Asymmetric Syntheses of Amino Polyols

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for the degree of Doctor of Philosophy

by

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Declaration

The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford from September 2014 until August 2018, under the supervision of Professor Stephen G. Davies. All of the work is my own unless otherwise stated and has not been submitted previously for any other degree at this or any other university.

Matthew S Kennedy

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Abstract

Matthew Kennedy D.Phil. Thesis

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This thesis centres on the asymmetric syntheses of three families of amino polyols.

Chapter 1 presents a review of literature reports relating to the isolation, biological activity and representative synthetic endeavours towards the three classes: (i) sphingoid bases and their analogues; (ii) piperidine iminosugars; and (iii) pyrrolidine iminosugars.

Chapter 2 describes the synthesis of three 3-deoxy-3-aminosphingoid bases; namely 3-deoxy-3-aminosafingol, 3-deoxy-3-aminophytosphingosine and 3-deoxy-3-aminosphinganine, exploring diastereoselective conjugate addition or aminohydroxylation methodologies as well as Wittig or Julia procedures to install the requisite long-chain hydrocarbon fragment.

Chapter 3 presents the synthesis of the piperidine iminosugar fagomine and three of its diastereoisomers using aminohydroxylation methodology and an asymmetric acetate aldol reaction as the key steps. A comparison of the spectroscopic and specific rotation data with literature reports is also undertaken.

Chapter 4 details a general route to the codonopsinol family of pyrrolidine iminosugars, culminating in the syntheses of three natural and one unnatural polyhydroxylated pyrrolidines, and a comparison of their data with literature reports.

Chapter 5 contains experimental procedures and characterisation data for all compounds synthesised in Chapters 2–4.

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Finally, to my parents and brother, for their endless support throughout my studies, and to whom I am eternally grateful.

Abbreviations

~	Approximately
(+)	Dextrorotary
(−)	Levorotatory
°	Degrees
$[\alpha]_D$	Specific rotation
δ	NMR chemical shift
μ	Micro
Δ	Difference
ν_{max}	Infrared absorption maximum
Å	Angstrom
Ac	Acetyl
app	Apparent
Ar	Aryl
atm	Atmospheres
ATP	Adenosine triphosphate
ATR	Attenuated total reflectance
aq	Aqueous
B.C.	Before Christ
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl

br	Broad
Bu	Butyl
Bus	*tert*-Butylsulfonyl
Bz	Benzoyl
c	Centi
c	Concentration
C	Celsius
cat	Catalytic
Cbz	Carboxybenzyl
cf.	Conferatur
CoA	Coenzyme A
conc	concentrated
Cp	Cyclopentadienyl
CSA	Camphorsulfonic acid
CSO	Camphorsulfonyloxaziridine
d	Doublet
D	Dextrorotary relative to (+)-glyceraldehyde
DAB-1	Dideoxy-1,4-imino-D-arabinitol
DBU	1,8-Diazabicyclo-[5.4.0]-undec-7-ene
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DEAD	Diethyl azodicarboxylate
dec	Decomposed

deg	Degrees
DHQ-PHAL	Hydroquinine 1,4-phthalazinediyl diether
DIBAL-H	Diisobutylalumnium hydride
DMSO	Dimethylsulfoxide
DMAP	4-Dimethylaminopyridine
DMDP	2,5-Dihydroxymethyl-3,4-dihydroxypyrrolidine
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMSO	Dimethylsulfoxide
DNJ	1-Deoxynojirimycin
dr	Diastereomeric ratio
E	Entgegen
e.g.	*Exampli gratia*
ee	Enantiomeric excess
ent	Enantiomer
epi	Epimer
er	Enantiomeric ratio
ESI^+	Positive electrospray ionisation
et al.	*Et alia*
Et	Ethyl
equiv	Equivalents
FT	Fourier transform

g	Grams
h	Hours
HMDS	Bis(trimethylsilyl)amide
HPLC	High-performance liquid chromatography
HRMS	High resolution mass spectrometry
Hz	Hertz
^{i}	Iso
IBX	2-Iodoxybenzoic acid
IR	Infrared
Ipc	Diisopinocampheyl
J	Coupling constant
L	Litres
LC/MS	Liquid chromatography–mass spectrometry
LDA	Lithium diisopropylamide
lit.	Literature
L-selectride	Lithium tri-*sec*-butylborohydride solution
m	Multiplet
m	Milli
m	Metre
m	Meta
M	Molar
M	Mega

m/*z*	Mass to charge ratio
m-CPBA	*meta*-Chloroperoxybenzoic acid
Me	Methyl
min	Minutes
MKR	Mutual Kinetic Resolution
mol	Moles
mp	Melting point
Ms	Methanesulfonyl
MS	Molecular sieves
N	Normality
n	Nano
NMO	4-Methylmorpholine *N*-oxide
nOe	Nuclear Overhauser effect
NMR	Nuclear magnetic resonance
Nu	Nucleophile
o	Ortho
p	Para
PCC	Pyridinium chlorochromate
pH	Potential of hydrogen
Ph	Phenyl
pin	Pinacolato
Piv	Pivaloyl

PKR	Parallel Kinetic Resolution
PMP	*para*-Methoxyphenyl
ppm	Parts per million
Pr	Propyl
PT	1-Phenyl-1*H*-tetrazole
py	Pyridine
q	Quartet
quant	Quantitative
R	Rectus
R	Unspecified organic group
R'	Unspecified organic group
®	Registered trademark
rt	Room temperature
s	Singlet
S	Sinister
S_N2	Bimolecular nucleophilic substitution
sec	Secondary
satd	Saturated
SPT	Serine palmitoyl tranferase
t	Tertiary
t	Triplet
TBAF	Tetrabutylammonium fluoride

TBAI	Tetrabutylammonium iodide
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
tert	Tertiary
TIPS	Triisopropylsilyl
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
THP	Tetrahydropyran
TLC	Thin layer chromatography
TMG	Tetramethylguanidine
TMP	2,2,6,6-Tetramethylpiperidide
TOCSY	Total correlation spectrscopy
Tol	*p*-Methylphenyl
Tr	Trityl
Ts	*p*-Toluenesulfonyl
UV	Ultraviolet
v	Volume
viz.	Videlicet
w	Weight
X_c	Chiral auxilliary
Z	Zusammen

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Chapter 1: Introduction

1.1 Alkaloid Natural Products

Alkaloids are a diverse class of nitrogenous secondary metabolites found in Nature which have a large variety of structural motifs and biological effects. They are loosely described as naturally occurring compounds which contain basic nitrogen atoms occurring mostly in the plant kingdom (but not excluding those of animal origin). Amino acids, peptides, proteins, nucleotides, nucleic acids and antibiotics are not normally regarded as alkaloids.[1] Their synthesis and biological evaluation is a well-researched area due to the number of potential synthetic targets and their significant bioactivity. Morphine **1** is probably the most well-known alkaloid due to its use as an analgesic and is the major component of opium, representing 10–15% of its dry weight. It was first isolated from the poppy *Papaver somniferum* in 1805 by Sertürner.[2] The first documented use of opium was in 1500 B.C. and its analgesic properties have not been matched by any synthetic drug or naturally occurring compound.[3] Strychnine **2** is the flagship member of the *Strychnos* alkaloid family; it was first isolated in 1818 by Pelletier and Caventou[4] from the seeds and bark of *Strychnos nux vomica* and was the subject of a landmark total synthesis by Woodward in 1954.[5] It is a potent neurotoxin which competitively blocks the neurotransmitter glycine resulting in convulsions. The primary cause of death resulting from strychnine poisoning is respiratory arrest due to spasm of the respiratory muscles.[6] Lycorine **3** is a phenanthridine alkaloid and belongs to the Amaryllidaceae family of natural products. A large number of alkaloids have been isolated from plants of the Amaryllidaceae family and exhibit a wide range of biological activities such as anti-viral,[7] anti-tumor,[8] and anti-inflammatory[9] effects. Lycorine **3** and its derivatives have been explored for their anti-plasmodial activity. A number of derivatives were tested but natural lycorine was found to be the most potent against *Plasmodium falciparum* F32 (Figure 1).[10]

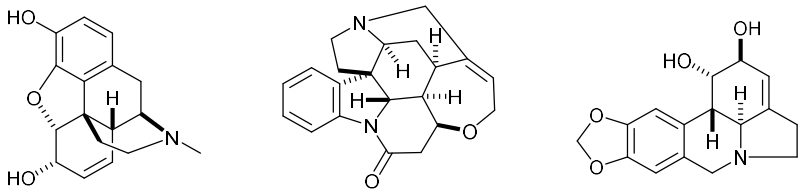


Figure 1. Examples of alkaloid natural products.

1.2 Amino Polyols

The amino polyol motif is a common unit in naturally occurring alkaloids and the structural diversity within the amino polyol class is vast. For example, long chain aliphatic amino polyols, such as myriocin **4** and sphingosine **5**, and iminosugars (here divided into polyhydroxylated pyrrolidines and piperidines) such as DMDP **6**, *N*-hydroxyethyl DAB **7**, prosopine **8** and deoxynojirimycin **9**, all belong to the amino polyol class despite their differing core scaffolds (Figure 2). The biochemistry and synthesis of these subclasses will be discussed in this introduction.

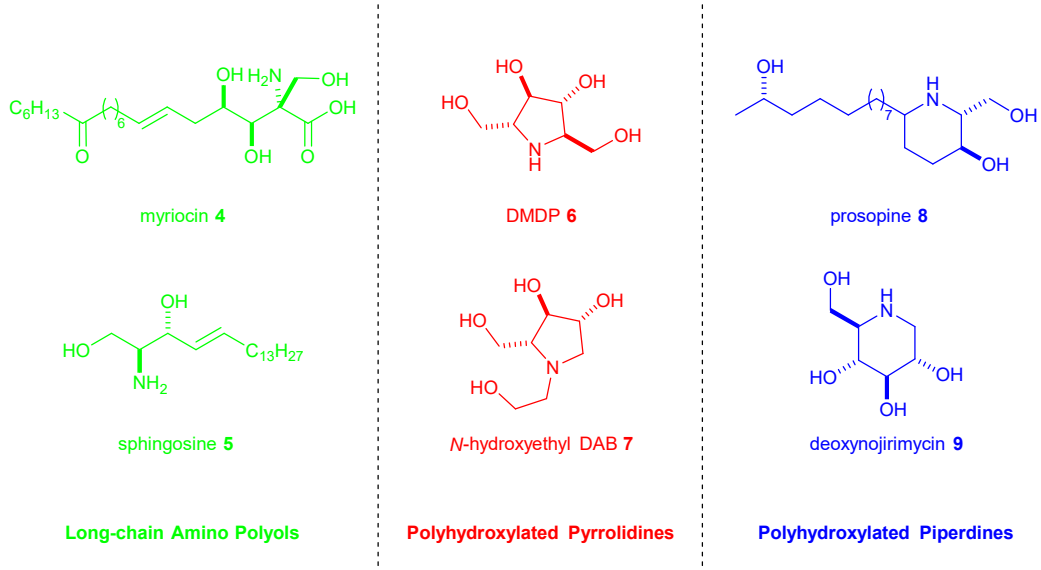
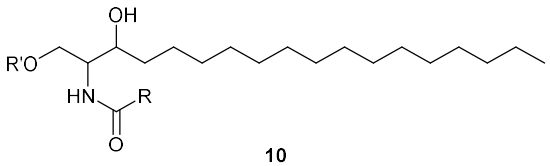


Figure 2: Selected examples of amino polyol natural products.

1.3 Sphingolipids

One class of aliphatic amino polyols are sphingolipids which comprise a sphingoid base, a polar head group (connected through the primary hydroxyl moiety), and are *N*-acetylated with

a fatty acid residue. They are structural components of cellular membranes with important roles in the regulation of cellular processes.[11] Sphingolipids are also a major constituent of the epidermis. In mammalian cells a variety of sphingolipids are known which are composed of 1 of at least 5 different sphingoid bases, 20 different fatty acids, and more than 500 different carbohydrate segments attached through the primary hydroxyl moiety (Figure 3). [12]

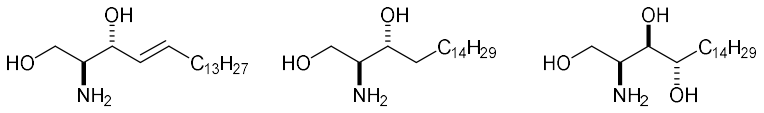


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Figure 3: General structure of the sphingolipids. [R = fatty acid chain, R' = polar head group].

1.4 Sphingoid Bases

Sphingoid bases, that form the backbone of the sphingolipids, are long chain amino polyols of which sphingosine **5** is the archetypal member. Sphingosine **5** has been extensively studied since its first isolation from the human brain by Thudichum in 1884[13] and its relative configuration was assigned in 1947.[14] The first total synthesis of **5** was completed by Shapiro and Segal in 1954.[15] Other members of this family vary in saturation of the hydrocarbon chain and the level of hydroxylation. Two saturated examples of sphingoid bases which illustrate these properties are sphinganine **11** and phytosphingosine **12** (Figure 4).



sphingosine **5** sphinganine **11** phytosphingosine **12**

Figure 4: Sphingoid bases sphingosine **5**, sphinganine **11** and phytosphingosine **12**.

