

δ_H (250 MHz, $CDCl_3$) 7.75-6.80 (24H, m, Ar*H*), 6.14 (1H, dd, *J* 9.0, 3.7, C_5HOH), 4.15-3.95 (2H, m, C1H_2), 3.92 (2H, d, *J* 13.7, NCH_XH_YPh × 2), 3.80 (3H, s, *Me*) 3.75 (2H, d, *J* 13.7 NCH_XH_YPh × 2), 3.73-3.68 (1H, m, C_2H), 3.35 (1H, dd, *J* 17.0, 8.8, $C_4H_CH_D$), 2.80 (1H, dd, *J* 17.0, 3.6, $C_4H_CH_D$), 1.90 (3H, s, *Me*), 1.10 (9H, s, ^tBu).

Minor diastereomer (diagnostic signals) 254D:

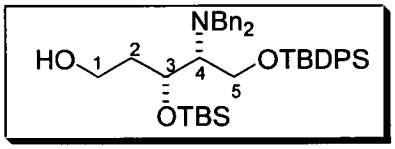
δ_H (200 MHz, $CDCl_3$) 3.15 (1H, dd, *J* 17.0, 8.8, $C_4H_CH_D$), 3.05 (1H, dd, *J* 17.0, 3.6, $C_4H_CH_D$), 1.92 (3H, s, *Me*), 1.13 (9H, s, ^tBu).

Methyl (3*R*,4*R*)-3-*tert*-Butyldimethylsilyloxy-5-*tert*-butyldiphenylsilyloxy-4-*N*,*N*-dibenzylaminopentanoate 271



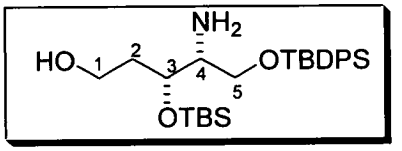
To a solution of ester **119** (508 mg, 0.870 mmol) in DCM (7 cm^3) was added 2,6-lutidine (0.230 cm^3, 1.92 mmol) followed by *tert*-butyldimethylsilyltrifluoromethanesulfonate (1.20 cm^3, 5.22 mmol). The solution was stirred for 18 hours at r.t.. The reaction mixture was diluted with DCM (40 cm^3) and the organic phase washed with saturated aqueous sodium bicarbonate (40 cm^3), brine (40 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:Et_2O (8:1)] to give the title compound (500 mg, 83%) as an oil. R_f [hexane:Et_2O (1:1)] 0.78; $[\alpha]_D$ –10.0 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 2930, 2857, 1739; δ_H (250 MHz, $CDCl_3$) 7.79-7.17 (20H, m, Ar*H*), 4.38 (1H, ddd, *J* 8.8, 6.7, 2.5, C_3HOTBS), 4.18 (1H, dd, *J* 10.3, 2.5, $C_5H_AH_BOTBDPS$), 4.14 (2H, d, *J* 13.1, $NCH_XH_YPh \times 2$), 4.02 (1H, dd, *J* 10.3, 7.0, $C_5H_AH_BOTBDPS$), 3.54 (2H, d, *J* 13.1, $NCH_XH_YPh \times 2$), 3.42 (3H, s, O*Me*), 2.89 (1H, ddd, *J* 8.8, 7.0, 2.5, C_4H), 2.82 (1H, dd, *J* 16.7, 2.5, $C_2H_CH_D$), 2.50 (1H, dd, *J* 16.7, 6.7, $C_2H_CH_D$), 1.13 (9H, s, ^tBu), 1.12 (9H, s, ^tBu), 0.87 (3H, s, *Me*), 0.86 (3H, s, *Me*); δ_C (62.9 MHz) 171.9 (C), 140.6 (2C), 135.7 (CH), 135.6 (CH), 133.5 (C), 133.3 (C), 129.7 (CH), 129.6 (CH), 129.1 (4 × CH), 128.9 (CH), 128.3 (CH), 127.9 (4 × CH), 127.7 (4 × CH), 127.6 (CH), 126.5 (CH), 70.1 (CH), 61.0 (CH_2), 55.9 (2 × CH_2), 51.1 (CH), 39.3 (CH_2), 26.9 (CH_3), 25.6 (3 × CH_3), 25.5 (3 × CH_3), 19.0 (C), 17.8 (C), -3.1 (CH_3), -3.7 (CH_3); m/z (FAB) 696 ($[M+H]^+$, 14%), 582 (16), 478 (33), 197 (19), 135 (32), 91 (100); HRMS (FAB) $C_{42}H_{58}NO_4Si$ $[M+H]^+$ requires 696.3904, found 696.3909.

(3*R*,4*R*)-3-*tert*-Butyldimethylsilyloxy-5-*tert*-butyldiphenylsilyloxy-4-*N*,*N*-dibenzylaminopentan-1-ol 272



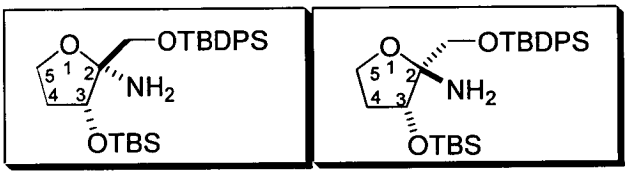
To a solution of methyl ester **271** (816 mg, 1.17 mmol) in toluene (5 cm^3) at –78 °C was added DIBAL-H (7.04 cm^3, 7.04 mmol). The mixture was stirred at –78 °C for 1 hour. MeOH (ca. 6 cm^3) was added very cautiously and the solution allowed to warm to r.t.. The mixture was diluted with DCM (50 cm^3) and the solution poured onto saturated aqueous sodium potassium tartrate (50 cm^3). The mixture was stirred vigorously for 5 hours when two distinct phases were apparent. The organic phase was separated and the aqueous phase was extracted with DCM (2 × 30 cm^3). The combined organic phases were washed with brine (50 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:Et_2O (6:1)] to give the title compound (650 mg, 83%) as an oil. R_f [hexane:Et_2O (1:1)] 0.46; $[\alpha]_D$ –18.0 (*c* 1.2, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3369, 2930, 2871, 1471; δ_H (250 MHz, $CDCl_3$) 7.76-7.25 (20H, m, Ar*H*), 4.35-4.24 (2H, m, C_3*H*OTBS + $C_5H_AH_B$OTBDPS), 4.25 (2H, d, *J* 13.2, NCH_XH_YPh × 2), 4.18 (1H, dd, *J* 11.7, 4.8, C_5H_A*H_B*OTBDPS), 3.69 (2H, d, *J* 13.2, NCH_XH_YPh × 2), 3.20-3.00 (2H, m, C_1H_2), 2.86-2.70 (1H, m, C_4*H*), 2.28-2.15 (1H, m, $C_2H_CH_D$), 1.78-1.65 (1H, m, $C_2H_CH_D$), 1.27 (9H, s, ^{t}*Bu*), 0.90 (9H, s, ^{t}*Bu*), 0.12 (3H, s, *Me*), 0.00 (3H, s, *Me*); δ_C (62.9 MHz) 140.7 (2C), 135.7 (2 × CH), 135.6 (2 × CH), 133.4 (C), 133.3 (C), 129.7 (CH), 129.6 (CH), 129.4 (4 × CH), 127.9 (4 × CH), 127.7 (2 × CH), 127.6 (2 × CH), 126.6 (2 × CH), 71.0 (CH), 65.7 (CH_2), 61.0 (CH_2), 60.5 (CH), 56.0 (2 × CH_2), 36.9 (CH_2), 26.9 (3 × CH_3), 25.7 (3 × CH_3), 19.0 (C), 17.8 (C), -4.8 (CH_3), -5.1 (CH_3); m/z (FAB) 668 ($[M+H]^+$, 71%), 578 (34), 488 (39), 478 (42), 340 (33), 262 (15), 197 (43), 181 (15), 91 (100); HRMS (FAB) $C_{41}H_{58}NO_3Si$ $[M+H]^+$ requires 668.3955, found 668.3964.

(3*R*, 4*R*)-3-*tert*-Butyldimethylsilyloxy-5-*tert*-butyldiphenylsilyloxy-4-*N*,*N*-aminopentanol 273



To a solution of the amino alcohol **272** (550 mg, 0.83 mmol) in methanol (8 cm^3) was added 20% $Pd(OH)_2/C$ (550 mg), the flask was flushed with argon before being stirred under an atmosphere of hydrogen for 8 hours. The reaction mixture was filtered through a layer of celite and concentrated under reduced pressure. The residue was chromatographed on silica gel [DCM:MeOH (25:1)] to give the title compound (380 mg, 94%) as a white foam. R_f [(DCM:MeOH (10:1)] 0.42; $[\alpha]_D$ – 24.0 (*c* 1.0, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3369, 3081, 2932, 2560, 1422; δ_H (250 MHz, $CDCl_3$) 7.67-7.25 (10H, m, Ar*H*), 4.64-4.50 (2H, br s, NH_2), 4.09 (1H, d, *J* 5.2, O*H*), 3.85-3.80 (1H, m, C_3HOTBS), 3.81 (1H, dd, *J* 10.0, 4.3, $C_5H_AH_B$OTBDPS), 3.68 (1H, dd, *J* 10.0, 6.4, $C_5H_AH_B$OTBDPS), 3.54 (1H, ddd, *J* 16.8, 14.5, 8.2, $C_1H_EH_F$OH), 3.68-3.54 (1H, m, $C_1H_EH_F$OH), 3.06 (1H, m, C_4H), 1.99-1.85 (1H, m, $C_2H_CH_D$), 1.74-1.65 (1H, m, $C_2H_CH_D$), 1.05 (9H, s, ^tBu), 0.80 (9H, s, ^tBu), -0.01 (3H, s, *Me*), -0.09 (3H, s, *Me*); δ_C (62.9 MHz) 135.4 (4 × CH), 132.8 (C), 132.7 (C), 129.7 (2 × CH), 127.7 (2 × CH), 127.6 (2 × CH), 68.1 (CH), 65.1 (CH_2), 56.1 (CH), 55.8 (CH_2), 38.2 (CH_2), 26.7 (3 × CH_3), 25.6 (3 × CH_3), 19.0 (C), 17.8 (C), -4.5 (CH_3), -5.3 (CH_3); m/z (FAB) 488 ($[M+H]^+$, 100%), 340 (13), 260 (7), 197 (37), 181 (6), 135 (32); HRMS (FAB) $C_{27}H_{46}NO_3Si_2$ $[M+H]^+$ requires 488.3016, found 488.3022.

(2*R*,3*R*)-2-Amino-2-*tert*-butyldimethylsilyloxy-3-*tert*-butyldiphenylsilyloxy furan 274 and (2*S*,3*R*)-2-Amino-2-*tert*-butyldimethylsilyloxy-3-*tert*-butyldiphenylsilyloxy furan 275



A suspension of IBX (46 mg, 0.16 mmol) in DMSO (0.5 cm^3) was stirred vigorously for 15 mins. By which time a clear solution was apparent. At this point amino alcohol **273** (80 mg, 0.16 mmol) in THF (1.5 cm^3) was added *via* syringe. The resulting solution was stirred at r.t. for 15 mins. Water (5 cm^3) was added and the mixture was diluted with EtOAc (5 cm^3). The white precipitate was filtered and the organic phase separated. The aqueous phase was extracted with Et_2O (2 × 10 cm^3). The combined organic phases were washed with brine (25 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:Et_2O (6:1)] to give a 55:45 inseparable mixture of the title compounds (70 mg, 91%). R_f [(hexane:Et_2O (1:1)] 0.26.

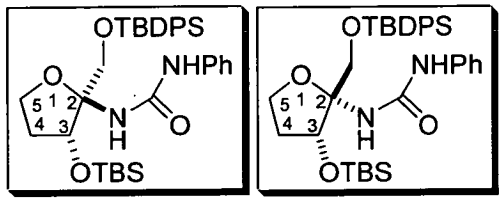
Major diasteromer 274:

δ_H (250 MHz, $CDCl_3$) 7.85-7.37 (10H, m, Ar*H*), 4.56 (1H, dd, *J* 6.2, 4.0, C_3*H*OTBS), 4.30 (1H, s, N*H*), 4.15 (1H, dd, *J* 8.4, 6.2, $C_5H_EH_F$), 4.00 (1H, td, *J* 8.4, 4.4, C_5H_E*H*$_F$), 3.90 (1H, s, N*H*), 3.86 (1H, d, *J* 11.0, C*H*$_A$H$_B$OTBDPS), 3.74 (1H, d, *J* 11.0, CH$_A$*H*$_B$OTBDPS), 2.48-2.30 (1H, m, $C_4H_CH_D$), 2.00-1.90 (1H, m, C_4H_C*H*$_D$), 1.02 (9H, s, ^{t}*Bu*), 0.84 (9H, s, ^{t}*Bu*), 0.23 (3H, s, *Me*), 0.22 (3H, s, *Me*); δ_C (62.9 MHz) 135.6, 135.5, 135.4, 135.1 (2C), 134.7, 133.2 (C), 133.1 (C), 133.0, 129.7, 129.6, 127.4, 77.1, 72.3, 67.6, 64.5, 34.2 (CH_2), 26.7 (3 × CH_3), 25.6 (3 × CH_3), 18.0 (C), 17.9 (C), -4.7 (CH_3), -4.8 (CH_3).

Minor diastereomer (diagnostic signals) 275:

δ_H (250 MHz, $CDCl_3$) 1.17 (9H, s, *^tBu*), 0.99 (9H, s, *^tBu*), 0.09 (3H, s, *Me*), 0.00 (3H, s, *Me*); δ_C (62.9 MHz) 72.9, 65.3, 34.7 (CH_2), 26.8 (3 × CH_3), 25.7 (3 × CH_3), 19.2 (C), 18.9 (C), -5.1 (CH_3), -5.2 (CH_3).

(2*R*,3*R*)-3-*tert*-Butyldimethylsilyloxy-2-*tert*-butyldiphenylsilyloxymethyl-2-*N*-phenylureido furan 276 and (2*S*,3*R*)-3-*tert*-Butyldimethylsilyloxy-5-*tert*-butyldiphenylsilyloxymethyl-2-*N*-phenylureido furan 277



To a solution of the mixture of anomeric amines **274** and **275** (50 mg, 0.10 mmol) in THF (1 cm^3) was added phenyl isocyanate (0.03 cm^3, 0.24 mmol). The resulting mixture was stirred for 18 hours before being concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (4:1)] to provide the title compounds (40 mg, 66%) as a 55:45 inseparable mixture. R_f [(hexane:EtOAc (4:1)] 0.40; m/z (FAB) 605 ($[M+H]^+$, 13%), 337 (23), 221 (20), 197 (30), 171 (23), 135 (38), 73 (100); HRMS (FAB) $C_{34}H_{49}N_2O_4Si_2$ $[M+H]^+$ requires 605.3231, found 605.3251.

Major diastereomer 276:

δ_H (250 MHz, $CDCl_3$) 7.88 (1H, br s, N*H*Ph), 7.72-7.56 (4H, m, Ar*H*), 7.42-7.02 (11H, m, Ar*H*), 5.22 (1H, s, N*H*), 4.45-4.39 (1H, m, C_3*H*OTBS), 4.14 (1H, dd, *J* 9.3, 3.6, $C_5H_EH_F$), 4.07-4.00 (1H, m, $C_5H_EH_F$), 3.98 (1H, d, *J* 10.4, CH_AH_BOTBDPS), 3.86 (1H, d, *J* 10.4, CH_AH_BOTBDPS), 2.51-2.41 (1H, m, $C_4H_CH_D$), 1.92-182 (1H, m, $C_4H_CH_D$), 1.04 (9H, s, *^tBu*), 1.03 (9H, s, *^tBu*), 0.11 (3H, s, *Me*), 0.06 (3H, s, *Me*), δ_C (62.9 MHz) 155.0 (C), 138.6 (C), 135.6, 135.5, 135.4, 133.1, 132.9, 132.5, 129.7,

129.5, 128.9, 128.5, 127.5, 123.0, 122.6, 120.0, 119.5, 71.4, 67.0, 65.5, 63.4, 62.8, 34.2, 32.0, 26.8 (3 × CH_3), 25.5 (3 × CH_3), 19.0 (C), 17.8 (C), -4.8 (2 × CH_3).

Minor diastereomer (diagnostic signals) 277:

δ_H (250 MHz, $CDCl_3$) 4.73 (1H, t, *J* 8.3, C_3*H*OTBS), 5.03 (1H, s, N*H*), 2.30-2.20 (1H, m, $C_4H_CH_D$), 2.11-2.00 (1H, m, $C_4H_CH_D$), 0.91 (9H, s, ^tBu), 0.90 (9H, s, ^tBu), 0.04 (3H, s, *Me*), -0.05 (3H, s, *Me*); δ_C (62.9 MHz) 26.6 (3 × CH_3), 25.6 (3 × CH_3), 17.9 (C).

Synthesis of 279

From aminopentanol:

A suspension of IBX (1.36 g, 4.86 mmol) in DMSO (5 cm^3) was stirred vigorously for 15 mins by which time a clear solution was apparent. A solution of 5-aminopentan-1-ol (500 mg, 4.86 mmol) in THF (4 cm^3) was added via syringe. The resulting mixture was stirred at r.t. for 20 mins. Water (20 cm^3) was added followed by Et_2O (10 cm^3). The white precipitate was filtered and the organic phase separated. The aqueous phase was extracted with Et_2O (2 × 10 cm^3). The combined organic phases were washed with brine (25 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was purified by silica gel chromatography [DCM:Et_2O (8:1)] to give the title compound (350 mg, 70%); R_f [hexane:Et_2O (1:1)] 0.20; δ_H (250 MHz, $CDCl_3$) 4.93-4.85 (1H, m), 4.05-3.94 (1H, m), 3.57-3.46 (2H, m), 1.85-1.62 (2H, m), 1.58-1.27 (3H, m); δ_C (62.9 MHz) 94.3 (CH), 63.7 (CH_2), 31.8 (CH_2), 25.1 (CH_2), 20.1 (CH_2).

