Applications Of A Serine Derived Aldehyde To Natural Product Synthesis

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February 2000

Dedicated to my parents, for their immeasurable support.

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.

Charles Hamilton Montgomery

Acknowledgements

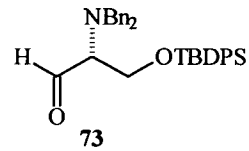
I would like to thank Dr. Alison N. Hulme, who supervised the work recorded herein, for her advice and encouragement throughout and for her thorough proof-reading of this thesis.

I would also like to thank Dr. Ian Sadler, John Millar, Wesley Kerr and Dr. David Reed for their excellent work on the department's various NMR machines. Thanks also go to Alan Taylor and Harry McKenzie for their mass spectrometry work and Simon Parsons for his x-ray diffraction work. Lastly and leastly to Stuart Johnstone for his magnificent glassblowing skills, but did the work really need to take so long!!!!!

Thanks also go to the many friends/drinking buddies I have made during my PhD: Craig Jamieson and Allan 'Baby' Davidson, who also doubled as flatmates in 'the pits of despair' 1 & 2. Stuart Johnstone (again), Big Daddy Garnet Howells for helping me out at the start of my time in lab 54 and for providing much hilarity throughout the years. Thanks also to Daren 'Dave' Pratt, Craig Walker and Ian Dodson for various excursions and hospitalisations, and all the members of labs 54, 55, 34 and 29 who are far too numerous to mention. Finally, to Mary Ognibene for her love, encouragement and for brightening up the last few years enormously.

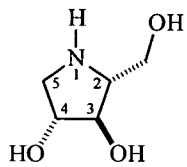
Abstract

This thesis documents the development of serine derived aldehyde **73** and its application to natural product synthesis.



73

Highly efficient syntheses of the biologically important natural products DAB1 **35** and nectrisine **36** from aldehyde **73** are discussed. The synthesis of these molecules made use of a highly efficient asymmetric boron mediated *syn* aldol reaction to generate a common intermediate, lactam **114**.



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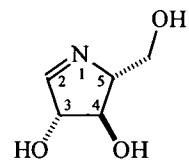

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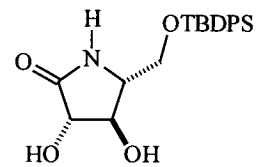

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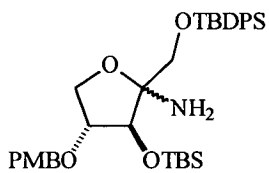
An alternate synthesis of lactam **114**, making use of the Sharpless asymmetric dihydroxylation reaction is also discussed, along with an extension of the aldol reaction methodology which allowed the development of syntheses directed towards the C_4Me analogue of **35** and the C_3Me analogue of **36**.

Finally the utility of aldehyde **73** towards the synthesis of the potential hydantocidin analogues **176** and **181**, and the synthesis of lactacystin analogue **183** was investigated.



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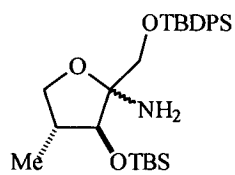

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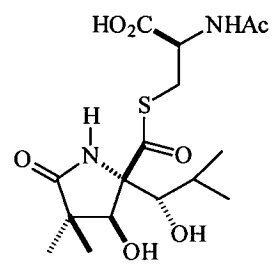

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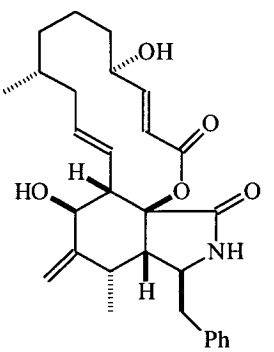
Contents

Chapter 1 : Introduction

1.0 α-Amino Acids and Their Derivatives

Chiral, non-racemic natural products including α-amino acids[1] have been part of the organic chemist's repertoire for many years. They have long been utilised as building blocks in synthetic strategies.[2] This is due to their presence in peptides and proteins and as starting material for the synthesis of naturally occurring biologically active compounds. Pertinent examples include the elegant syntheses of cytochalasine B **1**[3] and (+)-preussin **2**, **scheme 1**.[4] Nearly all the common *L*-amino acids have been employed in synthesis.[2] Such strategies have gained in stature primarily because efficient enzymatic processes, asymmetric syntheses, and new separation procedures have significantly expanded the number of available non-racemic amino acids. There has also been an increasing interest in the synthesis of proteinogenic and non-proteinogenic amino acids.[5]



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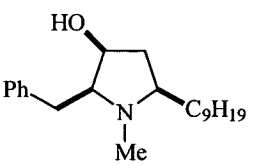

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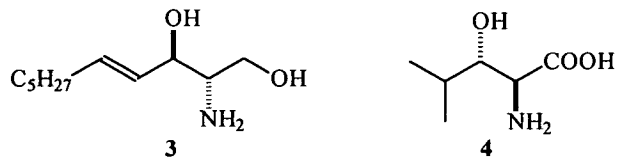
Scheme 1

Paralleling the interest in the synthesis and uses of α-amino acids has been the increased interest in compounds derived from these chiral pool building blocks, examples being, amino diols and β-hydroxy-α-amino acids, which are frequently found as key structural units in bioactive natural products. For instance, *D-erythro* sphingosine **3**[6] and it's derivatives were shown to be inhibitors of protein kinase C

and (2*S*,3*S*)-β-hydroxyleucine **4**, **scheme 2**, is a key constituent of a range of natural peptide antibiotics.[7] Amino alcohols in general also play an important role in modern organic chemistry as a class of versatile chiral ligands.[8] Indeed, a number of elegant processes have benefited from their presence including Sharpless asymmetric epoxidation/dihydroxylation methodology[9] and diastereoselective aldol condensation.[10]



Scheme 2

As chiral building blocks, *N*-protected amino aldehydes have found numerous applications in the synthesis of a wide variety of compounds.[11] In this respect, *N*-protected serinal has special importance as the presence of a β-hydroxy group in the side chain affords direct access to γ-hydroxy-β-amino alcohols and, moreover, provides a handle for further transformations.

1.1 Serine Derived Aldehydes

1.1.1 Serine

Since the interesting discovery of serine as a component of serecine, a silk protein,[12] it has been found in numerous biomolecules and has been employed as a building block for peptides and proteins.

Serine represents an attractive synthetic template for several reasons: (1) It is a naturally occurring, chiral amino acid, both enantiomers are readily available as economical raw materials; (2) each of the three carbon atoms bear a funtionality that can be selectively protected and elaborated upon; (3) many transformations can be carried out without adversely affecting optical integrity; (4) the skeleton of the corresponding 2-amino-1,3-diol is part of many naturally occurring substances,

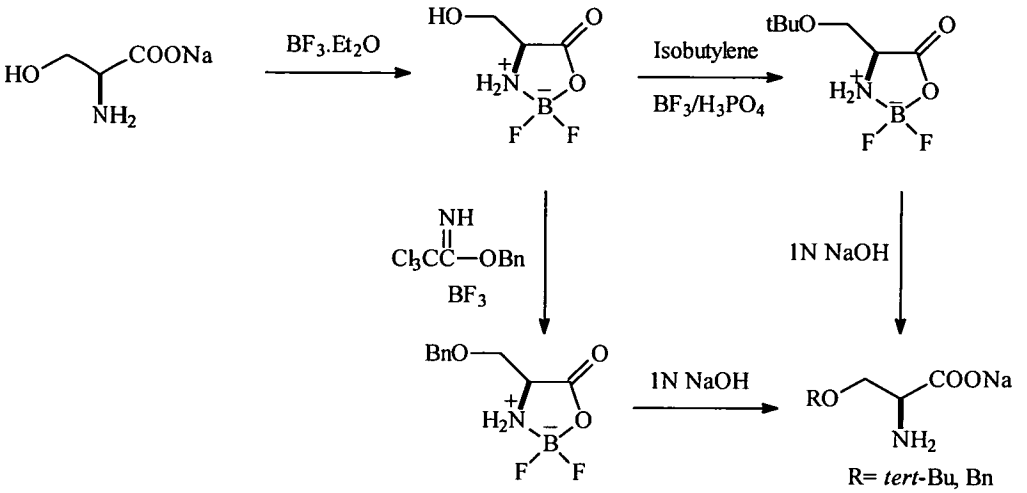
allowing the exploitation of the synthetic handle serine possesses in the synthesis of these substances.

1.1.2 Protection and Functionalisation Strategies For Serine

In general, a key aspect of synthetic elaboration is the judicious selection of protecting groups. In the protection of serine *en route* to a serinal derivative the synthetic chemist has many choices for each functionality (i.e. the amino group, the primary hydroxyl, and the carboxylic acid). The nitrogen terminus is most commonly protected as a carbamate (Boc,[13] Cbz,[14] or Fmoc[15]) using standard chemistry. The trityl group has been employed to a lesser extent.[16] More recently, the *N*,*N*-dibenzyl group has been added to the repertoire of *N*-protecting groups.[17]

A variety of groups have been employed for the protection of the primary alcohol in serine, including, benzyl,[18] *tert*-butyldimethylsilyl (TBS),[19] trityl,[20] *tert*-butyl[21] and tetrahydropyran (THP).[22] However, in these cases preprotection of the carboxylic acid/or amino group may be necessary.

Wang and co-workers have reported an interesting preparation of *O*-benzyl or *O*-*tert*-butyl serine, **scheme 3**.[18b] Serine is first treated with boron trifluoride to form a cyclic oxazaborolidinone. The crude oxazaborolidinone is reacted with either isobutylene under acid catalysis or with benzyl trichloroacetimidate/BF_3 to form the corresponding *O*-protected oxazaborolidinone. Workup with 1N sodium hydroxide liberates the hydroxyl protected serine, thus circumventing the need to protect the other functionalities prior to *O*-protection.



Scheme 3

Simultaneous nitrogen and hydroxyl protection with an isopropylidene group[23] or as an oxazolidinone[24] obviates the need for independent hydroxyl protection. Both the isopropylidene and oxazolidinone groups can be cleaved under relatively mild conditions.

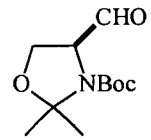
Protection/activation of the carboxyl group as a suitable ester is most common. In the majority of cases the acid functionality is required to be reduced to the corresponding alcohol or aldehyde before further elaboration.

1.1.3 Types of Serine Derived Aldehydes and Their Synthesis

As can be seen in the preceeding section there are a plethora of protecting groups that could be utilised in the synthesis of a serine derived aldehyde. The choices made will no doubt, in one way or another, affect additions of nucleophillic reagents to the aldehyde (especially protecting groups on the nitrogen atom). They may also affect the stereochemical integrity of the α-position. These represent crucial choices for the synthetic organic chemist to make when dealing with α-amino aldehydes. This section examines the differing types of serine derived aldehydes that have been developed and examples of their synthesis.

In general, protection of serine's different funtionalities takes place as described in section 1.1.2. It could therefore be perceived that many different (protected) aldehydes may have been developed, and, indeed, this is the case. In all cases the aldehyde group originates from the carboxylic acid funtionality of the amino acid.

Thus, Garner and co-workers have developed a cyclic oxazolidine aldehyde **5**,[23] **scheme 4**, while Rapaport reported both an acyclic *N*-(phenylsulfonyl)-protected aldehyde **6**[25] and an *N*-(9-phenylfluoren-9-yl) cyclic carbamate **7**.[26] There have been examples of *N*-Cbz **8**[27] protection and Reetz has more recently introduced the *N,N*-dibenzyl group **9a**[28] with *O*-TBS protection. *N,N*-dibenzyl with *O*-benzyl protection **9b**[29] and MOM protection **9c**[30] have also been reported, along with the more classical *N*-Boc **10**[31] protected aldehydes, here with *O*-benzyl protection.



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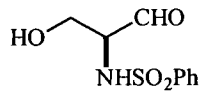

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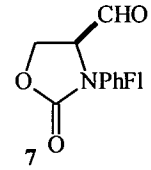

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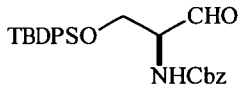

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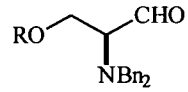
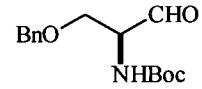


9a R=TBS
9b R=Bn
9c R=MOM



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Scheme 4

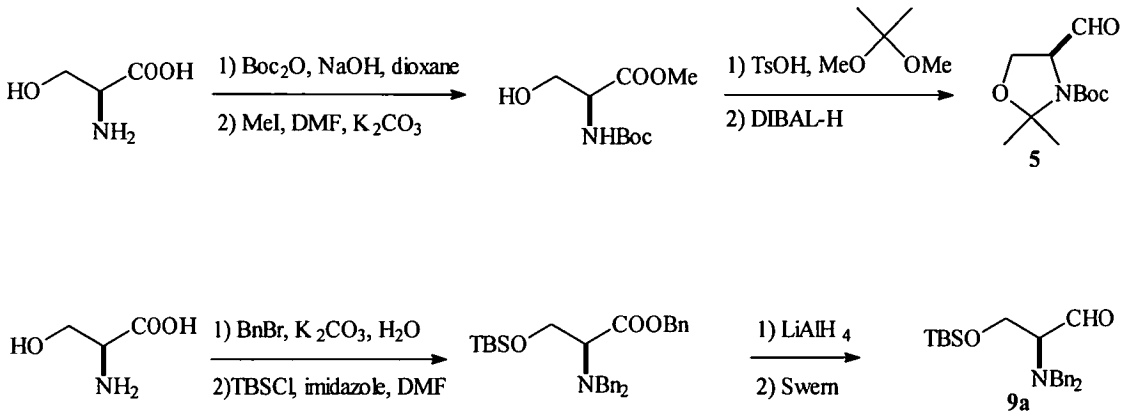
Some major disadvantages are present in the cases of the more classical carbamate protected aldehydes. Perhaps the most serious is that they show a tendancy to undergo racemization.[31] This necessitates their need to be handled in cold solvent and subjected to reaction as quickly as possible after their preparation. The very bulky 9-phenylfluoren-9-yl protecting group can confer enhanced configurational stability.[26] Additionally, *N,N*-dibenzyl amino aldehydes are configurationally stable at room temperature and are therefore much easier to handle.[28] The Garner aldehyde is also much more resilient to racemisation than its

straight chain Boc protected counterparts.[32] Storage for short periods of time, therefore, becomes a possibility. Thus, it is these newer types of aldehyde that have very much eclipsed the use of the more traditional carbamate protected derivatives.

The syntheses of these aldehydes in general follows the set pattern of initial protection of the nitrogen and primary hydroxyl units. These protective groups are easily introduced, be they carbamates (for *N*-protection) (e.g. Boc, Cbz),[27,31] which are introduced under basic conditions using CbzCl and Boc_2O, or benzyl groups (*O*- or *N*-protection), which are also introduced under basic conditions with BnBr.[28] Silicon protection,[33] MOM protection,[34] THP protection[22] and trityl protection[20] (examples of *O*-protection) are all introduced *via* standard procedures. This is then usually followed by a two step reduction/oxidation protocol, of the carboxylic acid (generally as an activated ester).

The reductions tend to be carried out with lithiumaluminium hydride,[17] diisobutylaluminium hydride,[35] lithium borohydride[36] or sodium borohydride.[37] In one or two cases authors have reported the direct reduction of an ester to an aldehyde with cold diisobutylaluminium hydride.[38] It has also been noted that conversion to the versatile Weinreb amide[39] followed by reduction of the amide with lithiumaluminium hydride (which gives exclusively the aldehyde; over reduction of the lithium salts is precluded by intramolecular complexation) leads to *N*-Boc protected aldehydes with greater optical purity than has hitherto been observed.[31]

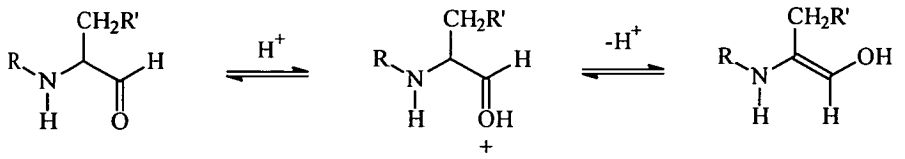
Following reductions to the primary alcohol an oxidation is required to provide the aldehyde moiety. This is conveniently carried out under Swern conditions,[40] or Dess-Martin conditions[41] in excellent yields. The syntheses of Garner's aldehyde **5**[23] and Reetz's *N*,*N*-dibenzyl amino aldehyde **9a**[28] are shown as examples in **scheme 5**. These are arguably the two most useful serine derived aldehydes to date, in terms of ease of synthesis, orthogonal protection, configurational stability and their ability to undergo diastereoselective reactions (to be discussed in **section 1.2**).



Scheme 5

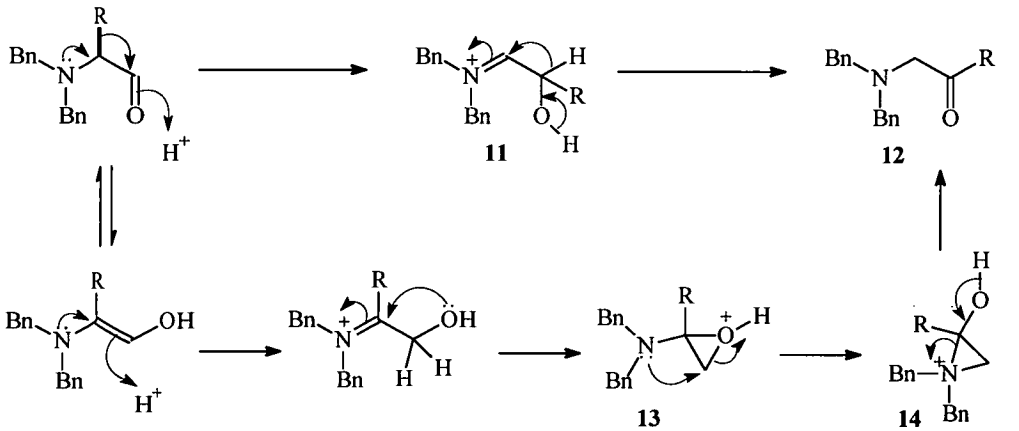
The synthesis of Garner's aldehyde (**5**) is straight forward, encompassing some classical protecting group chemistry, as mentioned in previous sections. Boc protection of the nitrogen and esterification followed by isopropylidine formation provided an ester with cyclic *O,N*-protection, which could be selectively reduced to the aldehyde with cold DIBAL-H. The optical purity of the material produced was in the range of 93-95% e.e. and the overall yield for the synthesis was in the range of 45-58%.[32] Reetz's synthesis began with di-benzylation of the amino functionality with concominant benzyl ester formation. The next step was protection of the primary hydroxyl as its silyl ether. Reduction of the ester to the primary alcohol followed by Swern oxidation provided the aldehyde in 51% overall yield and with an optical purity of >99% e.e.[28]

Chromatographic purification of the newly synthesised aldehydes, especially with mono-*N*-substitution is always detrimental and should be avoided unless absolutely necessary.[28] This is due, in many cases, to an increased tendency of these already unstable aldehydes to racemise under acidic conditions, **scheme 6**. Here, enolisation in the presence of acid causes racemisation. For some aldehydes this can occur very quickly during contact with silica gel.[42]



Scheme 6

Disturbingly, even the more configurationally stable *N,N*-dibenzylamino aldehydes are not immune to problems encountered through chromatography. In these cases alongside racemisation, an unusual rearrangement to give aminoketones **12**,[43] has been observed for a range of aldehydes, **scheme 7**. Two different mechanisms have been postulated as shown. In the first, a 1,2-R-group shift gives **11**, followed by a reverse 1,2-hydrogen shift to furnish the rearranged product. In the second, enol equilibration allows rearrangement *via* oxiranium ion **13** and aziridinium ion **14** to give **12**. The unstable nature of α-amino aldehydes means that in nearly all cases of their use they are in a crude isolated form, derived from either oxidation or reduction protocols.



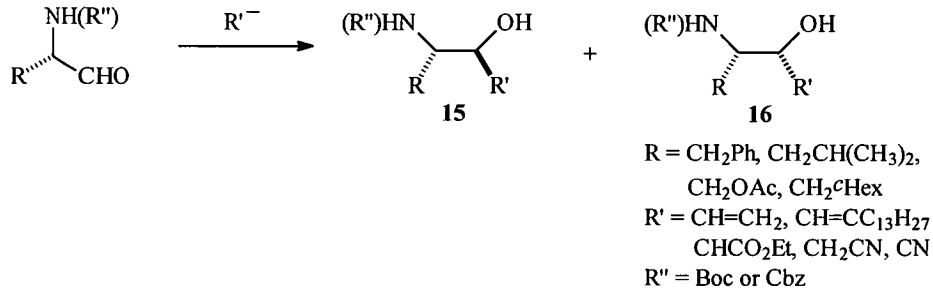
Scheme 7

1.2 Nucleophilic Additions

Once suitably protected α-amino aldehydes are reactive toward a variety of classic reagents used for addition to the aldehyde function, and their synthetic potential has been amply demonstrated.

1.2.1 Carbamate Protected α-Amino Aldehydes

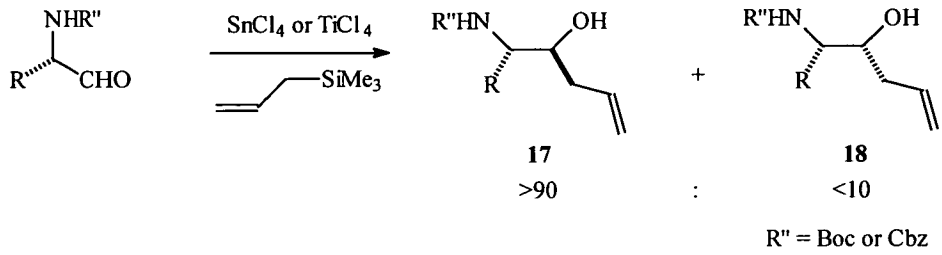
Until about 1987 α-amino aldehydes were protected at the nitrogen with, in general, carbamates (Boc, Cbz). A drawback of their use was the need to handle them in cold solvents prior to use because of ease of racemisation (as mentioned in section 1.1.3). A further limitation of their use is that in the vast majority of nucleophilic additions to them (with Grignard reagents, lithium enolates, KCN/H^+, and sulfur ylides), mixtures of chelation and non-chelation controlled adducts **15** and **16** respectively, **scheme 8**, were observed with poor levels of diastereoselection (in the range 1:1 to 3:1).[44]



Scheme 8

Rare cases of high selectivities have been observed. For instance, applying reagents which are capable of chelation can drastically enhance addition of nucleophiles to give adducts **15** predominantly. Reagents such as the bidentate Lewis acids: $TiCl_4$, $SnCl_4$, or $MgCl_2$ have been applied to the addition of allylsilanes, enolsilanes, zinc reagents and Me_3SiCN to α-alkoxy aldehydes[45] with excellent stereocontrol. This concept was subsequently applied to the reaction of allylsilane

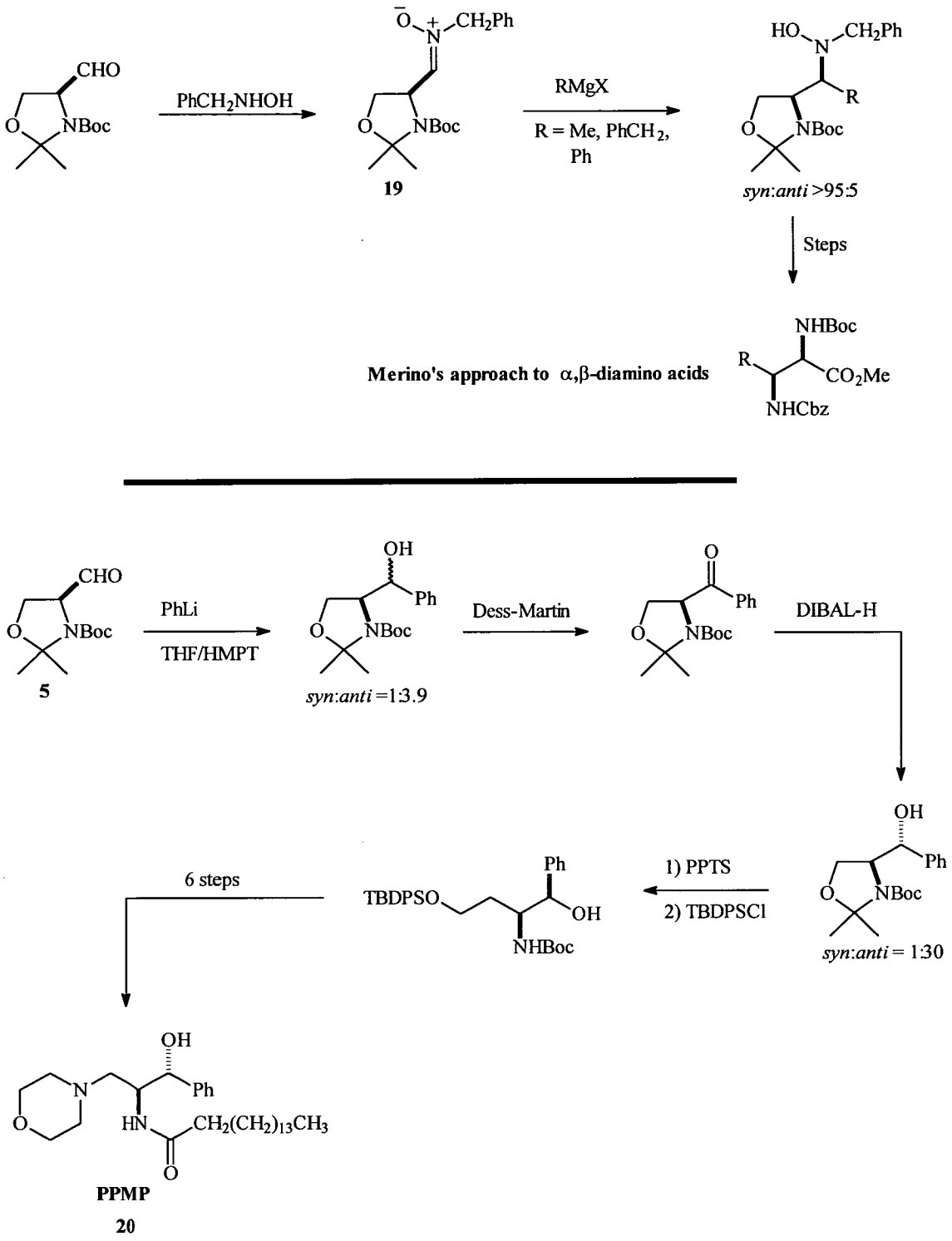
with α-amino aldehydes, in the presence of $SnCl_4$ or $TiCl_4$, **scheme 9**, to give chelation controlled adducts **17** with diasereomeric ratios (**17**:**18**) in the range >90:10.[46]



Scheme 9

However, with limited examples of excellent stereocontrol using reagents that promote chelation, combined with the mainly mediocre levels of diastereoselectivity achieved with the majority of nucleophiles, this class of aldehyde has been less frequently used in synthetic applications of late.[11,44]

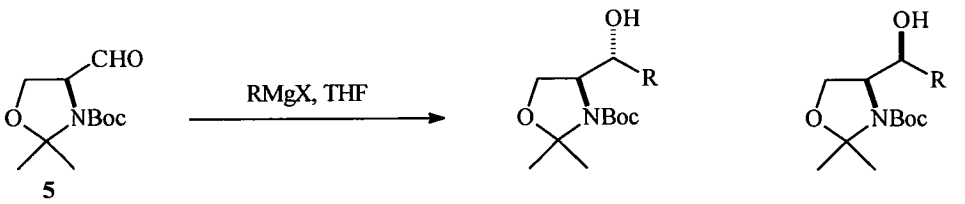
Garner's aldehyde **5** is probably the most popular serine derived aldehyde and has been used in the synthesis of a wide range of compounds.[47] For example, Merino's interesting approach to α,β-diamino acids utilises Garner's aldehyde as a key starting material.[47a] Highly stereoselective additions of Grignard reagents to α-amino nitrone **19** provided a means of generating the desired compounds. Nakagawa and co-workers have utilised the aldehyde in a stereoselective preparation of PPMP (1-phenyl-2-palmitoylamino-3-morpholino-1-propanol) **20**, **scheme 10**.[48] The key observation here is the relatively poor selectivity in addition of PhLi to the aldehyde. This was, however, rectified by conversion to a ketone followed by a stereoselective reduction using DIBAL-H.



Scheme 10

Though moderate to good selectivities are generally obtained, the facial selectivity in addition of Grignard reagents and other organometallic species to this

aldehyde has been shown to be reagent dependent. Moreover, both chelation and non-chelation controlled processes can occur concominantly, leading to diminished diastereoselectivity or even reversed facial selectivity, **scheme 11**, such that prediction of stereochemical outcome is tenuous.[49]



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R = Ph	5	:	1
R = *i*Pr	1	:	6

Scheme 11

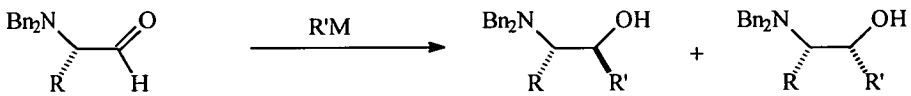
1.2.2 N,N-Dibenzylamino Aldehydes

In the 1990's, Reetz, introduced the idea of protecting group tuning[50] as a means of realising high levels of asymmetric control in organometallic additions involving *N,N*-dibenzylamino aldehydes. Their configurational stability at room temperature and the reliable and predictable high diastereoselectivity (ds >90% is a rule) observed with a battery of different organometallics have made them a family of extremely useful chiral building blocks.[30,51,52] Curiously, application of *N,N*-dibenzylaminoserine aldehyde in asymmetric synthesis has scarcely been reported in the literature.

Non-Chelation Controlled Addition:

The first reaction of an *N,N*-dibenzylamino aldehyde to be studied was the Grignard addition of phenylmagnesium bromide to alaninal **21a** (see **scheme 12**).[53] Because similar reactions using α-alkoxy aldehydes such as α-benzyloxy propanal had been known to occur non-selectively with formation of 2:1 mixtures of chelation and non-chelation controlled adducts,[54] there was little reason to assume that *N,N*-dibenzyl α-amino aldehydes would display any sort of diastereoselectivity. However,

experimentally only a single diastereomer in the reaction of alaninal **21a** with phenylmagnesium bromide was observed. It was argued that a tertiary amino group would be a better donor ligand for magnesium than an ether moiety (in analogy with reactions of α-alkoxy aldehydes) and chelation controlled adducts **22** would predominate. However, the product, in fact, turned out to be that of non-chelation control **23**.



21a: R = Me
21b: R = $BnOCH_2$
9a: R = *tert*-$BuMe_2SiOCH_2$

22 **23**

Scheme 12

Moreover, a variety of other organometallic reagents such as MeLi, $MeTi(O^iPr)_3$, $^nBuCeCl_2$ and MeMgX likewise react to form non-chelation controlled products **23**. In further experiments it was shown that non-chelation control is quite general for a wide variety of organometallic reagents. **Table 1** summarises some of these additions to alaninal **21a** and serine derived aldehydes (**21b** & **9a**).[55]

Table 1

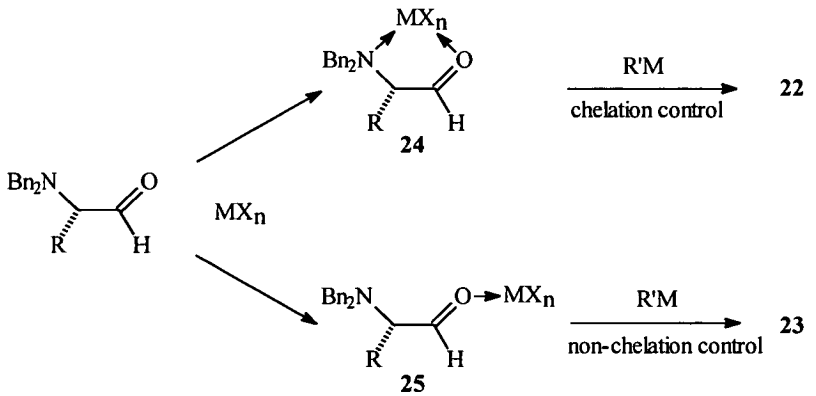
Entry	Aldehyde	Reagent	R' in **22/23**	Yield	**22 : 23**
1	**21a**	MeMgI	Me	87	5 : 95
2	**21a**	MeLi	Me	91	9 : 91
3	**21a**	$MeTi(O^iPr)_3$	Me	78	3 : 97
4	**21a**	Me_2CuLi	Me	80	25 : 75
5	**21a**	PhMgBr	Ph	85	3 : 97
6	**21a**	EtMgBr	Et	85	5 : 95
7	**21a**	*tert*-BuLi	*tert*-Bu	88	<3 : >97
8	**21a**	$Me_3SiCN/ZnBr_2$	CN	74	13 : 87
9	**21b**	EtMgBr	Et	71	<5 : >95
10	**21b**	*n*-$C_{15}H_{31}MgBr$	*n*-$C_{15}H_{31}$	79	<5 : >95
11	**21b**	*tert*-BuLi	*tert*-Bu	54	12 : 88
12	**21b**	PhMgBr	Ph	78	3 : 97

13	**9a**	MeMgBr	Me	85	<5 : >95
14	**9a**	^{i}PrMgCl	*i*Pr	>88	< 5 : >95
15	**9a**	*n*-PrMgCl	*n*-Pr	74	3 : 97
16	**9a**	*n*-BuLi	*n*-Bu	30	<5 : >95
17	**9a**	*n*-BuLi/$CeCl_3$	*n*-Bu	75	< 5 : >95
18	**9a**	*n*-$C_{13}H_{27}MgBr$	*n*-$C_{13}H_{27}$	77	6 : 94
19	**9a**	PhMgBr	Ph	81	3 : 97
20	**9a**	CH_2=CHMgBr	CH_2=CH	65	10 : 90
21	**9a**	*c*-C_3H_5Li	*c*-C_3H_5	84	10 : 90
22	**9a**	CH_2=$CHCH_2Ti(NEt_2)_3$	CH_2CHCH_2	83	16 : 84

Chelation Controlled Addition:

As can be seen in **Table 1** there is a distinct propensity for *N,N*-dibenzylamino aldehydes to undergo stereoselective non-chelation controlled reactions with a multitude of nucleophiles. It can therefore be envisaged that difficulties may arise when attempting to generate chelation controlled adducts. The reason for this has to do with steric factors arising from the two *N*-benzyl groups. Nevertheless, chelation control has been achieved in several cases.

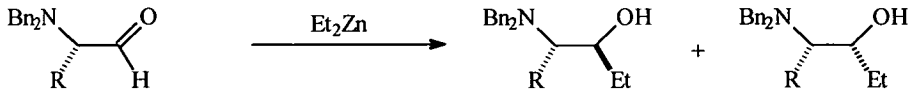
In most of the successful cases, a Lewis acid MX_n was employed in the hope of generating intermediates of the type **24**, **scheme 13**. However, it must be remembered that such Lewis acids can also form aldehyde adducts of the type **25** which would react with non-chelation control.[51]



Scheme 13

Some sporadic success has occurred in chelation controlled additions, for example, the highly Lewis acidic $MeTiCl_3$ leads to excellent stereocontrol in additions to *N,N*-dibenzylamino aldehydes. However, diastereoselectivity decreases drastically as the size of the R-group increases. The combination of $TiCl_4/Me_2Zn$ also leads to chelation controlled additions as do $SnCl_4$ mediated additions which can give good levels of diastereoselectivities. These types of chelation controlled additions, however, do not always give good levels of stereocontrol and it appears that in the case of Lewis acid mediated reactions several different types of complexes with *N,N*-dibenzylamino aldehydes exist and the direction and extent of the diastereoselectivity is difficult to predict.

In a completely different approach, diethylzinc was reacted with *N,N*-dibenzylamino aldehydes **21** at 0 °C, **scheme 14**, to afford chelation controlled adducts **22** preferentially, with diastereoselectivities in the range of 88-99% (**Table 2**).[56]



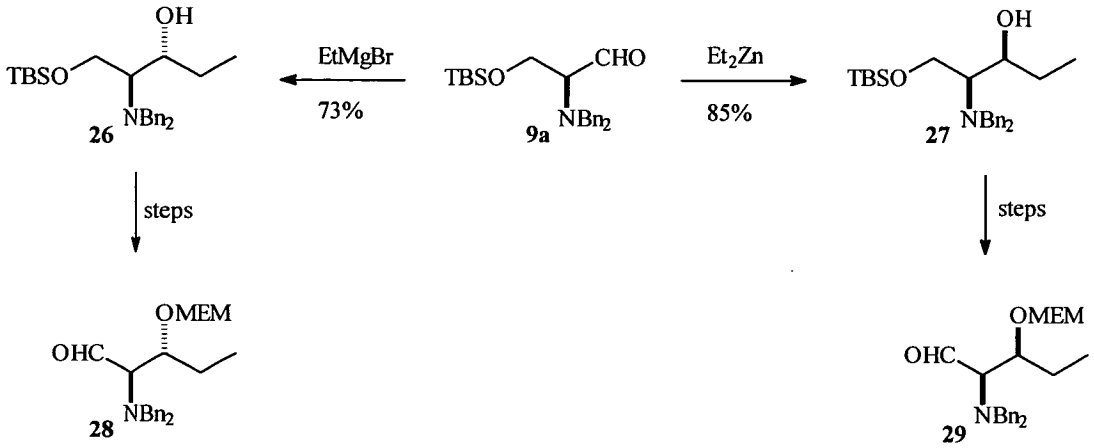
21a: R = Me
21d: R = $CH(CH_3)_2$
21e: R = $CH_2CH(CH_3)_2$
21f: R = CH_2Ph
21g: R = Ph
21h: R = CH_2OMEM

Scheme 14

Table 2

Entry	Aldehyde	Yield	**22 : 23**
1	**21a**	95	88 :12
2	**21d**	64	>99 : <1
3	**21e**	62	92 : 8
4	**21f**	70	90 : 10
5	**21g**	65	>99 : <1
6	**21h**	70	95 : 5

This reaction was used succesfully by Andres and Pedrosa in the synthesis of 2-aminopentan-1,3-diol diastereomers, **scheme 15**. Thus, serinal **9a** was transformed into the two diastereomeric 3-hydroxynorvinals **28** and **29** *en route* to the target molecules. The key step was addition of ethylmagnesium bromide to the aldehyde to give the *anti* (non-chelation controlled) product **26** or diethylzinc addition to **9a** to give the *syn* (chelation controlled) product **27**. Both additions were shown to occur in a highly stereoselective manner (90% and >99% ds respectively).[57]



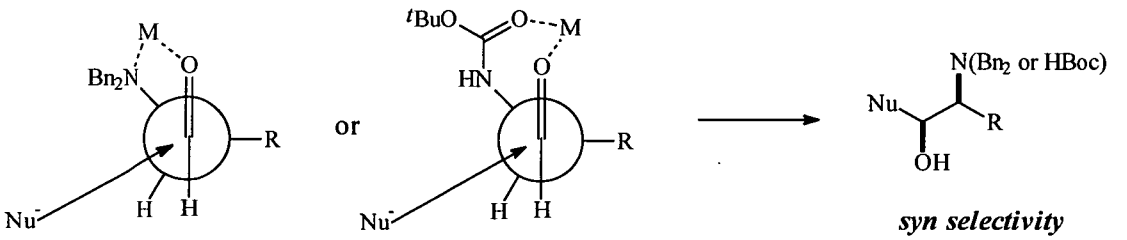
Scheme 15

These latter (chelation-controlled) results are unprecedented since all previously used organometallics such RLi, RMgX, RMnX, $RCeCl_2$, and R_2CuLi afford opposite diastereomers **23** selectively. The reason for this intriguing difference has not yet been pinpointed. However, it has been noted that the addition of diethylzinc to *N,N*-dibenzylamino aldehydes proceeds at unusually high rates. Normal aldehydes do not react with diethylzinc without the aid of promoters, such as $TiCl_4$,[58] or without the presence of catalysts such as β-amino alcohols.[59] Thus ligand acceleration promoted by the *N,N*-dibenzylamino group appears to be operating, perhaps in an autocatalytic fashion.[60] This result is interesting in that if other diorganozinc species react in a chelation controlled manner then this would represent a general method for preparing chelation controlled adducts from additions to *N,N*-dibenzyl amino aldehydes with high diastereoselectivity.

1.3 Models For Chelation and Non-Chelation Controlled Additions to α-Amino Aldehydes

1.3.1 Chelation Controlled Reactions:

Chelation controlled addition to α-amino aldehydes to give *syn*-α-amino-β-hydroxy compounds can be explained by a Cram chelate model, **scheme 16**.[61c] The incoming nucleophile adds to the carbonyl through attack at the least hindered face. For α-amino aldehydes complexation with a metal (M) can occur *via* the carbonyl oxygen and the nitrogen atom (e.g. in Et_2Zn additions to *N,N*-dibenzylaminoaldehydes) or *via* the carbonyl oxygen and the protecting group on the nitrogen (e.g. with Lewis acid promoted additions to Boc protected aldehydes). Whatever the complexation nature, the result of nucleophilic attack is the same and *syn* adducts are, in general, the end result.

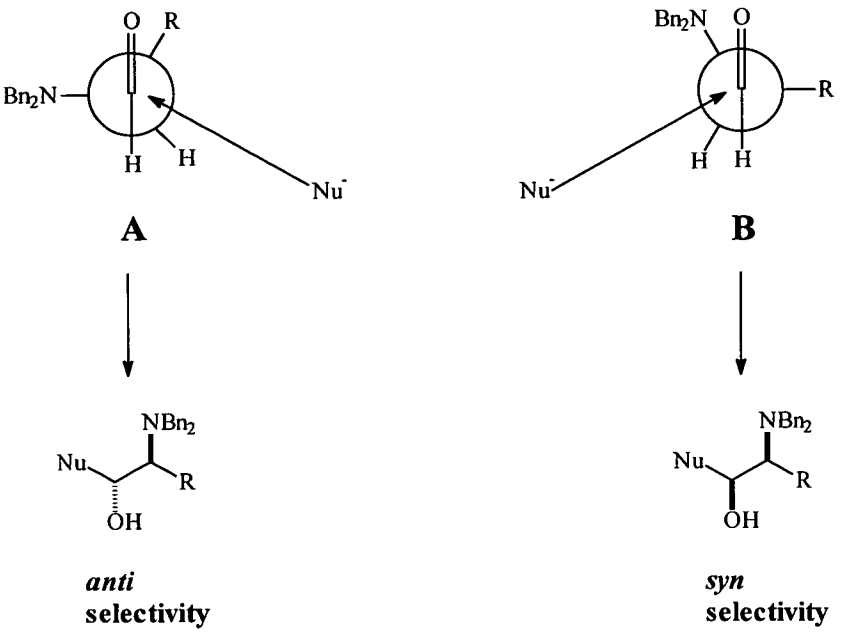


Scheme 16

1.3.2 Non-Chelation Controlled Reactions

Non-Chelation controlled additions to α-amino aldehydes can be rationalised by applying the Felkin-Anh model.[61] Two different conformers (**A** & **B**) may be predicted, **scheme 17**. In, for example, the case of *N,N*-dibenzyl amino aldehydes which undergo almost exclusively non-chelation controlled additions, conformer (**A**) predicts the observed *anti* selectivity, with the nucleophile approaching from the less hindered face of the aldehyde. For cases where the group (R) is very bulky

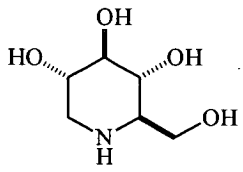
conformer (**B**) competes with conformer (**A**) and a diminished diastereoselectivity may result.[51]



Scheme 17

1.4 Iminosugars

Recently there has been increasing interest in a group of hydrophilic plant alkaloids due to their potentially useful biological activities. The compounds concerned are simple hydroxylated derivatives of the monocyclic and bicyclic nitrogen containing ring systems found in piperidine (e.g. deoxynojirimicin, **30**), pyrrolidine (e.g. DAB1, **31**), indolizidine (e.g. castanospermine, **32**), pyrrolizidine (e.g. australine, **33**) and *nor*tropane (e.g. calystegine, **34**) alkaloids, **scheme 18**.[62,63] Members of the group have been given various generic names in attempts to indicate their structural resemblance to sugars: iminosugars, polyhydroxylated alkaloids, azasugars and aminosugars have all been used.



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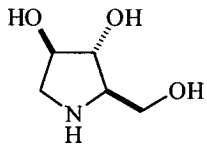

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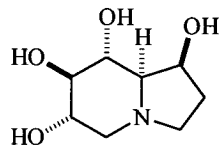

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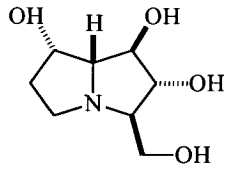

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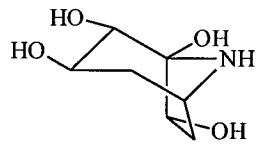

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Scheme 18

The biological activity of these iminosugars in the most part comes from their ability to inhibit glycosidases. Glycosidases are a class of enzyme which are extremely widespread in organisms.[64] These enzymes catalyze the hydrolysis of glycosidic bonds in carbohydrates and glycoconjugates. The net effect is the release of low molecular weight monosaccaharides and oligosaccharides.[62] Because glycosidases are important in many biochemical systems it is not surprising that compounds that inhibit them exhibit biological activity.

The enzymatic activity of iminosugars has been attributed to their structural resemblance to simple sugars. The extent and specificity of the inhibition was thought to be dependent on the position, number and stereochemistry of the hydroxyl groups on the molecule. However, experimental data have shown that the chirality of the hydroxyl groups on the iminosugars was not sufficient to predict their ability to inhibit enzymes.[62]

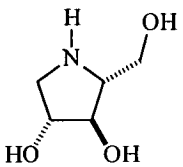
Some iminosugars inhibit glycosidases involved in glycoprotein processing. Glycoproteins belong to a class of glycoconjugates which also includes glycolipids. The processing is performed by glycosidase enzymes, which catalyze the trimming of saccharide units from the glycoprotein, creating new glycoproteins targetted to perform particular biological functions.

A number of iminosugars have been linked to anti-viral activity. For example, castanospermine **32** was found to inhibit AIDS-virus syncytium formation and virus replication. Other uses may include anti-cancer agents,[65] insecticides,[66] and plant growth regulators.[67]

As a group of compounds the iminosugars have a diverse range of uses: as pharmaceutical agents, and as agrochemicals to name but a few. With advances in isolation techniques and screening it is possible that more of these compounds will be isolated and developed as drugs.

1.5 Pyrrolidine Iminosugars

We, like others, have been interested in the synthesis of polyhydroxylated pyrrolidines, not least because of their biological activities. Our interest is focused upon the synthesis of the iminosugars DAB1 **35** (1,4-dideoxy-1,4-imino-*D*-arabinitiol) and nectrisine **36**, **scheme 19**.



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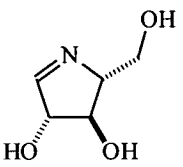

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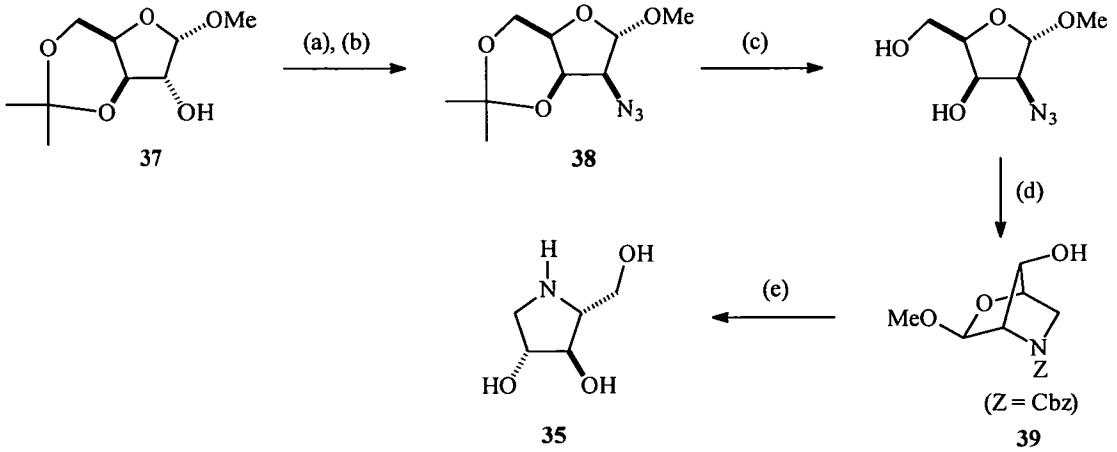
Scheme 19

1.5.1 Previous Syntheses of DAB1

DAB1 was isolated, almost simultaneously from the fruits of *Angylocalyx boutiqueanus*[68] and from *Arachniodes standishii*.[69] Extensive ^{1}H NMR studies deduced that its structure was that of **35** as shown in **scheme 19** (i.e. (2*R*,3*R*,4*R*)-3,4-dihydroxy-2-hydroxymethyl pyrrolidine). It was found to be a potent inhibitor of yeast α-glucosidase, with an IC_{50} of 1.8 x 10^{-7}M.[70] It has also been shown to be a potential AIDS-virus replication inhibitor.[71]

There have been several syntheses of DAB1 from carbohydrate precursors since the first by Fleet in 1985.[70,72] Fleet's original synthesis is highlighted in **scheme 20**. Thus, the acetonide **37**, which is readily available from *D*-xylose was esterified with triflic anhydride followed by treatment with sodium azide. Methanolysis of the acetonide afforded the *D*-ribofuranoside **38**. Tosylation of the primary hydroxyl group and hydrogenation of the azide function gave the bicyclic amine **39** (isolated as a carbamate) on heating with sodium acetate. Hydrolysis of **39** followed by borohydride reduction and removal of the carbamate protecting group furnished DAB1, in 15% overall yield as its hydrochloride salt.

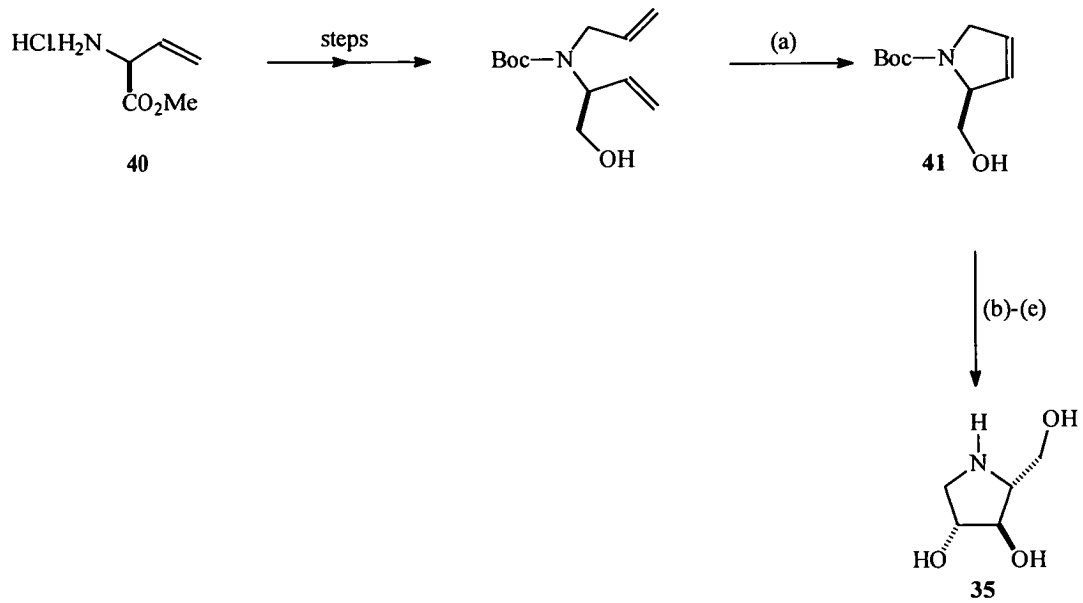


(a) $(CF_3SO_2)_2O$, py, $CHCl_2$; (b) NaN_3, DMF, 100 °C; (c) Dowex 50W-8X, MeOH; (d) TsCl, py, H_2, Pd black, EtOH/NaOAc; CbzCl, ether, $NaHCO_3$ (aq.); (e) CF_3COOH/water; $NaBH_4$, EtOH; H_2, Pd black, MeCOOH

Scheme 20

Other routes to achieve the synthesis of DAB1 have involved the use of aldolases to catalyze aldol condensations, prior to reductive amination and cyclisation to the pyrrolidine ring.[73]

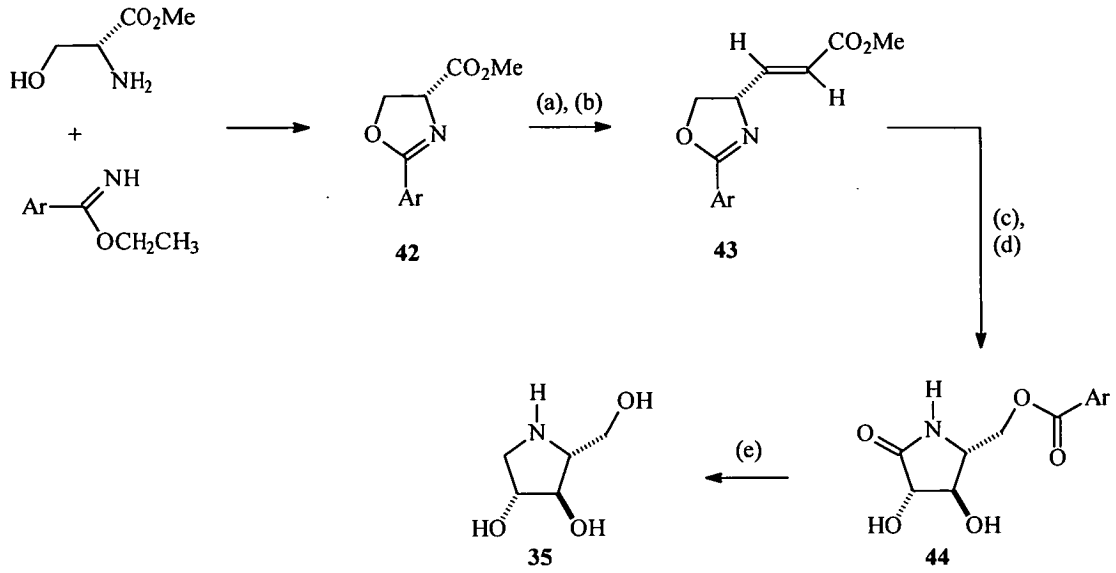
There have also been a few interesting syntheses utilising non-carbohydrate precursors. For example, Blechert and Huwe developed a racemic synthesis of DAB1 from vinyl glycine methyl ester **40**, **scheme 21**.[74] The synthesis relied upon a ring closing metathesis reaction to form dehydroprolinol derivative **41**. After tritylation of the primary hydroxyl group stereoselective epoxidation of the olefin was possible. Following epoxidation, a regioselective epoxide ring opening with potassium hydroxide furnished (after an acidic deprotection protocol) racemic DAB1 in 15% overall yield.



(a) 4 mol% $Cl_2(Pcy_3)_2Ru{=}CHCH{=}CPh_2$, Ph; (b) TrCl, Et_3N, DMAP, $CHCl_2$; (c) mCPBA, Et_2O; (d) KOH, water, DMSO, 95 °C; (e) HCl, MeOH, AcOMe

Scheme 21

Further syntheses have utilised a pyrrolidinone intermediate. A reduction of the carbonyl moiety leads to the required pyrrolidine.[75] One such route began with *D*-serine as the initial source of chirality.[75b] Formation of known oxazoline **42** from *D*-serine followed by reduction to the aldehyde and subsequent Wittig reaction gave *E*-olefin **43** (along with the separable *Z*-olefin (variable amounts)). Dihydroxylation of this olefin gave a mixture of diastereomeric diols in every case (including the use of the Sharpless asymmetric variant), fortunately these were separable. Treatment with aqueous hydrochloric acid afforded the pyrrolidin-2-one **44**. Finally, borane reduction gave the desired pyrrolidine, DAB1.



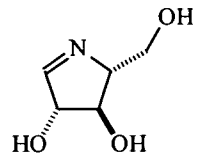
(a) DIBAL-H, $PhCH_3$; (b) $(Ph)_3P{=}CHCO_2Me$; (c) OsO_4, NMO, acetone/water (4:1); (d) 1.5 N HCl (aq.), THF; (e) B_2H_6, THF

Scheme 22

As can be seen from the above examples the literature is replete with examples of DAB1 syntheses. Most of the syntheses undertaken have utilised the inherent chirality of carbohydrate precursors.

1.5.2 Previous Syntheses of Nectrisine

In 1988 Shibata *et al.* described the isolation of a metabolite from the fungus *Nectria lucida* named FR-900483.[76] The structure of FR-900483 was shown to be **36** by extensive NMR studies and a synthesis from *D*-glucose.[77] The natural product was subsequently renamed nectrisine.



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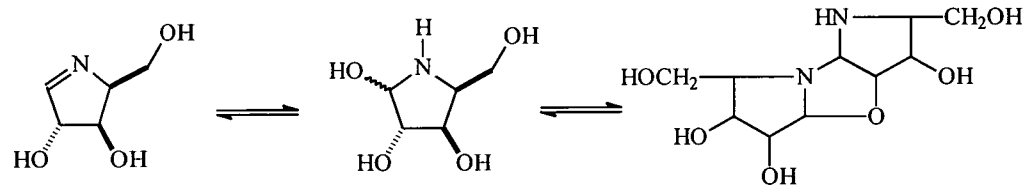
Scheme 23

Nectrisine **36** has subsequently been shown to be a powerful inhibitor of α-glucosidases (IC_{50} = 4.0 x 10^{-8}M; yeast α-glucosidase)[78] and to a slightly lesser extent α-mannosidases (IC_{50} = 3 x 10^{-6}M; Jack Bean α-mannosidase).[78] A novel kind of biological activity was also reported, in that nectrisine was found to be able to inhibit the suppression of lymphocyte production in mice.[77,79]

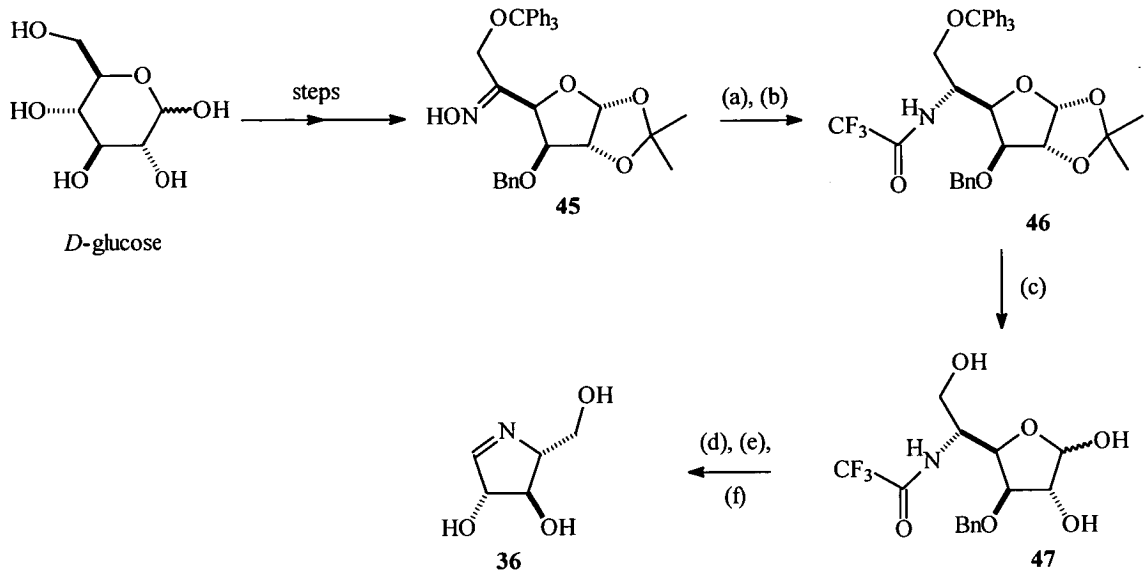
The first synthesis of nectrisine was by Kayakiri *et al.*[77] from *D*-glucose and served to identify the true structure as depicted in **scheme 23**. It must be noted that whilst nectrisine exists solely in its imine form (by NMR) other stereoisomers do not. This is exemplified by 4-*epi*-nectrisine whose solution structure turns out to be a rapidily equilibriating mixture of the imine, amino alcohol and a dimer, **scheme 24**.[80]



4-*epi*-nectrisine

Scheme 24

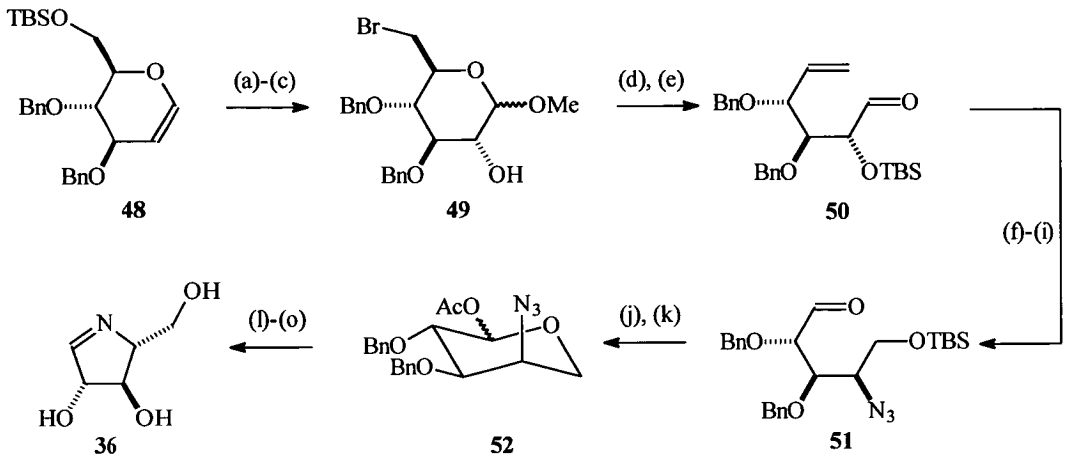
In Kayakiri's synthesis *D*-glucose was converted to the oxime **45** which was hydgrogenated over Raney nickel to provide compound **46** after trifluoroacetate protection, **scheme 25**.[77] Cleavage of the acetal protection with trifluoroacetic acid gave **47**. Oxidation with sodium periodate followed by hydrogenolysis of the benzyl protecting group and alkaline hydrolysis gave nectrisine.