Mammalian sphingoid bases are synthesised from the condensation of L-serine **13** and palmitoyl CoA **14**, catalysed by serine palmitoyl tranferase (SPT) in a pyridoxal-5'-phosphate-dependent manner.[16] The prevalence of 18-carbon sphingoid bases in mammals is due to the abundance of palmitoyl CoA.[17] The condensation of L-serine **13** with palmitoyl CoA **14** gives 3-ketodihydrosphingosine **15** which can be reduced to sphinganine **11** using reductase

catalysis. Subsequent acetylation of **11** under dihydroceramide synthase catalysis gives dihydroceramide **16** which can be dehydrogenated to give ceramide **17**. Deacetylation of **17** gives sphingosine **5** (Figure 5).[17]

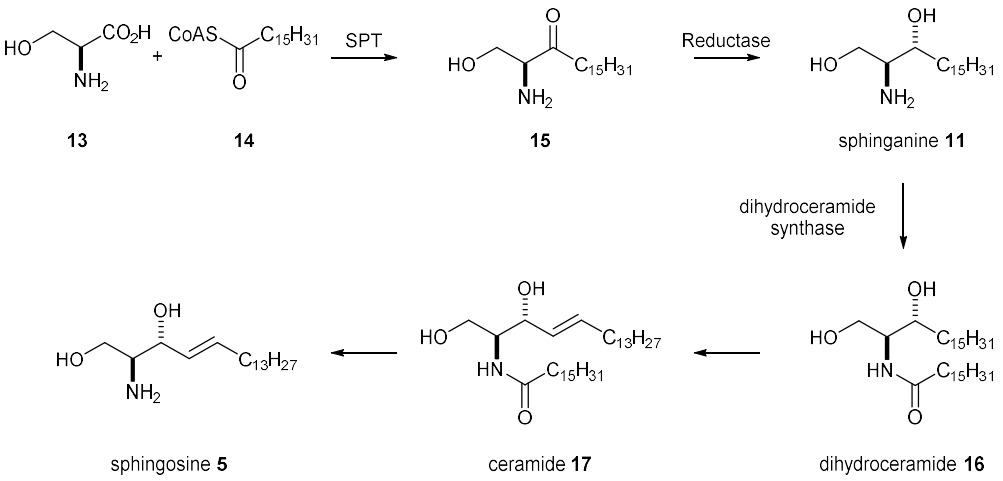
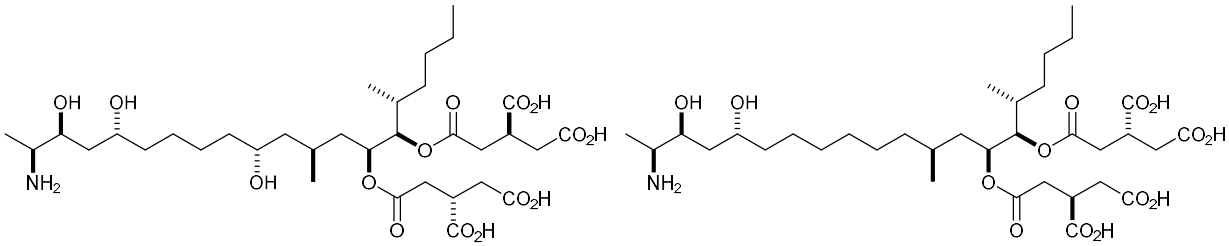


Figure 5: Biosynthetic pathway for ceramide **17**, dihydroceramide **16** and two sphingoid bases **5** and **11**.

1.4.1 Biological Significance

Recent research into the biological role of the sphingolipids has shown that they have pleiotropic effects on protein kinases as well as a role in regulating the actin cytoskeleton, apoptosis, endocytosis and the cell cycle.[18] Furthermore, recent studies have shown that sphingolipid metabolism plays a key role in gluco-lipotoxicity induced apoptosis and loss of function of pancreatic β-cells.[11] A metabolic product of sphingosine, sphingosine-1-phosphate, regulates cell growth and supresses cell death.[19] A family of sphingoid base analogues, known as the fumonisins, are ceramide synthase inhibitors which cause changes in the amounts of cellular sphingolipids and can disrupt cell function. The disruption of the sphingolipid biosynthetic pathway is a major contributor to the toxicity of the fumonisins.[20] For example, fumonisin B_1 **18** is the primary toxin produced by fungus *Fusarium verticillioides*, a common contaminant of corn and corn products.[21] Mouldy-corn syndrome, induced by the fumonisins, is fatal to pigs and horses.[22,23] Furthermore, fumonisin B_1 **18** has been reported to cause cirrhosis of the liver and hepatocellular carcinoma in rats.[24] The first total synthesis of Fumonisin B_2 **19** was reported by Kishi *et al*. in 1997 (Figure 6).[25]



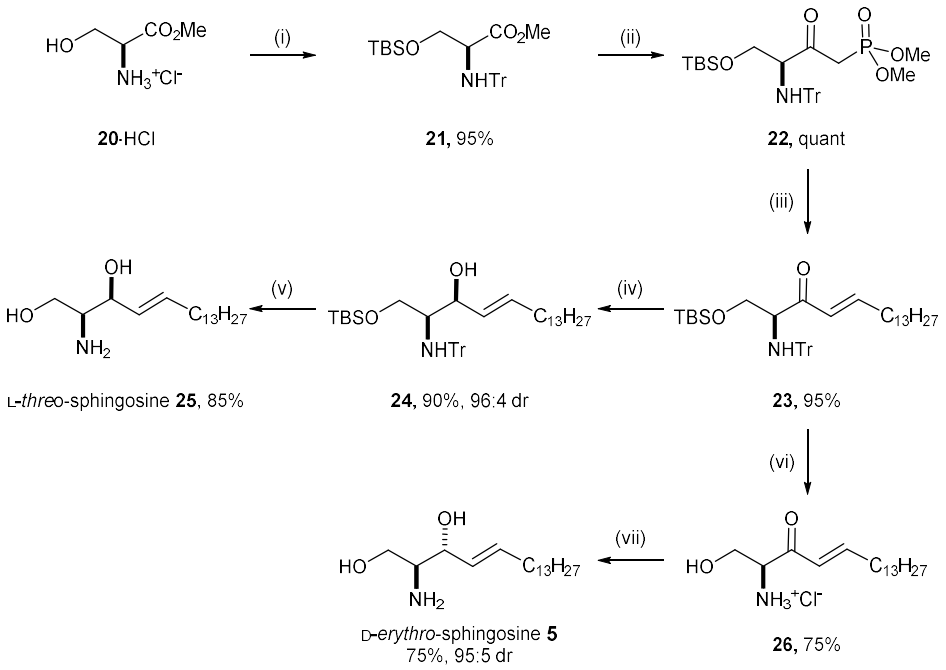
fumonisin B_1 **18** fumonisin B_2 **19**

Figure 6: Structures of fumonisin B_1 **18** and fumonisin B_2 **19**.

1.4.2 Syntheses

The synthesis of sphingoid bases and derivatives has been extensively studied due to their biological significance. The synthetic routes are wide-ranging although could be classified into three main classes: from chiral sugar starting materials, from serine and using asymmetric methods (e.g., asymmetric epoxidation).[26–28]

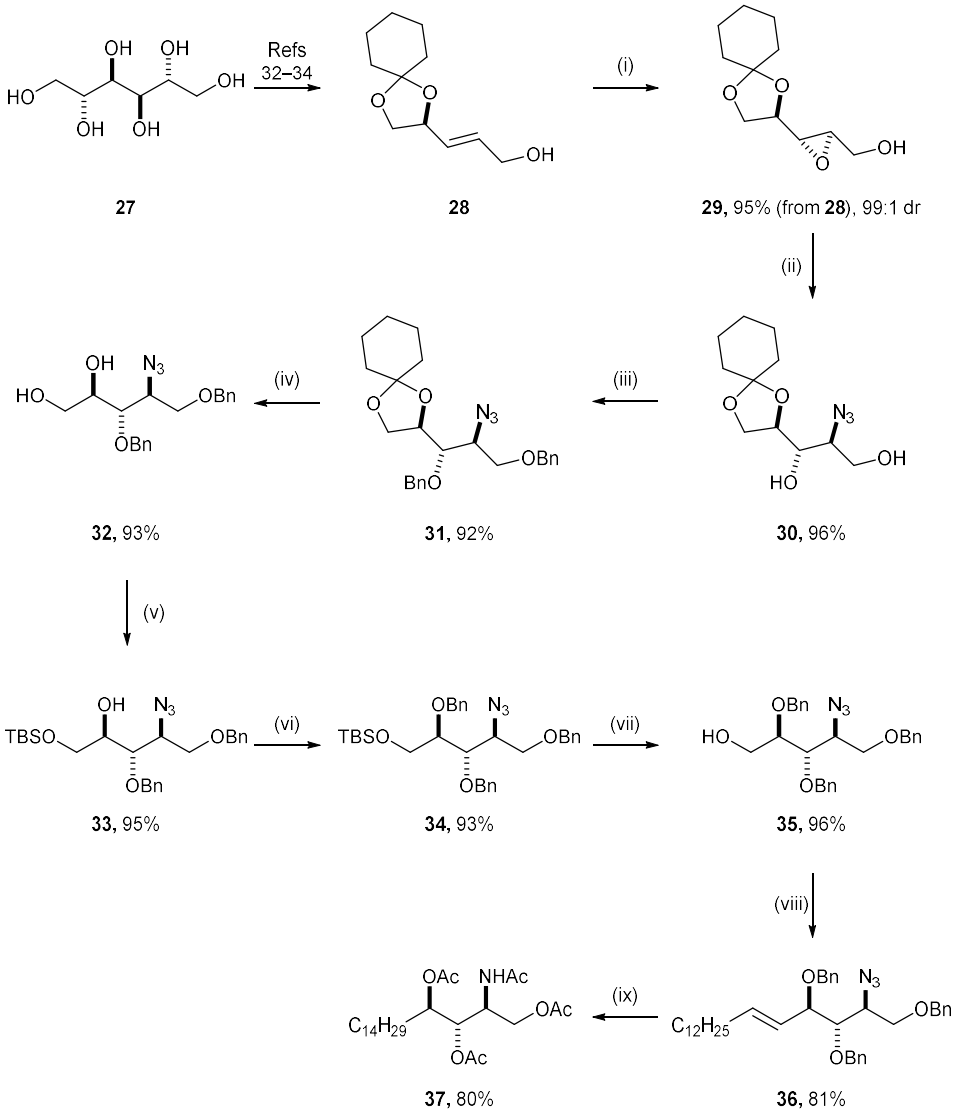
In 2002, Chung *et al*. reported a short synthesis of all four diastereoismers of sphingosine from serine using a diastereoselective reduction as the key stereodefining step.[29] *O*-Silylation of methyl L-serine hydrochloride **20**·HCl followed by *N*-tritylation gave its protected derivative **21** in 95% yield, which was converted quantitatively to phosphonate **22** by treatment with excess lithium dimethyl methylphosphonate in THF at –78 °C. Horner-Wadsworth-Emmons olefination of **22** with tetradecanal under Masamune-Rousch conditions[30] gave enone **23** in 95% yield. Reduction of **23** under Luche conditions gave diol **24** in 90% yield and 96:4 dr, which was deprotected to give L-*threo*-sphingosine **24** in 85% yield. Alternatively, *N*-deprotection of **23** gave **26**·HCl in 75% yield followed by reduction with $Zn(BH_4)_2$ gave access to diastereomeric D-*erythro*-sphingosine **5** in 75% yield and 95:5 dr (Scheme 1). It was reported that employing the same procedures on D-serine esters resulted in the synthesis of L-*erythro*- and D-*threo*-sphingosines in "*comparable yields and selectivities*".



Scheme 1. *Reagents and Conditions*: (i) TBSCl, Et_3N, CH_2Cl_2, rt, 48 h then TrCl, Et_3N, CH_2Cl_2, reflux, 2 h; (ii) $LiCH_2PO(OMe)_2$, THF, –78 °C to –20 °C; (iii) tetradecanal, DBU, LiCl, THF, rt, 5 h; (iv) $NaBH_4$, $CeCl_3{\cdot}7H_2O$, MeOH, 0 °C, 3 h; (v) 2 N HCl, MeOH/THF (10:3 v/v), 40 °C, 2 h; (vi) 2 N HCl, MeOH/THF (5:1 v/v), reflux, 1 h; (vii) $Zn(BH_4)_2$, THF, –78 °C, 5 h.

Mettu, Vaidya and co-workers synthesised peracetylated derivatives of D-*ribo*-phytosphingosine, D-*erythro*-sphingosine and sphinganine in 2012 starting from D-mannitol utilising a Sharpless epoxidation followed by ring-opening with azide.[31] Allylic alcohol **28** was prepared *via* known procedures[32–34] which allowed for Sharpless asymmetric epoxidation with diethyl D-tartrate, $Ti(O^iPr)_4$ and cumeme hydroperoxide to give epoxide **29** in 95% yield and 99:1 dr. Epoxide **29** was opened regioselectively[35] with NaN_3 in the presence of $B(OMe)_3$ to give azide **30** in 96% yield. Bis-*O*-benzylation of **30** with BnBr gave **31** in 92% yield, which was subjected to an acetal hydrolysis with HCl giving common synthetic intermediate **32** in 93% yield. Common intermediate **32** was diversified into **37**, **40** and **41** *via* chain elongation and deprotection. Firstly regioselective *O*-silylation of the primary hydroxyl group within **32** was achieved upon treatment with TBSCl, imidazole and DMAP to give **33** in 95% yield. *O*-Benzylation of the free secondary hydroxyl group within **33** using NaH and BnBr then gave **34** in 93% yield which could be desilylated with TBAF to give primary alcohol **35** in 96% yield. Oxidation of the primary hydroxyl moiety using IBX in DMSO followed by Wittig olefination of the resultant aldehyde gave olefin **36** in 81% yield.

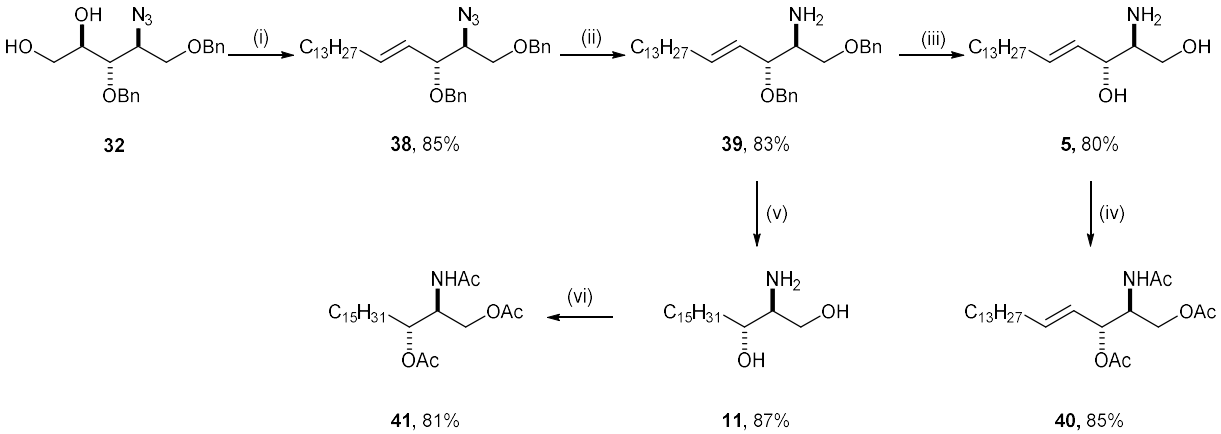
Hydrogenation/hydrogenolyis of **36** followed by acetylation with Ac_2O in pyridine gave peracetylated D-*ribo*-phytosphingosine **37** in 80% yield. This represents a synthesis of **37** in 43% overall yield from allylic alcohol **28**, itself derived from D-mannitol **27** (Scheme 2).