From tetrahydropyran 284:

To a solution 2,3-tetrahydropyran (0.50 cm^3, 6.46 mmol) in THF (5 cm^3) at 0 °C was added borane•THF (9.68 cm^3, 1.0 *M* in THF, 9.68 mmol). The solution was stirred at

0 °C for 2 hours before being warmed to r.t.. The solution was recooled to 0 °C and aqueous ammonium hydroxide (4.07 cm^3, 9.69 mmol) was added followed by aqueous sodium hypochlorite (12.4 cm^3, 9.69 mmol) dropwise. A white precipitate formed at this stage. The mixture was stirred at 0 °C for 15 mins then allowed to warm to r.t.. The reaction mixture was made acidic with 1N HCl and the aqueous phase was extracted with Et_2O (2 × 15 cm^3). The aqueous layer was basified with 3N NaOH and the aqueous phase was extracted with Et_2O (3 × 15 cm^3). The combined organic phases were washed with brine (25 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was purified by silica gel chromatography [DCM:Et_2O (8:1)] to give the title compound (85 mg, 42%); *all spectroscopic data was identical to the compound from 5-aminopentanol.*

References

[1] H. Umezawa, T. Aoyagi, H. Morishima, M. Matzuzaki, M. Hamada and T. Takeuchi, *J. Antibiot.*, **1970**, *23*, 259

[2] (a) K. L. Rinehart, J. B. Gloer and J. C. Cook, *J. Am. Chem. Soc.*, **1981**, *103*, 1857 (b) K. L. Rinehart, V. Nagaranjan, R. J. Lake, J. B. Gloer, F. A. Bozich, K. M. Li, R. E. Maleczka, W. L. Todsen, M. H. G. Munro, D. W. Sullins and R. Sakai, *J. Am. Chem. Soc.*, **1987**, *109*, 6846

[3] G. R. Petit, Y. Kamano, C. L. Herald, A. A. Tuinman, F. E. Boettner, H. Kizu, J. M. Schmidt, L. Baczynskyj, K. B. Tomer and Y. Kamano, *J. Am. Chem. Soc.*, **1987**, *109*, 6883

[4] K. Stratmann, D. L. Burgoyne, R. E. Moore and G. M. L. Patterson, *J. Org. Chem.*, **1994**, *59*, 7219

[5] M. C. Wani, H. L. Tayler, M. E. Wall, P. Coggon and A. T. McPhail, *J. Am. Chem. Soc.*, **1971**, *93*, 2325

[6] Y. Lu, C. Miet, N. Kunesch and J. E. Poisson, *Tetrahedron Asymm.*, **1993**, *4*, 893

[7] W. S. Liu and G. I. Glover, *J. Org. Chem.*, **1978**, *43*, 754

[8] W. S. Liu, S. C. Smith and G. I. Glover, *J. Med. Chem.*, **1979**, *22*, 577

[9] S. Masamune, W. Choy, J. S. Peterson and L. R. Sita, *Angew. Chem. Int. Ed. Engl.*,**1985**, *24*, 1

[10] (a) D. A. Evans, J. V. Nelson, E. Vogel and T. R. Taber, *J. Am. Chem Soc.*, **1981**, *103*, 3099; (b) D. A. Evans and T. L. Shih, *J. Am. Chem. Soc.*, **1981**, *103*, 2127; (c) D. A Evans, J. M. Takacs, L. R. McGee, M. D. Ennis, D. J. Mathre and J. Bartoli, *Pure and Appl. Chem.*, **1981**, *53*, 1109; (d) D. A. Evans, J. V. Nelson and T. R. Taber, *Topics in Stereochemistry*, **1982**, 13, 1

[11] (a) Y. Nagao, Y. Hagiwara, T. Kumagai, M. Ochiai, T. Inoue, K. Hashimoto and E. Fujita, *J. Org. Chem.*, **1986**, *51*, 2391; (b) W. Oppolzer, *Tetrahedron* **1987**, *43*, 1969; (c) T. Yan, A. Hung, H. Lee, C. Chang and W. Liu, *J. Org. Chem*, **1995**, *60*, 3301; (d) M. T. Crimmins, B. W. King and E. A. Tabet, *J. Am. Chem. Soc.*, **1997**, *33*, 7883

[12] T. Hintermann and D. Seebach, *Helv. Chim. Acta*, **1998**, *81*, 2093

[13] (a) M. Nerz-Stormes and E. R. Thornton, *Tetrahedron Lett.*, **1986**, *27*, 897; (b) M. Nerz-Stormes and E. R. Thornton, *J. Org. Chem.*, **1991**, *56*, 2489

[14] H. E. Zimmerman and M. D. Traxler, *J. Am. Chem. Soc.*, **1957**, *79*, 1920

[15] M. Braun, *Angew. Chem. Int. Ed. Engl.*, **1987**, *26*, 24

[16] R. W. Hoffman, K. Dittrich, S. Froech and D. Cremer, *Tetrahedron*, **1985**, *41*, 5517

[17] C. Gennari, R. Todeschini, M. G. Beretta, G. Favini and C. Scolastico, *J. Org. Chem.*, **1986**, *51*, 612

[18] (a) S. G. Davies, *Aldrichimica Acta*, **1990**, *23*, 31; (b) J. W. B. Cooke, S. G. Davies and A. Naylor, *Tetrahedron*, **1993**, *49*, 7955

[19] M. T. Reetz, *Angew. Chem. Int. Ed. Engl.*, **1991**, *30*, 1531

[20] (a) M. Cherest, H. Felkin and N. Prudent, *Tetrahedron Lett.*, **1968**, 2199; (b) N. T. Anh, *Top. Curr. Chem.*, **1980**, *88*, 145;

[21] M. T. Reetz, *Chem. Rev.*, **1999**, *99*, 123

[22] D. J. Cram and K. R. Kopecky, *J. Am. Chem. Soc.*, **1959**, *81*, 2748

[23] P. G. M. Wuts and S. R. Putt, *Synthesis*, **1989**, 951

[24] P. W. K. Woo, *Tetrahedron Lett.*, **1985**, *26*, 2973

[25] (a) C. Gennari, G. Pain and D. Moresca, *J. Org. Chem.*, **1995**, *60*, 6248; (b) C. Gennari, D. Moresca, A. Vulpetti and G. Pain, *Tetrahedron*, **1997**, *53*, 5593

[26] G. Veersha and A. Datta, *Tetrahedron Lett.*, **1997**, *38*, 5223

[27] M. Franciotti, A. Mann and M. Taddei, *Tetrahedron Lett.*, **1991**, *32*, 6783

[28] M. T. Reetz, M. W. Drewes, B. R. Matthews and K. Lennick, *J. Chem. Soc., Chem. Commun.*, **1989**, *1474*

[29] R. V. Hoffman and J. Tao, *J. Org. Chem.*, **1997**, *62*, 2292

[30] R. V. Hoffman and J. Tao, *J. Org. Chem.*, **1998**, *63*, 3979

[31] (a) B. D. Harris, K. L. Bhat and M.M. Joullié, *Tetrahedron Lett.*, **1987**, *28*, 2837; (b) B. D. Harris and M. M. Joullié, *Tetrahedron* **1988**, *44*, 3489

[32] J. Maibaum and D. H. Rich, *J. Org. Chem.*, **1988**, *53*, 869

[33] T. Nishi, M. Kitamura, T. Ohkuma and R. Noyori, *Tetrahedron Lett.*, **1988**, *29*, 6327

[34] (a) H. Kessler and M. Schudok, *Synthesis*, **1990**, 457; (b) U. Schmidt, M. Kroner and H. Griesser, *Synthesis*, **1989**, 832

[35] S. Sengupta and D. S. Sarma, *Tetrahedron Asymm.*, **1999**, *10*, 4633

[36] (a) U. Schmidt, B. Riedl, G. Haas, H. Griesser, A. Vetter and S. Weinbrenner, *Synthesis*, **1992**, 216; (b) M. Banzinger, J. F. McGarrity and T. Meul, *J. Org. Chem.*, **1993**, *58*, 4010; (c) J. A. Fehrentz, E. Bourdel, J. C. Califano, O. Chaloin, C. Devin, P. Garrouste, A. C. Lima-Leite, M. Llinares, F. Rieuner, J. Vizavonna, F. Winternitz, A. Loffet and J. Martinez, *Tetrahedron*, **1994**, *35*, 1557

[37] P. Jouin and B. Castro, *J. Chem. Soc. Perkin Trans. I*, **1987**, 1177

[38] M. Saiah, M. Bessodes and K. Antonakis, *Tetrahedron Asymm.*, **1991**, *2*, 111

[39] H. Kogen and T. Nishi, *J. Chem. Soc., Chem. Commun.*, **1987**, 311

[40] K. Shinozaki, K. Mizuno, H. Oda and Y. Masaki, *Bull. Chem. Soc. Jpn.*, **1996**, *69*, 1737

[41] (a) A. Bernardi, F. Micheli, D. Potenza, C. Scolastico and R. Villa, *Tetrahedron Lett.*, **1990**, *31*, 4949; (b) T. Ohta, S. Shiokawa, R. Sakamoto and S. Nozoe, *Tetarhedron Lett.*, **1990**, *31*, 7329; (c) W. J. Koot, R. van Ginkel, M. Kranenburg, H. Hiemstra, S. Louwrier, M. J. Moolenaar and W. N. Speckamp, *Tetrahedron Lett.*, **1991**, *32*, 401

[42] S. H. Kang and D. H. Ryu, *Bioorg. and Med. Chem. Lett.*, **1995**, *5*, 2959

[43] (a) R. M. Williams, P. J. Colson and W. Zhai, *Tetrahedron Lett.*, **1994**, *35*, 9371; (b) Y. Aoygai and R. M. Williams, *Tetrahedron*, **1998**, *54*, 10419

[44] P. L. Williams, P. Monerris, I. Gonzalez, G. Jou and E. Giralt, *J. Chem. Soc. Perkin Trans. 1*, **1994**, 1969

[45] R. J. Nash, E. A. Bell, G. W. J. Fleet, R. H. Jones and J. M. Williams, *J. Chem. Soc. Chem. Commun.*, **1985**, 738

[46] N. Asano, R. J. Nash, R. J. Molyneux and G. W. J. Fleet, *Tetrahedron Asymmetry*, **2000**, *11*, 1645

[47] A. M. Schofield, L. E. Fellows, R. J. Nash and G. W. J. Fleet, *Life Sciences*, **1986**, *39*, 645

[48] A. M. Schofield, P. Witham, R. J. Nash, G. C. Kite and L. E. Fellows, *Comp. Biochem. Physiol.*, **1995**, *112A*, 187

[49] N. Dell'Uomo, M. C. DiGiovanni, D. Misisti, G. Zappia and G. Delle Monache, *Tetrahedron Asymmetry*, **1996**, *7*, 181

[50] R. J. Molyneux, Y. T. Pan, J. E. Tropea, M. Benson, G. P. Kaushal and A. D. Elbien, *Biochem.*, **1991**, *30*, 9981

[51] G. Ceulemans, A. Van Aerschot, J. Rozenski and P. Herdewijn, *Tetrahedron*, **1997**, *53*, 14957

[52] L. M. Mascavage, Q. Ling, J. Vey, D. R. Dalton and P. J. Carroll, *J. Org. Chem.*, **2001**, *66*, 3621

[53] A. Barco, S. Benetti, C. De Risi, G. P. Pollini, R. Romanoli and V. Zanirato, *Tetrahedron Lett.*, **1996**, *37*, 7599

[54] (a) N. Ikota and A. Hanaki, *Heterocycles*, **1988**, *27*, 2535; (b) C. Herdeis, H. P. Hubmann and H. Lotter, *Tetrahedron Asymm.*, **1994**, *5*, 119

[55] D. Griffart-Brunet and N. Langlois, *Tetrahedron Lett.*, **1994**, *35*, 119

[56] C. M. Huwe and S. Blechert, *Tetrahedron Lett.*, **1995**, *36*, 1621

[57] Y. S. Kulkarni, *Aldrichim. Acta*, **1999**, *32*, 18

[58] J. Jurczak and A. Golebiowski, *Chem. Rev.*, **1989**, *89*, 149

[59] (a) L. Williams, Z. Zhang, X. Ding, and M. M. Joullie, *Tetrahedron Lett.*, **1995**, *36*, 7031; (b) B. H. Han, Y. C. Kim, M. K. Park and J. H. Park, *Heterocycles*, **1995**, 1909

[60] A. N. Hulme, C. H. Montgomery and D. K. Henderson, *J. Chem. Soc., Perkin Trans. 1.*, **2000**, 1837

[61] M. T. Reetz, M. W. Drewer and A. Schmitz, *Angew. Chem., Int. Ed. Engl.*, **1987**, *26*, 1141

[62] (a) J. M. Andres and R. Pedrosa, *Tetrahedron*, **1998**, *54*, 707; (b) T. Laib, J. Chastanet and J. Zhu, *J. Org. Chem.*, **1998**, *63*, 1709; (c) J. M. Andres and R. Pedrosa, *Tetrahedron Asymmetry*, **1998**, *9*, 2453; (d) J. M. Andres, N. de Elena and R. Pedrosa, *Tetrahedron*, **2000**, *56*, 1523

[63] M. T. Reetz, M. W. Drewes, A. Schmitz, X. Holdgrun, T. Wunsch and J. Binder, *J. Philos. Trans. R. Soc. London A*, **1988**, *326*, 573-578

[64] S. Nahm and S. M. Weinreb, *Tetrahedron Lett.*, **1981**, *22*, 3815

[65] K. Yoshida, S. Nakajima, T. Wakamatsu, Y. Ban and M. Shibasaki, *Heterocycles*, **1988**, *27*, 1167

[66] H. Ina and C. Kibayashi, *J. Org. Chem.*, **1993**, *58*, 52

[67] S. Hanessian and P. Lavallee, *Can. J. Chem.*, **1975**, *53*, 2975

[68] H. A. Staab, *Angew. Chem. Int. Ed.Engl.*, **1962**, *1*, 351

[69] R. Paul and G. W. Anderson, *J. Am. Chem. Soc*, **1960**, *82*, 4596

[70] P. F. Schuda, W. J. Greenlee, P. K. Chakravarty and P. Eskola, *J. Org. Chem.*, **1988**, *53*, 873

[71] M. M. Joullié, P. Portonovo, B. Liang and D. J. Ruchard, *Tetrahedron Lett.*, **2000**, *41*, 9373

[72] B. Li and R. W. Franck, *Bioorg. and Med. Chem. Lett.*, **1999**, *9*, 2629

[73] X. Wang, W. T. Monte, J. J. Napier and A. Ghannam, *Tetrahedron Lett.*, **1994**, 35, 9323

[74] J. March, Advanced Organic Chemistry, Wiley-Interscience, New York, **1992**

[75] J. McMurry, *Organic Reactions*, **1976**, *24*, 187

[76] R. E. Ireland and R. S. Meisser, *J. Org. Chem.*, **1991**, *56*, 4566

[77] M. T. Reetz, M. W. Drewes, K. Lennick, A. Schmitz and X. Holgrun, *Tetrahedron Asymm.*, **1990**, *1*, 375

[78] S. Chandrasekhar, C. R. Reddy and R. J. Rao, *Tetrahedron*, **2001**, *57*, 3435

[79] (a) A. Hirao, S. Itsuno, S. Nakahama and N. Yamazaki, *J. Chem. Soc., Chem. Comm.*, **1981**, 315; (b) S. Itsuno, Y. Sakuri, K. Ito, A. Hirao and S. Nakahama, *Bull. Chem. Soc. Jpn.*, **1987**, *60*, 395

[80] E. J. Corey, R. K. Bakshi and S. Shibata, *J. Am. Chem. Soc.*, **1987**, *109*, 5551

[81] E. J. Corey and C. J. Helal, *Angew. Chem. Int. Ed. Engl.*, **1998**, *37*, 1986

[82] L. Deloux and M. Srebnik, *Chem. Rev.*, **1993**, *93*, 763

[83](a) D. J. Mathre, T. K. Jones, L. C. Xavier, T. J. Blacklock, R.A. Reamer, J. J. Mohan, E. T. Turner-Jones, K. Hoogsteen, M. W. Baum and E. J. J. Grabowski, *J. Org. Chem.*, **1991**, *56*, 751; (b) D. J. Mathre, A.S. Thompson, A. W. Douglas, K. Hoogsteen, J. D. Carroll, E. G. Corley and E. J. J. Grabowski, *J. Org. Chem.*, **1993**, *58*, 2880

[84] R. Noyori and H. Takaya, *Acc. Chem. Res.*, **1990**, *23*, 345

[85] D. J. Ager and S. A. Laneman, *Tetrahedron Asymmetry*, **1997**, *8*, 3327

[86] U. Schmidt, V. Leitenberger, H. Griesser, J. Schmidt and R. Meyer, *Synthesis*, **1992**, 1248

[87] (a) S. A. King, A. S. Thompson, A. O. King and T. R. Verhoeven, *J. Org. Chem.*, **1992**, *57*, 6689; (b) R. F. Taber and L. J. Silverberg, *Tetrahedron Lett.*, **1991**, *32*, 4227

[88] P. Compain and O. R. Martin, *Biiorg. and Med. Chem.*, **2001**, *9*, 3077

[89] (a) K. Dax, M. Ebner, R. Peinsipp and A. E. Stutz, *Tetrahedron Lett.*, **1997**, *38*, 225; (b) E. Dechaux, P. Savy, S. Bouyain, C. Monneret and J. Florent, *J. Carbohydrate. Chem.*, **2000**, *19*, 485

[90] S. Hanessian, H. K. Huynh, G. V. Reddy, G. M. Smith, B. Ernst, H. C. Kolb, J. Magnani and C. Sweeley, *Biiorg. Med. Chem. Lett.*, **1998**, *8*, 2803

[91] K. Stratman, D. L. Burgoyne, R. E. Moore, G. M. L. Patterson and C. D. Smith, *J. Org. Chem.*, **1994**, *59*, 7219

[92] (a) T. Okuno, K. Ohmori, S. Nishiyama, S. Yamamura, K. Nakamura, K. N. Houk and K. Okamoto, *Tetrahedron*, **1996**, *52*, 14723, (b) B. Wagner, R. Beugelmans and J. Zhu, *Tetrahedron Lett.*, **1996**, *37*, 6557; (c) B. Wagner, G. I. Gonzalez, M. E. T. H. Dau and J. Zhu, *Bioorg. Med. Chem. Lett.*, **1999**, *7*, 737; (d) C. E. O'Connell, K. A. Salvato, Z. Meng, B. A. Littlefield and C. E. Schwartz, *Bioorg. Med. Chem. Lett.*, **1999**, *9*, 1541; (e) N. Kashihara, S. To-e, K. Nakamura, K. Umezawa, S. Yamamura and S. Nishiyama, *Bioorg. Med. Chem. Lett.*, **2000**, *8*, 101; (f) C. Hermann, G. C. G. Pais, A. Geyer, S. M. Kuhnert and M. E. Maier, *Tetrahedron*, **2000**, *56*, 8461

[93] (a) T. Q. Dinh and R. W. Armstrong, *J. Org. Chem.*, **1995**, *60*, 8118; (b) T.Q. Dinh, C. D. Smith and R.W. Armstrong, *J. Org. Chem.*, **1997**, *62*, 790

[94] T.Q. Dinh, C. D. Smith, X. Du and R.W. Armstrong, *J. Med. Chem.*, **1998**, *42*, 981

[95] K. Ohmori, T. Okuno, S. Nishiyama and S. Yamamura, *Tetrahedron Lett.*, **1996**, *37*, 3467

[96] A. K. Ghosh, W. Liu, Y. Xu and Z. Chen, *Angew. Chem. Int. Ed. Engl.*, **1996**, *35*, 74

[97] M. Haddad, C. Botuha and M. Larcheveque, *Synlett*, **1999**, 1118

[98] (a) G. C. Pais and M. E. Maier, *J. Org. Chem.*, **1999**, *64*, 4551; (b) M. E. Maier and C. Hermann, *Tetrahedron*, **2000**, *56*, 557

[99] (a) G. V. Reddy, G. V. Rao and D. S. Iyengar, *Chemistry Lett.*, **1999**, 703, (b) G. V. Reddy, G. V. Rao and D. S. Iyengar, *Chem. Commun.*, **1999**, 317

[100] C. R. O'Dowd, *Honours Project*, The University of Edinburgh, **1996**

[101] W. F. Huffman, R. F. Hall, J. A. Grant and K. G. Holden, *J. Med. Chem.*, **1978**, *21*, 413

[102] D. A. Evans, H. P. Ng and D. L. Reiger, *J. Am. Chem. Soc.*, **1993**, *115*, 11446

[103] (a) I. Maugras, J. Poncet and P. Jouin, *Tetrahedron*, **1990**, *46*, 2807; (b) F. Roux, I. Maugras, J. Poncet, G. Niel, and P. Jouin, *Tetrahedron*, **1994**, *50*, 5345

[104] (a) L. Andersson, T. Kuelhor and M. Nilsson, *Synthesis*, **1981**, 468; (b) N. G. Galakatos and D. S. Kemp, *J. Org. Chem.*, **1985**, *30*, 1302

[105] P. Q. Huang, S. L. Wang, J. L. Ye, Y. P. Ruan, Y. Q. Huang, H. Zheng and J. X. Gao, *Tetrahedron*, **1998**, *54*, 12547

[106] (a) C. H. Heathcock in J. D. Morrison : *Asymmetric Synth.*, **1984**, 2, chap. 2, Academic Press, New York; (b) D. A. Evans, J. V. Nelson and T. R. Taber, *Topics in Stereochemistry*, **1982**, *13*, 1

[107] B. Trost and H. Urabe, *J. Org. Chem.*, **1990**, *55*, 3982

[108] (a) M. T. Reetz, F. Kunisch and P. Heitmann, *Tetrahedron Lett.*, **1986**, *27*, 4721; (b) M. Muraoka, H. Kawasaki and K. Koga, *Tetrahedron Lett.*, **1988**, *29*, 337; (c) I. Paterson and J. M. Goodman, *Tetrahedron Lett.*, **1989**, *30*, 997