(a) Raney Ni, H_2, NH_4OH/MeOH; (b) $(CF_3CO)_2O$, Et_3N, CH_2Cl_2; (c) TFA, water; (d) $NaIO_4$, THF/water; (e) Pd black, H_2, HCO_2H, MeOH; (f) 1N NaOH

Scheme 25

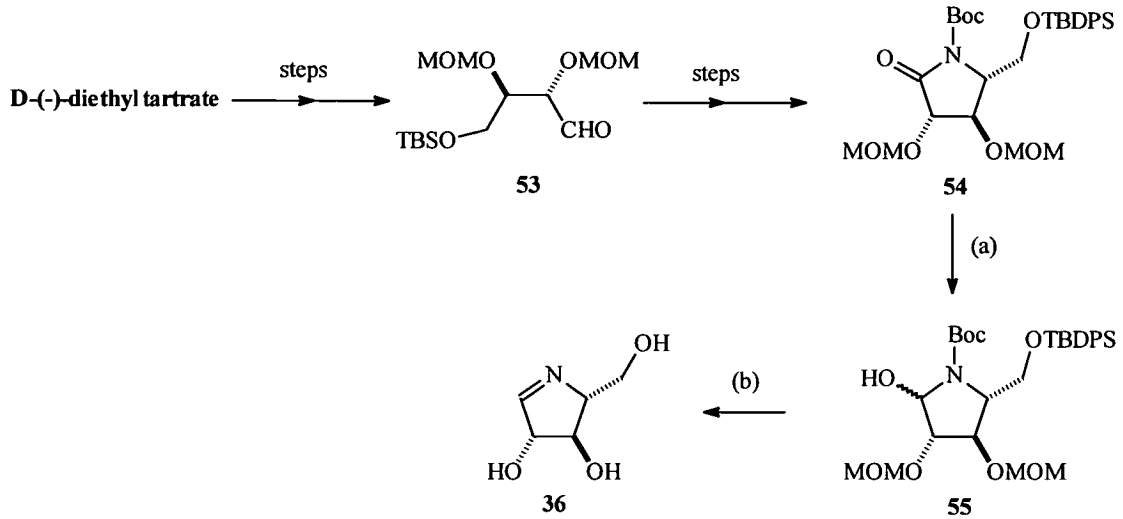
Through interest in applications of the Vasella reaction,[81] Danishefsky devised the synthesis outlined in **scheme 26**.[82] Thus glucal **48**, which is readily prepared from *D*-glucal, was reacted with mCPBA. De-silylation and bromination afforded **49**. Protection of the hydroxyl function and Vasella cleavage provided **50**. Reduction of the aldehyde gave rise to silyl migration to the primary alcohol. Inversion of the secondary alcohol by triflation followed by azidolysis, and ozonolysis afforded compound **51**. De-silylation and acetylation gave acetate **52**. Reduction of the azide moiety under hydrogenation conditions followed by protection with trifluoracetic anhydride, debenzylation and, finally treatment with 1N sodium hydroxide and Dowex resin (H^+ form) provided nectrisine **36**.



(a) mCPBA, MeOH; (b) TBAF, THF; (c) PPh_3, CBr_4; (d) TBSCl, imidazole, DMF; (e) Zn, EtOH/water; (f) $NaBH_4$; (g) Tf_2O; (h) NaN_3, DMF; (i) O_3, DCM; (j) TBAF; (k) Ac_2O; (l) Pd/Al_2O_3, H_2; (m) $(CF_3CO)_2O$; (n) $Pd(OH)_2$, H_2; (o) 1N NaOH (aq.), Dowex H^+

Scheme 26

An example of a synthesis which does not rely on carbohydrate precursors is the synthesis by Kim *et al.*[78] Their synthetic scheme started with diethyl tartrate derived aldehyde **53**. The synthesis was centred around the pyrrolidin-2-one intermediate **54**, which could be reduced to the corresponding amino alcohol **55** using Super Hydride®. From here, deprotection under acidic conditions and a purification using Dowex 1-X2 (OH^-) provided nectrisine, **scheme 27**.



(a) $LiEt_3BH$, THF; (b) 6N HCl, THF; Dowex 1-X2 (OH^-)

Scheme 27

1.6 Summary of Chapter 1

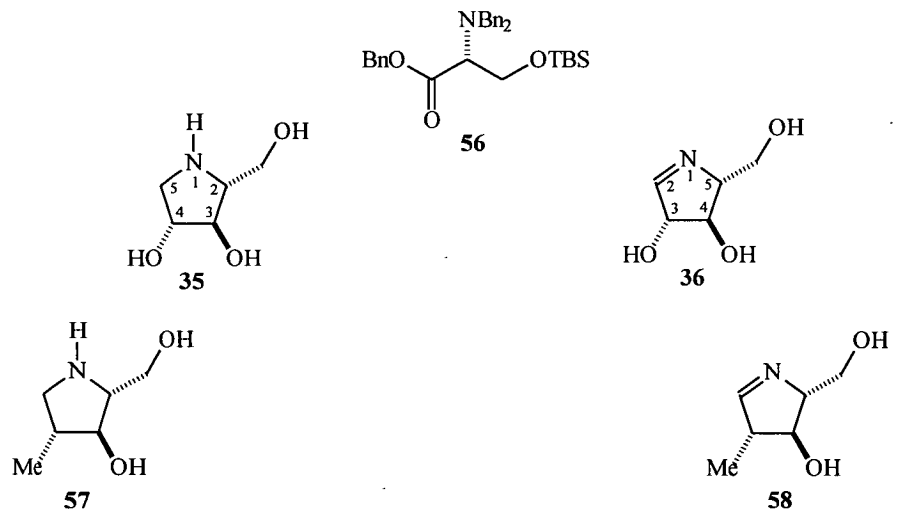
This chapter highlights the development and synthesis of α-amino aldehydes and of their reactions with nucleophiles. In particular, it contrasts the differing properties of *N*,*N*-dibenzyl protected aldehydes with their more classically *N*-carbamate protected counterparts. Latterly, an introduction to the synthetic targets DAB1 **35** and nectrisine **36** was made, along with examples of previous synthetic approaches to these natural products.

Chapter 2 : Results and Discussion Part 1

The Synthesis of Nectrisine

As explained in **chapter 1** we have been interested in the synthesis of polyhydroxylated pyrrolidines. We have also been interested in the use of *N,N*-dibenzyl protected serine aldehyde derivatives, of the type developed by Reetz **56**,[55] and of their applications in natural product synthesis. In particular our goal was to synthesise the biologically important iminosugars, nectrisine **36** and DAB1 **35**, **scheme 28**.

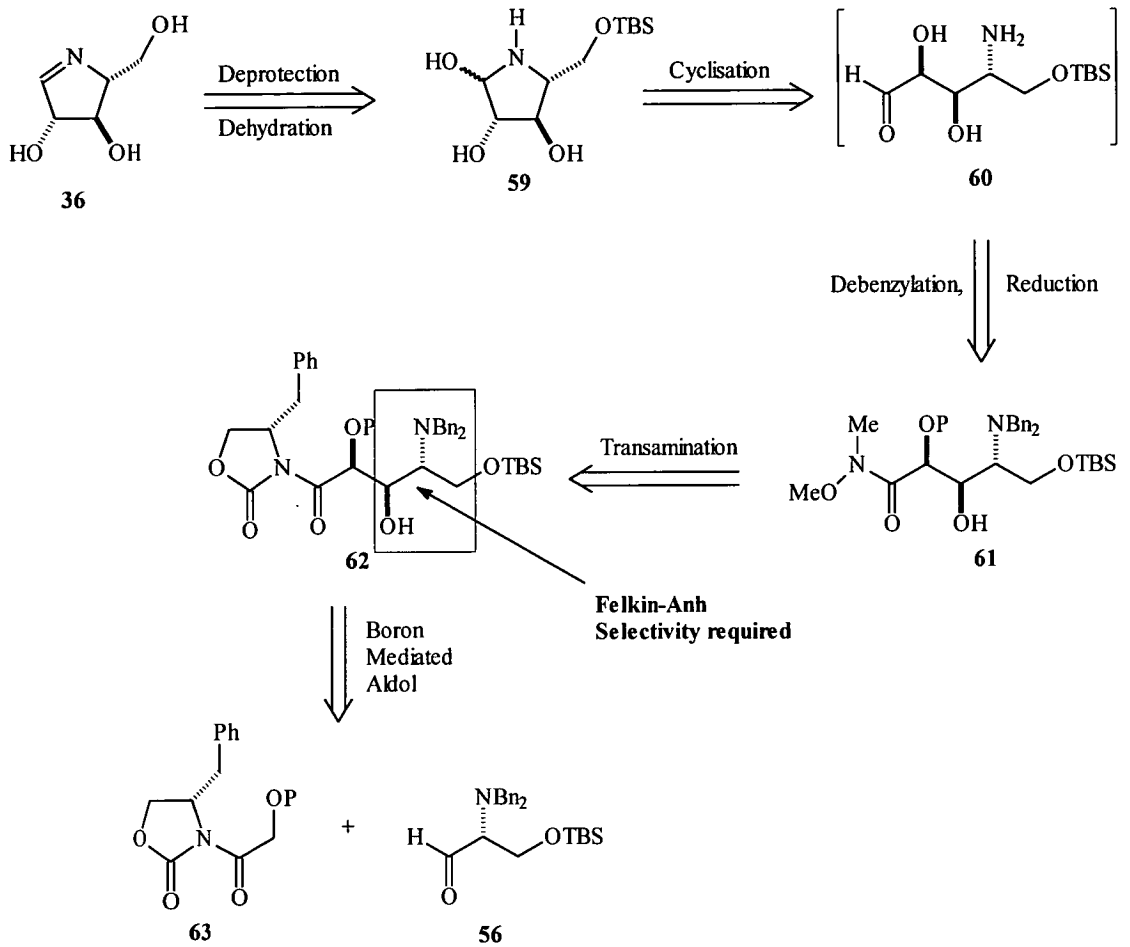
Underpinning the interest in the syntheses of these natural products was an interest in how *N,N*-dibenzyl protected serine aldehydes would behave in Evans type boron mediated aldol additions.[83] We wished to apply Evans methodology not only to the synthesis of these natural products, but also, to the synthesis of analogues of these molecules. In particular we sought to demonstrate the applicability of these aldehydes and judiciously selected aldol partners in synthesis. Our initial efforts were directed towards the synthesis of C_4Me DAB1 **57** and C_3Me nectrisine **58**. The methodology would then be expanded in order to construct many more analogues of these natural products and evaluate their biological activities.



Scheme 28

2.1 Retrosynthesis of Nectrisine

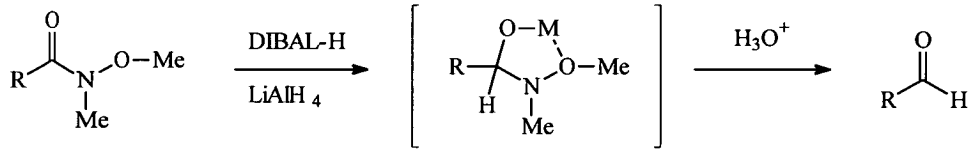
Our initial retrosynthetic analysis of nectrisine is shown in **scheme 29**. Our goal was to generate amino alcohol **59**. From here dehydration with concomitant deprotection would give nectrisine.



Scheme 29

We envisaged that the cyclic amino alcohol **59** would originate from amino aldehyde **60**. This amino aldehyde would in turn be generated from Weinreb amide **61**. After debenzylation we were confident that reduction of the amide with DIBAL-H or lithium aluminium hydride would be straightforward, and would selectively give the amino aldehyde with no over reduction. Our confidence was based on the fact that Weinreb[84] has shown that additions of nucleophiles to amides of this type

give no over addition products. The reason for this is due to the formation of a very stable metal chelated intermediate of the type **64**, which precludes further attack by nucleophiles. Hydrolysis of the intermediate on work-up would generate the desired aldehyde, **scheme 30**.



64

Scheme 30

Evans has shown that formation of Weinreb amides from corresponding oxazolidin-2-one imides is relatively straightforward and high yielding.[85] A boron mediated *syn* selective aldol reaction between Reetz's *N,N*-dibenzyl amino aldehyde **56** (derived from *D*-serine) and Evans type glycolate equivalent **63**, with suitable *O*-protection (probably some form of benzyl protecting group to allow deprotection concomitantly with the *N*-benzyl groups) would yield aldol adduct **62**.

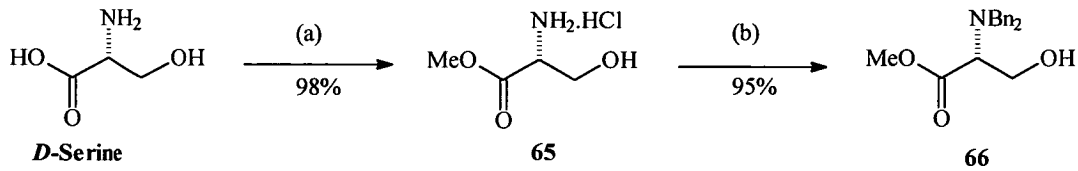
2.2 Synthesis of an *N,N*-dibenzyl Protected Serinal Derivative

We have been attracted to the *N,N*-dibenzyl protected serine aldehyde developed by Reetz for three main reasons. Firstly, Reetz and others have shown that additions to this aldehyde occur highly stereoselectively to give *anti* or Felkin-Anh type products,[11,17,22,53,57] in many cases almost exclusively. The aldehyde is stable to racemisation, unlike many other types of serine derived aldehyde (**chapter 1**) and can be stored for several days before use. Finally, we wished to address the utility of this aldehyde in synthesis, an area which, surprisingly, has not been exploited to date.

Reetz's synthesis provides the serine aldehyde in 51% overall yield with >99e.e., **scheme 5**.[55] The least efficient step was benzylation of the amine functionality with concomitant benzyl ester formation, which proceeded in mediocre yield. We wished to improve upon the overall efficiency of the synthesis thereby

making it more attractive for use in synthetic applications. The problem to address was, therefore, to increase the yield of nitrogen protection and ester formation.

We chose to synthesise *D*-serine methyl ester **65** followed by benzylation of the amine to give the desired ester **66**. The yield for this two step procedure was 93%, **scheme 31**, representing a significant increase on the tribenzyl protection protocol.[Ψ]

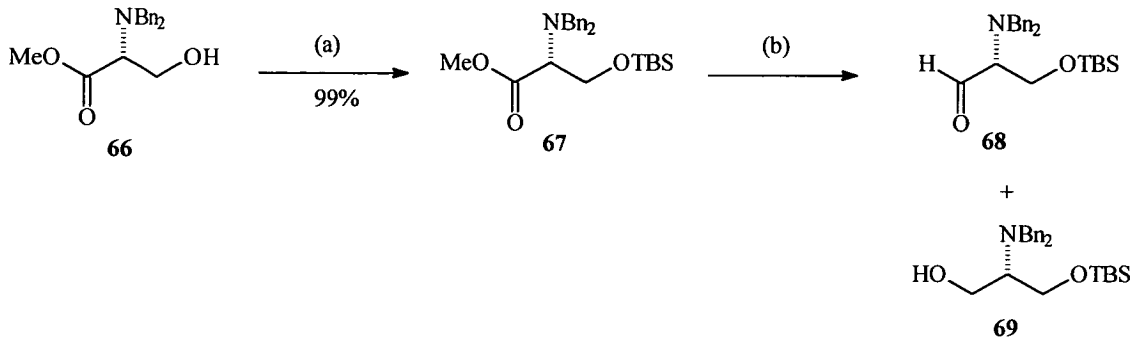


(a) MeOH, AcCl, reflux; (b) BnBr, K_2CO_3, MeCN

Scheme 31

We believed that silyl protection for the primary hydroxyl group as used by Reetz would offer suitable orthogonality with the benzyl groups, at the same time being easily removable at the end of the synthesis. We therefore opted for the *tert*-butyldimethylsilyl (TBS) group, which was conveniently introduced using TBSCl under basic conditions (imidazole) in DMF,[19,33a] **scheme 32**. At this stage we decided to attempt to reduce the ester functionality directly to the aldehyde moiety using DIBAL-H.[23,35] The reaction was attempted several times with varying temperatures in either toluene or THF (**Table 3**). Whilst aldehyde **68** was formed it was always accompanied by significant amounts of the over-reduced alcohol **69** and other impurities by t.l.c and ^{1}H NMR.

[Ψ] At the start of this project *D*-serine methyl ester.hydrochloride was not commercially available (unlike its enantiomer) thereby necessitating the need for its synthesis. However, the unnatural enantiomer is now available from Aldrich Chemical Company at reasonable cost (and less expensive than the natural enantiomer).



(a) TBSCl, Imidazole, DMF; (b) DIBAL-H

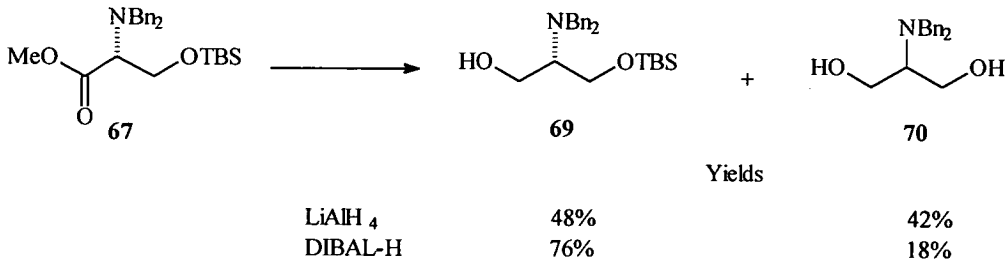
Scheme 32

Table 3

Attempt	Solvent	Temp (°C)	Aldehyde	Over Reduction
1	Toluene	-78	✓	✓
2	Toluene	-89	✓	✓
3	THF	-78	✓	✓
4	THF	-89	✓	✓
5	THF	-98	✓	✓

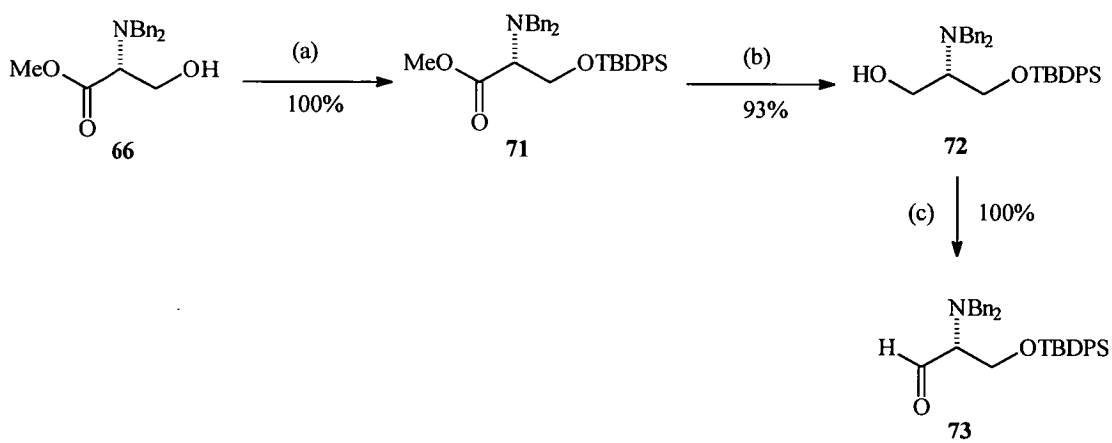
Moreover, the aldehyde was extremely unstable to silica gel (a 2D t.l.c analysis showed that the aldehyde decomposed to several different compounds after being in contact with silica gel for as little as 10 minutes) and it was therefore impossible to purify the crude aldehyde further.

Subsequently we decided to undertake a two step reduction/oxidation protocol (this being the method of choice for the majority α-amino aldehyde syntheses).[55,86] Reduction of the ester functionality to the primary alcohol was envisaged to be unproblematic, however, reduction with lithium aluminium hydride at -78 °C did not proceed cleanly. The sole impurity turned out to be the desilated *meso* diol **70**, which was formed in appreciable quantities (42%). Moreover, reduction with the milder DIBAL-H also gave rise to formation of the diol (18%), both reactions being carried out at -78 °C **scheme 33**.



Scheme 33

With the TBS protecting group proving to be too labile for our needs it was decided to introduce the less labile *tert*-butyldiphenylsilyl (TBDPS) group in an attempt to overcome these problems. Alcohol **66** was therefore protected as its TBDPS ether **71** in quantitative yield.[33b] Reduction of the ester using DIBAL-H at -78 °C gave the corresponding alcohol **72**, within 30 minutes, with excellent chemical yield and more importantly with no silyl group cleavage. From here a Swern oxidation[40] cleanly afforded the desired aldehyde **73** in excellent yield, **scheme 34**. The aldehyde was produced cleanly with no need for silica gel chromatography. This was fortunate, as this aldehyde was also extremely unstable to silica gel. The overall yield of 86%, from *D*-serine, means that this route represents a highly efficient synthesis of this synthetically important aldehyde.



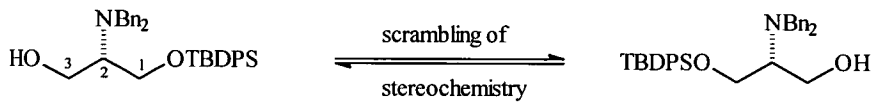
(a) TBDPSCl, imidazole, DMF; (b) DIBAL-H, toluene, -78 °C; (c) $(COCl)_2$, DMSO, Et_3N, DCM

Scheme 34

2.2.1 Enantiomeric Excess and Optical Stability of Aldehyde 73

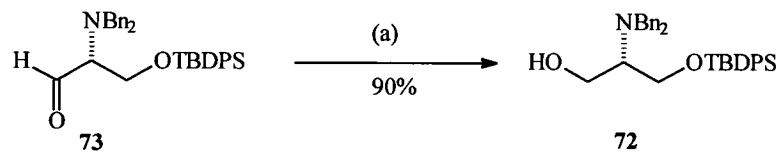
The enantiomeric excess of the aldehyde was to be measured by chiral HPLC (chiracel OD column). However, due to its instability when in contact with silica gel we decided to measure it indirectly *via* alcohol **72**. A racemic synthesis of alcohol **72** provided a means to optimise column conditions [hexane:propan-2-ol (19:1)] to give good baseline separation of the two enantiomer peaks. Freshly synthesised chiral non-racemic **72** was then analysed by HPLC under the same conditions. The optical purity of the alcohol was measured at >98% e.e.

We were concerned that alcohol **72** might racemise on storage as a result of silyl group migration (from C_1 to C_3), **scheme 35** (a phenomenon reported for a TBS protected serine amino alcohol).[37] As a result the enantiomeric excess of **72** was re-measured after storage (at –20 °C in a freezer) for a period of around one month. Gratifyingly, the alcohol's optical purity was still >98% e.e. as measured by chiral HPLC.



Scheme 35

The alcohol was then oxidised under Swern conditions to give aldehyde **73** in quantitative yield, **scheme 34**. We also wished to confirm that the aldehyde was not prone to racemisation. It was, therefore, stored in a refrigerator (4 °C) for a period of 48 hours, prior to being reduced back to alcohol **72**, with the aid of DIBAL-H, **scheme 36**.



73 **72**

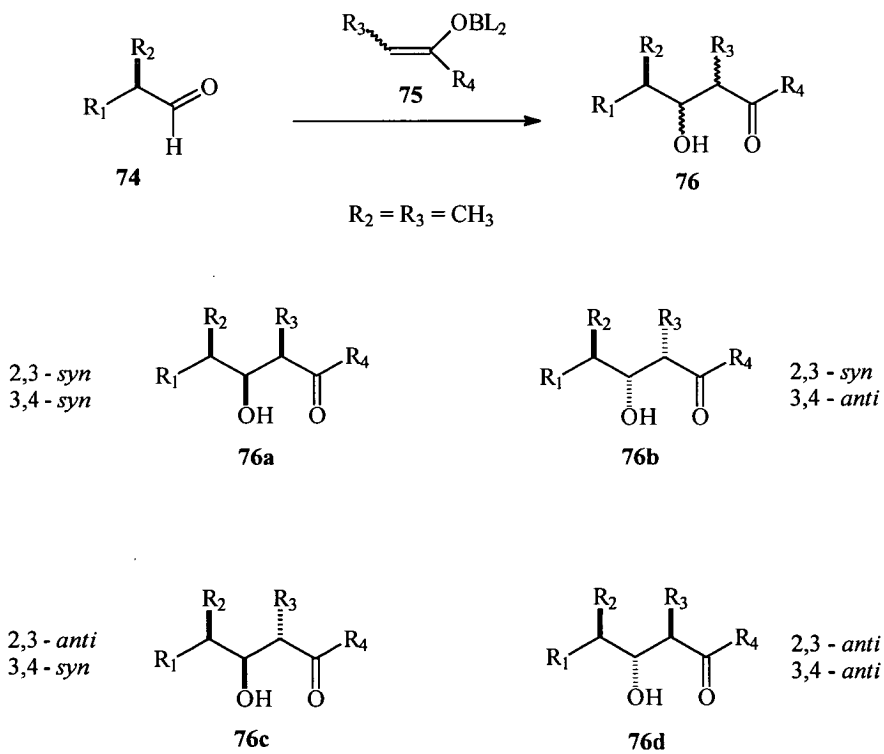
(a) DIBAL-H, toluene, -78°C

Scheme 36

The alcohol produced was subjected to chiral HPLC analysis, which showed that its optical purity was >98% e.e. Thus we can conclude that aldehyde **73** is stable with respect to racemisation, at least over a 48 hour storage period. In practice, however, the crude aldehyde was generally used in subsequent manipulations immediately following synthesis.

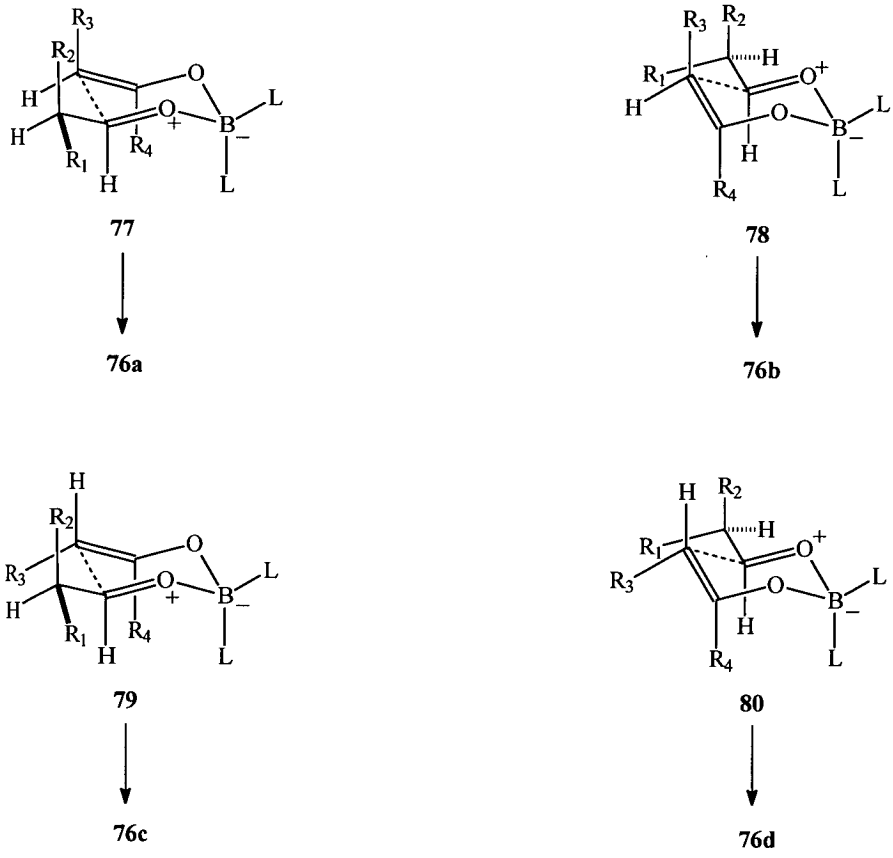
2.3 Asymmetric Boron Mediated Aldol Reactions

The venerable aldol reaction involves the reaction of an enolate and an aldehyde to form a new carbon-carbon bond. Recent intense and extensive studies on the reaction have covered a wide variety of reaction conditions and structural modifications,[87,88] and have disclosed that only a few sets of reaction parameters bring about high levels of stereoselection. In this regard, the use of chiral boron enolate reagents is notably successful, and will be discussed in this section.



Scheme 37

The aldol reaction creates two new chiral centres producing four possible stereoisomers **76a-d**, as exemplified for the reaction of a chiral aldehyde (R_2 = Me, in **74**) and the enolate (R_3 = Me in **75**) derived from an ethyl ketone, **scheme 37**. Two elements of control are necessary to achieve high stereoselectivity for this process. Assuming that the boron mediated aldol reaction proceeds through the accepted chair type cyclic transition state (Zimmerman-Traxler model),[89] then under kinetic control there are four possible reaction courses: (1) *Z*-enolate attacks the *Re* face of the aldehyde as shown in **scheme 38**, **77→76a**, (2) *Z*-enolate attacks the *Si* face of the aldehyde, **78→76b**, (3) *E*-enolate attacks *Re* face of aldehyde, **79→76c,** and (4) *E*-enolate attacks *Si* face of aldehyde, **80→76d**.[90 K]



Scheme 38

[K] Note: The aldehyde chain adopts a pseudo equatorial position in every case, thereby minimising 1,3-diaxial interactions

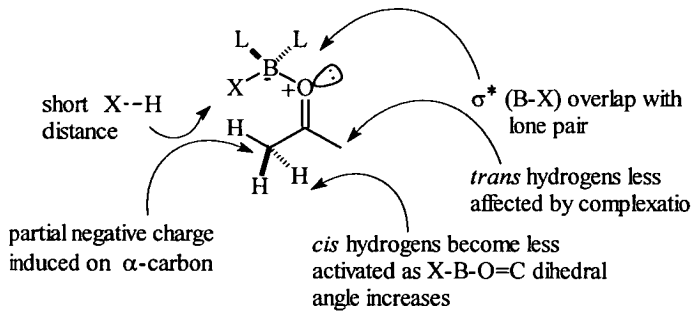
From this analogy it can be seen that (a) the enolate geometry directly affects the 2,3-stereochemistry of the products (i.e. *Z*-boron enolates give *syn* products and *E*-boron enolates give *anti* products)[83,91] and (b) the direction of enolate approach should determine the absolute configuration of the 3-hydroxy group, thereby providing control of the relative stereochemistry at the 3,4-positions.

2.3.1 Control of Enolate Geometry

As shown above, the relative stereochemistry of the kinetically controlled boron mediated aldol reaction is dependant on the geometry of the boron enolate (generated in the presence of a tertiary amine base). Thus, if the formation of the enolate could be controlled in order to preferentially form *Z* or *E* enolates the relative stereochemistry of an ensuing aldol reaction could be controlled precisely.

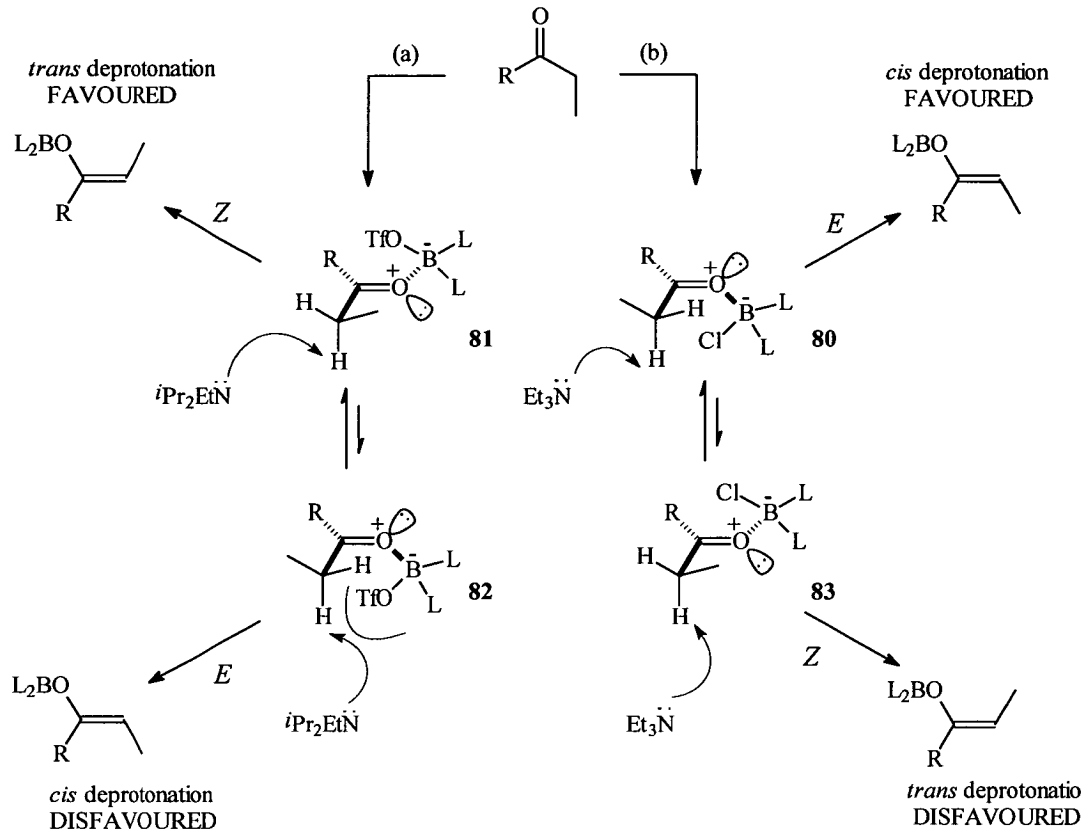
It turns out that steric requirements of the ligands (L) on the boron atom and the R_4 group on the enolate, **scheme 37**, can have a substantial effect on enolate geometry. L_2BX (X = leaving group) reagents with a variety of ligands and leaving groups have been used to generate either *E* or *Z*-boron enolates for a number of different substrates.[92] Brown has shown that L_2BX reagents with better leaving groups (e.g. mesylate or triflate) favour *Z*-enolates, whereas those with poorer leaving groups (e.g. chloride or bromide) favour *E*-enolates.[93]

Two hypotheses have been postulated in attempts to explain this selectivity. The hypothesis by Goodman and Paterson, formulated on the basis of molecular orbital calculations performed on $R_1R_2CO{\cdot}BH_2X$ complexes (X = F, Cl), shows that an anomeric effect between the uncomplexed lone pair on the carbonyl oxygen and the B-X antibonding orbital (σ^*) exists, causing the B-X bond to eclipse the C=O bond, **scheme 39**.[94,95]



Scheme 39

As can be seem in this acetone-boron complexed model, **scheme 39**, the halogen is directed toward one of the protons on the alkyl group to which it is adjacent or *cis* to. This has the effect of inducing a partial negative charge on this α-carbon, thereby, activating this alkyl group toward deprotonation by an unhindered base, such as, triethylamine. **Scheme 40** illustrates the formation of *Z* and *E*-enolates in accord with the above model.

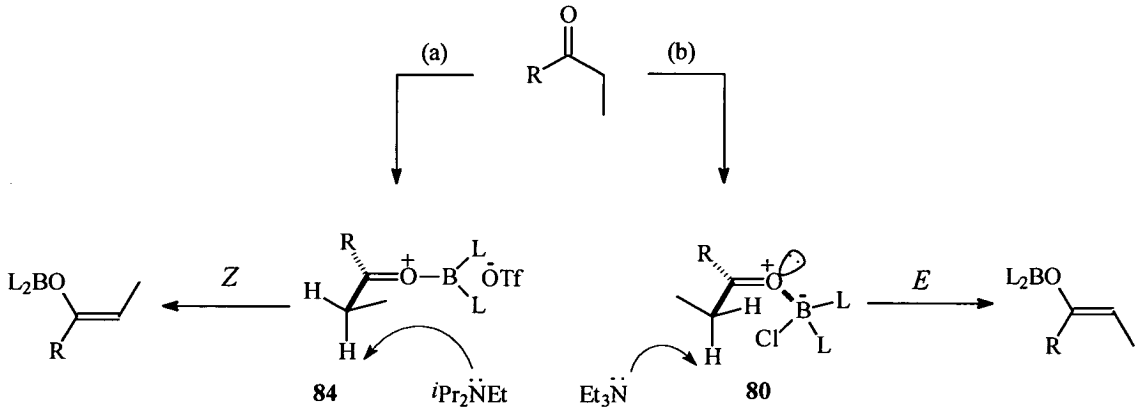


(a) L_2BOTf, $^iPr_2NEt$; (b) L_2BCl, Et_3N

Scheme 40

Thus, as can be seen in **scheme 40** sterically bulky triflate ligands hinder deprotonation of the alkyl group they are adjacent to, thereby allowing, deprotonation of the alkyl group which is distal or *trans* to the triflate group providing *Z*-enolates i.e. **81**→*Z*-enolate. In contrast, when chloride is the ligand, the electronic factors as described above mean that deprotonation of the adjacent alkyl group protons is now favoured giving *E*-enolates predominantly i.e. **80**→*E*-enolate.

Corey has proposed an alternate explanation in which the superior leaving group ability of the triflate group allows for the formation of a linear intermediate of the type **84**, **scheme 41**.[96]



(a) L_2BOTf, $^iPr_2NEt$; (b) L_2BCl, Et_3N

Scheme 41

In this hypothesis, a good leaving group allows deprotonation to give the *Z*-enolate *via* **84**. Poorer leaving groups ensure that the bent complex **80** predominates and, as above, deprotonation to give *E*-enolates takes place preferentially.

2.3.2 Evans Asymmetric Aldol Methodology

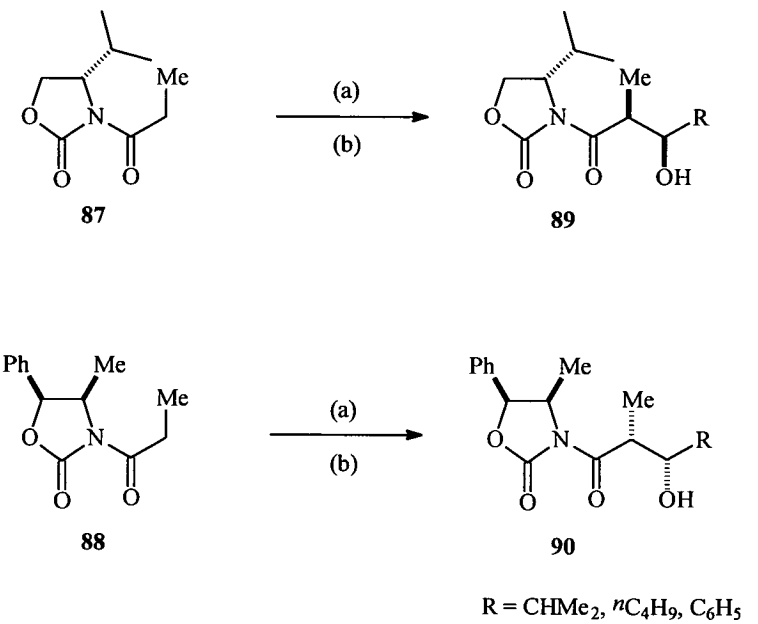
The boron enolate chemistry pioneered by Evans and utilising chiral *N*-acyloxazolidin-2-ones has become one of the most popular methods of generating aldol adducts, not least, because of the exceptionally high levels of diastereoselection that are possible.[83] The original work by Evans involved the pair of chiral oxazolidin-2-one auxiliaries **85** and **86** derived from commercially available *S*-valinol and (1*S*,2*R*)-norephedrine respectively, **scheme 42**.

85 **86**

Scheme 42

These oxazolidin-2-ones are conveniently acylated to give a variety of useful chiral acyl equivalents, which when reacted with either lithium amide bases or dibutyl boron triflate undergo highly stereoselective enolisation to form, almost exclusively, *Z*-enolates (*Z* : *E* selectivities >100:1).[83]

The corresponding *Z*-boron enolates, when reacted with achiral aldehydes, provide aldol adducts in which the 2,3-*syn* diastereoisomers are virtually the sole products. This is exemplified in the reaction of chiral propionyl equivalents **87** and **88**, which react with a variety of achiral aldehydes to give aldol adducts **89** and **90** as the sole products, in these cases enolate formation and the aldol reaction proceed with near perfect stereoselection (ca. 500:1), **scheme 43**.



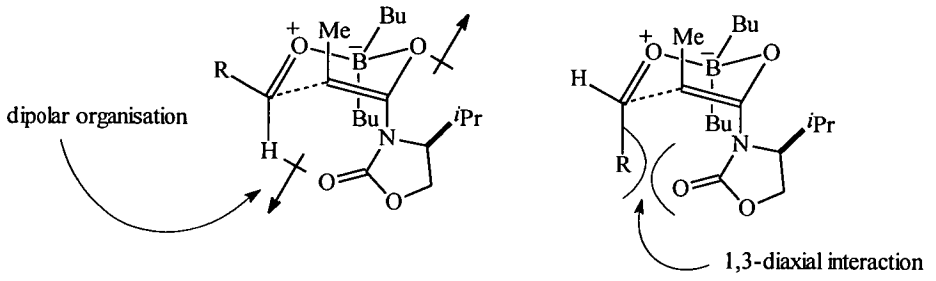
(a) Bu_2BOTf, $^iPr_2NEt$; (b) RCHO

Scheme 43

The above example serves to illustrate the fact that the easily produced *Z*-boron enolates of *N*-acyl oxazolidin-2-ones react with aldehydes to give *syn* aldol adducts exclusively. The absolute configuration of the two new chiral centres is controlled precisely by the chirality of the chiral auxiliary.

2.3.3 Double Asymmetric Induction in the Evans Aldol Reaction

In the above example we have seen that a chiral enolate is able to control the stereochemistry of the newly formed chiral centres in the aldol reaction. It is able to do this by discriminating between each face of the aldehyde it attacks. For example, if we take the *Z*-enolate derived from **87** and analyse the transition state (**91**) which leads to aldol adduct **89**, **scheme 44**, we can see that the *si* face of the aldehyde and the C_α *re* face of the enolate react to give the aldol adduct. It is intuitive from transition state **92** that the C_α *re* face of the enolate can not attack the *re* face of the aldehyde, due to unfavourable 1,3-diaxial interactions (as mentioned previously). Attack from the C_α *si* face of the enolate to either face of the aldehyde is also disfavoured, due to steric crowding over the C_α *si* face as a result of the substituent at the 4-position of the oxazolidin-2-one auxiliary. This selectivity means that *N*-acyl oxazolidin-2-one boron enolates are extremely useful in asymmetric synthesis.



91

***si* face of aldehyde & *re* face of enolate give aldol adduct 89**

92

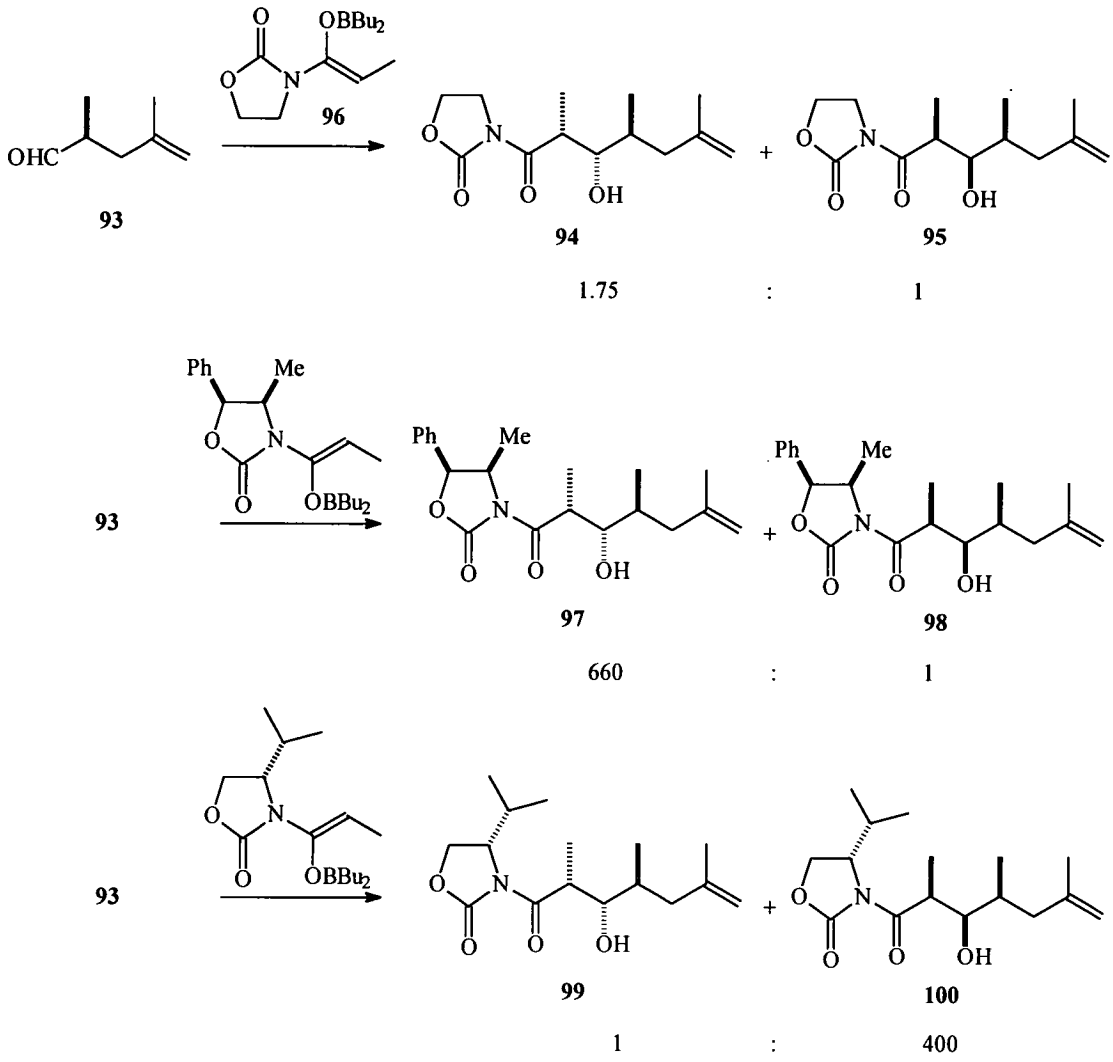
***re* face of aldehyde & *re* face of enolate**

Scheme 44

It follows that a chiral aldehyde should also be able to exert the same kind of diastereofacial selectivity.[97] Hence if a chiral enolate and a chiral aldehyde are reacted together then we can predict two possible outcomes: (1) the diastereofacial selectivity of both chiral partners is the same and aldol adducts with enhanced diatereoselectivity result (compared to outcomes from only one of the chiral species operating) and (2) the diastereofacial selectivites of the chiral partners is opposite

resulting in a diminished diastereoselectivity. The terms 'matched' and 'mismatched' pairs (respectively) have been introduced to described the effects of this double stereo induction.

An example which illustrates this effect, and also the power of the Evans chiral oxazolin-2-ones in synthesis is shown in **scheme 45**.[98] Here the chiral aldehyde **93** exerts only a modest level of diastereoinduction, providing aldol adducts **94** & **95** in a ratio of 1.75:1. The 'matched' reaction is shown directly below providing aldol adducts **97** & **98** with a drastically increased diastereomeric ratio of 660:1. The 'mismatched' reaction gives aldol adducts **99** & **100** in a ratio of 1:400. This auxiliary has the opposite sense of stereoinduction compared to the aldehyde, but the stereoinductive capability of the chiral oxazolidin-2-one is much greater than that of the aldehyde, thus, over turning the inductive capability of the aldehyde to give the 'mismatched' diastereomer with an excellent level of diastereoselectivity.

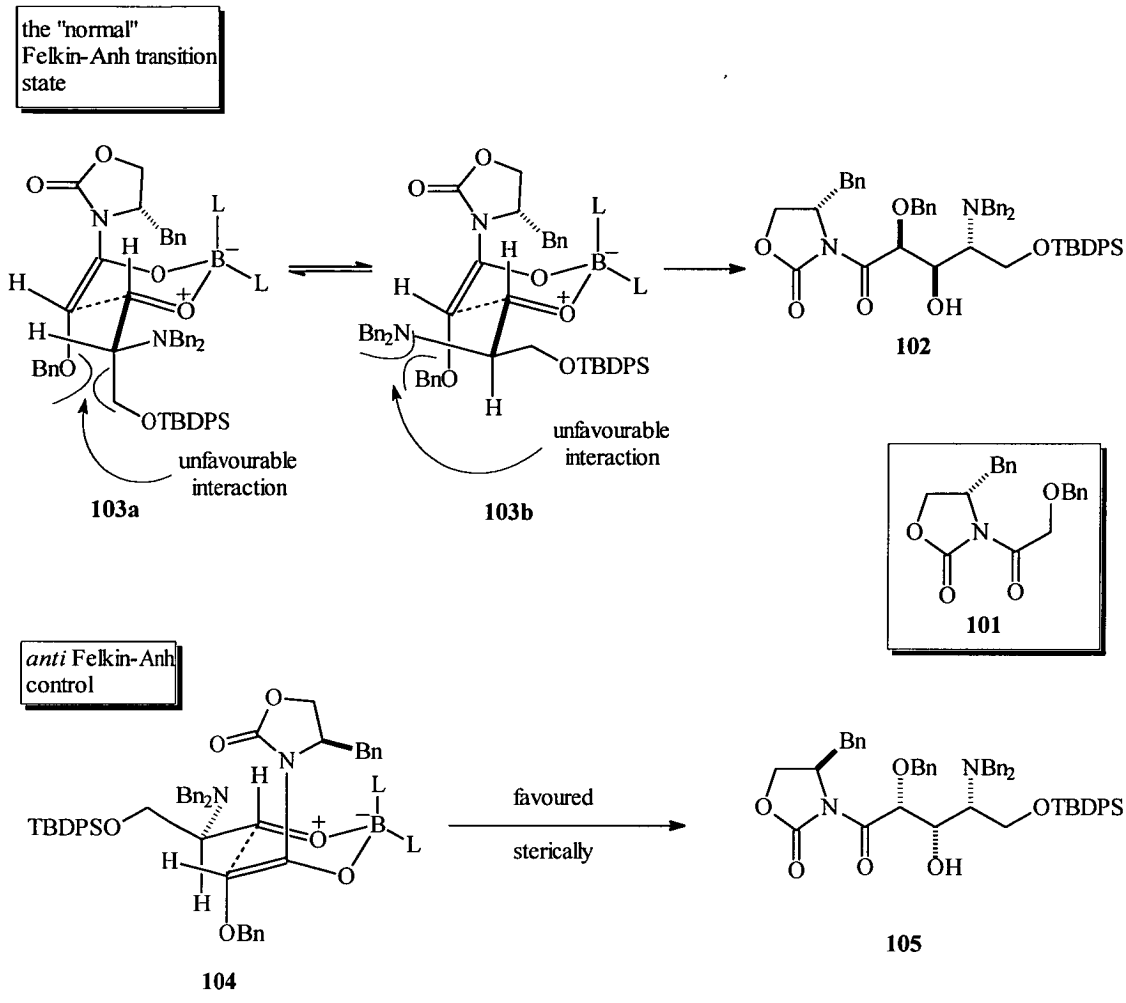


Scheme 45

The chiral auxiliaries can subsequently be removed under a variety of conditions, for example, transesterification (LiOBn,[99] $Ti(OBn)_4$,[100] BrMgOMe[101]), transamination ($Me_2AlN(OR)R$),[85] hydrolysis (LiOH[100] or LiOOH[102]) or reduction ($LiBH_4$).[85] They are then easily recovered and reused.

2.4 Application of Evans Aldol Methodology in Nectrisine Synthesis

As depicted in our retrosynthetic analysis of nectrisine, **scheme 29**, we believed an aldol reaction between the enolate of **101** (= **63**, with P = Bn) and our *N,N*-dibenzylamino serine aldehyde **73** would generate the required stereochemistry found in **102**, as a result of Felkin-Anh type attack by the enolate. Arguments by Roush[103] concerning aldol reactions of α-methyl chiral aldehydes and achiral propionate enolates prompted us to examine the transition states for the ensuing reaction between the enolate of **101** and aldehyde **73**, **scheme 46**. Thus transition state **103a** represents the Felkin-Anh transition state: the medium sized group (taken as the $CH_2OTBDPS$ group) is aligned *syn* to the carbonyl, and the developing C–C bond is *anti* to the largest substituent (taken as the NBn_2 group) thus giving the desired aldol adduct **102**. Rotation about α-carbon–carbonyl carbon bond provides transtition state **103b** which is also somewhat destabilised by steric interactions between NBn_2 and OBn. Roush's arguments suggest that the interactions shown might be serious enough to destabilise this transition state relative to the reaction of the enantiomeric enolate of *ent*-**101** and **73** which proceeds through sterically favoured transition state **104** to give aldol adduct **105**.



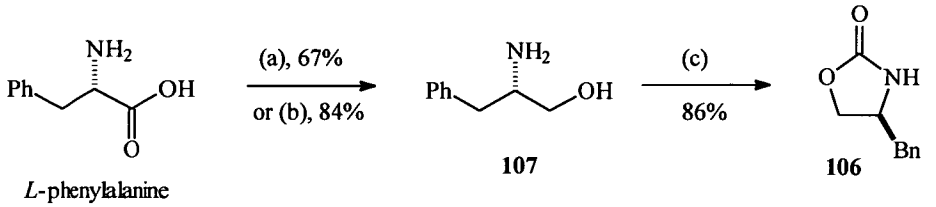
Scheme 46

We were therefore concerned that interactions of the type predicted by Roush might mean that the aldol reaction to give aldol adduct **102** would be less favourable than the reaction between aldehyde **73** and the enolate of *ent*-**101** which leads to aldol adduct **105**. We feared that diminished yields and/or diastereoselectivities might result. Nevertheless, we decided to investigate whether or not these arguments would hold in our case.

The glycolate equivalent **101** has been used by several others[104] and found to be highly effective in subsequent aldol reactions. We were interested in this *O*-benzyl protected glycolate equivalent as we believed that the *O*-benzyl protecting group would be easily removable under the same conditions as the *N*-benzyl groups, thereby, minimising the number of deprotection steps required in the synthesis of

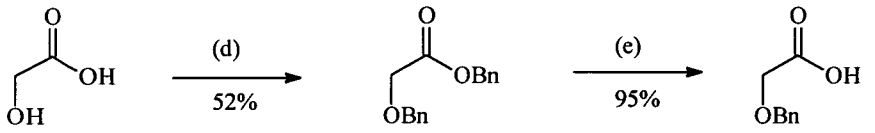
nectrisine. In fact, **101** was readily synthesised from *L*-phenylalanine as shown in **scheme 47**. Thus, the oxazolidinone **106** was synthesised *via* condensation of diethyl carbonate with *S*-phenyalaninol **107**. This was itself derived from *L*-phenylalanine *via* reduction of the carboxylic acid functionality under conditions described by Evans[83d] utilising borane·dimethylsulfide complex or by the method described by Meyers[105] using sodium borohydride. Benzyloxyacetic acid **109** was prepared either from glycolic acid, through dibenzylation to give ester **108** followed by hydrogenation over ammonium acetate poisoned 10% Pd/C to give the desired acid, or by reaction of the sodium salt of benzyl alcohol with bromo acetic acid. Acid **109** was then condensed with the lithiated oxazolidinone *via* its unsymmetrical anhydride, derived from pivaloyl chloride (trimethylacetyl chloride) to provide **101**.

Oxazolidinone Synthesis:



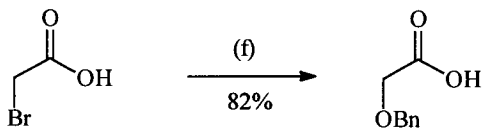
L-phenylalanine **107** **106**

Benzyloxyacetic acid Synthesis:



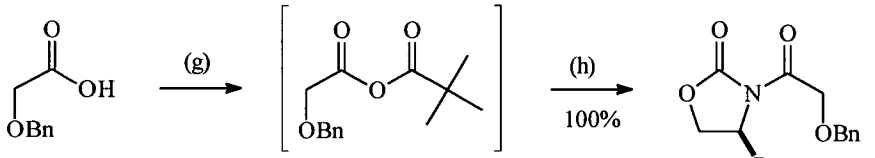
glycolic acid **108** **109**

or



bromoacetic acid **109**

Then:



109 **101**

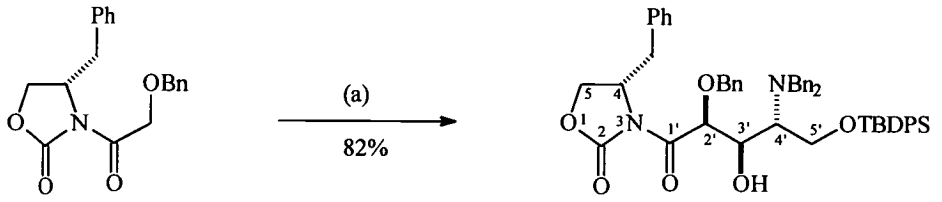
(a) $BF_3 \bullet Et_2O$, $BH_3 \bullet DMS$, THF; (b) $NaBH_4$, I_2, THF, reflux, then $KOH_{(aq)}$; (c) K_2CO_3, diethyl carbonate; (d) BnBr, K_2CO_3, MeCN; (e) NH_4OAc, 10% Pd/C, H_2, MeOH; (f) BnOH, NaH, THF; (g) Et_3N, pivaloyl chloride, THF; (h) **106**, BuLi, THF -78 °C

Scheme 47

In our hands, large scale syntheses were best carried out using the Meyers reduction route and synthesis of benzyloxy acetic acid *via* bromoacetic acid.

With glycolate equivalent **101** in hand we decided to attempt the aldol reaction that we believed would give aldol adduct **102**. Enolisation of **101** under

standard conditions (Bu_2BOTf, Et_3N; -78 °C→0 °C)[104] followed by addition of aldehyde **73** gave an aldol adduct (which was tentatively, at this stage, assigned the structure **102**) as a single diastereomer (by 600 MHz ^1H NMR) in excellent yield. The 2',3'-*syn* stereochemistry of the aldol adduct was easily determined *via* ^1H NMR coupling constants (the $C_{2'}$ proton was a clear doublet at 5.41 ppm with a coupling constant of 2.6 Hz).[ξ]



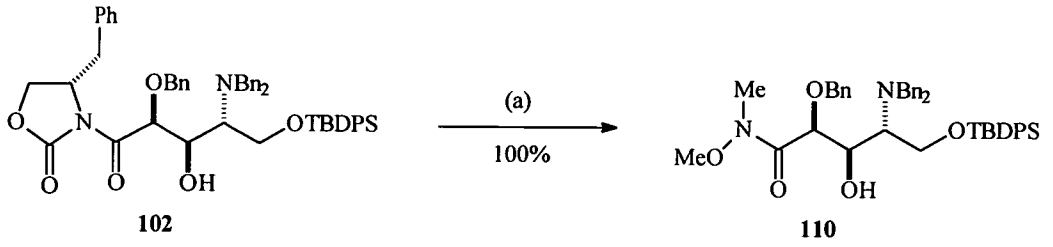
101 **102**

(a) Et_3N, Bu_2BOTf, DCM, -78 °C→0 °C (1.25 hours), recooled to -78 °C; **73** in DCM, -78 °C

Scheme 48

The Weinreb amide **110**, **scheme 49** was then synthesised using *N,O*-dimethylhydroxylamine•hydrochloride and trimethylaluminium. To our surprise, up to 40 equivalents of the hydroxylamine salt was required for the reaction to proceed to completion. This is in direct contrast to the 3 equivalents quoted by Evans[106] to effect the same kind of transformation. The hydroxylamine salt is extremely hygroscopic and we hypothesised that the presence of water might be hindering completion of the reaction. On thorough drying of the commercially obtained salt (several days in a vacuum oven), we subsequently found that only 15 equivalents were necessary to carry out the same transformation, in quantitative yield.

[ξ] In solution a β-hydroxy ketone exists in a chair-like conformation as a result of intramolecular hydrogen bonding. The bulk long chain adopts a more favoured equatorial position and the dihedral angle between α and β protons is ~60° for the *syn* arrangement and ~180° for the *anti* arrangement. As a result, the Karplus relationship predicts vicinal coupling constants to be ~3-5Hz for *syn* and ~7-12Hz for *anti* aldol adducts.

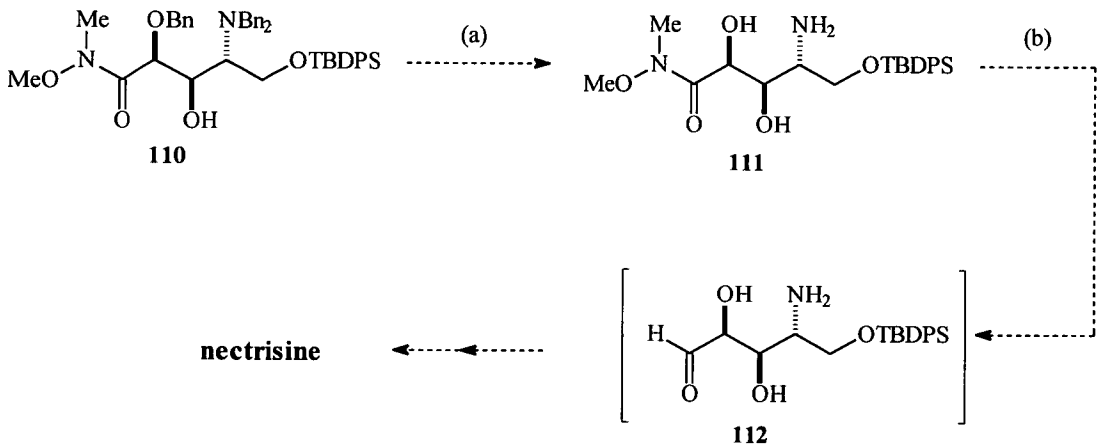


(a) (MeO)N(Me)H•HCl, $AlMe_3$, -30 °C→room temp.→-30 °C, THF; **102** in THF, -30 °C→room temp.

Scheme 49

2.4.1 An Unpredicted Cyclisation

Our initial synthetic scheme required the removal of the *N*-benzyl protecting groups with, we believed, concomitant *O*-benzyl deprotection to give the amine **111**. A DIBAL-H reduction of the Weinreb amide we predicted would give amino aldehyde **112** as an intermediate *en route* to nectrisine, **scheme 50**.

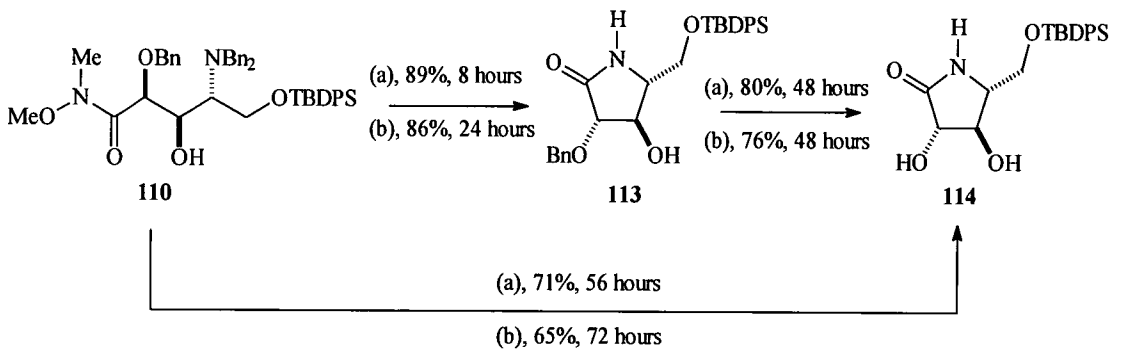


(a) Pd/C, H_2; (b) DIBAL-H

Scheme 50

However, exposure of Weinreb amide **110** to a hydrogen atmosphere in the presence of 10% Pd/C led to formation not of the desired amino diol **111**, but to the lactam **114**, **scheme 51**. The reaction typically took 3 days to generate **114** in good

yield. Furthermore, analysis of the reaction course by t.l.c showed that the starting material was consumed within around 24 hours, in conjunction with the formation of a new lower R_f spot. Interception of the reaction at this stage provided the intermediate **113**, the *O*-benzyl protected lactam. The *O*-benzyl protecting group then took a further 48 hours to undergo complete cleavage to provide the de-benzylated lactam **114**. This result is somewhat surprising as normally *O*-benzyl groups should be cleaved at a faster rate than *N*-benzyl groups.[107] Switching to the more active Pearlman's catalyst ($Pd(OH)_2/C$) did not affect the reaction time with respect to *O*-benzyl cleavage, however, *N*-benzyl cleavage was significantly faster, being complete within around 8 hours.