Scheme 2. *Reagents and Conditions*: (i) Diethyl D-tartrate, $Ti(O^iPr)_4$, cumene hydroperoxde, 4 Å MS, CH_2Cl_2, –20 °C, 72 h; (ii) NaN_3, $B(OMe)_3$, DMF, 50 °C, 8 h then $NaIO_4$, H_2O, rt, 30 min; (iii) NaH, BnBr, THF, Bu_4NI, 0 °C to rt, overnight; (iv) 10% HCl, MeCN, rt, 4 h; (v) TBSCl, imidazole, DMAP, CH_2Cl_2, 0 °C to rt, overnight; (vi) NaH, BnBr, Bu_4NI, THF; (vii) TBAF, THF, rt, 4 h; (viii) IBX, MeCN/DMSO, (4:1 v/v), rt, 24 h then tridecylphosphonium bromide, BuLi, THF, –78 °C to rt, 14 h; (ix) $Pd(OH)_2/C$, H_2, EtOAc/MeOH (1:1 v/v), rt then Ac_2O, py, DMAP, rt, 24 h.

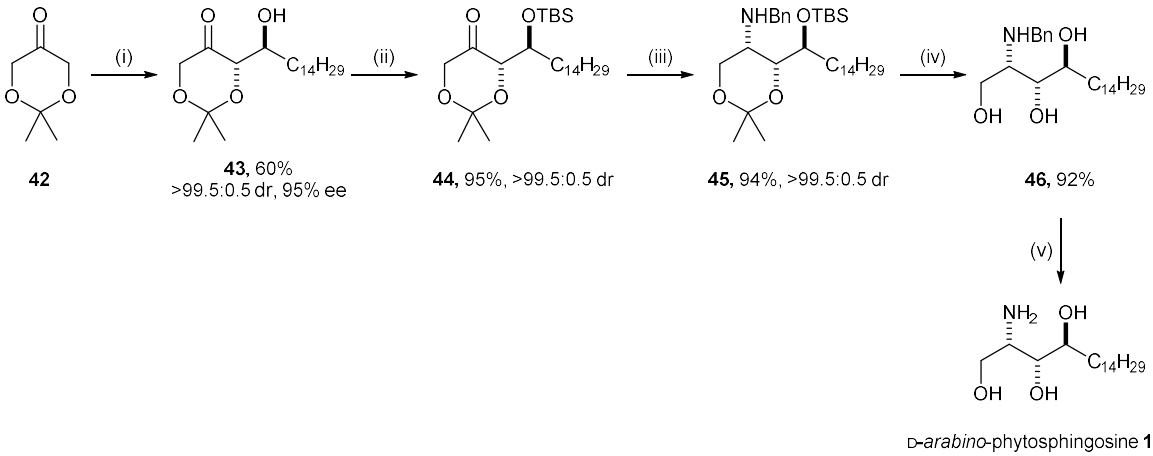
The other two target compounds were made, from the same synthetic intermediate **32**, beginning with an oxidative cleavage of the diol moiety and Wittig olefination of the resultant aldehyde with tridecyl phosphonium bromide to give olefin **38** in 85% yield. Reduction of the azide functionality using $Pd/CaCO_3$ under H_2 gave amine **39** in 83% yield, which was

followed by *O*-debenzylation using Birch conditions to give D-*erythro*-sphingosine **5** in 80% yield. Finally, peracetylation with Ac_2O in pyridine gave peracetylated D-*erythro*-sphingosine **40** in 85% yield, and in 37% overall yield from D-mannitol derived allylic alcohol **28**. Triacetylsphinganine **41** was also synthesised from amine **39** *via* hydrogenation/hydrogenolysis with Pearlman's catalyst to give sphinganine **11** in 87% yield, followed by subjection to the same acetylation procedure giving **41** in 81% yield, corresponding to 39% overall yield from **28** (Scheme 3).



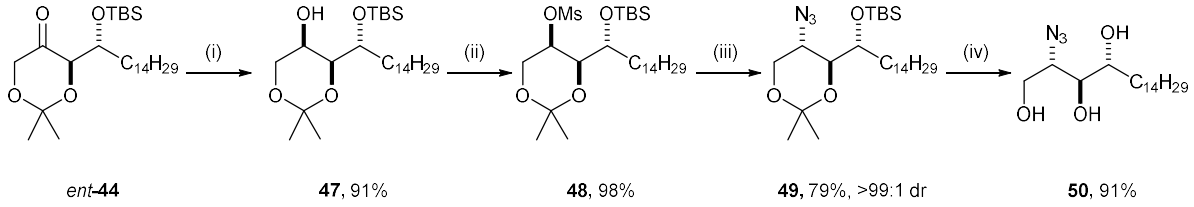
Scheme 3. *Reagents and Conditions*: (i) $NaIO_4$, MeCN/H_2O (3:2 v/v), rt, 30 min then tridecylphosphonium bromide, BuLi, THF, –78 °C to rt, 14 h; (ii) Pd/$CaCO_3$, H_2, EtOAc, rt, 8 h; (iii) Na, NH_3, THF, –78 °C, 45 min; (iv) Ac_2O, py, DMAP, rt, 16 h; (v) $Pd(OH)_2$/C, H_2, EtOAc/MeOH (1:1 v/v), rt, 48 h; (vi) Ac_2O, py, DMAP, rt, 16 h.

Enders *et al*. reported the synthesis of a range of sphingoid bases and their analogues including D-*arabino*-phytosphingosine **12** and 2-azidophytosphingsoine **50** using an (*S*)-proline-catalysed asymmetric aldol condensation.[36–38] (*S*)-Proline catalyses the addition of dioxanone **42** to pentadecanal giving **43** in 60% yield, >99.5:0.5 dr and 95% ee, then *O*-silyl protection with TBSOTf and 2,6-lutidine gave **44** in 95% yield and >99.5:0.5% dr. The amino moiety was installed by reductive amination with benzylamine, employing $NaBH(OAc)_3$ as the reducing agent, to give **45** in 94% yield and >99.5:0.5 dr. Finally, *O*-deprotection gave triol **46** in 92% yield and hydrogenolytic *N*-debenzylation gave D-*arabino*-phytosphingosine **12** in 99% yield (Scheme 4).



Scheme 4. *Reagents and Conditions*: (i) (*S*)-proline, pentadecanal, $CHCl_3$, rt, 96 h; (ii) TBSOTf, 2,6-lutidine, CH_2Cl_2, –20 °C, 2 h; (iii) $BnNH_2$, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, 2 °C; (iv) TBAF, THF, $MgSO_4$, 50 °C then TFA, THF, 50°C; (v) H_2, Pd/C, MeOH.

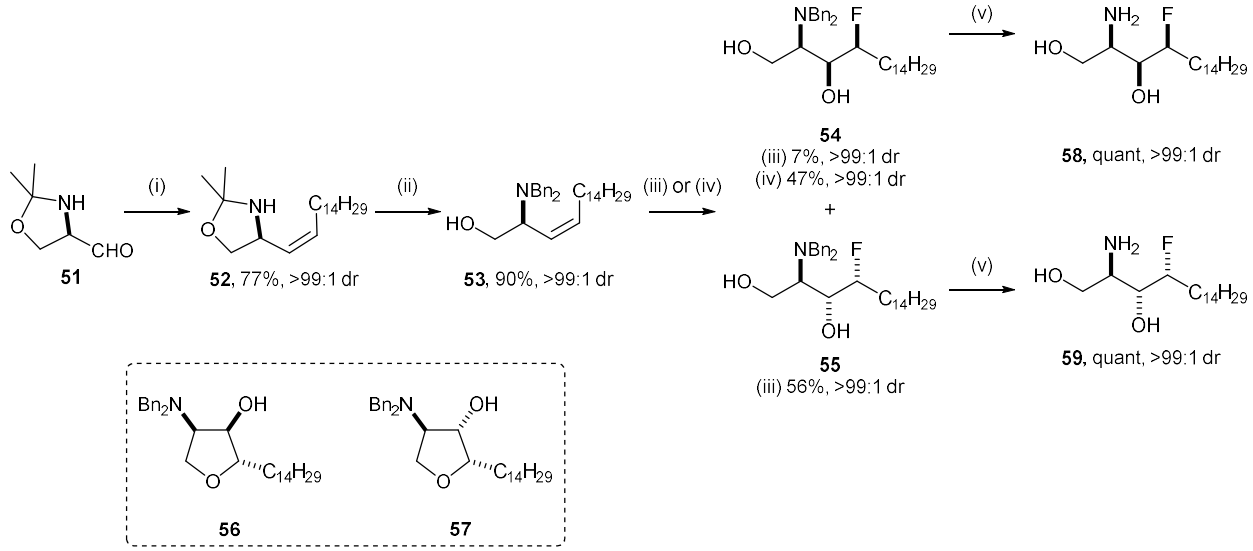
The enantiomeric *O*-silylated aldol product *ent*-**44** [which was made *via* the same synthetic route catalysed by (*R*)-proline] was submitted to reduction using L-selectride to give alcohol **47** in 91% yield, which could be mesylated with MsCl in 98% yield. Substitution of the mesylate with NaN_3 and 18-crown-6 occurred with inversion of configuration to give azide **49** in 79% and >99:1 dr, and subsequent deprotection afforded 2-azidophytosphingosine **50** in 91% yield (Scheme 5).



Scheme 5. *Reagents and Conditions*: (i) L-selectride, THF, –78 °C, 2 h; (ii) MsCl, DMAP, CH_2Cl_2, 0 °C to –10 °C, 15 h; (iii) NaN_3, 18-crown-6, DMF, 100 °C, 48 h; (iv) DOWEX 50WX2, MeOH, THF, 60 °C, 2 h.

Davies *et al*. prepared deoxyfluoro analogues of sphingoid bases using the hydroxyfluorination of allylic amines as the key step.[39,40] To prepare the allylic amine needed for the key step, Garner's aldehyde **51** was olefinated to give **52** in 77% yield. Protecting group manipulation of **52** gave **53** in 90% yield. The hydroxyfluorination could be carried out under two sets of conditions giving contrasting results. Upon treatment of **53** with 20 equivalents of HBF_4 followed by 4 equivalents of *m*-CPBA an 18:66:16 mixture of **54**, **55** and **56**, respectively, was obtained from which the major component **55** was isolated in 56%

yield and >99:1 dr, and the minor component **54** was isolated in 7% yield and >99:1 dr. A sample of tetrahydrofuran **56** was also isolated in 7% yield and >99:1 dr. However, with 2.0 equiv of HBF_4 followed by 2 equiv of *m*-CPBA, a 67:16:18 mixture of **54**, **55** and **57**, respectively, was produced from which **54** was isolated in 47% and >99:1 dr, and tetrahydrofuran **57** was isolated in 14% yield and >99:1 dr. *N*-Deprotection of **54** and **55**, under hydrogenolysis conditions, yielded **58** and **59**, respectively, in quantitative yield and >99:1 dr in both cases (Scheme 6).



Scheme 6. *Reagents and Conditions*: (i) $[C_{15}H_{31}PPh_3]^+Br^-$, NaHMDS, THF, hexane, –78 °C to rt, 42 h; (ii) conc aq HCl, MeOH, reflux, 17 h then BnBr, K_2CO_3, EtOH, reflux, 4 h; (iii) 20 equiv $HBF_4{\cdot}OEt_2$, CH_2Cl_2, then 4.0 equiv *m*-CPBA, CH_2Cl_2, rt, 18 h; (iv) 2.0 equiv $HBF_4{\cdot}OEt_2$, CH_2Cl_2, then 2.0 equiv *m*-CPBA, CH_2Cl_2, rt, 18 h; (v) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt, 24 h.

1.5 Iminosugars

Iminosugars are aza-sugar analogues where the endocyclic oxygen atom is replaced by nitrogen. They draw considerable interest from the synthetic and biochemical communities due to their glycosidase inhibitory activity, which is reported to be the origin of their therapeutic effects, in the treatment of cancers, diabetes and viral infections.[41,42] The mechanism of action is thought to be due to the resemblance of the protonated nitrogen atom, at physiological pH, to the cationic transition state formed during glycosidase catalysis.[43] Fleet classified these naturally-occurring polyhydroxylated azacycles into five structural classes: piperidines, pyrrolidines, indolizidines, pyrrolizidines and nortropanes.[24] Of these subclasses it

is the polyhydroxylated pyrrolidines and polyhydroxylated piperidines that will be discussed below.