[109] B. R. Lagu, H. M. Crane and D. C. Liotta, *J. Org. Chem.*, **1993**, *58*, 4191

[110] B. R. Lagu and D. C. Liotta, *Tetrahedron Lett.*, **1994**, *35*, 4485

[111] J. B. Goh, B. R. Lagu, J. Wurster and D. C. Liotta, *Tetrahedron Lett.*, **1994**, *35*, 6029

[112] I. Paterson and A. C. Mackay, *Tetrahedron Lett.*, **2001**, *42*, 9269

[113] H. C. Brown, R. K. Dhar, R. K. Bakashi, P. K. Pandiarajan and B. J. Singaram, *J. Am. Chem. Soc.*, **1989**, *111*, 3441

[114] H. He, L. A. Silo-Suh, J. Handelsman and J. Clardy, *Tetrahedron Lett.*, **1994**, *35*, 2499

[115] (a) D. B. Dess and J. C. Martin, *J. Org. Chem.*, **1983**, *48*, 4155; (b) D. B. Dess and J. C. Martin, *J. Am. Chem. Soc.*, **1991**, *113*, 7277

[116] C. Hartman and V. Meyer, *Chem. Ber.*, **1893**, *26*, 1717

[117] M. Frigerio and M. Santagostino, *Tetrahedron Lett.*, **1994**, *35*, 8019

[118] M. Frigerio, M. Santagostino, S. Sputore and G. Palmisano, *J. Org. Chem.*, **1995**, *60*, 7272

[119] (a) E. J. Corey and A. Palani, *Tetrahedron Lett.*, **1995**, *36*, 3485; (b) E. J. Corey and A. Palani, *Tetrahedron Lett.*, **1995**, *36*, 7945

[120] K. C. Nicolaou, Y. L. Zhong and P. S. Baran, *J. Am Chem. Soc.*, **2000**, *122*, 639

[121] M. Mülbaier and A. Giannis, *Angew. Chem. Int. Ed.*, **2001**, *40*, 4393

[122] C. H. Montgomery, *PhD Thesis*, The University of Edinburgh, **2000**

[123] T. W. Brandstetter, Y. Kim, J. C. Son, H. M. Taylor, P. M. Lilley, D. J. Watkin, L. N. Johnson, N. G. Oikonomakos and G. W. Fleet, *Tetrahedron Lett.*, **1995**, *36*, 2149

[124] (a) H. Huruyama, T. Takayama, T. Kinoshita, M. Kondo, M. Nakajima and T. Haneishi, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 1637; (b) M. Nakajima, K. Itoi, Y. Takamatsu, T. Kinoshita, T. Okazaki, K. Kawakubo, M. Shindo, T. Honma, M. Tohjigamori and T. Haneishi, *J. Antibiot.*, **1991**, *44*, 293

[125] S. F. Lee, R. J. Anderson and A. G. Toschi, *Plant Physiol.*, **1996**, *110*, 753

[126] S. Mio, M. Shiraishi , S. Sugai, H. Haruyama and S. Sato, *Tetrahedron*, **1991**, *47*, 2121

[127] S. Mio, M. Ueda, M. Hamura, J. Kitagawa and S. Sugai, *Tetrahedron*, **1991**, *47*, 2145

[128] P. M. Harrington and M. E. Jung, *Tetrahedron Lett.*, **1994**, *35*, 5145

[129] (a) P. Chemla, *Tetrahedron Lett.*, **1993**, *34*, 7391; (b) N. Nakajima, M. Matsumoto, M. Kirihara, M. Hashimoto, T. Katoh and S. Terashima, *Tetrahedron*, **1996**, *52*, 1177

[130] A. J. Fairbanks and G. W. J. Fleet, *Tetrahedron*, **1995**, *51*, 3881

[131] (a) S. Mio, H. Sano, M. Shindou, T. Honma and S. Sugai, *Agric. Biol. Chem.*, **1991**, *55*, 1105; (b) A. Renard, M. Kotera and J. Lhomme, *Tetrahedron Lett.*, **1998**, *39*, 3129

[132] (a) C. J. F. Bichard, E. P. Mitchell, M. R. Wormald, K. A. Watson, L. N. Johnson, S. E. Zographos, D. D. Koutra, N. G. Oikonomakos and G. W. J. Fleet, *Tetrahedron Lett.*, **1995**, *36*, 2145; (b) T. W. Brandstetter, M. R. Wormald, R. A. Dwek, T. D. Butters, F. M. Platt, K. E. Tsitsanou, S. E. Zographos, N. G. Oikonomakos and G. W. J. Fleet, *Tetrahderon Asymm.*, **1996**, *7*, 157; (c) E. Ösz, E. Sós, L. Somsák, L. Szilágyi and Z. Dinya, *Tetrahedron*, **1997**, *53*, 5813; (d) E. Ösz, L. Szilágyi, L. Somsák and A. Benyei, *Tetrahedron*, **1999**, *55*, 2419

[133] H. M^{c}Elroy, *MChem Honours Project*, The University of Edinburgh, **2001**

[134] G. W. Kabalka, K. A. R. Sastry, G. W. McCollum and H. Yoshioka, *J. Org. Chem.*, **1981**, *46*, 4296

[135] G. H. Coleman and H. C. Johnson, *Inorg. Synth.* **1939**, *1*, 59

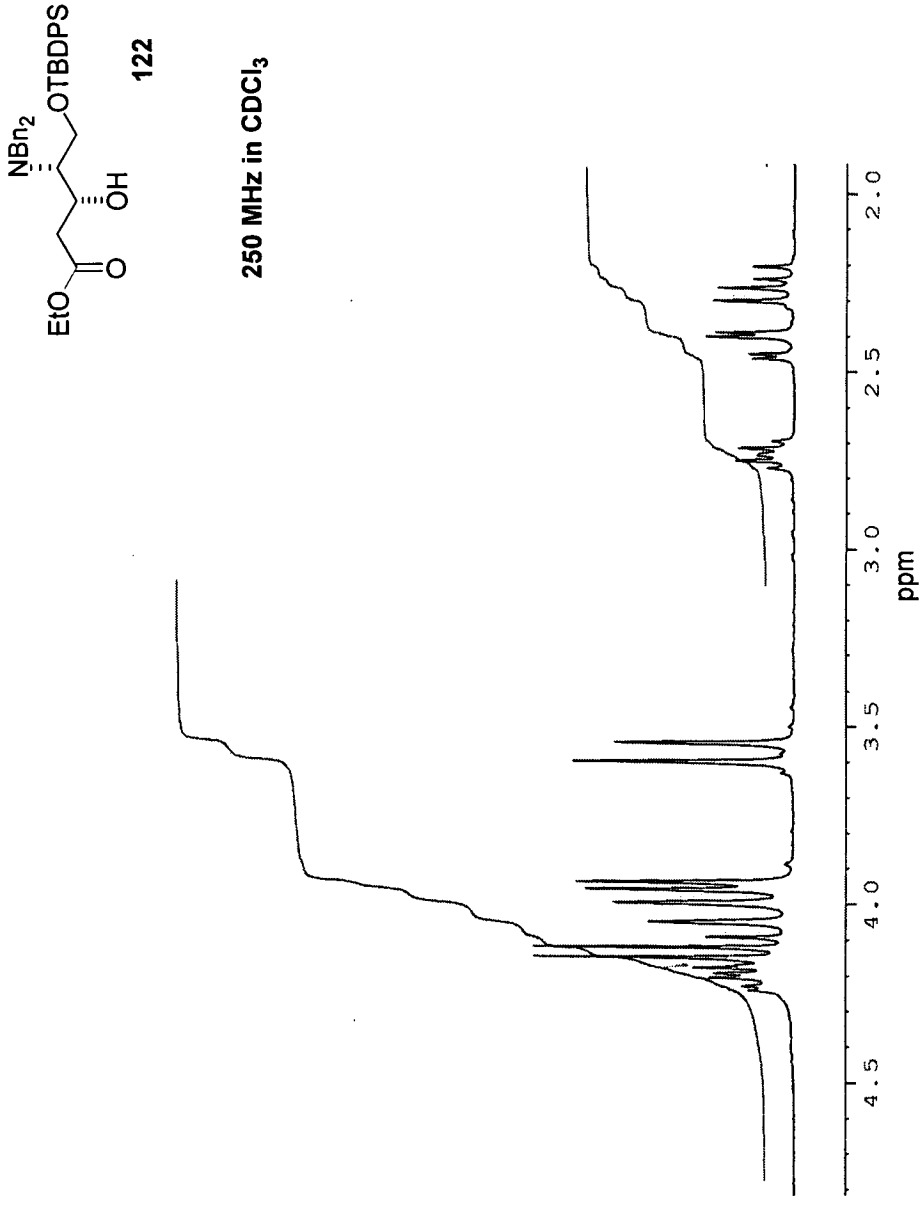
[136] G. W. Kabalka and Z. Wang, *Organometallics*, **1989**, *8*, 1093

[137] G. Zweifel and J. Plamondon, *J. Org. Chem*, **1970**, *35*, 898

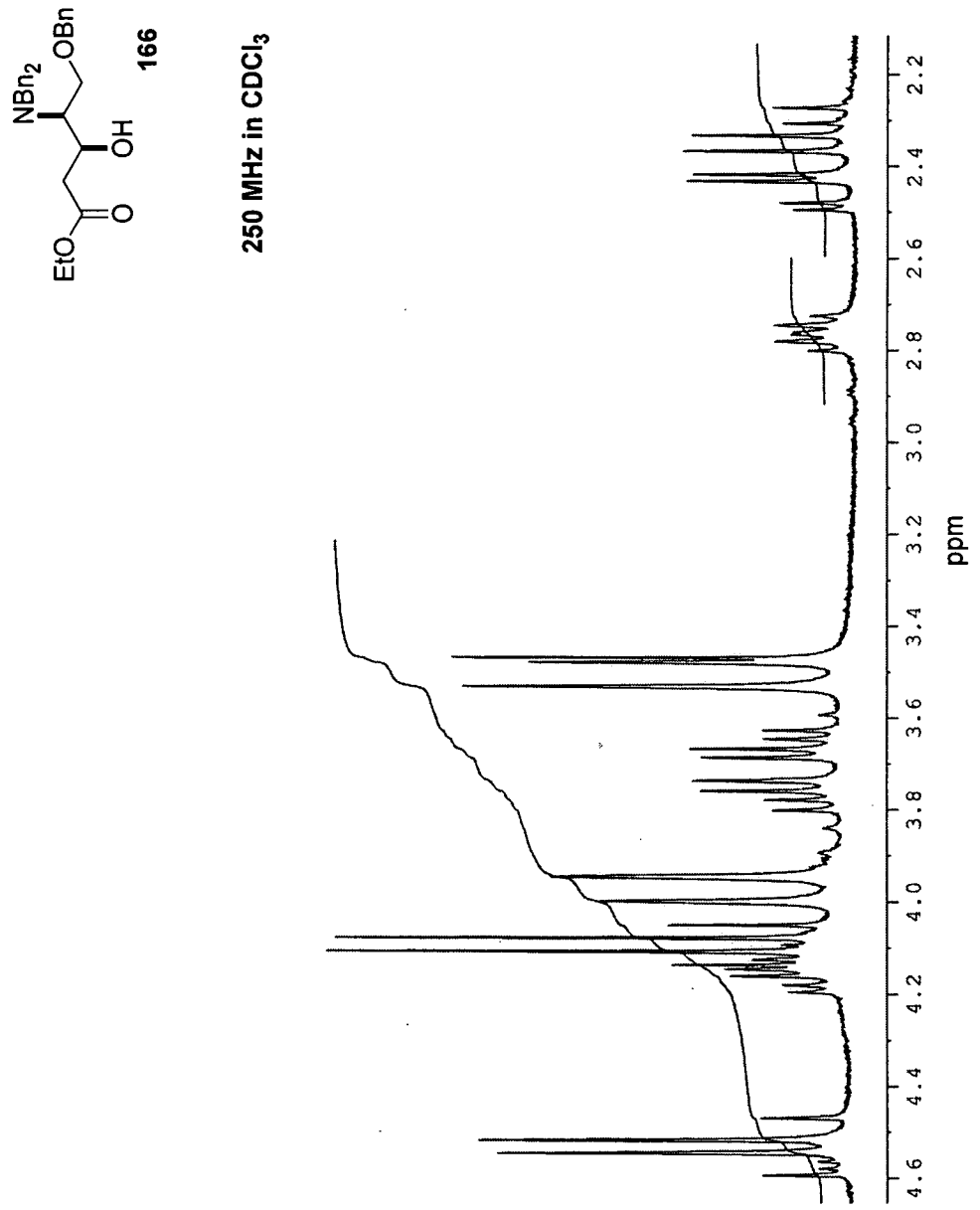
[138] J. W. Lown, R. R. Koganty and V. A. Joshua, *J. Org. Chem*, **1982**, *47*, 2027

[139] R. K. Dieter and R. R. Sharma, *J. Org. Chem.*, **1996**, *61*, 4180

^{1}H NMR spectrum of β-hydroxy alcohol 122



^{1}H NMR spectrum of β-hydroxy alcohol 166



^{1}H NMR spectrum of β-hydroxy alcohol 221

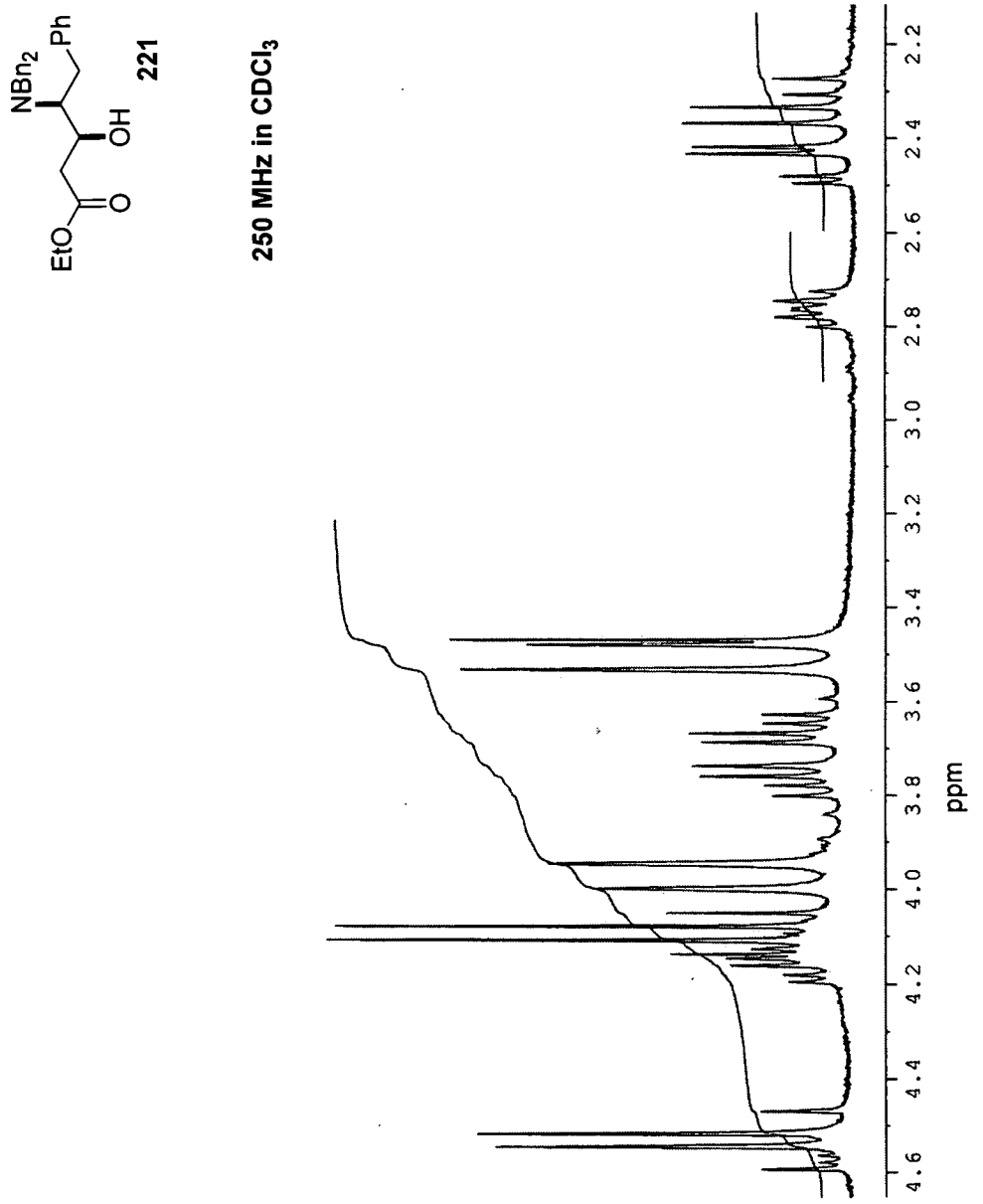


Table 1 *Crystal data and structure refinement for* ***90***

Part A: Crystal Data	
Empirical formula	$C_{21}H_{27}NO_3Si$
Formula weight	369.53
Wavelength	1.54184 Å
Temperature	150 (2) K
Crystal system	Monoclinic
Space group	P21
Unit cell dimensions	a = 12.555 (5) Å alpha = 90 deg b = 9.975 (7) Å beta = 98.10 (4) deg c = 16.749 (8) Å gamma = 90 deg
Volume	2076.6 (19) $Å^3$
Number of reflections for cell	56 (15 < theta< 22 deg.)
Z	4
Density (calculated)	1.182 Mg/m^3
Absorption coefficient	1.148 mm^{-1}
F(000)	792
Part B: Data Collection	
Crystal description	Colourless needle
Crystal size	0.04 × 0.08 × 0.78 mm
Instrument	Stoe Stadi-4
Theta range for data collection	2.66 to 69.63 deg.
Index ranges	-15<=h,<=15, -10<=k<=11, -15<=1<=20
Reflections collected	7259
Independent reflections	7034 [R(int) = 0.0767]
Scan type	Omega-2theta
Absorption correction	Gaussian Integration (T_{min} = 0.829, T_{max} = 0.959)
Part C :Solution and Refinement	
Solution	Patterson (DIRDIF)
Refinement type	**Full matrix least squares on F2**
Program used for refinement	SHELXL-97
Hydrogen atom placment	Geometric/difference map
Hydrogen atom treatment	Riding
Data/restraints/parameters	7034/1/474
Goodness of fit on F^2	1.070
Conventional R [F>4sigma (F)]	R1 = 0.0513 [5400 data]
Weighted R (F^2 and all data)	wR2 = 0.1459

Absolute structure parameter	-0.01 (4)
Extinction coefficient	0.0015 (3)
Final maximum delta/sigma	0.003
Weighting scheme	Calc w=1/[\s^2^(Fo^2^)+(0.0656P)^2^+1.2610P] where P=(Fo^2^+2Fc^2^)/3
Largest diff. Peak and hole	0.279 and –0.286 e. $Å^{-3}$