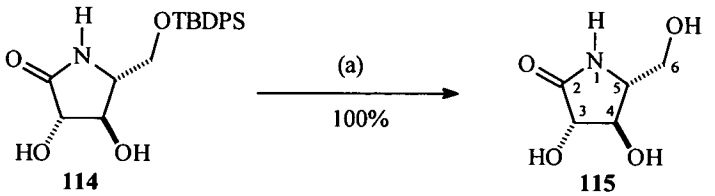


(a) 20% $Pd(OH)_2/C$, H_2, MeOH; (b) 10% Pd/C, H_2, MeOH

Scheme 51

We were initially surprised by the outcome of this reaction as we hadn't expected (MeO)N(Me) to be a particularly good leaving group. However, we recognised that the lactam **114** might also represent an important intermediate in the synthesis of nectrisine. In fact, by judicious choice of reduction conditions we believed it would be possible to access oxidation states corresponding to the amino alcohol and the amine. This unexpected cyclisation to give lactam **114**, therefore, proved to be quite fortuitous.

Furthermore, an opportunity to verify the stereochemistry of the asymmetric centres formed in the aldol reaction became possible at this stage. Thus, lactam **114** was deprotected in the presence of hydrofluoric acid to afford the known lactam **115**[72c,108], **scheme 52**.



(a) HF (48% in H_2O), MeCN/THF

Scheme 52

A comparison with ^1H NMR literature data is shown in **Table 4**, showing good correlation with **115**, proving that the correct stereochemistry had been assigned to aldol adduct **102**.

Table 4

Source	MHz	C_3H	C_4H	C_5H	C_6H_A	C_6H_B
Ref 72c	300	4.21	3.91	3.36	3.51	3.70
Ref 108	250	4.33	4.03	3.45-3.50	3.64	3.81
115	250	4.31	4.00	3.45	3.61	3.79
	Mult. /	*J* (Hz)				
Ref 72c		d, 8.0	t, 8.0	ddd, 8.0, 5.0, 4.0	dd, 12.5, 5.0	dd, 12.5, 4.0
Ref 108		d, 8.0	dd~t, 7.5	m	dd, 12.2, 4.9	dd, 12.2. 2.8
115		d, 8.0	dd~t, 8.0	ddd, 7.9, 4.9, 3.1	dd, 12.2, 4.9	dd, 12.2, 3.1

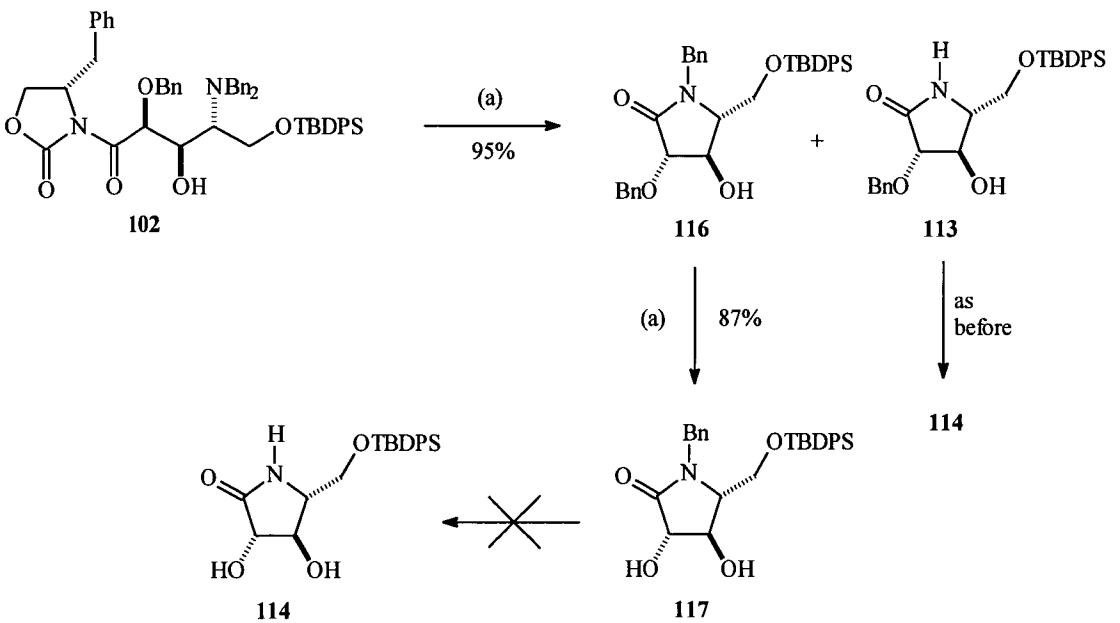
Note: the data for reference 72c consistently shows a deviation of around 0.1 ppm, compared to reference 108 and **115** which is possibly due to a referencing error.

Furthermore, the optical rotation [α_D] and melting point (mp) of **115** was also in excellent agreement with both literature compounds, **Table 5**.

Table 5

Source	α_D	mp
Ref 72c	+15.2 (c=0.40, H_2O)	135-138°C
Ref 108	+14.7 (c=0.58, D_2O)	130-133°C
115	+14.2 (c=0.40, D_2O)	131-133°C

With the potential of lactam **114** proving to be very high, we decided to attempt to shorten the number of steps required for its synthesis. We therefore, attempted a hydrogenation reaction with aldol adduct **102** as the substrate, thus potentially circumventing the need for transamination to the Weinreb amide **110**. Unfortunately, as we feared, the oxazolidin-2-one moiety was a far better leaving group than (MeO)N(Me) and cyclisation took place to give a mixture of lactam **116** along with **113** (essentially a 50:50 mixture). Prolonged reaction times with 20% $Pd(OH)_2/C$ provided lactam **117** (after 3 days) but never any trace of the desired lactam **114** (up to 21 days reaction time),[109] **scheme 53**.



(a) 20% $Pd(OH)_2/C$, H_2, MeOH

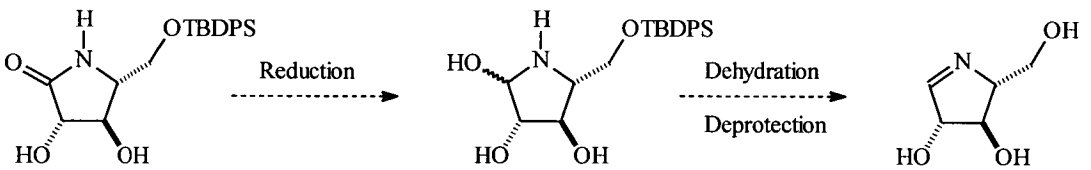
Scheme 53

As a result of this we decided to persevere with the two step protocol of transamination followed by hydrogenolysis, which was still a very efficient synthesis

of this lactam, as opposed to attempting further debenzylation protocols with regard to aldol adduct **102**.

2.4.2 Reduction of Lactam to Amino Alcohol

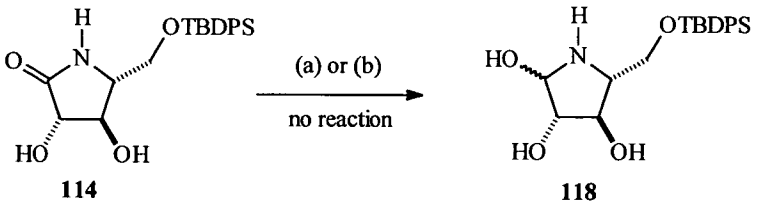
With recourse to our retrosynthetic analysis of nectrisine it was apparent that the next step in our synthesis should be a reduction of this lactam to provide the amino alcohol oxidation state **118**, as shown in **scheme 54**. This would then be followed by a dehydration step, which ideally might also cause deprotection of the silyl ether. A possibility for this transformation might involve the use of concentrated hydrochloric acid to enable dehydration, with concomitant silyl deprotection (TBDPS deprotection has been achieved in the presence of 6N HCl).[108]



114 **118** **36**

Scheme 54

We, therefore, attempted the reduction of lactam **114** with DIBAL-H at -78 °C, however, no reaction took place. Warming the reaction mixture to 0 °C had no effect on the reaction outcome. The same reaction was attempted using the reagent lithiumtriethylborohydride (Super Hydride®) which we thought might be more effectual. However, a similar outcome resulted, **scheme 55**. We did not wish to resort to using more powerful reducing agents, such as, lithium aluminium hydride or borane as we (**section 3.1.1**) and others[75] have shown that these are effective in reducing such lactams to the corresponding amines.



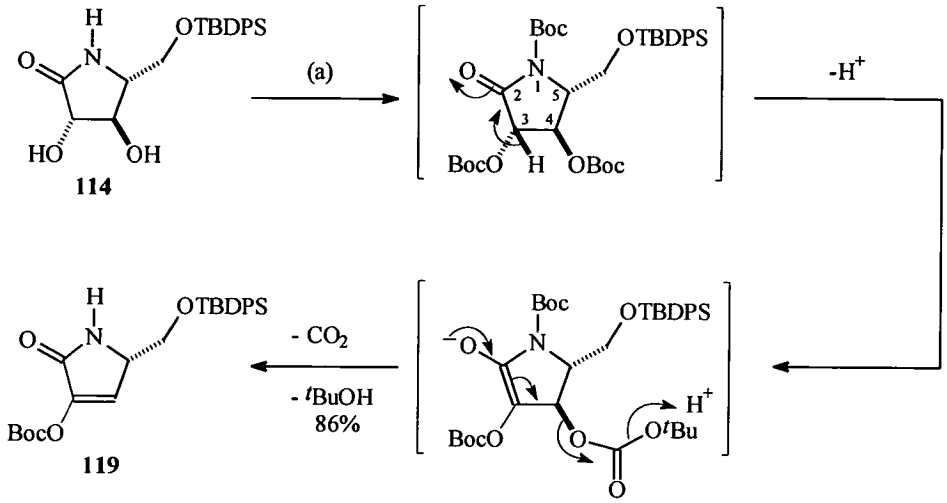
114 **118**

(a) DIBAL-H, toluene, -78 °C→0 °C; (b) $LiEt_3BH$, THF, -78 °C→0 °C

Scheme 55

We attributed this lack of reactivity to the carbonyl group being of relatively low electrophilicity, as a result we believed that increasing the electrophilicity of the carbonyl group would allow reduction to the target oxidation state. Several other groups have used this strategy to effect similar reductions.[110] The simplest way to increase the electrophilicity of the carbonyl group in these cases was to introduce an electron-withdrawing protecting group (such as a carbamate) to the nitrogen atom.

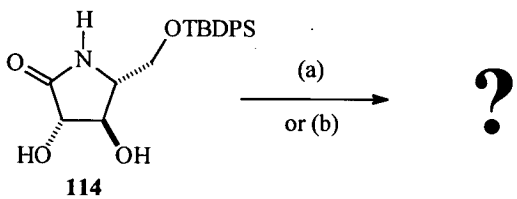
We, initially, attempted to introduce a Boc protecting group on to the nitrogen atom of lactam **114**. Unfortunately, whilst *N*-Boc protection in this case was possible, using forcing conditions (several equivalents of Boc_2 and Et_3N), the more nucleophilic hydroxyl groups were preferentially Boc protected. This had the effect of increasing the acidity of the proton at the C_3 position and as a result the dehydro compound **119** was formed in excellent yield, as shown in **scheme 56**.



(a) Boc_2O, Et_3N, DMAP, DCM

Scheme 56

We therefore surmised that preprotection of the secondary hydroxyl groups would be a wise course of action. Strangely, our initial attempts to introduce MOM or acetyl protecting groups (under standard conditions)[111] to the hydroxyl groups proved fruitless, with complex mixtures (by t.l.c.) being produced. As a result no attempt was made to purify these reaction mixtures further.

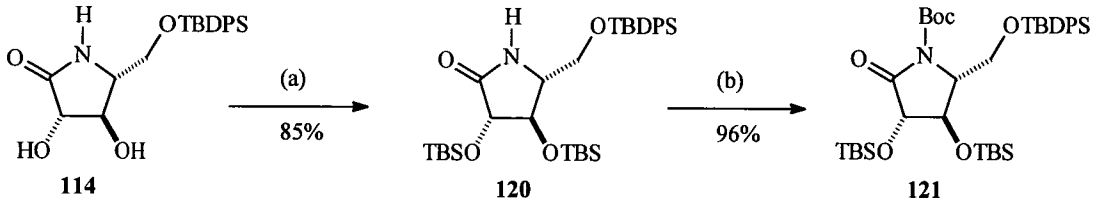


(a) MOMCl, $^{i}Pr_2NEt$, DCM; (b) Ac_2O, pyridine, DMAP, DCM

Scheme 57

Our initial strategy behind introduction of either MOM or acetate protecting groups was that they would be easily removable (along with the Boc group and the TBDPS group) under the acidic conditions we had chosen to effect the dehydration

of the amino alcohol oxidation state to give the imine. Thus as an alternative we next attempted to introduce further silicon protection, in the form of TBS groups. Reaction of lactam **114** with *tert*-butyldimethyltrifluoromethanesulfonate (TBSOTf) under mildly basic conditions (2,6-lutidine)[112] cleanly afford the di-TBS protected compound **120** in excellent yield. It was now possible to cleanly introduce the desired electron-withdrawing Boc group to the molecule to provide **121** in almost quantitative yield, **scheme 58**.



(a) TBSOTf, 2,6-lutidine, DCM; (b) Boc_2O, Et_3N, DMAP, DCM

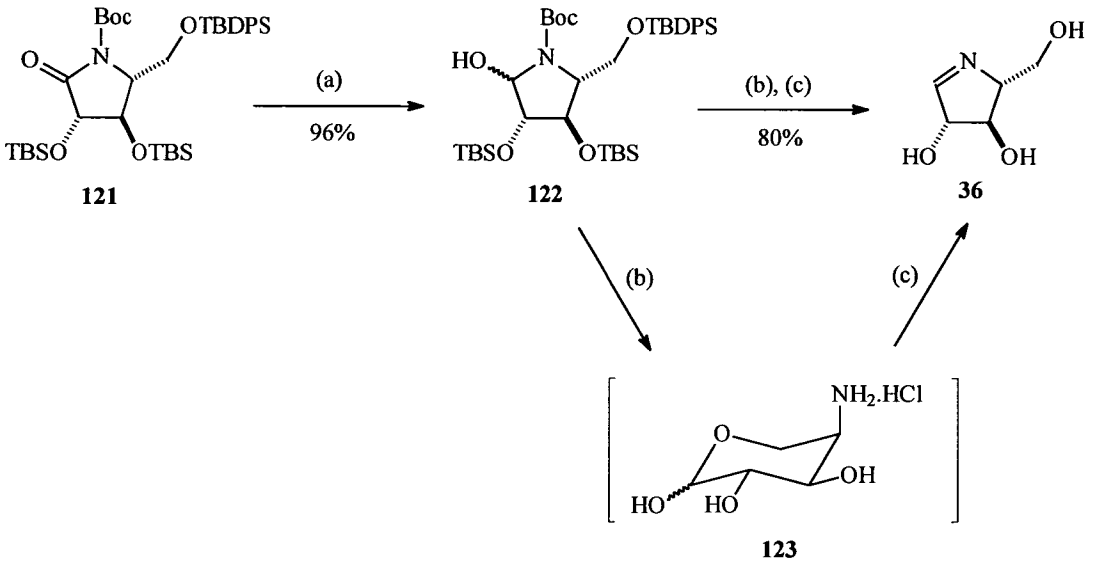
Scheme 58

Reduction of compound **121** with Super Hydride®, proceeded cleanly to afford the amino alcohol **122** in excellent chemical yield, **scheme 59**. Thus, introduction of the electron-withdrawing Boc group to the nitrogen atom appears to have had the desired effect of increasing the electrophilicity of the carbonyl group carbon, thereby, allowing reduction to occur at a much faster rate (only 15 minutes required for complete reduction), compared to the attempted reduction of **114**.

2.4.3 Imine Formation

A solution of **122** in THF was subsequently treated with 6N HCl. After heating to 50 °C for 2 hours the protecting groups were readily cleaved. Analysis by t.l.c. showed the presence of an extremely polar component, along with several high R_f impurities which were easily removed by silica gel column chromatography (eluent: 5:3:1 $CHCl_3$:MeOH:NH_3 (28% aqueous)). The polar component was eluted along with a large quantity of salts. This compound was not characterised. It was,

however, attributed to be intermediate **123**, by analogy with a reported synthesis of nectrisine, which also utilised an acidic deprotection protocol in the last step of the synthesis.[72f,108] A final purification by ion-exchange chromatography (Dowex 1X2 (OH^- form)) provided nectrisine **36** in excellent yield, **scheme 59**.



(a) $LiEt_3BH$, THF, -78 °C, 15 mins; (b) 6N HCl, THF; (c) Dowex 1X2 (OH^-), eluent = H_2O

Scheme 59

The correct stereochemistry of the 3 asymmetric centres had already been confirmed by the synthesis of lactam **115**. However, we wished to further confirm the identity **36** was indeed nectrisine by comparison with available literature physical data.[77,78] Unfortunately, it appears that literature ^1H NMR spectra were run on low field instruments and as a result the signals for nectrisine's protons were recorded as a multiplet[78] or not reported at all[77] (with the exception of the imino proton). ^{13}C NMR data was, however, in very close agreement with compound **36**, **Table 6**, as were optical rotations which are shown in **Table 7**, along with data for the imino proton.

Table 6

Source	MHz	δ_C (ppm)				
Ref 77	67.8	171.0	83.9	78.8	77.4	61.8
Ref 78	?	170.7	83.6	78.5	77.0	61.4
36	62.9	170.5	83.4	78.2	76.8	61.2

Note: Deviations in ppm between all 3 spectra are of a similar magnitude for each signal suggesting that the deviation is perhaps due to referencing differences

Table 7

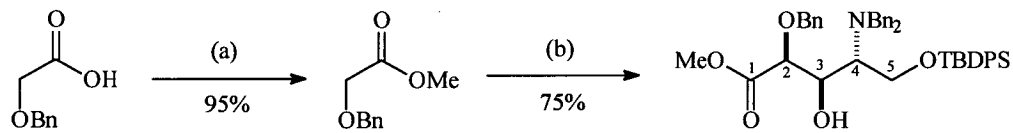
Source	MHz	Imino proton	α_D
Ref 77	270	7.71 (d, *J* 2.0 Hz)	+22.0 (c=0.6, H_2O)
Ref 78	?	7.67 (brs)	+21.8 (c=0.6, H_2O)
36	600	7.72 (d, *J* 2.4 Hz)	+21.0 (c=0.4, H_2O)

On the basis of the above comparisons and also with literature comparisons of lactam **115** we were confident that we had successfully synthesised nectrisine. With an overall yield of 31% (12 steps) this represents a highly efficient synthesis of this biologically important natural product.

2.5 Examination of the Aldol Reaction Leading to Adduct 102

With the success of the synthesis of nectrisine we wished to take a closer look at the aldol reaction which gave adduct **102**. In particular we wished to ascertain whether this was a 'matched' or a 'mismatched' process. In order to do this we surmised that an aldol reaction between a suitable achiral glycolate enolate equivalent and our chiral non-racemic aldehyde **73** would provide us with the sense and magnitude of the diastereoinduction that aldehyde **73** exerts in the aldol reaction.

Therefore, the *Z*-boron enolate of benzyloxy acetic acid methyl ester **124** was reacted with aldehyde **73**. The ensuing aldol reaction proceeded cleanly to afford a *syn* aldol adduct (the C_2 proton was a clear doublet at 4.38 ppm with a *syn* coupling constant of 1.4 Hz) (tentatively assigned as **125**) in good yield as a single diastereomer, **scheme 60**.

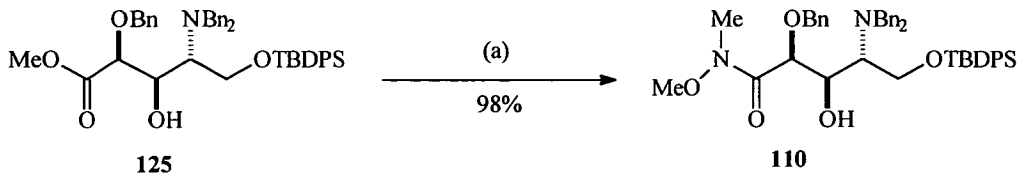


109 **124** **125**

(a) MeOH, AcCl, reflux; (b) Bu_2BOTf, $^iPr_2NEt$, diethyl ether, -78 °C, 90 mins; **73** in diethyl ether, -78 °C

Scheme 60

Aldol adduct **125** subsequently underwent transamination with *N,O*-dimethylhydroxylamine•HCl/$AlMe_3$ to cleanly afford Weinreb amide **110**, **scheme 61**, in excellent yield within 18 hours. The Weinreb amide was identical in all respects (NMR, IR, $[\alpha]_D$, R_f) to the amide synthesised from aldol adduct **102**.



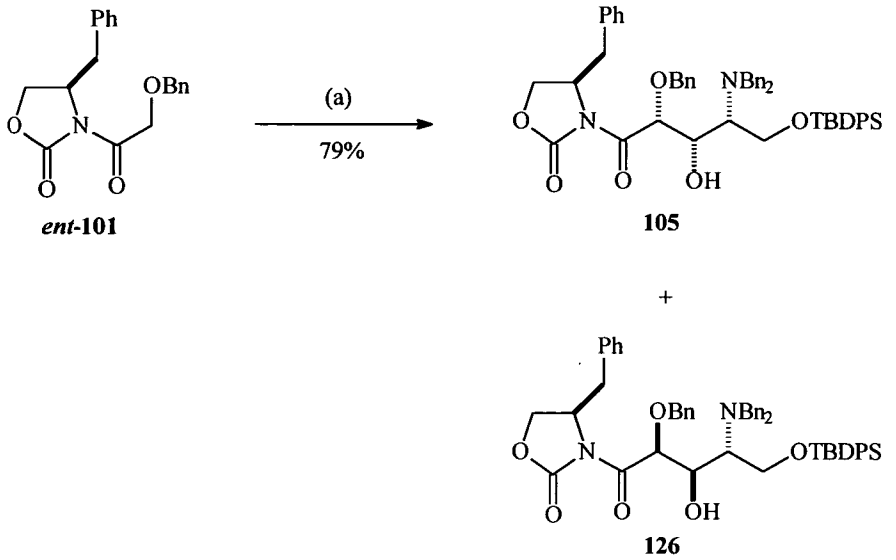
125 **110**

(a) (MeO)N(Me)H•HCl, $AlMe_3$, THF, -30 °C→room temp.→-30 °C, THF; **125**, THF -30 °C→room temp.

Scheme 61

This shows that the stereoinductive capability of the aldehyde alone is enough to provide the desired Felkin-Anh product. It is therefore probable that since a single diastereomer was obtained in the reaction of chiral enolate **101** with **73**, then it is very likely that this reaction represents a 'matched' case.

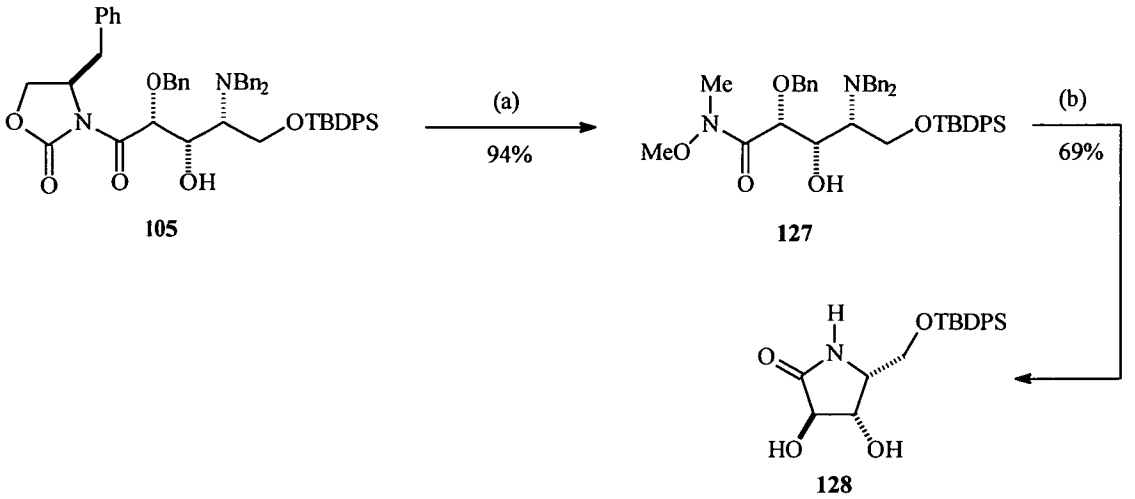
In order to fully confirm that this was the case, the same aldol reaction was attempted with the *Z*-boron enolate of *ent*-**101** (synthesised in an analogous manner to **101**, from *D*-phenylalanine). The reaction yielded a mixture of *syn* aldol adducts **105** (C_2 proton a clear doublet at 5.22 ppm J = 2.4 Hz) and **126** (C_2 proton a clear doublet at 5.46 ppm J = 1.7 Hz) (with a 9:1 diastereomeric ratio) which were readily separable by column chromatography, **scheme 62**. This, therefore, must represent a 'mismatched case', with the chiral auxiliary having the opposite sense of stereoinduction to the aldehyde. This reaction once again shows the power of the Evans *N*-acyl oxazolidin-2-one chiral auxiliaries, here being able to overturn the stereoinductive capability of aldehyde **73** in order to give the aldol adduct **105** preferentially.



(a) Bu_2BOTf, Et_3N, DCM, -78 °C→0 °C, 1.25 hours, recooled to -78 °C; **73** in DCM at -78 °C

Scheme 62

The aldol adduct **126** was readily transformed into Weinreb amide **110** (quantitative yield, identical in all respects to the Weinreb amide synthesised from **102**) and aldol adduct **105** was transformed into its Weinreb amide **127**, **scheme 63**. The Weinreb amide **127** was subsequently transformed into lactam **128**, proving that this aldol process would give rise to a different stereoisomeric form of nectrisine, although such investigations are beyond the scope of this project.

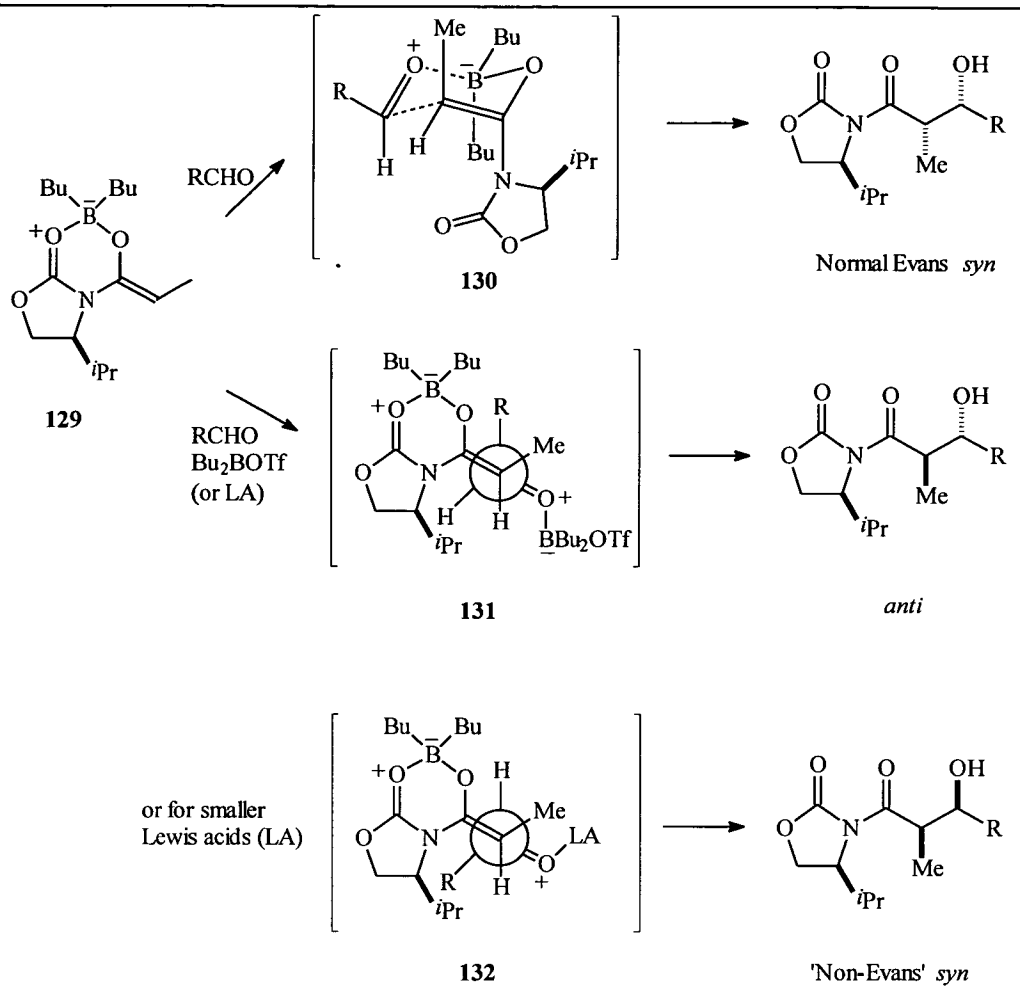


(a) (MeO)N(Me)H•HCl, $AlMe_3$, THF, -30 °C→room temp.→-30 °C; **125**, THF -30 °C→room temp.; (b) $Pd(OH)_2/C$, H_2, MeOH

Scheme 63

2.5.1 Formation of Anti and 'Non-Evans' Syn Aldol Adducts

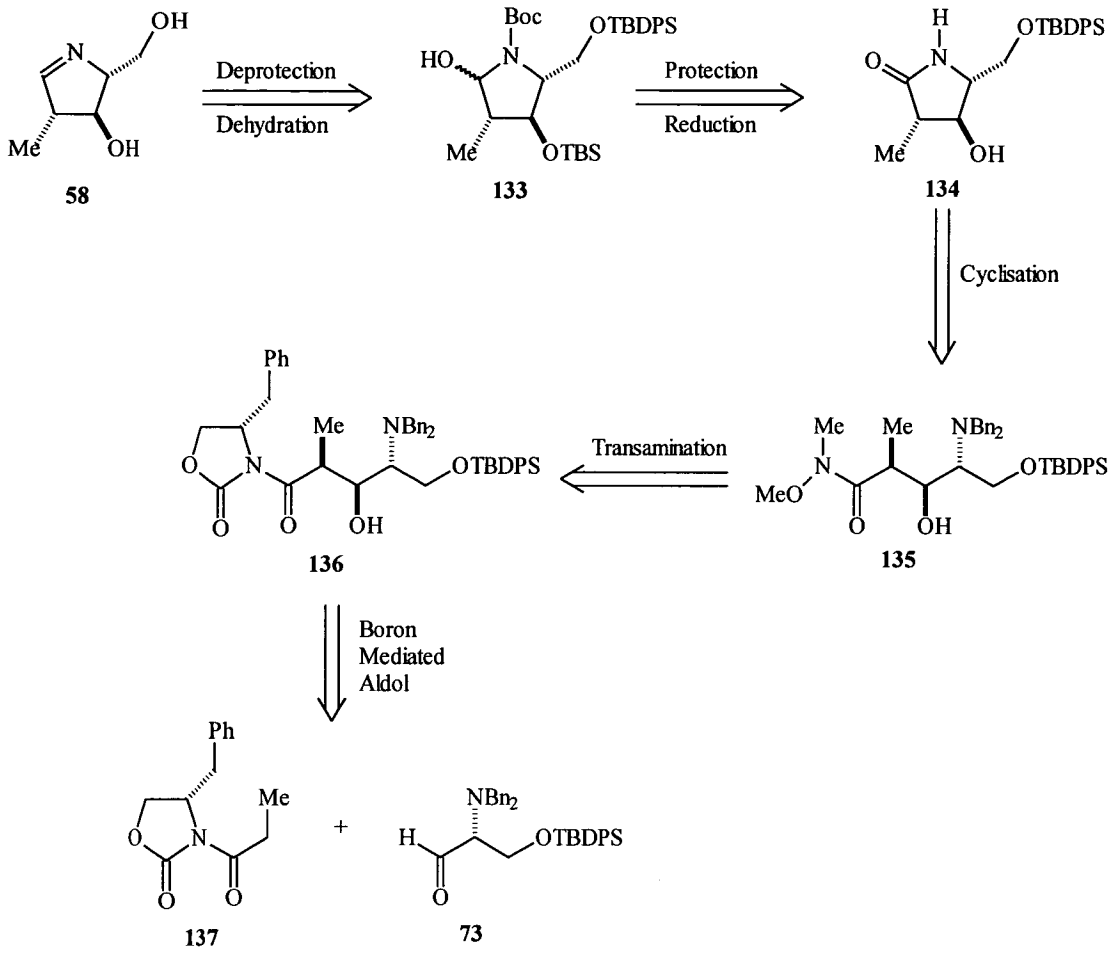
To obtain such high diastereoselectivities in our aldol process, which gave adduct **102**, it was necessary to strictly adhere to the published protocol for formation of the required *syn* aldol adducts (1.2 equivalents of dibutylboron triflate and 1.3 equivalents of base). Although time did not permit its investigation it is worth noting the results obtained by Heathcock,[113] who was able to generate *anti* and 'non-Evans' *syn* aldol adducts by increasing the number of equivalents of Lewis acid used. A mechanistic explanation is shown in **scheme 64** with the reaction of propionate *Z*-enolate **129** and an aldehyde RCHO. The normal 'closed' transition state (Zimmerman-Traxler) **130** is shown along with the proposed 'open' transition state **131** which leads to *anti* aldol adducts. The open transition state **132** leads to 'non Evans' *syn* aldol adducts and is favoured for smaller Lewis acids (e.g. $SnCl_4$ or $TiCl_4$).[114]



Scheme 64

2.6 Synthesis of a C_3Me Analogue of Nectrisine

In keeping with our initial aims we wished to expand on the synthesis of the natural product nectrisine, by synthesising it's C_3Me analogue **58**. A retrosynthetic analysis using the methodology developed in the synthesis of nectrisine (i.e. cyclisation to lactam followed by reduction and dehydration) is shown in **scheme 65**. Thus, we believed that a propionate aldol reaction between aldehyde **73** and the chiral propionate equivalent **137** would provide aldol adduct **136** as a single diastereomer, in analogy with the highly successful glycolate aldol reaction giving **102**. From then on we believed that the chemistry undertaken for the synthesis of nectrisine would be directly applicable to its C_3Me analogue.

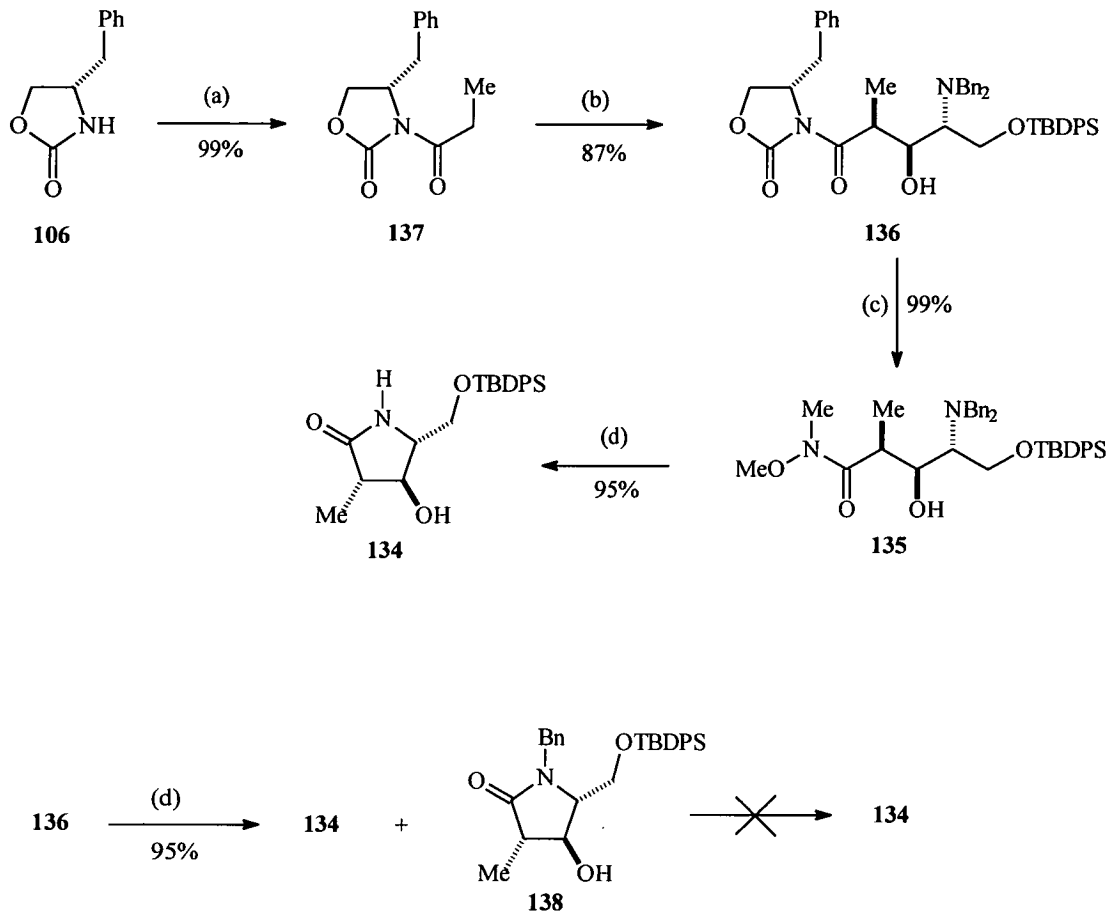


Scheme 65

The chiral propionate equivalent **137** was synthesised straightforwardly from the lithiated oxazolidin-2-one **106** which was condensed with freshly distilled propionyl chloride to provide **137** in virtually quantitative yield.

As anticipated, the propionate aldol reaction proceeded smoothly to provide aldol adduct **136** in excellent yield as a single diastereoisomer. Transamination gave the Weinreb amide **135** in virtually quantitative yield, although once again a vast excess of the aluminium amide was necessary to drive the reaction to completion. Hydrogenation of the Weinreb amide provided the desired lactam **134** in excellent yield, within 12 hours. We also attempted hydrogenation of propionate aldol adduct **136** which as it turned out mirrored the attempt made with the glycolate aldol adduct

in that a mixture of the desired lactam **134** and the *N*-benzyl protected lactam **138** (approx. 50:50 ratio) was formed. This is summarised in **scheme 66**.

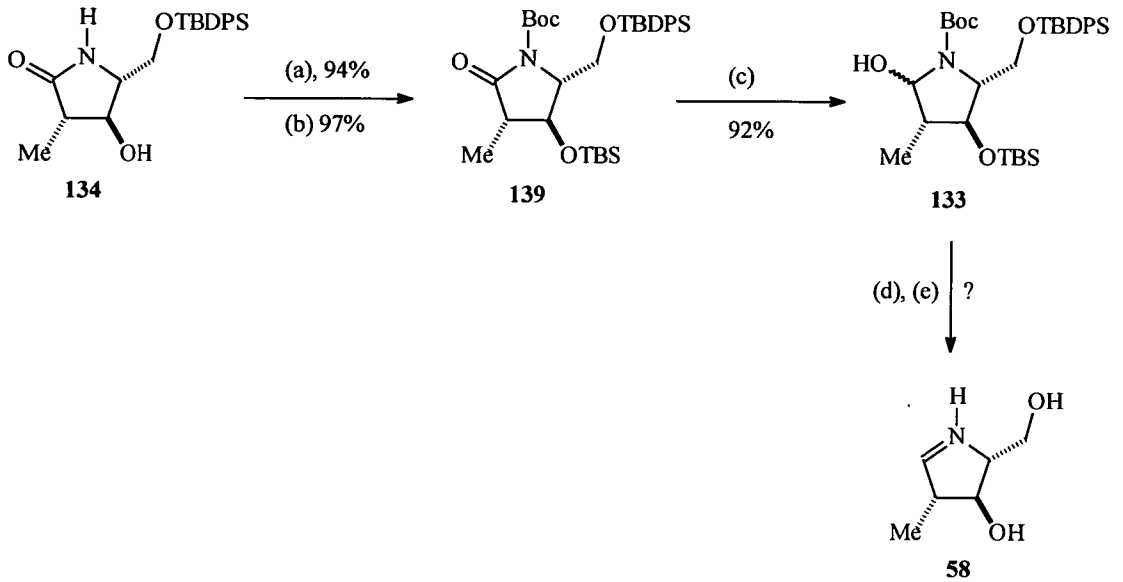


(a) BuLi, THF; C_2H_5COCl; (b) Bu_2BOTf, Et_3N, DCM, 0 °C, (15 mins), cooled to -78 °C; **73** in DCM at -78 °C; (c) (MeO)N(Me)H•HCl, $AlMe_3$, THF, -30 °C→room temp.→-30 °C; **132**, THF -30 °C→room temp.; (d) 10% Pd/C, H_2, MeOH

Scheme 66

With the lactam **134** in hand we were able to apply the same reaction parameters that afforded nectrisine to the synthesis of its C_3Me analogue. Thus, protection of the secondary hydroxyl group as its TBS ether and Boc protection of the nitrogen atom afforded fully protected lactam **139**. From here reduction with Super Hydride® provided **133**, which was subsequently treated with 6N HCl, thus effecting the removal of all of the protecting groups (as observed by t.l.c.). A final

ion-exchange purification using Dowex 1X2 (OH^-) failed to provide the C_3Me analogue of nectrisine, no material was recovered from the ion-exchange resin, **scheme 67**, and unfortunately time did not permit further attempts to isolate the desired imine.



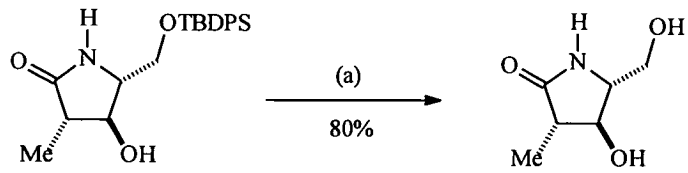
(a) TBSOTf, 2,6-lutidine, DCM; (b) Boc_2O, Et_3N, DMAP, DCM; (c) $LiEt_3BH$, THF, -78 °C; (d) 6N HCl, THF; (e) Dowex 1X2 (OH^-)

Scheme 67

2.6.1 Deprotection of Lactam 134

It occurred to us that deprotected lactams **115** and **140** might also be of biological interest. The deprotection of lactam **114** to give **115** is documented in **section 2.4.1** through a protocol involving hydrofluoric acid. We, therefore, deprotected lactam **134** using *tert*-butylammoniumfluoride (TBAF)[φ] (another popular desilylating agent)[115] which is far less toxic than hydrofluoric acid. The deprotection proceeded cleanly affording lactam **140**, **scheme 68** in excellent yield.

[φ] The deprotection of lactam **114** was also attempted using TBAF, however, purification of the deprotected lactam **115** was found to be much more tedious than with the HF protocol.



134 **140**

(a) TBAF, THF, 1 min

Scheme 68

2.7 Summary of Chapter 2

We have successfully completed the synthesis of the natural product nectrisine **36** with an excellent overall chemical yield (31%, 12 steps). The aldol reaction that generated the desired stereochemical relationships between both the hydroxyl and amino groups was thoroughly investigated and found to be the 'matched' case. The 'mismatched' reaction was found to be capable of generating the opposite *syn* aldol adduct with excellent diastereoselectivity. Finally, the synthesis of the C_3Me analogue of nectrisine **58** was undertaken. Disappointingly, the synthesis failed to provide the desired compound at the final stage. We are confident, however, that if more time had been available this situation would have been rectified and the synthesis of **58** would have been achieved.

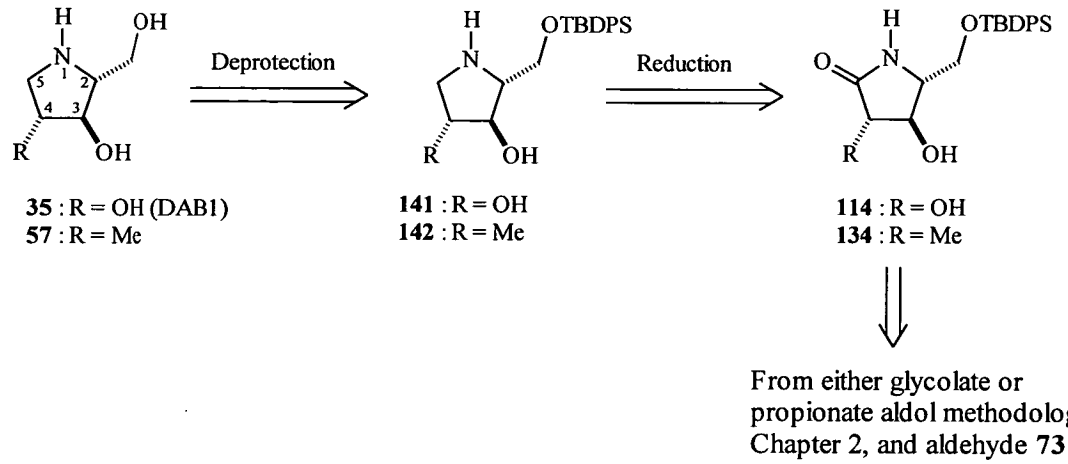
Chapter 3 : Results and Discussion Part 2

The Synthesis of 1,4-Dideoxy-1,4-imino-*D*-arabinitol (DAB1)

3.1 Application of Lactam Methodology to DAB1 Synthesis

As discussed in **chapter 2**, it soon became clear that lactam **114**, was potentially, a very useful intermediate in the synthesis of pyrrolidine type iminosugars. The powerful aldol methodology used in connection with aldehyde **73** allowed the construction of this lactam in a highly stereocontrolled manner. Subsequent selective reductions of this lactam should, therefore, allow access to either the amino alcohol (as in nectrisine synthesis) or to the amine oxidation state.

Chapter 2 details the reduction of lactam **114** to the amino alcohol oxidation state with subsequent elaboration of this amino alcohol to the desired natural product. Our attention was then, unsurprisingly, focused on the possibility that reduction of lactam **114** to the amine would permit the efficacious synthesis of our second synthetic target DAB1 **35**. A brief retrosynthetic analysis, **scheme 67**, shows our proposed synthetic strategy, which we also wished to expand to include the synthesis of the C_4Me analogue of DAB1 from lactam **134**.



35 : R = OH (DAB1)
57 : R = Me

141 : R = OH
142 : R = Me

114 : R = OH
134 : R = Me

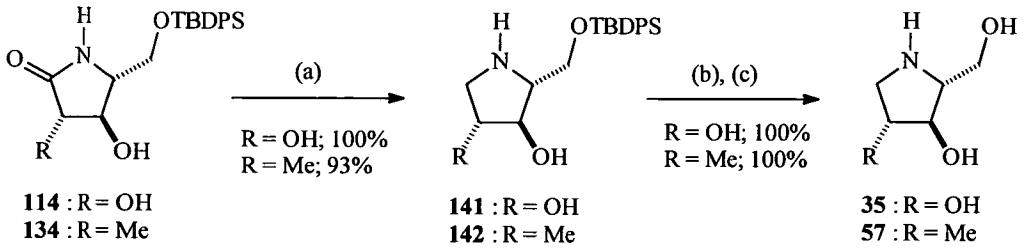
Scheme 68

3.1.1 Forward Synthesis of DAB1 and its C_4Me Analogue

The synthesis of DAB1 effectively starts from lactam **114**, the synthesis of which required 8 synthetic steps (50% overall yield) and is discussed in **chapter 2**. We believed that the use of borane[75b] or lithium aluminium hydride[75a] would allow reduction of the carbonyl group to provide the amine. Reduction of such lactams with these reagents has been documented in the literature.

Treatment of lactam **114** with borane•THF complex provided the corresponding amine in quantitative yield. All that remained was a final deprotection. This was initially attempted with TBAF in THF; however, it proved impossible to purify the natural product, as it appeared to co-run with TBAF on silica gel. Ion-exchange chromatography was also unsuccessful in purifying the reaction mixture. We therefore ventured to deprotect amine **141** using hydrofluoric acid (HF). Treatment of **114** with HF[116] rapidly afforded the deprotected compound. Moreover, excess fluoride was removed by treating the concentrated reaction mixture with methoxytrimethyl silane (excess fluoride reacts with this reagent to generate trimethylsilylfluoride, the boiling point of which is approx. 15 °C, this can then be removed conveniently by rotary evaporation).[117] High R_f impurities were removed simply by trituration to give DAB1 **35** as its hydrofluoride salt in quantitative yield. This is shown in **scheme 69** along with the reaction scheme that afforded the C_4Me

analogue **57**. The HF salts were subjected to ion-exchange chromatography (Dowex 1X2 (OH^-)) to give the free bases of **35** and **57**.



114 : R = OH
134 : R = Me

141 : R = OH
142 : R = Me

35 : R = OH
57 : R = Me

(a) BH_3•THF, THF, reflux; (b) HF (48% aqueous), MeCN; (c) Dowex (OH^-)

Scheme 57

3.1.2 Structure Confirmation

In order to confirm that we had indeed synthesised DAB1 a comparison of **35**•HF, with literature physical data for DAB1•HCl from several reports was made.[72c,75b,118] This is summarised in **Tables 8** and **9**. It can be seen that NMR details for the HF salt of **35** are in excellent agreement with those reported for the HCl salt of DAB1.

Table 8 *Comparison of ^1H NMR data with HF salt of* **35**

Source	Form	MHz	C_2H	C_3H	C_4H	C_5H_A	C_5H_B	C_6H_A	C_6H_B
Ref 118	HCl salt	300	3.62	4.10	4.34	3.37	3.58	3.84	3.96
Ref 72c	HCl salt	400	3.65	4.13	4.36	3.39	3.60	3.86	3.98
Ref 75b	HCl salt	300	3.55	4.02	4.26	3.29	3.51	3.76	3.88
35	HF salt	600	3.61	4.12	4.36	3.38	3.61	3.86	3.98
	Mult. / *J*	(Hz)							
Ref 118			ddd, 8.4, 4.6, 4.1	dd, 4.1, 2.5	dd, 4.6, 2.6	dd, 12.7, 2.6	dd, 12.7, 4.6	dd, 12.3, 8.4	dd, 12.3, 4.6
Ref 72c			dt, 8.4, 4.2	t, 3.4	dd, 4.7, 2.8	dd, 12.5, 2.8	dd, 12.6, 4.7	dd, 12.2, 8.3	dd, 12.2, 4.7
Ref 75b			ddd, 8.1, 5.7, 3.9	dd, 3.6, 3.3	ddd, 4.5, 3.3, 2.4	dd, 12.6, 2.4	dd, 12.6, 4.5	dd, 12.3, 8.1	dd, 12.0, 5.7
35			dt, 8.2, 4.2	t, 3.7	dd, 5.0, 2.7	dd, 12.6, 2.7	dd, 12.6, 5.0	dd, 12.2, 8.2	dd, 12.2, 4.6

Table 9 *Comparison of ^{13}C NMR data with HF salt* **35**

Source	Form	MHz	δ_C				
Ref 118	HCl salt	100.5	76.4	75.1	67.4	59.7	50.8
Ref 72c	HCl salt	100.5	78.5	77.1	69.4	61.7	52.8
Ref 75b	HCl salt	75	75.7	74.3	66.5	58.9	50.0
35	HF salt	62.9	75.5	74.2	66.6	58.9	49.9

Note: data for references 118 & 72c show consistent deviations compared with ref 75b and **35**, which could be due to referencing differences.

Comparison with data for the free base is shown in **Tables 10** and **11**. Most reports have concentrated on supplying data for the HCl salt, however, data for the free base of **35** correlates well with data from the original paper on DAB1's isolation,[68] which served to establish its structure.

Table 10 *Comparison of ^1H NMR data with free base of* ***35***

Source	MHz	C_2H	C_3H	C_4H	C_5H_A	C_5H_B	C_6H_A	C_6H_B
Ref 68	400	2.87	3.70	4.01	2.72	2.99	3.53	3.60
35	600	2.99	3.85	4.16	2.84	3.12	3.67	3.75
	Mult.	/ *J* (Hz)						
Ref 68		ddd, 6.4, 5.3, 4.9	dd, 5.3, 3.7	dd, 5.8, 3.7	dd, 12.1, 3.8	dd, 12.1, 5.8	dd, 11.6, 6.4	dd, 11.6, 4.9
35		dt 6.1, 4.8	dd, 5.3, 3.9	dd, 5.8, 3.9	dd, 12.2, 3.9	dd, 12.2, 5.8	dd, 11.6, 6.4	dd, 11.6, 4.8

Note: the deviations in chemical shift for each signal are approx. constant. This might be due to referencing differences, or, it has come to our attention that the ^{1}H NMR signals for DAB1 are very pH dependant and this may also account for these deviations.[119]

Table 11 *Comparison of ^{13}C NMR data with free base of* ***35***

Source	MHz	δ_C				
Ref 68	75.4	79.9	78.4	66.4	62.9	51.6
35	62.9	79.9	77.4	65.0	62.0	50.4

Comparisons with reported optical rotations[70,72b,72c] were also made and are summarised in **Table 12**.

Table 12 *Comparison of Optical Rotation data with* ***35***

Source	Form	$[\alpha]_D$
Ref 70	HCl salt	+ 37.9 (c=0.53, H_2O)
Ref 70	Free base	+7.8 (c=0.46, H_2O)
Ref 72b	HCl salt	+ 34.7 (c=0.78, H_2O)
Ref 72b	Free base	+8.1 (c=0.98,H_2O)
Ref 72c	HCl salt	+ 27.3 (c=0.47, H_2O)
35	HF salt	+ 26.3 (c=0.30, H_2O)
35	Free base	+8.2 (c=0.25, H_2O)

Thus we were confident that we had indeed synthesised the desired natural product DAB1 **35**. This synthesis represents a highly efficient synthetic route, the

target compound being synthesised with an overall yield of 50% (10 steps). Its C_4Me analogue was also synthesised in a highly efficient manner (65% overall, 10 steps). The stereochemical assignment of **57** was made by analogy to the glycolate aldol process.

3.2 Summary of Natural Product Synthesis

As demonstrated in this and the previous chapter, we have developed highly efficient syntheses of the natural products DAB1 **35** and nectrisine **36**. Both natural products originating from selective reductions of the carbonyl function of lactam **114**. We have also extended this methodology to encompass the synthesis of the C_4Me analogue of DAB1 **57**. Additionally, the precursor to the C_3Me analogue of nectrisine **58** was also prepared. Both were accessed by judicious choice of aldol partner (glycolate or propionate equivalent) with aldehyde **73**.

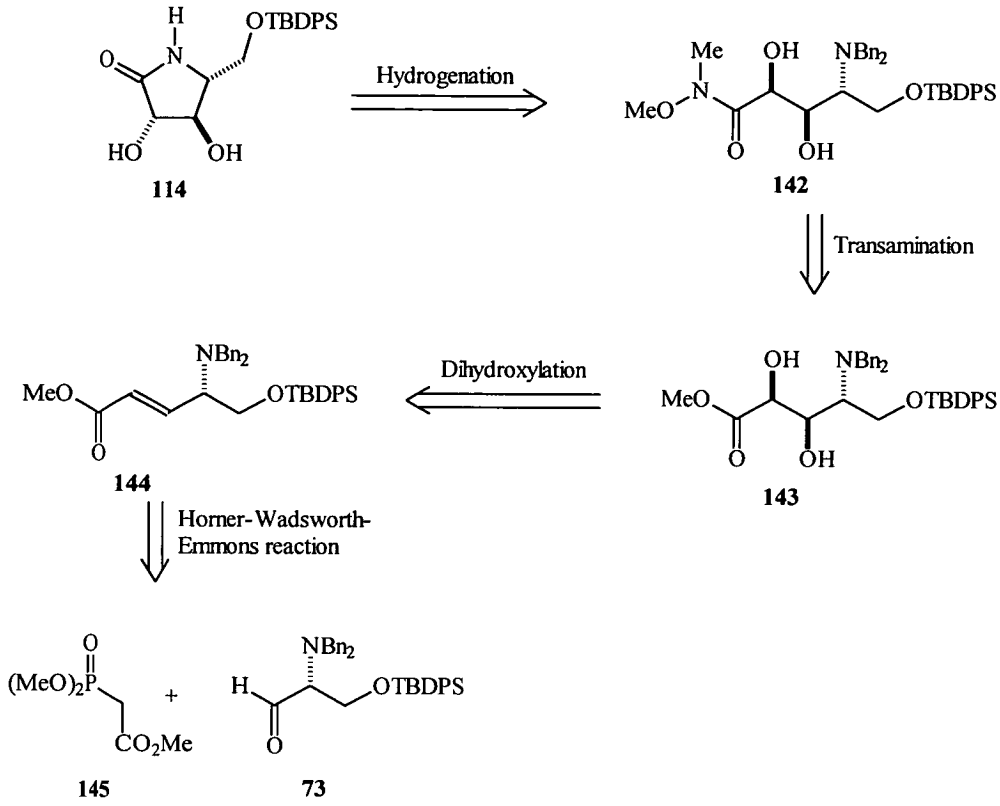
Chapter 4 : Results and Discussion Part 3

Synthesis of Lactam 114 *via* Osmium Catalysed Dihydroxylation

With the success of the boron mediated aldol reaction in generating the desired *syn*-hydroxyl stereochemistry required for the synthesis of DAB1 and nectrisine (*via* lactam **114**), we sought to probe how effective an osmium tetroxide dihydroxylation protocol might be in generating lactam **114**.

4.1 Retrosynthetic Analysis of Lactam 114

Scheme 58 represents a retrosynthesis of lactam **114**, encompassing a dihydroxylation protocol that would generate the desired *syn*-diol stereochemistry. We believed that *E*-olefin **144** would be a good candidate for osmium catalysed dihydroxylation, since generation of such olefins can conveniently be achieved by exploiting the Horner-Wadsworth-Emmons reaction. In this case aldehyde **73** and commercially available trimethylphosphonoacetate **145** are required to undergo reaction to provide compound **144**. From here we believed formation of Weinreb amide **142** followed by hydrogenolysis of the *N*-benzyl protecting groups (*vide supra*) would provide lactam **114**.

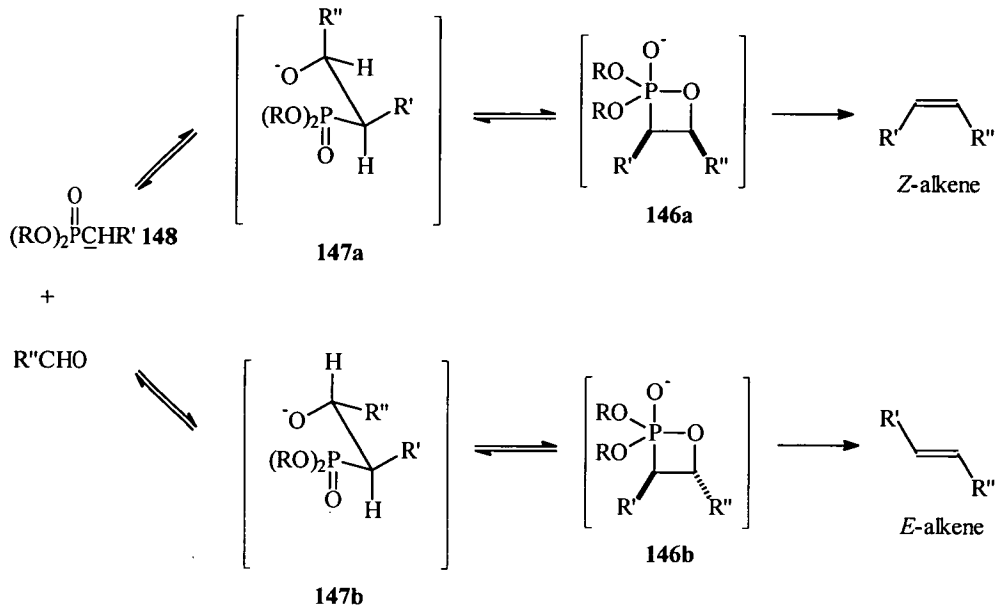


Scheme 58

4.2 The Horner-Wadsworth-Emmons Reaction

The Horner-Wadsworth-Emmons (HWE) reaction, a variant of the Wittig reaction, is an extremely versatile method for the formation of α,β-unsaturated compounds from phosphonates, **148**. It has several advantages over the Wittig reaction, in that the ylides derived from phosphonates are more reactive than the corresponding ylides derived from phosphoranes (Wittig reaction). In addition the phosphorus by-product is a phosphate ester and hence soluble in water, unlike, triphenylphosphine oxide (the by-product of a Wittig reaction) making purification of the reaction mixtures more straightforward. The mechanism of the reaction is summarised in **scheme 59**. The phosphoryl-stabilised carbanion attacks the carbonyl in a stepwise manner, to give oxyanion intermediates **147a** and **b**,[120] which then decompose *via* transient four centred oxyphosphetane intermediates **146a** and **b**[121] to yield the olefin. The stereochemistry is determined by a combination of the

stereoselectivity in the initial C-C bond forming step, and perhaps, reversibility of the intermediates. Several different types of reaction parameters have been developed to form predominantly either *E* or *Z* olefins.[121]



Scheme 59

4.2.1 Barium Hydroxide Mediated HWE Reaction and Aldehyde 73

Paterson *et. al.* found that the use of barium hydroxide as a base in the HWE reaction was an extremely mild and effective way of carrying out the reaction.[122] *E*-olefins were obtained exclusively and the barium hydroxide caused no epimerisation of base sensitive aldehydes. The microcrystalline structure of the barium hydroxide was found to be crucial to its activity, and C200 barium hydroxide (produced by heating $Ba(OH)_2.8H_2O$ at 200 °C for 3 hours)[123] was discovered to be the most active form. Paterson also found that heating commercial $Ba(OH)_2.8H_2O$ at 100-140 °C for 2 hours gave good results in HWE reactions.

We were attracted to these mild conditions, believing that they would be ideal for use with aldehyde **73**. Thus treatment of trimethylphosphonoacetate **145** with barium hydroxide followed by addition of aldehyde **73** lead to the formation of *E*-α,β-unsaturated ester **144** exclusively, **scheme 60**, (the *E*-geometry of the olefin was

determined *via* ^{1}H NMR spectroscopy. The C_2H-C_3H coupling constant was measured at 15.9Hz).[3]

145 **144**

(a) activated $Ba(OH)_2$, THF/H_2O (40:1); **73**, THF/H_2O (40:1), room temperature

Scheme 60

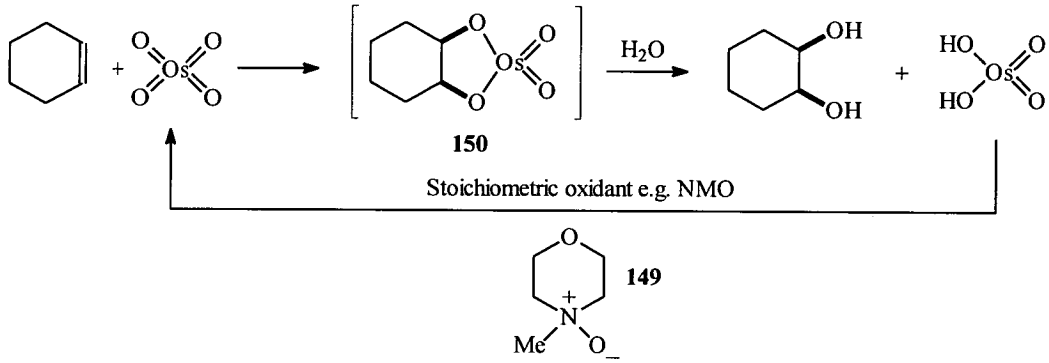
Although the conditions employed in the reaction were mild we decided to check that the stereochemical integrity of the α-position was not being compromised by prolonged exposure to barium hydroxide. The aldehyde was thus stirred for 24 hours (typical length of time for the HWE reaction) in the presence of barium hydroxide (in THF/H_2O (40:1)) before being reduced to the corresponding alcohol **72** (as in **section 2.2.1**). The enantiomeric excess of the alcohol was measured by chiral HPLC and was gratifyingly found to be >98%e.e. We were, therefore, confident that olefin **144** was being formed without any epimerisation at the C_4 position.