1.5.1 Polyhydroxylated Piperidines

The first isolation of a piperidine iminosugar was nojirimycin **60** in 1966 from *Steptomyces* as a novel antibiotic. Since then, more than 100 polyhydroxylated alkaloids have been isolated from plants and microorganisms.[44] The first isolation of 1-deoxynojirimycin (DNJ) **9** from a natural source was reported by Yagi *et al*. in 1976 from an extract of *Morus* species.[45] Since its initial isolation **9** has been found in a variety of natural sources including plants,[46,47] animals[48] and microorganisms.[49,50] As with other iminosugars the biological activity of DNJ **9** centres on its glycosidase inhibitory effects.[51] Furthermore, much research has been invested in the synthesis and biological study of analogues of DNJ especially focussing on *N*-substitution and as such two analogues, *N*-butyl-DNJ **61** and *N*-hydroxyethyl-DNJ **62** have been developed as Miglustat **61** and Miglitol **62**, respectively. Miglustat **61**, marketed as Zavesca®, is used as a treatment for type I Gaucher's disease[52] and miglitol **62**, marketed as Glyset®, is a treatment for type II diabetes (Figure 7).[53]

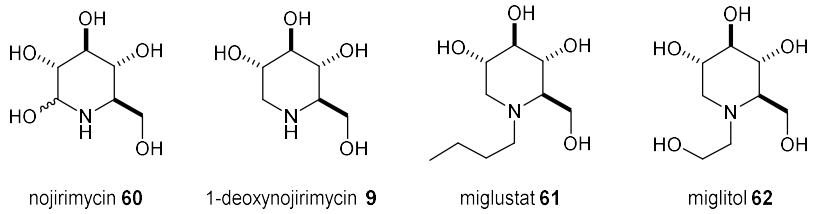
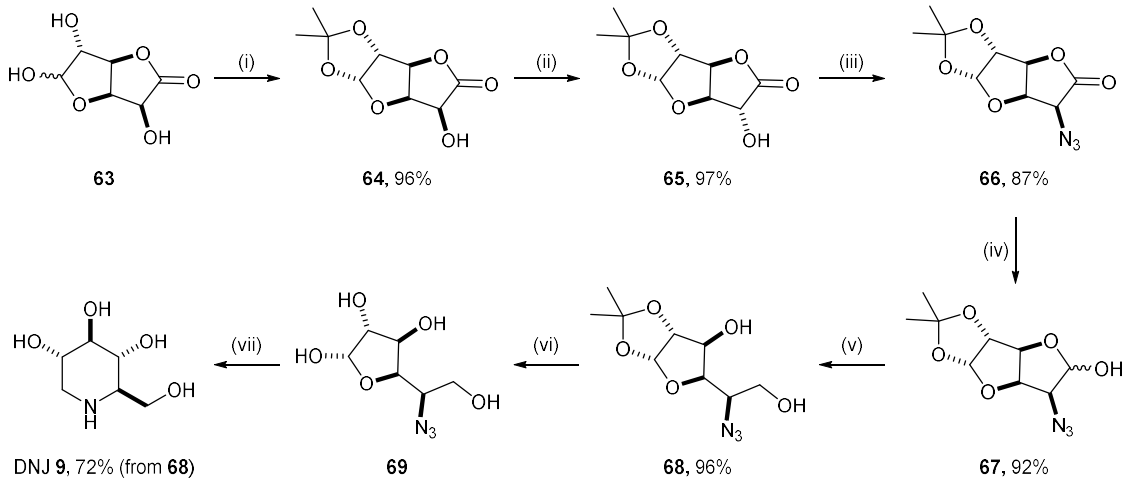


Figure 7. Examples of polyhydroxylated piperidine iminosugars.

1.5.1.1 Syntheses

Due to the biological effects of DNJ and its derivatives, the synthetic community has devoted a large amount of time to their synthesis. Many of the syntheses begin with sugar starting materials,[54–56] although there are also reports starting from achiral starting materials[57] or using enzymatic methods.[58,59] A selection of syntheses is discussed below.

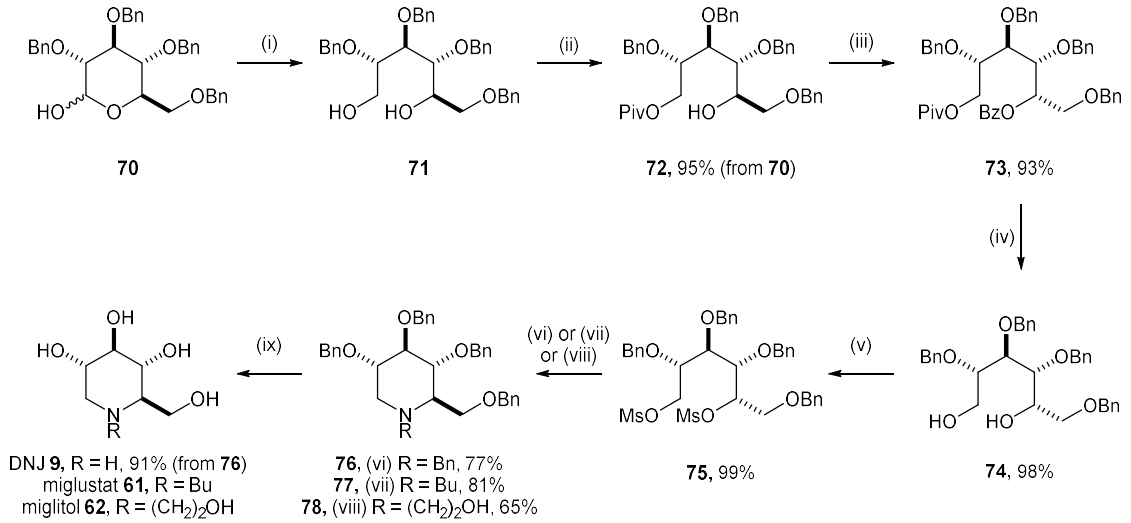
In 2010 Fleet *et al*. reported large scale syntheses of a number of iminosugars including DNJ **9** and its enantiomer from D-glucuronolactone **63**.[60] Acetonide protection of D-glucuronolactone gave **64** in 96% yield. The free hydroxyl group within **64** was inverted (*via* the intermediacy of the corresponding triflate) to give **65** in 97% yield (the yield of **65** *via* crystallisation was 73% on over 100 g scale). Triflation of **65** followed by S_N2 displacement of the corresponding triflate with NaN_3 in DMF gave azide **66** in 87% yield. The two-step reduction of **66** to diol **68** was required for optimal yields of **68** as direct reductions were reported to be low yielding; reduction to lactol **67** with DIBAL-H in CH_2Cl_2 occurred in 92% yield, which could subsequently be reduced with $NaBH_4$ in MeOH to give **68** in 96% yield. Acidic cleavage of the acetonide protecting group followed by reductive hydrogenation afforded DNJ **9** in 72% yield, and 52% overall yield from D-glucuronolactone **63** (Scheme 7).



Scheme 7. *Reagents and Conditions*: (i) conc H_2SO_4, acetone, rt, 5 h; (ii) Tf_2O, py, CH_2Cl_2, –30 °C, 2 h then CF_3CO_2Na, DMF, rt, 1 h; (iii) Tf_2O, py, CH_2Cl_2, –30 °C, 2 h then NaN_3, DMF, –20 °C, 1 h; (iv) DIBAL-H, CH_2Cl_2, –78 °C, 1 h; (v) $NaBH_4$, MeOH, –10 °C, 1 h; (vi) DOWEX 50WX2. H_2O, 70 °C, 2 h; (vii) Pd/C, H_2, H_2O, rt, 2 h.

Another synthesis from a sugar precursor was reported by Wang and co-workers in 2011.[55] The synthesis of DNJ **9**, miglustat **61** and miglitol **62** were all achieved from tetrabenzyl glucopyranose **70**. Reduction of **70** followed by selective protection of the primary hydroxyl group within **71** with PivCl gave **72** in 95% yield over two steps. Mitsunobu reaction of **72** with benzoic acid, DEAD and PPh_3 occurred with inversion of configuration to give benzoate **73** in 93% yield. Hydrolysis of the pivalate and benzoate esters within **73** upon treatment with

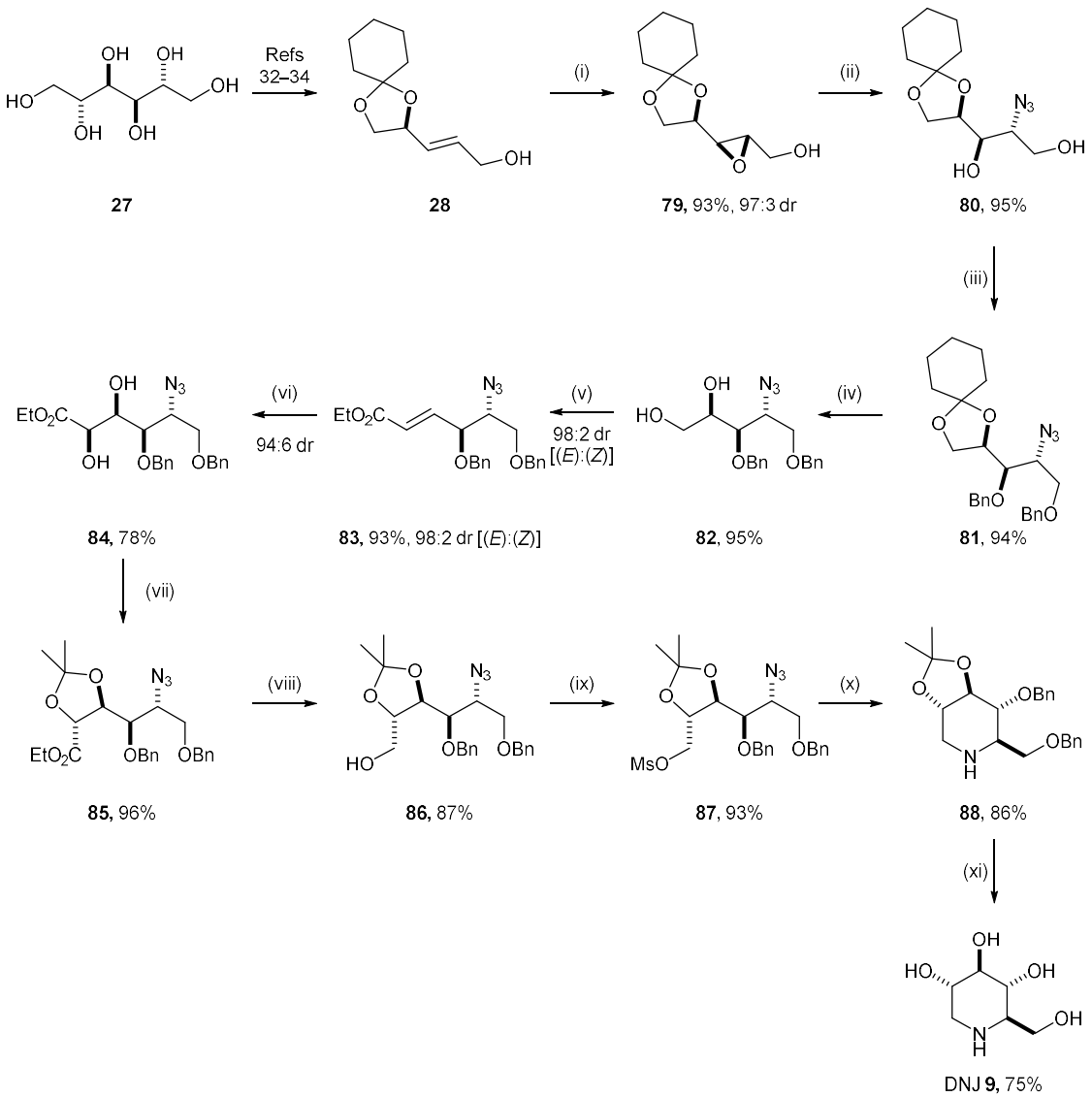
NaOMe in MeOH afforded diol **74** in 96% yield, which was transformed into bis-mesylate **75** with MsCl in pyridine in 99% yield. Reaction of **75** with the requisite primary amines, *viz*. benzylamine, butylamine or 2-hydroxyethylamine, allowed for cyclisation to give *N*-subustituted piperidines **76**–**78** in 65–81% yield, which could be debenzylated under hydrogenolytic conditions to give **9**, **61** and **62**, respectively. The authors only reported the yield for the synthesis of **9** (91%) (Scheme 8).



Scheme 8. *Reagents and Conditions*: (i) $NaBH_4$, MeOH, rt, 12 h; (ii) PivCl, py, CH_2Cl_2, rt, overnight; (iii) Ph_3P, DEAD, $PhCO_2H$, PhMe, 0 °C to rt, overnight; (iv) NaOMe, MeOH, rt, 5 h; (v) MsCl, py, rt, 5 h; (vi) $BnNH_2$, 50 °C, 4 days; (vii) $BuNH_2$, 50 °C, 4 days; (viii) $HO(CH_2)_2NH_2$, 50 °C, 4 days; (ix) Pd(OH)/C, H_2, EtOH/$CHCl_3$ (4:1), rt, 20 h.

Following their synthesis of the sphingoid bases (*vide supra*) Mettu *et al*. reported the synthesis of DNJ **9**, using a similar synthetic strategy, from the same allylic alcohol **28** derived from D-mannitol **27**.[56] Allylic alcohol **28** was subjected to a Sharpless catalytic asymmetric epoxidation using diethyl L-tartrate, $Ti(O^iPr)_4$ and cumene hydroperoxide which gave epoxide **79** in 93% yield and 97:3 dr (previously diastereomeric epoxide **29** was synthesised using diethyl D-tartrate). Regioselective ring-opening[35] of **79** with NaN_3 and $B(OMe)_3$ afforded azide **80** in 95% yield. Benzylation of both hydroxyl moieties within **80** gave **81** in 94% yield, which could be converted to diol **82** *via* an acidic acetonide deprotection in 95% yield. Periodate cleavage of 1,2-diol **82** gave the corresponding aldehyde, which could be trapped *in situ* with a phosphonate reagent under Masamune-Rousch conditions[30] to give

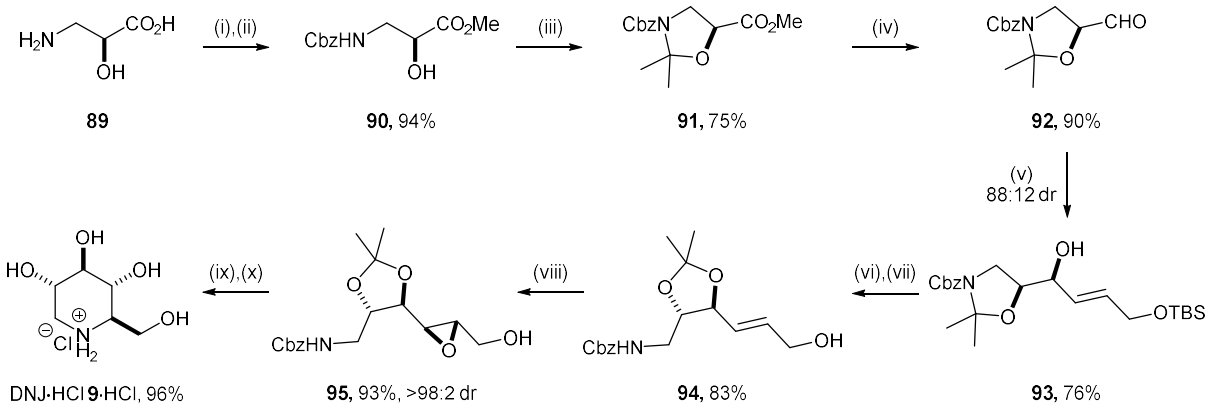
α,β-unsaturated ester **83** in 93% yield and 98:2 dr [(*E*):(*Z*)]. Dihydroxylation of **83** with AD-mix-α gave diol **84** in 94:6 dr, from which pure **84** was isolated in 78% yield. Acetonide protection of the newly formed diol unit within **84** occurred in 96% yield, and was followed by reduction of the ester within **85**, with $NaBH_4$ and LiCl, to give primary alcohol **86** in 87% yield. The primary hydroxyl group within **86** was mesylated with MsCl and cyclisation of **87** occurred upon treatment with H_2 and Lindlar's catalyst, giving **88** in 86% yield. Final deprotection of **88** gave DNJ **9** in 75% yield, and 32% overall yield from allylic alcohol **28** (Scheme 9).