Table 2: *Atomic coordinates ($\times 10^4$) and equivalent isotropic displacement parameters ($A^2 \times 10^3$) for XX. U(eq) is defined as one third of the trace of the orthogaonalised Uij tensor.*

	x	**y**	**z**	**U (eq)**
Si (1)	1608 (1)	103 (1)	2834 (1)	26 (1)
N (1A)	1945 (3)	1001 (4)	331 (2)	30 (1)
C (2A)	2319 (3)	2049 (4)	913 (2)	26 (1)
O (3A)	1554 (2)	4069 (3)	300 (2)	37 (1)
(C 3A)	1367 (3)	3011 (4)	844 (2)	27 (1)
C (4A)	397 (3)	2170 (4)	502 (3)	31 (1)
O (5A)	377 (2)	122 (4)	-308 (2)	46 (1)
C (5A)	869 (3)	990 (4)	122 (2)	30 (1)
C (6A)	2617 (3)	1475 (4)	1745 (2)	27 (1)
O (7A)	1668 (2)	921 (3)	1992 (2)	29 (1)
C (8A)	2994 (3)	-444 (4)	3286 (2)	29 (1)
C (9A)	3470 (4)	-1601 (5)	3059 (3)	48 (1)
C (10A)	4507 (4)	-1962 (7)	3378 (4)	67 (2)
C (11A)	5112 (4)	-1143 (6)	3926 (3)	56 (1)
C (12A)	4672 (4)	34 (6)	4152 (3)	54 (1)
C (13A)	3619 (4)	371 (5)	3850 (3)	42 (1)
C (14A)	1102 (3)	1301 (4)	3561 (2)	28 (1)
C (15A)	1173 (3)	1024 (5)	4382 (3)	38 (1)
C (16A)	805 (4)	1934 (5)	4909 (3)	43 (1)
C (17A)	368 (4)	3143 (5)	4615 (3)	42 (1)
C (18A)	287 (4)	3439 (5)	3812 (3)	39 (1)
C (19A)	640 (3)	2515 (5)	3282 (3)	34 (1)
C (20A)	600 (3)	-1276 (5)	2521 (2)	31 (1)
C (21A)	524 (4)	-2237 (5)	3227 (3)	46 (1)
C (22A)	-512 (3)	-604 (6)	2266 (3)	46 (1)
C (23A)	898 (4)	-2058 (5)	1801 (3)	42 (1)
Si (2)	3724 (1)	8753 (1)	-2551 (1)	29 (1)

N (1B)	4623 (3)	7525 (4)	-95 (2)	29 (1)
C (2B)	4535 (3)	6398 (4)	-648 (2)	26 (1)
O (3B)	3588 (2)	4716 (3)	-2 (2)	35 (1)
C (3B)	3423 (3)	5805 (4)	-557 (3)	29 (1)
C (4B)	2818 (3)	6957 (5)	-226 (3)	33 (1)
O (5B)	3537 (2)	8971 (3)	486 (2)	44 (1)
C (5B)	3674 (3)	7946 (5)	102 (3)	32 (1)
C (6B)	4605 (3)	6847 (4)	-1496 (2)	29 (1)
O (7B)	3785 (2)	7806 (3)	-1746 (2)	31 (1)
C (8B)	5128 (3)	9217 (4)	-2694 (2)	30 (1)
C (9B)	5815 (3)	9808 (4)	-2057 (3)	33 (1)
C (10B)	6876 (3)	10128 95)	-2114 (3)	36 (1)
C (11B)	7288 (3)	9859 (5)	-2825 (3)	40 (1)
C (12B)	6646 (4)	9261 (5)	-3463 (3)	43 (1)
C (13B)	5577 (4)	8944 (5)	-3399 (3)	39 (1)
C (14B)	3081 (3)	7750 (5)	-3436 (2)	33 (1)
C (15B)	3049 (4)	8194 (5)	-4233 (3)	41 (1)
C (16B)	2615 (4)	7400 (6)	-4883 (3)	45 (1)
C (17B)	2181 (4)	6172 (6)	-4745 (3)	48 (1)
C (18B)	2187 (4)	5722 (6)	-3965 (3)	47 (1)
C (19B)	2633 (3)	6525 (5)	-3317 (3)	38 (1)
C (20B)	2871 (3)	10222 (5)	-2330 (3)	37 (1)
C (21B)	2602 (4)	11083 (6)	-3098 (3)	49 (1)
C (22B)	1815 (4)	9703 (6)	-2079 (3)	53 (1)
C (23B)	3435 (4)	11115 (6)	-1653 (3)	55 (1)

Table 3 *bond lengths Å for* ***90***

Bond	**Length Å**
Si (1)-O (7A)	1.641 (3)
Si (1)-C (8A)	1.877 (4)
Si (1)-C (14A)	1.879 (4)
Si (1)-C (20A)	1.893 (5)
N (1A)-C (5A)	1.346 (5)
N (1A)-C (2A)	1.462 (5)
C (2A)-C (6A)	1.504 (5)
C (2A)- C (3A)	1.524 (5)
O (3A)- C (3A)	1.436 (5)
C (3A)- C (4A)	1.522 (6)
C (4A)- C (5A)	1.500 (6)

O (5A)-C (5A)	1.235 (5)
C (6A)-O (7A)	1.427 (4)
C (8A)- C (9A)	1.378 (6)
C (8A)- C (13A)	1.401 (6)
C (9A)- C (10A)	1.383 (7)
C (10A)- C (11A)	1.375 (8)
C (11A)- C (12A)	1.374 (8)
C (12A)- C (13A)	1.388 (6)
C (14A)- C (15A)	1.394 (6)
C (14A)- C (19A)	1.394 (6)
C (15A)- C (16A)	1.389 (6)
C (16A)- C (17A)	1.387 (7)
C (17A)- C (18A)	1.366 (7)
C (18A)- C (19A)	1.394 (6)
C (20A)- C (23A)	1.526 (6)
C (20A)- C (21A)	1.536 (6)
C (20A)- C (22A)	1.553 (6)
Si (2)- O (7B)	1.639 (3)
Si (2)- C (8B)	1.870 (4)
Si (2)- C (14B)	1.874 (5)
Si (2)- C (20B)	1.882 (5)
N (1B)- C (5B)	1.347 (5)
N (1B)- C (2B)	1.452 (5)
C (2B)- C (6B)	1.504 (5)
C (2B)- C (3B)	1.543 (5)
O (3B)- C (3B)	1.426 (5)
C (3B)- C (4B)	1.524 (6)
C (4B)- C (5B)	1.505 (6)
O (5B)- C (5B)	1.233 (5)
C (6B)- O (7B)	1.425 (5)
C (8B)- C (9B)	1.405 (6)
C (8B)- C (13B)	1.386 (6)
C (9B)- C (10B)	1.389 (6)
C (10B)- C (11B)	1.381 (7)
C (12B)- C (13B)	1.397 (6)
C (14B)- C (19B)	1.371 (7)
C (14B)- C (15B)	1.402 (6)
C (15B)- C (16B)	1.394 (7)
C (16B)- C (17B)	1.374 (8)
C (17B)- C (18B)	1.380 (7)
C (18B)- C (19B)	1.401 (7)
C (20B)- C (23B)	1.534 (7)
C (20B)- C (22B)	1.535 (6)
C (20B)-C (21B)	1.534 (6)

Table 4 *Bond angles (degrees) for* ***90***

Bond	Angle (degrees)
O (7A)-Si (1)-C (8A)	109.79 (16)
O (7A)-Si (1)-C (14A)	107.52 (18)
C (8A)-Si (1)-C (14A)	107.62 (18)
O (7A)-Si (1)-C (20A)	103.46 (17)
C (8A)-Si (1)-C (20A)	116.5 (2)
C (14A)-Si (1)-C (20A)	111.58 (18)
C (5A)-N (1A)-C (2A)	113.3 (3)
N (1A)-C (2A)- C(6A)	111.1 (3)
N (1A)-C (2A)-C (3A)	108.3 (3)
C (6A)-C (2A)-C (3A)	105.0 (3)
O (3A)-C (3A)-C (4A)	104.4 (3)
O (3A)-C (3A)-C (2A)	123.9 (4)
C (4A)-C (3A)-C (2A)	127.1 (4)
C (5A)-C (4A)-C (3A)	109.0 (4)
O (5A)-C (5A)-C (4A)	107.9 (3)
O (5A)-C (5A)-N (1A)	125.7 (2)
N (1A)-C (5A)-C (4A)	116.7 (4)
O (7A)-C (6A)-C (2A)	123.1 (3)
C (6A)-O (7A)-Si (1)	120.1 (3)
C (9A)-C (8A)-C (13A)	122.3 (5)
C (9A)-C (8A)-Si (1)	120.3 (5)
C (13A)-C (8A)-Si (1)	119.1 (5)
C (8A)-C (9A)-C (10A)	120.5 (5)
C (11A)-C (10A)-C (9A)	121.2 (5)
C (12A)-C (11A)-C (10A)	117.9 (4)
C (11A)-C (12A)-C (13A)	122.2 (3)
C (12A)-C (13A)-C (8A)	119.9 (3)
C (15A)-C (14A)-C (19A)	121.1 (4)
C (15A)-C (14A)-Si (1)	119.6 (4)
C (19A)-C (14A)-Si (1)	120.5 (4)
C (16A)-C (15A)-C (14A)	119.8 (4)
C (17A)-C (16A)-C(14A)	121.0 (4)
C (18A)-C (17A)-C (16A)	109.8 (4)
C (17A)-C (18A)-C (19A)	108.3 (4)
C (18A)-C (19A)-C (14A)	109.3 (4)
C (23A)-C (20A)-C (21A)	111.2 (3)
C (23A)-C (20A)-C (22A)	110.6 (3)
C (21A)-C (20A)-C (22A)	107.6 (3)
C (23A)-C (20A)-Si (1)	108.20 (16)
C (21A)-C (20A)-Si (1)	107.91 (19)

C (22A)-C (20A)-Si (1)	109.84 (19)
O (7B)-Si (2)-C (8B)	104.42 (18)
O (7B)-Si (2)-C (14B)	113.9 (2)
C (8B)-Si (2)-C (14B)	112.2 (2)
O (7B)-Si (2)-C (20B)	114.1 (3)
C (8B)-Si (2)-C (20B)	111.3 (4)
C (14B)-Si (2)-C (20B)	102.8 (3)
C (5B)-N (1B)-C (2B)	112.4 (3)
N (1B)-C (2B)-C (6B)	111.9 (3)
N (1B)-C (2B)-C (3B)	107.8 (3)
C (6B)-C (2B)-C (3B)	104.6 (3)
O (3B)-C (3B)-C (4B)	105.1 (3)
O (3B)-C (3B)-C (2B)	125.4 (4)
C (4B)-C (3B)-C (2B)	126.1 (4)
C (5B)-C (4B)-C (3B)	108.5 (4)
O (5B)-C (5B)-N (1B)	110.0 (3)
O (5B)-C (5B)-C (4B)	125.2 (2)
N (1B)-C (5B)-C (4B)	116.3 (4)
O (7B)-C (6B)-C (2B)	119.7 (3)
C (6B)-O (7B)-Si (2)	123.9 (3)
C (9B)-C (8B)-C (13B)	122.5 (4)
C (9B)-C (8B)-Si (2)	119.5 (4)
C (13B)-C (8B)-Si (2)	119.9 (4)
C (10B)-C (9B)-C (8B)	120.0 (4)
C (9B)-C (10B)-C (11B)	121.7 (4)
C (12B)-C (11B)-C (10B)	117.5 (4)
C (11B)-C (12B)-C (13B)	120.1 (3)
C (12B)-C (13B)-C (8B)	122.4 (4)
C (19B)-C (14B)-C (15B)	121.3 (5)
C (19B)-C (14B)-Si (2)	119.7 (5)
C (15B)-C (14B)-Si (2)	120.0 (5)
C (16B)-C (15B)-C (14B)	119.7 (5)
C (17B)-C (16B)-C (15B)	121.7 (4)
C (14B)-C (19B)-C (18B)	108.6 (4)
C (23B)-C (20B)-C (22B)	108.5 (5)
C (22B)-C (20B)-C (21B)	108.7 (4)
C (23B)-C (20B)-Si (2)	112.4 (3)
C (22B)-C (20B)-Si (2)	109.2 (4)
C (21)-C (20B)-Si (2)	109.5 (3)

Symmetry transformations used to generate equivalent atoms:

Table 5 *Anisotropic displacement parameters (A^2 x 10^3) for xx. The anisotropic displacement factor exponent takes the form: -2 pi^2 [H^2 a*^ U11 + ... + 2 h k a* b* U12]*

	U11	U22	U33	U23	U13	U12
Si (1)	24 (1)	24 (1)	31 (1)	1 (1)	6 (1)	0 (1)
N (1A)	27 (2)	29 (2)	35 (2)	-3 (2)	12 (1)	2 (2)
C (2A)	22 (2)	24 (2)	32 (2)	0 (2)	6 (2)	-5 (2)
O (3A)	27 (2)	32 (2)	53 (2)	16 (1)	6 (1)	-4 (1)
C (3A)	23 (2)	22 (2)	38 (2)	8 (2)	7 (2)	-1 (2)
C (4A)	25 (2)	25 (3)	42 (2)	1 (2)	6 (2)	-5 (2)
O (5A)	42 (2)	42 (2)	52 (2)	-11 (2)	4 (1)	-14 (2)
C (5A)	27 (2)	28 (3)	36 (2)	0 (2)	9 (2)	-6 (2)
C (6A)	18 (2)	27 (2)	37 (2)	3 (2)	7 (2)	0 (2)
O (7A)	23 (1)	31 (2)	36 (2)	7 (1)	9 (1)	1 (1)
C (8A)	27 (2)	26 (2)	34 (2)	1 (2)	4 (2)	-1 (2)
C (9A)	34 (2)	41 (3)	65 (3)	-18 (2)	0 (2)	6 (2)
C (10A)	38 (3)	51 (4)	110 (5)	-23 (4)	0 (3)	13 (3)
C (11A)	29 (2)	53 (4)	82 (4)	-3 (3)	-9 (2)	11 (3)
C (12A)	33 (2)	51 (3)	74 (3)	-11 (3)	-8 (2)	-3 (3)
C (13A)	35 (2)	34 (3)	57 (3)	-8 (2)	6 (2)	1 (2)
C (14A)	21 (2)	27 (2)	37 (2)	0 (2)	6 (2)	-4 (2)
C (15A)	36 (2)	40 (3)	38 (2)	3 (2)	8 (2)	11 (2)
C (16A)	49 (3)	49 (3)	33 (2)	-2 (2)	7 (2)	8 (2)
C (17A)	37 (2)	41 (3)	49 (3)	-10 (2)	10 (2)	4 (2)
C (18A)	36 (2)	37 (3)	45 (3)	0 (2)	9 (2)	6 (2)
C (19A)	35 (2)	33 (3)	34 (2)	1 (2)	8 (2)	5 (2)
C (20A)	29 (2)	26 (2)	39 (2)	2 (2)	7 (2)	-1 (2)
C (21A)	53 (3)	41 (3)	44 (3)	4 (2)	5 (2)	-17 (3)
C (22A)	25 (2)	37 (3)	61 (3)	2 (3)	5 (2)	-3 (2)
C (23A)	44 (3)	33 (3)	44 (3)	-10 (2)	6 (2)	-6 (2)
Si (2)	23 (1)	26 (2)	34 (1)	6 (1)	4 (1)	1 (1)
N (1B)	24 (2)	41 (3)	34 (2)	0 (2)	4 (1)	1 (2)
C (2B)	19 (2)	52 (3)	37 (2)	3 (2)	8 (2)	3 (2)
O (3B)	27 (2)	37 (3)	51 (2)	13 (1)	10 (1)	1 (1)
C (3B)	25 (2)	32 (1)	38 (2)	7 (2)	5 (2)	0 (2)
C (4B)	20 (2)	30 (2)	49 (3)	8 (2)	8 (2)	-1 (2)
O (5B)	35 (2)	23 (2)	66 (2)	-13 (2)	16 (1)	4 (1)
C (5B)	26 (2)	29 (2)	43 (2)	7 (2)	12 (2)	6 (2)
C (6B)	22 (2)	24 (2)	37 (2)	3 (2)	8 (2)	7 (2)
O (7B)	23 (1)	30 (3)	32 (2)	8 (1)	5 (1)	5 (1)
C (8B)	25 (2)	38 (2)	39 (2)	8 (2)	4 (2)	3 (2)
C (9B)	32 (2)	25 (2)	40 (2)	6 (2)	5 (2)	1 (2)

C (10B)	31 (2)	27 (3)	50 (2)	9 (2)	0 (2)	-1 (2)
C (11B)	30 (2)	25 (2)	63 (3)	12 (2)	13 (2)	-3 (2)
C (12B)	41 (3)	29 (3)	52 (3)	5 (2)	21 (2)	-5 (2)
C (13B)	42 (2)	41 (3)	39 (2)	1 (2)	8 (2)	1 (2)
C (14B)	23 (2)	38 (3)	37 (2)	4 (2)	7 (2)	2 (2)
C (15B)	37 (2)	40 (3)	40 (2)	4 (2)	1 (2)	-3 (2)
C (16B)	40 (2)	44 (3)	37 (2)	2 (2)	0 (2)	1 (2)
C (17B)	37 (2)	55 (4)	42 (3)	-13 (3)	-2 (2)	-4 (3)
C (18B)	40 (3)	64 (4)	54 (3)	2 (2)	7 (2)	-11 (2)
C (19B)	31 (2)	48 (3)	40 (2)	6 (2)	7 (2)	-4 (2)
C (20B)	32 (2)	35 (3)	44 (2)	3 (2)	6 (2)	8 (2)
C (21B)	45 (3)	46 (3)	55 (3)	14 (2)	8 (2)	13 (2)
C (22B)	35 (2)	67 (4)	60 (3)	15 (3)	18 (2))	17 (2)
C (23B)	50 (3)	48 (4)	66 (3)	-12 (3)	7 (2)	12 (3)

Table 6 *Hydrogen coordinates (× 10^4) and isotropic displacement parameters (A^2 × 10 ^3) for* ***90***

	x	y	z	U (eq)
H (1A)	2379	433	136	38 (13)
H (2A)	2956	2514	743	31
H (3A)	866	4430	219	90 (20)
H (3A1)	1274	3381	1385	32
H (4A1)	-12	1878	936	37
H (4A2)	-89	2684	96	37
H (6A1)	3171	770	1739	32
H (6A2)	2913	2187	2125	32
H (9A)	3073	-2171	2671	57
H (10A)	4803	-2780	3217	81
H (11A)	5825	-1387	4144	67
H (12A)	5090	620	4517	65
H (13A)	3316	1170	4030	51
H (15A)	1478	199	4585	45
H (16A)	852	1729	5467	52
H (17A)	123	3772	4975	50
H (18A)	-9	4272	3616	47
H (19A)	564	2715	2723	40
H (21A)	317	-1734	3684	69
H (21B)	1224	-2664	3389	69
H (21C)	-18	-2926	3060	69
H (22A)	-1052	-1296	2101	69

H (22B)	-467	8	1815	69
H (22C)	-719	-100	2723	69
H (23A)	1595	-2498	1953	62
H (23B)	944	-1441	1352	62
H (23C)	346	-2737	1636	62
H (1B)	5241	7901	95	100 (2)
H (2B)	5112	5727	-471	31
H (3B)	2869	4322	12	73 (18)
H (3B1)	3042	5497	-1090	35
H (4B1)	2304	7370	-660	40
H (4B2)	2416	6639	205	40
H (6B1)	5320	7250	-1522	35
H (6B2)	4520	6065	-1863	35
H (9B)	5542	9995	-1568	39
H (10B)	7317	10529	-1671	43
H (11B)	8012	10086	-2871	48
H (12B)	6931	9064	-3946	52
H (13B)	5144	8534	-3843	47
H (15B)	3329	9053	-4332	49
H (16B)	2618	7707	-5420	53
H (17B)	1878	5631	-5186	58
H (18B)	1889	4871	-3868	57
H (19B)	2625	6213	-2782	45
H (21D)	2149	11840	-2985	73
H (21E)	2217	10535	-3531	73
H (21F)	3270	11420	-3265	73
H (22D)	1972	9202	-1573	79
H (22E)	1455	9112	-2501	79
H (22F)	1345	10463	-2004	79
H (23D)	2945	11831	-1537	82
H (23E)	4081	11510	-1824	82
H (23F)	3638	10574	-1168	82

Abbreviations

Ac	acetyl
aq.	aqueous
Ar	aryl
atm.	atmosphere
Boc	*tert*-butoxycarbonyl
Bn	benzyl
Bu	butyl
Cbz	benzlyoxycarbonyl
DCM	dichloromethane
DEAD	diethyl azodicarboxylate
DIBAL-H	diisobutylaluminium hydride
DMF	*N*,*N*-dimethylformamide
DMAP	4-dimethylaminopyridine
DMSO	dimethylsulfoxide
de	diastereomeric excess (i.e. % of major diastereomer- % of minor diasteromer)
ee	enatiomeric excess (i.e. % of major diastereomer- % of minor diasteromer)
EI	electron impact ionisation
Et	ethyl
Ether	diethyl ether
FAB	fast atom bombardment
Fmoc	fluorenylmethylcarbonyl
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrum
Hz	hertz
IR	infra red
M	unspecified metal
M	mol dm^{-3}

Me	methyl
MOM	methoxymethyl
NMR	nuclear magnetic resonance
NU^-	nucleophile
P	unspecified protecting group
Ph	phenyl
PMB	*para*-methoxybenzyl
Pr	propyl
ppm	parts per million
Py	pyridine
R_t	retention time for HPLC
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
THF	tetrahydrofuran
t.l.c.	thin layer chromatography
TMS	trimethylsilyl
TsCl	*para*-toluene sulphonyl chloride

Approaches to the synthesis of (2*R*,3*S*)-2-hydroxymethylpyrrolidin-3-ol (CYB-3) and its C(3) epimer: a cautionary tale

Alison N. Hulme* and Karen S. Curley

Department of Chemistry, The University of Edinburgh, Kings Buildings, West Mains Road, Edinburgh, UK EH9 3JJ

Received (in Cambridge, UK) 14th January 2002, Accepted 22nd February 2002
First published as an Advance Article on the web 26th March 2002

The syntheses of (2*R*,3*S*)-2-*tert*-butyldiphenylsilyloxymethylpyrrolidin-3-ol (TBDPS-protected CYB-3) (**21**) and its C(3) epimer (**25**) have been achieved in 9 and 8 steps respectively from D-serine. However, chiral HPLC analysis of the key β-hydroxy ester intermediates in these syntheses (**17** and **18**) revealed that appreciable levels of racemisation had occurred in the aldol and Claisen condensation reactions used in this synthetic sequence.