4.3 Osmium Catalysed Dihydroxylation

Dihydroxylation of an olefin using osmium tetroxide is a stereospecific reaction in which a *syn*-diol is produced.[124] Classically the osmium tetroxide would be used in stoichiometric quantities which would be costly and would cause increased exposure to this highly toxic oxidant. Catalytic osmylation utilising sodium or potassium chlorate[125] or hydrogen peroxide[126] to regenerate the osmium tetroxide can be useful but frequently results in over oxidation of the newly formed diol to provide α-ketols. These problems have been overcome by the development of a

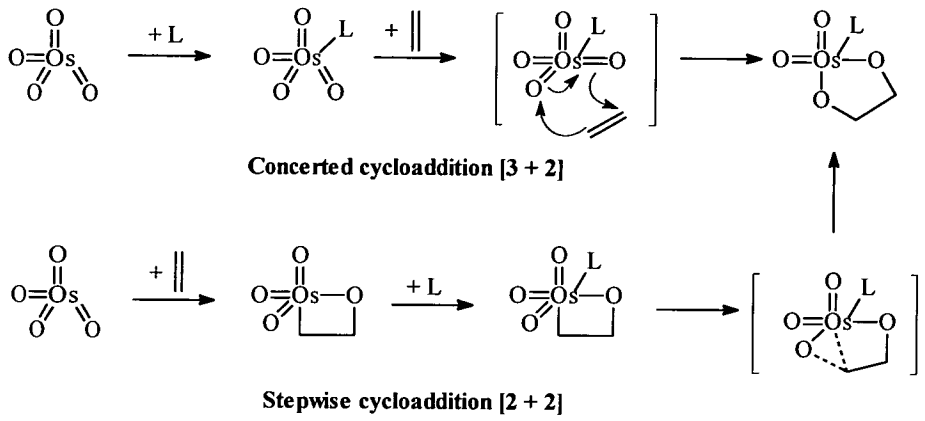
[3] Vicinal coupling constants for *Z*-olefins are generally in the range 6-14 Hz (typicallyl0 Hz). Coupling constants for *E*-olefins are generally in the range 14-20Hz (typically 16 Hz)

catalytic osmylation process, which uses tertiary amine oxides (in particular, *N*-methylmorpholine *N*-oxide (NMO) **149**)[127] to regenerate the oxidant. This method has become the most widely used catalytic osmylation method. The process is exemplified in **scheme 61**. The dihydroxylation of cyclohexene is shown here as an example, proceeding through osmate ester intermediate **150**. One advantage of dihydroxylation using osmium tetroxide is that it is a very general reaction, electron rich, electron-deficient, and electronically 'neutral' alkenes will all undergo reaction, as will heavily substituted alkenes.[128]



Scheme 61

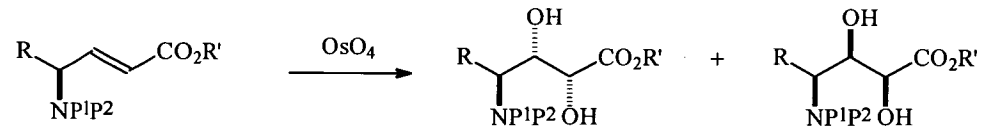
The precise mechanism for the formation of osmate ester intermediates of the type **150** is a source of contention and is still under debate.[129] Two paths generating the same intermediate have been hypothesised and are shown in **scheme 62**. In the first a concerted [3 + 2] cycloaddition in the presence of an amine ligand (L) (known to accelerate osmium tetroxide dihydroxylations)[130] gives the osmate ester. In the second proposal a stepwise [2 + 2] cycloaddition provides the same ester.



Scheme 61

4.3.1 Osmium Catalysed Dihydroxylation of 144

We were initially uncertain as to what the outcome of the osmium catalysed dihydroxylation reaction with **144** would be. Others have previously reported low facial bias in related reactions of allylic amine derivatives.[130,131] However, Reetz has recently performed this reaction on both Boc protected and *N,N*-dibenzyl protected allylic amines of the type **151**, which are very similar in structure to **144**.[132] Reetz found that depending on the protecting group used, the reaction could be biased towards a particular diastereomer (thus demonstrating the concept of protecting group tuning), **scheme 62**.

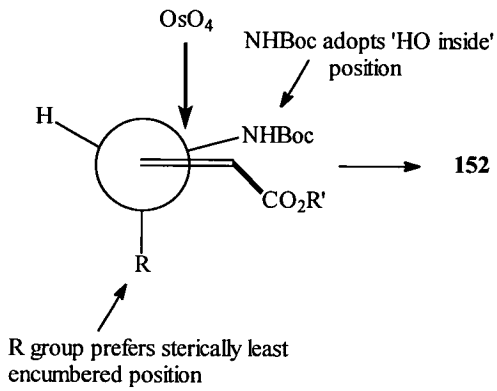


151 **152** **153**

R = CH_3; $PhCH_2$;
$CH(CH_3)_2$; $CH_2CH(CH_3)_2$
R' = CH_3 or C_2H_5
P1P2 = HBoc or Bn_2

Scheme 62

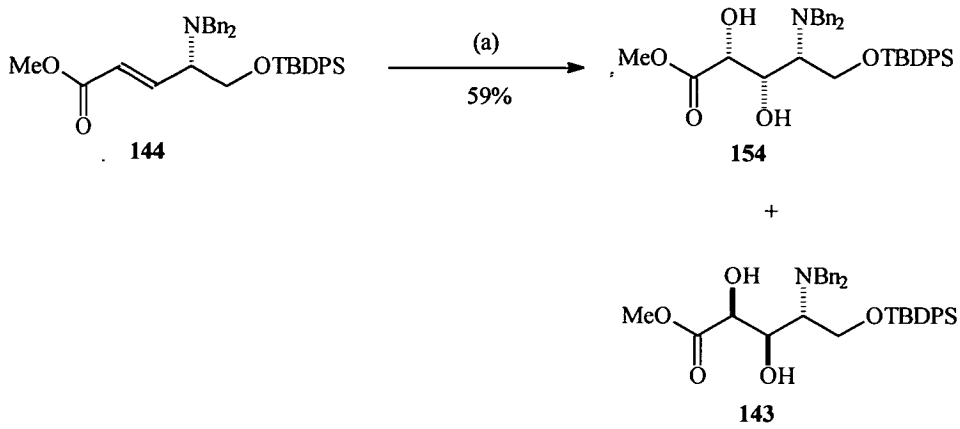
Boc protected derivatives favoured diastereomers of the type **152** with diastereoselectivities ranging form 51:49 to 81:19. The use of *N,N*-dibenzyl protection resulted in predominant formation of the diastereomers with the opposite sense, of the type **153**, with slightly better diastereoselectivities, in the range 24:76 to 8:92. The sense of diastereoselectivity in the Boc protected derivatives is the same as in the well studied cases of stereoselective dihydroxylation reactions of allylic alcohols and ethers. Reetz has shown that these dihydroxylations are in keeping with the Stork-Houk model **scheme 63**.



Scheme 63

In the absence of detailed mechanistic studies it is currently difficult to explain the results obtained when dihydroxylations were carried out on *N,N*-dibenzyl protected derivatives. Nevertheless, it is clear that changing protecting groups can have a marked effect on the outcome of the reaction.

Compound **144** was thus subjected to standard osmium catalysed dihydroxylation conditions (OsO_4, NMO). We found it necessary to employ up to 18 mol% of OsO_4 in order to shorten the reaction time. (1 mol% - 7 days for 100% conversion; 18 mol% - 5 hours for 100% conversion). The diastereomeric ratio was not affected by the increased amounts of osmium tetroxide. The reaction gave a mixture of diastereomers which were readily separable by column chromatography in a ratio of 65:35 in favour of diastereomer **154** in moderate overall yield, **scheme 64**.



(a) OsO_4, NMO, acetone/water (8:1)

Scheme 64

Compound **154** was isolated as a crystalline solid and its structure was unambiguously determined by single crystal X-ray diffraction, **figure 1**. These results are, therefore, in keeping with those reported by Reetz. Thus, the dihydroxylation reaction has preferentially produced the opposite diastereomer to that required for the synthesis of lactam **114**.

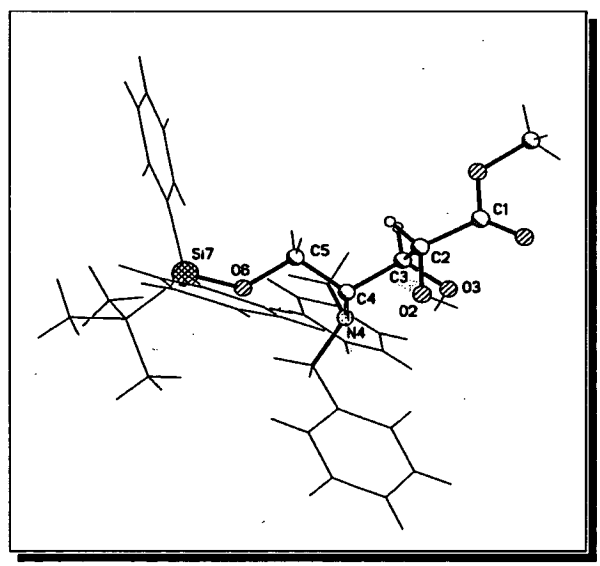


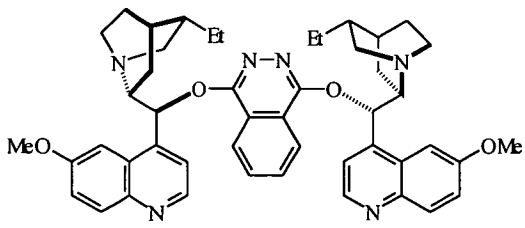
Figure 1 *x-ray crystal structure of 154*

We believed that by using the procedure developed by Sharpless, using chiral amine ligands, we would, hopefully, be able to effect the outcome of the reaction through reagent control.

4.4 Sharpless Asymmetric Dihydroxylation

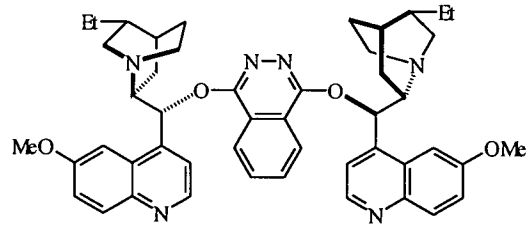
It is well known that prochiral substrates such as aldehydes, ketones, alkenes or dienes having at least one stereogenic centre react with achiral reagents or catalysts to provide two possible diastereomeric products. Ideally, variation of reagents, solvents or reaction conditions should allow access to either diastereomer. If the asymmetric induction is poor inspite of such efforts, the principle of double stereodifferentiation using chiral reagents or catalysts offers a way out of this synthetic dilemma.[97]

The Sharpless asymmetric dihydroxylation (AD) is an extremely efficient way of carrying out enantioselective dihydroxylations. Developments in this reaction[133] by Sharpless pinnacled with the introduction of the pair of chiral amine ligands **155** and **156** in 1992.[134] The ligands are constructed around a phthalazine core ustilising dihydroquinidine (DHQD) or dihydroquinine (DHQ), which are both commercially available natural products, and are shown in **scheme 65**.



155

$(DHQD)_2$-PHAL
Ligand used in AD-mix-β



156

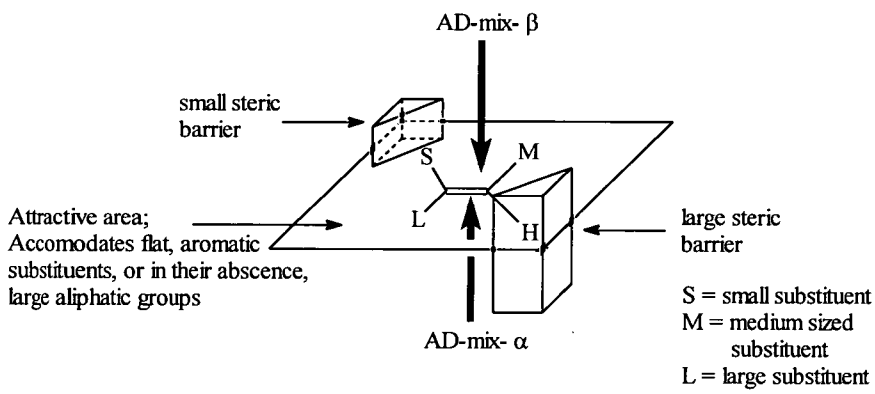
$(DHQ)_2$-PHAL
Ligand used in AD-mix-α

Scheme 65

Dihydroxylations using these ligands are carried out using potassium ferricyanide as co-oxidant in conjunction with osmium tetroxide. Mixtures of these

components are now commercially available, AD-mix-α (with DHQD ligand) and AD-mix-β (with DHQ ligand), and their use in natural product synthesis has been well documented.[135] A full mechanistic understanding of the Sharpless asymmetric dihydroxylation process is not yet available and there is still considerable debate over certain aspects of the reaction. For instance Corey has recently provided evidence, through X-ray crystallographic studies, that a U-shaped enzyme-like binding pocket exists and that this is crucial to the enantioselective dihydroxylation of olefins.[136] The group of Sharpless has however rejected this model.[137]

A simple pictorial 'working model' for the catalytic site, which at least accounts for the experimentally observed selectivity has been developed and is shown in **scheme 66**. The olefin is orientated to minimise steric interactions with the catalyst. Once this is achieved the chiral osmium tetroxide catalysts' attack the olefin with facial selectivity dependent on which chiral ligand is used. Thus as depicted, AD-mix-β delivers the hydroxyl groups from the top face and AD-mix-α delivers the hydroxyl groups from the bottom face.



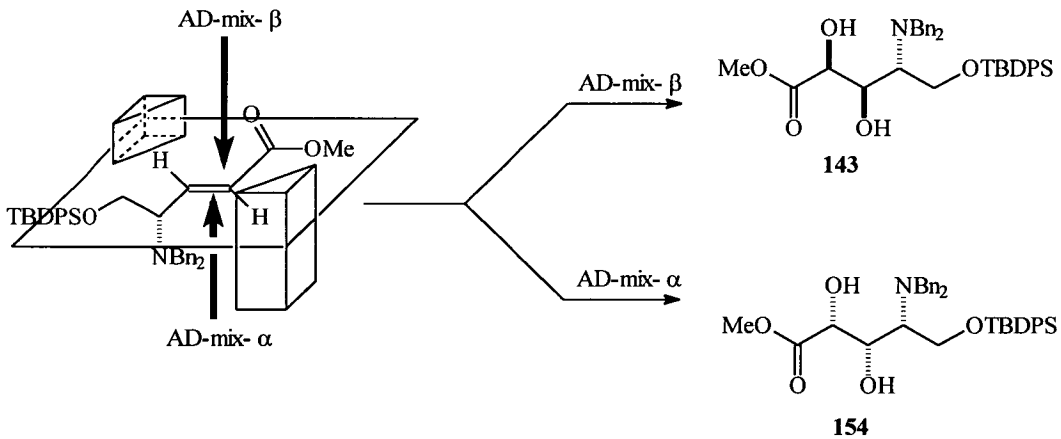
Scheme 66

4.4.1 Sharpless Asymmetric Dihydroxylation of 144

The use of the chiral dihydroxylation reagents AD-mix-α and AD-mix-β in the dihydroxylation of α,β-unsaturated ester **144** brings about, once again, the possibility of having 'matched' and 'mismatched' stereochemical outcomes. Since

the dihydroxylation reaction using achiral osmium tetroxide gave predominantly **154**, **scheme 64**, then the AD-mix which would also generate this diastereomer would clearly represent the 'matched' case and we would therefore expect to obtain higher degrees of diasteroselectivity. However, for an efficient synthesis of lactam **114** by this dihydroxylation method we would need to generate diastereomer **143** predominantly. The appropriate AD-mix would be required to override the intrinsic diastereoinduction observed in the reaction with achiral osmium tetroxide and this would therefore represent a 'mismatched' reaction.

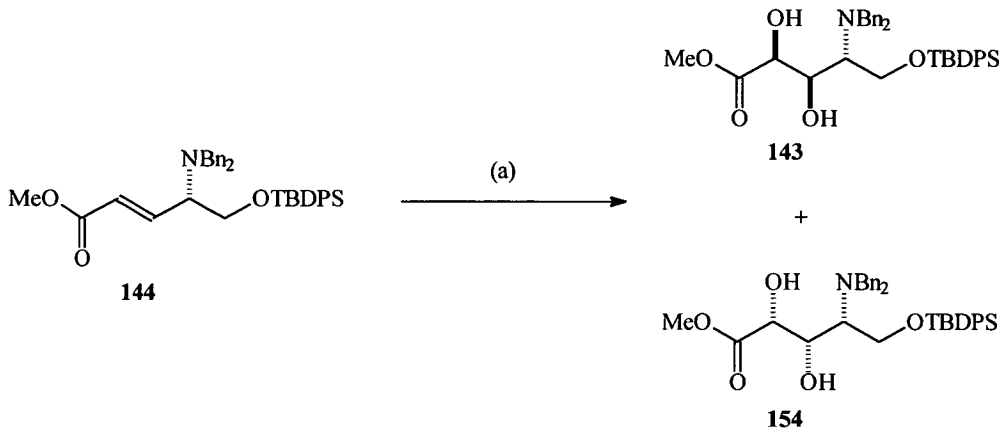
On subjecting **144** to analysis using the above mnemonic device it is clear that AD-mix-α should generate diastereomer **154** and therefore should represent the 'matched'case. AD-mix-β should generate diastereomer **143** predominantly and accordingly in a 'mismatched' fashion, **scheme 67**.



Scheme 67

The results of the dihydroxylation of **144** with both AD-mixes-α and β are summarised in **scheme 68** and **table 13**. When AD-mix-β was used a reversal of diastereoselectivity compared with the achiral case was indeed observed (68:32 in favour of **143**). Surprisingly, AD-mix-α provided no enhancement of the intrinsic diastereoselection of the reaction and provided diols **143** and **154** with the same diastereoselectivity as was found in the achiral case. Moreover, both reactions were frustratingly sluggish and after 7 days reaction time only 28% of **144** had reacted (72% of starting material recovered) in the case of AD-mix-α. In the case of AD-

mix-β better conversions were observed, however, 25% of **144** still remained unreacted after 7 days. (Note: the use of methane sulfonamide in such reactions has been shown to increase the rate of osmate ester hydrolysis for non-terminal olefins, hence its presence).[134]



(a) AD-mix-α or β, $MeSO_2NH_2$, Acetone/Water (3:1)

Scheme 68

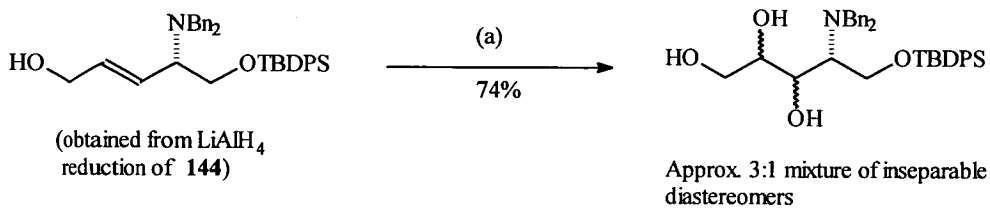
Table 13

AD-mix	% Conversion	Yield[a]	**143 : 154**
α	28%	65%	34 : 66
β	75%	68%	68 : 32

[a]Yields based on recovered starting material

As can be seen the Sharpless asymmetric dihydroxylation was of moderate use in generating desired diol **143**. The reasons for the sluggish reactions, and lower than expected diastereoselectivity in the case of AD-mix-α, are difficult to explain and might possibly be due to steric complications. Electronic factors may also have some part to play, as it is well known that electronically rich olefins react at a faster rate than electron poor olefins, with OsO_4. Indeed, in a brief examination of the achiral dihydroxylation reaction (OsO_4, NMO) involving the coresponding allylic

alcohol of **144**, **scheme 69,** we observed much faster rates for the reaction compared with the α,β unsaturated ester (completion of reaction within 24 hours with only 1 mol% OsO_4). Hence, removal of the deactivating ester functionality appears to drastically improve the rate of reaction.



(obtained from $LiAlH_4$ reduction of **144**)

Approx. 3:1 mixture of inseparable diastereomers

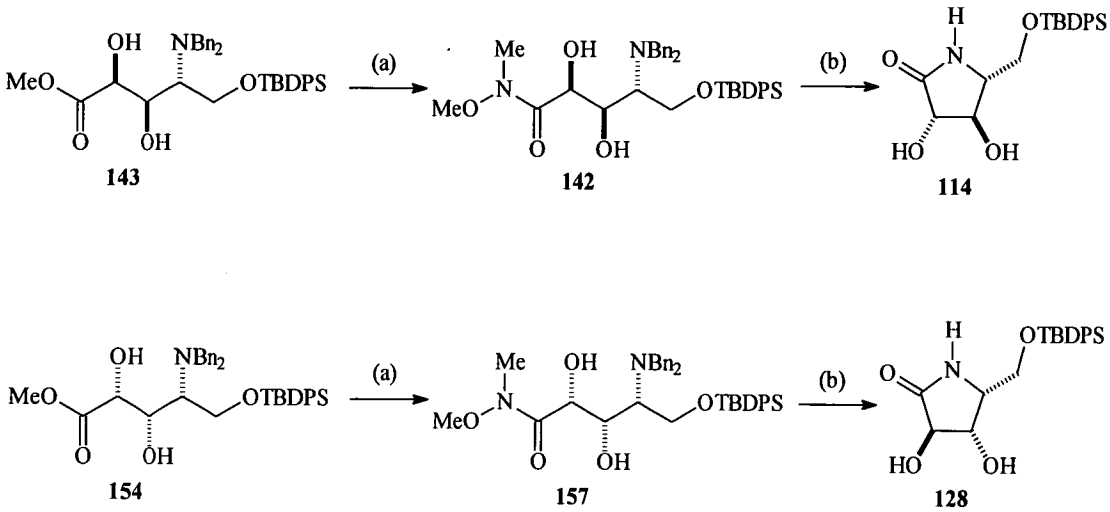
(a) OsO_4, NMO, acetone/water (8:1)

Scheme 69

There have been similar reports of poorer than expected levels of diastereoselectivity and conversions in AD-mix catalysed dihydroxylations.[75b] It is perhaps worth noting that in the achiral dihydroxylation of **144** the addition of more osmium tetroxide increased the rate of the reaction considerably. It may be possible to optimise conditions for the asymmetric variant in order to gain increased olefin conversion *via* increasing the amount of osmium tetroxide and of course chiral ligand present in each AD-mix.[138] Time, however, did not permit further investigations into this reaction.

4.5 Formation of Lactams 114 and 128 From Diols 143 and 154

Synthesis of lactams **114** and **128** was expected to proceed without incident and indeed this was the case. Formation of Weinreb amides **142** and **157** under previously described conditions proceeded with excellent yields over a 24 hour reaction period. The Weinreb amides were subsequently subjected to hydrogenolysis conditions ($Pd(OH)_2/C$) which lead to spontaneous cyclisation and generation of the desired lactams, **scheme 70**.



(a) (MeO)N(Me)H•HCl, $AlMe_3$, THF, -30 °C→room temp.→-30 °C; **143/154**, THF –30 °C→room temp; (b) $Pd(OH)_2/C$, H_2, MeOH

Scheme 70

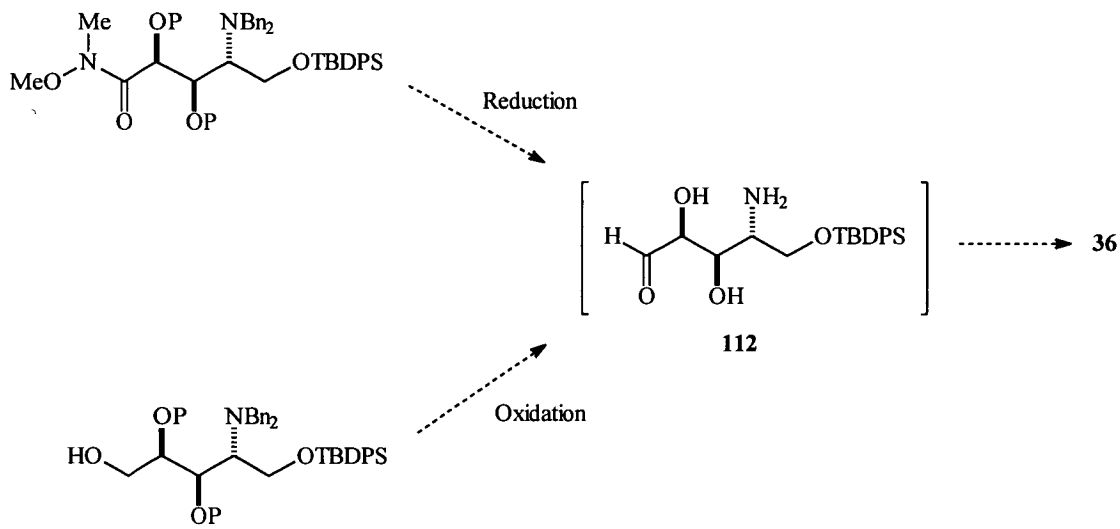
Since the crystal structure of **154** has been determined it is now very clear that this stereochemical arrangement gives rise to lactam **128** and by default the stereochemical arrangement in **143** and therefore aldol adduct **102** must give rise to lactam **114**. Thus providing further evidence that the correct stereochemistry was indeed assigned to lactam **114** and hence aldol adduct **102**.

Chapter 5 : Results and Discussion Part 4

Further Applications of Serine Aldehyde 73 to Natural Product Synthesis

5.1 Application to Hydantocidin Analogue Synthesis

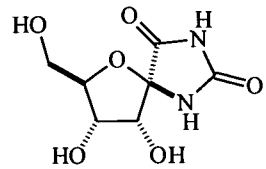
During our initial synthetic work on the synthesis of nectrisine **36** we had focused on generating amino aldehyde intermediate **112**. In order to do this we had envisaged the aldehyde moiety coming from either a reductive protocol (from the corresponding Weinreb amide) or, perhaps, an oxidative protocol (from the corresponding primary alcohol), **scheme 71**. Eventually, the synthesis of nectrisine as discussed in **chapter 2** turned out to the most successful method of generating the natural product. However, the failings of our studies directed toward the synthesis of amino aldehyde **112** led to the interesting discovery that hydantocidin analogues could be synthesised *via* aldehyde **73**.



P = H or suitable protection

Scheme 71

Hydantocidin **158**, **scheme 72**, was isolated from the fermentation broth of *Streptomyces hygrocopicus* and provided the first example of a spirohydantoin nucleus at the anomeric position of a sugar.[139] Because of the potent herbicidal and plant growth regulatory activity[140] considerable interest has been shown in the synthesis hydantocidin and its stereoisomers by aldol,[141] dihydroxylation,[142] and other procedures.[143] Various deoxyhydantocidins have also been described.[144] As yet no proposal has been made for the mode of action of hydantocidin.

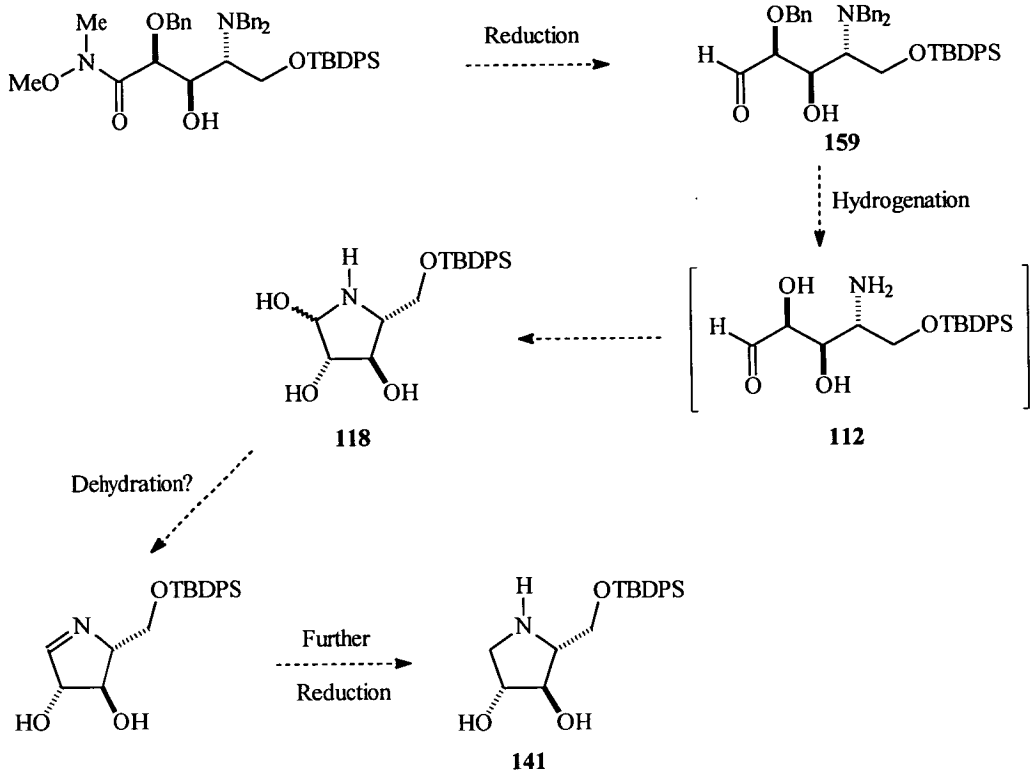


158

Scheme 72

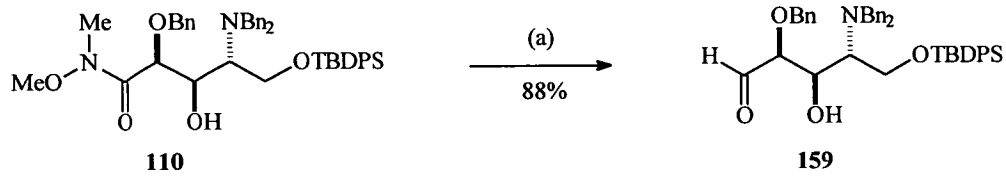
5.1.1 Attempts to Generate Nectrisine via a Reductive Protocol

We have learned in **chapter 2** that debenzylation of Weinreb amide **110** to yield the free amine was impossible due to spontaneous lactamisation. We therefore, ventured that reduction of the Weinreb amide moiety to the aldehyde functionality followed by hydrogenolysis of the benzyl protecting groups might be more effectual in generating nectrisine *via* intermediate amino aldehyde **112**. We believed that the amino aldehyde would be reactive enough to cyclise rapidly on generation. This would therefore provide the corresponding lactol **118**. We were, however, unsure how stable this lactol would be. If dehydration occurred under the hydrogenation conditions then the likelihood would be that further reduction of the resulting imine would occur, thus yielding the corresponding amine **141**. If this did happen, however, all would not have been lost, as this would still represent an attractive route toward the synthesis of our second natural product target, DAB1 **35**. These initial thoughts are summarised in **scheme 73**.



Scheme 73

Reduction of Weinreb amides to aldehydes was discussed in **chapter 2, section 2.1**. Thus, treatment of Weinreb amide **110** with DIBAL-H at -78 °C led to the smooth formation of the desired aldehyde **159** in excellent yield, **scheme 74**. The aldehyde was slightly unstable to silica gel, in that heating a sample of the aldehyde on a t.l.c. plate with the aid of a heat gun led to the sample quickly turning brown on the plate. Column chromatography was carried out as quickly as possible and the aldehyde was isolated as a single diastereomer. The optical integrity of the α-position was, however, of some concern. A sample of the aldehyde was left in acidic deuterochloroform for a period of ca. 72 hours. Re-examination of the ^{1}H NMR spectrum showed that the sample was now a mixture of inseparable diastereomers (approximately 92:8 ratio). The aldehyde could, however, be stored at -20 °C for at least one month without showing any signs of epimerisation.

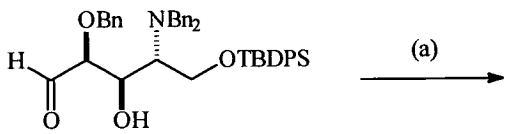


110 **159**

(a) DIBAL-H, toluene, -78 °C, 15 mins

Scheme 74

The hydrogenation reaction (in the presence of 20% $Pd(OH)_2/C$) **scheme 75**, was, however, extremely disappointing. The starting material slowly reacted to give a multi-component reaction mixture, by t.l.c. None of the desired product(s) could be isolated and as a result this reaction course was summarily abandoned.



159

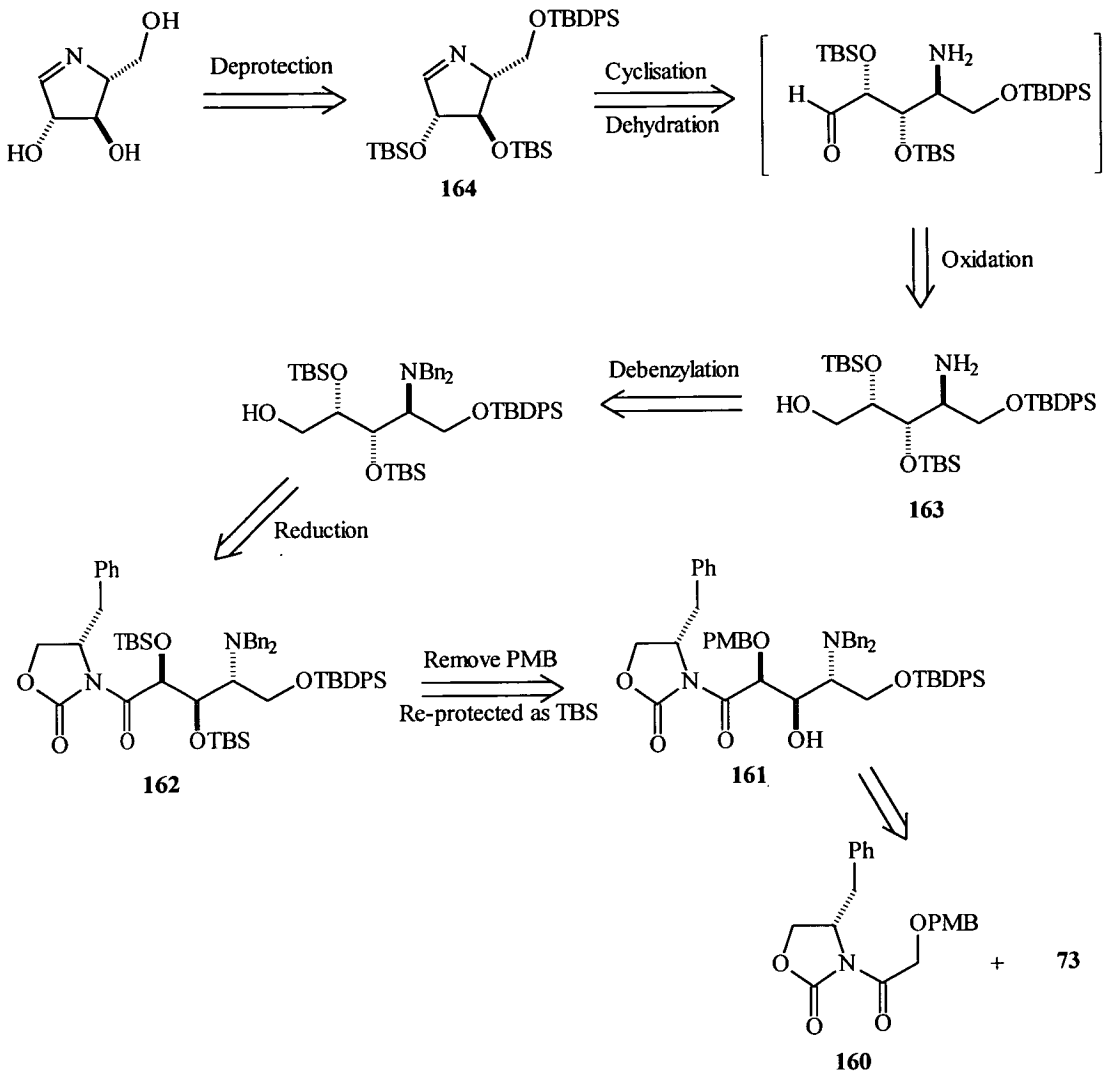
(a) $Pd(OH)_2/C$, H_2, MeOH

Scheme 75

5.1.2 Attempts to Generate Nectrisine via an Oxidative Protocol

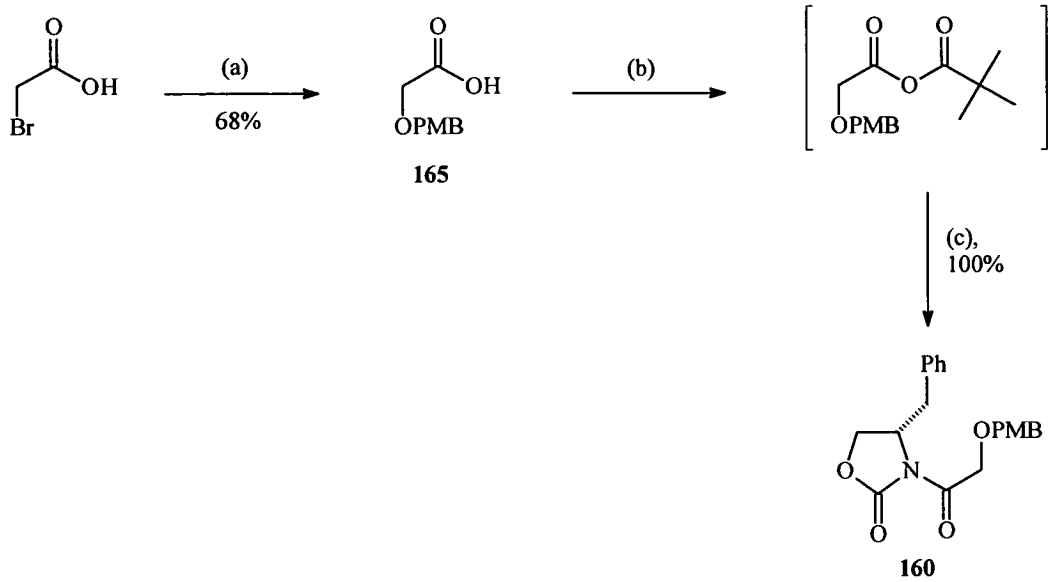
A retrosynthetic analysis of nectrisine showing our proposed route, encompassing an oxidative method of generating desired amino aldehyde **112** is shown in **scheme 76**. We believed that aldol adduct **161** would be more useful in this synthetic scheme than adduct **102**. This reasoning was due to the fact that we were sure we could remove the *p*-methoxybenzyl (PMB) group from this aldol adduct and replace it with a TBS ether, at the same time protecting the neighbouring free hydroxyl group. Reduction of aldol adduct **162** to yield a primary hydroxyl group, followed by debenzylation would provide compound **163** (we believed that *O*-benzyl protecting groups would also be cleaved under these conditions and would subsequently present problems in the oxidation step, hence replacement with the TBS group). Oxidation of the primary hydroxyl and cyclisation would provide, after

dehydration, imine **164**. The silyl ether protecting groups could then be removed in one step to afford nectrisine.



Scheme 76

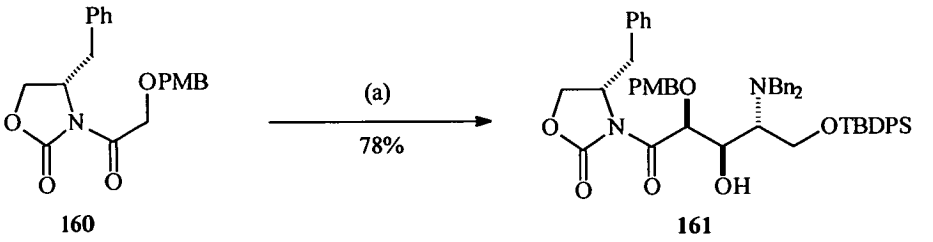
The PMB protected chiral glycolate equivalent **160** was synthesised in an analogous manner to equivalent **101**. Thus, bromoacetic acid was condensed with the sodium salt of *p*-methoxybenzylalcohol to provide *p*-methoxybenzyloxyacetic acid **165**. Conversion of **165** to the unsymmetrical anhydride derived from pivaloylchloride and reaction with lithiated **106** provided **160** in excellent yield, **scheme 77**.[104b]



(a) NaH, PMBOH, THF, reflux; (b) **165**, pivaloylchloride, Et_3N, THF, -78 °C (c) **106**, BuLi, THF, -78 °C

Scheme 77

The ensuing aldol reaction between **160** and **73** (**scheme 78**) provided the desired *syn* aldol adduct **161** in good yield as a single diastereomer (the relative C_2-C_3 *syn* stereochemistry was assigned, as before, on the basis of ^1H NMR coupling constants; the C_2 proton was a clear doublet at 5.37 ppm, J = 2.7 Hz). The Felkin-Anh selectivity was made on the basis of precedent (**chapter 2**). It is worth noting that this aldol reaction had to be performed within very strict reaction parameters.[145] The reaction was performed in toluene (no aldol adduct was detected when DCM was the solvent) and enolisation temperatures had to be maintained between -30 and -50 °C to obtain good yields of the aldol adduct **161**.

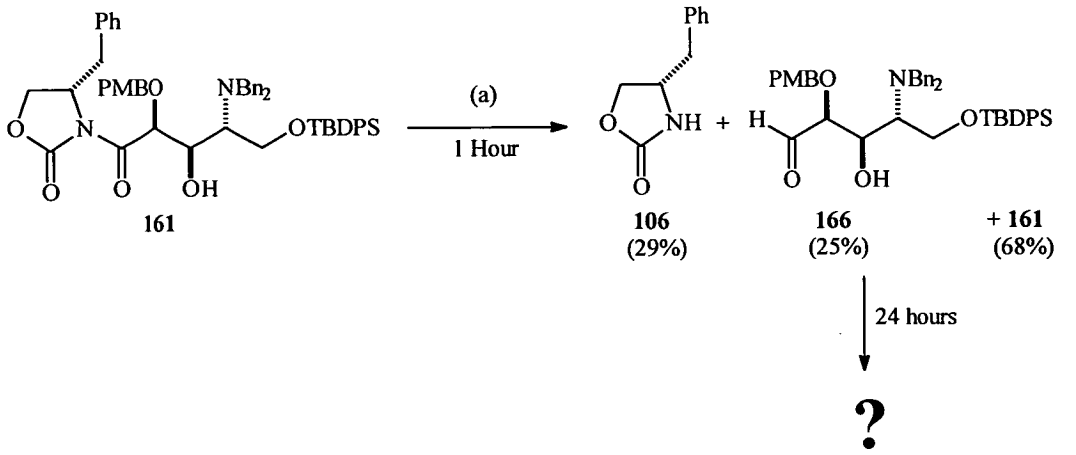


(a) Bu_2BOTf, Et_3N, toluene, -50 °C→-30 °C→-78 °C; **73** in toluene at -78 °C

Scheme 78

5.1.3 Attempted Removal of p-Methoxybenzyl Protection

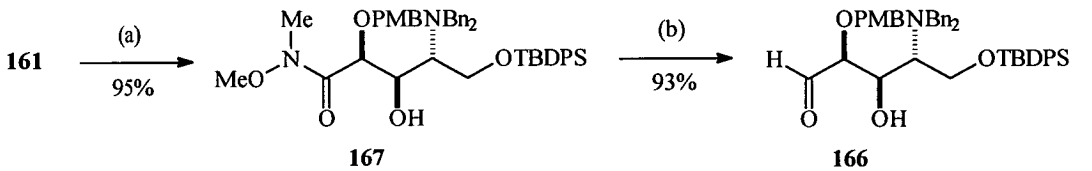
The next course of action was to be removal of the PMB protecting group. Initially we believed that this would be a straightforward process. The literature is replete with examples of oxidative removal of PMB groups utilising the reagent DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone).[83b] Reaction of aldol adduct **161** with 1.3 equivalents of DDQ did not, however, provide any of the de-protected product. The reaction was quenched after 1 hour, and t.l.c. showed that the reaction mixture was essentially starting material, however, two other components were apparent. Separation of these components was easily achieved by column chromatography to provide recovered starting material, oxazolidin-2-one **106** and aldehyde **166**. In a separate experiment conducted under the same conditions but over a 24 hour period no aldehyde was detected and t.l.c. analysis showed that several other components were now present. NMR and IR suggested that oxidation of the *N*-benzyl protecting groups was now occurring along with oxidation of the aldehyde to the carboxylic acid functionality, **scheme 79**. At present we are unable to explain these results.



(a) DDQ, DCM/H_2O (9:1), 1-24 hours

Scheme 79

Aldehyde **166** could also be generated *via* reduction of Weinreb amide **167** using DIBAL-H at -78 °C, **scheme 80**. The aldehyde obtained was identical in all respects to the aldehyde synthesised from aldol adduct **161** (*vide supra*).



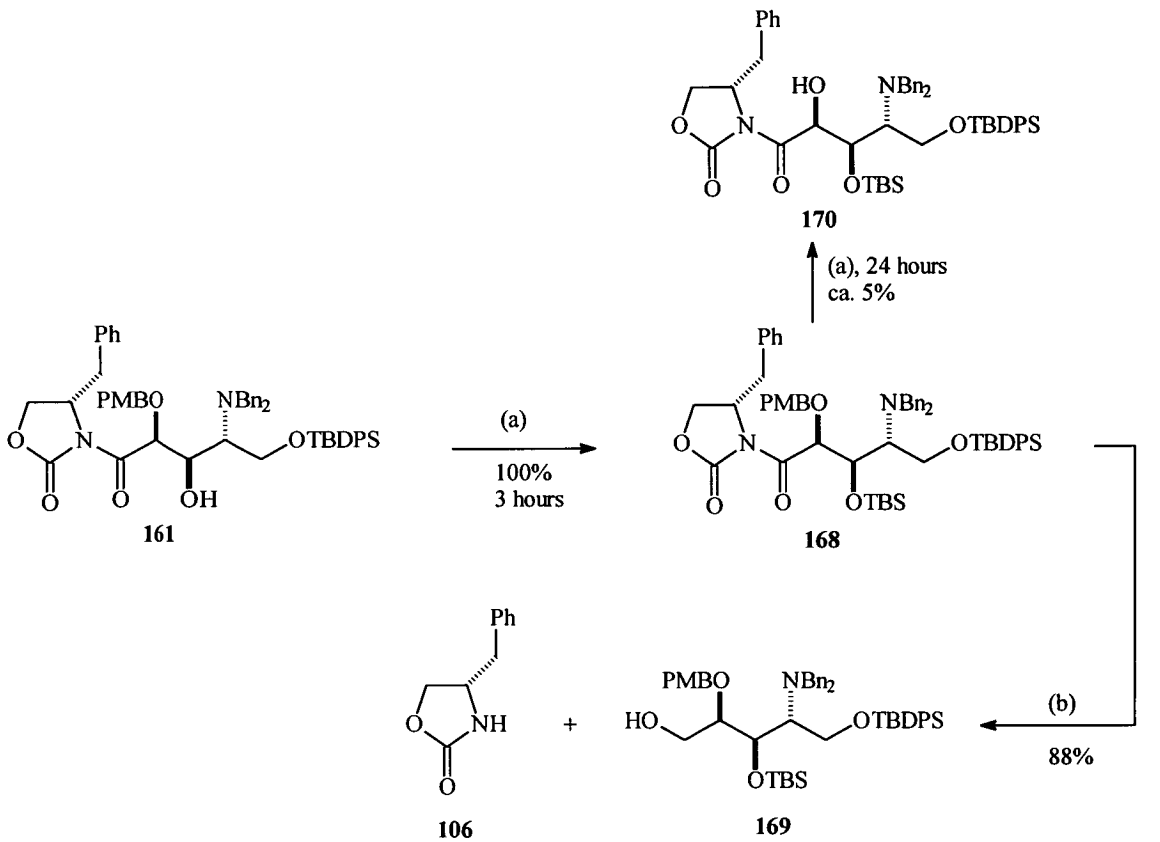
(a) (MeO)N(Me)H•HCl , $AlMe_3$, -30 °C→room temp.→-30 °C; **161**, -30 °C→room temp. (b) DIBAL-H, toluene, -78 °C, 15 mins

Scheme 80

5.1.4 Retention of PMB Group in the Synthesis of an Hydantocidin Analogue

With the apparent failure in removing the PMB group from aldol adduct **161** we decided to continue with our synthetic plan, however, retaining the PMB group. TBS protection of the free secondary hydroxyl group was undertaken utilising

TBSOTf in the presence of 2,6-lutidine to provide the protected aldol adduct **168** in quantitative yield. It is worth noting that prolonged reaction times (24 hours) generated small traces (ca. 5%) of the PMB de-protected compound **170** (presumably caused by the presence of triflic acid from hydrolysed TBSOTf). Short reaction times (3 hours) completely prevented this. Reductive cleavage of the oxazolidin-2-one chiral auxiliary using lithium borohydride, as described by Evans,[85b] proceeded without incident to afford alcohol **169** in excellent yield (**scheme 81**) along with recovered oxazolidin-2-one **106**.

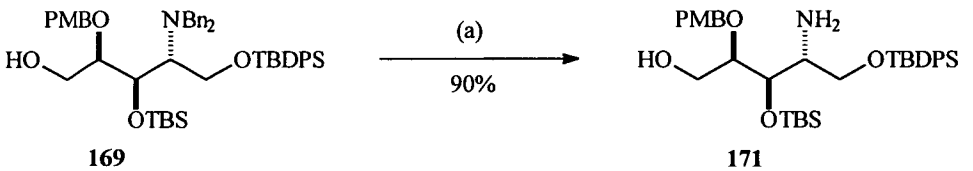


(a) TBSOTf, 2,6-lutidine, DCM; (b) $LiBH_4$, THF, MeOH

Scheme 81

We had initially believed that debenzylation of the *N*-benzyl groups, under hydrogenolysis conditions, would also cleave any *O*-benzyl protecting groups (including OPMB) (hence our earlier attempt to remove the PMB group in order to replace it with a TBS ether). However, we decided to continue with the

hydrogenolysis protocol and address any issues regarding oxidation of the primary hydroxyl in the presence of a secondary hydroxyl group at a later date, if required. As it turned out exposure of **169** to a hydrogen atmosphere in the presence of Pearlman's catalyst effectively removed the *N*-benzyl protecting groups without cleaving the *p*-methoxybenzyl group to give **171** in excellent yield, **scheme 82**. This result was slightly surprising but fortunate as it meant we no longer had to address the issue of oxidising a primary hydroxyl group in the presence of both a secondary alcohol and a secondary amine.



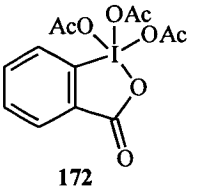
169 **171**

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

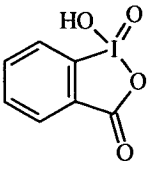
Scheme 82

5.1.5 IBX Oxidation of Amino Alcohol 171

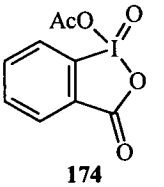
There has been considerable interest, during the last decade or so, in hypervalent iodine derivatives due to their recognised versatility in preparative organic synthesis.[41,146] Of the various iodo-based reagents, the Dess-Martin periodinane (DMP) **172** (**scheme 83**) has attracted particular attention because it is one of the mildest reagents available for the oxidation of alcohols to carbonyls. Recently, the iodinane oxides **173** (*o*-IodoxyBenzoic Acid (IBX))[147] and **174**[148] have been used to convert alcohols to aldehydes. These iodinane oxides seem to share some oxidising properties with DMP, for example, they all oxidise primary alcohols to aldehydes without over oxidation to carboxylic acids. In fact, it has also been claimed[148] that **174** is the actual oxidant in aged but still effective batches of DMP. However IBX differs from DMP in the oxidation of 1,2-diols. DMP cleaves the glycol bond whereas IBX oxidises them to α-ketols or α-diketones without cleavage of the 1,2-diol bond.



172



173

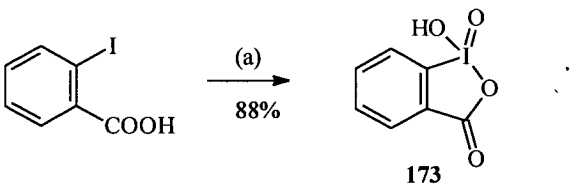


174

Scheme 83

IBX has been utilised to a much lesser extent than DMP due, in the most part, to its insolubility in common organic solvents. However, the discovery that IBX was readily soluble in DMSO and that THF could be used as a co-solvent for DMSO insoluble compounds has led to an increase in use of this oxidant, and it is now seen an extremely important addition to the repertoire of oxidising agents presently available.

IBX was synthesised by Garnet Howells according to the published procedure of Dess and Martin[149] from *o*-Iodoxybenzoic acid, **scheme 84**.



173

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

Scheme 84

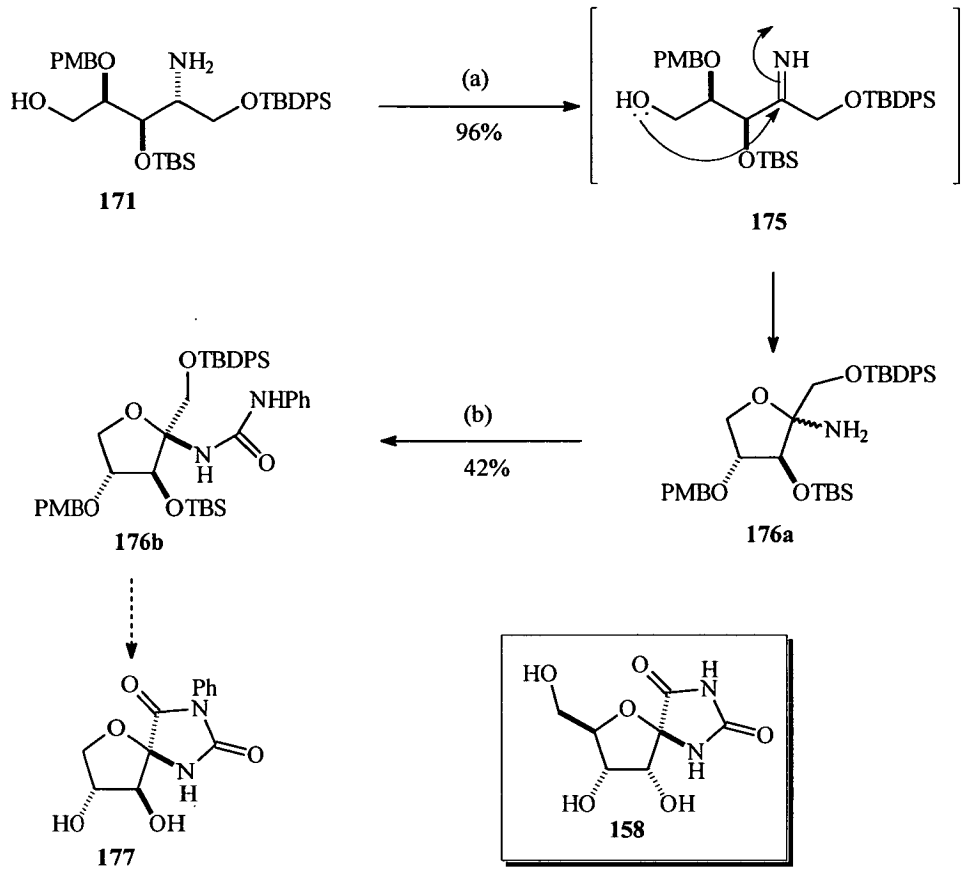
We were attracted to the use of IBX in the oxidation of the primary hydroxyl group of amino alcohol **171** as a result of a report that showed it to selectively oxidise primary alcohols in the presence of primary, secondary and tertiary amines.[150] Thus to a clear solution of one equivalent of IBX in DMSO (the IBX solubilises after ca. 15 minutes) was added a solution of **171** in THF. After approximately 15 minutes t.l.c. showed that the starting material had been completely consumed and a new spot had appeared. Careful analysis of this compound showed that it was not the desired lactol, which would have been formed

via oxidation of the primary hydroxyl, but the cyclic sugar **176a** present as a 3:2 mixture of anomers. Thus, contrary to literature precedent oxidation of the amine has occurred. The resulting imine **175** was presumably then trapped by the primary hydroxyl group to afford **176a**, **scheme 85**, (in a very clean reaction no other oxidation products were observed).

Although one might expect hydrolysis of amine **176a** to occur in the presence of water,[151] evidence for the retention of the nitrogen atom can be seem in the high resolution mass spectrum (**176a**-$C_{35}H_{52}NO_5Si_2$ $[M+H]^+$ within 0.12 ppm *vs* $C_{35}H_{50}O_6Si_2$ $[M^+]$, with 38 ppm deviation). Whilst the ^{13}C NMR signal for the anomeric carbon atom is perhaps higher than might be anticipated, similar stable anomeric amines have been observed by Fleet,[152a] through reduction of azide precursors. Furthermore, the facile oxidation of secondary amines to imines using a hypervalent iodine species has previously been reported.[152b]

Further evidence for the trapping of imine intermediates can also be seen in the work of Fleet towards the synthesis of 5-*epi*hydantocidin[153] and other analogues of hydantocidin.[154] In these examples the imine intermediates were generated by azide disproportionation in the presence of TPAP[153] and by NBS oxidation of an amine,[154] respectively.

To confirm that **176a** was indeed the proposed anomeric amine a small portion of the compound was reacted with phenyl isocyanate. After flash column chromatography the urea **176b** was isolated in a pure form. The stereochemical relationship at the anomeric position was assigned on the basis of ^1H NMR nOe experiments. Signals for the urea N*H* protons were clearly visible in the ^1H NMR spectrum (at 7.71 and 5.17 ppm), the formation of the urea was further confirmed by IR and HRMS. A ^1H NMR of the crude reaction mixture also showed the presence of the diastereomeric urea, however, this could not be isolated in a pure form.



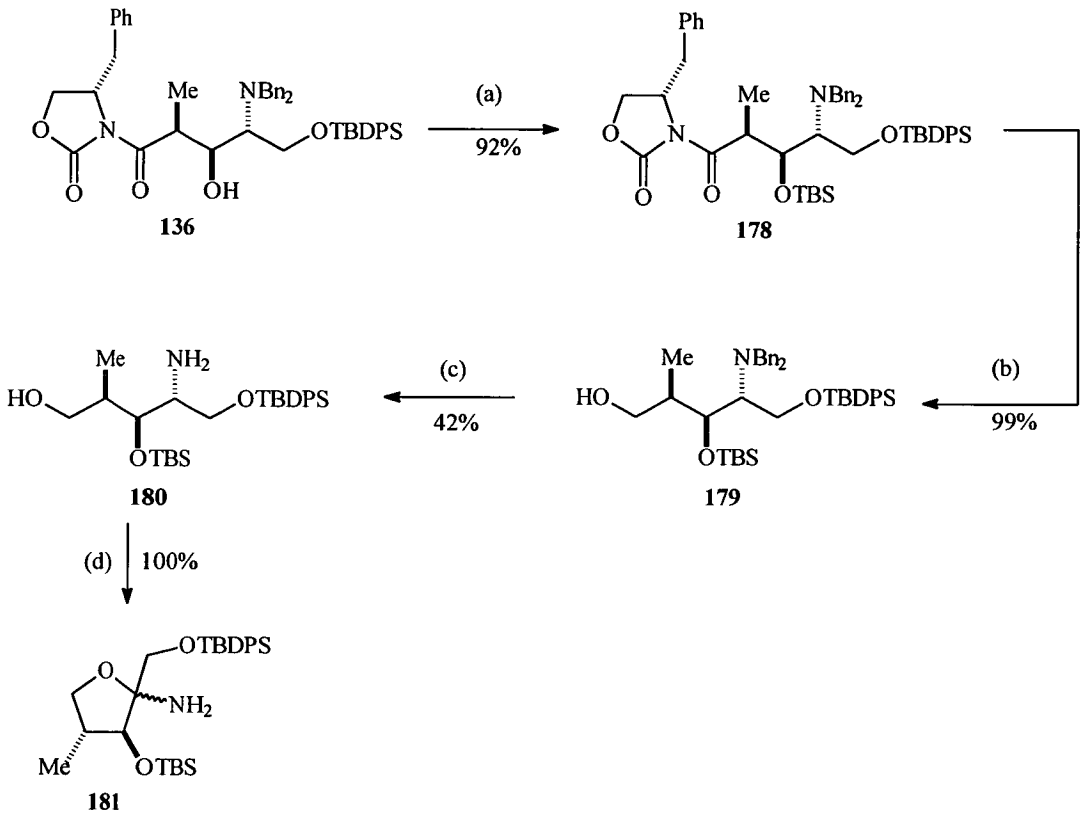
(a) IBX, DMSO, THF; (b) PhNCO, THF

Scheme 85

Although this result was disappointing from the point of view that nectrisine could not be synthesised in this manner, it is clear that **176b** is structurally similar to the sugar core of hydantocidin **158**. Formation of the hydantoin ring would, therefore, provide us with an analogue of hydantocidin **177** that might be of biological interest. This, therefore, turned out to be a most useful discovery. Unfortunately, further studies into the formation of the hydantoin ring and completion of the synthesis of the analogue was not possible due to time constraints. However, this chemistry is at present being actively pursued within the Hulme group, along with the synthesis of other analogues of hydantocidin.

5.2 Use of Propionate Aldol Adduct 136 to Provide Another Potential Hydantocidin Analogue

The chemistry developed in the above example was expanded to include the propionate aldol adduct **136**. The same chemistry was utilised and is shown in **scheme 86**. Due to time constraints the synthesis of amino alcohol **180** was not optimised and full characterisation of **180** and **181** was not possible, however, NMR data strongly supported their synthesis.