Scheme 9. *Reagents and Conditions*: (i) diethyl L-tartrate, $Ti(O^iPr)_4$, cumene hydroperoxide, 4 Å MS, CH_2Cl_2, –20 °C, 72 h; (ii) $B(OMe)_3$, NaN_3, DMF, 50 °C, 6 h then $NaIO_4$; (iii) NaH, BnBr, Bu_4NI, THF, 0 °C to rt, 16 h; (iv) 10% HCl, MeCN, rt, 4 h; (v) $NaIO_4$, MeCN/H_2O (3:2 v/v), rt, 30 min then $(EtO)_2P(O)CH_2CO_2Et$, LiCl, $^iPr_2NEt$, MeCN, rt, 24 h; (vi) AD-mix-α, $(DHQ)_2$-PHAL, $MeSO_2NH_2$, $NaHCO_3$, OsO_4, $^tBuOH/H_2O$ (1:1 v/v), 0 °C, 3 days; (vii) 2,2-dimethoxypropane, acetone, TsOH, rt, overnight; (viii) LiCl, $NaBH_4$, THF/EtOH (1:1 v/v), rt, overnight; (ix) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 3 h; (x) Pd/$CaCO_3$, H_2, MeOH, rt, 6 h then K_2CO_3, reflux, 3 h; (xi) Pd/C, H_2, MeOH, 6 N HCl, rt, 48 h then DOWEX 50WX8.

In 2011 Li and coworkers reported the synthesis of DNJ·HCl **9**·HCl from (*S*)-isoserine **89** *via* a diastereoselective reductive coupling.[61] (*S*)-Isoserine **89** was protected as its methyl ester and *N*-Cbz carbamate **90** in 94% yield. Cyclic *N*,*O*-acetal **91** was formed from **90** upon treatment with 2,2-dimethoxypropane in 75% yield which then could be reduced to aldehyde **92** using DIBAL-H in 90% yield. Diastereoselective reductive coupling of **92** with protected 3-hydroxypropyne occurred with $ZrCp_2HCl$ and Et_2Zn in 76% yield and good diastereoselectivity (88:12 dr). Removal of the *N*,*O*-acetal and *O*-silyl protecting group by

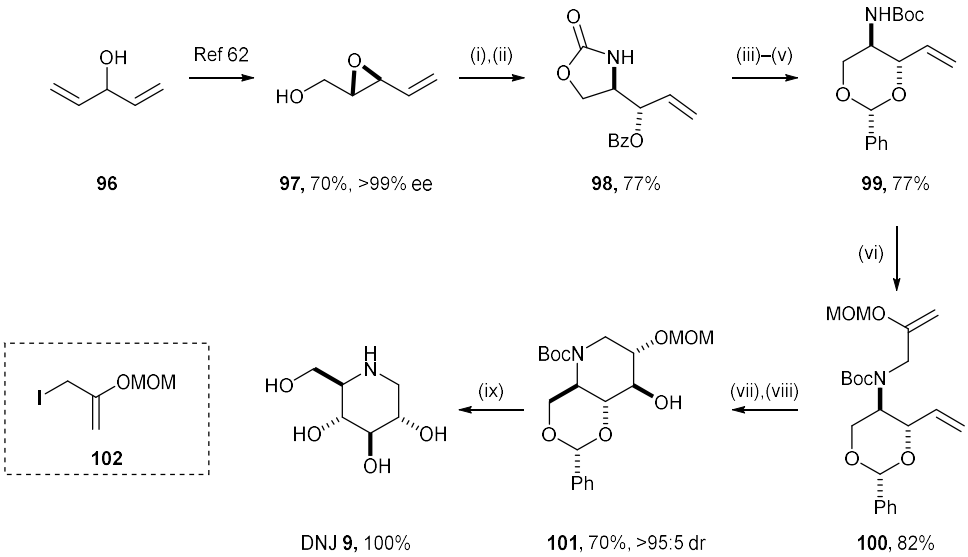
exposure to TsOH followed by protection of the subsequent diol gave acetonide **94** in 83% yield over two steps. Asymmetric Sharpless epoxidation using diethyl L-tartrate, $Ti(O^iPr)_4$ and ^{t}BuOOH gave epoxide **95** in 93% yield and high diastereoselectivity (>98:2 dr). Hydrogenolysis of the *N*-Cbz protecting occurred with *in situ* cyclisation followed by deprotection in aqueous acid to give **9**·HCl in 96% yield (Scheme 10).



Scheme 10. *Reagents and Conditions*: (i) $SOCl_2$, MeOH, rt, 16 h; (ii) benzyl chloroformate, satd aq $NaHCO_3$, CH_2Cl_2, 0 °C; (iii) 2,2-dimethoxypropane, $BF_3{\cdot}OEt_2$, acetone, rt, overnight; (iv) DIBAL-H, PhMe, –70 °C, 2.5 h; (v) $ZrCp_2HCl$, 3-*tert*-butyldimethylsilyloxyprop-1-yne, Et_2Zn, –30 °C to 0 °C, overnight; (vi) TsOH, MeOH, rt, 20 h; (vii) 2,2-dimethoxypropane, TsOH, DMF, rt, overnight; (viii) diisopropyl L-tartrate, $Ti(O^iPr)_4$, 4 Å MS, ^{t}BuOOH, CH_2Cl_2, –20 °C overnight; (ix) Pd/C, EtOH, H_2, reflux, overnight; (x) HCl, 40 °C, 3 h.

In 2009, Poisson and co-workers reported the asymmetric synthesis of DNJ **9** from achiral starting materials using a one-pot ring-closing metathesis/hydroboration as the key step.[57] Diene **96** was subjected to Sharpless asymmetric epoxidation conditions followed by base-catalysed Payne rearrangement to give epoxy alcohol **97** in 70% yield and >99% ee.[62] Reaction of **97** with benzoyl isocyanate proceeded by epoxide-opening, benzoyl migration and oxazolidinone formation to give **98** in 77% yield. *N*-Boc protection of **98** followed by hydrolysis of the oxazolidinone and benzoyl protecting group with NaOEt, and subsequent protection of the diol as the benzylidene acetal gave **99** in 77% yield. *N*-Alkylation with allylic iodide **102** afforded **100** in 82% yield, which then underwent ring-closing metathesis in the presence of Hoveyda-Grubbs 2nd generation catalyst, followed by hydroboration with $BH_3{\cdot}SMe_2$, to give **101** in 70% yield and >95:5 dr. Acidic deprotection of **101** with HCl in

EtOH gave DNJ·HCl **9**·HCl in 100% yield (from **101**), and in 24% overall yield from known epoxy alcohol **97** (Scheme 11).



Scheme 11. *Reagents and Conditions*: (i) BzNCO, Et_2O, rt, 2 h; (ii) K_2CO_3, $(C_{12}H_{25})NMe_3Cl$, CH_2Cl_2/H_2O (1:1 v/v), rt, 16 h; (iii) Boc_2O, Et_3N, DMAP, CH_2Cl_2, rt, 1.5 h; (iv) NaOEt, EtOH, 0 °C to rt, 2 h; (v) $PhCH(OMe)_2$, CSA, CH_2Cl_2, rt, 6 h; (vi) NaH, **102**, DMF, rt, 1 h; (vii) Hoveyda-Grubbs 2nd generation catalyst, benzoquinone, PhMe, reflux, 4.5 h; (viii) $BH_3·SMe_2$, THF, rt, 7 h then $NaBO_3·4H_2O$, rt, 18 h; (ix) 1% HCl in EtOH, reflux, 18 h.

1.5.2 Polyhydroxylated Pyrrolidines

The first pyrrolidine iminosugar isolated from a natural source was 2,5-dihydroxymethyl-3,4-dihydroxypyrrolidine [DMDP] **6** in 1976 from the leaves of *Derris elliptica* and since then it has been found in plants, animals and microorganisms, demonstrating that it is a fairly common metabolite and termed by Fleet[63] as "*probably the most widely naturally occurring iminosugar*".[64] As well as being a glycosidase inhibitor,[65,66] it also has inhibitory effects of the ATP-dependant efflux pump, a pump that removes chemotherapy drugs from multidrug resistant cancer cells.[67] It also has potential insecticidal effects as a feeding inhibitor.[68] 1,4-Dideoxy-1,4-imino-D-arabinitol **103**, commonly known as DAB-1, was isolated from *Angylocalyx boutqueanus* fruit by Williams *et al.* in 1985[69] and was reported to be a strong competitive inhibitor of yeast α-glucosidase.[70] Nectrisine **104** was isolated from the fungus *Nectria lucida* in 1988 and was found to have immunomodulatory effects.[71] It was also

reported to be an inhibitor of α-glucosidase, α- and β-mannosidases, β-glucosidase and β-*N*-acetylglucosaminidase (Figure 8).[72]

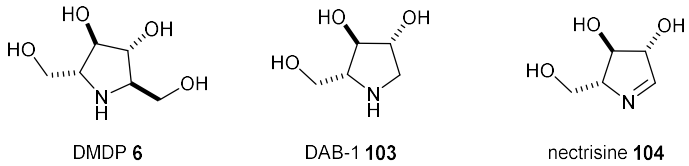
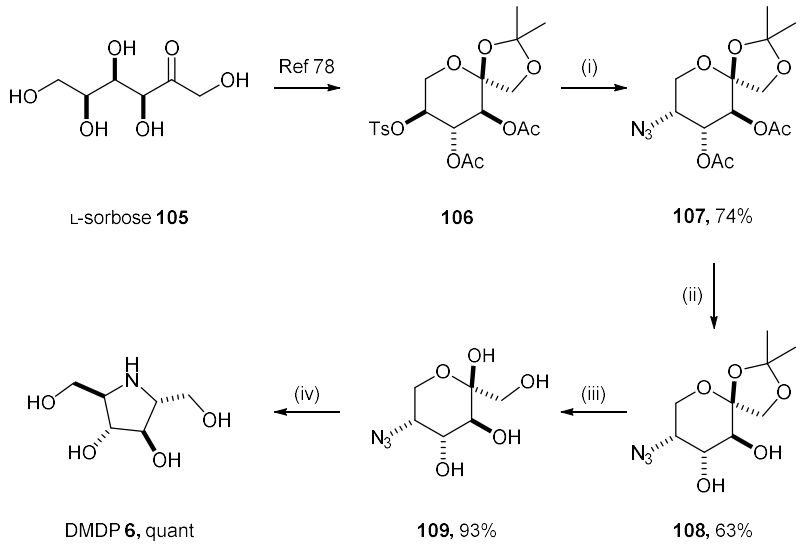


Figure 8. Examples of pyrrolidine iminosugars.

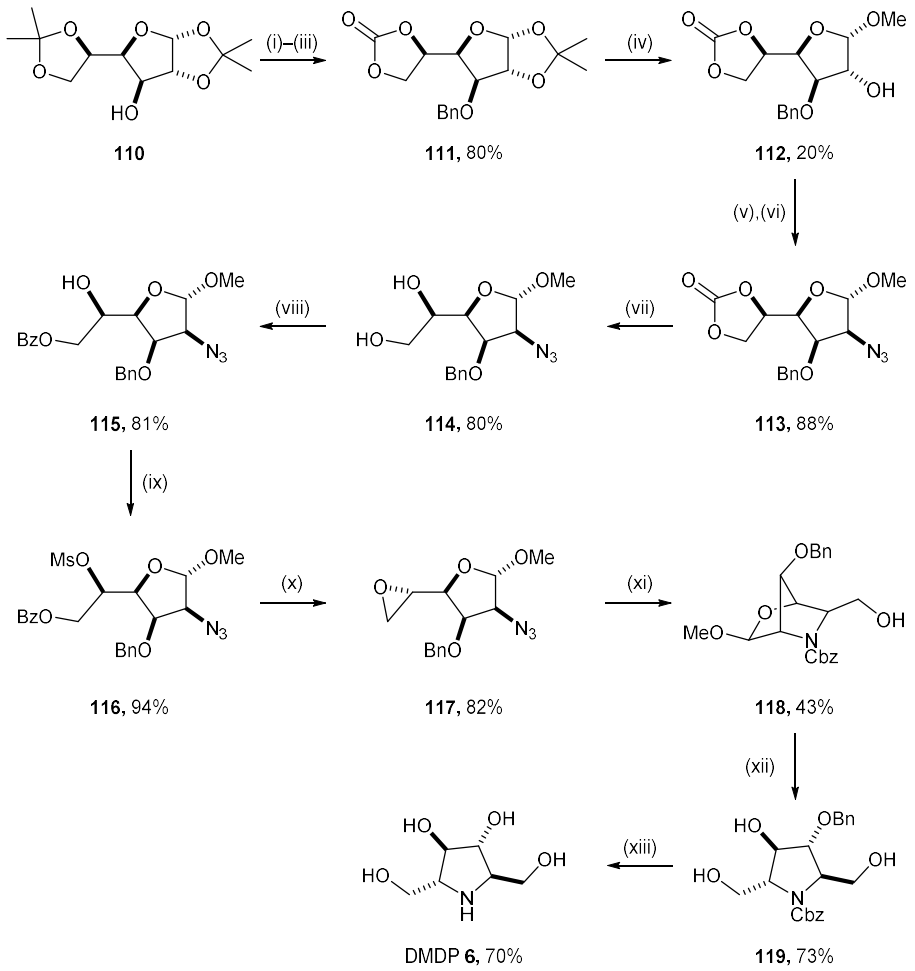
1.5.2.1 Syntheses

Due to its high abundance and biological properties **6** has been targeted by synthetic chemists in a variety of ways including from sugars,[73–75] using enzymatic methods[58] or *via* reduction of pyrroles.[76] The first reported synthesis of DMDP **6** was by Card and Hitz in 1984.[77] L-Sorbose **105** was converted to **106** in three steps using known procedures,[78] and then **106** was treated with LiN_3 in DMF to afford azide **107** (with inversion of configuration) in 74% yield. Diacetate **107** was deprotected with NaOMe in MeOH to give **108** in 63% yield, then the acetonide protecting group was removed to give tetraol **109** in 93% yield. Reduction of the azide group under Pd/C catalysis gave DMDP **6** quantitatively (Scheme 12).