Introduction

The hydroxypyrrolidine CYB-3 (**1**),[1] shares its biological source (a tree from *Castanospermum australe* sp.) with the more well known indolizidine alkaloid castanospermine (**2**) (Fig. 1).[2]

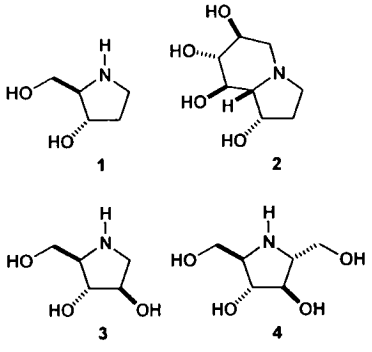


Fig. 1 Alkaloid glycosidase inhibitors.

Although CYB-3 exhibits only modest inhibitory activity against several insect[3] and mammalian[4] glycosidase targets when compared with other pyrrolidine alkaloids such as 1,4-dideoxy-1,4-imino-D-arabinitol (DAB-1) (**3**),[5] and (2*R*,3*R*,4*R*,5*R*)-2,5-bis(hydroxymethyl)-3,4-dihydroxypyrrolidine (DMDP) (**4**),[6] it has been proposed as both a chemical[7] and biosynthetic[8] precursor for a number of more active indolizidine alkaloids and has also been used in the synthesis of modified oligonucleotides.[9]

Several chemical syntheses of CYB-3 (**1**) have been reported recently which rely upon readily available chiral pool starting materials. In approaches utilising the amino acid serine (**5**), a number of different strategies have been used to achieve the required two-carbon homologation; the most common of these involving allylation and subsequent oxidative cleavage to remove the "extra" carbon.[10] However, two-carbon homologation has also been achieved through the use of vinyl Grignard addition[9] and Horner–Wadsworth–Emmons (HWE)/cyclocarbamation reactions,[7] as well as the tandem Michael/Henry reaction of a nitroethylene precursor.[11] Other popular chiral pool starting materials for the synthesis of CYB-3 include pyroglutamic acid† (**6**)[12] and sugars such as mannose (**7**)

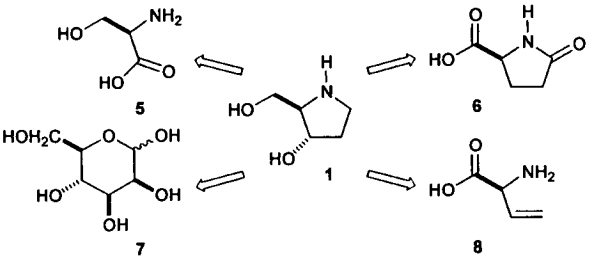


Fig. 2 Chiral pool precursors to CYB-3.

(Fig. 2).[13] One final approach from the chiral pool utilises the olefin metathesis of a derivative of vinyl glycine (**8**) as the key step.[14]

We have recently reported the syntheses of both the iminosugar DAB-1 (**3**),[15] and the antibiotic anisomycin (**9**),[16] utilising stereocontrolled glycolate aldol couplings to D-serine- and D-tyrosine-derived aldehydes **10** and **11** respectively to provide the acyclic backbone of each of these natural products in high yield (Fig. 3).

As part of a continued interest in the synthesis of bioactive iminosugars through the use of the aldol reaction, we were

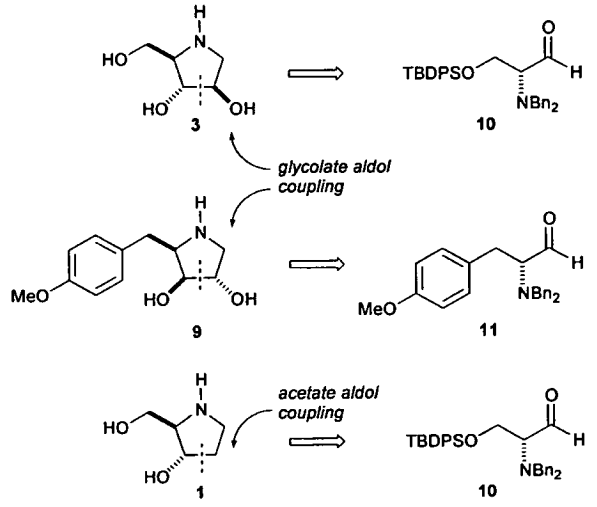


Fig. 3 An aldol based approach to the syntheses of the hydroxylated pyrrolidines DAB-1, anisomycin and CYB-3.

† Pyroglutamic acid is also known as 5-oxoproline.

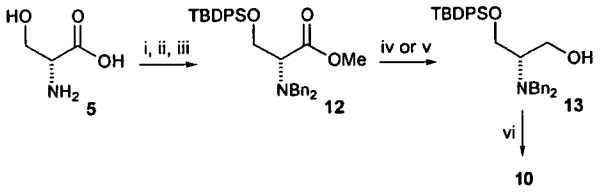
DOI: 10.1039/b200415a

attracted to the possibility of an acetate aldol approach to the synthesis of CYB-3 (**1**), combining the lithium enolate of methyl, or ethyl acetate with our readily accessible D-serine-derived aldehyde **10**. Previous reports of such acetate aldols have shown that high levels of substrate-derived stereocontrol might be achieved in the case of simple *N*,*N*-dibenzyl α-amino aldehydes,[17] and that this strategy might be successfully extended to the reaction of more sterically demanding aldehydes such as that derived from isoleucinal.[18]

Results and discussion

Synthesis of (2*R*,3*S*)-2-*tert*-butyldiphenylsilyloxymethylpyrrolidin-3-ol

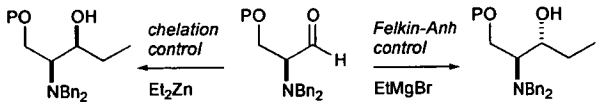
The synthesis of aldehyde **10** from D-serine (**5**) was carried out in five steps as described in our previous paper (Scheme 1).[15]



Scheme 1 *Reagents and conditions*: i. CH_3COCl, MeOH, reflux, 3 h (98%); ii. K_2CO_3, BnBr, CH_3CN, rt, 24 h (95%); iii. TBDPSCl, imidazole, DMF, rt, 18 h (100%); iv. DIBAL-H, $PhCH_3$, −78 °C, 30 min (93%); v. $LiBH_4$, Et_2O : MeOH (60 : 1), 0 °C ⟶ reflux, 4 h (95%); vi. $(COCl)_2$, DMSO, CH_2Cl_2, −78 °C, 1 h, Et_3N (100%).

However, on a gram scale the removal of copious quantities of aluminium salts from the DIBAL-H reduction of methyl ester **12** was found to be troublesome, and $LiBH_4$ reduction of the ester **12** to the corresponding alcohol **13** was preferred (95%). Using this modified protocol, aldehyde **10** could routinely be prepared in 88% overall yield from serine.

High levels of substrate based stereocontrol have been observed in the reactions of L-serine-derived *N*,*N*-dibenzyl α-amino aldehyde **14a** and its TBDMS-protected analogue **14b** with simple nucleophiles, by ourselves[19] and Andrés and Pedrosa.[20] Thus aldehydes **14a,b** have been shown to react with Grignard reagents to give the *anti* addition products **15a,b** with >95 : 5 selectivity due to Felkin–Anh control (Fig. 4),

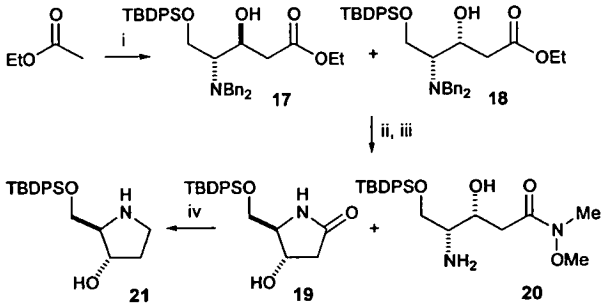


16a d.r. >99:1
16b d.r. >99:1
14a P = TBDPS
14b P = TBDMS
15a d.r. 95:5
15b d.r. 95:5

Fig. 4 Felkin–Anh and chelation control in the reaction of simple nucleophiles with *N*,*N*-dibenzyl α-amino aldehydes **14**.

whereas the reaction of dialkylzinc reagents has been shown to proceed with excellent selectivity for the *syn* addition products **16a,b**, presumably due to a chelation controlled mechanism.

With the knowledge that these simple nucleophilic addition reactions to the enantiomeric protected serine-derived aldehyde **14a** proceeded with excellent stereocontrol, and the precedent of high substrate-derived selectivity in previous reactions of methyl, or ethyl acetate aldol reactions with simple *N*,*N*-dibenzyl α-amino aldehydes,[17,18] we were confident in achieving high levels of stereocontrol when following the synthetic pathway towards CYB-3 **1** outlined in Scheme 2. However, when aldehyde **10** was condensed with the lithium enolate of ethyl acetate the aldol adducts **17** and **18** were generated in good



Scheme 2 *Reagents and conditions*: i. LiHMDS, THF, −78 °C, 20 min; **10**, THF, −78 °C ⟶ 0 °C, 3 h (85%); ii. (MeO)NHMe·HCl, Me_3Al, THF, 0 °C ⟶ 35 °C, 3 h (98%); iii. $Pd(OH)_2$/C cat., MeOH, H_2, rt, 12 h (81% **19**, 12% **20**); iv. BH_3·THF, THF, 0 °C ⟶ reflux, 24 h (85%).

yield (85%),‡ but disappointingly were obtained as a 6 : 1 inseparable mixture of diastereomers [as determined by integration of the C(2) signals in the crude proton NMR spectrum].§

To complete the synthesis of CYB-3 we chose to pursue a similar route to that used in the synthesis of DAB-1,[15] namely cyclisation to give the pyrrolidin-2-one followed by borane reduction to give the requisite protected pyrrolidine. To facilitate the complete removal of the *N*-benzyl protecting groups from the mixture of aldol adducts[15] they were first converted in excellent yield into the corresponding Weinreb amides. These amides were then treated under standard deprotection conditions [$Pd(OH)_2$/C, H_2] to yield a readily separable mixture of products in which the Weinreb amide resulting from desired aldol adduct **17** had undergone a spontaneous cyclisation to give pyrrolidinone **19** (81%), whilst the minor diastereomer was isolated as the acyclic amino amide **20** (12%). The pyrrolidinone **19** was found to be a crystalline solid, allowing its structure to be determined unequivocally by X-ray diffraction. This fortuitous separation allowed the subsequent borane reduction to be conducted on a single diastereomer, and conversion of pyrrolidinone **19** to the desired protected pyrrolidine **21** was achieved in high yield (85%).

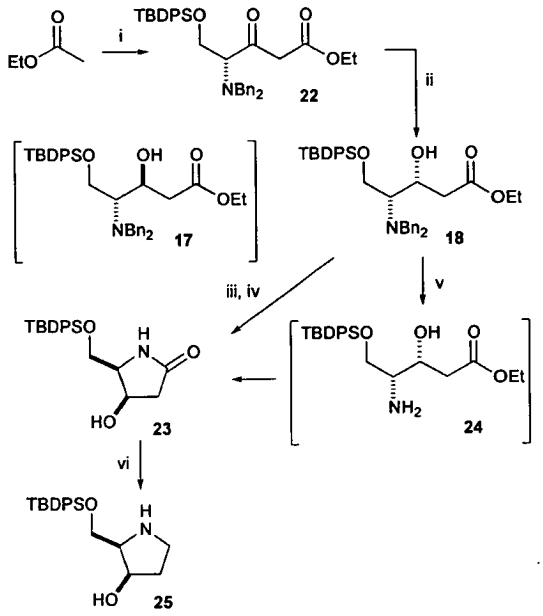
Thus a 9 step synthesis of TBDPS-protected CYB-3 **21** has been achieved in 50% overall yield. This protected derivative is ideally suited towards further synthetic manipulation such as that followed by Herdewijn *et al.* in the synthesis of modified oligonucleotides.[9] Furthermore, **21** and its protected pyrrolidinone precursor **19**, offer the opportunity for the development of new selective glycomimetic-based glycosyltransferase inhibitors,[21] through selective glycosylation of the CYB-3 core. [There are for example, only a few reported syntheses of motifs related to the oligosaccharide sialyl Lewis X currently reported in the literature based on mono- or disaccharide derivatives of a pyrrolidinone,[22] or pyrrolidine core.[23]]

Synthesis of (2*R*,3*R*)-2-*tert*-butyldiphenylsilyloxymethylpyrrolidin-3-ol

In tackling the synthesis of the C(3) epimer we felt that we should make use of the high substrate-derived selectivity that is normally observed in the Felkin–Anh controlled reduction of *N*,*N*-dibenzyl α-amino ketones.[17a] The *N*,*N*-dibenzyl α-amino ketone that was required for this strategy was obtained from the

‡ R_t *anti* diastereomers (aldol major) **17** and *ent*-**17**, 8.3 and 9.0 min; R_t *syn* diastereomers (Claisen major) **18** and *ent*-**18**, 9.1 and 10.8 min [4.6 × 250 mm Chiracel OD column, solvent (5% isopropyl alcohol (IPA) in hexane), flow rate 0.5 mL min^{-1}].

§ Unfortunately, all attempts to improve the diastereoselectivity of this acetate aldol reaction through the use of 'matched' chiral acetate boron enolates (from either the phenylalanine-derived acylated Evans oxazolidinone, or valine-derived acylated thiazolidinethione) were unsuccessful. These reactions resulted in lower yields of reaction products, with no significant improvement in the diastereoselectivity.



Scheme 3 *Reagents and conditions:* i. LiHMDS, THF, −78 °C, 25 min; **12**, THF, −78 °C ⟶ 0 °C, 4 h (78%); ii. $NaCNBH_3$, AcOH, Et_2O : MeOH (8 : 3), 0 °C ⟶ rt, 7 h (81%); iii. (MeO)NHMe, Me_3Al, THF, 0 °C ⟶ 35 °C, 3 h (95%); iv. $Pd(OH)_2/C$, MeOH, H_2, rt, 12 h; SiO_2; MeOH, reflux, 24 h (72%); v. $Pd(OH)_2$, MeOH, H_2, rt, 12 h; SiO_2; MeOH, reflux, 24 h (78%); vi. BH_3·THF, THF, 0 °C ⟶ reflux, 24 h (86%).

Claisen condensation of methyl ester **12** (Scheme 1) with the lithium enolate of ethyl acetate to give **22** in good yield (78%, Scheme 3). Several different reagents, including sodium and lithium borohydride, were used for the selective reduction of the ketone functionality. Due to the hindered nature of this protected α-amino ketone this reaction was found to be extremely sluggish at 0 °C and heating to room temperature was required to drive the reaction to completion. This resulted in considerable concomitant reduction of the ester to give the corresponding diastereomeric diols. Thus although reasonable selectivity favouring the desired *syn* stereochemistry in **18** (typically 5 : 1 to 8 : 1) could be achieved, the yields of **18** and **17** were low. A solution was finally obtained with the use of sodium cyanoborohydride which, despite longer reaction times and the need for a greater excess of the reagent to drive the reaction to completion, resulted in a marked decrease in ester reduction. This allowed the synthesis of diastereomeric β-hydroxy esters **18** and **17** as a 10 : 1 mixture of diastereomers [as determined by integration of the C(2) signals in the crude ^1H NMR spectrum]. In this diastereomeric mixture, **18** was found to be amenable to chromatographic separation and could be isolated in 81% yield (along with 6% of **17**).

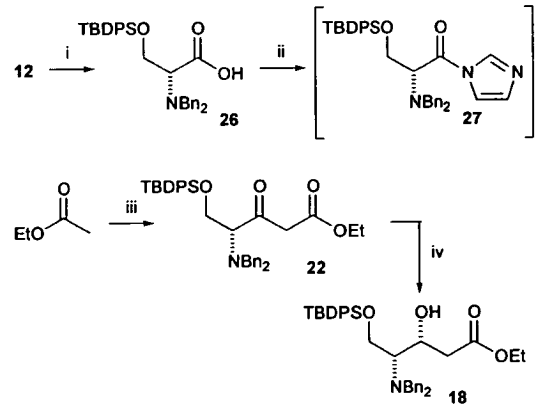
Two separate routes to the completion of the synthesis of the C(3) epimer of CYB-3 were pursued. In the first, the ester **18** was converted to the Weinreb amide as in the previous synthetic sequence [(MeO)NHMe·HCl, Me_3Al, 95%] and this was subjected to debenzylation [$Pd(OH)_2/C$, H_2] to give the amino amide **20**. This amide was filtered through a short pad of silica and then heated at reflux in methanol for 24 h, to give the pyrrolidinone **23** in 78% yield. The second, more direct route made use of the relatively lower reactivity towards cyclisation imparted on this stereoisomer by its conformation. (Thus debenzylation of the amino ester **18** might be expected to go to completion, without concomitant cyclisation to give a mixture of the desired product **23** and the corresponding benzyl protected pyrrolidinone.) When **18** was treated under standard conditions [$Pd(OH)_2/C$, H_2] for debenzylation, amino ester **24** was indeed isolated in excellent yield (100% crude material). Filtration through a short pad of silica and heating to reflux in methanol once again yielded pyrrolidinone **23** in high yield (78%). Borane reduction of pyrrolidinone **23** gave the desired protected pyrrolidine **25** in high yield (86%). Using the second (shorter) of these routes, a 7 step synthesis of the TBDPS-protected C(3) epimer of CYB-3 (**25**) from the amino acid serine, has been achieved in 39% overall yield.

The cautionary tale

There is literature precedent for the aldol reactions of simple lithium enolates with *N,N*-dibenzyl α-amino aldehydes, and little discussion of any loss of stereochemical integrity during the course of these reactions.[17,18] However, it is known that racemisation may occur in the Claisen condensation reaction of simple *N,N*-dibenzyl α-amino esters,[24] where the resultant enantiomeric excess may be reduced to as low as 78–90%. We were anxious to investigate whether, and if so the extent to which, racemisation had occurred in our current synthetic work.