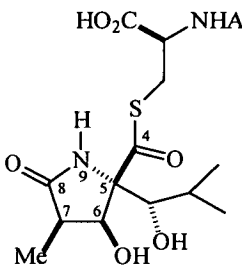


(a) TBSOTf, 2,6-lutidine, DCM; (b) $LiBH_4$, THF, MeOH; (c) $Pd(OH)_2/C$, H_2, MeOH; (d) IBX, DMSO, **180**, THF

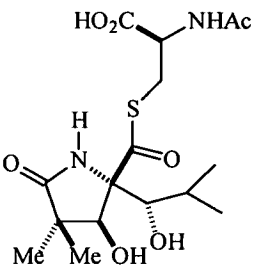
Scheme 86

5.3 Use of an Asymmetric Chromium Mediated Reformatsky Reaction in the Synthesis of a Lactacystin Analogue

Lactacystin **182** is a microbial product first isolated by Omura *et. al.*[152] and found to be a remarkably selective and potent inactivator of the 20*S* proteosome. Because of this and the scarcity of naturally derived **182** there has been intense interest in the synthesis of **182** and its analogues.[153] Corey subsequently found that the *gem*-dimethyl analogue **183** was an even more potent inhibitor.[154]



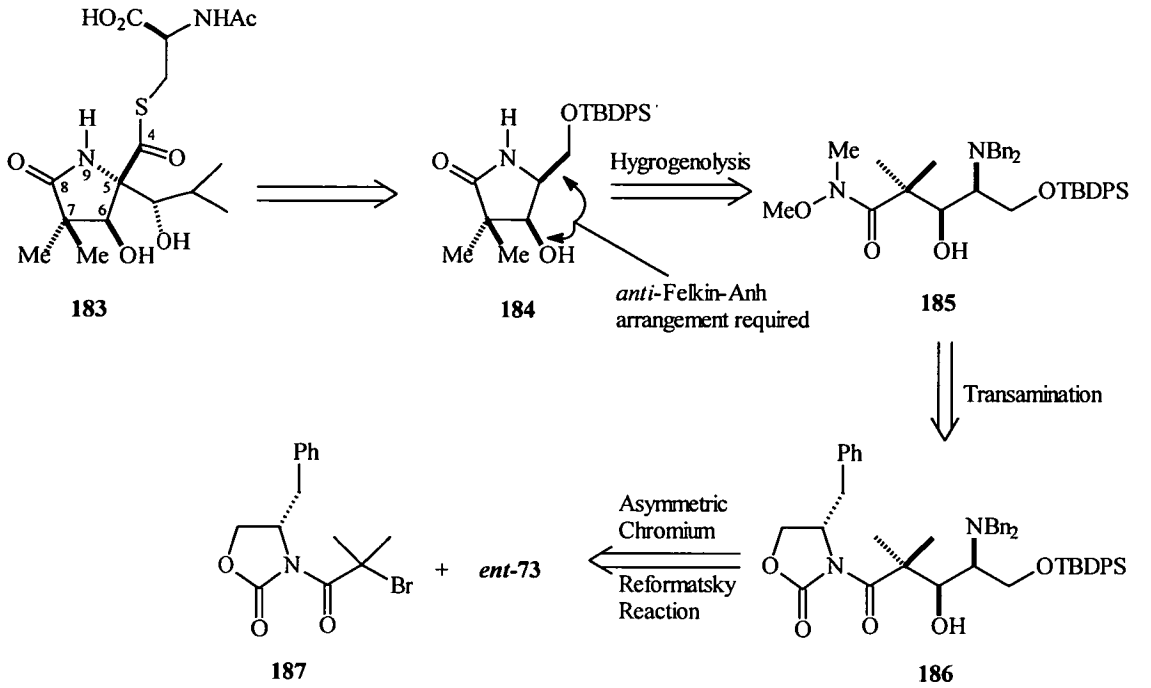
182



183

Scheme 87

We believed that the methodology which allowed for the formation of lactams **114** and **134** would be useful in a synthetic strategy directed toward lactacystin analogues of the type **183**. Directing our synthesis, initially, towards this *gem*-dimethyl analogue would negate the need to control the relative stereochemistry between the C_6 and C_7 substituents (synthesis of **182** would require an *anti* aldol type reaction to generate the required stereochemistry). However, in order to generate the required *anti*-Felkin-Anh stereochemical relationship between substituents at the C_5 and C_6 positions a 'mismatched' aldol type process would be required. Our initial goal was, therefore, to efficiently generate lactam **184, scheme 88**.

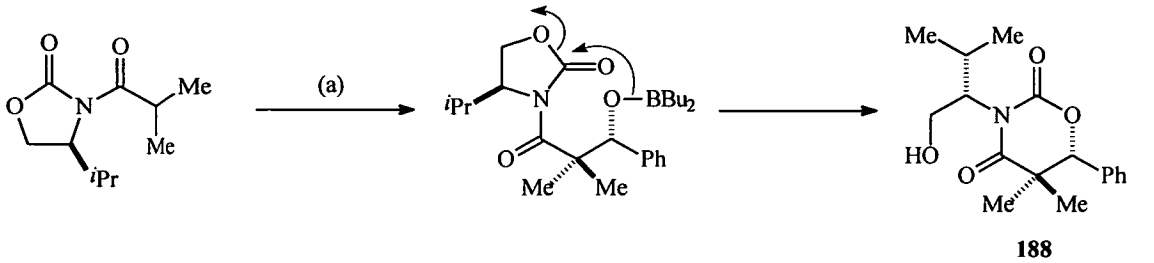


Scheme 88

The above retrosynthetic analysis highlights the chemistry which we believed would generate the desired lactam **184**. As before, hydrogenolysis of Weinreb amide **185** should lead to the desired lactam which, it was thought, would be attainable from aldol adduct **186**. The synthesis of **186** would be achieved *via* an asymmetric chromium mediated Reformatsky reaction, between the chromium enolate of **187** and *ent*-**73**.

5.3.1 The Asymmetric Chromium Mediated Reformatsky Reaction

The introduction of a quaternary centre in the asymmetric Evans boron mediated aldol reaction has been shown to be problematic, in that ring opening of the oxazolidin-2-one as shown in **scheme 89** is known to occur generating oxazinediones of the type **188**.[155]



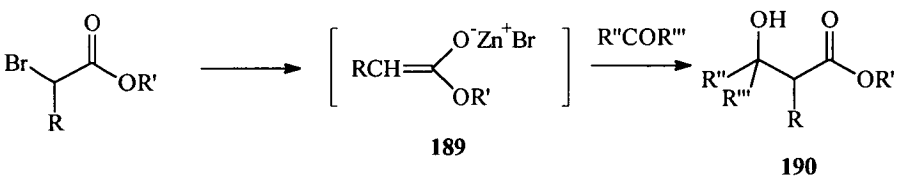
188

(a) (i) Bu_2BOTf, Et_3N, (ii) PhCHO

Scheme 89

Utilising other types of auxiliaries, for example, imidazolidin-2-ones,[156] can prevent this. However, we wished to continue utilising the Evans type oxazolidin-2-ones, and instead, overcome this problem by generating the desired aldol adduct *via* an asymmetric chromium mediated Reformatsky reaction, recently developed by Wessjohann.[157]

The Reformatsky reaction, **scheme 90**, like the aldol reaction, can be regarded as a two step reaction with formation of an enolate (traditionally using Zn) **189** and reaction with an aldehyde or ketone to yield a β-hydroxy ester **190**.

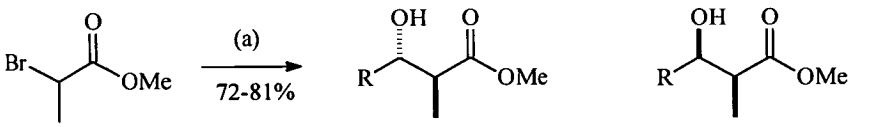


189 190

Scheme 90

Wessjohann recently reported that the reaction of α-bromo ester **191** with isobutyraldehyde or benzaldehyde in the presence of $CrCl_2$ and LiI gave good yields of β-hydroxy esters **192** and **193**, **scheme 91** (this has now been greatly expanded upon to include many other types of bromo compounds and reaction partners).[160d] The traditional Reformatsky reaction using zinc, in general, suffers from low reactivity of the zinc species (use of activated zinc can be useful)[158] and poor reproducibility. The chromium mediated Reformatsky reaction was, on the other hand, found to be capable of generating aldol adducts with reproducible yields,

excellent chemoselectivity, and also, without any retro-reaction,[160b] which is a drawback of many base catalysed aldolisations.

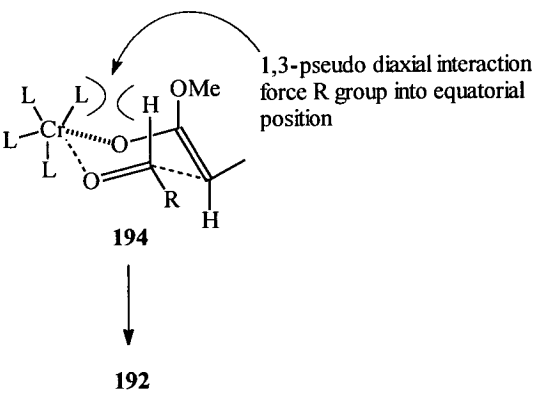


191 R = ^{i}Pr or Ph **192** **193**

(a) $CrCl_2$, LiI, THF

Scheme 91

Additionally, the reaction produced predominantly *anti* aldol adducts **192**, with relatively low selectivities. This was explained by invoking the Zimmerman-Traxler model **194, scheme 92**, in which a slight preference for the *E*-enolate exists, providing *anti* diastereomers **192**.



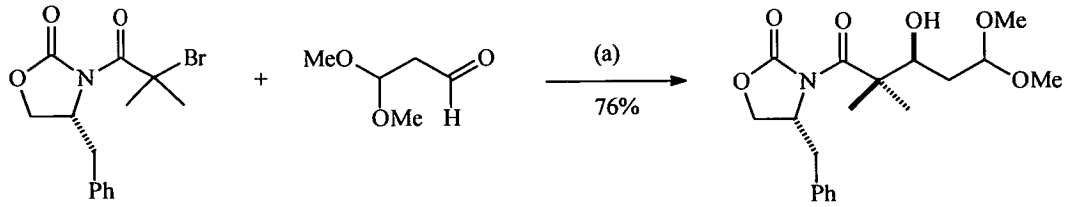
194

192

Scheme 92

Wessjohann has subsequently shown that it is possible, under these conditions, to introduce quaternary centres to aldol adducts in an asymmetric fashion. Using Evans oxazolidin-2-one chiral equivalent *ent*-**187**,[160c] the corresponding aldol adduct **195** was generated as a single diastereomer, **scheme 93**, with the absolute stereocontrol being determined by the chirality of the auxiliary, in the same manner as the previously discussed boron mediated aldol reaction, **chapter 2**. However, the

problem associated in generating such aldol adducts with asymmetric boron-enolate chemistry (ring opening of oxazolidin-2-one, described above) was not observed.



ent-**187** **195**

(a) $CrCl_2$, LiI, THF

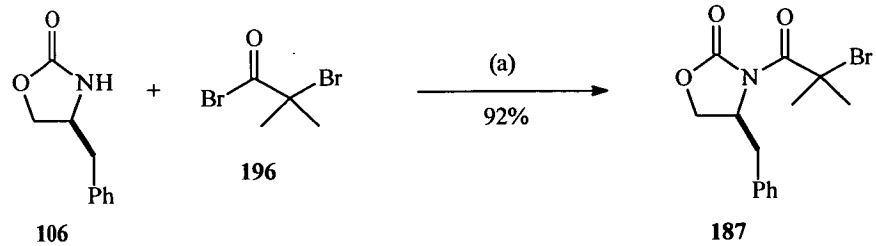
Scheme 93

5.3.2 Asymmetric Chromium Mediated Reformatsky Reaction with Aldehyde 73

We believed that the high levels of stereoselectivity observed for the 'mismatched' boron mediated aldol reaction (**scheme 62**) between the boron-enolate of *ent*-**101** and **73** might also be observed in the chromium mediated Reformatsky reaction. For the correct absolute stereochemistry (generating **186**) this would require a reaction between the chromium-enolate of **187** and *ent*-**73** (a 'mismatched' reaction, by analogy with the boron aldol process).

Initially, however, we chose to perform the reaction with the chromium-enolate of **187** and aldehyde **73**, which we believed would give the Felkin-Anh type product and represent the 'matched' reaction. This was in order to ascertain whether the chromium Reformatsky reaction would be compatible with aldehyde **73**, and if so, how selective it would be compared with the 'matched' boron mediated aldol process.

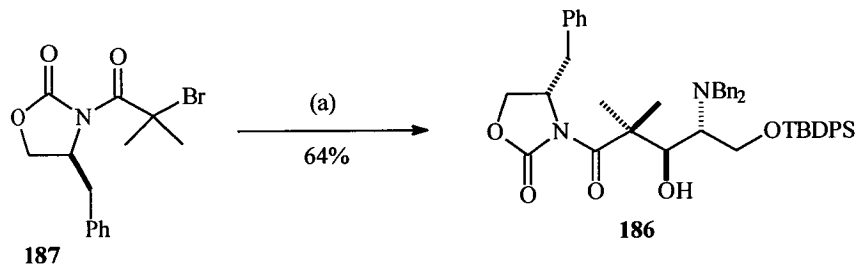
The reaction of lithiated **106** and 2-bromo-2-methylpropionylbromide **196** provided chiral component **187** in excellent yield, **scheme 94**.



(a) BuLi, THF, -78 °C; **196**

Scheme 94

Reaction between **187** and **73** in the presence of $CrCl_2$ and LiI[ξ] in THF cleanly afforded the desired aldol adduct as a single diastereomer in good yield. The Felkin-Anh stereochemistry was assigned by analogy to the previously described boron mediated aldol process. The quality of the $CrCl_2$ was found to be crucial. Aged samples, inevitably, contained some of the oxidised Cr(III) species which resulted in lower isolated yields of the desired adduct. As a result all manipulations involving chromium (II) chloride were carried out in a glove bag under an argon atmosphere. Good supplies of chromium (II) chloride resulted in reproducibly good yields for the reaction, **scheme 95**.

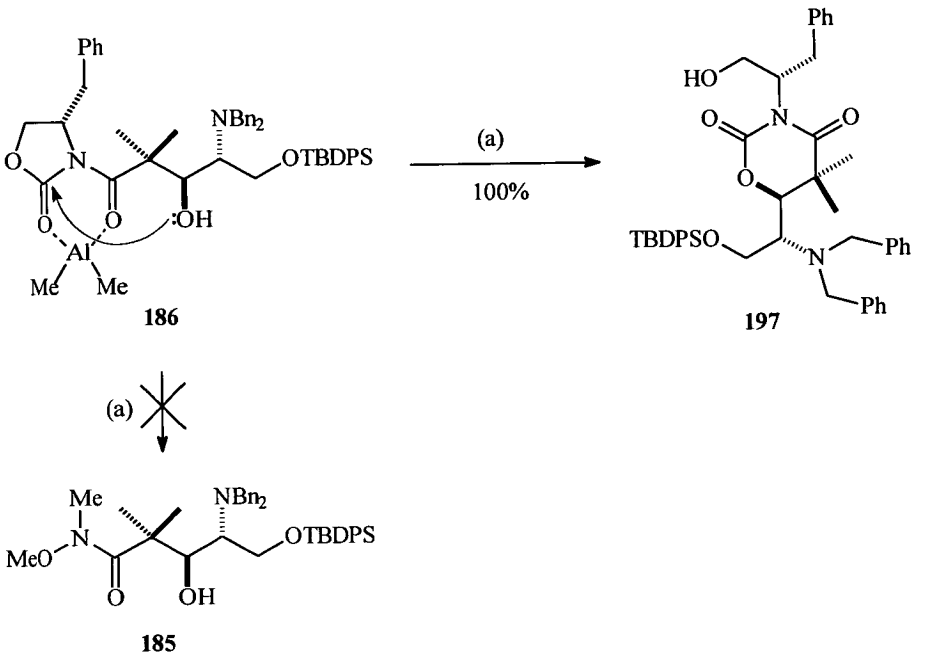


(a) $CrCl_2$, LiI, **73**, THF, room temperature

Scheme 95

[ξ] Addition of lithium iodide results in clean reactions and higher yields. The effect of its addition includes general Lewis acid and nucleophilic iodide catalysis. However, the main influence of its addition is thought to be through its ability to solubilise and modify the nature of the chromium dichloride. The active species has been proposed by Wessjohann to be a $Li_2[CrX_4L_2]$ species or similar complex.

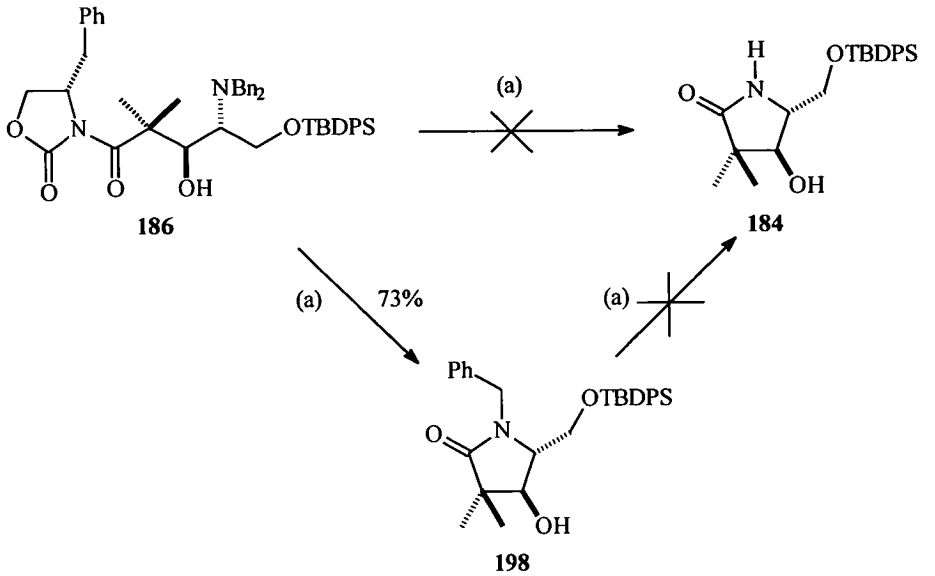
Attempts to generate Weinreb amide **185** under the usual transamination conditions ($AlMe_3$/(MeO)N(Me)H•HCl) was unsuccessful. Formed in quantitative yield, the product from the reaction was discovered to be oxazine-2,4-dione **197**. This must have been the result of attack from the secondary hydroxyl group onto the $AlMe_3$ activated oxazolidin-2-one carbonyl group, as shown in **scheme 96**. This being the product we had initially sought to avoid by moving away from boron-enolate chemistry.



(a) (MeO)N(Me)H•HCl, $AlMe_3$, THF, -30 °C→room temp.→-30 °C; **186**, THF, -30 °C→room temp.

Scheme 96

As a result of this we decided to investigate whether lactamisation (to generate the desired lactam **184**) would be possible through debenzylation of aldol adduct **186**. We believed that the hindered *exo*-cyclic carbonyl group would allow for the removal of both benzyl protecting groups before cyclisation could take place. However, exposure of **186** to a hydrogen atmosphere in the presence of Pearlman's catalyst, disappointingly, afforded only the *N*-benzyl protected lactam **198** in good yield, **scheme 97**. Once again, prolonged exposure to hydrogen under these conditions did not result in the desired deprotected lactam being formed.

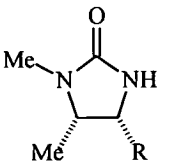


(a) $Pd(OH)_2/C$, H_2, MeOH

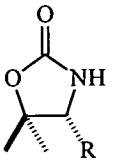
Scheme 97

Clearly the failing of this route was due to the unsuitability of the Evans chiral oxazolidin-2-one. The formation of oxazinediones is documented in boron mediated aldol reactions of Evans oxazolidin-2-ones, as described at the beginning of this section. However, circumvention of this problem *via* the successful use of a chromium mediated Reformatsky reaction inevitably proved futile, with formation of the undesired oxazine-2,4-dione **197** taking place in the next stage of the synthesis.

We believe that the use of alternative chiral auxiliaries, for example, imidazolidin-2-ones, of the type **199** (mentioned previously) or the 'SuperQuat' type auxiliaries **200** developed by Davies[159] might prove to be more successful, **scheme 98**. The carbonyl group of these auxiliaries is more resistant to nucleophilic attack, compared with Evans type oxazolidin-2-ones, as a result of electronic (increased deactivation of carbonyl by *N*-Me moiety in **199**) and steric (5,5-dimethyl substituent of SuperQuats hinders approach of nucleophile) factors respectively. Unfortunately, time did not permit further investigations.



199



200

Scheme 98

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), Bruker AC250 (250 MHz), Bruker AM360 (360 MHz) or Varian Inova 600 (600 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), Bruker AC250 (62.9 MHz) or Bruker AM360 (90.6 MHz) instruments and are reported in ppm on the δ scale.

Infra-red spectra were recorded on a Biorad FTS-7 or 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 $60F_{254}$ (0.25 mm) glass backed silica plates

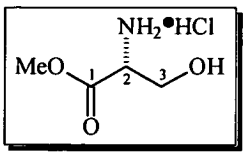
and visualised by ultraviolet (UV) light and/or ammonium molybdate stain.[φ] Flash column chromatography was carried out on Merck Kieselgel 60 (Merck 9385) under positive pressure by means of a hand pump. Eluent compositions are quoted as v/v ratios. Chiral high performance liquid chromatography (HPLC) was carried out on a Waters 786 instrument with a Chiracel OD column (internal diameter 4.6 mm) equipped with a UV detector. A standard flow rate of 0.5 cm^3/min was used. All HPLC samples were filtered through 0.45 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.[163] Dichloromethane (DCM), dimethylformamide (DMF), triethylamine, diisoproylethylamine and 2,6-lutidine were distilled from calcium hydride and stored over calcium hydride under an argon atmosphere. Tetrahydrofuran (THF) was distilled from sodium metal/benzophenone ketyl and stored under an argon atmosphere. Acetyl and propionyl chloride were distilled immediately prior to use. 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 or flame dried under argon prior to use. Standard techniques for the handling of air-sensitive materials were employed.[164]

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

Methyl (2*R*)-2-amino-3-hydroxypropanoate•hydrochloride *65*

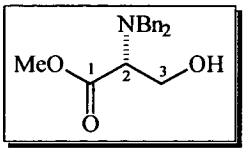


Acetyl chloride (56.1 g, 50.8 cm^3, 0.71 mol) was added dropwise to methanol (300 cm^3) at 0 °C. The mixture was stirred for ca. 15 mins and *D*-Serine (25.0 g, 0.24 mol) was then added portionwise to the solution. The resulting mixture was heated to reflux and held at reflux for 3 hours. Concentration under reduced pressure provided the title compound (36.2 g, 98%) as a solid. Recrystallisation from methanol provided an analytical sample, mp 164-166 °C; $[\alpha]_D$ -8.9 (*c* 0.64, MeOH) [lit., (Aldrich) mp 163-166 °C, $[\alpha]_D$ -4.0 (*c* 4.0, EtOH)]; δ_H (200 MHz, D_2O) 4.13 (1H, t, *J* 3.8, C_2H), 3.95 (1H, dd, *J* 12.7, 4.1, $C_3H_AH_B$), 3.83 (1H, dd, *J* 12.7, 3.5, $C_3H_AH_B$), 3.70 (3H, s, O*Me*); δ_C (50.3 MHz) 168.6, 58.8, 54.3, 53.3; (Found : C, 30.57; H, 6.33; N, 8.79. $C_4H_9NO_3$.HCl requires C, 30.87; H, 6.43; N, 9.00%).

Methyl (2*S*)-2-amino-3-hydroxypropanoate•hydrochloride *ent-65*

Synthesised in an analogous manner to the (*R*)-isomer, from *L*-serine. Thus, acetyl chloride (4.1 cm^3, 57.6 mmol), methanol (25 cm^3) and *L*-serine (2.0 g, 18.9 mmol) gave the title compound (2.8 g, 95%) as a colourless crystalline solid, mp 163 °C (dec.), $[\alpha]_D$ +4.2 (*c* 1.0, MeOH) [lit., (Aldrich) mp 163 °C (dec.), $[\alpha]_D$ +3.4 (*c* 4, MeOH).

Methyl (2*R*)-2-dibenzylamino-3-hydroxypropanoate *66*

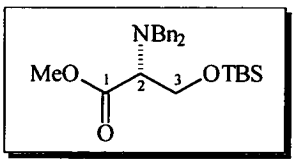


To a solution of *D*-serine methylester•hydrochloride (15.0 g, 96.5 mmol) in anhydrous acetonitrile (240 cm^3) was added potassium carbonate (66.6 g, 0.48 mol) followed by benzyl bromide (41.1 g, 28.6cm^3, 0.24 mol). The mixture was stirred for 24 hours. Water (300cm^3) was added and the aqueous phase was extracted with EtOAc (3 x 300 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (4:1)] to give the title compound (27.5 g, 95%) as an oil, R_f [hexane:EtOAc (5:1)] 0.23; $[\alpha]_D$ +174.6 (*c* 0.8, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3455, 3061, 3028, 2950, 2844, 1731, 1491, 1453; δ_H (200 MHz, $CDCl_3$) 7.39-7.21 (10H, m, Ar*H*), 3.92 (2H, d, *J* 13.4, NCH_AH_BPh x 2) 3.80 (3H, s, O*Me*), 3.80-3.69 (2H, m, C_2H + CH_XH_YOH), 3.69 (2H, d, *J* 13.4, NCH_AH_BPh x 2), 3.59 (1H, dd, *J* 15.0, 7.5, CH_XH_YOH), 2.58 (1H, brs, O*H*); δ_C (50.3 MHz) 171.1, 138.6 (2C), 128.9 (4C), 128.4 (4C), 127.3 (2C), 61.6, 59.2, 54.6 (2C), 51.2; m/z (FAB) 299 ($[M+H]^+$, 59%), 268 (100), 240 (96), 181 (41), 92 (41); HRMS (FAB) ($C_{18}H_{21}NO_3$ requires 299.1521, found 299.1576).

Methyl (2*S*)-2-dibenzylamino-3-hydroxypropanoate *ent-66*

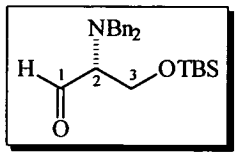
Synthesised in analogous manner to the (*R*)-isomer from *ent*-**65**. Thus, *ent*-**65** (2.21 g, 14.6 mmol), potassium carbonate (9.75 g, 70.5 mmol) and benzyl bromide (4.2 cm^3, 35.4 mmol) in acetonitrile (45 cm^3) gave the title compound (4.08 g, 94%) as a colourless oil, $[\alpha]_D$ -127.7 (*c* 1.1, $CHCl_3$).

Methyl (*2R*)-3-*t*-butyldimethylsilyloxy-2-dibenzylaminopropanoate *67*



To a solution of ester **66** (3.86 g, 12.8 mmol) and *tert*-butyldimethyllsilyl chloride (3.85 g, 25.6 mmol) in anhydrous DMF (20 cm^3) was added imidazole (3.50 g, 51.2 mmol). The mixture was stirred for 18 hours. Brine (150 cm^3) was added and the aqueous phase was extracted with DCM (3 x 150cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:EtOAc (5:1)] to give the title compound (5.21 g, 99%) as a colourless oil, R_f [hexane:EtOAc (4:1)] 0.83; $[\alpha]_D$ +49.6 (*c* 1.35, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1737, 1602, 1585, 1494; δ_H (200 MHz, $CDCl_3$) 7.42-7.19 (10H, m, Ar*H*), 4.00 (1H, dd, *J* 9.8, 6.6, CH_AH_BOTBS), 3.97 (2H, d, *J* 13.9, NCH_XH_YPh x 2), 3.88 (1H, dd, *J* 9.7, 6.2, CH_AH_BOTBS), 3.75 (3H, s, O*Me*), 3.67 (2H, d, *J* 14.0, NCH_XH_YPh x 2), 3.56 (1H, dd~t, *J* 6.1, C_2H), 0.86 (9H, s, ^tBu), 0.00 (6H, s, *Me* x 2); δ_C (50.3 MHz) 172.0, 139.8 (2C), 128.6 (4C), 128.1 (4C), 126.8 (2C), 62.8, 62.5, 55.3 (2C), 50.9, 25.6 (3C), 17.9, -5.8 (2C); m/z (FAB) 413 ($[M+H]^+$, 11%), 354 (29), 268 (26), 91 (100), 73 (72); HRMS (FAB) ($C_{24}H_{35}NO_3Si$ requires 413.2386, found 413.2421).

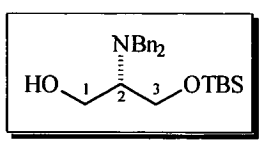
Attempted synthesis of Aldehyde *68 via* DIBAL-H reduction of Ester *67*

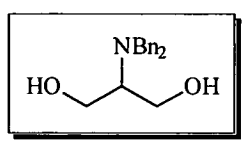


General Procedure:

To a solution of ester **67** in toluene or THF at either -78, -89, or -98 °C was added diisobutylaluminium hydride (1 equivalent (1.0 *M* in toluene)). The resulting solution was stirred until the starting material had been consumed (by t.l.c.). The reaction was quenched at the reaction temperature by addition of methanol and allowed to warm to room temperature. The resulting mixture was then poured onto a rapidly stirred biphasic mixture of saturated aqueous sodium potassium tartrate solution and DCM and stirred for 1 hour. In each case t.l.c. and ^{1}H NMR showed that the aldehyde was not formed as the sole product. It was also discovered that the aldehyde was extremely unstable to silica gel and as a result the reaction mixtures were not purified further.

(2*S*)-2-Dibenzylamino-3-*tert*-butyldimethylsilyloxypropan-1-ol *69* and 2-Dibenzylaminopropan-1,3-diol *70* from reduction of TBS ester *67*





$LiAlH_4$ Procedure:

To a suspension of lithium aluminium hydride (20 mg, 0.53 mmol) in THF (4 cm^3) at -78 °C was added ester **67** (100 mg, 0.24 mmol) in THF (4 cm^3) at -78 °C. The

resulting mixture was stirred at -78 °C for 3 hours. The reaction was quenched by sequential addition of water (1 cm^3), 15% aqueous sodium hydroxide solution (1 cm^3) and finally, water (1 cm^3). The organic phase was separated and the aqueous phase was extracted with diethyl ether (3 x 10 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (5:1)→(1:1)] to elute first the desired alcohol **69** (45 mg, 48%) as a colourless oil, followed by the undesired *meso* diol impurity **70** (28 mg, 42%) as a colourless solid.

DIBAL-H Procedure:

To a solution of ester **67** (100 mg, 0.24 mmol) in toluene (3 cm^3) at -78 °C was added diisobutylaluminium hydride (0.53 cm^3, (1.0 *M* in toluene), 0.53 mmol). The reaction mixture was stirred at -78 °C for 40 minutes. The reaction was quenched by addition of methanol (0.5 cm^3) and allowed to warm to room temperature before being diluted with DCM (10 cm^3). A saturated aqueous solution of sodium potassium tartrate (10 cm^3) was added and the resulting mixture was stirred vigorously for 3 hours. The organic phase was separated and the aqueous phase was extracted with DCM (3 x 10 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (5:1)→(1:1)] to elute first the desired alcohol **69** (67 mg, 76%) followed by the *meso* diol **70** (12 mg, 18%).

Data for alcohol **69**:

Obtained as colourless oil,

R_f [hexane:EtOAc (5:1)] 0.38; $[\alpha]_D$ –66.8 (*c* 0.6, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3451, 1601, 1492; δ_H (200 MHz, $CDCl_3$) 7.27-7.10 (10H, m, Ar*H*), 3.82 (2H, d, *J* 13.2, NC$H_A$$H_B$Ph x 2), 3.77 (1H, dd, *J* 10.6, 5.9, C$H_X$$H_Y$OTBS), 3.64 (1H, dd, *J* 10.6, 5.9, C$H_X$$H_Y$OTBS), 3.57 (2H, d, *J* 13.5, NC$H_A$$H_B$Ph x 2), 3.50-3.45 (2H, m, CH_2OH), 2.98-2.89 (1H, m, C_2H), 2.84 (1H, brs, O*H*), 0.84 (9H, s, ^tBu), 0.00 (6H, s, *Me* x 2);

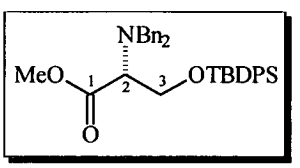
δ_C (50.3 MHz) 139.5 (2C), 128.8 (4C), 128.3 (4C), 127.0 (2C), 60.8, 59.6, 59.4, 53.9 (2C), 25.7 (3C), 18.0, -5.7 (2C); m/z (FAB) 386 ([M+H]$^+$, 57%), 354 (49), 296 (17), 240 (55), 91 (100), 73 (93); HRMS (FAB) ($C_{23}H_{35}NO_2Si$ requires 386.2515, found 386.2515).

Data for diol **70**:

Obtained as a colourless solid,

R_f [hexane:EtOAc (1:1)] 0.24; mp 83-85 °C; ν_{max} (neat)/cm^{-1} 3324, 1602, 1584, 1493; δ_C (200 MHz, $CDCl_3$) 7.40-7.11 (10H, m, Ar*H*), 3.78 (4H, s, NC*H*$_2$Ph x 2), 3.74 (2H, dd, *J* 11.0, 7.7, C*H*$_X$H$_Y$OH x 2), 3.61 (2H, dd, *J* 11.0, 5.7, CH$_X$*H*$_Y$OH x 2), 3.00 (1H, tt, *J* 7.7, 5.8, C$_2$*H*), 2.69 (2H, brs, O*H* x 2); δ_C (50.3 MHz) 139.2 (2C), 128.9 (4C), 128.4 (4C), 127.2 (2C), 59.9, 59.7 (2C), 53.9 (2C); m/z (FAB) 272 ([M+H]$^+$, 60%), 240 (55), 182 (18), 105 (17), 91 (100), 73 (23); HRMS (FAB) ($C_{17}H_{21}NO_2$ requires 272.1651, found 272.1650).

Methyl (2*R*)-3-*tert*-butyldiphenylsilyloxy-2-dibenzylaminopropanoate *71*



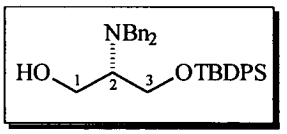
To a solution of ester **66** (11.4 g, 37.8 mmol) and *tert*-butyldiphenylsilyl chloride (20.8 g, 19.7 cm^3, 75.6 mmol) in anhydrous DMF (60 cm^3) was added imidazole (10.5 g, 151.2 mmol). The mixture was stirred for 18 hours. Brine (150 cm^3) was added and the aqueous phase was extracted with DCM (3 x 150cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:EtOAc (15:1)] to give the title compound (20.42 g, 100%) as a colourless oil, R_f [hexane:EtOAc (10:1)] 0.77; $[\alpha]_D$ +30.9 (*c* 2.22, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3060, 2948, 1734, 1592, 1455; δ_H (200 MHz, $CDCl_3$)

7.67-7.22 (20H, m, Ar*H*), 4.06 (1H, dd, *J* 10.2, 6.2, C*H*$_A$H$_B$OTBDPS), 4.03 (2H, d, *J* 14.3, NC*H*$_X$H$_Y$Ph x 2), 4.00 (1H, dd, 10.2, 6.2, CH$_A$*H*$_B$OTBDPS), 3.77 (2H, d, *J* 14.3, NCH$_X$*H*$_Y$Ph x 2), 3.76 (3H, s, O*Me*), 3.70 (1H, t, *J* 6.2, C$_2$*H*), 1.05 (9H, s, ^{t}*Bu*); δ_C (62.9 MHz) 171.8, 139.6 (2C), 135.4 (4C), 133.0 (2C), 129.5 (2C), 128.5 (4C), 128.1 (4C), 127.5 (4C), 126.8 (2C), 63.2, 62.8, 55.3 (2C), 51.0, 26.5 (3C), 19.0, m/z (FAB) 537 (M^+, 100%), 478 (40), 268 (35), 135 (25); HRMS (FAB) ($C_{34}H_{39}NO_3Si$ requires 537.2699, found 537.2721).

Methyl (2*S*)-3-*tert*-butyldiphenylsilyloxy-2-dibenzylaminopropanoate *ent-71*

Synthesised in an analogous manner to the (*R*)-isomer from *ent*-**66**. Thus, *ent*-**66** (2.11 g, 6.86 mmol), *tert*-butyldiphenylsilylchloride (3.77 g, 1.37 mmol) and imidazole (1.87 g, 2.74 mmol) in DMF (11 cm^3) gave the title compound (3.75 g, 100%) as a colourless oil, $[\alpha]_D$ -26.7 (*c* 1.06, $CHCl_3$).

(2*S*)-3-*tert*-Butyldiphenylsilyloxy-2-dibenzylaminopropan-1-ol *72*



To a solution of ester **71** (3.0g, 5.6 mmol) in anhydrous toluene (20 cm^3) at -78 °C was added diisobutylaluminium hydride (14.0 cm^3, (1.0M in toluene), 14.0 mmol). The mixture was stirred at -78 °C for 30 minutes then quenched by dropwise addition of methanol (ca. 10 cm^3). The resulting mixture was allowed to warm to room temperature and diluted with DCM (100 cm^3). A saturated aqueous solution of sodium potassium tartrate (75 cm^3) was added and the biphasic mixture was stirred vigorously for 3 hours by which time two clear phases were apparent. The organic phase was separated and the aqueous phase was extracted with DCM (3 x 100 cm^3).

The combined organic extracts were dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (5:1)], to give the title compound (2.64 g, 93%) as a colourless oil, R_f [hexane:EtOAc (5:1)] 0.38; $[\alpha]_D$ -58.4 (*c* 1.15, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3451, 3061, 3028, 2933, 2858, 1593, 1456; δ_H (200 MHz, $CDCl_3$) 7.74-7.19 (20H, m, Ar*H*), 3.90 (1H, dd, *J* 10.7, 6.0, C$H_A$$H_B$OTBDPS), 3.88 (2H, d, *J* 13.4, NC$H_X$$H_Y$Ph x 2), 3.75 (1H, dd, *J* 10.7, 6.0, CH$_A$$H_B$OTBDPS), 3.61 (2H, d, *J* 13.4, NCH$_X$$H_Y$Ph x 2), 3.58 (2H, d, *J* 7.5, C$_1$$H_2$), 3.10 (1H, ddd, *J* 7.4, 6.0, 6.0, C$_2$*H*), 2.92 (1H, brs, O*H*), 1.10 (9H, s, ^tBu); δ_C (62.9 MHz) 139.4 (2C), 135.5 (4C), 132.9 (2C), 129.8 (2C), 129.7 (2C), 128.8 (4C), 128.3 (4C), 127.7 (4C), 61.3, 59.9, 59.4, 53.9 (2C), 26.7 (3C), 19.0; m/z (FAB) 510 ([M+H]$^+$, 91%), 480 (92), 240 (99), 197 (100), 77 (50); HRMS (FAB) ($C_{33}H_{40}NO_2Si$ requires 510.2828, found 510.2829).

(2*R*)-3-*tert*-Butyldiphenylsilyloxy-2-dibenzylaminopropan-1-ol *ent-72*

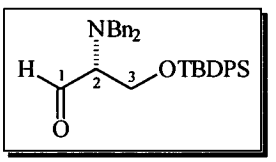
Synthesised in an analogous manner to the (*S*)-isomer from *ent*-**71**. Thus, *ent*-**71** (1.02 g, 1.88 mmol) and diisobutylaluminium hydride (3.95 cm^3, (1.5 *M* in toluene), 5.63 mmol) in toluene (4.0 cm^3) gave the title compound (878 mg, 91 %) as a colourless oil, $[\alpha]_D$ +45.2 (*c* 1.06, $CHCl_3$).

***Via* Reduction of Aldehyde 73:**

To a solution of aldehyde **73** (78 mg, 0.15 mmol) in toluene (1 cm^3) at -78 °C was added diisobutylaluminium hydride (0.21 cm^3, (1.0 *M* in toluene), 0.21 mmol). The mixture was stirred at -78 °C for 5 mins. The reaction was quenched by the sequential addition of water (50 µl), aqueous sodium hydroxide (50 µl, 1.0 *M*) and water (1 cm^3). The resulting mixture was allowed to warm to room temperature and extracted with DCM (3 x 2 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel

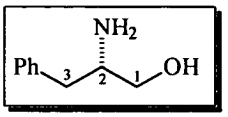
[hexane:EtOAc (5:1)] to give alcohol **72** (70 mg, 90%) as a colourless oil, HPLC [hexane:propan-2-ol (19:1)] (*S* enantiomer) R_t = 5.2 minutes, (*R* enantiomer) R_t = 6.2 minutes, >98% e.e.

(2*R*)-3-*tert*-Butyldiphenylsilyloxy-2-dibenzylaminopropanal *73*



To a solution of oxalyl chloride (0.45 g, 0.31 cm^3, 3.6 mmol) in anhydrous DCM (15 cm^3) at -78 °C was added a solution of DMSO (0.57 g, 0.43 cm^3, 4.5 mmol) in DCM (0.5 cm^3) dropwise. The mixture was stirred for ca. 5 minutes when it became cloudy. A solution of the alcohol **72** (1.57 g, 3.08 mmol) in DCM (5.0 cm^3) at -78 °C was introduced *via* cannula. The resulting clear solution was stirred at -78 °C for 1 hour. Triethylamine (1.20 g, 1.63 cm^3, 11.72 mmol) was added and the resulting cloudy solution was allowed to warm to room temperature over ca. 15 minutes. Water (10 cm^3) was added producing two clear phases. The organic phase was separated and the aqueous phase was extracted with DCM (3 x 10 cm^3). The combined organic extracts were washed sequentially with 1% HCl (20 cm^3), water (20 cm^3), a saturated aqueous solution of sodium bicarbonate (20 cm^3) and brine (20 cm^3), then dried and concentrated under reduced pressure to give the title compound (1.56 g, 100%) as a very pale yellow oil which was used in subsequent stages without further purification, R_f [hexane:EtOAc (5:1)] 0.66; ν_{max} (neat)/cm^{-1} 3068, 3028, 2930, 2856, 2711, 1731, 1427, 1112; 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, 5.6, CH_AH_BOTBDPS), 4.09 (1H, dd, *J* 11.0, 5.6, CH_AH_BOTBDPS), 3.98 (2H, d, *J* 13.9, NCH_XH_YPh x 2), 3.90 (2H, d, *J* 13.9, NCH_XH_YPh x 2), 3.52 (1H, t, *J* 5.8, C_2H), δ_C (50.3 MHz) 202.8, 139.3 (2C), 135.6 (2C), 135.5 (2C), 132.8, 132.7, 129.8 (2C), 128.6 (4C), 128.3 (4C), 127.7 (4C), 127.1 (2C), 67.8, 60.5, 55.6 (2C), 26.7 (3C), 19.9.

(2*S*)-2-Amino-3-phenylpropan-1-ol *107*



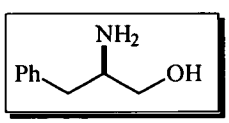
Meyers Route:

To a mixture of *L*-phenylalanine (80.0 g, 0.48 mol) and sodium borohydride (43.7 g, 1.15 mol) in sodium dried THF (750 cm^3) at 0 °C was added a solution of iodine (122 g, 0.48 mol) in sodium dried THF (250 cm^3). After gas evolution had ceased the resulting mixture was heated to reflux and held at reflux for 18 hours. The mixture was cooled to 0 °C and the remaining sodium borohydride was quenched by careful addition of methanol (~80 cm^3). The resulting clear solution was stirred for 30 mins before being concentrated under reduced pressure to a colourless paste. This paste was taken up into 20% aqueous potassium hydroxide solution (1.0 L) and stirred at room temperature for 18 hours. The mixture was extracted with DCM (3 x 750 cm^3) and the combined organic extracts were dried and concentrated under reduced pressure to a colourless solid which was recrystallised from toluene to give the title compound (60.8 g, 84%) as a colourless crystalline solid, mp 91-93 °C; $[\alpha]_D$ -22.9 (*c* 1.2, EtOH) [lit.,[83d] mp 89.5-91.5 °C, $[\alpha]_D$ -24.7 (*c* 1.03, EtOH)]; ν_{max} ($CHCl_3$ soln.)/cm^{-1} 3679, 3623, 3368, 1580, 1520, 1498; δ_H (200 MHz, $CDCl_3$) 7.33-7.09 (5H, m, Ar*H*), 3.59 (1H, dd, *J* 10.6, 3.5, $C_1H_AH_B$), 3.37 (1H, dd, *J* 10.6, 7.3, $C_1H_AH_B$), 3.09 (1H, dddd, *J* 8.8, 7.3, 5.0, 3.5, C_2H), 2.77 (1H, dd, *J* 13.6, 5.0, $C_3H_XH_Y$), 2.63 (2H, brs, NH_2), 2.49 (1H, dd, *J* 13.6, 8.8, $C_3H_XH_Y$); δ_C (50.3 MHz) 138.5, 128.9 (2C), 128.3 (2C), 126.2, 65.6, 53.9, 40.2, m/z (FAB) 152 ($[M+H]^+$, 100%), 91 (40), 77 (5). All spectroscopic data was in good agreement with that of the literature.

Evans Route:

To a solution of *L*-phenylalanine (5.0 g, 30.3 mmol) in THF (15 cm^3) was added borontrifluoride•etherate (3.73 cm^3, 30.3 mmol). The mixture was heated to reflux and held at reflux for 1 hour, by which time all solid material had dissolved. The temperature of the reaction mixture was then lowered to just below reflux and borane•dimethylsulfide (30.3 cm^3, (1.0 *M* in DCM), 30.3 mmol) was added dropwise. Hydrogen evolution was observed and dimethylsulfide was allowed to distil off as it was liberated. The solution was then heated to reflux and held at reflux for 6 hours. The reaction mixture was cooled to 0 °C and the remaing borane was quenched by careful addition of THF/water (1:1) (10 cm^3). Aqueous sodium hydroxide (25 cm^3, 5.0 *M*) was added and the reaction mixture was heated to reflux and held at reflux for 16 hours. Concentration under reduced pressure removed THF and the remaining aqueous mother liquor was extracted with DCM (5 x 20 cm^3). The combined organic extracts were dried and concentrated under reduced pressure to give a solid which was recrystallised from EtOAc to give the title compound (3.05 g, 67%) as colourless needles, mp 92-94 °C; *all spectroscopic data was identical to the compound synthesised above.*

(2*R*)-2-Amino-3-phenylpropan-1-ol *ent-107*



Meyers Route:

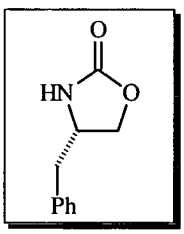
Synthesised in an analogous manner to (2*S*)-2-amino-3-phenylmethylpropan-1-ol from *D*-phenylalanine. Thus *D*-phenylalanine (20.0 g, 0.12 mol), sodium borohydride (10.93 g, 0.29 mol) and iodine (30.5g, 0.12 mol) in THF (250 cm^3) gave after recrystallisation from toluene the title compound (13.9 g, 76%) as a colourless

crystalline solid, mp 87-89 °C, $[\alpha]_D$ +22.3 (*c* 1.0, EtOH) [lit.,[165] mp 88-89 °C, $[\alpha]_D$ +22.1 (*c* 1.5, EtOH)].

Evans Route:

Synthesised in an analogous manner from *D*-phenylalanine (5.0 g, 30.3 mmol), borontrifluoride•etherate (3.73 cm^3, 30.3 mmol) and borane•dimethylsulfide (30.3 cm^3, (1.0 *M* in DCM), 30.3 mmol) in THF (15 cm^3) to give the title compound (2.91 g, 64%) after recrystallisation from EtOAc as a colourless crystalline solid, mp 87-89 °C.

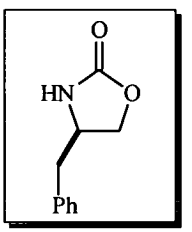
(4*S*)-4-Phenylmethyloxazolidin-2-one *106*



A dry 1L 3-necked flask equipped with a thermometer and a 45 cm Vigreaux distillation column was charged with *S*-phenylalaninol **107** (48.5 g, 0.32 mol), potassium carbonate (4.4 g, 0.032 mol) and diethyl carbonate (79.0 cm^3, 0.65 mol). The mixture was carefully heated to 135-140 °C and ethanol was allowed to distil off as it was formed (over ca. 2 hours). The reaction mixture was allowed to cool to room temperature and diluted with DCM (800 cm^3). Potassium carbonate was removed by filtration and the organic phase was washed with a saturated aqueous solution of sodium bicarbonate (400 cm^3) before being dried and concentrated under reduced pressure. The residue crystallised on standing and recrystallisation from [hexane:EtOAc] provided the title compound (47.3 g, 86%) as colourless needles, mp 87-88 °C; $[\alpha]_D$ +5.2 (*c* 1.06, EtOH) [lit.,[83d] mp 87-88.5 °C, $[\alpha]_D$ +4.9 (*c* 1.10, EtOH); ν_{max} ($CHCl_3$ soln./cm^{-1}) 3455, 1757, 1604, 1541, 1498; δ_H (200 MHz, $CDCl_3$) 7.36-

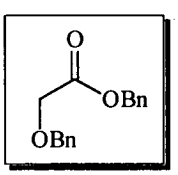
7.15 (5H, m, Ar*H*), 6.46 (1H, brs, N*H*), 4.43-4.32 (1H, m, C_4H), 4.12 (1H, dd, *J* 10.7, 5.2, $C_5H_AH_B$), 4.12-4.05 (1H, m, $C_5H_AH_B$), 2.90 (1H, dd, *J* 13.8, 6.0, CH_XH_YPh) 2.80 (1H, dd, *J* 13.8, 6.3, CH_XH_YPh); δ_C (50MHz) 159.7, 137.8, 128.9 (2C), 128.7 (2C), 127.0, 69.2, 53.5, 41.0; m/z (EI) 178 ($[M+H]^+$, 100), 117 (18.7). All spectroscopic data was in good agreement with that of the literature.

(4*R*)-4-Phenylmethyloxazolidin-2-one *ent-106*



The *R*-enantiomer was synthesised in an analogous manner to the *S*-enantiomer. Thus, *R*-phenylalaninol *ent*-**107** (10.0 g, 66.67 mmol), diethylcarbonate (16.4 cm^3, 133.34 mmol) and potassium carbonate (0.92 g, 6.67 mmol) provided the title compound (9.8 g, 83%) as a colourless solid, mp 86-88 °C; $[\alpha]_D$ -4.5 (*c* 1.2, EtOH) [lit.,**Error! Bookmark not defined.** mp 86-88 °C, $[\alpha]_D$ -4.58 (*c* 1.1, EtOH)].

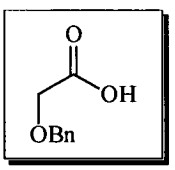
Benzyl benzyloxyacetate *108*



To a solution of glycolic acid (3.0 g, 39.5 mmol) in anhydrous acetonitrile (30 cm^3) was added potassium carbonate (21.8 g, 158.0 mmol) and benzyl bromide (11.0 cm^3, 92.4 mmol). The reaction mixture was stirred for 16 hours and then diluted with water (50 cm^3). The organic phase was separated and the aqueous phase was

extracted with DCM (3 x 50 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (1:1)] to give the title compound (5.25 g, 52%) as a colourless oil, R_f [hexane:EtOAc (1:1)] 0.63; ν_{max} (neat)/cm^{-1} 1755, 1603, 1585, 1496; δ_H (200 MHz, $CDCl_3$) 7.41-7.39 (10H, m, Ar*H*), 5.24 (2H, s, CO_2CH_2Ph), 4.67 (2H, s, $COCH_2OBn$), 4.18 (2H, s, OCH_2Ph); δ_C (50.3 MHz) 169.0, 135.9, 134.2, 127.4 (4C), 127.2 (4C), 127.1 (2C), 72.0, 65.8, 65.2; m/z (FAB) 257 ($[M+H]^+$, 14.6%), 181 (41.2), 137 (22.5), 91 (100), 77 (7.3).

Benzyloxyacetic acid *109*



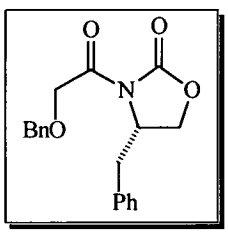
***Method A*:**

To a solution of benzyloxyacetic acid benzyl ester **108** (256 mg, 1.0 mmol) in MeOH (5 cm^3) was added 10% Pd/C (20 mg) and ammonium acetate (45 mg, 0.5 mmol). The mixture was exposed to a hydrogen atmosphere (1 atm.) and stirred under hydrogen for 30 minutes. The reaction mixture was filtered through a pad of celite and concentrated under reduced pressure to give the title compound (160 mg, 95%) as a colourless oil, R_f [hexane:EtOAc (2:1)] 0.31; ν_{max} (neat)/cm^{-1} 3450, 1731, 1650, 1556, 1496, 1455; δ_H (200 MHz, $CDCl_3$) 10.5 (1H, brs, CO_2H), 7.39-7.25 (5H, m, Ar*H*), 4.64 (2H, s, $COCH_2OBn$), 4.15 (2H, s, OCH_2Ph); δ_C (50.3 MHz) 175.4, 136.5, 128.5 (2C), 128.1, 128.0 (2C), 73.3, 66.4; m/z (EI) 166 (M^+, 27.9%), 107 (99.3), 91 (100), 77 (35.5).

Method B:

To a suspension of sodium hydride (12.96 g, (60% oil dispersion), 322 mmol) in THF (200 cm^3) at 0 °C was added bromoacetic acid (10.0 g, 71.8 mmol). Benzyl alcohol (7.75 g, 71.8 mmol) was added dropwise to the mixture followed by tetra-*n*-butylammonium bromide (1.15 g, 3.60 mmol). The reaction mixture was warmed to reflux and held at reflux for 4 hours. The reaction was carefully quenched by addition of water at 0 °C and the resulting mixture was concentrated under reduced pressure to provide a colourless slurry. This slurry was diluted with diethyl ether (175 cm^3) and extracted with a saturated aqueous solution of sodium bicarbonate (3 x 175 cm^3). The combined aqueous extracts were acidified to pH1 by addition of concentrated sulfuric acid and extracted with diethyl ether (3 x 300 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The resulting residue was chromatographed on silica gel [hexane:EtOAc (2:1)] to give the title compound (9.83 g, 82%) as a colourless oil, *all spectroscopic data was identical to the acid obtained from* ***Method A.***

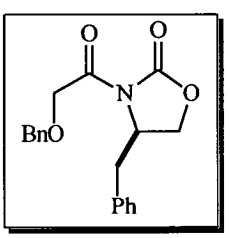
(4*S*)-3-(2'-Benzyloxy-1'-oxoethyl)-4-phenylmethyloxazolidin-2-one *101*



To a solution of benzyloxyacetic acid **109** (4.95 g, 29.0 mmol) in THF (170 cm^3) at -78 °C was added triethylamine (3.96 cm^3, 29.0 mmol) and pivaloyl chloride (3.67 cm^3, 29.0 mmol). The resulting slurry was allowed to warm to 0 °C and stirred at 0 °C for 20 minutes before being re-cooled to -78 °C. Meanwhile in a separate flask, a solution of oxazolidinone **106** (5.40 g, 29.0 mmol) in THF (30 cm^3) at -78 °C was

treated with *n*-butyllithium (20.7 cm^3, 1.6 *M* in hexanes, 29.0 mmol). The lithiated oxazolidinone was then cannulated into the flask containing the mixed anhydride and the resulting mixture was stirred for 1 hour. A saturated aqueous solution of ammonium chloride (100 cm^3) was added producing two clear phases. The organic phase was separated and the aqueous phase was extracted with DCM (3 x 100 cm^3). The combined organic extracts were washed sequentially with saturated aqueous sodium bicarbonate solution (150 cm^3) and brine (150 cm^3) then dried and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:EtOAc (1:1)] to give the title compound (9.89 g, 100%) as a colourless crystalline solid, R_f [hexane:EtOAc (1:1)] 0.62; mp 69-71 °C; $[\alpha]_D$ +57.9 (*c* 1.14, $CHCl_3$) [lit.,[166] mp 67-69 °C, $[\alpha]_D$ +56.0 (*c* 1.71, $CHCl_3$)]; ν_{max} ($CHCl_3$ soln./cm^{-1}) 1778, 1714, 1603, 1584, 1496; δ_H (200 MHz, $CDCl_3$) 7.44-7.19 (10H, m, Ar*H*), 4.71-4.74-4.59 (5H, m, C_2H_2 + OCH_2Ph + C_4H), 4.28 (1H, t, *J* 9.0, $C_5H_AH_B$), 4.22 (1H, dd, *J* 9.0, 3.0, $C_5H_AH_B$), 3.34 (1H, dd, *J* 13.2, 2.9, CH_XH_YPh), 2.82 (1H, dd, *J* 13.2, 9.3, CH_XH_YPh); δ_C (50.3 MHz) 170.0, 153.2, 137.0, 134.8, 129.3 (2C), 128.9 (2C), 128.4 (2C), 128.0 (2C), 127.9, 127.3, 73.4, 69.5, 67.1, 54.7, 37.6; m/z (EI) 326 ($[M+H]^+$, 26.0%), 195 (100), 178 (47.6), 91 (18.8); HRMS (EI) ($C_{19}H_{20}NO_4$ requires 326.1392, found 326.1392). All spectroscopic data was in good agreement with that of the literature.

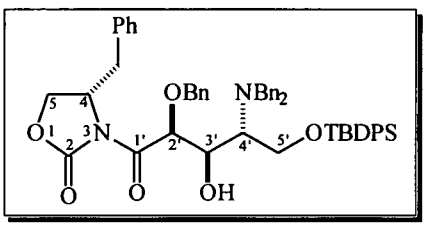
(4*R*)-3-(2'-Benzyloxy-1'-oxoethyl)-4-phenylmethyloxazolidin-2-one *ent-101*



Synthesised in an analogous manner to the *S*-enantiomer from *ent*-**106**. Thus, oxazolidin-2-one *ent*-**106** (3.0 g, 16.95 mmol), ^{n}BuLi (10.60 cm^3, 1.6 *M* in hexanes, 16.95 mmol), benzyloxyacetic acid (2.83 g, 16.95 mmol), pivaloyl chloride (2.0 cm^3,

16.95 mmol) and triethylamine (2.38 cm^3, 16.95 mmol) in THF (80 cm^3) provided the title compound (5.4 g, 98%) as a colourless solid, mp 67-69 °C; $[\alpha]_D$ -58.3 (*c* 1.1, $CHCl_3$) [lit.,[104a] mp 67-69 °C, $[\alpha]_D$ -57.45 (*c* 2.0, $CHCl_3$)].

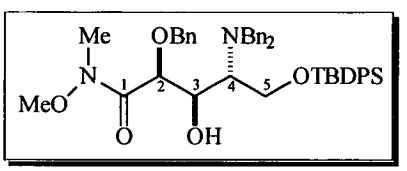
(2'*S*,3'*R*,4*S*,4'R)-3-(2'-Benzyloxy-5'-*tert*-butyldiphenylsilyloxy-4'-*N*,*N*-dibenzylamino-3'-hydroxy-1'-oxopentyl)-4-phenylmethyloxazolidin-2-one *102*



To a solution of the glycolate equivalent **101** (3.42 g, 10.56 mmol) in DCM (57 cm^3) at -78 °C was added triethylamine (1.39 g, 1.91 cm^3, 13.73 mmol) followed by dropwise addition of dibutylboron triflate (12.76 cm^3, 1.0 *M* in DCM, 12.76 mmol). The solution was stirred at -78 °C for 45 mins and then allowed to warm to 0 °C over 30 mins and stirred at 0 °C for 1.25 hours. The solution was then recooled to -78 °C and a -78 °C solution of aldehyde **73** (1.47 g, 2.89 mmol) in DCM (7.5 cm^3) was added dropwise *via* cannula. The reaction mixture was stirred at –78 °C for 1 hour 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 methanol (40 cm^3) followed by aqueous pH 7 phosphate buffer solution (25 cm^3). Hydrogen peroxide (30% aqueous solution) (10 cm^3) in methanol (10cm^3) was added dropwise to the solution and the mixture was stirred and warmed to room temperature over ca. 1 hour. The organic phase was separated and the aqueous phase was extracted with DCM (3 x 75 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:EtOAc (3.5:1)] to give the title compound (1.98 g, 82%) as a solid, R_f [hexane:EtOAc (1:1)] 0.79; mp 62-63 °C; $[\alpha]_D$ +14.48 (*c* 0.87, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3559, 3062, 3011, 2932, 2857, 1781, 1706;

δ_H (600 MHz, $CDCl_3$) 7.74-7.13 (30H, m, Ar*H*), 5.41 (1H, d, *J* 2.6, C_2-*H*), 4.47 (1H, dddd, *J* 10.1, 7.1, 3.2, 2.1, C_4-*H*), 4.26 (1H, d, *J* 11.0, OCH_AH_BPh), 4.26-4.24 (1H, m, C_3-*H*), 4.11 (1H, dd, *J* 9.1, 2.1, $C_5H_XH_Y$), 4.08-4.05 (3H, m, $CH_2OTBDPS$ + $C_5H_XH_Y$), 4.06 (1H, d, *J* 11.0, OCH_AH_BPh), 3.86 (2H, d, *J* 13.8, NCH_SH_TPh x 2), 3.61 (2H, d, *J* 13.8, NCH_SH_TPh x 2), 3.29 (1H, q, *J* 5.4, C_4-*H*), 3.22 (1H, dd, *J* 13.4, 3.2, CH_PH_QPh), 3.05 (1H, brd, *J* 8.1, O*H*), 2.58 (1H, dd, *J* 13.4, 10.1, CH_PH_QPh), 1.04 (9H, s, ^tBu); δ_C (62.9 MHz) 171.1, 152.9, 139.9 (2C), 137.2, 135.7 (3C), 135.6 (3C), 135.2, 133.0, 132.8, 129.6 (2C), 129.3 (2C), 129.0 (3C), 128.8 (2C), 128.3 (2C), 128.0 (4C), 127.6 (3C), 127.6 (3C), 127.2, 126.7 (2C), 78.3, 72.5, 72.1, 66.6, 61.3, 59.6, 55.8, 54.6 (2C), 37.2, 26.7 (3C), 18.9; m/z (FAB) 833 ($[M+H]^+$, 26%), 478 (15); HRMS (FAB) ($C_{52}H_{57}N_2O_6Si$ requires 833.3985, found 833.3954).

(2*S*,3*R*,4*R*)-2-Benzyloxy-5-*tert*-butyldiphenysilyloxy-4-*N*,*N*-dibenzylamino-3-hydroxypentanoic acid methoxy methyl amide *110*



To a suspension of *N*,*O*-dimethylhydroxylamine•hydrochloride (4.20 g, 43 mmol) in anhydrous THF (7.5 cm^3) at -30 °C was added trimethylaluminium (21.5 cm^3, 2.0 *M* in toluene, 43 mmol). The solution was allowed to warm to room temperature over ca. 15 minutes, after which time a clear solution remained. The solution was recooled to -30 °C and a -30 °C solution of the aldol adduct **102** (1.43 g, 1.72 mmol) in THF (5 cm^3) was added dropwise via cannula. The mixture was warmed to 0 °C and stirred at 0 °C for 2 hours. The reaction mixture was then cannulated into a rapidly stirred biphasic mixture of DCM (50 cm^3) and saturated aqueous sodium potassium tartrate solution (50 cm^3) and stirred for 5 hours when two clear phases were apparent. The organic phase was separated and the aqueous phase was extracted with DCM (3 x 50

cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:EtOAc (4:1)] to give the title compound (1.23 g, 100%) as a solid, R_f [hexane:EtOAc (2:1)] 0.40; mp 42-43 °C; $[\alpha]_D$ -30.4 (*c* 1.09, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3458, 3059, 3023, 2930, 2854, 1664, 1425; δ_H (600 MHz, $CDCl_3$) 7.74-7.16 (25H, m, Ar*H*), 4.62 (1H, brs, C_2H), 4.36 (1H, d, *J* 10.7, OCH_AH_BPh), 4.20 (1H, td, *J* 7.8, 2.1, C_3H), 4.10 (1H, dd, *J* 11.0, 4.5, $C_5H_XH_YOTBDPS$), 4.07 (1H, dd, *J* 11.0, 5.6, $C_5H_XH_YOTBDPS$), 3.93 (1H, d, *J* 10.7, OCH_AH_BPh), 3.89 (2H, d, *J* 14.0, NCH_SH_TPh x 2), 3.72 (2H, d, *J* 14.0, NCH_SH_TPh x 2), 3.40 (3H, s, O*Me*), 3.20 (1H, ddd, *J* 7.8, 5.6, 4.5, C_4H), 3.15 (3H, s, N*Me*), 2.75 (1H, brd, *J* 6.8, O*H*), 1.08 (9H, s, ^tBu); δ_C (62.9 MHz) 171.4, 140.0 (2C), 137.5, 135.7 (2C), 135.6 (2C), 133.3, 133.0, 129.6 (2C), 128.7 (4C), 128.1 (4C), 127.9 (2C), 127.9 (2C), 127.6 (2C), 127.5 (2C), 127.4, 126.7 (2C), 75.2, 71.4, 70.9, 60.9, 60.8, 59.3, 54.8 (2C), 32.1, 26.7 (3C), 18.9; m/z (FAB) 717 ($[M+H]^+$, 30%), 639 (11), 478 (100), 278 (37), 135 (77), 91 (92); HRMS (FAB) ($C_{44}H_{53}N_2O_5Si$ requires 717.3724, found 717.3728).