Scheme 12. *Reagents and Conditions*: (i) LiN_3, DMF, 70 °C, 72 h; (ii) NaOMe, MeOH, rt, 1 h; (iii) Biol-Rad AG 50Q-X8, H_2O/EtOH (10:3 v/v), 45 °C, 2 h; (iv) H_2, Pd/C, EtOH.

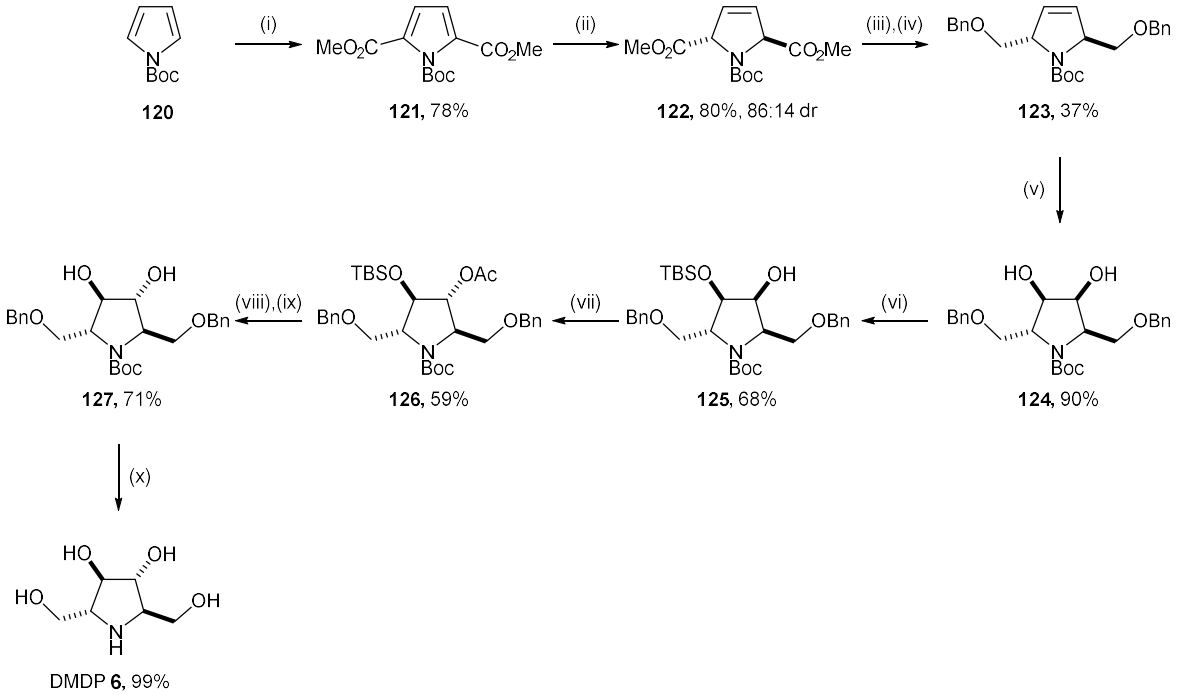
Another early synthesis of **6** was reported by Fleet and Smith in 1987 from diacetone D-glucose **110**.[79] The free alcohol within **110** was protected with NaH, BnBr and TBAI, then the terminal acetonide group was selectively hydrolysed and the resultant diol was protected as a carbonate to give **111** in 80% yield over 3 steps. DOWEX 50WXH resin promoted the cleavage of the remaining acetonide protecting group within **111** and the formation of methyl glycoside **112** in 20% yield (the other anomer was isolated in 52% yield). The hydroxyl moiety within **112** was activated as the triflate, using Tf_2O and pyridine, which was subsequently substituted with azide to give **113** in 88% yield. Deprotection of the carbonate functionality within **113** occurred in 80% yield and was followed by regioselective protection of the primary alcohol within **114** with benzoyl chloride to give **115** in 81% yield. Mesylation of **115** with MsCl in pyridine gave secondary mesylate **116** in 94% yield. Hydrolysis of benzoate ester within **116** with NaOMe in DMF, followed by ring-closure gave epoxide **117** in 82% yield. Epoxide **117** was reduced under H_2 with palladium black, then protected with benzyl chloroformate to give bicycle **118** in 43% yield. Treatment of **118** with TFA gave pyrrolidine **119** in 73% yield which could be fully deprotected to give target compound DMDP **6** in 70% yield (Scheme 13).



Scheme 13. *Reagents and Conditions*: (i) NaH, BnBr, Bu_4NI, THF, reflux, 45 min; (ii) aq HCl, MeOH, rt, 20 h; (iii) NaOMe, dimethyl carbonate, reflux, 3 h; (iv) DOWEX 50WXH, MeOH, reflux, 12 h; (v) Tf_2O, py, CH_2Cl_2, –30 °C, 20 min; (vi) NaN_3, DMF, 50 °C, 24 h; (vii) NaOMe, MeOH, rt, 6 h; (viii) BzCl, py, rt, 4 h; (ix) MsCl, py, rt, 4 h; (x) NaOMe, DMF, 50 °C, 3 h; (xi) H_2, Pd black, EtOH, 1 h then benzyl chloroformate, rt, 2 h; (xii) TFA, H_2O, rt, 15 min then $NaBH_4$, EtOH/H_2O (2:1 v/v), rt, 10 min; (xiii) H_2, Pd black, AcOH, rt, 13 h.

Donohoe and co-workers reported the synthesis of **6** from pyrrole using selective reduction conditions to give the pyrrolidine scaffold.[76] Double lithiation of commercially available *N*-Boc pyrrole **120** followed by addition of methyl chloroformate allowed for the synthesis of **121** in 78% yield. Reduction using Birch-like conditions followed by quenching with NH_4Cl gave an 86:14 mixture of diastereoisomers, with *trans*-**122** being the major component, which was isolated in 80% yield as a single compound (using 2,6-*di*-*tert*-butyl phenol as the proton source allowed for synthesis of the *cis* isomer exclusively, in 80% yield). Reduction of diester **122** with $LiBHEt_3$ followed by *O*-benzylation with BnBr and Ag_2O gave **123** in 37% yield, which allowed for the oxidation using OsO_4 to give tetrasubstituted pyrrolidine **124** in 90% yield. *O*-Silyl protection with TBSOTf and 2,6-lutidine gave **125** in 68% yield, which

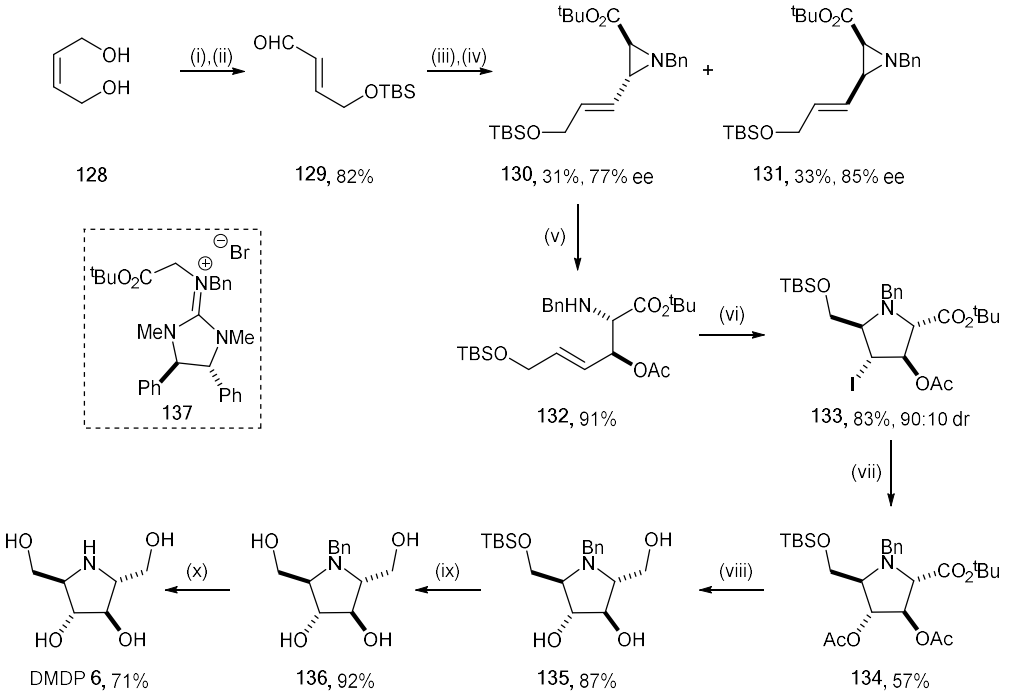
resulted in inversion of configuration at the stereocentre bearing the free alcohol functionality (*via* the triflate) to give acetate **126** in 59% yield. Basic hydrolysis removed the acetate protecting group and acidic conditions cleaved the *O*-silyl protecting group giving diol **127** in 71% yield. Hydrogenolysis followed by conc HCl in MeOH removed the *N*-Boc and *O*-benzyl protecting groups and gave DMDP **6** in 99% yield (Scheme 14).



Scheme 14. *Reagents and Conditions*: (i) LiTMP, methyl chloroformate, THF, –78 °C, 30 min; (ii) Li, NH_3, THF, –78 °C, 30 min then NH_4Cl; (iii) $LiBHEt_3$, THF, rt, 24 h; (iv) Ag_2O, BnBr, CH_2Cl_2, rt, 20 h; (v) OsO_4, NMO, quinuclidine, acetone/H_2O (4:1), rt, overnight; (vi) TBSOTf, 2,6-lutidine, CH_2Cl_2, –78 °C to rt, overnight; (vii) Tf_2O, py, CH_2Cl_2, 0 °C to rt, 1 h then KOAc, DMF, 18-crown-6, rt, 1 h; (viii) Na, MeOH, rt, 1 h; (ix) conc HCl, MeOH, rt, 1 h; (x) H_2, Pd/C, rt, 16 h; (xi) conc HCl, MeOH, rt, 24 h.

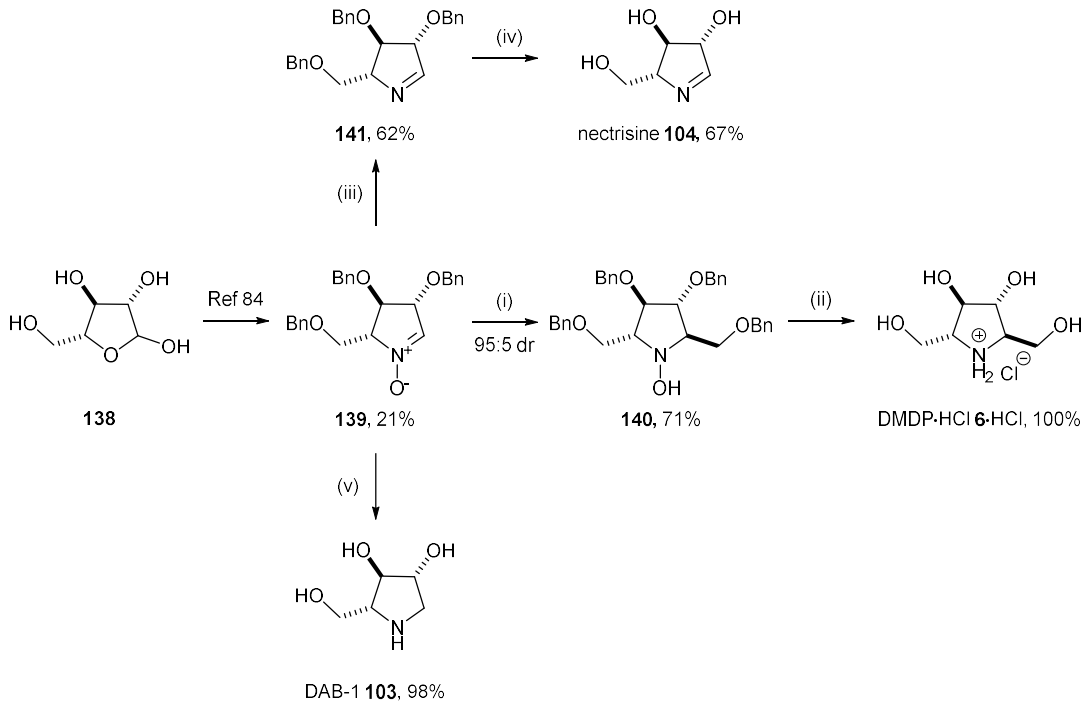
In 2012, Ishikawa *et al*. reported their synthesis of **6** from achiral starting materials using asymmetric aziridination.[80] Partial protection of *cis*-1,4-dihydroxybut-2-ene **128** with NaH and TBSCl followed by oxidative isomerisation using PCC gave unsaturated aldehyde *trans*-**129** in 82% yield. Treatment of **129** with guanidinium bromide **137** and tetramethylguanidine (TMG),[81] followed by Ac_2O gave aziridines *trans*-**130** and *cis*-**131** which could be isolated in 31% yield and 77% ee, and 33% yield and 85% ee, respectively. *trans*-Aziridine **130** could be ring-opened in acetic acid to give α-amino-β-acetoxy ester **132** in 91% yield. Treatment of **132** with I_2 and K_2CO_3 in EtOAc allowed for the 5-*exo*-trig[82]

iodocyclisation product **133** in 83% yield and 90:10 dr, which were subjected to a Prévost displacement with AgOAc/AcOH to give **134** in 57% yield as a single diastereoisomer [the aromatic pyrrole with loss of the C(3) and C(4) substituents was also isolated in 26% yield]. Reduction of the ester and acetate groups within **134** with $LiBH_4$ gave triol **135** in 87% yield, which could be *O*-desilylated with TBAF in 92% yield followed by hydrogenolysis to give DMDP **6** in 71% yield (Scheme 15).



Scheme 15. *Reagents and Conditions*: (i) NaH, TBSCl, THF, rt, 17 h; (ii) PCC, NaOAc, CH_2Cl_2, rt, 3.5 h; (iii) **137**, TMG, THF, rt, 17 h; (iv) Ac_2O, MeCN, rt, 1 h; (v) AcOH, rt, 1.5 h; (vi) I_2, K_2CO_3, EtOAc, –40 °C, 1 h; (vii) AgOAc, AcOH, 40 °C, 15 h; (viii) $LiBH_4$, THF, reflux, 10 h; (ix) TBAF, THF, rt, 0.5 h; (x) H_2, $Pd(OH)_2/C$; MeOH/HCl, rt, 1 h.