We have previously shown that the synthetic sequence outlined in Scheme 1 allows the production of aldehyde **10** (and hence its precursors) with no appreciable racemisation (>98% ee by chiral HPLC) and indeed that high yields of a single diastereomer might be obtained in subsequent glycolate aldol couplings, suggesting no appreciable racemisation in the reaction of **10**.[15] In order to rapidly identify all four possible stereoisomers from the acetate aldol coupling, the synthesis of **17** and **18** was carried out using the route shown in Scheme 2 starting from a sample of aldehyde **10** prepared from racemic serine. The resultant β-hydroxy esters were separable by chiral HPLC using a standard analytical Chiracel OD column and a solvent mix of 5% IPA in hexane.‡ Comparison of this HPLC trace with those obtained from the aldol reaction of chiral non-*racemic* D-serine-derived aldehyde **10**, allowed us to draw the unhappy conclusion that our aldol adduct **17** was of only 90% ee. Worse still, the β-hydroxy ester **18** derived from the Claisen reaction of methyl ester **12** and subsequent cyanoborohydride reduction was shown to vary in enantiomeric excess from 0% to 70% in an extremely capricious manner.

In an effort to address the latter problem, alternative substrates for the Claisen condensation were sought. Saponification of the methyl ester to acid **26** and conversion to the imidazolide (acylimidazole) **27** is well-precedented in the literature for other α-amino esters.[24,25] However, in itself this presented problems in that methyl ester **12** was found to be relatively unreactive towards saponification under a range of standard conditions, including those recently published for sterically congested methyl esters of this type.[24] The most efficient conditions were found to be heating ester **12** to reflux in a THF–water solvent mixture in the presence of LiOH (Scheme 4). There was a delicate balance between the yield of

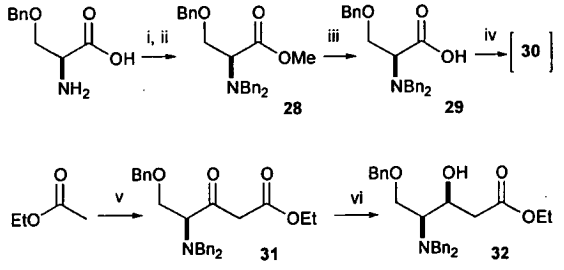


Scheme 4 *Reagents and conditions:* i. LiOH, THF : H_2O (4 : 1), reflux, 6 h (58%); ii. CDI, THF, rt, 2 h; iii. LiHMDS, THF, −78 °C, 20 min; **27**, THF, −78 °C ⟶ 0 °C, 2 h (91% from **26**); iv. $NaCNBH_3$, AcOH, Et_2O : MeOH (8 : 3), 0 °C ⟶ rt, 7 h (81%).

acid **26** and the eventual enantiomeric excess of product **18**; longer reaction times (24 h) resulting in high yields of the acid (90%) but with considerable racemisation and concomitant loss of the TBDPS protecting group. Conversion to the imidazolide **27** using carbonyldiimidazole (CDI) was efficient, but in general **27** was not isolated, rather it was treated directly with the lithium enolate of ethyl acetate to give the amino ketone **22** in high yield (91% from acid **26**). Reduction under the previously optimised conditions ($NaCNBH_3$) allowed the synthesis and isolation of **18** and assessment of its enantiomeric purity by chiral HPLC. Using this route we were able to produce the β-hydroxy ester **18** with a reliable enantiomeric excess of 70%. This material was then converted through to the desired (2*R*,3*S*)-2-*tert*-butyldiphenylsilyloxymethylpyrrolidin-3-ol **25**, giving an 8 step synthesis of this protected hydroxypyrrolidine in 26% overall yield.

Since the enantiomeric excess observed in β-hydroxy ester **18** produced *via* the route shown in Scheme 4 was shown to be extremely dependent upon the conditions used for the saponification of methyl ester **12**, this suggested that in itself the use of the CDI-mediated Claisen condensation was not contributing greatly to the racemisation process (as compared to the direct condensation of methyl ester **12**). Indeed CDI-mediated coupling has been used in conjunction with a number of other *N*,*N*-dibenzylamino acids, without any apparent loss of stereochemical integrity.[24] This suggested that the problem perhaps arose from the extremely hindered nature of methyl ester **12**, due in part to the choice of the TBDPS protecting group. Thus a further solution to the problem of racemisation in the condensation route to the C(3) epimer of CYB-3 was sought through the synthesis of an *O*-benzyl protected acid derivative, which it was hoped would offer the same acid stability as its TBDPS counterpart, but with reduced steric bulk.

In order to test this hypothesis, the synthesis of methyl ester **28**, was undertaken in two steps from commercially available L-*O*-benzyl serine (Scheme 5). Saponification of ester **28** was



Scheme 5 *Reagents and conditions:* i. CH_3COCl, MeOH, reflux, 3 h (96%); ii. K_2CO_3, BnBr, CH_3CN, rt, 24 h (94%); iii. LiOH, THF : H_2O (4 : 1), reflux, 4 h (100%); iv. CDI, THF, rt, 2 h; v. LiHMDS, THF, −78 °C, 20 min; **30**, THF, −78 °C ⟶ 0 °C, 2.5 h (92% from **29**); vi. $NaCNBH_3$, AcOH, Et_2O : MeOH (2 : 1), 0 °C ⟶ rt, 8 h (90%).

found to be far more facile than its TBDPS counterpart **12**, and high yields of the desired acid **29** were achieved under a range of conditions including the use of LiOH, $Ba(OH)_2$, and KOH. The most efficient conditions were found to mimic those used for the TBDPS protected ester; heating a mixture of the ester **28** and LiOH to reflux in a THF–water solution (100%).¶ CDI-mediated coupling with the lithium enolate of ethyl acetate to give β-keto ester **31** was found to proceed extremely smoothly (92% from acid **29**). Finally, sodium cyanoborohydride reduction to amino alcohol **32** was used to assess the enantiomeric excess of the material that had been produced through comparison with an HPLC trace produced from a sample of racemic material.‖ However, in line with an observed $[\alpha]_D$ of 0° for both the acid **29** and α-amino ketone **31**, chiral HPLC confirmed that we once again had an enantiomeric excess of 0%.[26] Thus, despite this representing a higher-yielding approach to the desired protected CYB-3 C(3) epimer, this route was not pursued further.

Conclusions

We have shown that the aldol and imidazolide-mediated Claisen reactions of the lithium enolate of ethyl acetate with aldehyde **10** and acid **26** provide extremely attractive routes to the synthesis of silyl-protected CYB-3 and its C(3) epimer, in terms of both the number of steps and overall efficiency of the process. However, chiral HPLC analysis has revealed that for our TBDPS protected serine-derived system this efficiency is achieved at a price. Thus aldol adduct **17** is isolated in only 90% ee and Claisen–reduction product **18** is isolated in a modest 70% ee.

Our studies have highlighted in particular, problems with the synthesis of certain *O*-protected serine-derived *N*,*N*-dibenzyl α-amino acids required for use in this Claisen based approach to the C(3) epimer of CYB-3. However, a recent report of the synthesis of the *tert*-butyldimethylsilyl protected analogue of acid **26**, *via* deprotection of the corresponding allyl ester suggests that alternative routes to the desired acid might be possible.[27] Preliminary studies in our laboratories with other *N*,*N*-dibenzyl protected α-amino acids indicate that problems of racemisation using this route appear to be confined to the serine derivatives. Hence, we are currently undertaking studies to investigate the application of this approach to the synthesis of other pyrrolidine glycomimetics.

Experimental

General

All reactions involving air or water sensitive reagents were carried out under an atmosphere of argon using flame or oven-dried glassware. Unless otherwise noted, starting materials and reagents were obtained from commercial suppliers and were used without further purification. THF was distilled from Na–benzophenone ketyl immediately prior to use. Toluene, CH_2Cl_2, Et_3N, and DMF were distilled from calcium hydride. Anhydrous methanol and acetonitrile were used as supplied by Aldrich. Unless otherwise indicated, organic extracts were dried over anhydrous magnesium sulfate and concentrated under reduced pressure using a rotary evaporator. Purification by flash column chromatography was carried out using Merck Kieselgel 60 silica gel as the stationary phase. Chiral HPLC was performed using a Waters instrument equipped with a UV detector and a Chiracel OD column (internal diameter 4.6 mm, length 250 mm). All solvents for use in HPLC analysis were vacuum filtered and degassed prior to use, and a standard flow rate of 0.5 mL min^{-1} was used. IR spectra were measured as thin films on NaCl plates, unless otherwise stated. Melting points were determined on a Gallenkamp Electrothermal Melting Point apparatus and are uncorrected. Optical rotations were measured (10^{-1} deg cm^2 g^{-1}) on a AA-1000 polarimeter with a path length of 1.0 dm, at the sodium D line, at room temperature. ^1H and ^{13}C NMR spectra were recorded on a Varian Gemini 200, a Bruker AC250 or a Bruker AM360 spectrometer. Coupling constants *J* are reported in Hz. Elemental analysis was carried on a Perkin Elmer 2400 CHN Elemental Analyser. Fast atom bombardment (FAB) mass

¶ Prolonged exposure to these conditions (24 h) at room temperature was found to result in no conversion of the ester **28** to acid **29**.

‖ *R*, *syn* diastereomers **32** and *ent*-**32**, 18.3 and 23.1 min [4.6 × 250 mm Chiracel OD column, solvent (5% IPA in hexane), flow rate 0.5 mL min^{-1}].

spectra were obtained using a Kratos MS50TC mass spectrometer at The University of Edinburgh.

Synthesis of TBDPS-protected CYB-3

(2*S*)-3-*tert*-Butyldiphenylsilyloxy-2-(*N*,*N*-dibenzylamino)-propan-1-ol 13. To a solution of ester **12** (4.20 g, 7.82 mmol),[15] in anhydrous ether (60 cm^3) at 0 °C was added lithium borohydride (0.99 g, 49.9 mmol) followed by anhydrous methanol (1 cm^3). The mixture was stirred at 0 °C until effervescence ceased and then heated to reflux and held at reflux for 4 hours. Saturated aqueous NH_4Cl (140 cm^3) was added cautiously and the aqueous phase was extracted with DCM (3 × 100 cm^3). The combined organic phases were washed with brine (200 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane : EtOAc (5 : 1)] to give alcohol **13** (3.80 g, 95%) as an oil. R_f [hexane : EtOAc (4 : 1)] 0.55; all spectroscopic data were in good agreement with those reported previously.[15]

Ethyl (3*S*,4*R*)-5-*tert*-butyldiphenylsilyloxy-4-(*N*,*N*-dibenzylamino)-3-hydroxypentanoate 17. To a solution of LiHMDS (8.84 cm^3, 1.06 M in THF, 9.37 mmol) at −78 °C was added ethyl acetate (0.871 cm^3, 8.84 mmol). The solution was stirred at −78 °C for 20 minutes. A solution of the aldehyde **10** (1.49 g, 2.94 mmol) in THF (6 cm^3) was added dropwise *via* cannula. The reaction mixture was stirred at −78 °C for 30 minutes then allowed to warm to 0 °C over a period of 2 hours, then stirred at 0 °C for 20 minutes. Saturated aqueous NH_4Cl (50 cm^3) was added and the aqueous phase extracted with DCM (3 × 60 cm^3). The combined organic phases were washed with brine (60 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane : Et_2O (5 : 1)] to give the title compound (1.48 g, 85%) as a 6 : 1 mixture of diastereomers. ν_{max} (neat)/cm^{-1} 3469, 2930, 1736, 1720, 1427; *m/z* (FAB) 596 ([M + H]$^+$, 14%), 478 (13), 268 (18), 135 (26), 91 (100); HRMS (FAB) $C_{37}H_{46}NO_4Si$ [*M* + H]$^+$ requires 596.3196, found 596.3192.

Spectroscopic data for major diastereomer 17. R_f [hexane : Et_2O (1 : 1)] 0.40; δ_H (250 MHz, $CDCl_3$) 7.76–7.19 (20H, m, Ar*H*), 4.39–4.32 (1H, m, C(3)*H*OH), 4.25 (2H, q, *J* 7.2, OCH_2CH_3), 4.23–4.17 (1H, m, C(5)H_AH_BOTBDPS), 4.07 (1H, dd, *J* 10.6, 5.3, C(5)H_AH_BOTBDPS), 3.89 (2H, d, *J* 13.6, NCH_XH_YPh × 2), 3.58 (2H, d, *J* 13.6, NCH_XH_YPh × 2), 3.45 (1H, br s, O*H*), 2.98 (1H, dd, *J* 16.3, 2.7, C(2)H_CH_D), 2.78 (1H, br ddd, *J* 10.6, 8.7, 5.3, C(4)*H*), 2.31 (1H, dd, *J* 16.3, 8.7, C(2)H_CH_D), 1.28 (3H, t, *J* 7.2, OCH_2CH_3), 1.09 (9H, s, *'Bu*); δ_C (62.9 MHz) 173.0 (C), 139.6 (C), 135.6 (CH), 132.8 (C), 132.7 (C), 128.9 (CH), 128.7 (CH), 128.2 (CH), 127.7 (CH), 126.9 (CH), 68.1 (CH), 61.2 (CH), 60.9 (CH_2), 60.4 (CH_2), 55.1 (CH_2), 50.0 (CH_2), 39.5 (CH_2), 26.8 (CH_3), 19.0 (C), 14.1 (CH_3).

Spectroscopic data for minor diastereomer 18. R_f [hexane : Et_2O (1 : 1)] 0.38; δ_H (250 MHz, $CDCl_3$) data were in good agreement with those reported below, diagnostic signal at 2.45 (1H, dd, *J* 15.2, 3.0, C(2)H_CH_D).

(4*S*,5*R*)-5-*tert*-Butyldiphenylsilyloxymethyl-4-hydroxypyrrolidin-2-one 19. *Preparation of the Weinreb amides.* To a slurry of *N*,*O*-dimethylhydroxylamine·hydrochloride (494 mg, 5.04 mmol) in THF (3 cm^3) at 0 °C was added trimethylaluminium (2.52 cm^3, 2.0 M in toluene, 5.04 mmol). The solution was stirred at 0 °C for 5 minutes then allowed to warm to room temperature over *ca.* 15 minutes, after which time a clear solution remained. The (6 : 1) mixture of aldol adducts **17** and **18** (500 mg, 0.839 mmol) in THF (4 cm^3) was added dropwise *via* cannula. The reaction mixture was warmed to 35 °C and stirred for 3 hours. The reaction mixture was cooled and then cannulated rapidly into a mixture of DCM (30 cm^3) and saturated aqueous potassium sodium tartrate (30 cm^3) and stirred vigorously for 5 hours whereupon two distinct phases were apparent. The aqueous phase was extracted with DCM (3 × 30 cm^3). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane : EtOAc (4 : 1)] to give a 6 : 1 mixture of diastereomeric amides (506 mg, 98%) as a colourless oil. ν_{max} (neat)/cm^{-1} 3457, 3069, 2937, 2856, 1643, 1427; *m/z* (FAB) 611 ([M + H]$^+$, 27%), 478 (36), 210 (11) 197 (20) 135 (41), 91 (100); HRMS (FAB) $C_{37}H_{47}N_2O_4Si$ [*M* + H]$^+$ requires 611.3305, found 611.3290.

Spectroscopic data for major diastereomer (from 17): (3S,4R)-5-tert-butyldiphenylsilyloxy-4-(N,N-dibenzylamino)-3-hydroxy-N-methoxy-N-methylpentanamide. R_f [hexane : EtOAc (4 : 1)] 0.35; δ_H (360 MHz, $CDCl_3$) 7.83–7.24 (20H, m, Ar*H*), 4.39–4.32 (1H, m, C(3)*H*OH), 4.27 (1H, dd, *J* 10.9, 4.0, C(5)H_AH_BOTBDPS), 4.14 (1H, dd, *J* 10.9, 6.4, C(5)H_AH_BOTBDPS), 3.99 (2H, d, *J* 13.7, NCH_XH_YPh × 2), 3.80 (2H, d, *J* 13.7, NCH_XH_YPh × 2), 3.66 (3H, s, O*Me*), 3.21 (3H, s, *Me*), 2.89–2.82 (1H, m, C(4)*H*), 2.80–2.73 (1H, br m, C(2)H_AH_B), 2.32–2.25 (1H, br m, C(2)H_AH_B), 1.18 (9H, s, *'Bu*); δ_C (62.9 MHz) 174.8 (C), 140.7 (C), 136.3 (CH), 136.2 (CH), 133.8 (C), 133.6 (C), 130.2 (CH), 129.6 (CH), 129.4 (CH), 128.6 (CH), 128.3 (CH), 128.2 (CH), 127.3 (CH), 67.6 (CH), 66.6 (CH_3), 62.2 (CH), 61.7 (CH_2), 55.7 (CH_2), 37.1 (CH_2), 32.3 (CH_3), 27.4 (CH_3), 19.6 (C).

Spectroscopic data for minor diastereomer (from 18). R_f [hexane : EtOAc (4 : 1)] 0.34; δ_H (360 MHz, $CDCl_3$) data were in good agreement with those reported below, diagnostic signals at 3.60 (3H, s, O*Me*), 2.69–2.58 (1H, br m, C(2)H_CH_D).

Reaction of the Weinreb amides. To a solution of the 6 : 1 mixture of Weinreb amides (420 mg, 0.689 mmol) in methanol was added 20% $Pd(OH)_2$/C (420 mg), the flask was flushed with argon before being stirred under an atmosphere of hydrogen for 12 hours. The reaction mixture was filtered through a layer of Celite and concentrated under reduced pressure. The residue was chromatographed on silica gel [DCM : MeOH (50 : 1)] to give pyrrolidinone **19** (206 mg, 81%) as a white solid and amino amide **20** (35 mg, 12%) as a colourless oil.

R_f [DCM : MeOH (10 : 1)] 0.32; mp 117–118 °C (hexane : EtOAc); $[\alpha]_D$ +17.2 (*c* 0.36, $CHCl_3$) (90% ee); ν_{max} (solution cell)/cm^{-1} 3200, 2910, 1678, 1426; δ_H (250 MHz, $CDCl_3$) 7.64–7.59 (4H, m, Ar*H*), 7.43–7.32 (6H, m, Ar*H*), 6.40 (1H, s, N*H*), 4.30–4.28 (1H, m, C(4)*H*OH), 3.63–3.60 (4H, m, C(3)H_2 + C(5)*H* + O*H*), 2.74 (1H, dd, *J* 17.2, 6.8, CH_AH_BOTBDPS), 2.30 (1H, dd, *J* 17.2, 2.9, CH_AH_BOTBDPS), 1.00 (9H, s, *'Bu*); δ_C (62.9 MHz) 176.4 (C), 135.4 (CH), 135.3 (CH), 132.6 (C), 132.4 (C), 129.8 (CH), 127.7 (CH), 69.5 (CH), 64.7 (CH_2), 64.5 (CH), 40.0 (CH_2), 26.6 (CH_3), 18.9 (C); *m/z* (FAB) 370 ([M + H]$^+$, 68%), 312 (15), 292 (53), 234 (27), 214 (61), 135 (100); HRMS (FAB) $C_{21}H_{28}NO_3Si$ [*M* + H]$^+$ requires 370.1838, found 370.1830.

(3R,4R)-4-Amino-5-tert-butyldiphenylsilyloxy-3-hydroxy-N-methyl-N-methoxypentanamide 20. R_f [DCM : MeOH (10 : 1)] 0.12; δ_H (250 MHz, $CDCl_3$) 8.14–8.12 (2H, br s, NH_2), 7.60–7.32 (10H, m, Ar*H*), 4.25–4.20 (1H, br m, C(3)*H*OH), 4.01–3.85 (2H, m, C(5)H_2OTBDPS), 3.50 (3H, s, O*Me*), 2.97 (3H, s, *Me*), 2.90–2.82 (2H, br m, C(2)H_CH_D + C(4)*H*), 2.39–2.30 (1H, br m, C(2)H_CH_D), 1.08 (9H, s, *'Bu*).