110 from aldol adduct ***126***

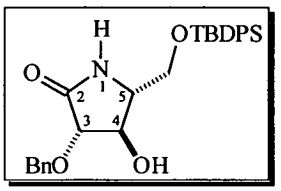
In an analogous manner to that described above aldol adduct **126** (150 mg, 0.18 mmol), *N,O*-dimethylhydroxylamine•HCl (440 mg, 4.5 mmol), trimethylaluminium (2.25 cm^3, (2.0 *M* in toluene), 4.5 mmol) in THF (3 cm^3) gave Weinreb amide **110** (120 mg, 93%) as a colourless solid. Mixed melting point with authentic **110**: 42-43 °C. All other spectroscopic data was identical with the previously synthesised Weinreb amide (*vide supra*).

110 from aldol adduct ***125***

In an analogous manner to that described above aldol adduct **126** (100 mg, 0.15 mmol), *N,O*-dimethylhydroxylamine•HCl (440 mg, 4.5 mmol), trimethylaluminium (2.25 cm^3, (2.0 *M* in toluene), 4.5 mmol) in THF (3 cm^3) gave Weinreb amide **110**

(102 mg, 91%) as a colourless solid. Mixed melting point with authentic **110**: 42-43 °C. All other spectroscopic data was identical with the previously synthesised Weinreb amide (*vide supra*).

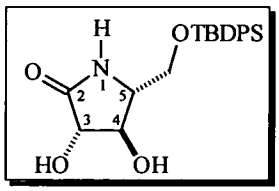
(3*S*,4*R*,5*R*)-3-Benzyloxy-5-*tert*-butyldiphenylsilyloxymethyl-4-hydroxy pyrrolidine-2-one *113*



A solution of the Weinreb amide **110** (1.0 g, 1.4 mmol) and 20% $Pd(OH)_2/C$ (1.0 g) in methanol (10 cm^3) was exposed to a hydrogen atmosphere (1 atm) and stirred vigorously for 8 hours. The mixture was then filtered through a pad of celite and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane-EtOAc (2:3)] to give the title compound (591 mg, 89%) as a colourless oil, R_f [hexane:EtOAc (1:1)] 0.38; $[\alpha]_D$ -30.0 (*c* 0.6, CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3381, 1708; δ_H (200 MHz, $CDCl_3$) 7.66-7.10 (15H, m, Ar*H*), 5.69 (1H, brs, N*H*), 5.06 (1H, d, *J* 11.7, OCH_AH_BPh), 4.67 (1H, d, *J* 12.1, OCH_AH_BPh), 4.05-3.93 (2H, m, C_3H + C_5H), 3.74 (1H, dd, *J* 10.2, 4.0, $CH_XH_YOTBDPS$), 3.54 (1H, dd, *J* 10.3, 7.0, $CH_XH_YOTBDPS$), 3.45-3.32 (1H, m, C_4H), 2.11 (1H, brs, O*H*), 0.98 (9H, s, ^tBu); δ_C (50.3 MHz) 172.2, 137.7, 135.5 (2C), 132.5, 130.0 (2C), 128.5 (2C), 128.1 (4C), 127.9 (4C), 127.8 (2C), 81.8, 75.2, 72.7, 64.6, 57.8, 26.6 (3C), 19.0; m/z (FAB) 476 ($[M+H]^+$, 41%), 307 (29), 154 (98), 136 (76), 91 (100); HRMS (FAB) ($C_{28}H_{34}NO_4Si$ requires 476.2257, found 476.2258).

In an analogous manner Weinreb amide ***110*** (100 mg, 0.14 mmol), Pd/C (100 mg) in methanol (1 cm^3) was stirred under a hydrogen atmosphere for 24 hours to provide the title compound (57 mg, 86%) as a colourless oil. *Spectroscopic data was identical to that obtained above.*

(3*S*,4*R*,5*R*)-5-*tert*-Butyldiphenylsilyloxymethyl-3,4-dihydroxypyrrolidin-2-one *114*



A solution of the Weinreb amide **110** (1.0 g, 1.4 mmol) and 20% $Pd(OH)_2/C$ (1.0 g) in methanol (10 cm^3) was exposed to a hydrogen atmosphere (1 atm.) and stirred vigorously for 72 hours. The mixture was then filtered through a pad of celite and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:EtOAc (2:3)] to give the title compound (383 mg, 71%) as a colourless foam, R_f [hexane:EtOAc (1:1)] 0.11; $[\alpha]_D$ +11.52 (c 1.05, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3424, 2931, 2863, 1720; δ_H (600 MHz, $CDCl_3$) 7.61-7.25 (10H, m, Ar*H*), 6.15 (1H, brs, N*H*), 4.67 (1H, brs, O*H*), 4.28 (1H, d, *J* 7.7, C_3H), 3.98 (1H, t, *J* 7.4, C_4H), 3.88 (1H, dd, *J* 10.7, 3.5, CH_AH_BOTBDPS), 3.79 (1H, brs, O*H*), 3.61 (1H, dd, *J* 10.7, 7.3, CH_AH_BOTBDPS), 3.51 (1H, dt, *J* 7.3, 3.5, C_5H), 1.03 (9H, s, ^tBu); δ_C (50.3 MHz) 174.2, 135.5 (4C), 132.6 (2C), 130.0 (2C), 127.9 (4C), 75.7 (2C), 64.4, 58.0, 26.6 (3C), 19.0; m/z (FAB) 386 ($[M+H]^+$, 15%), 307 (40), 154 (100), 107 (75), 77 (61); HRMS (FAB) ($C_{21}H_{28}NO_4Si$ requires 386.1787, found 386.1776).

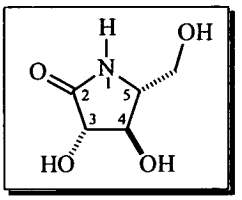
From ***113***:

A solution of **113** (591 mg, 1.24 mmol) and 20 % $Pd(OH)_2$ (600 mg) in methanol (10 cm^3) was stirred under hydrogen for 48 hours to provide **114** (385 mg, 80%).

Or:

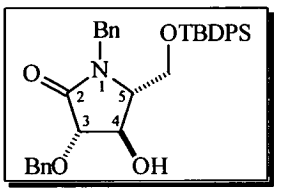
A solution of **113** (57 mg, 0.12 mmol) and 10% Pd/C (60 mg) in methanol (0.5 cm^3) was stirred under hydrogen for 48 hours to provide **114** (35 mg, 76%). *Spectroscopic data was identical to that obtained above.*

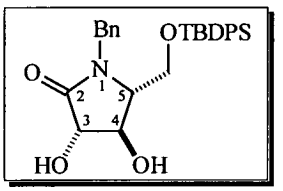
(3*S*,4*R*,5*R*)-3,4-Dihydroxy-5-hydroxymethylpyrrolidin-2-one *115*



To a solution of the TBDPS protected lactam **114** (43 mg, 0.112 mmol) in MeCN/THF (1:1) (1.5 cm^3) was added HF (48% aqueous solution) (0.3 cm^3, ~5 eq.). The mixture was stirred for 15 minutes. Methoxytrimethylsilane (3.0 cm^3) was added cautiously and the mixture was concentrated. The residue was again treated with methoxtrimethylsilane (3 cm^3) and concentrated. This process was repeated once more and the remaining residue was chromatographed on silica gel [$CHCl_3$:MeOH:NH_3 (28 % aqueous) (5:3:1)] to give the title compound (17 mg, 100%) as a colourless solid, R_f [$CHCl_3$:MeOH:NH_3 (28% aqueous) (5:3:1)] 0.14; mp 131-133 °C; $[\alpha]_D$ +14.2 (*c* 0.4, D_2O) [lit.[108] mp 130-133, $[\alpha]_D$ +14.7 (*c* 0.58, D_2O)]; δ_H (250 MHz, D_2O) 4.31 (1H, d, *J* 8.0, C_3H), 4.00 (1H, dd, *J* 8.0, 7.3, C_4H), 3.79 (1H, dd, *J* 12.2, 3.1, CH_AH_BOH), 3.61 (1H, dd, *J* 12.2, 4.9, CH_AH_BOH), 3.45 (1H, ddd, *J* 7.3, 4.9, 3.1, C_5H); δ_C (75 MHz) 175.5, 75.5, 74.6, 60.0, 57.9; m/z (FAB) 148 ($[M+H]^+$, 47.2), 133 (21.9, 105 (32.1), 73 (100); HRMS (FAB) ($C_5H_{10}NO_4$ requires 148.0610, found 148.0613). All spectroscopic data was in good agreement with that of the literature.

(3*S*,4*R*,5*R*)-*N*-Benzyl-3-benzyloxy-5-*tert*-butyldiphenylsilyloxymethyl-4-hydroxypyrrolidin-2-one *116* and (3*S*,4*R*,5*R*)-*N*-Benzyl-5-*tert*-butyldiphenylsilyloxymethyl-3,4-dihydroxypyrrolidin-2-one *117*





A solution of aldol adduct **102** (200 mg, 0.24 mmol) and 20% $Pd(OH)_2/C$ (200 mg) was exposed to a hydrogen atmosphere (1 atm.) and stirred vigorously for 24 hours. The mixture was filtered through a pad of celite and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:EtOAc (2:1)] to give **116** (72 mg, 53%) and **113** (48 mg, 42%). Re-exposure of **116** (70 mg, 0.12 mmol) and 20% $Pd(OH)_2/C$ (100 mg) to a hydrogen atmosphere for 72 hours gave, after chromatography on silica gel [hexane:EtOAc (1:1)], lactam **117** (50 mg, 87%).

Data for **116**:

Obtained as a colourless oil,

R_f [hexane:EtOAc (1:1)] 0.72; $[\alpha]_D$ -2.4 (*c* 0.50, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3374, 1682; δ_H (200 MHz, $CDCl_3$) 7.64-6.94 (20H, m, Ar*H*), 5.15 (1H, d, *J* 12.1, OCH_AH_BPh), 4.98 (1H, d, *J* 15.4, NCH_XH_YPh), 4.86 (1H, d, *J* 12.1, OCH_AH_BPh), 4.35 (1H, brddd, *J* 10.2, 6.5, 3.5, C_4H), 4.13 (1H, d, *J* 7.0, C_3H), 3.77 (1H, dd, *J* 11.0, 3.7, $CH_SH_TOTBDPS$), 3.75 (1H, d, *J* 15.4, NCH_xH_YPh), 3.67 (1H, dd, *J* 11.0, 4.6, $CH_SH_TOTBDPS$), 3.15 (1H, ddd, *J* 6.2, 4.4, 3.7, C_5H), 1.05 (9H, s, ^tBu); δ_C (50.3 MHz) 171.0, 137.9, 135.7, 135.6 (2C), 135.4 (2C), 132.5 (2C), 130.0, 129.9, 128.6 (2C), 128.4 (2C), 128.0 (2C), 127.9 (2C), 127.8 (2C), 127.8 (2C), 127.5 (2C), 81.8, 73.3, 72.4, 60.7 (2C), 43.6, 26.7 (3C), 19.0; m/z (FAB) 566 ($[M+H]^+$, 31%), 386 (77), 296 (15), 217 (29), 91 (100); HRMS (FAB) ($C_{35}H_{40}NO_4Si$ requires 566.2727, found 566.2724).

Data for **117**:

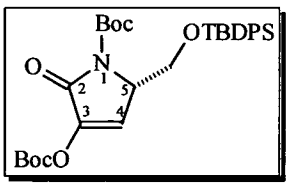
Obtained as a colourless oil,

R_f [hexane:EtOAc (1:1)] 0.32; $[\alpha]_D$ -10.8 (*c* 0.3, CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3357, 1685; δ_H (250 MHz, $CDCl_3$) 7.65-6.91 (15H, m, Ar*H*), 5.03 (1H, d, *J* 15.3, NCH_AH_BPh), 4.39-4.34 (2H, m, C_3H + $CH_XH_YOTBDPS$), 3.98 (1H, brt, *J* 3.9, C_4H), 3.75 (1H, d, *J* 15.5, NCH_AH_BPh), 3.74 (1H, dd, *J* 10.0, 6.5, $CH_XH_YOTBDPS$), 3.23 (1H, dt, *J* 6.7, 3.3, C_5H), 1.04 (9H, s, ^tBu); δ_C (62.9 MHz) 172.5, 135.5 (2C), 134.5, 130.0, 129.9, 129.3, 128.7, 128.6 (2C), 127.9 (2C), 127.8 (3C), 127.6 (3C), 127.5, 76.1, 74.0, 60.6, 59.7, 43.7, 26.8 (3C), 19.1; m/z (FAB) 476 ($[M+H]^+$, 14%), 325 (13), 217 (80), 91 (100), 73 (25); HRMS (FAB) ($C_{28}H_{34}NO_4Si$ requires 476.2257, found 476.2254).

Attempted Reduction of Lactam 114

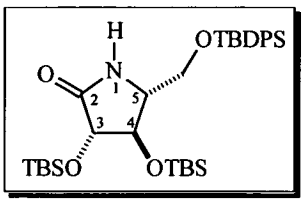
To a -78 °C solution of lactam **114** (100 mg, 0.26 mmol) in toluene (2 cm^3) or THF (2 cm^3) was added either diisobutylaluminum hydride (0.26 cm^3, (1.0 *M* in toluene), 0.26 mmol) or lithiumtriethylborohydride (Super Hydride®) (0.26 cm^3, (1.0 *M* in THF), 0.26 mmol). The resulting mixtures were stirred at -78 °C for 1 hour. T.l.c. indicated that no reaction had taken place in both cases. As a result the reaction mixtures were warmed to room temperature and stirred at room temperature for 3 hours. T.l.c showed that no reaction had occurred. Further additions of the reducing agents had no effect on the reaction outcome. The reactions were summarily abandoned.

(5*R*)-1-(*tert*-Butoxycarbonyl)-3-(*tert*-butoxycarbonyloxy)-5-(*tert*-butyldiphenylsilyloxymethyl)-1H-pyrrol-2 (5H)-one *119*



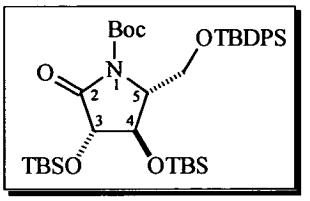
To a solution of the lactam **114** (96 mg, 0.25 mmol) in DCM (1.0 cm^3) was added triethylamine (115 μl, 0.825 mmol), di-*tert*-butyldicarbonate (327 mg, 1.5 mmol) and dimethylaminopyridine (6 mg, 0.05 mmol). The reaction mixture was stirred for 30 minutes then diluted with DCM (5.0 cm^3) and washed with saturated aqueous sodium bicarbonate solution (5.0 cm^3) and brine (5.0 cm^3). The organic phase was concentrated under reduced pressure and the remaining residue was chromatographed on silica gel [hexane:EtOAc (5:1)] to give the title compound (121 mg, 86%) as a colourless oil, R_f [hexane:EtOAc (5:1)] 0.30; ν_{max} (neat)/cm^{-1} 1768 (2 carbonyls, one partially obscured) 1719, 1656; δ_H (250 MHz, $CDCl_3$) 7.63-7.32 (10H, m, Ar*H*), 7.05 (0.2H, d, *J* 2.5, C_4H), 7.00 (0.2H, d, *J* 2.4, C_4H), 6.91 (0.6H, d, *J* 2.4, C_4H), 4.63 (0.4H, m, C_5H) 4.59 (0.6H, ddd, *J* 6.2, 3.2, 2.5, C_5H), 4.38-4.28 (0.4H, m, CH_AH_BOTBDPS), 4.09 (0.6H, dd, *J* 9.8, 3.3, CH_AH_BOTBDPS), 4.00-3.88 (0.4H, m, CH_AH_BOTBDPS), 3.83 (0.6H, dd, *J* 9.8, 6.2, CH_AH_BOTBDPS), 1.54 (5.4H, s, O^t*Bu*), 1.53 (1.8H, s, O^t*Bu*), 1.53 (1.8H, s, O^t*Bu*), 1.50 (1.8H, s, O^t*Bu*), 1.49 (1.8H, s, O^t*Bu*), 1.44 (5.4H, s, O^t*Bu*), 1.01 (5.4H, s, Si^t*Bu*), 0.92 (1.8H, s, Si^t*Bu*), 0.91 (1.8H, s, Si^t*Bu*); δ_C (62.9 MHz) 162.6, 149.4, 148.8, 141.9, 135.4 (2C), 135.3 (2C), 135.0, 132.7, 132.6, 129.8, 127.7 (4C), 127.1, 84.6, 83.3, 62.8, 58.4, 27.9 (3C), 27.4 (3C), 26.6 (3C), 19.1; m/z (FAB) 590 ($[M + Na]^+$, 1.1%), 412 (20), 197 (17.1), 91 (27.8), 57 (100).

(3*S*,4*R*,5*R*)-5-*tert*-Butyldiphenylsilyloxymethyl-3,4-di-*tert*-butyldimethylsilyloxypyrrolidin-2-one *120*



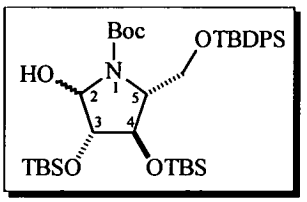
To a solution of the lactam **114** (230 mg, 0.60 mmol) in DCM (5 cm^3) was added 2,6-lutidine (150 μl, 1.32 mmol) followed by *tert*-butyldimethylsilyltrifluoromethane sulfonate (826 μl, 3.60 mmol). The mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with DCM (30 cm^3) and washed with saturated aqueous sodium bicarbonate solution (15 cm^3) and brine (15 cm^3). The organic phase was concentrated under reduced pressure and the residue was chromatographed on silica gel [hexane:EtOAc (6:1)] to give the title compound (310 mg, 85%) as a colourless foam, R_f [hexane:EtOAc (4:1)] 0.66; $[\alpha]_D$ -8.6 (*c* 0.93, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3212, 1720; δ_H (250 MHz, $CDCl_3$) 7.64-7.25 (10H, m, Ar*H*), 5.53 (1H, brs, N*H*), 4.12 (1H, d, *J* 5.8, C_3H), 3.87 (1H, t, *J* 5.5, C_4H), 3.76 (1H, dd, *J* 10.0, 3.4, CH_AH_BOTBDPS), 3.54 (1H, dd, *J* 10.0, 8.1, CH_AH_BOTBDPS), 3.41 (1H, ddd, *J* 8.1, 5.1, 3.4, C_5H), 1.04 (9H, s, ^tBu), 0.90 (9H, s, ^tBu), 0.89 (9H, s, ^tBu), 0.18 (3H, s, *Me),* 0.12 (3H, s, *Me*), 0.03 (3H, s, *Me*), -0.11 (3H, s, *Me*); δ_C (62.9 MHz) 173.0, 135.4 (2C), 135.3 (2C), 132.8, 132.7, 129.9, 129.8, 127.8 (4C), 77.7, 76.7, 64.9, 60.0, 26.7 (3C), 25.7 (3C), 25.6 (3C), 19.1, 18.1, 17.7, -3.7, -4.2, -4.3, -4.8, m/z (FAB) 614 ($[M+H]^+$, 62.2%), 556 (25.7), 478 (10.6), 73 (100), HRMS (FAB) ($C_{33}H_{56}NO_4Si_3$ requires 614.3517, found 614.3496).

(3*S*,4*R*,5*R*)-*N*-*tert*-Butoxycarbonyl-3,4-di-*tert*-butyldimethylsilyloxy-5-*tert*-butyldiphenylsilyloxymethylpyrrolidin-2-one *121*



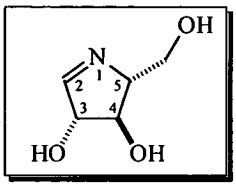
To a solution of the lactam **120** (210 mg, 0.343 mmol) in DCM (4 cm^3) was added triethylamine (60 μl, 0.428mmol) followed by di-*tert*-butyldicarbonate (100 mg, 0.457 mmol) and *N*,*N*-dimethylaminopyridine (9 mg, 0.069 mmol). The resulting mixture was stirred at room temperature for 90 minutes. The reaction mixture was diluted with EtOAc (10 cm^3) and washed with saturated aqueous sodium bicarbonate (10 cm^3) and brine (10 cm^3). The organic phase was concentrated under reduced pressure and the remaining residue was chromatographed on silica gel [hexane:EtOAc (8:1)] to give the title compound (235 mg, 96%) as a colourless oil, R_f [hexane:EtOAc (8:1)] 0.56; $[\alpha]_D$ -33.1 (*c* 0.75, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1761, 1719; δ_H (250 MHz, $CDCl_3$) 7.66-7.25 (10H, m, Ar*H*), 4.31 (1H, t, *J* 1.5, C_4H), 4.00-3.96 (1H, d, *J* 1.6, C_3H), 3.99 (1H, m, C_5H), 3.82 (1H, dd, *J* 9.8, 7.2, CH_AH_BOTBDPS), 3.77 (1H, dd, *J* 9.8, 5.0, CH_AH_BOTBDPS) 1.38 (9H, s, O^tBu), 1.05 (9H, s, Si^tBu), 0.88 (9H, s, Si^tBu), 0.86 (9H, s, Si^tBu), 0.15 (3H, s, *Me*), 0.13 (3H, s, *Me*), 0.12 (3H, s, *Me*), 0.10 (3H, s, *Me*); δ_C (62.9 MHz) 172.0, 149.7, 135.4 (4C), 133.0, 132.9, 129.7 (2C), 127.7 (4C), 82.9, 78.8, 72.0, 66.7, 62.6, 27.8 (3C), 26.7 (3C), 25.7 (3C), 25.6 (3C), 19.1, 18.0, 17.8, -4.5, -4.6 (2C), -5.2; m/z (FAB) 736 ([M + Na]$^+$, 29.6%), 636 (100), 614 (85.1); HRMS (FAB) ($C_{38}H_{63}NO_6Si_3Na$ requires 736.3861, found 736.3854).

(2*RS*,3*S*,4*R*,5*R*)-*N*-*tert*-Butoxycarbonyl-3,4-di-*tert*-butyldimethylsilyloxy-5-*tert*-butyldiphenylsilyloxymethyl-2-hydroxypyrrolidine *122*



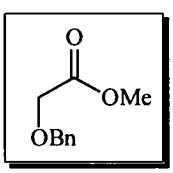
To a solution of the lactam **121** (132 mg, 0.185 mmol) in THF (3 cm^3) at -78 °C was added lithiumtriethylborohydride (Super Hydride®) (241 μl, 1.0M in THF, 0.241 mmol). The mixture was stirred at -78 °C for 15 minutes. The reaction was quenched with methanol (0.5 cm^3) and a saturated aqueous solution of sodium bicarbonate (2 cm^3). The resulting foamy slurry was warmed to room temperature and vigorously extracted with EtOAc (3 x 5 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The remaining residue was chromatograhed on silica gel [hexane:EtOAc (6:1)] to give the title compound (127 mg, 96%) as a colourless oil, R_f [hexane:EtOAc (4:1)] 0.54; $[\alpha]_D$ -7.3 (*c* 1.1, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3460, 1701; δ_H (250 MHz, CD_3OD) 7.78-7.43 (10H, m, Ar*H*), 5.46-5.40 (1H, brm, C_2H), 4.60-4.55 (1H, brm, C_3H), 4.06 (1H, dd, *J* 5.0, 2.6, C_4H), 4.09-3.95 (1H, brm, C_5H), 3.84-3.81 (2H, brm, CH_2OTBDPS), 1.42 (9H, brs, O^tBu), 1.16 (9H, s, Si^tBu), 1.01 (9H, s, Si^tBu), 0.98 (9H, s, Si^tBu), 0.23 (6H, s, *Me* x 2), 0.22 (6H, s, *Me* x 2); δ_C (62.9 MHz) 155.2, 134.8 (4C), (132.5 (2C), 129.1 (2C), 127.0 (4C), 81.2, 77.4, 75.7, 66.2, 62.3, 26.8 (3C), 25.7 (3C), 24.7 (3C), 25.7 (3C), 18.1(2C), 17.3, 16.8, -5.9, -6.0, -6.3, -6.5; m/z (FAB) 738 $[M + Na]^+$, 29.5%), 698 (34.3), 598 (100), 540 (97.5), 520 (61.0), 135 (32.7), 73 (90.5); HRMS (FAB) ($C_{38}H_{65}NO_6Si_3Na$ requires 738.4018, found 738.4031).

Nectrisine *36*



To a solution of the multi-protected pyrrolidine **122** (115 mg, 0.16 mmol) in THF (3 cm^3) was added a solution of 6N HCl (1.8 cm^3) in THF (1 cm^3). The mixture was heated to 50 °C and held at this temperature for 2 hours. The reaction mixture was concentrated and the remaining residue was chromatographed on silica gel [$CHCl_3$:MeOH:NH_3 (28% aqueous) (5:3:1)] to give a colourless solid which was subjected to a final purification by ion-exchange [Dowex OH^-, (prepared by treating Dowex 1-X2 with 1N aqueous sodium hydroxide and washing with de-ionised water until eluent was at pH7)] to give nectrisine (17 mg, 80%) as a colourless oil R_f [$CHCl_3$:MeOH:NH_3 (28% aqueous) (5:3:1)] 0.25; $[\alpha]_D$ +21.0 (*c* 0.4, H_2O) [lit.[78] $[\alpha]_D$ +21.8 (*c* 0.6, H_2O)]; δ_H (600 MHz, D_2O) 7.72 (1H, d, *J* 2.4, C_2H), 4.75 (1H, dt, *J* 5.2, 1.0, C_3H), 4.11 (1H, t, *J* 5.3, C_4H), 3.91 (1H, dd, *J* 11.5, 3.9, CH_AH_BOH), 3.88 (1H, ddddd, *J* 5.3, 4.2, 3.9, 2.3, 1.2, C_5H), 3.79 (1H, dd, *J* 11.6, 4.2, CH_AH_BOH); δ_C (62.9 MHz) 170.5, 83.4, 78.2, 76.8, 61.2; m/z (FAB) 131 (M^+, 38.1%), 91 (100); HRMS (FAB) ($C_5H_9NO_3$ requires 131.0582, found 131.0582). All spectroscopic data was in good agreement with that of the literature.

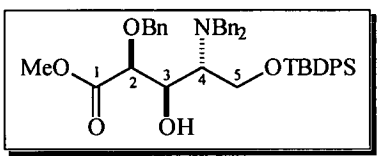
Methyl benzyloxyacetate *124*



To methanol (80 cm^3) at 0 °C was added acetyl chloride (13.62 cm^3, 173.5 mmol) followed by benzyloxyacetic acid **109** (9.60 g, 57.8). The reaction mixture was

warmed to reflux and held at reflux before being concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (3:1)] to give the title compound (9.86 g, 95%) as a colourless oil, R_f [hexane:EtOAc (2:1)] 0.62; ν_{max} (neat)/cm^{-1} 1756, 1605, 1557, 1496; δ_H (200 MHz, $CDCl_3$) 7.37-7.30 (5H, m, Ar*H*), 4.62 (2H, s, COCH_2OBn), 4.10 (2H, s, CH_2OBn), 3.74 (3H, s, O*Me*); δ_C (50MHz) 170.5, 136.8, 128.3 (3C). 127.8 (2C), 73.0, 66.8, 51.5; m/z (FAB) 181 ([M+H]$^+$, 56.7), 91 (100).

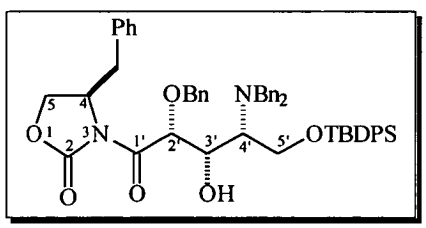
Methyl (2*S*,3*R*,4*R*)-2-benzyloxy-5-*tert*-butyldiphenylsilyloxy-4-*N*,*N*-dibenzylamino-3-hydroxypentanoate *125*

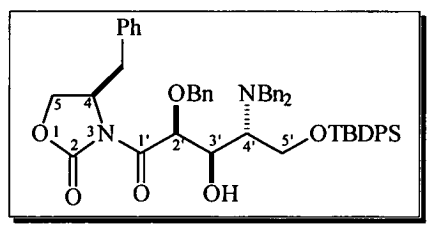


To a solution of diisopropylethylamine (207 µl, 1.19 mmol) in anhydrous diethylether (2.5 cm^3) at -78 °C was added dibutylboron triflate (1.01 cm^3, (1.0 *M* in DCM), 1.01 mmol). To this cloudy mixture was added ester **124** (178 mg, 0.99 mmol) in diethylether (1.0 cm^3) *via* cannula. The resulting mixture was stirred for 90 mins at -78 °C before a -78 °C solution of the aldehyde (500 mg, 0.99 mmol) in diethylether (1.5 cm^3) was added *via* cannula. The resulting mixture was stirred at -78 °C for 1 hour and 0 °C for 1 hour. The reaction was quenched by addition of aqueous pH 7 phosphate buffer solution (0.5 cm^3) followed by methanol (0.5 cm^3). Finally, hydrogen peroxide (1.0 cm^3) in methanol (1.0 cm^3) was added dropwise and the resulting cloudy solution was stirred for 30 minutes at 0 °C and 30 minutes at room temperature. The mixture was diluted with DCM (10 cm^3) and the organic phase was separated. The aqueous phase was extracted with DCM (3 x 5 cm^3). The combined organic extracts were washed with a saturated aqueous solution of sodium bicarbonate (10 cm^3) and brine (10 cm^3), dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc

(4:1)] to give the title compound (510 mg, 75 %) as a colourless foam, R_f [hexane:EtOAc (3:1)] 0.69; $[\alpha]_D$ -32.2 (*c* 1.94, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3546, 1751, 1601, 1588, 1494; δ_H (250 MHz, $CDCl_3$) 7.82-7.15 (25H, m, Ar*H*), 4.40 (1H, d, *J* 10.2, OCH_AH_BPh), 4.38 (1H, d, *J* 1.4, C_2H), 4.18 (1H, dd, *J* 10.7, 5.7, $C_5H_AH_BOTBDPS$), 4.17-4.10 (1H, m, C_3H), 4.09 (1H, dd, *J* 10.7, 5.7, $C_5H_AH_BOTBDPS$), 3.91 (2H, d, *J* 13.5, NCH_XH_YPh x 2), 3.77 (3H, s, O*Me*), 3.62 (2H, d, *J* 13.5, NCH_XH_YPh x 2), 3.52 (1H, d, *J* 10.2, OCH_AH_BPh), 3.18 (1H, dt, *J* 9.1, 5.5, C_4H), 1.12 (9H, s, ^tBu); δ_C (62.9 MHz) 172.3, 140.0 (2C), 137.4, 135.6 (2C), 135.5 (2C), 133.1, 132.9, 129.7, 129.6, 129.2 (4C), 128.2 (4C), 127.9 (4C), 127.6 (4C), 127.5, 126.9 (2C), 77.3, 72.8, 72.1, 61.2, 59.1, 54.8 (2C), 51.8, 26.7 (3C), 18.9; m/z (FAB) 688 ($[M+H]^+$, 62.0%), 599 (25.0), 478 (19.5), 217 (40.8), 91 (100); HRMS (FAB) ($C_{43}H_{50}NO_5Si$ requires 688.3458, found 688.3458).

(2'*R*,3'*S*,4*R*,4'*R*)-3-(2'-Benzyloxy-5'-*tert*-butyldiphenylsilyloxy-4'-*N*,*N*-dibenzylamino-3'-hydroxy-1'-oxopentyl)-4-phenylmethyloxazolidin-2-one *105* and (2'*S*,3'*R*,4*R*,4'*R*)-3-(2'-Benzyloxy-5'-*tert*-butyldiphenylsilyloxy-4'-*N*,*N*-dibenzylamino-3'-hydroxy-1'-oxopentyl)-4-phenylmethyloxazolidin-2-one *126*





Synthesised in an analogous manner to **102**, from *R*-imide *ent*-**101** to give a mixture of diastereomers **105**:**126** (9:1 ratio). Thus, the imide *ent*-**101** (590 mg, 1.82 mmol), aldehyde **73** (370 mg, 0.729 mmol), dibutylborontriflate (2.18 cm^3, (1.0 *M* in DCM), 2.18 mmol), triethylamine (331 µl, 2.37 mmol) in DCM (17 cm^3) gave **105** (424 mg, 70%) and **126** (52 mg, 8.6%) as a colourless oil and a colourless foam respectively,

Data for **105**:

Obtained as colourless oil,

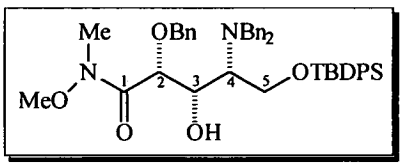
R_f [hexane:EtOAc (3:1)] 0.28; $[\alpha]_D$ -29.2 (*c* 0.9, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3331, 1773, 1708; δ_H (360 MHz, $CDCl_3$) 7.81-7.07 (30H, m, Ar*H*), 5.22 (1H, d, *J* 2.4, C_2-*H*), 4.56-4.52 (1H, m, C_3-*H*), 4.52 (1H, d, *J* 11.5, OCH_AH_BPh), 4.50 (1H, ddt, *J* 9.8, 6.2, 3.1, C_4-*H*), 4.27 (1H, d, *J* 11.5, OCH_AH_BPh), 4.15-4.11 (1H, m, $C_5H_XH_Y$), 4.13 (1H, dd, *J* 11.3, 4.4, C_5-H_MH_NOTBDPS) 4.04 (1H, dd, *J* 11.3, 8.0, C_5-H_MH_NOTBDPS), 3.93 (2H, d, *J* 13.1, NCH_SH_TPh x 2), 3.86-3.81 (2H, m, NCH_SH_TPh x 2), 3.84 (1H, dd, *J* 9.5, 2.5, $C_5H_XH_Y$), 3.56 (1H, dt, 8.0, 4.4, C_4-*H*), 3.30 (1H, dd, *J* 13.3, 3.1, $CHPH_QPh$), 2.72 (1H, dd, *J* 13.3, 9.8, CH_PH_QPh), 1.94 (9H, s, ^tBu); δ_C (90.6 MHz) 170.7, 153.7, 139.5 (2C), 137.7, 136.2 (4C), 135.8, 133.6, 130.3, 130.2, 129.9 (2C), 129.7 (3C), 129.4 (2C), 129.0, 128.9 (3C), 128.8, 128.7, 128.6 (2C), 128.2 (4C), 128.1 (2C), 127.9, 127.8, 127.6 (2C), 72.8 (2C), 68.2, 67.2, 62.3 (2C), 60.3, 56.2 (2C), 38.2, 27.6 (3C), 19.6.

Data for **126**:

Obtained as a colourless foam,

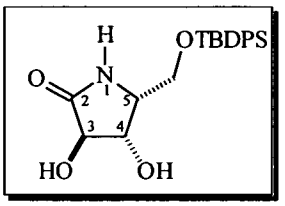
R_f [hexane:EtOAc (3:1)] 0.35; α_D -33.6 (*c* 1.00, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3451, 1779, 1705; δ_H (360 MHz, $CDCl_3$) 7.77-7.19 (30H, m, Ar*H*), 5.46 (1H, d, *J* 1.7, C_2-*H*), 4.70 (1H, dddd, *J* 10.3, 6.8, 5.2, 3.2, C_4-*H*), 4.38 (1H, brd, *J* 7.6, O*H*), 4.26 (1H, d, *J* 10.7, OCH_AH_BPh), 4.20 (1H, brdd, *J* 7.2, 2.1, C_3-*H*), 4.19 (1H, dd, *J* 13.5, 5.1, C_5-H_XH_YOTBDPS), 4.22-4.11 (3H, m, C_5H_2 + C_5-H_XH_YOTBDPS), 3.99 (1H, d, *J* 10.7, OCH_AH_BPh), 3.98 (2H, d, *J* 13.7, NH_SH_TPh x 2), 3.67 (2H, d, *J* 13.7, NCH_SH_TPh x 2), 3.41 (1H, dt~q, *J* 5.3, C_4-*H*), 3.30 (1H, dd, *J* 13.5, 3.2, CH_MH_NPh), 2.74 (1H, dd, *J* 13.5, 9.4, CH_MH_NPh), 1.10 (9H, s, ^tBu); δ_C (50.3 MHz) 171.7, 153.1, 140.0 (2C), 137.4, 135.7 (2C), 135.6 (2C), 135.0, 133.1, 133.0, 129.7 (2C), 129.3 (2C), 129.1 (4C), 128.8 (2C), 128.1 (2C), 128.0 (4C), 127.9 (2C), 127.7 (4C), 127.5, 127.2, 126.7 (2C), 78.3, 77.2, 72.0, 66.7, 61.5, 59.7 (2C), 54.7 (2C), 37.7, 26.7 (3C), 18.9.

(2*R*,3*S*,4*R*)-2-Benzyloxy-5-*tert*-butyldiphenysilyloxy-4-*N*,*N*-dibenzylamino-3-hydroxy-pentanoic acid methoxy-methyl-amide *127*



An analogous protocol to that described for the synthesis of Weinreb amide **110** was undertaken. Thus, aldol adduct **105** (300 mg, 0.36 mmol), *N*,*O*-dimethylhydroxylamine•HCl (880 mg, 9.0 mmol), trimethylaluminium (4.5 cm^3, (2.0 *M* in toluene), 9.0 mmol) in THF (6 cm^3) gave, after chromatography on silica gel [hexane:EtOAc (1:1)], the title compound (253 mg, 98%) as a colourless oil, R_f [hexane:EtOAc (1:1)] 0.56; α_D -14.2 (*c* 1.25, $CHCl_3$), ν_{max} (neat)/cm^{-1} 3424, 1664; δ_H (360 MHz, $CDCl_3$) 7.74-6.97 (25H, m, Ar*H*), 4.59 (1H, d, *J* 2.1, C_2H), 4.36 (1H, brs, O*H*), 4.12 (1H, d, *J* 12.0, OCH_AH_BPh), 4.13-4.11 (1H, brm, OCH_AH_BPh), 3.98 (2H, d, *J* 13.2, NCH_XH_YPh x 2), 3.92 (1H, dd, *J* 9.3, 2.1, C_3H), 3.87-3.81 (2H, m, $C_5H_2OTBDPS$), 3.77 (2H, d, *J* 13.3, NCH_XH_YPh x 2), 3.45 (1H, brdt, *J* 10.0, 6.2, C_4H), 3.32 (3H, s, O*Me*), 3.19 (3H, s, N*Me*), 1.17 (9H, s, ^tBu); δ_C (50.3 MHz) 170.1, 139.0 (2C), 137.4, 135.7 (4C), 132.9, 132.8, 129.8 (2C), 129.1 (4C), 128.3 (4C), 128.1 (2C), 127.7 (4C), 127.5 (2C), 127.4, 127.0 (2C), 71.2, 67.5, 61.4, 60.5, 59.3 (2C), 54.5 (2C), 32.5, 26.8 (3C), 19.0.

(3*R*,4*S*,5*R*)-5-*tert*-Butyldiphenylsilyloxymethyl-3,4-dihydroxypyrrolidin-2-one *128*



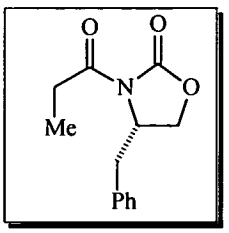
From Weinreb amide 127:

A solution of the Weinreb amide **127** (200 mg, 0.279 mmol) and 20% $Pd(OH)_2/C$ (200 mg) in methanol (5 cm^3) was exposed to a hydrogen atmosphere and stirred under hydrogen for 72 hours. The reaction mixture was filtered through a pad of celite and concentrated under reduced pressure. The residue obtained was chromatographed on silica gel [hexane:EtOAc (2:3)] to give the title compound (74 mg, 69%) as a colourless foam, R_f [hexane:EtOAc (1:3)] 0.23; $[\alpha]_D$ +40.2 (*c* 1.25, $CHCl_3$); ν_{max} 3305, 1689; δ_H (250 MHz, $CDCl_3$) 7.67-7.25 (10H, m, Ar*H*), 6.52 (1H, brs, N*H*), 5.00 (1H, brs, O*H*), 4.42 (1H, brd, *J* 2.7, C_3H), 4.12-3.98 (1H, brm, C_4H), 3.83 (1H, dd, *J* 10.8, 5.2, $CH_AH_BOTBDPS$), 3.72 (1H, dd, *J* 10.8 7.6, $CH_AH_BOTBDPS$), 3.69-3.61 (1H, brm, C_5H), 1.00 (9H, s, ^tBu); δ_C (62.9 MHz) 175.4, 135.5 (2C), 135.4 (2C), 132.6, 132.4, 129.8, 129.8, 127.8 (4C), 74.9 (2C), 62.6, 55.5, 26.7 (3C), 18.9.

From Weinreb amide 157

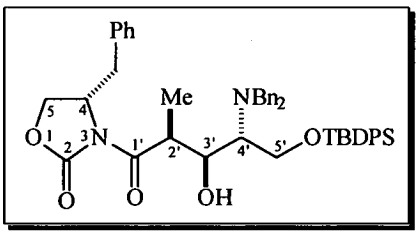
Analogous to the above protocol, Weinreb amide **157** (165 mg, 0.263 mmol) and 20% $Pd(OH)_2/C$ (165 mg) in methanol (4 cm^3) under a hydrogen atmosphere (1 atm.) gave after 24 hours lactam **128** (86 mg, 85%) as a colourless foam. *Spectroscopic data was identical to the lactam obtained from 127.*

(4*S*)-3-(1'-Oxopropyl)-4-phenylmethyloxazolidin-2-one *137*



To a solution of the oxazolidinone **106** (7.50 g, 43.4 mmol) in THF (100 cm^3) at -78 °C was added n-butyllithium (1.6 *M* in hexanes) (29.0 cm^3, 42.4 mmol). The mixture was stirred for 5 minutes and freshly distilled propionyl choride (11.2 cm^3, 127.2 mmol) was added slowly *via* syringe. The resulting mixture was stirred at -78 °C for 15 mins. The reaction was quenched by addition of a saturated aqueous solution of ammonium chloride (50 cm^3), producing two clear phases. The organic phase was separated and the aqueous phase was extracted with DCM (3 x 100 cm^3). The combined organic extracts were washed sequentially with saturated aqueous sodium bicarbonate solution (75 cm^3) and brine (75 cm^3) dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (3:1)] to give the title compound (9.80 g, 99%) as a colourless crystalline solid, R_f [hexane:EtOAc (3:1)] 0.46; mp 45-47 °C; $[\alpha]_D$ +94.7 (*c* 1.5, EtOH) [lit.,[167] mp 44-46 °C, $[\alpha]_D$ +92.9 (*c* 1.01, EtOH)]; ν_{max} (Nujol mull/cm^{-1}) 1795, 1708, 1557; δ_H (200 MHz, $CHCl_3$) 7.38-7.18 (5H, m, Ar*H*), 4.66 (1H, dddd, *J* 9.9, 9.6, 6.4, 3.3, C_4H), 4.18 (2H, m, C_5H_2), 3.29 (1H, dd, *J* 13.4 3.3, CH_AH_BPh), 2.98 (2H, q, 7.3, $C_2'H_2$), 2.76 (1H, dd, *J* 13.4, 9.6, CH_AH_BPh), 1.19 (3H, t, *J* 7.4, CH_3); δ_C (50.3 MHz) 174.0, 153.4, 135.2, 129.3 (2C), 128.8 (2C), 127.2, 66.0, 54.9, 37.7, 28.9, 8.0; m/z (EI) 233 (M^+, 20.4%), 142 (37.4), 91 (50.2), 57 (100). All spectroscopic data was in good agreement with that of the literature.

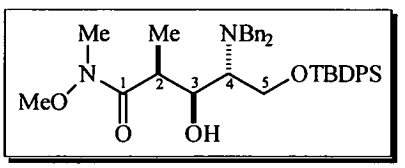
(2'*S*,3'*S*,4*S*,4'*R*)-3-(5'-*tert*-Butyldiphenylsilyloxy-4'-*N*,*N*-dibenzylamino-3'-hydroxy-2'-methyl -1'-oxopentyl)-4-phenylmethyloxazolidin-2-one *136*



To a solution of imide **137** (3.50 g, 14.8 mmol) in DCM (24 cm^3) at 0 °C was added Bu_2BOTf (17.8 cm^3, (1.0 *M* in DCM), 17.8 mmol). Triethylamine (2.71 cm^3, 19.3 mmol) was added to the orange coloured solution and the mixture became bright yellow colour in colour. This mixture was stirred at 0 °C for 15 mins before being cooled to -78 °C. A -78 °C solution of the aldehyde **73** (2.50 g, 4.39 mmol) was introduced *via* cannula and resulting mixture was stirred at -78 °C for 1 hour then 0 °C for 30 mins. The reaction was quenched at 0 °C by addition of aqueous pH 7 phosphate buffer solution (10 cm^3) followed by methanol (15 cm^3). Methanol:hydrogen peroxide (1:1) (25 cm^3) was then cautiously added and the resulting mixture was stirred at 0 °C for 1 hour. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 30 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (3:1)] to give the title compound (3.18 g, 87 %) as a colourless solid, R_f [hexane:EtOAc (3:1)] 0.51; mp 63-65 °C; $[\alpha]_D$ +19.7 (*c* 0.88, $CHCl_3$); ν_{max} ($CHCl_3$ soln.)/cm^{-1} 3551, 1782, 1679; δ_H (250 MHz, $CDCl_3$) 7.81-7.16 (25H, m, Ar*H*), 4.63-4.56 (1H, m, C_4H), 4.35 (1H, qd, *J* 7.1, 1.5, C_2H), 4.22 (1H, dd, *J* 11.1, 3.5, $C_5H_AH_B$), 4.20-4.15 (3H, m, C_3H + C_5H_2), 4.06 (1H, dd, *J* 11.1, 5.6 $C_5H_AH_B$), 3.94 (2H, d, *J* 13.7, NCH_AH_BPh x 2), 3.64 (2H, d, *J* 13.7, NCH_AH_BPh x 2), 3.26 (1H, d, *J* 2.61, O*H*), 3.19 (1H, dd, *J* 13.3, 3.3, CH_XH_YPh), 2.80 (1H, td, *J* 5.6, 3.2, C_4HNBn_2), 2.71 (1H, dd, *J* 13.3, 9.5, CH_XH_YPh), 1.12 (9H, s, ^tBu), 0.71 (3H, d, *J* 7.1, *Me*); δ_C (62.9 MHz) 178.7, 152.4, 139.8 (2C), 135.8 (2C), 135.6 (2C), 135.0, 133.3, 133.0, 129.7 (2C), 129.3 (2C), 129.1 (4C),

128.8 (2C) 128.2 (4C), 127.7 (2C), 127.6 (2C), 127.2, 126.8 (2C), 77.1, 69.1, 66.0, 60.7, 58.1, 55.5 (2C), 54.8, 38.8, 37.6, 26.9 (3C), 19.1, 9.5; m/z (FAB) 741 ($[M+H]^+$, 29.8%), 625 (35.1), 479 (46.9), 91 (100); HRMS (FAB) ($C_{46}H_{53}N_2O_5Si$ requires 741.3725, found 741.3718).

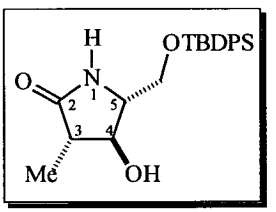
(2*S*,3*S*,4*R*)-5-*tert*-Butyldiphenylsilyloxy-4-*N*,*N*-dibenzylamino-3-hydroxy-2-methyl pentanoic acid methoxy-methyl amide *135*



To a suspension of *N*,*O*-dimethylhydroxylamine•HCl (7.60 g, 78.0 mmol) in THF (15 cm^3) at -30 °C was carefully added trimethylaluminium (39.0 cm^3, (2.0 *M* in toluene), 78.0 mmol) over 5 minutes. Vigorous effervescence occurred and the mixture was allowed to warm to room temperature over ca. 15 minutes after which time a clear solution remained. This solution was recooled to -30 °C and a -30 °C solution of the aldol adduct **136** (1.90 g, 2.62 mmol) in THF (10 cm^3) was added *via* cannula. The mixture was warmed to 0 °C and stirred at 0 °C for 2.5 hours. The reaction mixture was then cannulated into a rapidly stirred biphasic mixture of DCM (150 cm^3) and saturated aqueous sodium potassium tartrate solution (150 cm^3), the resulting mixture was stirred at room temperature for 18 hours when two clear phases were apparent. The organic phase was separated and the aqueous phase was extracted with DCM (3 x 150 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (3:1)] to give the title compound (1.59 g, 99%) as a colourless solid, R_f [hexane:EtOAc (3:1)] 0.31; mp 100-102 °C; $[\alpha]_D$ -8.6 (*c* 0.93, $CHCl_3$); ν_{max} ($CHCl_3$ soln.)/cm^{-1} 3474, 1627; δ_H (250 MHz, $CDCl_3$) 7.82-7.18 (20H, m, Ar*H*), 4.23 (1H, dd, *J* 11.0, 3.2, $C_5H_AH_BOTBDPS$), 4.14 (1H, brdd, *J* ~9.7 (2nd coupling obscured), C_3H), 4.03 (1H, dd, *J* 11.2, 6.1, $C_5H_AH_BOTBDPS$), 3.93 (2H, d,

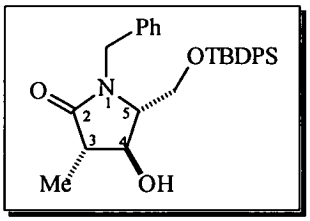
J 13.8, CH_XH$_Y$Ph x 2), 3.75 (2H, d, *J* 13.8, CH$_A$*H*$_B$Ph x 2), 3.54 (3H, s, O*Me*), 3.48-3.44 (1H, m, C$_2$*H*), 3.14 (3H, s, *Me*), 2.78 (1H, ddd, *J* 9.2, 6.1, 3.1, C$_4$*H*), 1.14 (9H, s, ^{t}*Bu*), 0.57 (3H, d, *J* 7.0, C$_2$*Me*); δ_C (62.9 MHz) 178.9, 140.1 (2C), 135.7 (2C), 135.6 (2C), 133.4, 133.1, 129.6 (2C), 128.9 (4C), 128.0 (4C), 127.6 (2C), 127.5 (2C), 126.8 (2C), 77.1, 69.1, 61.3, 61.0, 57.9, 55.2 (2C), 35.0, 26.9 (3C), 19.1, 8.7 (1C); m/z (FAB) 625 ([M+H]$^+$, 39.8), 535 (44.2), 478 (39.0), 355 (27.3), 91 (100); HRMS (FAB) ($C_{38}H_{49}N_2O_4Si$ requires 625.3461, found 625.3466).

(3*S*,4*S*,5*R*)-5-*tert*-Butyldiphenylsilyloxymethyl-4-hydroxy-3-methylpyrrolidin-2-one *134*



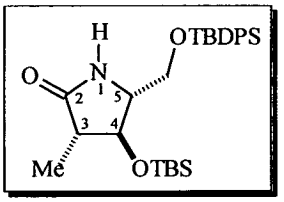
To a solution of Weinreb amide **135** (254 mg, 0.41 mmol) in methanol (4 cm^3) was added 10 % Pd/C (254 mg). The mixture was exposed to a hydrogen atmosphere and stirred under hydrogen for 12 hours. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (1:3)] to give the title compound (102 mg, 65%) as a colourless foam, R_f [hexane:EtOAc (2:3)] 0.31; $[\alpha]_D$ -6.4 (*c* 0.95, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3385, 3272, 1696; δ_H (250 MHz, $CDCl_3$) 7.66-7.25 (10H, m, Ar*H*), 5.28 (1H, brs, N*H*), 3.80 (1H, dd, *J* 10.2, 4.4, C*H*$_A$H$_B$OTBDPS), 3.72 (1H, m, C$_4$*H*), 3.63 (1H, dd, *J* 10.2, 6.6, CH$_A$*H*$_B$OTBDPS), 3.52 (1H, dt, *J* 6.7, 4.5, C$_5$*H*), 2.82 (1H, brs, O*H*), 2.38 (1H, dq~qn, *J* 7.2, C$_3$*H*), 1.18 (3H, d, *J* 7.2, C*H*$_3$), 1.05 (9H, s, ^{t}*Bu*); δ_C (62.9 MHz) 176.6, 135.4 (4C), 132.6, 129.9 (2C), 127.8 (4C), 76.9, 65.1, 61.2 (2C), 44.9, 16.7 (3C), 19.0, 13.0; m/z (FAB) 384 ([M+H]$^+$, 100%), 306 (35.7), 199 (80.1),137 (58.7), 75 (16.2); HRMS (FAB) ($C_{22}H_{30}NO_3Si$ requires 384.1995, found 384.1995).

(3*S*,4*S*,5*R*)-*N*-Benzyl-5-*tert*-butyldiphenylsiloxymethyl-4-hydroxy-3-methyl pyrrolidin-2-one *138*



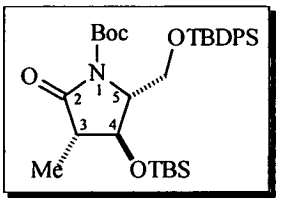
To a solution of the aldol adduct **136** (90 mg, 0.124 mmol) in methanol (1.5 cm^3) was added 10% Pd/C (90 mg). The mixture was exposed to a hydrogen atmosphere and stirred under hydrogen for 18 hours. The mixture was filtered through a pad of celite and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (1:1)] to give the title compound (30 mg, 0.063 mmol, 51%) as a colourless foam, along with lactam **134** (21 mg, 0.054 mmol, 44%) as a colourless foam, R_f [hexane:EtOAc (1:1)] 0.45; $[\alpha]_D$ +14.9 (*c* 0.41, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3380, 1667; δ_H (250MHz, $CDCl_3$) 7.64-7.18 (15H, m, Ar*H*), 5.00 (1H, d, *J* 15.1, NC$H_A$$H_B$Ph), 4.00 (1H, dd, *J* 7.6, 6.1 C_4H), 3.80 (1H, dd, *J* 11.0, 3.3, C$H_X$$H_Y$OTBDPS), 3.67 (1H, d, *J* 14.6, NC$H_A$$H_B$Ph), 3.65 (1H, dd, *J* 11.0, 5.2, C$H_X$$H_Y$OTBDPS), 3.19 (1H, ddd, *J* 6.0, 5.2, 3.2, C_5H), 2.45 (1H, dq~qn, *J* 7.2, C_3H), 1.29 (3H, d, 7.2, *Me*) 1.04 (9H, s, ^tBu); δ_C (62.9 MHz) 174.9, 136.0, 135.5 (2C), 135.4 (2C), 132.5, 132.4, 130.0, 129.9, 128.5 (2C), 127.9 (2C), 127.8 (2C), 127.7 (2C), 127.3, 75.4, 63.2, 61.5, 44.6, 43.7, 26.7 (3C), 19.0, 13.8; m/z (FAB) 474 ($[M+H]^+$, 100%), 416 (10.1), 199 (32.6), 91(83.5); HRMS (FAB) ($C_{29}H_{36}NO_3Si$ requires 474.2451, found 474.2451).

(3*S*,4*S*,5*R*)-4-*tert*-Butyldimethylsilyloxy-5-*tert*-butyldiphenylsilyloxy-3-methylpyrrolidin-2-one



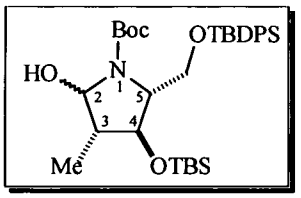
To a solution of the lactam **134** (63 mg, 0.164 mmol) in DCM (1.5 cm^3) was added 2,6-lutidine (23 μl, 0.197 mmol) followed by *tert*-butyldimethylsilyltrifluoromethanesulfonate (104 μl, 0.452 mmol). The mixture was stirred at room temperature for 3 hours. The reaction mixture was then diluted with EtOAc (5 cm^3) and washed with a saturated aqueous solution of sodium bicarbonate (5 cm^3) and brine (5 cm^3). The organic phase was dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel to give the title compound (77 mg, 94 %) as a colourless oil, R_f [hexane:EtOAc (3:1)] 0.38; $[\alpha]_D$ +8.1 (*c* 0.52, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3203, 1705; δ_H (250 MHz, $CDCl_3$) 7.64-7.34 (10H, m, Ar*H*), 5.66 (1H, brs, N*H*), 3.79-3.73 (1H, m, C$H_A$$H_B$OTBDPS), 3.67 (1H, dd, *J* 7.2, 5.2, C_4H), 3.53-3.45 (2H, m, C_5H + C$H_A$$H_B$OTBDPS), 2.40 (1H, dq~qn, *J* 7.2, C_3H), 1.17 (3H, d, *J* 7.2, *Me*), 1.04 (9H, s, ^tBu), 0.80 (9H, s, ^tBu), 0.00 (3H, s, *Me*), -0.12 (3H, s, *Me*); δ_C (62.9 MHz) 176.5, 135.4 (2C), 135.3 (2C), 132.5 (2C), 129.9 (2C), 127.8 (4C), 76.5, 64.7, 62.0, 45.3, 26.6 (3C), 25.4 (3C), 19.0, 17.6, 13.4, -4.4, -4.9; m/z (FAB) 498 ($[M+H]^+$, 100%), 440 (24.6), 374 (26.9), 197 (37.6), 135 (60.3), 73 (92.6); HRMS (FAB) ($C_{28}H_{44}NO_3Si_2$ requires 498.2860, found 498.2866).

(3*S*,4*S*,5*R*)-*N*-*tert*-Butoxycarbonyl-4-*tert*-butyldimethylsilyloxy-5-*tert*-butyldiphenylsilyloxy-3-methylpyrrolidin-2-one *139*



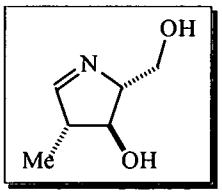
To a solution of the newly TBS protected lactam (*vide supra*) (50 mg, 0.1 mmol) in DCM (1.5 cm^3) was added triethylamine (18 μl, 0.13 mmol), di-*tert*-butyldicarbonate (31 mg, 0.14 mmol) and *N,N*-dimethylaminopyridine (7 mg, 0.05 mmol). The reaction mixture was stirred at room temperature for 18 hours then diluted with EtOAc (5 cm^3) and washed with saturated aqueous sodium bicarbonate solution (5 cm^3) and brine (5 cm^3). The organic phase was dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (8:1)] to give the title compound (58 mg, 97%) as a colourless oil, R_f [hexane:EtOAc (3:1)] 0.57; $[\alpha]_D$ -30.0 (*c* 0.2, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1754, 1715 ; δ_H (250 MHz, $CDCl_3$) 7.63-7.33 (10H, m, Ar*H*), 4.14 (1H, dd, *J* 3.7, 2.2, C_4H), 3.90-3.85 (2H, m, C_5H + CH_AH_BOTBDPS), 3.73 (1H, dd, *J* 12.4, 4.6, CH_AH_BOTBDPS), 2.48 (1H, dq, *J* 7.2, 3.7, C_3H), 1.43 (9H, s, ^tBu), 1.24 (3H, d, *J* 7.2, *Me*), 1.04 (9H, s, ^tBu), 0.85 (9H, s, ^tBu), 0.56 (3H, s, *Me*), 0.00 (3H, s, *Me*); δ_C (50.3 MHz) 175.5, 149.8, 135.5 (4C), 132.8, 132.5, 129.8 (2C), 127.7 (4C), 82.8, 72.7, 66.8, 62.0, 47.8, 27.8 (3C), 26.8 (3C), 25.5 (3C), 19.1, 17.7, 14.5, -4.5, -4.7; m/z (FAB) 598 ($[M+H]^+$, 3.0%), 498 (19.1), 325 (40.8), 217 (100), 109(83.7), 91 (98.6); HRMS (FAB) ($C_{33}H_{52}NO_5Si_2$ requires 598.3384, found 598.3380).

(2*RS*,3*S*,4*S*,5*R*)-*N*-*tert*-Butoxycarbonyl-5-*tert*-butyldiphenylsilyloxymethyl-4-*tert*-butyldimethylsilyloxy-2-hydroxy-3-methylpyrrolidine *133*



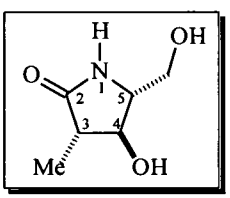
To a solution of the lactam **139** (48 mg, 0.08 mmol) in THF (1.5 cm^3) at -78 °C was added lithiumtriethylborohydride (Super Hydride®) (104 μl, (1.0M in THF), 0.104 mmol). The mixture was stirred at -78 °C for 15 minutes. The reaction was quenched with methanol (0.3 cm^3) and a saturated aqueous solution of sodium bicarbonate (1 cm^3). The resulting foamy slurry was warmed to room temperature and vigorously extracted with EtOAc (3 x 5 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (6:1)] to give the title compound (44 mg, 93%) as a colourless oil and as an approximately 1:1 mixture of diastereomers (from C_2 proton integration), R_f [hexane:EtOAc (3:1)] 0.59; $[\alpha]_D$ -11.1 (*c* 0.35, $CHCl_3$); ν_{max} 3467, 1690; δ_H (250 MHz, $CDCl_3$) 7.68-7.24 (10H, m, Ar*H*), 5.38 (0.5H, brdd, *J* 7.4, 5.7, C_2H), 5.21 (0.5H, dd, *J* 8.9, 5.0, C_2H), 4.30-3.40 (3H, m, C_4H + C_5H + CH_AH_BOTBDPS), 3.00 (1H, dd, *J* 10.9, 8.1, CH_AH_BOTBDPS), 1.99-1.95 (1H, brm, C_3H), 1.60-1.30 (12H, m, O^tBu + C_3Me), 1.20-0.96 (9H, m, Si^tBu), 0.90-0.70 (9H, m, Si^tBu), 0.05 (1.5 H, s, Si*Me*), 0.00 (1.5H, s, Si*Me*), -0.12 (1.5H, s, Si*Me*), -0.21 (1.5H, s, Si*Me*); δ_C (62.9 MHz) 153.7, 152.9, 135.7 (2C)*, 135.5 (2C)*, 133.0*, 132.4*, 130.0*, 129.8*, 127.8 (2C)*, 127.6 (2C)*, 88.6*, 80.0*, 67.8*, 66.5, 66.0, 61.5, 60.4, 46.7, 46.0, 28.3 (3C)*, 26.8 (3C)*, 25.5 (3C)*, 19.0*, 18.9*, 11.7*, -4.5 (2C)*, (* denotes signals common to both diastereomers); m/z (FAB) no parent ion mass, 582 $[(M\text{-}OH)^+$ 21%), 482 ($[M\text{-}C_5H_9O_3]^+$ (i.e. –(OH + Boc)) 26%), 404 (21), 325 (25), 217 (66); HRMS (FAB) for ion at m/z 482 ($C_{28}H_{42}NO_2Si_2$ requires 482.2911, found 482.2911).