In 2008, Merino, Goti and co-workers reported their synthesis of a number of iminocyclitols including DMDP **6**, DAB-1 **103** and nectrisine **104** from sugars.[83] The work centres on the addition of organometallic reagents to chiral nitrones, e.g. **139**, which was synthesised from D-arabinose **138** in four steps using known methods.[84] Addition of $LiCH_2OBn$ to **139** occurred in 95:5 dr, giving **140** in 71% yield. Hydrogenolysis of **140** gave DMDP·HCl **6**·HCl in 100% yield. Direct hydrogenolytic reduction of nitrone **139** gave DAB-1 **103** in 98% yield. Deoxygenation of nitrone **139** with trimethyl phosphite gave **141** in 62% yield, which could be *O*-debenzylated to give nectrisine **104** in 67% yield (Scheme 16).



Scheme 16. *Reagents and Conditions*: (i) $LiCH_2OBn$, THF, –80 °C, 15 min; (ii) H_2 (20 atm), $Pd(OH)_2/C$, HCl/MeOH, rt, 6 h; (iii) $P(OMe)_3$, PPh_3, Et_3N, reflux, 4 h; (iv) BCl_3, CH_2Cl_2, –78 °C to –40 °C, 3 h; (v) H_2, Pd/C, rt, 15 h then DOWEX WX8200.

1.6 Thesis Aims

This thesis describes the synthesis of three families of amino polyols: acyclic 3-deoxy-3-aminosphingoid bases, fagomines and codonopsinols. The syntheses of the 3-deoxy-3-aminosphingoid bases (e.g., **146**) and fagomines (e.g., **149**) relies on the diastereoselective addition of chiral lithium amide reagents to α,β-unsaturated esters **142**. The synthesis of the codonopsinol family (e.g., **153**) relies on the addition of aryl Grignard reagents to a chiral *N*-sulfinyl imine **150** derived from tartaric acid. The synthesis of all of the members of the codonopsinol family will allow for a confirmation of their chemical structure (Figure 9).

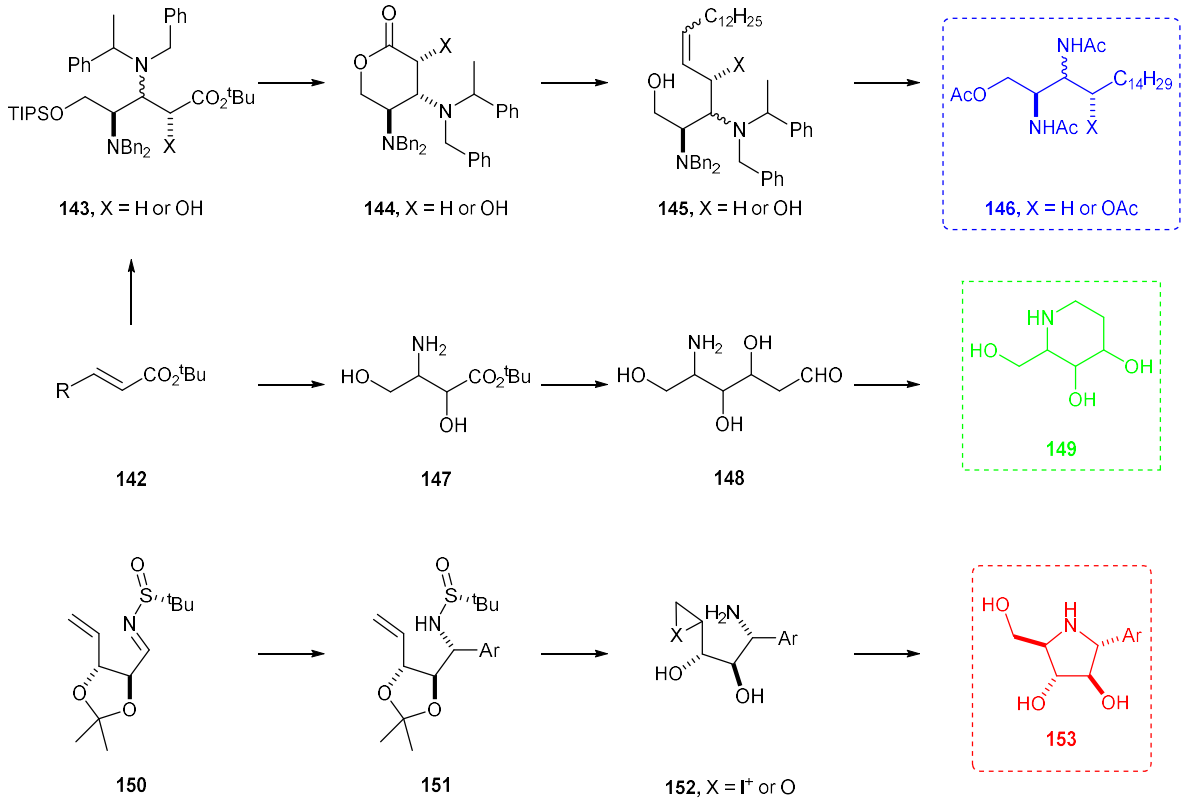


Figure 9. Thesis aims.

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Chapter 2: Asymmetric Synthesis of 3-Deoxy-3-Aminosphingoid Bases

2.1 Chapter Overview

This chapter details the asymmetric synthesis of three 3-deoxy-3-aminosphingoid bases *viz*. 3-deoxy-3-aminosafingol, 3-deoxy-3-aminophytosphingosine and 3-deoxy-3-aminosphinganine, all derived from L-serine. Installation of the stereogenic centres relies on diastereoselective conjugate addition or aminohydroxylation methodologies and Wittig or Julia procedures were used to lengthen the carbon chain.

2.2 Initial Proposal

It was originally envisaged that addition of a chiral lithium amide to α,β-unsaturated ester **154** would give β,γ-diamino ester **154** which could be lactonised to give **156**. Reduction of **156** and olefination to give a mixture of olefins (*E*)-**157** and (*Z*)-**158**, followed by deprotection and acetylation would then give the target compound **159** (Figure 10).

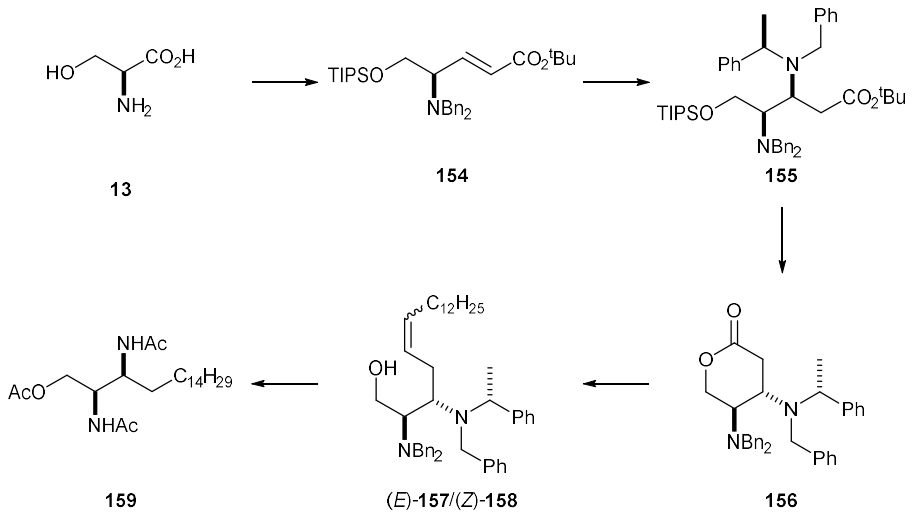
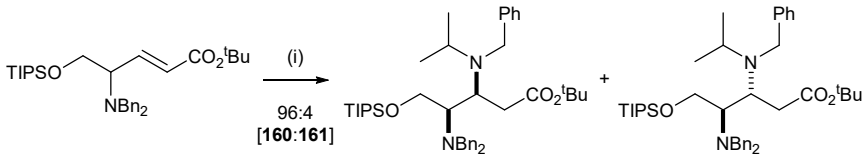


Figure 10. Proposed synthetic route to peracetylated 3-deoxy-3-aminosafingol **159**.

2.3 Previous Work

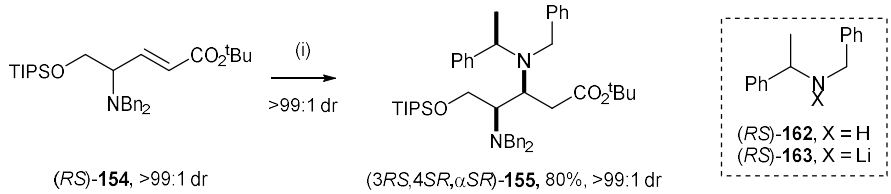
Previous work by Davies *et al*. showed that peracetylated 3-deoxy-3-aminosafingol **159** could be synthesised from enantiopure α,β-unsaturated ester (*R*)-**154** (derived from L-serine) using

lithium amide conjugate addition methodology as the stereodefining step.[1] Lithium *N*-isopropyl-*N*-benzylamide has been shown to be a good achiral model to probe the substrate control of conjugate addition of enantiopure α-methylbenzyl-derived amides (*vide infra*).[2] Therefore the addition of lithium *N*-benzyl-*N*-isopropylamide to (*RS*)-**154** was attempted. Addition of lithium *N*-isopropyl-*N*-benzylamide to **154** gave a 96:4 mixture of **160** and **161**, respectively, from which the major component **160** was isolated in 57% yield and >99:1 dr and the minor component **161** was isolated in 2% yield and >99:1 dr. This shows that the substrate control for addition of an achiral lithium amide reagent to α,β-unsaturated ester **154** was in favour of 3,4-*syn* addition (Scheme 17).[1]



Scheme 17. *Reagents and Conditions*: (i) lithium *N*-isopropyl-*N*-benzylamide, THF, –78 °C, 2 h.

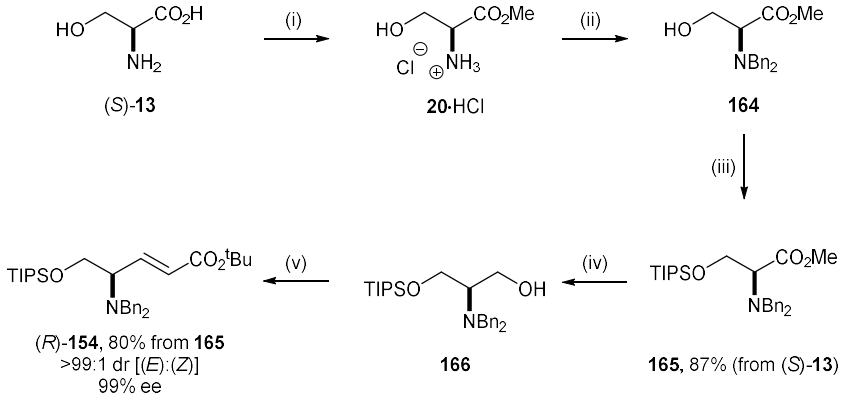
Given the high level of substrate control shown and the known, high diastereoselectivity of lithium amide reagents[3] a mutual kinetic resolution (MKR) was also attempted and showed high enantiorecognition. Addition of (*RS*)-**163** [created by deprotonation of (*RS*)-**162** with BuLi] to α,β-unsaturated ester (*RS*)-**154** gave a ^{1}H NMR spectrum of the crude reaction mixture which displayed signals consistant with high diastereoselectivity (>99:1 dr) from which (3*RS*,4*SR*,α*SR*)-**155** was isolated in 80% yield and >99:1 dr (Scheme 18).[1]



Scheme 18. *Reagents and Conditions*: (i) (*RS*)-**163**, THF, –78 °C, 2 h.

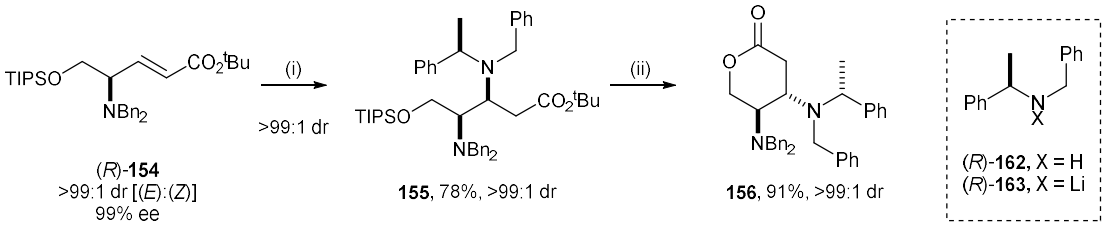
Given these two results, the synthesis of 3-deoxy-3-aminosafingol was attempted.[1] Homologation of L-serine (*S*)-**13** to α,β-unsaturated ester (*R*)-**154** [derived from L-serine (*vide*

infra)], using a telescoped procedure, began with esterification, chemoselective *N*-benzylation and *O*-silylation which gave **165** in 87% yield. Reduction of **165** followed by oxidation and olefination gave the required enantiopure α,β-unsaturated ester (*R*)**-154** in 80% yield and >99:1 dr (Scheme 19).



Scheme 19. *Reagents and conditions*: (i) AcCl, MeOH, reflux, 3 h; (ii) K_2CO_3, BnBr, MeCN, rt, 24 h; (iii) imidazole, TIPSCl, DMF, rt 16 h; (iv) DIBAL-H, PhMe, –78 °C, 1 h; (v) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 1 h then Et_3N, –78 °C, 20 min then rt, 20 min, then $Ph_3PCHCO_2{}^tBu$ **167**, CH_2Cl_2, rt, 18 h.