(2*R*,3*S*)-2-*tert*-Butyldiphenylsilyloxymethylpyrrolidin-3-ol 21. To a solution of the pyrrolidinone **19** (120 mg, 0.332 mmol) in THF (5 cm^3) at 0 °C was added BH_3·THF complex (4.95 cm^3, 1.0 M in THF, 4.95 mmol). The solution was stirred at 0 °C until effervescence ceased and then stirred at reflux for 24 hours. Methanol was added cautiously to the cooled (0 °C) reaction mixture. The resulting mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel [DCM : MeOH (50 : 1)] to give the pyrrolidine **21** (100 mg, 85%) as a white solid. R_f [DCM : MeOH (10 : 1)] 0.27; mp 105–106 °C; $[\alpha]_D$ +33.3 (*c* 0.09, $CHCl_3$) (90% ee); δ_H (250 MHz, $CDCl_3$)

7.65–7.61 (4H, m, Ar*H*), 7.50–7.37 (6H, m, Ar*H*), 4.35 (1H, ddd, *J* 11.0, 7.4, 4.3, C(3)*H*OH), 4.19 (1H, dd, *J* 11.1, 3.0, CH_AH_BOTBDPS), 3.80 (1H, dd, *J* 11.1, 2.4, CH_AH_BOTBDPS), 3.37 (1H, ddd, *J* 11.7, 8.0, 7.4, C(5)H_EH_F), 3.21 (1H, ddd, *J* 11.7, 9.4, 4.3, C(5)H_EH_F), 2.94 (1H, ddd, *J* 11.0, 3.0, 2.4 C(2)*H*), 2.14 (1H, ddt, *J* 16.2, 9.4, 7.4, C(4)H_CH_D), 1.99 (1H, ddt, *J* 16.2, 8.0, 4.3, C(4)H_CH_D), 1.74 (1H, br s, O*H*), 1.06 (9H, s, *'Bu*); δ_C (62.9 MHz) 135.4 (CH), 132.2 (CH), 131.8 (C), 130.1 (CH), 127.9 (CH), 74.0 (CH), 73.1 (CH), 59.5 (CH_2), 53.0 (CH_2), 34.1 (CH_2), 26.8 (CH_3), 19.2 (C); *m/z* (FAB) 356 ([M + H]$^+$, 65%), 278 (26), 197 (53), 183 (22), 135 (100); HRMS (FAB) $C_{21}H_{30}NO_2Si$ [*M* + H]$^+$ requires 356.2046, found 356.2046.

Synthesis of the C(3) epimer of TBDPS-protected CYB-3

(2*R*)-3-*tert*-butyldiphenylsilyloxy-2-(*N*,*N*-dibenzylamino)-propanoic acid 26. To a solution of methyl ester **12** (500 mg, 0.931 mmol) in THF (15 cm^3) was added dropwise a slurry of LiOH·H_2O (195 mg, 4.65 mmol) in H_2O (3.75 cm^3). The solution was heated to reflux and held at reflux for 6 hours. The solution was cooled to room temperature and H_2O (15 cm^3) was added. The aqueous phase was extracted with EtOAc (2 × 25 cm^3) then the mixture was acidified to pH 3 with 1 M HCl and the aqueous phase was extracted with Et_2O (3 × 20 cm^3). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to give acid **26** (280 mg, 58%) as a tacky solid. R_f [hexane : EtOAc (4 : 1)] 0.20; $[\alpha]_D$ −15.45 (*c* 0.22, $CHCl_3$) (70% ee); ν_{max} (neat)/cm^{-1} 3200, 3069, 2930, 2856, 1709, 1428; δ_H (250 MHz, $CDCl_3$) 7.79–7.29 (20H, m, Ar*H*), 4.21–4.12 (2H, m, CH_2OTBDPS), 4.09 (2H, d, *J* 13.5, NCH_XH_YPh × 2), 4.03 (2H, d, *J* 13.5, NCH_XH_YPh × 2), 3.09 (1H, dd, *J* 8.5, 5.1, C(2)*H*), 1.16 (9H, s, *'Bu*); δ_C (62.9 MHz) 172.3 (C), 137.2 (C), 136.1 (CH), 135.9 (CH), 133.0 (C), 132.9 (C), 130.5 (CH), 129.5 (CH), 129.3 (CH), 128.5 (CH), 128.4 (CH), 128.1 (CH), 63.5 (CH), 62.3 (CH_2), 55.6 (CH_2), 27.4 (CH_3), 19.6 (C); *m/z* (FAB) 524 ([M + H]$^+$, 56%), 154 (44), 136 (37), 107 (16), 91 (100); HRMS (FAB) $C_{33}H_{38}NO_3Si$ [*M* + H]$^+$ requires 524.2621, found 524.2622.

Ethyl (4*R*)-5-*tert*-butyldiphenylsilyloxy-4-(*N*,*N*-dibenzylamino)-3-oxopentanoate 22. *From methyl ester 12.* To a solution of LiHMDS (2.79 cm^3, 1.06 M in THF, 2.79 mmol) at −78 °C was added ethyl acetate (0.270 cm^3, 1.21 mmol) and the solution stirred at −78 °C for 25 min. Methyl ester **12** (300 mg, 0.560 mmol) in THF (4 cm^3) was added *via* cannula and the resultant solution stirred at −78 °C for 3 hours then warmed to 0 °C and stirred at 0 °C for 1 hour. The reaction was quenched by the addition of saturated aqueous NH_4Cl (10 cm^3) and the aqueous phase was extracted with DCM (3 × 10 cm^3). The combined organic phases were washed with brine (20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane : Et_2O (10 : 1)] to give the β-keto ester **22** as a pale yellow oil (260 mg, 78%). R_f [hexane : EtOAc (4 : 1)] 0.62; ν_{max} (neat)/cm^{-1} 3069, 2930, 2856, 1745, 1716, 1427; δ_H (250 MHz, $CDCl_3$) 7.80–7.21 (20H, m, Ar*H*), 4.18 (2H, q, *J* 7.2, OCH_2CH$_3$), 4.17–4.09 (2H, m, CH_2OTBDPS), 3.92 (2H, d, *J* 13.6, NCH_XH_YPh × 2), 3.81 (2H, d, *J* 13.6 NCH_XH_YPh × 2), 3.76–3.72 (1H, m, C(4)*H*), 3.69 (1H, d, *J* 16.0, C(2)H_CH_D), 3.58 (1H, d, *J* 16.0, C(2)H_CH_D), 1.27 (3H, t, *J* 7.2, OCH$_2$CH_3), 1.14 (9H, s, *'Bu*); δ_C (62.9 MHz) 203.3 (C), 167.8 (C), 139.6 (C), 136.1 (CH), 136.0 (CH), 135.7 (C), 135.2 (C), 130.3 (CH), 129.4 (CH), 128.9 (CH), 128.7 (CH), 128.2 (CH), 128.1 (CH), 127.2 (CH), 67.6 (CH), 61.6 (CH_2), 60.7 (CH_2), 55.6 (CH_2), 47.5 (CH_2), 27.3 (CH_3), 19.6 (C), 14.5 (CH_3); *m/z* (FAB) 594 ([M + H]$^+$, 12%), 478 (204), 199 (12), 181 (7), 135 (33), 91 (100); HRMS (FAB) $C_{37}H_{44}NO_4Si$ [*M* + H]$^+$, requires 594.3040, found 594.3039

From acid 26. To a solution of acid **26** (500 mg, 0.958 mmol) in THF (10 cm^3) was added 1,1'-carbonyldiimidazole (542 mg, 3.35 mmol). The solution was stirred at room temperature for 2 hours to generate imidazolide **27**. Meanwhile to a solution of LiHMDS (2.88 cm^3, 1.0 M in THF, 2.88 mmol) at −78 °C was added ethyl acetate (0.280 cm^3, 2.88 mmol) and the resultant solution was stirred for 20 min at −78 °C. The solution of imidazolide **27** in THF was added *via* cannula. The reaction mixture was stirred at −78 °C for 20 min and allowed to warm to 0 °C over 30 min and stirred for a further 1 hour at 0 °C. The reaction was quenched by the addition of saturated aqueous NH_4Cl (15 cm^3) and the aqueous phase was extracted with DCM (3 × 15 cm^3). The combined organic phases were washed with brine (30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane : EtOAc (10 : 1)] to give the title compound **22** as a pale yellow oil (510 mg, 90%). R_f [hexane : EtOAc (4 : 1)] 0.62; $[\alpha]_D$ +33.6 (*c* 0.27, $CHCl_3$) (70% ee); all other spectroscopic data were identical to those obtained from the Claisen reaction of methyl ester **12**.

Ethyl (3*R*,4*R*)-5-*tert*-butyldiphenylsilyloxy-4-(*N*,*N*-dibenzylamino)-3-hydroxypentanoate 18. To a solution of β-keto ester **22** (360 mg, 0.621 mmol) in Et_2O (8 cm^3) and MeOH (3 cm^3) was added acetic acid (*ca.* 1 cm^3) until the solution was pH 4. The solution was cooled to 0 °C and sodium cyanoborohydride (385 mg, 6.22 mmol) was added. Once effervescence had ceased the resulting solution was stirred at room temperature for 7 hours. The reaction was quenched by the addition of a saturated solution of NH_4Cl (30 cm^3) and the aqueous phase was extracted with DCM (3 × 30 cm^3). The combined organic phases were washed with brine (40 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane : Et_2O (7 : 1)] to give the amino alcohol **18** (290 mg, 81%) as a colourless oil and amino alcohol **17** (21 mg, 6%) as a colourless oil.

Spectroscopic data for major diastereomer 18. R_f [hexane : Et_2O (1 : 1)] 0.38; $[\alpha]_D$ −18.75 (*c* 1.6, $CHCl_3$) (70% ee); ν_{max} (neat)/cm^{-1} 3456, 3070, 2931, 2858, 1732, 1428; δ_H (250 MHz, $CDCl_3$) 7.76–7.24 (20H, m, Ar*H*), 4.24–4.20 (1H, m, C(3)*H*OH), 4.19 (2H, q, *J* 7.1, OCH_2CH$_3$), 4.18–4.06 (2H, m, CH_2OTBDPS), 4.05 (2H, d, *J* 13.3, NCH_XH_YPh × 2), 3.60 (2H, d, *J* 13.3, NCH_XH_YPh × 2), 2.77–2.72 (1H, m, C(4)*H*), 2.45 (1H, dd, *J* 15.2, 3.0, C(2)H_CH_D), 2.30 (1H, dd, *J* 15.2, 9.0, C(2)H_CH_D), 1.28 (3H, t, *J* 7.1, OCH$_2$CH_3), 1.15 (9H, s, *'Bu*); δ_C (62.9 MHz) 172.4 (C), 139.5 (C), 136.2 (CH), 136.1 (CH), 133.3 (C), 133.2 (C), 130.5 (CH), 130.4 (CH), 129.5 (CH), 128.9 (CH), 128.3 (CH), 127.7 (CH), 65.8 (CH), 63.4 (CH), 60.9 (CH_2), 60.6 (CH_2), 54.9 (CH_2), 40.1 (CH_2), 27.4 (CH_3), 19.6 (C), 14.6 (CH_3); *m/z* (FAB) 596 ([M + H]$^+$, 40%), 478 (51), 326 (12), 197 (12), 135 (26), 91 (100); HRMS (FAB) $C_{37}H_{46}NO_4Si$ [*M* + H]$^+$ requires 596.3196, found 596.3197.

Spectroscopic data for minor diastereomer 17. R_f [hexane : Et_2O (1 : 1)] 0.40; spectroscopic data were in good agreement with those reported above.

(4*R*,5*R*)-5-*tert*-Butyldiphenylsilyloxymethyl-4-hydroxypyrrolidin-2-one 23. *Via the Weinreb amide.* To a slurry of *N*,*O*-dimethylhydroxylamine·hydrochloride (371 mg, 3.82 mmol) in THF (4 cm^3) at 0 °C was added trimethylaluminium (3.82 cm^3, 2.0 M in toluene, 7.64 mmol). The solution was stirred at 0 °C for 5 minutes then allowed to warm to room temperature over *ca.* 15 minutes, after which time a clear solution remained. Ester **18** (380 mg, 0.637 mmol) in THF (4 cm^3) was added dropwise *via* cannula. The mixture was warmed to 35 °C and stirred for 3 hours. The reaction mixture was cooled and then rapidly transferred by cannula into a mixture of DCM (30 cm^3) and saturated aqueous potassium sodium tartrate (30 cm^3) and stirred vigorously for 5 hours whereupon two distinct phases were apparent. The aqueous phase was extracted with DCM (3 × 30 cm^3).The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure. The residue was

chromatographed on silica gel [hexane : EtOAc (4 : 1) to give the Weinreb amide (370 mg, 95%) as a colourless oil.

(3R,4R)-5-tert-Butyldiphenylsilyloxy-4-(N,N-dibenzylamino)-3-hydroxy-N-methoxy-N-methylpentanamide. R_f [hexane : EtOAc (4 : 1)] 0.34; $[\alpha]_D$ −4.74 (*c* 0.45, $CHCl_3$) (70% ee); ν_{max} (neat)/cm^{-1} 3460, 3075, 2925, 2826, 1644, 1428; δ_H (360 MHz, $CDCl_3$) 7.82–7.24 (20H, m, Ar*H*), 4.28–4.20 (1H, m, C(3)*H*OH), 4.10 (1H, dd, *J* 10.9, 8.0, C(5)H_AH_BOTBDPS), 4.04 (2H, d, *J* 13.4, NCH_XH_YPh × 2), 4.00 (1H, dd, *J* 10.9, 5.4, C(5)H_AH_BOTBDPS), 3.91 (2H, d, *J* 13.4, NCH_XH_YPh × 2), 3.60 (3H, s, O*Me*), 3.20 (3H, s, *Me*), 2.80–2.73 (1H, m, C(4)*H*), 2.69–2.58 (1H, br m, C(2)H_CH_D), 2.30–2.19 (1H, br m, C(2)H_CH_D), 1.12 (9H, s, *'Bu*); δ_C (90.6 MHz) 173.6 (C), 140.2 (C), 136.2 (CH), 136.1 (CH), 133.6 (C), 133.5 (C), 130.4 (CH), 130.3 (CH), 129.6 (CH), 128.7 (CH), 128.3 (CH), 127.4 (CH), 66.7 (CH), 63.6 (CH_3), 61.5 (CH), 61.4 (CH_2), 55.4 (CH_2), 37.2 (CH_2), 32.4 (CH_3), 27.4 (CH_3), 19.6 (C); *m/z* (FAB) 416 ([M + H]$^+$, 72%), 478 (81), 341 (17), 197 (43), 181 (16), 135 (70), 105 (34), 91 (100); HRMS (FAB) $C_{37}H_{47}N_2O_4Si$ [*M* + H]$^+$ requires 611.3305, found 611.3305.

Synthesis of amino amide 20. To a solution of the Weinreb amide derived from ester **18** (300 mg, 0.492 mmol) in methanol (5 cm^3) was added 20% $Pd(OH)_2$/C (300 mg), the flask was flushed with argon before being stirred under an atmosphere of hydrogen for 12 hours. The reaction mixture was filtered through a layer of Celite and concentrated under reduced pressure. The residue was chromatographed on silica gel [DCM : MeOH (50 : 1)] to give the amino amide **20** (210 mg, 100%) as an oil. R_f [DCM : MeOH (10 : 1)] 0.12; spectroscopic data were in good agreement with those reported above.

Conversion to pyrrolidinone 23. A solution of amino amide **20** (100 mg, 0.234 mmol) in MeOH (3 cm^3) was heated to reflux and held at reflux for 24 hours. The solution was cooled and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [DCM : MeOH (50 : 1)] to give pyrrolidinone **23** (62 mg, 72%) as a white solid; R_f [DCM : MeOH (10 : 1)] 0.30; mp 110–112 °C; $[\alpha]_D$ +11.30 (*c* 0.2, $CHCl_3$) (70% ee); ν_{max} (neat)/cm^{-1} 3385, 2931, 1682, 1427; δ_H (250 MHz, $CDCl_3$) 7.66–7.25 (10H, m, Ar*H*), 6.20 (1H, br s, N*H*), 4.61 (1H, ddd, *J* 10.4, 7.0, 4.2, C(4)*H*OH), 3.95 (1H, dd, *J* 10.5, 5.8, CH_AH_BOTBDPS), 3.81 (1H, dd, *J* 10.5, 4.8, CH_AH_BOTBDPS), 3.78 (1H, dt, *J* 10.4, 5.5, C(5)*H*), 3.29 (1H, br s, O*H*), 2.68 (1H, dd, *J* 17.3, 7.0, C(3)H_CH_D), 2.41 (1H, dd, *J* 17.3, 4.2, C(3)H_CH_D), 1.05 (9H, s, *'Bu*); δ_C (62.9 MHz) 176.0 (C), 135.4 (CH), 135.3 (CH), 132.4 (C), 132.2 (C), 130.0 (CH), 128.0 (CH), 68.2 (CH), 63.0 (CH_2), 59.2 (CH), 40.3 (CH_2), 26.7 (CH_3), 19.0 (C); *m/z* (FAB) 370 ([M + H]$^+$, 59%), 292 (34), 234 (37), 214 (66), 199 (80), 135 (94), 105 (46); HRMS (FAB) $C_{21}H_{28}NO_3Si$ [*M* + H]$^+$ requires 370.1838, found 370.1838.

***Via* amino ester 24.** To a solution of β-hydroxy ester **18** (270 mg, 0.451 mmol) in methanol (5 cm^3) was added 20% $Pd(OH)_2$/C (270 mg), the flask was flushed with argon before being stirred under an atmosphere of hydrogen for 12 hours. The reaction mixture was filtered through a layer of Celite and concentrated under reduced pressure. The residue was chromatographed on silica gel [DCM : MeOH (50 : 1)] to give the amino ester **24** (186 mg, 100%) as an oil.

Ethyl (3R,4R)-5-tert-butyldiphenylsilyloxy-4-amino-3-hydroxypentanoate 24. R_f [DCM : MeOH (10 : 1)] 0.20; $[\alpha]_D$ −11.1 (*c* 1.2, $CHCl_3$) (70% ee); ν_{max} (neat)/cm^{-1} 3363, 2932, 2888, 1724, 1426; δ_H (250 MHz, $CDCl_3$) 7.76–7.06 (10H, m, Ar*H*), 4.22 (2H, q, *J* 7.0, OCH_2CH$_3$), 3.78–3.47 (5H, br m, C(3)*H*OH + C(5)H_2 + NH_2), 3.10–3.00 (1H, m, C(4)*H*), 2.65 (1H, dd, *J* 15.0, 3.2, C(2)H_AH_B), 2.30 (1H, dd, *J* 15.0, 8.9, C(2)H_AH_B), 1.31 (3H, t, *J* 7.0, OCH$_2$CH_3), 1.13 (9H, s, *'Bu*); δ_C (50.3 MHz) 169.9 (C), 134.7 (CH), 132.2 (CH), 131.3 (C), 129.9 (C), 128.9 (CH), 128.0 (CH), 126.9 (CH), 64.7 (CH), 61.5 (CH), 60.1 (CH_2), 59.9 (CH_2), 45.6 (CH_2), 25.5 (CH_3), 18.2 (C), 14.9 (CH_3); *m/z* (FAB) 416 ([M + H]$^+$, 100%), 199 (20), 142 (7), 135 (38), 105 (12), 95 (11); HRMS (FAB) $C_{23}H_{34}NO_4Si$ [*M* + H]$^+$ requires 416.2257, found 416.2252.

A solution of amino ester **24** (186 mg, 0.448 mmol) in MeOH (4 cm^3) was heated to reflux and held at reflux for 24 hours. The solution was cooled and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel gel [DCM : MeOH (50 : 1) to give pyrrolidinone **23** (130 mg, 78%) as an oil. R_f [DCM : MeOH (10 : 1)] 0.30; all spectroscopic data were identical to those obtained from the cyclisation of the Weinreb amide derived from ethyl ester **18**.