Attempted Synthesis of C_3Me Nectrisine Analogue *58*



To a solution of the multi-protected pyrrolidine **133** (35 mg, 0.06 mmol) in THF (1 cm^3) was added a solution of 6N HCl (0.7 cm^3) in THF (0.7 cm^3). The mixture was heated to 50 °C and held at this temperature for 2 hours. The reaction mixture was concentrated and the remaining residue was chromatographed on silica gel [$CHCl_3$:MeOH:NH_3 (28% aqueous) (5:3:1)] to give a colourless solid (large quantities of salts were present), which was subjected to a final purification by ion-exchange chromatography (Dowex OH^-). No material was recovered from the ion-exchange resin after eluting with methanol, water and 28% aqueous ammonia.

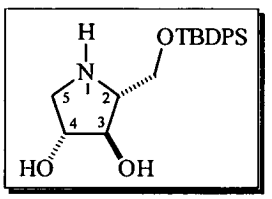
(3*S*,4*S*,5*R*)-4-Hydroxy-5-hydroxymethyl-3-methylpyrrolidin-2-one *140*



To a solution of the TBDPS protected lactam **134** (30 mg, 0.078 mmol) in THF (1.0 cm^3) was added TBAF (156 μl, 0.156 mmol). The solution immediately turned yellow and the mixture was concentrated under reduced pressure. The residue was chromatographed on silica gel [EtOAc, followed by methanol] to give the title compound (9 mg, 80%) as a colourless amorphous solid, mp 126-128 °C; R_f [hexane:EtOAc (1:3)] 0.10; $[\alpha]_D$ +21.5 (*c* 0.26, MeOH); ν_{max} (neat)/cm^{-1} 3377, 3280, 3208, 1643; δ_H (250 MHz, CD_3OD) 3.86 (1H, dd, *J* 7.3, 5.9, C_4H), 3.83 (1H, dd, *J* 11.6, 3.3, $CH_AH_BOTBDPS$), 3.62 (1H, dd, *J* 11.6, 5.9, $CH_AH_BOTBDPS$), 3.47 (1H,

td, *J* 5.9, 3.3, C_2H), 2.43 (1H, dq~qn, *J* 7.2, C_3H), 1.27 (3H, d, *J* 7.3, CH_3); δ_C (62.9 MHz) 177.9, 74.8, 61.9, 61.2, 44.8, 11.8; m/z (FAB) 146 ($[M+H]^+$, 34.5%), 109 (25.5), 91 (100), 73 (30.3); HRMS (FAB) ($C_6H_{12}NO_3$ requires 146.0817, found 146.0816).

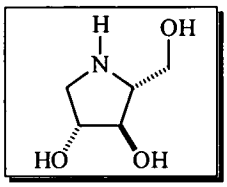
(2*R*,3*R*,4*R*)-2-*tert*-Butyldiphenysilyloxymethyl-3,4-dihydroxypyrrolidine *141*



To a solution of lactam **114** (160 mg, 0.42 mmol) in dry THF (2.0 cm^3) at 0 °C was added BH_3•THF (6.23 cm^3, (1.0 *M* in THF), 6.23 mmol). After ca. 10 minutes the mixture was heated to reflux and held at reflux for 18 hours. The solution was cooled to 0 °C and methanol (ca. 8 cm^3) was added to destroy unreacted borane. The solution was then concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (1:1)] to give the title compound (157 mg, 100%) as a solid, R_f [hexane:EtOAc (1:3)] 0.78; mp 150 °C; $[\alpha]_D$ -8.08 (*c* 0.99, MeOH); ν_{max} (neat)/cm^{-1} 3542, 3489, 3350, 3180, 2928, 2845, 1426; δ_H (600 MHz, CD_3OD) 7.73-7.70 (4H, m, Ar*H*), 7.45-7.39 (6H, m, Ar*H*), 5.22 (1H, brs, N*H*), 4.20 (1H, dt, *J* 5.0, 1.6, C_4H), 4.08 (1H, dd, *J* 10.6, 4.8, $CH_AH_BOTBDPS$), 4.03 (1H, dt, *J* 4.4, 1.8, C_3H), 3.85 (1H, dd, *J* 10.6, 2.6, $CH_AH_BOTBDPS$), 3.14 (1H, brdd, *J* 12.5, 6.4, $C_5H_XH_Y$), 3.04 (1H, dq, *J* 12.5, 2.6, $C_5H_XH_Y$), 2.76 (1H, dqn, *J* 4.9, 2.7, C_2H), 1.07 (9H, s, ^tBu); δ_C (50.3 MHz) 134.9 (4C), 132.2 (2C), 129.2 (2C), 127.1 (4C), 78.5, 75.1, 73.1, 59.8, 59.0, 25.4 (3C), 18.3; m/z (FAB) 372 ($[M+H]^+$, 100), 198 (4), 49 (6); HRMS (FAB) ($C_{21}H_{30}NO_3Si$ requires 372.1995, found 372.1995).

(2*R*,3*R*,4*R*)-3,4-Dihydroxy-2-hydroxymethylpyrrolidine

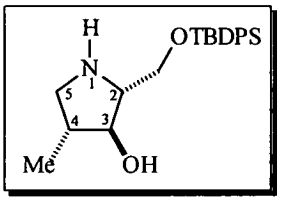
(1,4-Dideoxy-1,4-imino-*D*-arabinitol) *35*



To a solution of the silyl protected compound **141** (19 mg, 0.051 mmol) in acetonitrile (0.75 cm^3) was added hydrofluoric acid (0.141 cm^3 (48% solution in water), ca. 5eq). The mixture was stirred for 15 mins before being concentrated under reduced pressure and treated with methoxytrimethylsilane (2 cm^3). This mixture was then re-concentrated. The residue was treated with methoxytrimethylsilane (2 cm^3) and re-concentrated. The resulting residue obtained was triturated with EtOAc (3 x 1.0 cm^3) to give the hydrofluoride salt of the title compound (8 mg, 100%) as a tacky solid, $[\alpha]_D$ +26.3 (c 0.30, H_2O) [lit.[72c] +27.3 (*c* 0.47, H_2O)]; δ_H (600 MHz, D_2O) 4.36 (1H, dt, *J* 5.0, 2.7, C_4H), 4.12 (1H, brt, *J* 3.7, C_3H), 3.98 (1H, dd, *J* 12.2, 4.6, CH_AH_BOH), 3.86 (1H, dd, *J* 12.2, 8.2, CH_AH_BOH), 3.65 (1H, dt, *J* 8.2, 4.2, C_2H), 3.61 (1H, dd, *J* 12.6, 5.0, $C_5H_XH_Y$), 3.38 (1H, dd, *J* 12.6, 2.7, $C_5H_XH_Y$); δ_C (62.9 MHz) 75.5, 74.2, 66.6, 58.9, 49.9; m/z (FAB) 134 ($[M+H]^+$, 30%), 116 (26), 102 (47), 91 (21); HRMS (FAB) ($C_5H_{12}NO_3$ requires 134.0817, found 134.0817). All spectroscopic data was in good agreement with that of the literature.

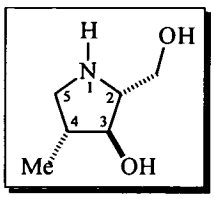
The HF salt was subjected to ion-exchange chromatography [Dowex OH^-] (prepared by treating Dowex 1-X2 with 1N aqueous NaOH, followed by water until pH of eluent returned to 7) eluting with water to give the free base (quantitative recovery) as a sticky oil, R_f [$CHCl_3$:MeOH:28% aq. NH_3 (5:3:1)] 0.21; $[\alpha]_D$ +8.2 (*c* 0.25, H_2O) [lit.[72b] +8.1 (*c* 0.98, H_2O)]; δ_H (600 MHz, D_2O) 4.16 (1H, dt, *J* 5.8, 3.9, C_4H), 3.85 (1H, dd, *J* 5.7, 3.9, C_3H), 3.75 (1H, dd, *J* 11.6, 4.8, CH_AH_BOH), 3.67 (1H, dd, *J* 11.6, 6.4, CH_AH_BOH), 3.12 (1H, dd, *J* 12.2, 5.8, $C_5H_XH_Y$), 2.99 (1H, dt, *J* 6.1, 4.8, C_2H), 2.84 (1H, dd, *J* 12.2, 3.9, $C_5H_XH_Y$); δ_C (62.9 MHz) 79.9, 77.4, 65.0, 62.0, 50.4. All spectroscopic data was in good agreement with that of the literature.

(2*R*,3*S*,4*R*)-2-*tert*-Butyldiphenylsilyloxymethyl-3-hydroxy-4-methylpyrrolidine *142*



To a solution of the lactam **134** (103 mg, 0.27 mmol) in THF (2.0 cm^3) at 0 °C was added borane•THF (4.05 cm^3, (1.0 *M* in THF), 4.05 mmol). After the initial effervescence had ceased the mixture was warmed to reflux and held at reflux for 24 hours. Methanol was cautiously added to the cooled (0 °C) reaction mixture to destroy unreacted borane. The resulting mixture was concentrated under reduced pressure to a colourless paste. This paste was chromatographed on silica gel [hexane:EtOAc (2:3)] to give the title compound (92 mg, 93%) as a colourless oil, R_f [hexane:EtOAc (6:1)] 0.25; $[\alpha]_D$ +17.0 (*c* 1.26, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3468, 3255; δ_H (250 MHz, $CDCl_3$) 7.66-7.25 (10H, m, Ar*H*), 4.36 (1H, brs, O*H*), 4.15 (1H, dd, *J* 11.3, 3.0, $C_5H_AH_B$), 3.76 (1H, dd, *J* 11.3, 1.9, $C_5H_AH_B$), 3.70 (1H, t, *J* 7.9, C_3H), 3.26 (1H, ddd, *J* 8.3, 5.7, C_2H), 2.87-2.79 (2H, m, CH_2OTBDPS), 2.23 (1H, dq~qn, *J* 7.6, C_4H), 1.07 (3H, d, *J* 6.8, *Me*), 1.07 (9H, s, ^tBu); δ_C (62.9 MHz) 135.4 (4C), 132.3, 131.9, 130.1 (2C), 127.9 (4C), 77.1, 72.6, 58.6, 58.4, 38.5, 26.8 (3C), 19.1, 15.5; m/z (FAB) 370 ($[M+H]^+$, 40.5), 382(100), 199 (82.2), 135 (50.3); HRMS (FAB) ($C_{22}H_{32}NO_2Si$ requires 370.2202, found 370.2205).

(3*R*,4*R*,5*R*)-4-Hydroxy-5-hydroxymethyl-3-methylpyrrolidine and it's HF salt *57*

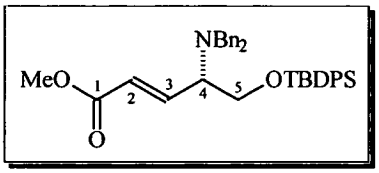


To a solution of the TBDPS protected pyrrolidine **142** (45 mg, 0.122 mmol) in acetonitrile (1.5 cm^3) was added hydrofluoric acid (48% aqueous solution) (0.3 cm^3, ~5 eq). The reaction mixture was stirred for 20 minutes. Methoxytrimethylsilane (3.0 cm^3) was added cautiously and the mixture was concentrated under reduced pressure. The remaining residue was again treated with methoxytrimethylsilane (3.0cm^3) and concentrated. This procedure was repeated once more. The remaining residue was chromatographed on silica gel [$CHCl_3$:MeOH:NH_3 (28% aqueous) (5:3:1)] to elute the hydrofluoride salt of the title compound (17 mg, 94%) as a colourless oil, R_f [$CHCl_3$:MeOH:NH_3(28% aqueous) (5:3:1)] 0.45. The HF salt was subjected to ion-exchange chromatography (Dowex 1X2, OH^-) using MeOH to elute the free base (16 mg, 100%) as a colourless oil,

Data for HF salt: $[\alpha]_D$ +6.3 (*c* 0.4, MeOH); δ_H (250 MHz, CD_3OD) 3.97 (1H, dd, *J* 11.9, 3.5, C*H*$_A$H$_B$OH), 3.82 (1H, dd, *J* 11.9, 6.0, CH$_A$*H*$_B$OH), 3.78 (1H, t, *J* 8.3, C$_3$*H*), 3.59 (1H, dd, *J* 11.7, 8.0, C$_5$*H*$_A$H$_B$), 3.42 (1H, ddd, *J* 8.0, 6.1, 3.6, C$_2$*H*), 2.96 (1H, dd~t, *J* 11.5, C$_5$H$_A$*H*$_B$), 2.25 (1H, m, C$_4$*H*), 1.23 (3H, d, *J* 6.6, *Me*); δ_C (75 MHz) 75.2, 65.3, 57.6, 48.3, 39.2, 12.5.

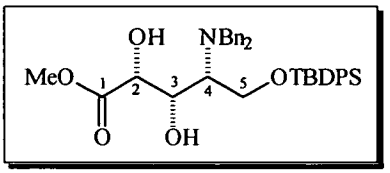
Data for free base: $[\alpha]_D$ -2.3 (*c* 0.35, MeOH) δ_H (250 MHz, CD_3OD) 3.97 (1H, dd, *J* 11.3, 3.9, C*H*$_A$H$_B$OH), 3.68 (1H, dd, *J* 11.3, 5.8, CH$_A$*H*$_B$OH), 3.55 (1H, t, *J* 7.4, C$_3$*H*), 3.22 (1H, dd, *J* 10.9, 7.9, C$_5$*H*$_X$H$_Y$), 3.00 (1H, ddd, *J* 7.3, 5.8, 3.9, C$_2$*H*), 2.65 (1H, dd, *J* 10.8, 8.6, C$_5$H$_X$*H*$_Y$), 2.13 (1H, qn, *J* 7.4, C$_4$*H*), 1.16 (3H, d, *J* 6.8, *Me*); δ_C (62.9 MHz) 78.3, 65.9, 60.8, 56.1, 41.0, 14.3; m/z (FAB) 132 ([M+H]$^+$, 44.0%), 322 (100); HRMS (FAB) ($C_6H_{14}NO_2$ requires 132.1024, found 132.1024).

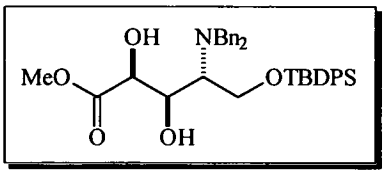
Methyl (2*E*,4*S*)-5-*tert*-butyldiphenylsilyloxy-4-*N*,*N*-dibenzylaminopent-2-eneoate *144*



To a solution of trimethylphosphonoacetate (0.18 cm^3, 1.47 mmol) in THF/H_2O (40:1) (20 cm^3) was added $Ba(OH)_2$ (activated)$^{\Psi}$ (240 mg, 1.47 mmol). After approximately 30 minutes a white suspension had formed and a solution of the aldehyde **73** (386 mg, 0.726 mmol) in THF (3 cm^3) was added. The resulting mixture was stirred for 18 hours. The mixture was then diluted with DCM (150 cm^3) and washed with a saturated aqueous solution of sodium bicarbonate (150 cm^3) and brine (150 cm^3). The organic phase was dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (4:1)] to give the title compound (320 mg, 78%) as a colourless oil, R_f [hexane:EtOAc (4:1)] 0.57; $[\alpha]_D$ +61.5 (*c* 1.06, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1724, 1652, 1600, 1566, 1492; δ_H (250 MHz, $CDCl_3$) 7.53-7.24 (20H, m, Ar*H*), 7.04 (1H, dd, *J* 15.9, 7.0, C_2H), 6.03 (1H, dd, *J* 15.9, 1.4, C_3H), 3.93 (1H, dd, *J* 10.3, 6.3, $C_5H_AH_B$OTBDPS), 3.82 (2H, d, *J* ~15.6 (obscured), NCH_AH_BPh x 2), 3.81 (1H, dd, *J* 10.3, 7.4, $C_5H_AH_B$OTBDPS), 3.77 (3H, s, *Me*), 3.60 (2H, d, *J* 14.0, NCH_AH_BPh x 2), 3.52 (1H, ddd, *J* 7.7, 6.3, 1.3, C_4H), 1.04 (9H, s, ^tBu); δ_C (62.9 MHz, $CDCl_3$) 166.6, 146.0, 139.6 (2C), 135.5 (4C), 133.0 (2C), 129.7 (2C), 128.3 (4C), 128.2 (4C), 127.7 (4C), 126.9 (2C), 123.5, 63.7, 60.3, 54.4 (2C), 51.4, 26.6(3C), 18.9; m/z (FAB) 564 ($[M+H]^+$, 75.6), 294 (100), 197 (98.8), 135 (60.8), 105 (44.9), 92 (23.3); HRMS (FAB) ($C_{36}H_{42}NO_3Si$ requires 564.2934, found 564.2934).

Methyl (2*R*,3*S*,4*R*)-5-*tert*-butyldiphenylsilyloxy-4-*N*,*N*-Dibenzylamino-2,3-dihydroxypentanoate *154* and Methyl (2*S*,3*R*,4*R*)-5-*tert*-butyldiphenylsilyloxy-4-*N*,*N*-dibenzylamino-2,3-dihydroxypentanoate *143*





To a solution of the α,β-unsaturated ester **144** (850 mg, 1.51 mmol) in acetone/water (8:1) (8.5 cm^3) was added NMO (534 mg, 4.53 mmol) and osmium tetroxide (4% aqueous solution) (1.77 cm^3, 0.266 mmol). The mixture was vigorously stirred for 5 hours. Saturated aqueous sodium sulfite solution (approx. 5 cm^3) was added and the resulting mixture was stirred for 1 hour, before being partitioned between DCM (25 cm^3) and brine (25 cm^3). The organic phase was separated and the aqueous phase was extracted with DCM (3 x 15 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica [hexane:EtOAc (4:1)] to give the title compounds as a 65:35 mixture of diastereomers ((2*R*, 3*S*, 4*R*):(2*S*, 3*R*, 4*R*)) (525 mg, 59%),

Data for (2*R*,3*S*,4*R*) diastereomer **154**: obtained (340 mg, 38%) as a colourless crystalline solid, R_f [hexane:EtOAc (4:1)] 0.22; mp 112-113 °C; $[\alpha]_D$ -32.9 (*c* 1.4, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3530, 1747; δ_H (250 MHz, $CDCl_3$) 7.73-7.17 (20H, m, Ar*H*), 4.30 (1H, brs, O*H*), 3.98 (2H, d, *J* 11.3, NCH_AH_BPh x 2), 3.97-3.87 (4H, m, C_2H + C_3H + CH_2OTBDPS), 3.78 (3H, s, O*Me*), 3.53 (2H, d, *J* 13.1, NCH_AH_BPh x 2), 3.13 (1H, ddd~dt, *J* 8.2, 4.0, C_4H), 2.85 (1H, brs, O*H*), 1.11 (9H, s, ^tBu); δ_C (50.3 MHz) 173.3, 138.5 (2C), 135.6 (2C), 135.6 (2C), 132.5 (2C), 130.0, 129.9, 129.0 (4C), 128.4 (4C), 127.8 (4C), 127.3 (2C), 70.5, 68.2, 59.5, 59.0, 54.4 (2C), 52.2, 26.7 (3C), 18.9; m/z (FAB) 598 ([M+H]$^+$, 44.1), 478 (48.3), 328 (20.1), 197 (16.4), 135 (15.5,

$^\Psi$ Barium hydroxide was activated by heating in an oven at a temperature of 120°C for 2 hours.

91 (100); HRMS (FAB) ($C_{36}H_{44}NO_5Si$ requires 598.2989, found 598.2989); single crystal x-ray diffraction: see appendix.

Data for (2*S*,3*R*,4*R*) diastereomer **143**: obtained (185 mg, 21%) as a colourless oil, R_f [hexane:EtOAc (4:1)] 0.17; $[\alpha]_D$ -30.6 (*c* 1.15, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3482, 1738; δ_H (250 MHz, $CDCl_3$) 7.74-7.20 (20H, m, Ar*H*), 4.66 (1H, brs, O*H*), 4.12-4.07 (4H, m, C_2H + C_3H + CH_2OTBDPS), 4.06 (2H, d, *J* 12.9, CH_AH_BPh x 2), 3.77 (3H, s, O*Me*), 3.53 (2H, d, *J* 13.4, CH_AH_BPh x 2), 3.04 (1H, dt, *J* 9.4, 5.7, C_4H), 2.75 (1H, brs, O*H*), 1.08 (9H, s, ^tBu); δ_C (50 MHz, $CDCl_3$) 174.3, 139.3 (2C), 135.6 (2C), 135.5 (2C), 132.6, 132.5, 129.9 (2C), 128.9 (4C), 128.2 (4C), 127.8 (4C), 127.0 (2C), 72.4, 70.5, 61.5, 58.7, 54.9 (2C), 52.3, 26.7 (3C), 18.9.

Synthesis of Diols *via* AD-mix-α

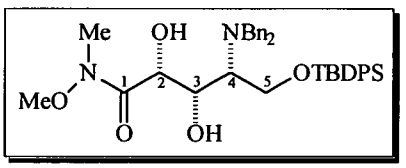
To a solution of the α,β-unsaturated ester **144** (150 mg, 0.266 mmol) in acetone/water (3:1) (5 cm^3) was added AD-mix-α (1.4 g) and methanesulfonamide (26 mg, 0.266 mmol). The reaction mixture was stirred vigorously for 7 days. Saturated aqueous sodium sulfite solution (approx. 3 cm^3) was added and the mixture was stirred for 1 hour, before being partitioned between DCM (15 cm^3) and brine (15 cm^3). The organic phase was separated and the aqueous phase was extracted with DCM (3 x 10 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (4:1)] to give unreacted starting material (108 mg, 72%), the (2*R*,3*S*,4*R*) diastereomer (19 mg, 43% (based on recovered starting material)) and the (2*S*,3*R*,4*R*) diastereomer (10 mg, 22% (based on recovered starting material)).

Synthesis of Diols *via* AD-mix-β

The synthesis of the diols using AD-mixβ was carried out in an identical manner to the synthesis with AD-mix-α. Chromatography provided unreacted starting material

(38 mg, 25 %), the (2*R*,3*S*,4*R*) diastereomer (26 mg, 22% (based on recovered starting material)) and the (2*S*,3*R*,4*R*) diastereomer (55 mg, 46% (based on recovered starting material)).

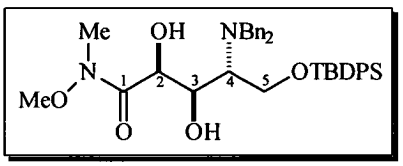
(2*R*,3*S*,4*R*)-5-*tert*-Butyldiphenylsilyloxy-4-*N*,*N*-dibenzylamino-2,3-dihydroxy pentanoic acid methoxy-methyl-amide *157*



To a suspension of *N*,*O*-dimethylhydroxylamine•HCl (1.15 g, 11.68 mmol) in THF (6 cm^3) at -30 °C was added trimethylaluminium (5.84 cm^3, (2.0 *M* in toluene),11.68 mmol). The resulting mixture was allowed to warm to room temperature during which time vigorous gas evolution was observed. After 20 minutes gas evolution had ceased and the clear solution was recooled to -30 °C and a 30 °C solution of methyl ester **154** (220 mg, 0.389 mmol) in THF (2 cm^3) was added *via* cannula. The resulting mixture was allowed to warm to room temperature and stirred at room temperature for 24 hours. The reaction mixture was then cannulated into a rapidly stirred biphasic solution of DCM (50 cm^3) and saturated aqueous sodium potassium tartrate (50 cm^3). The resulting cloudy mixture was stirred vigorously for 5 hours when two clear phases separated. The organic phase was separated and the aqueous phase was extracted with DCM (3 x 30 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (3:1)] to give the title compound (227 mg, 93%) as a colourless oil, R_f [hexane:EtOAc (3:1)] 0.24; $[\alpha]_D$ -21.9 (*c* 0.98, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3446, 1664, 1589, 1495; δ_H (250 MHz, $CDCl_3$) 7.78-7.20 (20H, m, Ar*H*), 4.24 (1H, brs, C_2H), 4.07 (1H, dd, *J* 11.4, 6.7, $C_5H_AH_B$OTBDPS), 3.96 (2H, d, *J* 13.2, NCH_XH_YPh x 2), 3.94 (1H, dd, *J* 11.4, 4.2, $C_5H_AH_B$OTBDPS), 3.85 (1H, dd, *J* 9.1, 1.0, C_3H), 3.62 (2H, d, *J* 13.2, NCH_XH_YPh x 2), 3.42 (3H, s,

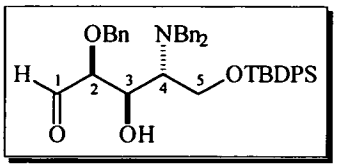
O*Me*), 3.31 (1H, ddd, *J* 9.1, 6.7, 4.2, C_4H), 3.20 (3H, s, *Me*), 1.15 (9H, s, ^tBu); δ_C (62.9 MHz) 172.5, 138.7 (2C), 135.6 (4C), 132.9, 132.7, 129.8 (2C), 129.0 (4C), 128.3 (4C), 127.7 (4C), 127.1 (2C), 77.1, 68.6, 67.4, 60.7, 60.6, 59.9, 54.6 (2C), 26.8 (3C), 19.1; m/z (FAB) 627 ($[M+H]^+$, 68.5%), 478 (61.6), 357 (13.0), 135 (51.1), 91 (100); HRMS (FAB) ($C_{37}H_{47}N_2O_5Si$ requires 627.3254, found 627.3252).

(2*S*,3*R*,4*R*)-4-*N*,*N*-Dibenzylamino-5-*tert*-butyldiphenylsiloxy-2,3-dihydroxy pentanoic acid methoxy-methyl-amide *142*



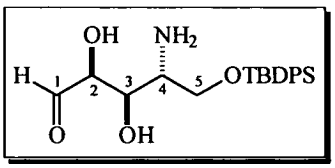
The synthesis of the (2*S*,3*R*,4*R*) diastereomer was carried out in an identicle manner to the (2*R*,3*S*,4*S*) diastereomer. Thus, *N*,*O*-dimethylhydroxylamine•hydrochloride (770 mg, 7.81 mmol), trimethylaluminium (3.91 cm^3, (2.0 *M* in toluene), 7.81 mmol) and methylester **143** (147 mg, 0.26 mmol) provided the title compound (138 mg, 85%) as a colourless oil, after chromatography, R_f [hexane:EtOAc (3:1)] 0.24; $[\alpha]_D$ -25.0 (*c* 0.97, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3448, 1654, 1493, 1453; δ_H (250 MHz, $CDCl_3$) 7.77-7.18 (20H, m, Ar*H*), 4.93 (1H, brd, *J* 4.7, O*H*), 4.27 (1H, brd, *J* 8.8, C_2H), 4.15-4.11 (1H, m, $C_5H_AH_B$OTBDPS) 4.11 (1H, dd, *J* 10.8, 4.5, $C_5H_AH_B$OTBDPS), 4.06 (1H, dd, *J* 7.8, 4.7, C_3H), 4.00 (2H, d, *J* 13.3, NCH_XH_YPh x 2), 3.64 (2H, d, *J* 13.3, NCH_XH_YPh x 2), 3.42 (3H, s, O*Me*), 3.24 (3H, s, *Me*), 3.08 (1H, dt, *J* 9.2, 4.7, C_4H), 1.09 (9H, s, ^tBu); δ_C (75 MHz) 173.5, 139.5 (2C), 135.6 (2C), 135.5 (2C), 132.9, 132.6, 129.7 (2C), 128.3 (4C), 128.1 (4C), 127.7 (2C), 127.6 (2C), 126.8 (2C), 77.1, 70.8, 68.2, 60.9, 59.1, 54.9 (2C), 26.8 (3C), 19.0.

(2*S*,3*R*,4*R*)-2-Benzyloxy-5-*tert*-butyldiphenylsilyloxy-4-*N*,*N*-dibenzylamino-3-hydroxy pentanal *159*



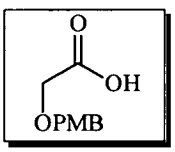
To a solution of Weinreb amide **110** (70mg, 0.098 mmol) in toluene (1.5 cm^3) at -78 °C was added diisobutylaluminium hydride (244 μl, 0.244mmol). The resulting mixture was stirred at -78 °C for 20 mins and carefully quenched by addition of methanol (ca. 0.5 cm^3) and warmed to room temperature. The resulting mixture was diluted with DCM (10 cm^3) and saturated aqueous sodium potassium tartrate solution (10 cm^3) was added. The resulting cloudy biphasic mixture was stirred for 3 hours after which two clear phases separated. The organic phase was separated and the aqueous phase was extracted with DCM (3 x 10 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The remaining residue was quickly chromatographed on silica gel [hexane:EtOAc (2:1)] to give the title compound (59 mg, 88%) as a colourless oil, R_f [hexane:EtOAc (2:1)] 0.56; $[\alpha]_D$ -38.7 (*c* 0.3, CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3445, 1729; δ_H (200 MHz, $CDCl_3$) 9.60 (1H, d, *J* 1.1, C*H*O), 7.69-7.04 (25H, m, Ar*H*), 4.10 (1H, d, *J* 11.0, OCH_AH_BPh), 4.10-3.97 (4H, m, C_2H + C_3H +C_5H_2OTBDPS), 3.79 (2H, d, *J* 13.5, NCH_XH_YPh x 2), 3.64 (1H, d, *J* 11.0, OCH_AH_BPh), 3.45 (2H, d, *J* 13.5, NCH_XH_YPh x 2), 3.09 (1H, dt, *J* 9.5, 5.1, C_4H), 1.00 (9H, s, ^tBu); δ_C (50.3 MHz) 204.8, 139.7 (2C), 137.3 (2C), 135.7 (2C), 135.6 (2C), 133.0, 132.7, 129.8 (2C), 129.2 (4C), 128.3 (4C), 128.2 (2C), 128.0 (2C), 127.8 (4C), 127.1 (2C), 83.3, 72.7, 71.8, 60.9, 59.1, 54.9 (2C), 26.8 (3C), 18.9; m/z (FAB) 658 ($[M+H]^+$, 1.8%), 541 (5), 478 (70), 135 (21.9), 91 (100); HRMS (FAB) ($C_{42}H_{48}NO_4Si$ requires 658.3353, found 658.3352).

Debenzylation of *159*: Attempted Synthesis of Amino Aldehyde *112*



A solution of **159** (50 mg, 0.073 mmol) and 20% $Pd(OH)_2/C$ (50 mg) in methanol (1 cm^3) was exposed to a hydrogen atmosphere (1 atm.) and stirred vigorously for 72 hours. T.l.c. showed that the reaction mixture was composed of several different components. As a result the reaction mixture was not purified further.

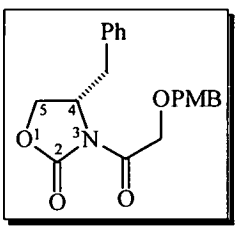
p*-Methoxybenzyloxyacetic acid *165



To a suspension of sodium hydride (17.60 g (60% oil dispersion), 0.44 mol) in THF (400 cm^3) at 0 °C was added bromoacetic acid (15.0 g, 0.11 mol). *p*-Methoxybenzyl alcohol (15.18 g, 0.11 mol) was added dropwise to the mixture followed by tetra-*n*-butyl ammonium bromide (1.76 g, 5.50 mmol). The reaction mixture was heated to reflux and held at reflux for 4 hours. The reaction was carefully quenched by addition of water at 0 °C and the resulting mixture was concentrated under reduced pressure to a slurry. This slurry was diluted with diethyl ether (300 cm^3) and extracted with a saturated aqueous solution of sodium bicarbonate (3 x 300 cm^3). The combined aqueous extracts were acidified to pH 1 by addition of concentrated sulphuric acid and extracted with diethyl ether (3 x 500 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (1:1)] to give a pale yellow oil which crystallised on standing. Recrystallisation from diethylether provided the title

compound (14.3 g, 68%) as a colourless crystalline solid, R_f [hexane:EtOAc (1:1)] 0.42; mp 50-52 °C; ν_{max} (nujol)/cm^{-1} 3480, 1713, 1612, 1513, 1462; δ_H (200 MHz, $CDCl_3$) 9.78 (1H, brs, COO*H*), 7.28 (2H, d, *J* 8.4, Ar*H*(ortho to methoxy)), 6.88 (2H, d, *J* 8.4, Ar*H* (meta to methoxy)), 4.57 (2H, s, CH_2COOH), 4.11 (2H, s, OCH_2ArOMe), 3.80 (3H, s, O*Me*); δ_C (50.3 MHz) 175.1, 159.4, 129.7 (2C), 128.5, 113.7 (2C), 72.7, 65.9, 55.0; m/z (FAB) 196 (M^+, 17.9), 137 (30.9), 121 (100).

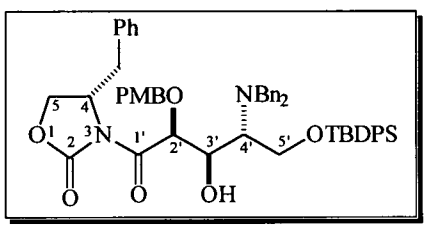
(4*S*)-3-(2'-*p*-Methoxybenzyloxy-1'-oxoethyl)-4-phenylmethyloxazolidin-2-one *160*



To a solution of *p*-methoxybenzyloxyacetic acid **165** (5.54 g, 28.3 mmol) in THF (150 cm^3) at -78 °C was added triethylamine (3.97 cm^3, 28.3 mmol) and pivaloyl chloride (3.32 cm^3, 28.3 mmol). The resulting slurry was allowed to warm to 0 °C and stirred at 0 °C for 20 minutes before being recooled to -78 °C. Meanwhile, in a separate flask a solution of the oxazolidinone **106** (5.00 g, 28.3 mmol) in THF (30 cm^3) at -78 °C was treated with n-butyllithium (1.6 *M* in hexanes) (17.66 cm^3, 28.3 mmol). The lithiated oxazolidinone was then cannulated into the flask containing the mixed anhydride and the resulting mixture was stirred for 1 hour. A saturated solution of ammonium chloride (100 cm^3) was added producing to clear phases. The organic phase was separated and the aqueous phase was extracted with DCM (3 x 100 cm^3). The combined organics were washed sequentially with saturated aqueous sodium bicarbonate (150 cm^3) and brine (150 cm^3) then dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (1:1)] to give the title compound (10.0 g, 100%) as a colourless solid, R_f [hexane:EtOAC (1:1)] 0.56; mp 63-65 °C; $[\alpha]_D$ +52.0 (*c* 1.25, $CHCl_3$) [lit.,[104b] for

(*R*)-isomer, mp 67-68 °C, $[\alpha]_D$ -69.2 (*c* 1.32, CH_2Cl_2)]; ν_{max} (nujol)/cm^{-1} 1764, 1713, 1615, 1583, 1515, 1463; δ_H (200MHz, $CDCl_3$) 7.37-7.12 (7H, m, Ar*H*), 6.89 (2H, dd, *J* 6.6, 1.4, Ar*H* (meta to methoxy), 4.74-4.67 (3H, m, C*H*$_2$OPMB + C_4H), 4.62 (2H, s, OC*H*$_2$ArOMe), 4.24-4.20 (2H, m, C_5H_2), 3.80 (3H, s, O*Me*), 3.30 (1H, dd, *J* 13.5, 3.3, CH_AH_BPh), 2.80 (1H, dd, *J* 13.5, 9.5, CH_AH_BPh); δ_C (50.3 MHz) 170.2, 159.4, 153.3, 134.9, 129.7 (2C), 129.3, 129.1 (2C), 128.9 (2C), 127.3, 113.8 (2C), 73.0, 69.2, 67.1, 55.1, 54.6, 37.5; m/z (FAB) 355 (M^+, 20.0%), 307 (100), 154 (55.4), 121 (30.3).

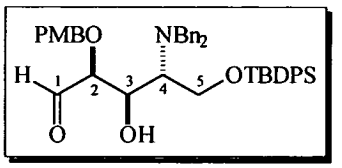
(2'*S*,3'*R*,4*S*,4'*R*)-3-(5'-*tert*-Butyldiphenylsilyloxy-4-*N*,*N*-dibenzylamino-3'-hydroxy-2'-*p*-methoxybenzyloxy-1'-oxopentyl)-4-phenylmethyloxazolidin-2-one *161*



To a -78 °C solution of imide **160** (2.80 g, 7.89 mmol) in toluene (30 cm^3) was added dibutylborontriflate (8.86 cm^3, (1.0 *M* in DCM), 8.86 mmol)), followed by triethylamine (1.42 cm^3, 9.47 mmol). The resulting mixture was warmed to between -50 and -40 °C and stirred for 1 hour before being warmed to -30 °C and stirred for a further 1 hour. The mixture was then re-cooled to -78 °C and a -78 °C solution of the aldehyde **73** (1.0 g, 1.97 mmol) in toluene (10 cm^3) was added *via* cannula. The resulting solution was stirred at -78 °C for 1 hour and warmed to 0 °C and stirred for a further 45 minutes. The reaction was quenched by addition of methanol (10 cm^3) and pH 7 phosphate buffer solution (10 cm^3). Hydrogen peroxide (12 cm^3) in methanol (12 cm^3) was added cautiously and the resulting cloudy solution was stirred at 0 °C for 1 hour. The solution was diluted by addition of DCM (100 cm^3). The

organic phase was separated and the aqueous phase was extracted with DCM (3 x 20 cm^3). The combined organic extracts were washed with saturated aqueous sodium bicarbonate solution (60 cm^3) and brine (60cm^3) then dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (2:1)] to give the title compound (1.32 g, 78%) as a colourless solid, R_f [hexane:EtOAc (1:1)] 0.77; mp 56-58 °C; $[\alpha]_D$ +23.1 (*c* 0.88, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3534, 1779, 1705, 1609, 1511, 1490; δ_H (600 MHz, $CDCl_3$) 7.71-7.16 (25H, m, Ar*H*), 7.10 (2H, dd, *J* 8.5, 1.9, Ar*H* ortho to methoxy), 6.76 (2H, dd, *J* 8.8, 2.1, Ar*H* meta to methoxy), 5.37 (1H, d, *J* 2.7, C_2-*H*), 4.44 (1H, dddd, *J* 10.3, 7.4, 3.1, 2.1, C_4*H*), 4.22 (1H, td, *J* 8.2, 2.7, C_3-*H*), 4.14 (1H, d, *J* 10.7, CH_AH_BArOMe), 4.08 (1H, dd, *J* 9.0, 2.1, $C_5H_XH_Y$), 4.06 (1H, d, *J* 10.9, CH_AH_BArOMe), 4.06 (2H, m, CH_2OTBDPS), 4.03 (1H, dd, *J* 8.3, 7.4, $C_5H_XH_Y$), 3.84 (2H, d, *J* 13.9, NCH_SH_TPh x 2), 3.72 (3H, s, O*Me*), 3.62 (2H, d, *J* 13.9, NCH_SH_TPh x 2), 3.25 (1H, q, *J* 5.7, C_4-*H*), 3.18 (1H, dd, *J* 13.4, 3.1, CH_PH_QPh), 3.00 (1H, d, *J* 8.4, O*H*), 2.53 (1H, dd, *J* 13.4, 10.3, CH_PH_QPh), 1.04 (9H, s, ^tBu); δ_C (62.9 MHz) 171.2, 159.2, 152.9, 139.9 (2C), 135.7 (2C), 135.6 (2C), 135.2, 133.0, 132.9, 130.1 (2C), 129.6 (2C), 129.2 (2C), 129.0 (4C), 128.8 (2C), 128.0 (4C), 127.6 (2C), 127.5 (2C), 127.2 (2C), 126.7 (2C), 113.4 (2C), 77.9, 72.2, 72.1, 66.6, 61.4, 59.7, 55.7, 55.1, 54.6 (2C), 37.5, 26.7 (3C), 19.0; m/z (FAB) 863 ($[M+H]^+$, 20.1%), 593 (6.7), 478 (70.7), 121 (100), 91 (91.1); HRMS (FAB) ($C_{53}H_{59}N_2O_7Si$ requires 863.4092, found 863.4090).

Attempted Oxidative Removal of *p*-Methoxybenzyl Group: Synthesis of (2*S*,3*R*,4*R*)-5-*tert*-Butyldiphenylsilyloxy-4-*N*,*N*-dibenzylamino-3-hydroxy-2-*p*-methoxybenzyloxypentanal *166*

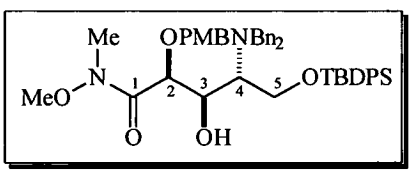


To a solution of aldol adduct **161** (50 mg, 0.058 mmol) in DCM/Water (9:1) (2 cm^3) was added 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (16 mg, 0.0696 mmol). The initial dark brown colour changed to a dark green colour over ca. 20 minutes. Stirring was continued for 1 hour. Saturated aqueous sodium bicarbonate (2 cm^3) was added and the organic phase was separated. The aqueous phase was extracted with DCM (3 x 2 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (1:1)] to provide recovered starting material (34 mg, 68%), oxazolidin-2-one **106** (3 mg, 91% (based on recovered starting material)) and aldehyde **166** (10 mg, 78% (based on recovered starting material)) as a colourless oil, R_f [hexane:EtOAc (1:1)] 0.76; $[\alpha]_D$ -26.3 (*c* 0.4, CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3448, 1728, 1610, 1585, 1512; δ_H (200 MHz, $CDCl_3$) 9.54 (1H, d, *J* 1.1, C*H*O), 7.68-7.12 (20H, m, Ar*H*), 7.06 (2H, dd, *J* 8.4, 2.2, Ar*H* ortho to methoxy), 6.73 (2H, dd, *J* 8.8, 2.2, Ar*H* meta to methoxy), 4.10-4.04 (3H, m, C_2H + C_3H + $C_5H_AH_B$OTBDPS), 4.00 (1H, d, *J* 10.6, CH_XH_YArOMe), 3.79 (2H, d, *J* 13.3, NCH_SH_TPh x 2), 3.70 (3H, s, O*Me*), 3.70-3.67 (1H, m, $C_5H_AH_B$OTBDPS), 3.65 (1H, d, *J* 10.6, CH_XH_YArOMe), 3.47 (2H, d, *J* 13.3, NCH_SH_TPh x 2), 3.06 (1H, dt, *J* 9.5, 5.5, C_4H), 1.00 (9H, s, ^tBu); δ_C (50.3 MHz) 204.9, 159.4, 139.7 (2C), 135.7 (2C), 135.6 (4C), 133.0, 132.8, 129.8 (2C), 129.2 (4C), 128.3 (4C), 127.7 (4C), 127.1 (2C), 113.6 (2C), 83.0, 72.4, 71.7, 60.9, 59.2, 55.0, 54.9 (2C), 29.5, 26.8 (3C), 18.9; m/z (FAB) 688 ($[M+H]^+$, 1.4%), 478 (62), 197 (23), 101 (98), 91 (100); HRMS (FAB) ($C_{43}H_{50}NO_5Si$ requires 688.3458, found 688.3454).

From Weinreb Amide *167*

To a -78 °C solution of Weinreb amide **167** (100 mg, 0.134 mmol) in toluene (2 cm^3) was added diisobutylaluminium hydride (335 µl, (1.0 *M* in toluene), 0.335 mmol). The resulting mixture was stirred at -78 °C for 20 mins and carefully quenched by addition of methanol (ca. 0.5 cm^3) and warmed to room temperature. The resulting mixture was diluted with DCM (10 cm^3) and saturated aqueous sodium potassium tartrate solution (10 cm^3) was added. The resulting cloudy biphasic mixture was stirred for 3 hours after which time two clear phases separated. The organic phase was separated and the aqueous phase was extracted with DCM (3 x 10 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The remaining residue was quickly chromatographed on silica gel [hexane:EtOAc (2:1)] to give the title compound (82 mg, 93%) as a colourless oil, *spectroscopic data was identical to that from the aldehyde obtained from aldol adduct 161.*

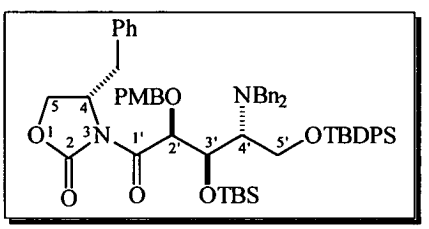
(2*S*,3*R*,4*R*)-5-*tert*-Butyldiphenysilyloxy-4-*N*,*N*-dibenzylamino-3-hydroxy-2-*p*-methoxybenzyloxy pentanoic acid methoxy-methyl-amide *167*



To a suspension of *N*,*O*-dimethylhydroxylamine•hydrochloride (1.02 g, 10.44 mmol) in anhydrous THF (5 cm^3) at -30 °C was added trimethylaluminium (5.22 cm^3 (2.0 *M* in toluene), 10.44 mmol). The solution was allowed to warm to room temperature over ca. 15 minutes, after which time a clear solution remained. The solution was recooled to -30 °C and a -30 °C solution of the aldol adduct **161** (300 mg, 0.35 mmol) in THF (2 cm^3) was added dropwise *via* cannula. The mixture was warmed to 0 °C and stirred at 0 °C for 2 hours. The reaction mixture was then cannulated into a rapidly stirred biphasic mixture of DCM (30 cm^3) and saturated aqueous sodium

potassium tartrate solution (30 cm^3) and stirred for 5 hours when two clear phases were apparent. The organic phase was separated and the aqueous phase was extracted with DCM (3 x 50 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:EtOAc (1:1)] to give the title compound (247 mg, 95%) as a colourless oil, R_f [hexane:EtOAc (1:1)] 0.56; $[\alpha]_D$ -20.4 (*c* 0.68, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3443, 1668, 1611, 1585, 1512; δ_H (200 MHz, $CDCl_3$) 7.75-7.09 (22H, m, Ar*H*), 6.79 (2H, dd, *J* 6.6, 1.9, Ar*H* meta to methoxy), 4.60 (1H, d, *J* 1.9, C_2H), 4.27 (1H, d, *J* 10.6, OCH_AH_BPh), 4.19 (1H, brdd, *J* 7.7, 2.4, C_3H), 4.14-4.06 (2H, m, $C_5H_XH_YOTBDPS$ + OCH_AH_BPh), 3.95-3.90 (1H, m, $C_5H_XH_YOTBDPS$), 3.89 (2H, d, *J* 14.3, NCH_SH_TPh x 2), 3.79 (3H, s, ArO*Me*), 3.70 (2H, d, *J* 14.3, NCH_SH_TPh x 2), 3.39 (3H, s, NO*Me*), 3.21-3.14 (1H, m, C_4H), 3.14 (3H, s, N*Me*), 2.69 (1H, brd, *J* 7.3, O*H*), 1.07 (9H, s, ^tBu); δ_C (50.3 MHz) 171.5, 159.1, 140.1 (2C), 135.7 (3C), 135.6 (2C), 133.4, 133.0, 129.6 (4C), 128.8 (4C), 128.0 (4C), 127.6 (3C), 126.7 (2C), 113.3 (2C), 75.0, 71.0, 70.9, 60.9, 59.4, 55.1, 54.7 (2C), 32.2, 26.8 (3C), 18.9; m/z (FAB) 747 ($[M+H]^+$, 33%), 657 (4), 478 (15), 325 (11), 217 (91), 121 (42), 91 (100), 73 (17); HRMS (FAB) ($C_{45}H_{55}N_2O_6Si$ requires 747.3829, found 747.3826).

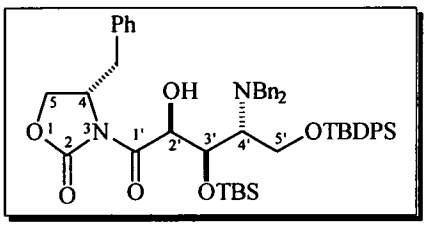
(2'*S*,3'*R*,4*S*,4'*R*)-3-(3'-*tert*-Butyldimethylsilyloxy-5'-*tert*-butyldiphenylsilyloxy-4'-*N*,*N*-dibenzylamino-2'-*p*-methoxybenzyloxy-1'-oxopentyl)-4-phenylmethyloxazolidin-2-one *168*



To a solution of the aldol adduct **161** (980 mg, 1.14 mmol) in DCM (10 cm^3) was added 2,6-lutidine (1.7 cm^3, 7.13 mmol) followed by *tert*-

butyldimethyltrifluoromethanesulfonate (534 μl, 4.56 mmol). The resulting mixture was stirred at room temperature for 3 hours then diluted with EtOAc (50 cm^3) and washed with saturated aqueous sodium bicarbonate solution (30 cm^3) and brine (30 cm^3). The organic phase was dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (3:1)] to give the title compound (1.24 g, 100%) as a colourless sticky foam, R_f [hexane:EtOAc (3:1)] 0.62; $[\alpha]_D$ +31.6 (*c* 0.94, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1782, 1702, 1611, 1586, 1513; δ_H (250 MHz, $CDCl_3$) 7.73 (27H, m, Ar*H*), 6.78 (2H, dd, *J* 6.7, 2.1, Ar*H* meta to methoxy), 5.24 (1H, d, *J* 6.9, $C_{2'}$*H*), 4.43 (1H, d, *J* 11.4, CH_AH_BArOMe), 4.38 (1H, dd, *J* 7.0, 2.3, $C_{3'}$*H*), 4.14 (1H, d, *J* 11.4, CH_AH_BArOMe), 3.97 (1H, m, $C_{5'}H_XH_YOTBDPS$), 3.97 (2H, d, *J* 14.6, NCH_SH_TPh x 2), 3.87 (1H, dd, *J* 11.6, 3.3, $C_{5'}H_XH_YOTBDPS$), 3.80 (1H, dd, *J* 8.6, 1.8, $C_5H_PH_Q$), 3.70 (3H, s, O*Me*), 3.63 (2H, d, *J* 14.6, NCH_SH_TPh x 2), 3.53 (1H, dd, *J* 8.3, 7.6, $C_5H_pH_Q$), 3.40 (1H, m, C_4*H*), 3.06 (1H, dt, *J* 9.0, 3.1, $C_{4'}$*H*), 2.72 (1H, dd, *J* 13.5, 3.1, CH_MH_NPh), 2.11 (1H, dd, *J* 13.8, 10.5, CH_MH_NPh), 1.15 (9H, s, ^tBu), 0.61 (9H, s, ^tBu), -0.02 (3H, s, *Me*), -0.08 (3H, s, *Me*); δ_C (50.3 MHz) 171.2, 159.3, 152.6, 140.3 (2C), 135.7 (4C), 135.2, 133.4, 133.1, 130.0 (2C), 129.6 (2C), 129.4 (2C), 129.2 (2C), 128.6 (2C), 128.3 (4C), 128.0 (4C), 127.5 (2C), 127.1 (2C), 126.3 (2C), 113.4 (2C), 79.1, 73.0 (2C), 66.2, 62.7, 55.0, 54.9, 53.8 (2C), 37.0, 26.9 (3C), 26.0 (3C), 25.5, 19.1, 18.2, -3.3, -4.8; m/z (FAB) 977 (MH^+, 5.7%), 478 (46.2), 197 (11.4), 135 (25.9), 121 (100), 91 (93.1), 73 (31.0); HRMS (FAB) ($C_{59}H_{73}N_2O_7Si_2$ requires 977.4956, found 977.4962).

(2'*S*,3'*R*,4*S*,4'*R*)-3-(3'-*tert*-Butyldimethylsilyloxy-5'-*tert*-butyldiphenylsilyloxy-4'-*N*,*N*-dibenzylamino-2'-hydroxy-1'-oxopentyl)-4-phenylmethyloxazolidin-2-one *170*



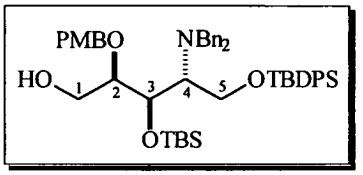
Small traces of this compound could be isolated if the above reaction was left for over 3 hours. For example, after 24 hours approximately 5% of the product was identified as **170**.

Data for **170**:

Obtained as a colourless solid,

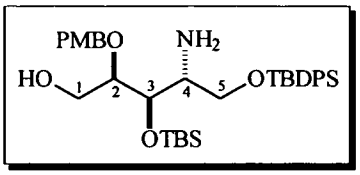
R_f [hexane:EtOAc (3:1)] 0.35; mp 123-125 °C; $[\alpha]_D$ +33.0 (*c* 2.7, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3541, 1785, 1695, 1600, 1492; δ_H (250 MHz, $CDCl_3$) 7.80-7.15 (25H, m, Ar*H*), 5.47 (1H, brs, C_2-*H*), 4.48 (1H, dddd, *J* 9.9, 7.3, 4.3, 2.9, C_4-*H*), 4.15 (1H, dd, *J* 9.2, 2.3, C_3-*H*), 4.06 (2H, s, NCH_AH_BPh x 2), 3.98 (2H, s, NCH_AH_BPh x 2), 4.11-3.86 (5H, m, C_4-*H* + C_5-*H*$_2$OTBDPS + C_5H_2) 3.27 (1H, dd, *J* 13.4, 2.9, CH_AH_BPh), 2.70 (1H, dd, *J* 13.4, 9.9, CH_AH_BPh), 1.20 (9H, s, ^tBu), 0.58 (9H, s, ^tBu), -0.26 (3H, s, *Me*), -0.45 (3H, s, *Me*); δ_H (62.9 MHz) 172.7, 152.6, 139.8 (2C), 135.8 (2C), 135.6 (2C), 135.2 (2C), 133.2, 132.9, 129.7 (2C), 129.6 (3C), 129.4 (2C), 128.9 (2C), 128.0 (3C), 127.7 (2C), 127.6 (3C), 127.2, 126.7 (2C), 71.6, 70.3, 66.2, 64.3, 61.7, 55.8 (2C), 55.7, 37.1, 27.0 (3C), 25.7 (3C), 19.0, 17.6, -4.6, -5.0; m/z (FAB) 857 ($[M+H]^+$, 71%), 587 (4.4), 478 (100), 197 (32), 135 (58), 91 (98), 73 (66); HRMS (FAB) ($C_{51}H_{65}N_2O_6Si_2$ requires 857.4381, found 857.4388).

(2*R*,3*R*,4*R*)-3-*tert*-Butyldimethylsilyloxy-5-*tert*-butyldiphenylsilyloxy-4-*N*,*N*-dibenzylamino-2-*p*-methoxybenzyloxypentan-1-ol *169*



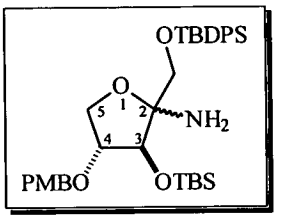
To a solution of the aldol adduct **167** (758 mg, 7.76 mmol) in THF (12 cm^3) at 0 °C was added lithium borohydride (854 mg, 38.8 mmol) followed by MeOH (1.58 cm^3, 38.8 mmol). The mixture was warmed to room temperature and stirred at room temperature for 18 hours. 1N aqueous sodium hydroxide (5 cm^3) was cautiously added to destroy unreacted borohydride. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 10 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (4:1)] to give the title compound (530 mg, 88%) as a colourless foam, R_f [hexane:EtOAc (2:1)] 0.63; $[\alpha]_D$ +22.8 (*c* 0.58, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3446, 1612, 1587, 1513; δ_H (250 MHz, $CDCl_3$) 7.74-7.23 (20H, m, Ar*H*), 7.18 (2H, dd, *J* 7.1, 1.9, Ar*H* ortho to methoxy), 6.85 (2H, dd, *J* 6.7, 2.0, Ar*H*2 meta to methoxy), 4.35 (1H, d, *J* 11.3, CH_AH_BArOMe), 4.16 (1H, d, *J* 11.3, CH_AH_BArOMe), 3.94 (2H, d, *J* 13.6, NCH_XH_YPh x 2), 3.95-3.85 (1H, m, $C_5H_AH_BOTBDPS$), 3.87 (1H, q, *J* 4.3, C_2H), 3.85-3.75 (1H, m, $C_5H_AH_BOTBDPS$), 3.80 (3H, s, O*Me*), 3.73 (2H, d, *J* 13.6, NCH_XH_YPh x 2), 3.45 (1H, dd, *J* 7.1, 4.1, C_3H), 3.36 (1H, m, C_4H), 3.36-3.15 (2H, m, C_1H), 1.15 (9H, s, ^tBu), 0.65 (9H, s, ^tBu), -0.11 (3H, s, *Me*), -0.17 (3H, s, *Me*); δ_C (62.9 MHz) 159.0, 140.3 (2C), 135.7 (2C), 135.6 (2C), 133.4 (2C), 130.6, 129.6 (4C), 129.1 (4C), 127.9 (4C), 127.6 (4C), 126.6 (2C), 113.6 (2C), 80.4, 72.3, 71.6, 63.4, 61.3, 59.9, 55.0 (3C), 26.9 (3C), 25.7 (3C), 19.0, 17.9, -3.7, -4.9; m/z (FAB) 804 ($[M+H]^+$, 39%), 478 (19.0), 197 (5.0), 121 (100), 91 (50.2); HRMS (FAB) ($C_{49}H_{66}NO_5Si_2$ requires 804.4480, found 804.4460).

(2*R*,3*R*,4*R*)-4-Amino-3-*tert*-butyldimethylsilyloxy-5-*tert*-butyldiphenylsilyloxy-2-*p*-methoxybenzyloxy pentan-1-ol *171*



A solution of the benzyl protected amino alcohol **168** (500 mg, 0.635 mmol) and 20% $Pd(OH)_2/C$ (500mg) in MeOH (10 cm^3) was exposed to a hydrogen atmosphere and stirred under hydrogen for 17 hours. The reaction mixture was filtered through a plug of celite and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (1:1)] to give the title compound (334 mg, 90%) as a colourless oil, R_f [hexane:EtOAc (1:1)] 0.44; $[\alpha]_D$ +26.1 (*c* 1.14, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3567, 3466, 1611, 1587, 1513; δ_H (200 MHz, $CDCl_3$) 7.66-7.25 (10H, m, Ar*H*), 7.08 (2H, d, *J* 8.4, Ar*H* ortho to methoxy), 6.72 (2H, d, *J* 8.4, Ar*H* meta to methoxy), 4.58 (1H, d, *J* 11.4, CH_AH_BArOMe), 4.23 (1H, d, *J* 11.4, CH_AH_BArOMe), 3.94 (1H, dd~t, *J* 10.1, C_3H), 3.76 (3H, s, O*Me*), 3.75-3.62 (3H, m, $C_5H_2OTBDPS + C_2H$), 3.48-3.40 (3H, brm, $NH_2 + C_4H$), 3.20 (2H, m, C_1H_2), 1.06 (9H, s, ^tBu), 0.81 (9H, s, ^tBu), -0.09 (3H, s, *Me*), -0.10 (3H, s, *Me*); δ_C (50.3 MHz) 159.1, 135.5 (2C), 133.7, 130.4 (2C), 129.6 (2C), 129.1 (4C), 127.6 (4C), 113.6 (2C), 80.7, 72.7, 70.1, 65.1, 57.0, 56.3, 54.8, 26.7 (3C), 25.5 (3C), 19.0, 17.7, -4.5, -5.0; m/z (FAB) 624 ($[M+H]^+$, 0.7%), 325 (11.3), 217 (62.6), 91 (84.8), 45 (100); HRMS (FAB) $C_{35}H_{54}NO_5Si_2$ requires 624.3541, found 624.3541).

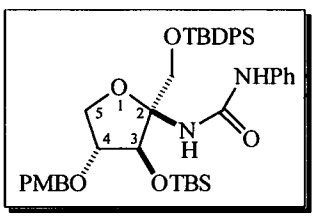
(2*RS*,3*S*,4*R*)-2-Amino-2-*tert*-butyldiphenylsilyloxymethyl-3-*tert*-butyldimethylsilyloxy-4-*p*-methoxybenzyloxy furan *176a*



A suspension of IBX (65.2 mg, 0.233 mmol) in DMSO (0.5 cm^3) was stirred vigorously for approximately 20 minutes by which time a clear solution was apparent. At this point the amino alcohol **170** (145 mg, 0.233 mmol) in THF (3.5 cm^3) was added *via* syringe. The resulting mixture was stirred at room temperature for 15 minutes. Water (1.5 cm^3) was added and the mixture was diluted with EtOAc (5 cm^3). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 5 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The residue remaining was chromatographed on silica gel [hexane:EtOAc (4:1)] to give the title compound (138 mg, 96%) as a colourless oil, R_f [hexane:EtOAc (4:1)] 0.44; $[\alpha]_D$ +7.1 (*c* 0.05, CH_2Cl_2); ν_{max} (neat)/cm^{-1} 3399, 1611, 1587, 1512; δ_H (600 MHz, $CDCl_3$) 7.73-7.30 (10H, m, Ar*H*), 7.23 (0.8H, dd, *J* 8.5, 2.1, Ar*H* ortho to methoxy), 7.12 (1.2H, dd, *J* 8.5, 2.2, Ar*H* ortho to methoxy), 6.86 (0.8H, dd, *J* 8.5, 2.1, Ar*H* meta to methoxy), 6.81 (1.2H, dd, *J* 8.5, 2.0, Ar*H* meta to methoxy), 4.50 (0.4H, d, *J* 11.5, CH_AH_BArOMe), 4.45 (0.4H, d, *J* 11.5, CH_AH_BArOMe), 4.36 (0.6H, d, *J* 11.3, CH_AH_BArOMe), 4.34 (0.6H, d, *J* 11.3, CH_AH_BArOMe), 4.08 (0.6H, d, *J* 2.4, C_3H), 4.05 (1.0H, dd, *J* 9.7, 5.2, $C_5H_XH_Y$), 3.98 (0.4H, d, *J* 3.2, C_3H), 3.90 (0.6H, dt, *J* 5.1, 2.5, 2.5, C_4H), 3.83-3.79 (0.4H, m, C_4H), 3.79 (1.2H, s, O*Me*), 3.79 (1.8H, s, O*Me*), 3.81-3.77 (0.4H, m, $CH_SH_TOTBDPS$), 3.76 (0.4H, d, *J* 10.7, $CH_SH_TOTBDPS$), 3.70 (0.6H, d, *J* 10.3, $CH_SH_TOTBDPS$), 3.67 (0.6H, d, *J* 10.3, $CH_SH_TOTBDPS$), 3.62 (1.0H, dd, *J* 9.8, 2.8, $C_5H_XH_Y$), 1.06 (3.6H, s, ^tBu), 1.05 (5.4H, s, ^tBu), 0.88 (5.4H, s, ^tBu), 0.70 (3.6H, s, ^tBu), 0.08 (1.8H, s, *Me*), 0.08 (1.8H, s, *Me*), -0.03 (1.2H, s, *Me*), -0.10 (1.2H, s, *Me*); δ_C (62.9MHz) 159.0*, 135.6* (2C), 135.5* (2C), 133.3, 133.1, 129.8*, 129.7*, 129.5*, 129.4, 129.1, 129.0*

(2C), 127.5* (4C), 113.7 (2C), 113.6 (2C), 95.2, 94.2, 84.9, 84.3, 80.5, 76.4, 71.2*, 70.1, 68.7, 66.8, 66.7, 55.2*, 26.8 (3C)*, 25.6 (3C)*, 19.1*, 17.9, 17.7, -4.8, -4.9, -5.0, -5.3 (*-denotes signals common to both diastereomers); m/z (FAB) 622 ($[M+H]^+$, 5.9%), 564 (1.8), 383 (2.5), 121 (100), 73 (23.8); HRMS (FAB) ($C_{35}H_{52}NO_5Si_2$ requires 622.3384, found 622.3385).