(4*R*,5*R*)-2-*tert*-Butyldiphenylsilyloxymethylpyrrolidin-3-ol 25. To a solution of pyrrolidinone **23** (120 mg, 0.330 mmol) in THF (5 cm^3) at 0 °C was added BH_3·THF complex (4.95 cm^3, 1.0 M in THF, 4.95 mmol). The solution was stirred at 0 °C until effervescence ceased and then stirred at reflux for 24 hours. Methanol (*ca.* 5 cm^3) was added cautiously to the cooled (0 °C) reaction mixture. The resulting mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel [DCM : MeOH (50 : 1)] to give the pyrrolidine **25** (105 mg, 86%) as a white solid. R_f [DCM : MeOH (10 : 1)] 0.25; mp 100–101 °C; $[\alpha]_D$ +8.5 (*c* 0.5, $CHCl_3$) (70% ee); δ_H (250 MHz, $CDCl_3$) 7.69–7.60 (4H, m, Ar*H*), 7.52–7.25 (6H, m, Ar*H*), 6.20 (1H, s, N*H*), 4.56 (1H, ddd, *J* 11.4, 6.5, 4.5, C(3)*H*OH), 4.52–4.51 (1H, br s, O*H*), 4.23 (1H, dd, *J* 11.2, 4.8, CH_AH_BOTBDPS), 4.20 (1H, dd, *J* 11.2, 8.0, CH_AH_BOTBDPS) 3.59 (1H, ddd, *J* 11.4, 8.0, 4.8, C(2)*H*), 3.06 (1H, ddd, *J* 12.7, 7.6, 6.0, C(5)H_EH_F), 2.97 (1H, ddd, *J* 12.7, 6.5, 4.5, C(5)H_EH_F), 2.19 (1H, ddt, *J* 16.1, 6.0, 4.5, C(4)H_CH_D), 1.94 (1H, ddt, *J* 16.1, 7.6, 6.5, C(4)H_CH_D), 1.08 (9H, s, *'Bu*); δ_C (62.9 MHz) 135.5 (CH), 135.3 (CH), 131.6 (C), 131.2 (C), 130.3 (CH), 128.0 (CH), 73.8 (CH), 69.0 (CH), 60.3 (CH_2), 52.8 (CH_2), 32.5 (CH_2), 26.8 (CH_3), 19.0 (C); *m/z* (FAB) 356 ([M + H]$^+$, 65%), 278 (26), 197 (53), 183 (22), 135 (100); HRMS (FAB) $C_{21}H_{30}NO_2Si$ [*M* + H]$^+$ requires 356.2046, found 356.2043.

Methyl (2*S*)-2-(*N*,*N*-dibenzylamino)-3-benzyloxypropanoate 28

Synthesis of methyl ester hydrochloride salt. Acetyl chloride (2.20 cm^3, 30.8 mmol) was added dropwise to methanol (24 cm^3) at 0 °C. The mixture was stirred for 15 min and L-*O*-benzylserine (2.00 g, 10.3 mmol) was then added portionwise to the solution. The resulting mixture was heated to reflux and held at reflux for 3 hours. Concentration under reduced pressure provided the methyl ester hydrochloride salt (2.25 g, 96%) as a solid.

Methyl (2S)-2-amino-3-benzyloxypropanoate·hydrochloride salt. Mp 162–164 °C (methanol); $[\alpha]_D$ +15.2 (*c* 1.4, MeOH); δ_H (250 MHz, D_2O) 7.37–7.26 (5H, m, Ar*H*), 4.57 (1H, d, *J* 12.0, OCH_EH_FPh), 4.47 (1H, d, *J* 12.0, OCH_EH_FPh), 4.28 (1H, br t, *J* 3.7, C(2)*H*), 3.93 (1H, dd, *J* 11.0, 4.2, C(3)H_AH_B), 3.83 (1H, dd, *J* 11.0, 3.0, C(3)H_AH_B), 3.71 (3H, s, O*Me*); δ_C (62.9 MHz) 169.0 (C), 137.1 (C), 129.1 (CH), 128.9 (CH), 128.8 (CH), 73.5 (CH_2), 66.7 (CH_2), 54.1 (CH_3), 53.5 (CH); *m/z* (FAB) 210 ([M + H]$^+$, 95%), 196 (8), 150 (5), 120 (10), 102 (10), 91 (100); HRMS (FAB) $C_{11}H_{16}NO_3$ [*M* + H]$^+$ requires 210.1130, found 210.1133.

Conversion to *N*,*N*-dibenzyl protected methyl ester 28. To a solution of the methyl ester (2.00 g, 8.71 mmol) in anhydrous acetonitrile (30 cm^3) was added anhydrous potassium carbonate (5.55 g, 43.6 mmol) followed by benzyl bromide (2.38 cm^3, 21.8 mmol). The mixture was stirred at room temperature for 24 hours. H_2O (50 cm^3) was added and the aqueous phase was extracted with EtOAc (3 × 30 cm^3). The combined organic phases were washed with brine (100 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane : EtOAc (10 : 1)] to

give protected methyl ester **28** (3.20 g, 94%) as a colourless oil. R_f [hexane : EtOAc (4 : 1)] 0.60; $[a]_D$ −48.5 (*c* 1.07, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3062, 3028, 2948, 2855, 1735, 1602, 1494, 1453; δ_H (250 MHz, $CDCl_3$) 7.41–7.21 (15H, m, Ar*H*), 4.52–4.30 (2H, m, OCH_EH_FPh), 3.96 (2H, d, *J* 13.9, NCH_XH_YPh × 2), 3.89 (1H, t, *J* 2.8, C(2)*H*), 3.85–3.79 (1H, m, $C(3)H_AH_B$), 3.78 (3H, s, O*Me*), 3.75–3.68 (1H, m, $C(3)H_AH_B$), 3.72 (2H, d, *J* 13.9, NCH_XH_YPh × 2); δ_C (62.9 MHz) 171.8 (C), 139.5 (C), 137.9 (C), 128.6 (CH), 128.2 (CH), 128.1 (CH), 127.4 (CH), 126.9 (CH), 73.0 (CH_2), 69.4 (CH_2), 60.8 (CH), 55.2 (CH_2), 51.2 (CH_3); *m/z* (FAB) 390 ([M + H]$^+$, 15%), 330 (32), 282 (8), 268 (41), 181 (9), 91 (100); HRMS (FAB) $C_{25}H_{28}NO_3$ [*M* + H]$^+$ requires 390.2069, found 390.2070.

(2*SR*)-2-(*N*,*N*-Dibenzylamino)-3-benzyloxypropanoic acid 29

To a solution of the ester **28** (300 mg, 0.771 mmol) in THF (8 cm^3) was added a slurry of $LiOH·H_2O$ (194 mg, 4.63 mmol) in H_2O (2 cm^3). The mixture was heated to reflux and held at reflux for 4 hours. The solution was cooled to room temperature, water (15 cm^3) was added and the mixture was acidified to pH 3 with 1 M HCl. The aqueous phase was extracted with Et_2O (3 × 15 cm^3). The combined organic phases were dried ($MgSO_4$) and concentrated under reduced pressure to give acid **29** (288 mg, 100%). R_f [hexane : EtOAc (4 : 1)] 0.13; ν_{max} (neat)/cm^{-1} 4059, 3067, 3028, 2923, 2854, 1715, 1495; δ_H (250 MHz, $CDCl_3$) 7.67–7.03 (15H, m, Ar*H*), 4.63 (1H, d, *J* 11.9, OCH_EH_FPh), 4.55 (1H, d, *J* 11.9, OCH_EH_FPh), 4.17 (1H, dd, *J* 10.3, 4.6, $C(3)H_AH_B$), 4.06 (2H, d, *J* 13.3, NCH_XH_YPh × 2), 4.01–3.67 (2H, m, $C(3)H_AH_B$ + C(2)*H*), 3.94 (2H, d, *J* 13.3, NCH_XH_YPh × 2); δ_C (62.9 MHz) 171.1 (C), 137.5 (C), 135.8 (C), 129.2 (CH), 128.7 (CH), 128.4 (CH), 128.1 (CH), 127.8 (CH), 127.2 (CH), 73.4 (CH_2), 67.5 (CH_2), 61.5 (CH), 55.1 (CH_2); *m/z* (FAB) 376 ([M + H]$^+$, 100%), 330 (16), 286 (31), 240 (12) 181 (20), 91 (91); HRMS (FAB) $C_{24}H_{26}NO_3$ [*M* + H]$^+$ requires 376.1913, found 376.1914.

Ethyl (4*SR*)-5-benzyloxy-4-(*N*,*N*-dibenzylamino)-3-oxopentanoate 31

To a solution of acid **29** (300 mg, 0.825 mmol) in THF (8 cm^3) was added 1,1′-carbonyldiimidazole (404 mg, 2.49 mmol). The solution was stirred at room temperature for 2 hours to generate imidazolide **30**. Meanwhile to a solution of LiHMDS (2.49 cm^3, 1.0 M in THF, 2.49 mmol) at −78 °C was added ethyl acetate (0.240 cm^3, 2.49 mmol) and the solution stirred for 20 min. The solution of imidazolide **30** in THF was added *via* cannula and the solution stirred at −78 °C for 30 min then warmed to 0 °C over a period of 1 hour. The mixture was stirred at 0 °C for 1 hour before being quenched with saturated aqueous NH_4Cl (20 cm^3). The aqueous phase was extracted with DCM (3 × 20 cm^3). The combined organic phases were washed with brine (30 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane : EtOAc (10 : 1)] to give the β-keto ester **31** (340 mg, 92%) as a pale yellow oil. R_f [hexane : EtOAc (4 : 1)] 0.53; ν_{max} (neat)/cm^{-1} 3062, 3029, 2081, 2926, 2860, 1744, 1716, 1494, 1453; δ_H (250 MHz, $CDCl_3$) 7.43–7.22 (15H, m, Ar*H*), 4.62 (1H, d, *J* 12.0, OCH_EH_FPh), 4.55 (1H, d, *J* 12.0, OCH_EH_FPh), 4.14 (2H, q, *J* 7.2, OCH_2CH_3), 4.01 (1H, dd, *J* 9.2, 6.5, $C(5)H_AH_B$), 3.94 (1H, dd, *J* 9.2, 4.0, $C(5)H_AH_B$), 3.85 (2H, d, *J* 13.1, NCH_XH_YPh × 2), 3.75–3.65 (1H, m, C(4)*H*), 3.73 (1H, d, *J* 16.0, $C(2)H_CH_D$), 3.70 (2H, d, *J* 13.1, NCH_XH_YPh × 2), 3.54 (1H, d, *J* 16.0, $C(2)H_CH_D$), 1.23 (3H, t, *J* 7.2, OCH_2CH_3); δ_C (62.9 MHz) 202.7 (C), 167.3 (C), 138.9 (C), 137.9 (C), 128.9 (CH), 128.5 (CH), 128.3 (CH), 127.5 (CH), 127.1 (CH), 126.8 (CH), 73.4 (CH_2), 66.1 (CH), 65.4 (CH_2), 61.0 (CH_2), 55.0 (CH_2), 46.5 (CH_2), 13.9 (CH_3); *m/z* (FAB) 446 ([M + H]$^+$, 100%), 356 (39), 330 (53), 240 (22), 196 (17), 132 (9), 106 (37), 91 (97); HRMS (FAB) $C_{28}H_{32}NO_4$ [*M* + H]$^+$ requires 446.2331, found 446.2332.

Ethyl (3*SR*, 4*SR*)-5-benzyloxy-4-(*N*,*N*-dibenzylamino)-3-hydroxypentanoate 32

To a solution of β-keto ester **31** (80 mg, 0.18 mmol) in Et_2O (4 cm^3) and MeOH (2 cm^3) was added acetic acid (*ca.* 0.5 cm^3) until the solution was pH 4. The solution was cooled to 0 °C and sodium cyanoborohydride (60 mg, 1.4 mmol) was added. Once effervescence ceased the solution was warmed to room temperature and stirred for 8 hours. The solution was quenched by the addition of a saturated solution of NH_4Cl (15 cm^3) and the aqueous phase was extracted with DCM (3 × 15 cm^3). The combined organic phases were washed with brine (20 cm^3), dried ($MgSO_4$) and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane : EtOAc (6 : 1)] to give the amino alcohol **32** (72 mg, 90%) as an oil. R_f [hexane : EtOAc (4 : 1)] 0.38; ν_{max} (neat)/cm^{-1} 3371, 2936, 1726, 1452; δ_H (250 MHz, $CDCl_3$) 7.43–7.19 (15H, m, Ar*H*), 4.59 (1H, d, *J* 12.0, OCH_EH_FPh), 4.52 (1H, d, *J* 12.0, OCH_EH_FPh), 4.19 (1H, ddd, *J* 11.2, 8.5, 3.6, C(3)*H*OH), 4.14 (2H, q, *J* 7.2, OCH_2CH_3), 4.05 (2H, d, *J* 13.2, NCH_XH_YPh × 2), 3.80 (1H, dd, *J* 10.2, 5.5, $C(5)H_AH_B$), 3.69 (1H, dd, *J* 10.2, 4.8, $C(5)H_AH_B$), 3.53 (2H, d, *J* 13.2, NCH_XH_YPh × 2), 3.47 (1H, s, O*H*), 2.80–2.72 (1H, m, C(4)*H*), 2.50 (1H, dd, *J* 15.4, 3.6, $C(2)H_CH_D$), 2.37 (1H, dd, *J* 15.4, 8.5, $C(2)H_CH_D$), 1.23 (3H, t, *J* 7.2, OCH_2CH_3); δ_C (62.9 MHz) 172.0 (C), 138.8 (C), 137.8 (C), 129.0 (CH), 128.4 (CH), 127.7 (CH), 127.5 (CH), 127.1 (CH), 73.2 (CH_2), 66.3 (CH_2), 65.7 (CH_2), 61.3 (CH), 60.4 (CH), 54.3 (CH_2), 39.45 (CH_2), 14.0 (CH_3); *m/z* (FAB) 448 ([M + H]$^+$, 20%), 330 (19), 326 (5), 210 (2), 181 (4), 91 (100); HRMS (FAB) $C_{28}H_{34}NO_4$ [*M* + H]$^+$ requires 448.2488, found 448.2489.

Acknowledgements

We thank the EPSRC (GR/L60166/01 to K.S.C.) for support.

References

1 R. J. Nash, A. E. Bell, G. W. J. Fleet, R. H. Jones and M. J. Williams, *J. Chem. Soc., Chem. Commun.*, 1985, 738.
2 L. D. Hohenschutz, E. A. Bell, P. J. Jewess, D. P. Leworthy, R. J. Pryce, E. Arnold and J. Clardy, *Phytochemistry*, 1981, **20**, 811.
3 A. M. Schofield, P. Witham, R. J. Nash, G. C. Kite and L. E. Fellows, *Comp. Biochem. Physiol.*, 1995, **112A**, 187.
4 A. M. Schofield, L. E. Fellows, R. J. Nash and G. W. J. Fleet, *Life Sci.*, 1986, **39**, 645.
5 (*a*) J. Furukawa, S. Okuda, K. Saito and S.-I. Hatanaka, *Phytochemistry*, 1985, **24**, 593; (*b*) R. J. Nash, E. A. Bell and J. M. Williams, *Phytochemistry*, 1985, **24**, 1620.
6 (*a*) A. D. Elbein, M. Mitchell, B. A. Stanford, L. E. Fellows and S. V. Evans, *J. Biol. Chem.*, 1984, **259**, 12409; (*b*) S. V. Evans, L. E. Fellows and E. A. Bell, *Biochem. Syst. Ecol.*, 1985, **13**, 271; (*c*) A. Welter, J. Jadot, G. Dardenne, M. Marlier and J. Casimir, *Phytochemistry*, 1976, **15**, 747; (*d*) absolute stereochemistry: G. W. Fleet and P. W. Smith, *Tetrahedron*, 1987, **43**, 971.
7 N. Dell'Uomo, M. C. DiGiovanni, D. Misiti, G. Zappia and G. Delle Monache, *Tetrahedron: Asymmetry*, 1996, **7**, 181.
8 *N*-Hydroxyethyl derivative of CYB-3 as biosynthetic precursor for castanospermine and australine: R. J. Molyneux, Y. T. Pan, J. E. Tropea, M. Benson, G. P. Kaushal and A. D. Elbein, *Biochemistry*, 1991, **30**, 9981.
9 G. Ceulemans, A. Van Aerschot, J. Rozenski and P. Herdewijn, *Tetrahedron*, 1997, **53**, 14957.
10 (*a*) Reaction with (allyl)B(Ipc)$_2$: L. M. Mascavage, Q. Lu, J. Vey, D. R. Dalton and P. J. Carroll, *J. Org. Chem.*, 2001, **66**, 3621; (*b*) reaction with allyl bromide/$CrCl_2$: Y Aoyagi, H. Inaba, Y. Hiraiwa, A. Kuroda and A. Ohta, *J. Chem. Soc., Perkin Trans. 1*, 1998, 3975.
11 A. Barco, S. Benetti, C. De Risi, G. P. Pollini, R. Romagnoli and V. Zanirato, *Tetrahedron Lett.*, 1996, **37**, 7599.
12 (*a*) C. Herdeis, H. P. Hubmann and H. Lotter, *Tetrahedron: Asymmetry*, 1994, **5**, 119; (*b*) D. Griffart-Brunet and N. Langlois, *Tetrahedron Lett.*, 1994, **35**, 119.
13 (*a*) B. M. Malle, I. Lundt and R. H. Furneaux, *J. Carbohydr. Chem.*, 2000, **19**, 573; (*b*) A. G. H. Wee, D. D. McLeod and T. J. Rankin, *Heterocycles*, 1998, **48**, 2263.
14 C. M. Huwe and S. Blechert, *Synthesis*, 1997, 61.

15 A. N. Hulme, C. H. Montgomery and D. K. Henderson, *J. Chem. Soc., Perkin Trans. 1*, 2000, 1837.
16 A. N. Hulme and E. M. Rosser, *Org. Lett.*, 2002, **4**, 265.
17 (*a*) M. T. Reetz, *Chem. Rev.*, 1999, **99**, 1121; (*b*) M. T. Reetz, *Angew. Chem., Int. Ed. Engl.*, 1991, **30**, 1531.
18 (*a*) With isoleucine derived aldehyde: M. T. Reetz, M. W. Drewes, A. Schmitz, X. Holdgrun, T. Wunsch and J. Binder, *J. Philos. Trans. R. Soc. London A*, 1988, **326**, 573; (*b*) with dimethyl tartrate derived aldehyde: H. Ina and C. Kibayashi, *J. Org. Chem.*, 1993, **58**, 52.
19 A. N. Hulme, and C. H. Montgomery, unpublished results.
20 J. M. Andrés and R. Pedrosa, *Tetrahedron*, 1998, 5607.
21 P. Compain and O. R. Martin, *Bioorg. Med. Chem.*, 2001, **9**, 3077.
22 S. Hanessian, H. K. Huynh, G. V. Reddy, G. McNaughton-Smith, B. Ernst, H. C. Kolb, J. Magnani and C. Sweeley, *Bioorg. Med. Chem. Lett.*, 1998, **8**, 2803.
23 (*a*) E. Dechaux, P. Savay, S. Bouyain, C. Monneret and J.-C. Florent, *J. Carbohydr. Chem.*, 2000, **19**, 485; (*b*) K. Dax, M. Ebner, R. Peinsipp and A. E. Stütz, *Tetrahedron Lett.*, 1997, **38**, 225.
24 R. V. Hoffmann and J. Tao, *J. Org. Chem.*, 1997, **62**, 2292 and references cited therein.
25 M. T. Reetz, M. W. Drewes, B. R. Matthews and K. Lennick, *J. Chem. Soc., Chem. Commun.*, 1989, 1474.
26 This result is somewhat surprising as a two-step synthesis of acid **29** from *O*-benzylserine (i. BnBr; ii. KOH) has been reported to occur without racemisation; M. T. Reetz, M. W. Drewes, K. Lennick, A. Schmitz and X. Holdgrün, *Tetrahedron: Asymmetry*, 1990, **1**, 375. However, experimental details for this conversion have not been reported.
27 S. Chansrasekhar, Ch. R. Reddy and R. J. Rao, *Tetrahedron*, 2001, **57**, 3435.