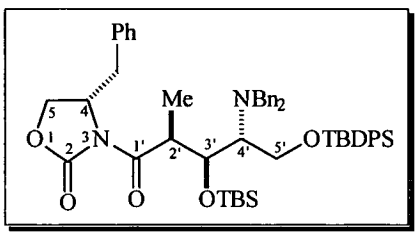
(2*R*,3*S*,4*R*)-2-*tert*-butyldiphenylsilyloxymethyl-3-*tert*-butyldimethylsilyloxy-4-*p*-methoxybenzyloxy-2-*N*-phenylureido furan *176b*



To a solution of the mixture of anomeric amines **176a** (2.4 mg, 3.86 μmol) in THF (0.5 cm^3) was added phenyl isocyanate (1 μl, 9.1 μmol). 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 compound (1.2 mg, 42%) as a colourless oil, R_f [hexane:EtOAc (4:1)] 0.41; ν_{max} (neat)/cm^{-1} 3686, 1678; δ_H (600 MHz, $CDCl_3$) 7.71 (1H, brs, N*H*Ph), 7.65 (2H, dd, *J* 7.9, 1.4, Ar*H* ortho to silicon), 7.60 (2H, dd, *J* 7.9, 1.4, Ar*H* ortho to silicon), 7.42-7.07 (12H, m, Ar*H*), 6.96 (1H, tt, *J* 7.3, 1.3, Ar*H* para to NH of urea), 6.88 (2H, dd, *J* 6.6, 2.0, Ar*H* meta to methoxy), 5.17 (1H, brs, N*H* (at anomeric centre)), 4.63 (1H, d, *J* 5.5, C_3H), 4.52 (1H, d, *J* 11.5, CH_AH_BArOMe), 4.37 (1H, d, *J* 11.5, CH_AH_BArOMe), 4.06 (1H, ddd, *J* 6.7, 5.5, 4.4, C_4H), 4.02 (1H, dd, *J* 9.2, 6.7, $C_5H_XH_Y$), 3.93 (1H, d, *J* 11.5, CH_SH_TOTBDPS), 3.81 (3H, s, O*Me*), 3.77 (1H, dd, *J* 9.2, 4.4, $C_5H_XH_Y$), 3.65 (1H, d, *J* 11.5, CH_SH_TOTBDPS), 1.04 (9H, s, ^tBu), 0.90 (9H, s, ^tBu), 0.13 (3H, s, Si*Me*), 0.06 (3H, s, Si*Me*); nOe experiments: irradiation of the signal at 3.65 ppm caused enhancement of the signals at 3.93 ppm (15%) and 4.63 ppm (2.5%), irradiation at 3.93 ppm caused enhancement of signal at 3.65 ppm

(13%), irradiation at 4.37 ppm caused enhancement of signal at 4.52 ppm (17%), irradiation of signal at 4.52 ppm caused enhancement of signal at 4.37 ppm (12%); m/z (FAB) 741 ($[M+H]^+$, 5.3%), 683 (14.2), 383 (15.9), 121 (100) ; HRMS (FAB) ($C_{42}H_{57}N_2O_6Si_2$ requires 741.3755, found 741.3758)

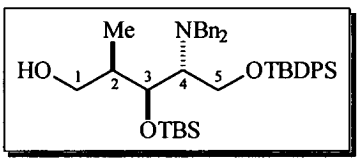
(2'*S*,3'*S*,4*S*,4'*R*)-3-(3'-*tert*-Butyldimethylsilyloxy-5'-*tert*-butyldiphenylsilyloxy-4'-*N*,*N*-dibenzyl-2'-methyl-1'-oxopentyl)-4-phenylmethyloxazolidin-2-one *178*



To a solution of the aldol adduct **136** (373 mg, 0.50mmol) in DCM (6 cm^3) was added 2,6-lutidine (147 µl, 1.25 mmol) followed by *tert*-butyldimethylsilyltrifluoromethanesulphonate (292 µl, 1.25 mmol). The mixture was stirred at room temperature for 1.5 hours then diluted with EtOAc (40 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 and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (8:1)] to give the title compound (394 mg, 92%) as a colourless solid, R_f [hexane:EtOAc (3:1)] 0.71; mp 56-57 °C; $[\alpha]_D$ +31.3 (*c* 0.88, $CHCl_3$); δ_H (250 MHz, $CDCl_3$) 7.81-7.13 (25H, m, Ar*H*), 4.46 (1H, dddd, *J* 9.9, 9.6, 6.6, 3.3, C_4*H*), 4.33 (1H, dq, *J* 7.2, 2.0, C_2*H*), 4.12 (1H, dd, *J* 10.9, 4.1, C_5*H*$_A$H$_B$OTBDPS), 4.10 (3H, m, C_5H_2 + $C_5H_AH_B$OTBDPS), 4.06 (2H, d, *J* 13.8, NC*H*$_X$H$_Y$Ph x 2), 3.96 (1H, dd, *J* 8.5, 2.0, C_3*H*), 3.90 (2H, d, *J* 13.4, NCH$_X$*H*$_Y$Ph x 2), 3.14 (1H, dd, *J* 13.3, 3.3, C*H*$_S$H$_T$Ph), 3.10 (1H, dt, *J* 9.9, 4.1, C_4*H*), 2.65 (1H, dd, *J* 13.3, 9.6, CH$_S$*H*$_T$Ph), 1.20 (9H, s, ^{t}*Bu*), 0.75 (3H, d, *J* 7.2, C_2*Me*), 0.59 (9H, s, ^{t}*Bu*), -0.13 (3H, s, Si*Me*), -0.27 (3H, s, Si*Me*); δ_C (62.9 MHz) 175.6, 152.4, 140.2 (2C), 135.6 (2C), 135.4 (2C), 135.1, 133.1 (2C),

129.5, 129.3, 129.1 (4C), 128.6 (4C), 127.8 (4C), 127.4 (4C), 126.9, 126.3 (2C), 71.1, 65.6, 64.8, 60.8, 55.4 (2C), 54.8, 41.0, 37.6, 26.8 (3C), 25.7 (3C), 18.9, 18.0, 10.2, -4.1, -5.1; m/z (FAB) 854 (M^+, 59.9%), 797 (31.2), 678 (24.7), 585 (27.4), 478 (100); HRMS (FAB) ($C_{52}H_{67}N_2O_5Si_2$ ($[M+H]^+$) requires 855.4589, found 855.4573).

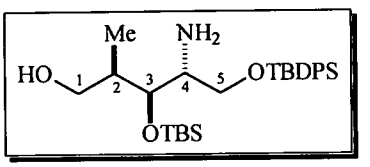
(2*R*,3*S*,4*R*)-3-*tert*-Butyldimethylsilyloxy-5-*tert*-butyldiphenylsilyloxy-4-*N*,*N*-dibenzylamino-2-methyl pentan-1-ol *179*



To a solution of the aldol adduct **177** (320 mg, 0.37 mmol) in THF (5 cm^3) was added lithium borohydride (0.925 cm^3, 1.85 mmol (2.0 *M* in THF)) followed by methanol (40 μl). The reaction mixture was stirred for 30 minutes at room temperature. The reaction was quenched by addition of a 1N sodium hydroxide solution (ca. 1 cm^3) and partitioned between water (10 cm^3) and EtOAc (10 cm^3). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 10 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (6:1)] to give the title compound (252 mg, 99%) as a colourless oil, R_f [hexane:EtOAc (3:1)] 0.69; $[\alpha]_D$ -17.4 (*c* 1.9, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3445, 1615, 1590, 1521; δ_H (250 MHz, $CDCl_3$) 7.83-7.21 (20H, m, Ar*H*), 4.00 (2H, d, *J* 13.3, NCH_AH_BPh x 2), 4.00 (2H, m, $C_5H_2OTBDPS$), 3.86 (2H, d, *J* 13.3, NCH_AH_BPh x 2), 3.60 (1H, dd, *J* 8.3, 1.4, C_3H), 3.27 (2H, d, *J* 7.5, CH_2OH), 3.17 (1H, td, *J* ~9.5, 4.8, C_4H), 2.15 (1H, ddd, *J* 7.5, 6.6, 1.3, C_2H), 1.23 (9H, s, ^{t}Bu), 0.62 (9H, s, ^{t}Bu), 0.25 (3H, d, *J* 6.6, C_2Me), -0.11 (3H, s, Si*Me*), -0.31 (3H, s, Si*Me*); δ_C (62.9 MHz) 140.6 (2C), 135.7 (2C), 135.6 (2C), 133.4, 133.3, 129.6 (2C), 129.4 (4C), 128.0 (4C), 127.6 (2C), 127.6 (2C), 126.7 (2C), 71.5, 65.2, 65.1, 59.8, 55.4 (2C), 38.1, 27.0 (3C), 25.7 (3C), 19.0, 17.9, 9.2, -4.2, -4.4; m/z (FAB) 682 ($[M+H]^+$, 50.1%), 478 (62.6), 197

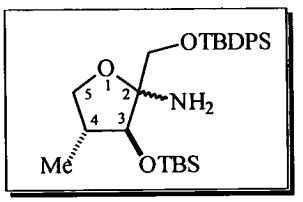
(31.2), 135 (83.8), 91 (60.7), 73 (100); HRMS (FAB) ($C_{42}H_{60}NO_3Si_2$ requires 682.4117, found 682.4096).

(2*R*,3*S*,4*R*)-4-Amino-3-*tert*-butyldimethylsilyloxy-5-*tert*-butyldiphenylsilyloxy-2-methylpentan-1-ol *180*



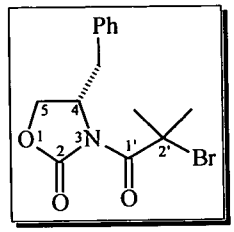
To a solution of *N*,*N*-dibenzylamino alcohol **178** (114 mg, 0.167 mmol) in methanol (2.0 cm^3), was added 20% $Pd(OH)_2/C$ (114 mg). The reaction mixture was exposed to a hydrogen atmosphere (1 atm.) and stirred under hydrogen for 18 hours. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane: EtOAc (1:1) + 5% Et_3N) to give the title compound (35 mg, 42%) as a colourless oil, R_f [hexane: EtOAc (3:1)] 0.11; δ_H (200 MHz, $CDCl_3$) 7.68-7.27 (10H, m, Ar*H*), 3.80-3.57 (4H, m, CH_2OTBDPS + C_3H + $C_1H_AH_BOH$), 3.31 (1H, dd, *J* 11.4, 5.4, $C_1H_AH_BOH$), 3.18 (1H, dt, *J* 9.1, 4.5, C_4H), 2.62 (2H, brs, NH_2), 1.83-1.79 (1H, brm, C_4H), 1.08 (9H, s, ^tBu), 0.90 (3H, d, *J* 7.3, C_2Me), 0.83 (9H, s, ^tBu), 0.00 (3H, s, Si*Me*), -0.06 (3H, s, Si*Me*); δ_C (50.3 MHz) 135.5 (4C), 129.7 (2C), 127.7 (4C), 75.8, 65.8, 61.7, 57.8, 41.1, 26.3 (3C), 25.6 (3C), 19.0, 17.7, 13.9, -4.3, -4.8.

(2*RS*,3*S*,4*R*)-2-Amino-2-*tert*-butyldiphenylsilyloxymethyl-3-*tert*-butyldimethylsilyloxy-4-methyl furan *181*



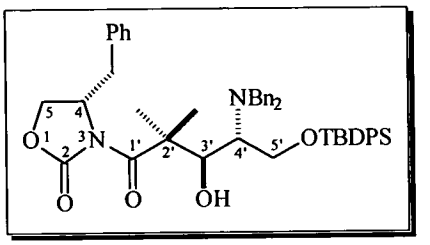
A suspension of IBX (17 mg, 0.06 mmol) in DMSO (0.1 cm^3) was stirred vigorously for approximately 20 minutes by which time a clear solution was apparent. At this point the amino alcohol **179** (30 mg, 0.06 mmol) in THF (0.3 cm^3) was added *via* syringe. The resulting mixture was stirred at room temperature for 2 minutes. Water (1.5 cm^3) was added and the mixture was diluted with EtOAc (2 cm^3). The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 2 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The residue remaining was chromatographed on silica gel [hexane:EtOAc (5:1)] to give the title compound (29 mg, 100%) as a colourless oil, R_f [hexane:EtOAc (1:1)] 0.93; δ_H (200 MHz, $CDCl_3$) 7.78-7.27 (10H, m, Ar*H*), 4.07 (0.7H, dd~t, *J* 8.2, $C_5H_AH_B$), 3.92 (0.3H, dd~t, *J* 8.4, $C_5H_AH_B$), 3.86 (1H, d, *J* 7.0, C_3H), 3.74 (0.3H, d, *J* 10.3, CH_AH_BOTBDPS), 3.64 (0.3H, d, *J* 10.6, CH_AH_BOTBDPS), 3.55 (1.4H, s, CH_AH_BOTBDPS), 3.49 (0.3H, dd~t, *J* 8.4, $C_5H_AH_B$), 3.32 (0.7H, dd~t, *J* 8.6, $C_5H_AH_B$), 2.40 (1H, dqn, *J* 8.4, 7.0, C_4H), 1.84 (2H, brs, NH_2), 1.08 (9H, s, ^tBu), 1.06 (3H, d, *J* 7.0, C_4Me), 0.90 (6.3H, s, ^tBu), 0.80 (2.7H, s, ^tBu), 0.10 (2.1H, s, Si*Me*), 0.05 (0.9H, s, Si*Me*), 0.03 (0.9H, s, Si*Me*), 0.02 (2.1H, s, Si*Me*); δ_C (50.3 MHz) 135.7 (2C), 135.3 (2C), 133.3 (2C), 129.6 (2C), 127.6 (4C), 92.8, 78.7, 70.3, 67.4, 40.8, 26.7 (3C), 25.6 (3C), 19.1, 17.5, 15.4, -4.5, -5.0.

(4*S*)-3-(2'-Bromo-2'-methyl-1'-oxopropyl)-4-phenylmethyloxazolidin-2-one *187*



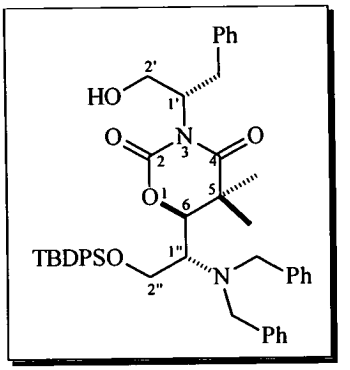
To a solution of the oxazolidinone **106** (2.0 g, 11.3 mmol) in THF (50 cm^3) at -78 °C was added ^{n}BuLi (7.1 cm^3, (1.6 *M* in hexanes), 11.3 mmol) followed by 2-bromo-2-methylpropionylbromide (3.38 g, 2.42 cm^3, 14.7 mmol). The mixture was stirred at -78 °C for 1 hour. The reaction was quenched by addition of a saturated aqueous solution of ammonium chloride (ca. 40 cm^3). The organic phase was separated and the aqueous phase was extracted with DCM (3 x 50 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The residue was chromatographed on silica gel [hexane:EtOAc (4:1)] to give the title compound (3.38 g, 92%) as a colourless crystalline solid, R_f [hexane:EtOAc (3:1)] 0.56; mp 68-70 °C; $[\alpha]_D$ +28.9 (*c* 1.07, $CHCl_3$); ν_{max} (neat)/cm^{-1} 1789, 1681, 1603, 1583, 1546; δ_H (200 MHz, $CDCl_3$) 7.39-7.21 (5H, m, Ar*H*), 4.73 (1H, tdd, *J* 9.8, 3.6, 2.9, C_4H), 4.26 (1H, dd~t, *J* 9.1, $C_5H_AH_B$), 4.17 (1H, dd, *J* 9.1, 3.0, $C_5H_AH_B$), 3.24 (1H, dd, *J* 13.3. 3.6, CH_XH_YPh), 2.82 (1H, dd, *J* 13.3, 9.5, CH_XH_YPh), 2.14 (3H, s, *Me*), 2.09 (3H, s, *Me*); δ_C (50.3 MHz) 171.1, 151.1, 135.1, 129.4 (2C), 128.9 (2C), 127.3, 66.0, 57.5, 56.7, 37.4, 31.3, 30.2; m/z (FAB) 328 (M^+, ^{81}Br 99%) 326 (M^+, ^{79}Br 100%), 247 (45), 178 (49), 117 (56), 91 (71).

(3'*S*,4*S*,4'*R*)-3-(5'-*tert*-Butyldiphenylsiloxy-4'-*N*,*N*-dibenzylamino-2',2'-dimethyl-3'-hydroxy-1'-oxopentyl)-4-phenylmethyloxazolidin-2-one *186*



To a solution of **186** (321 mg, 0.985 mmol) and aldehyde **73** (200 mg, 0.394 mmol) in THF (3 cm^3) was added LiI (5 mg, 0.0394 mmol) and $CrCl_2$ (241 mg, 1.97 mmol) (Note: all manipulations involving $CrCl_2$ were performed in a glove bag under an atmosphere of argon). A slight exotherm occurred on addition of the $CrCl_2$ and the mixture was stirred at room temperature for 90 minutes. Saturated aqueous sodium chloride solution (1 cm^3) was added to the green solution and the resulting mixture was stirred for 15 minutes. The organic phase was separated and the aqueous phase was extracted with EtOAc (3 x 2 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (4:1)] to give the title compound (190 mg, 64%) as a colourless oil, R_f [hexane:EtOAc (3:1)] 0.52; $[\alpha]_D$ -22.4 (*c* 0.4, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3508, 1778, 1684; δ_H (200 MHz, $CDCl_3$) 7.82-7.18 (25H, m, Ar*H*), 4.98-4.94 (1H, brm, C_3-*H*), 4.71 (1H, tdd, *J* 9.9, 7.0, 3.3, C_4-*H*), 4.14 (1H, dd, *J* 11.4, 7.3, C*H*$_A$H$_B$OTBDPS), 4.24-4.00 (3H, m, C_5H_2 + CH$_A$*H*$_B$OTBDPS), 3.86 (2H, d, *J* 13.9, NC*H*$_X$H$_Y$Ph x 2), 3.60 (2H, d, *J* 13.9, NCH$_X$*H*$_Y$Ph x 2), 3.19 (1H, dd, *J* 13.2, 2.9, C*H*$_S$H$_T$Ph), 3.00 (1H, brdt~q, *J* 5.1, C_4-*H*), 2.66 (1H, dd, *J* 13.2, 9.9, CH$_S$*H*$_T$Ph), 1.23 (3H, s, *Me*), 1.12 (9H, s, ^{t}*Bu*), 1.07 (3H, s, *Me*); δ_C (62.9 MHz) 177.4, 152.6, 139.7 (2C), 135.7 (3C), 135.5, 132.5, 129.3 (3C), 129.1 (3C), 128.8, 128.7 (2C), 128.0 (3C), 127.8 (3C), 127.7 (3C), 127.2 (2C), 127.1, 126.7 (2C), 74.6, 66.1, 66.0, 62.4, 57.6, 54.5 (2C), 51.5, 37.8, 26.8 (3C), 20.1, 19.4, 18.9; m/z (FAB) 755 ([M+H]$^+$, 9.1%), 665 (3.2), 325 (14), 217 (96), 91 (100); HRMS (FAB) ($C_{47}H_{55}N_2O_5Si$ requires 755.3880, found 755.3876).

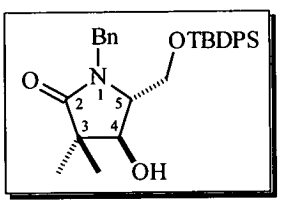
(1'*S*,1''*R*,6*R*)-6-(2''-*tert*-Butyldiphenylsilyloxy-1''-*N*,*N*-dibenzylamino)-3-(2'-hydroxy-1'-phenylmethyl)-5,5-dimethyl oxazine-2,4-dione *197*



To a suspension of *N*,*O*-dimethylhydroxylamine•HCl (194 mg, 1.98 mmol) in THF (1.5 cm^3) at -30 °C was added trimethylaluminium (0.99 cm^3, (2.0 *M* in toluene), 1.98 mmol). The solution was warmed to room temperature and stirred for ca. 15 minutes when a clear solution remained. The solution was re-cooled to -30 °C and a -30 °C solution of aldol adduct **185** (50 mg, 0.066 mmol) in THF (1.0 cm^3) was added *via* cannula. The resulting mixture was stirred at -30 °C for 30 minutes and slowly warmed to 0 °C and stirred at 0 °C for 1.25 hours. The reaction was quenched by addition of MeOH (ca. 1.0 cm^3) and allowed to warm to room temperature. The resulting cloudy solution was diluted with DCM (10 cm^3) and a saturated aqueous solution of sodium potassium tartrate (10 cm^3) was added. The mixture was stirred vigorously for 2 hours by which time two clear phases remained. The organic phase was separated and the aqueous phase was extracted with DCM (3 x 10 cm^3). The combined organic extracts were dried and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (4:1)] to give the title compound (41 mg, 100%) as a colourless oil, R_f [hexane:EtOAc (3:1)] 0.38; $[\alpha]_D$ -13.9 (*c* 0.71, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3446, 1755, 1697; δ_H (250 MHz, $CDCl_3$) 7.87-7.11 (25H, m, Ar*H*), 5.06 (1H, tdd, *J* 11.2, 6.8, 3.8, $C_{1'}$-*H*Bn), 4.12 (1H, dd, *J* 11.7, 7.9, $C_{2''}$-H_AH_BOTBDPS), 3.99 (1H, dd, *J* 11.7, 7.2, $C_{2''}$-H_AH_BOTBDPS), 3.83 (2H, d, *J* 14.0, NCH_XH_YPh x 2), 3.81 (1H, dd, *J* 11.8, 3.8, $C_{2'}$-H_SH_TOH), 3.70 (1H, dd,

J 11.8, 3.8, $C_2H_S\mathit{H}_T$OH), 3.65 (1H, m, $C_6\mathit{H}$), 3.48 (2H, d, *J* 14.0, $NCH_X\mathit{H}_Y$Ph x 2), 3.16 (1H, dd, *J* 13.9, 11.2, $C\mathit{H}_P\mathit{H}_Q$Ph), 3.05-2.96 (2H, m, $CH_P\mathit{H}_Q$Ph + $C_{1'}\mathit{H}NBn_2$), 1.09 (9H, s, $^t\mathit{Bu}$), 0.56 (3H, s, *Me*), 0.53 (3H, s, *Me*); δ_C (62.9 MHz) 174.5, 150.8, 139.1 (2C), 137.3, 135.6 (2C), 135.5 (2C), 133.1, 132.7, 129.8, 129.7, 128.9 (2C), 128.7 (4C), 128.4 (2C), 128.1 (4C), 127.7 (2C), 127.6 (2C), 127.0 (2C), 126.7, 81.5, 63.4, 60.9, 57.6, 55.6, 54.1 (2C), 41.5, 33.2, 26.8 (3C), 20.4, 19.0, 17.8; m/z (FAB) 755 ($[M+H]^+$, 48.0%), 478 (27.5), 197 (25.1), 135 (36.8), 91 (100); HRMS (FAB) ($C_{47}H_{55}N_2O_5Si$ requires 755.3880, found 755.3814).

(4*S*,5*R*)-5-*tert*-Butyldiphenylsilyloxymethyl-3,3-dimethyl-4-hydroxypyrrolidin-2-one *198*



A solution of aldol adduct **185** (50 mg, 0.066 mmol) and 20% $Pd(OH)_2/C$ (50 mg) in methanol (2 cm^3) was exposed to a hydrogen atmosphere (1 atm.) and stirred under hydrogen for 18 hours. The reaction mixture was filtered through a pad of celite and concentrated under reduced pressure. The remaining residue was chromatographed on silica gel [hexane:EtOAc (3:1)] to give the title compound (19 mg, 73%) as a colourless oil, R_f [hexane:EtOAc (3:1)] 0.27; $[\alpha]_D$ -15.6 (*c* 0.36, $CHCl_3$); ν_{max} (neat)/cm^{-1} 3390, 1666; δ_H (250 MHz, $CDCl_3$) 7.65-6.93 (15H, m, Ar*H*), 5.04 (1H, d, *J* 15.0, $NC\mathit{H}_A\mathit{H}_B$Ph), 4.02 (1H, brdd, *J* 7.3, 4.7, $C_4\mathit{H}$), 3.82 (1H, dd, *J* 11.0, 3.0, $C\mathit{H}_X\mathit{H}_Y$OTBDPS), 3.69 (1H, dd, *J* 11.0, 4.7, $CH_A\mathit{H}_B$OTBDPS), 3.62 (1H, d, *J* 15.0, $NCH_A\mathit{H}_B$Ph), 3.06 (1H, ddd, *J* 7.3, 4.7, 3.0, $C_5\mathit{H}$), 1.24 (3H, s, *Me*), 1.07 (3H, s, *Me*), 1.05 (9H, s, $^t\mathit{Bu}$); δ_C (62.9 MHz) 178.1, 136.1, 135.6 (2C), 135.4 (2C), 132.5, 130.0, 129.9, 128.5 (3C), 127.9 (3C), 127.7 (3C), 127.3, 76.2, 61.0, 60.9, 43.7, 43.3, 26.8 (3C), 22.9, 19.1, 17.6; m/z (FAB) 488 ($[M+H]^+$, 53%), 325 (6), 217 (43), 91 (100), 73 (82); HRMS (FAB) ($C_{30}H_{38}NO_3Si$ requires 488.2620, found 488.2624).

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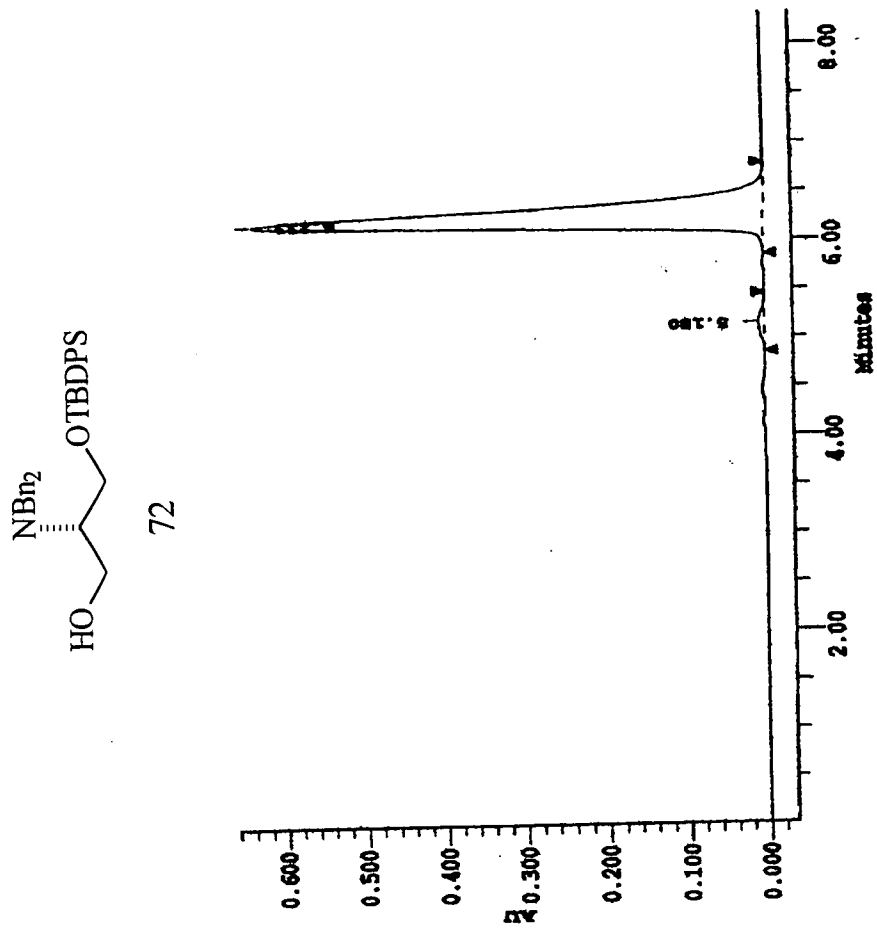
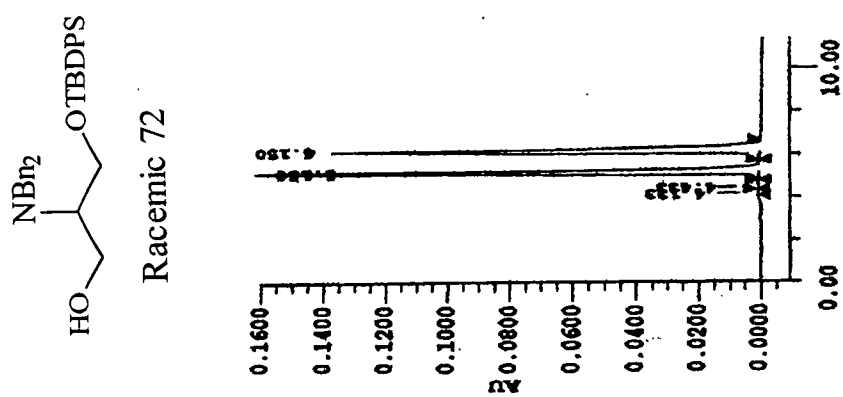
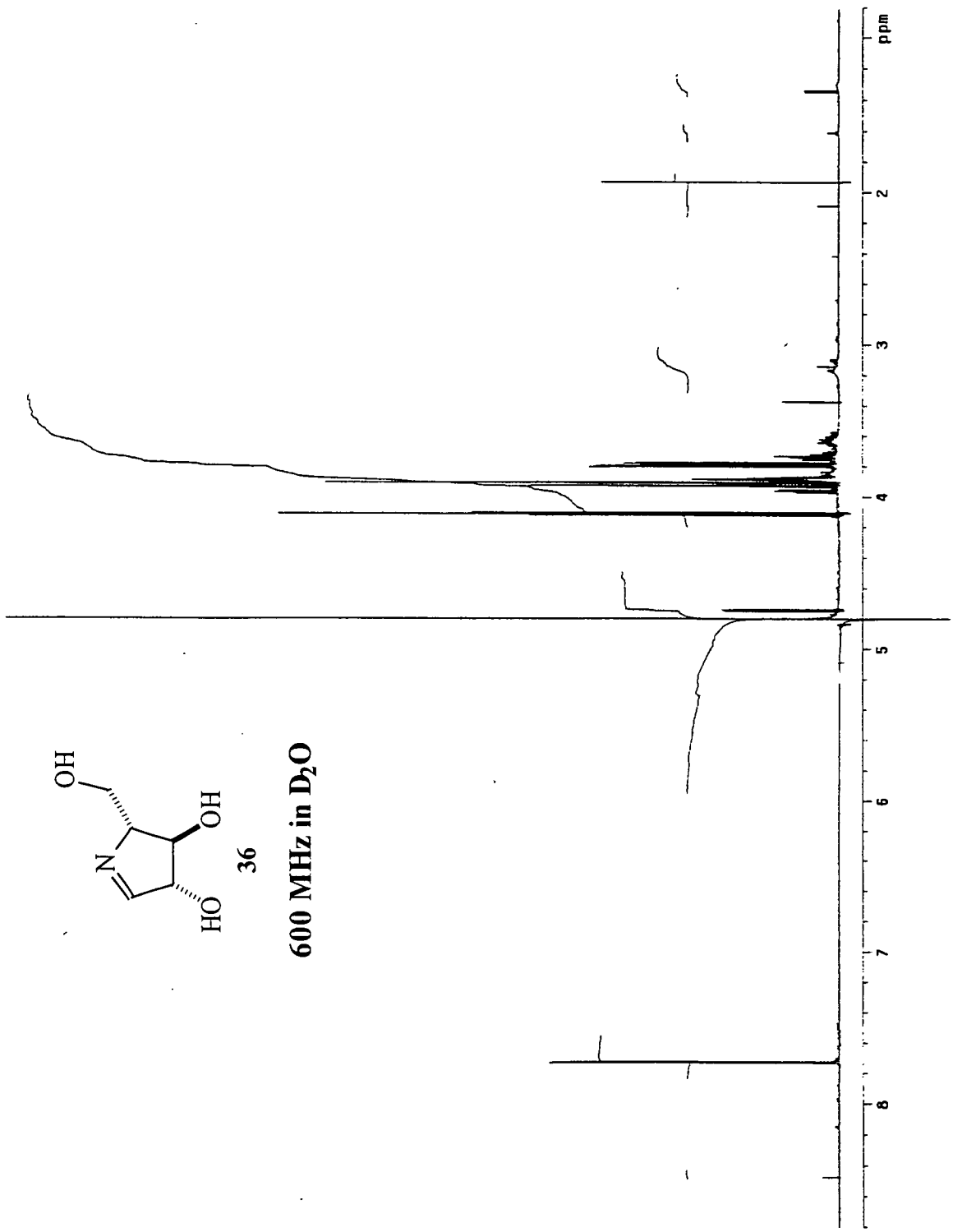
HPLC Traces For Alcohol 72

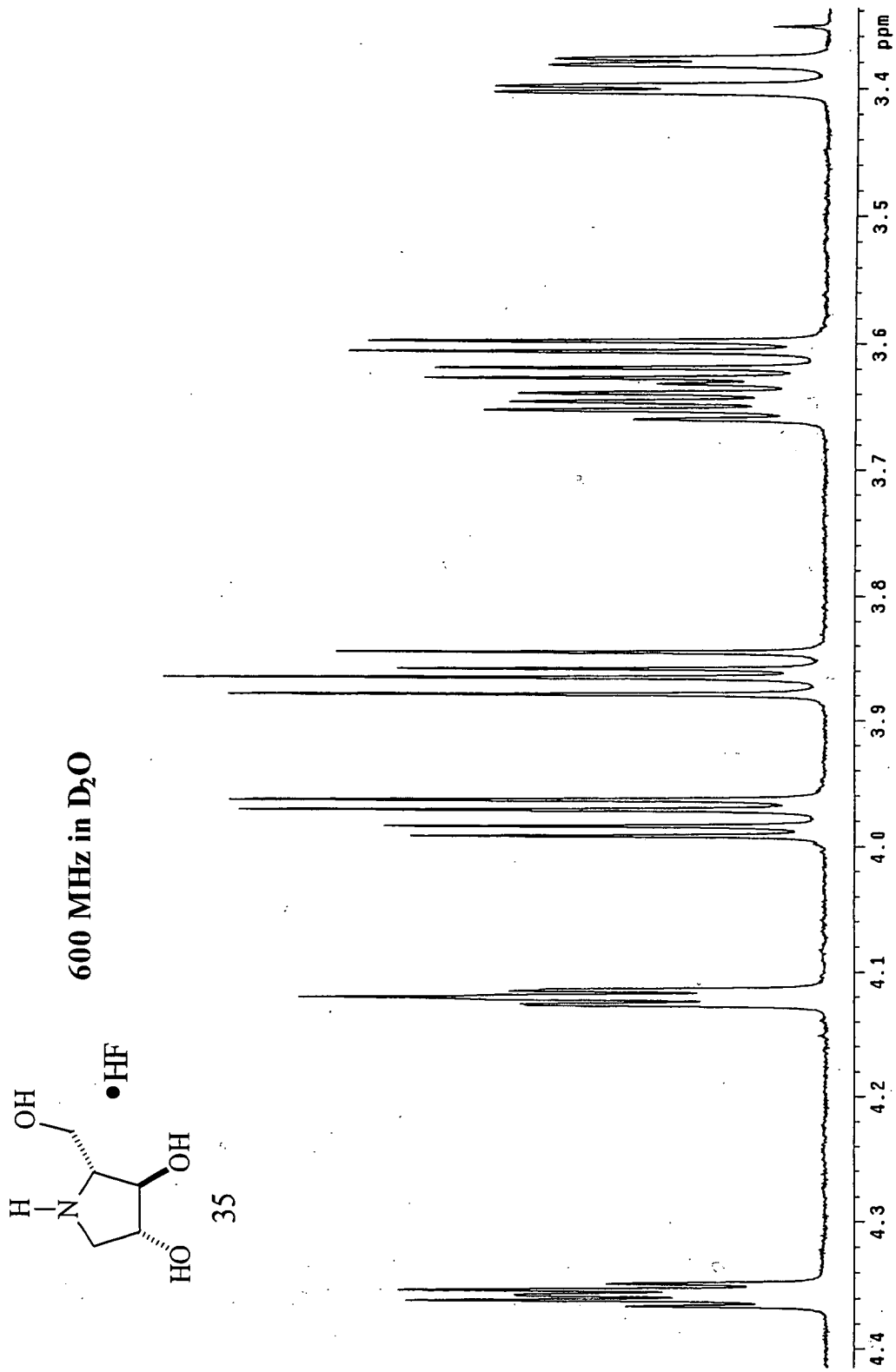




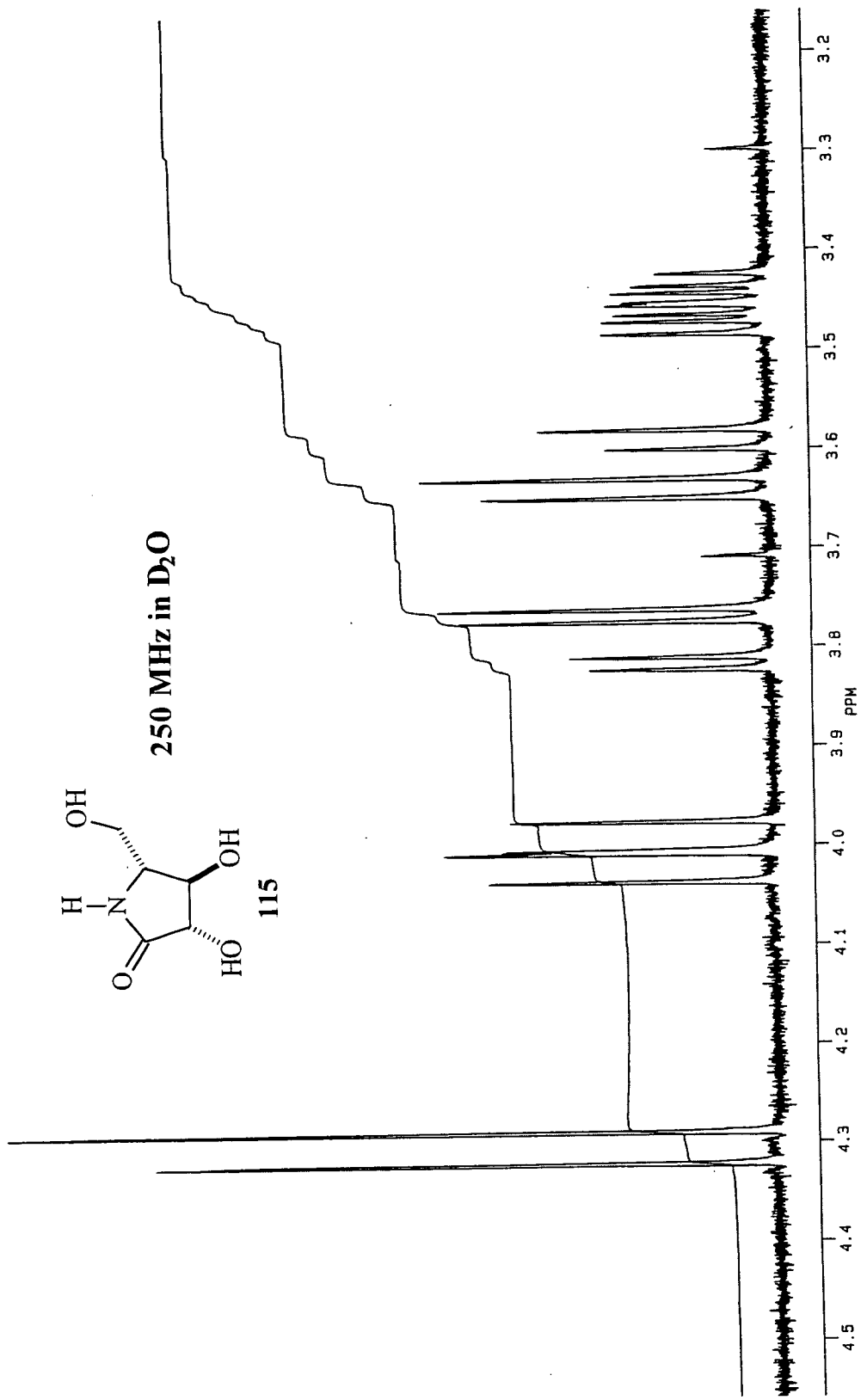
^{1}H NMR Spectrum of Nectrisine *36*



^{1}H NMR Spectrum of DAB1•HF *35*



^{1}H NMR Spectrum of Lactam *115*



X-ray Crystal Structure of 154

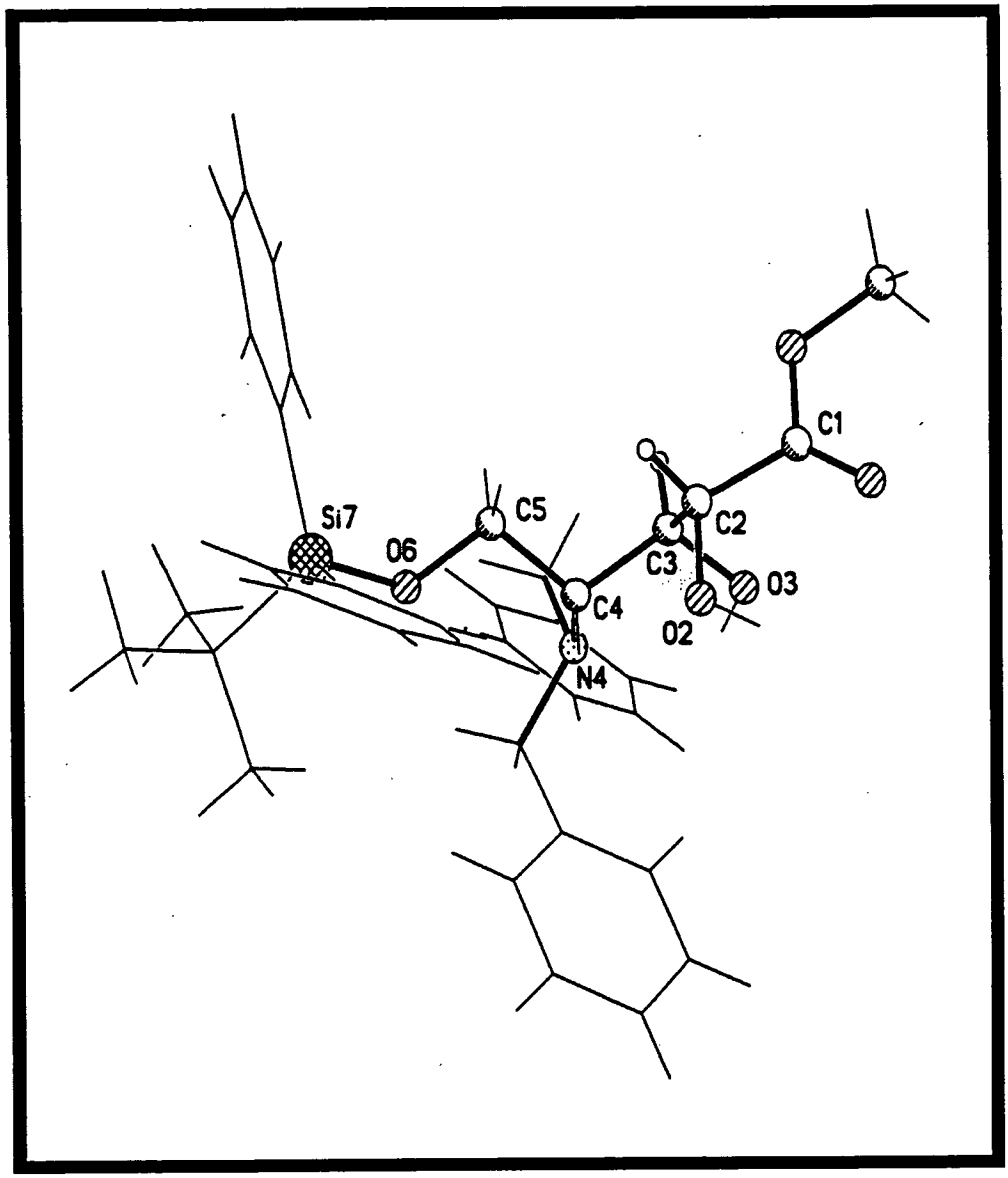


Table 1 *Crystal data and structure refinement for* ***154***

Part A: Crystal Data	
Empirical formula	$C_{36}H_{43}NO_5Si$
Formula weight	597.80
Wavelength	1.54184 Å
Temperature	150 (2) K
Crystal system	Monoclinic
Space group	P21
Unit cell dimensions	a = 10.4970 (6) Å alpha = 90 deg. b = 14.4596 (9) Å beta = 113.316 (4) deg. c = 11.7189 (7) Å gamma = 90 deg.
Volume	1633.46 (17) $Å^3$
Number of reflections for cell	82 (20 < theta <22 deg.)
Z	2
Density (calculated)	1.215 Mg/m^3
Absorption coefficient	0.971 mm^{-1}
F (000)	640
Part B: Data Collection	
Crystal description	Colourless Plate
Crystal size	0.58 x 0.31 x 0.12 mm
Theta range for data collection	4.11 to 70.23 deg.
Index ranges	-12<=h<=11, -3<=k<=16, 0<=1<=14
Reflections collected	4051
Independent reflections	3867 [R (int) = 0.0314]
Scan type	Omega-theta
Absorption correction	Optimised numerical (T_{min} = 0.597, T_{max} = 0.906
Part C: Solution and Refinement	
Solution	Patterson (DIRDIF)

Refinement type	Full-matrix least squares on F^2
Program used for refinement	SHELXL-97
Hydrogen atom placement	Geometric/difference map
Hydrogen atom treatment	Riding/rotating group
Data/restraints/parameters	3867/1/396
Goodness of fit on F^2	1.037
Conventional R [F>4sigma (F)]	R1 = 0.0322 [3674 data]
Weighted R (F^2 and all data)	wR2 = 0.0873
Absolute structure parameter	0.01 (4)
Extinction coefficient	0.0017 (3)
Final maximum delta/sigma	0.021
Weighting scheme	calc w=1/[\s^2^(Fo^2^)+(0.0611P)^2^+0.1997 P] where P=(Fo^2^+2Fc^2^)/3
Largest diff. Peak and hole	0.436 and –0.301 e.Å^3

Table 2 *Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for* ***154****. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor*

	x	y	z	U (eq)
C(1)	-3866 (2)	-866 (2)	-1760 (2)	24 (1)
O (1)	-5037 (2)	-657 (2)	-2348 (2)	41 (1)
O (1M)	-3214 (2)	-1559 (2)	-2053 (2)	37 (1)
C (1M)	-4058 (3)	-2087 (3)	-3132 (3)	54 (1)
C (2)	-2937 (2)	-395 (2)	-566 (2)	25 (1)
O (2)	-3726 (2)	232 (2)	-189 (2)	40 (1)
C (3)	-1708 (2)	75 (2)	-722 (2)	22 (1)
O (3)	-2271 (2)	672 (2)	-1764 (2)	36 (1)
C (4)	-824 (2)	633 (2)	447 (2)	20 (1)
N (4)	2 (2)	1325 (1)	103 (2)	20 (1)
C (41)	342 (2)	2148 (2)	919 (2)	24 (1)
C (42)	1256 (2)	933 (2)	21 (2)	26 (1)
C (41A)	-920 (2)	2706 (2)	792 (2)	23 (1)
C (42A)	-1733 (2)	3112 (2)	-343 (2)	27 (1)
C(43A)	-2849 (3)	3666 (2)	-456 (3)	32 (1)
C (44A)	-3193 (3)	3819 (2)	557 (3)	37 (1)
C (45A)	-2415 (3)	3405 (2)	1679 (3)	37 (1)
C (46A)	-1293 (3)	2846 (2)	1789 (2)	32 (1)
C (41B)	1979 (2)	1590 (2)	-529 (2)	25 (1)
C (42B)	1252 (2)	2165 (2)	-1533 (2)	27 (1)
C (43B)	1962 (3)	2760 (2)	-2009 (2)	29 (1)
C (44B)	3401 (3)	2777 (2)	-1505 (2)	34 (1)
C (45B)	4128 (3)	2195 (2)	-1533 (2)	27 (1)
C (46B)	3416 (2)	1614 (2)	-42 (2)	30 (1)
C (5)	-12 (2)	-29 (2)	1498 (2)	22 (1)
O (6)	674 (2)	474 (1)	2632 (1)	22 (1)
Si (7)	950 (1)	44 (1)	4017 (1)	18 (1)
C (71A)	1756 (2)	-1127 (2)	4129 (2)	20 (1)
C (72A)	1412 (2)	-1899 (2)	4662 (2)	27 (1)
C (73A)	2007 (3)	-2758 (2)	4681 (3)	33 (1)
C (74A)	2975 (2)	-2872 (2)	4156 (2)	30 (1)
C (75A)	3343 (3)	-2124 (2)	3633 (2)	29 (1)
C (76A)	2746 (2)	-1262 (2)	3615 (2)	25 (1)
C (71B)	-766 (2)	-59 (2)	4170 (2)	24 (1)
C (72B)	-1993 (2)	207 (2)	3194 (2)	32 (1)
C (73B)	-3269 (2)	116 (3)	3286 (3)	44 (1)
C (74B)	-3340 (3)	-221 (2)	4359 (3)	49 (1)
C (75B)	-2145 (3)	-473 (2)	5340 (3)	45 (1)
C (76B)	-873 (3)	-401 (2)	5246 (2)	31 (1)
C (71C)	2154 (2)	888 (2)	5161 (2)	21 (1)
C (72C)	2266 (3)	652 (2)	6479 (2)	27 (1)

C (73C)	1594 (3)	1873 (2)	4840 (2)	27 (1)
C (74C)	3606 (2)	833 (2)	5140 (2)	30 (1)

Table 3 *bond lengths Å for* ***154***

Bond	Length Å
C (1)-O (1)	1.186 (3)
C (1)-O (1M)	1.332 (3)
C (1)-C (2)	1.515 (3)
O (1M)-C (1M)	1.442 (3)
C (2)-O (2)	1.411 (3)
C (2)-C (3)	1.532 (3)
C (3)-O (3)	1.419 (3)
C (3)-C (4)	1.542 (3)
C (4)-N (4)	1.481 (3)
C (4)-C (5)	1.526 (3)
N (4)-C (42)	1.472 (3)
N (4)-C 41)	1.478 (3)
C (41)-C (41A)	1.507 (3)
C (42)-C (41B)	1.510 (3)
C (41A)-C (46A)	1.386 (3)
C (41A)-C (42A)	1.394 (3)
C (42A)-C (43A)	1.381 (4)
C (43A)-C (44A)	1.389 (4)
C (44A)-C (45A)	1.380 (4)
C (45A)-C (46A)	1.393 (4)
C (41B)-C (46B)	1.386 (3)
C (41B)-C (42B)	1.395 (4)
C (42B)-C (43B)	1.391 (4)
C (43B)-C (44B)	1.387 (4)
C (44B)-C (45B)	1.381 (4)
C (45B)-C (46B)	1.390 (3)
C (5)-O (6)	1.434 (3)
O (6)-Si (7)	1.6538 (16)
Si (7)-C (71A)	1.874 (3)
Si (7)-C (71C)	1.882 (2)
Si (7)-C (71B)	1.885 (2)
C (71A)-C (72A)	1.395 (4)
C (71A)-C (76A)	1.406 (3)
C (72A)-C (73A)	1.387 (4)
C (73A)-C (74A)	1.391 (4)
C (74A)-C (75A)	1.371 (4)
C (75A)-C (76A)	1.392 (4)
C (71B)-C (72B)	1.396 (3)
C (71B)-C (76B)	1.400 (3)

C (72B)-C (73B)	1.392 (3)
C (73B)-C (74B)	1.377 (5)
C (75B)-C (76B)	1.373 (5)
C (75B)-C (76B)	1.386 (3)
C (71C)-C (73C)	1.530 (3)
C (71C)-C (74C)	1.537 (3)
C (71C)-C (72C)	1.540 (3)

Table 4 *Bond angles (degrees) for* ***154***

Bond	**Angle (degrees)**
O (1)-C (1)-O (1M)	124.2 (2)
O (1)-C (1)-C (2)	124.1 (2)
O (1M)-C (1)-C (2)	111.60 (19)
C (1)-O (1M)-C (1M)	115.1 (2)
O (2)- C(2)-C (1)	109.60 (18)
O (2)-C (2)-C (3)	112.3 (2)
C (1)-C (2)-C (3)	110.72 (17)
O (3)-C (3)-C (2)	106.77 (17)
O (3)-C (3)-C (4)	110.2 (2)
C (2)-C (3)-C (4)	111.41 (16)
N (4)-C (4)-C (5)	116.33 (17)
N (4)-C (4)-C (3)	108.86 (17)
C (5)-C (4)-C (3)	109.7 (2)
C (42)-N (4)-C (41)	111.07 (18)
C (42)-N (4)-C (4)	113.09 (19)
C (41)-N (4)-C (4)	112.70 (17)
N (4)-C (41)-C (41A)	112.90 (18)
N (4)-C (42)-C (41B)	113.5 (2)
C (46A)-C (41A)-C (42A)	118.2 (2)
C (46A)-C (41A)-C (41)	121.7 (2)
C (42A)-C (41A)-C (41)	120.1 (2)
C (43A)-C (42A)-C (41A)	120.7 (2)
C (42A)-C (43A)-C (44A)	120.5 (2)
C (45A)-C (44A)-C (43A)	119.3 (2)
C (44A)-C (45A)-C (46A)	120.0 (2)
C (41A)-C (46A)-C (45A)	121.2 (2)
C (46B)-C (41B)-C (42B)	118.3 (2)
C (46B)-C (41B)-C (42)	119.2 (2)
C (42B)-C (41B)-C (42)	122.4 (2)
C (43B)-C (42B)-C (41B)	120.4 (2)
C (44B)-C (43B)-C (42B)	120.4 (2)
C (45B)-C (44B)-C (43B)	119.6 (2)
C (44B)-C (45B)-C (46B)	119.8 (2)
C (41B)-C (46B)-C (45B)	121.4 (2)

O (6)-C (5)-C (4)	110.2 (2)
C (5)-O (6)-Si (7)	123.19 (15)
O (6)-Si (7)-C (71A)	107.88 (10)
O (6)-Si (7)-C (71C)	105.25 (10)
C (71A)-Si (7)-C (71C)	112.27 (10)
O (6)-Si (7)-C (71B)	108.67 (9)
C (71A)-Si (7)-C (71B)	110.10 (12)
C (71C)-Si (7)-C (71B)	112.40 (10)
C (72A)-C (71A)-C (76A)	116.6 (2)
C (72A)-C (71A)-Si (7)	124.40 (17)
C (76A)-C (71A)-Si (7)	119.01 (19)
C (73A)-C (72A)-C (71A)	122.0 (2)
C (72A)-C (73A)-C (74A)	120.2 (3)
C (75A)-C (74A)-C (73A)	119.2 (3)
C (74A)-C (75A)-C (76A)	120.6 (2)
C (75A)-C (76A)-C (71A)	121.5 (2)
C (72B)-C (71B)-C (76B)	117.3 (2)
C (72B)-C (71B)-Si (7)	120.48 (18)
C (76B)-C (71B)-Si (7)	122.23 (18)
C (73B)-C (72B)-C (71B)	121.0 (3)
C (74B)-C (73B)-C (72B)	120.3 (3)
C (75B)-C (74B)-C (73B)	119.8 (2)
C (74B)-C (75B)-C (76B)	120.2 (3)
C (75B)-C (76B)-C (71B)	121.4 (3)
C (73C)-C (71C)-C (74C)	109.3 (2)
C (73C)-C (71C)-C (72C)	108.8 (2)
C (74C)-C (71C)-C (72C)	108.82 (18)
C (73C)-C (71C)-Si (7)	110.13 (15)
C (74C)-C (71C)-Si (7)	110.24 (16)
C (72C)-C (71C)-Si (7)	109.52 (17)

Symmetry transformations used to generate equivalent atoms:

Table 5 *Anisotropic displacement parameters (A^2 x 10^3) for* ***154****. The anisotropic displacement factor exponent takes the form: -2 pi^2 [h^2 a*^2 U11 + ... +2 h k a* b* U12]*

	U11	**U22**	**U33**	**U23**	**U13**	**U12**
C (1)	25 (1)	19 (1)	28 (1)	4 (1)	10 (1)	-2 (1)
O (1)	26 (1)	40 (1)	44 (1)	1 (1)	0 (1)	4 (1)
O (1M)	29 (1)	28 (1)	44 (1)	-14 (1)	3 (1)	2 (1)
C (1M)	45 (2)	52 (2)	57 (2)	-32 (2)	12 (1)	-11 (1)
C (2)	28 (1)	21 (1)	26 (1)	0 (1)	11 (1)	-1 (1)
O (2)	35 (1)	42 (1)	49 (1)	-15 (1)	22 (1)	-3 (1)
C (3)	26 (1)	19 (1)	19 (1)	1 (1)	7 (1)	-2 (1)
O (3)	46 (1)	26 (1)	25 (1)	8 (1)	3 (1)	-13 (1)

C (4)	24 (1)	15 (1)	22 (1)	1 (1)	8 (1)	-1 (1)
N (4)	24 (1)	12 (1)	24 (1)	0 (1)	9 (1)	0 (1)
C (41)	28 (1)	15 (1)	25 (1)	8 (1)	3 (1)	-13 (1)
C (42)	28 (1)	21 (1)	31 (1)	3 (1)	12 (1)	4 (1)
C (41A)	24 (1)	15 (1)	29 (1)	-2 (1)	9 (1)	-3 (1)
C (42A)	30 (1)	21 (1)	33 (1)	6 (1)	14 (1)	0 (1)
C (43A)	29 (1)	24 (2)	41 (1)	10 (1)	11 (1)	2 (1)
C (44A)	29 (1)	20 (1)	48 (2)	-2 (1)	15 (1)	1 (1)
C (45A)	37 (1)	37 (2)	37 (1)	-13 (1)	15 (1)	0 (1)
C (46A)	35 (1)	28 (2)	28 (1)	-3 (1)	8 (1)	4 (1)
C (41B)	30 (1)	17 (1)	29 (1)	-4 (1)	13 (1)	-1 (1)
C (42B)	29 (1)	24 (1)	28 (1)	-2 (1)	11 (1)	-2 (1)
C (43B)	42 (1)	18 (1)	32 (1)	0 (1)	18 (1)	1 (1)
C (44B)	44 (1)	22 (2)	42 (1)	-6 (1)	24 (1)	-9 (1)
C (45B)	29 (1)	31 (2)	45 (1)	-5 (1)	14 (1)	-7 (1)
C (46B)	27 (1)	26 (2)	32 (1)	0 (1)	9 (1)	0 (1)
C (5)	28 (1)	17 (1)	21 (1)	0 (1)	7 (1)	-2 (1)
O (6)	27 (1)	16 (1)	19 (1)	0 (1)	6 (1)	-2 (1)
Si (7)	20 (1)	14 (1)	20 (1)	0 (1)	7 (1)	0 (1)
C (71A)	20 (1)	16 (1)	20 (1)	-3 (1)	4 (1)	-2 (1)
C (72A)	26 (1)	20 (1)	38 (1)	(1)	15 (1)	-1 (1)
C (73A)	35 (1)	17 (2)	49 (2)	6 (1)	17 (1)	1 (1)
C (74A)	32 (1)	17 (1)	38 (1)	-4 (1)	9 (1)	6 (1)
C (75A)	29 (1)	28 (2)	32 (1)	-2 (1)	14 (1)	10 (1)
C (76A)	29 (1)	19 (1)	29 (1)	1 (1)	13 (1)	4 (1)
C (71B)	25 (1)	16 (1)	33 (1)	-7 (1)	12 (1)	-3 (1)
C (72B)	25 (1)	30 (2)	39 (1)	-8 (1)	10 (1)	3 (1)
C (73B)	27 (1)	42 (2)	60 (2)	-14 (2)	12 (1)	2 (1)
C (74B)	34 (1)	42 (2)	84 (2)	-17 (2)	37 (2)	-10 (1)
C (75B)	51 (2)	34 (2)	64 (2)	-8 (2)	40 (2)	-8 (2)
C (76B)	38 (1)	22 (1)	42 (1)	-3 (1)	25 (1)	-2 (1)
C (71C)	23 (1)	16 (1)	22 (1)	-1 (1)	7 (1)	1 (1)
C (72C)	35 (1)	22 (1)	22 (1)	-1 (1)	10 (1)	-1 (1)
C (73C)	34 (1)	15 (1)	28 (1)	-2 (1)	8 (1)	3 (1)
C (74C)	25 (1)	26 (2)	37 (1)	-4 (1)	11 (1)	-4 (1)

Table 6 *Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for* ***154***

	x	**y**	**z**	**U (eq)**
H (1M1)	-4906	-2288	-3044	81
H (1M2)	-3538	-2630	-3208	81
H (1M3)	-4303	-1702	-3877	81
H (2)	-2563	-879	92	29
H (2A)	-4367	452	-819	61

H (3)	-1116	-404	-887	26
H (3A)	-1764	1141	-1651	54
H(4)	-1481	981	715	25
H (41A)	990	2546	715	28
H (41B)	820	1946	1793	28
H (42A)	999	366	-494	31
H (42B)	1913	752	864	31
H (42C)	-1517	3006	-1047	33
H (43A)	-3384	3945	-1233	38
H (44A)	-3956	4204	478	39
H (45A)	-2644	3502	2377	44
H (46A)	-773	2555	2561	38
H (42D)	267	2151	-1893	32
H (43B)	1458	3156	-2683	35
H (44B)	3882	3188	-1828	40
H (45B)	5114	2191	-195	42
H (46B)	3924	1226	640	35
H (5A)	-653	-488	1611	27
H (5B)	683	-367	1283	27
H (72A)	750	-1835	5023	32
H (73A)	1954	-3270	5055	40
H (74A)	3377	-3461	158	36
H (75A)	4011	-2195	3280	35
H (76A)	3015	-752	3248	30
H (72B)	-1957	453	2456	38
H (73B)	-4095	288	2606	53
H (74B)	-4212	-280	4420	59
H (75B)	-2190	-697	6058	54
H (76B)	-56	-587	5927	37
H (72C)	2974	1044	7085	41
H (72D)	2526	0	6660	41
H (72E)	1369	760	6532	41
H (73C)	2203	2303	5464	41
H (73D)	657	1905	4830	41
H (73E)	1563	2041	4020	41
H (74C)	3531	905	4284	45
H (74D)	4024	232	5464	45
H (74E)	4189	1328	5658	45

Abbreviations

Ac	Acetyl
AD	asymmetric dihydroxylation
aq.	aqueous
Ar	aryl
atm.	atmosphere
Boc	*tert*-butoxycarbonyl
Bn	Benzyl
Bu	Butyl
Cbz	benzyloxycarbonyl
DCM	dichloromethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIBAL-H	diisobutylaluminium hydride
DMP	Dess-Martin periodinane
DMF	*N*,*N*-dimethylformamide
DMAP	4-dimethylaminopyridine
DMS	dimethylsulfide
DMSO	dimethylsulfoxide
ds	diastereoselectivity
e.e.	enantiomeric excess (i.e. % of major enantiomer - % of minor enantiomer)
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
IBX	iodoxybenzoic acid
IR	infra red
L	unspecified ligand

M	unspecified metal
M	mol dm^{-3}
mCPBA	*meta*-chloroperbenzoic acid
Me	methyl
MOM	methoxymethyl
Mult.	Multiplicity
NBS	*N*-bromosuccinamide
NMO	*N*-methylmorpholine *N*-oxide
NMR	nuclear magnetic resonance
Nu^-	unspecified nucleophile
P	unspecified protecting group
Ph	phenyl
PMB	*para*-methoxybenzyl
Pr	propyl
ppm	parts per million
py	pyridine
R_t	retention time for HPLC
Tf, triflate	trifluoromethanesulfonate
TBAF	tetrabutylammonium fluoride
TBS	*tert*-butyldimethylsilyl
TBDPS	*tert*-butyldiphenylsilyl
THF	tetrahydrofuran
t.l.c.	thin layer chromatography
TMS	trimethylsilyl
TPAP	tetra-*n*-propyl ammonium perruthenate