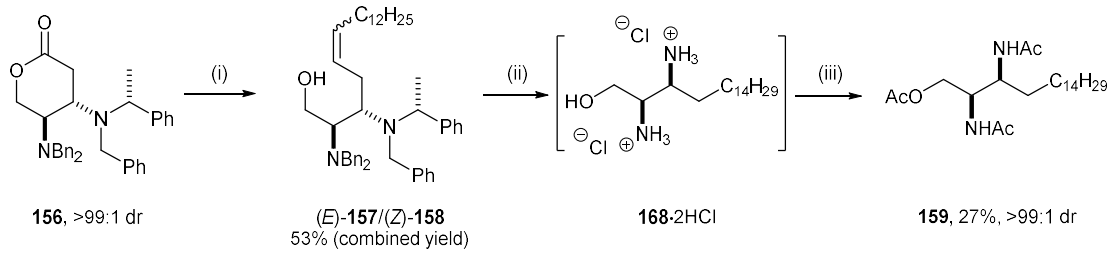
The doubly diastereoselective addition of enantiopure lithium amide (*R*)**-163** to enantiopure (*R*)**-154** occurred with high diastereoselectivity, giving only **155**, which was isolated in 78% yield and >99:1 dr. Deprotection of the silyl protecting group with TBAF occurred with concomitant lactonisation in 24 h to give lactone **156** in 91% yield as a single diastereoisomer (Scheme 20).[1]



Scheme 20. *Reagents and conditions*: (i) (*R*)**-163**, THF, –78 °C, 2 h; (ii) TBAF, THF, rt, 24 h.

Reduction of lactone **156**, with DIBAL-H, and subsequent olefination with the ylide derived from tridecylphosphonium bromide occurred in 53% yield as a mixture of olefin isomers with an undetermined diastereomeric ratio. Tandem hydrogenation/hydrogenolysis followed by

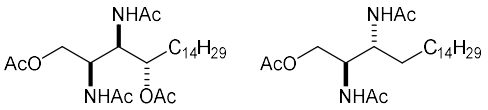
acetylation gave peracetylated 3-deoxy-3-aminosafingol **159** in 27% yield from a mixture of (*E*)-**157** and (*Z*)-**158**, and 7% overall yield from L-serine (*S*)-**13** (Scheme 21).[1]



Scheme 21. *Reagents and conditions* (i) DIBAL-H, PhMe, –78 °C, then $[C_{13}H_{27}PPh_3]^+[Br]^-$, BuLi, reflux, 1 h; (ii) H_2, $Pd(OH)_2/C$, 1.25 M HCl in MeOH, rt, 48 h; (iii) Ac_2O, py, DMAP, rt, 18 h.

2.4 Project Aims

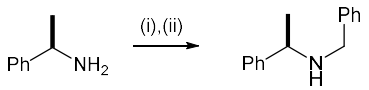
Although the initial work into the synthesis of peracetylated 3-deoxy-3-aminosafingol **159** was completed the route remained unoptimised. Therefore, the initial aim of this project was to optimise the final steps of the synthesis of **159** and also apply this methodology to the synthesis of peracetylated 3-deoxy-3-aminophytosphingosine **169** and peracetylated 3-deoxy-3-aminosphinganine **170** (Figure 11).



169 170

Figure 11. Peracetylated 3-deoxy-3-aminophytosphingosine **169** and 3-deoxy-3-aminosphinganine **170**.

The requisite enantiopure amine (*R*)-**162** was made *via* reductive amination of (*R*)-α-methylbenzylamine (*R*)-**171** with benzaldehyde, using $NaBH_4$ as the reducing agent, in 73% yield. Secondary amine (*R*)-**162** was determined to be >95:5 er from ^{1}H NMR spectroscopic analysis in the presence of the chiral solvating agent (*S*)-*O*-acetylmandelic acid, and comparison with an authentic racemic sample. However, given that primary amine **171** was deemed to be 98% ee and that no racemisation has previously been observed it can be assumed that (*R*)-**162** has an enantiomeric excess of 98% (Scheme 22).



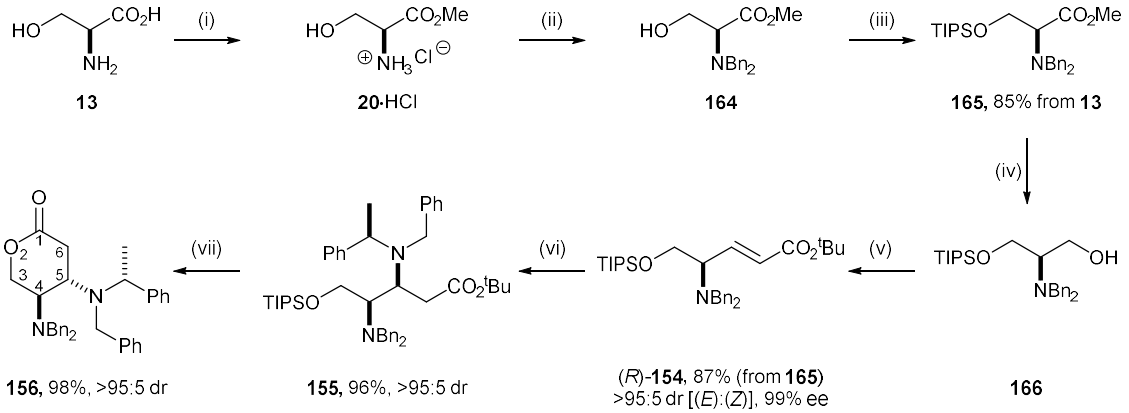
(*R*)-**171**, 98% ee (*R*)-**162**, 73%, 98% ee

Scheme 22. *Reagents and Conditions*: (i) PhCHO, EtOH, 78 °C, 2 h; (ii) $NaBH_4$, 0 °C to rt, 48 h.

2.5 Doubly Diastereoselective Conjugate Addition

α,β-Unsaturated ester (*R*)-**154** was synthesised *via* the established route[1] from L-serine. Esterification of L-serine (*S*)-**13** with AcCl in MeOH gave methyl serine hydrochloride **20**·HCl which was followed by chemoselective *N*-benzylation with BnBr and K_2CO_3 in MeCN to give **164** then *O*-silylation with TIPSCl, imidazole and DMAP in CH_2Cl_2 gave fully protected serine (*S*)-**165** in 85% yield over three steps. Reduction of **165** with DIBAL-H in PhMe gave alcohol **166** which could be subjected to a one-pot Swern oxidation-olefination procedure with **167** (which was synthesised in 89% yield from *tert*-butyl bromoacetate and PPh_3) to give α,β-unsaturated ester (*R*)-**154** in 87% yield, as a single diastereoisomer, from ester **165**. Chiral HPLC analyses of (*RS*)-**154** and (*R*)-**154** allowed the enantiomeric purity of the sample of (*R*)-**154** to be determined as 99% ee. With enantiopure (*R*)-**154** in hand, the well-established Davies lithium amide conjugate addition methodology could be employed. Conjugate addition of lithium amide (*R*)-**163** [generated from the treatment of secondary amine (*R*)-**162** with BuLi] to (*R*)-**154** gave β,γ-diamino ester **155** as the only observable diastereoisomer in the crude reaction mixture, which was isolated in 96% yield and >95:5 dr. Following previous work,[1] *O*-silyl deprotection of **155** upon treatment with TBAF in THF proceeded with concomitant lactonisation to give, after purification, lactone **156** in 98% yield and >95:5 dr (Scheme 23). In order to understand the conformation of **156**, analysis of the ^{1}H NMR ^3J coupling constants within **156** was considered. The quartet multiplicity of the C(5)*H* resonance within **156** indicates that the coupling between C(5)*H* with both C(4)*H* and C(6)H_2 are similar in magnitude, suggesting axial-equatorial and equatorial-equatorial interactions (^3J = 4.7 Hz). A large coupling constant representing an axial-axial relationship is absent. Therefore, the ^{1}H NMR ^3J coupling constants within **156** was consistent with the lactone

adopting a half-chair conformation in solution with the bulky amino substituents adopting a pseudo-diaxial relationship, presumably to minimise 1,2-strain.

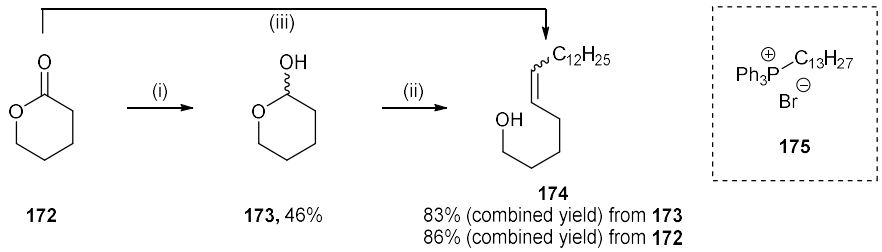


Scheme 23. *Reagents and Conditions*: (i) AcCl, MeOH, 70 °C, 3 h; (ii) BnBr, K_2CO_3, MeCN, rt, 36 h; (iii) TIPSCl, imidazole, DMAP, CH_2Cl_2, rt, 36 h; (iv) DIBAL-H, PhMe, –78 °C, 1 h; (v) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 1 h then Et_3N, –78 °C, 20 min then rt, 20 min then $Ph_3PCHCO_2{}^tBu$ **167**, rt, 18 h; (vi) (*R*)-**163**, THF, –78 °C, 2 h; (vii) TBAF, THF, 0 °C to rt, 24 h.

2.6 Elaboration to Peracetylated 3-Deoxy-3-Aminosafingol 159

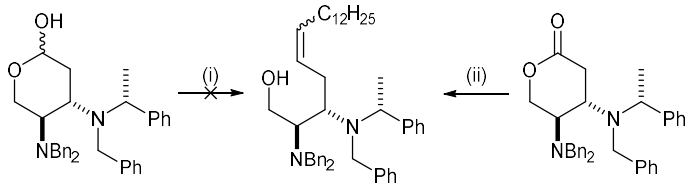
2.6.1 One-pot Reduction/Wittig Olefination Optimisation – Previous Work

Previously, the initial exploration of the lactone olefination started on a model system, δ-valerolactone **172**, where it was shown that reduction with DIBAL-H gave lactol **173** in 46% yield, which could be olefinated when treated with BuLi in THF then the ylide derived from **175** to give olefin **174** in 83% yield. A one-pot procedure was also attempted whereby reduction of δ-valerolactone followed by addition of ylide in THF gave olefin **174** in 86% yield (Scheme 24).[1]



Scheme 24. *Reagents and conditions*: (i) DIBAL-H, CH_2Cl_2, –78 °C, 30 min; (ii) BuLi, THF, –78 °C, 1 h then **175**, BuLi, reflux, 1 h; (iii) DIBAL-H, PhMe, –78 °C, then **175**, BuLi, THF, reflux, 1 h.

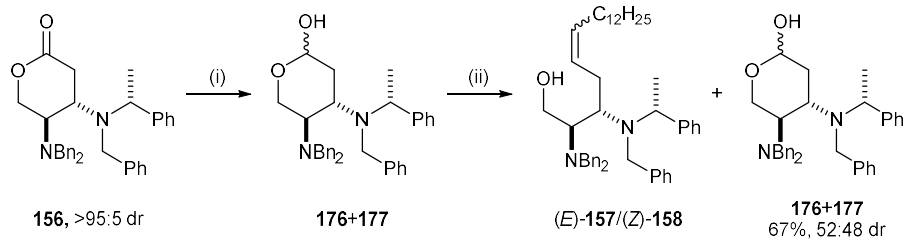
Attempted reduction/olefination of lactone **156** *via* both routes showed that the one-pot procedure gave a mixture of olefins (*E*)-**157** and (*Z*)-**158** in 53% combined yield however the stepwise reduction then olefination gave a mixture containing returned starting material **176** and **177**, the phosphonium salt and unidentified impurities, from which a mixture of epimeric lactols **176** and **177** was isolated in 40% combined yield (Scheme 25).[1]



Scheme 25. *Reagents and conditions* (i) BuLi, THF, –78 °C, 1 h then $[C_{13}H_{27}PPh_3]^+[Br]^-$, BuLi, reflux, 1 h; (ii) DIBAL-H, PhMe, –78 °C, then **175**, BuLi, THF, reflux, 1 h.

2.6.2 One-pot Reduction/Wittig Olefination Optimisation

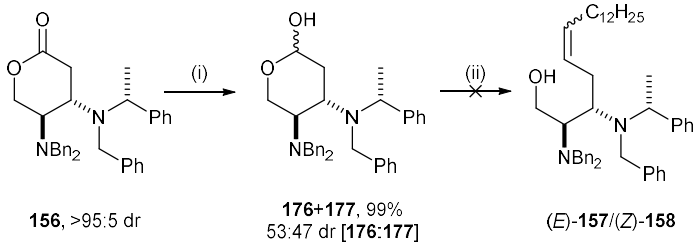
It seemed that the DIBAL-H present in the one-pot procedure was critical to allow the olefination to occur however the reaction parameters needed to be explored further. Firstly, a stepwise procedure was attempted: reduction of **156** with DIBAL-H gave lactols **176** and **177**. After workup, this mixture was treated with DIBAL-H in THF followed by the ylid derived from **175**, which gave starting material **176** and **177** in 67% isolated yield and 52:48 dr (Scheme 26).



Scheme 26. *Reagents and conditions* (i) DIBAL-H, CH_2Cl_2, –78 °C, 30 min; (ii) DIBAL-H, THF, –78 °C, 1 h then **175**, BuLi, reflux, 1 h.

This procedure was also attempted with a sample of purified lactols **176** and **177**, which were synthesised from **156** in 99% yield and 53:47 dr. Once again, treatment of **176** and **177** with

DIBAL-H followed by the ylide derived from **175** gave no sign of the target olefins in the complex ^{1}H NMR spectrum of the crude reaction mixture (Scheme 27).



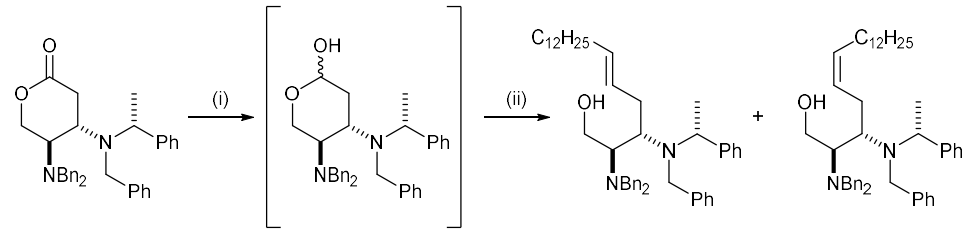
156, >95:5 dr

176+**177**, 99%
53:47 dr [**176**:**177**]

(*E*)-**157**/(*Z*)-**158**

Scheme 27. *Reagents and conditions* (i) DIBAL-H, CH_2Cl_2, –78 °C, 30 min; (ii) DIBAL-H, PhMe, –78 °C, 1 h then **175**, BuLi, THF, reflux, 1 h.

As the stepwise procedure seemed unproductive the one-pot procedure was further investigated. It was suggested that the solvent system for the one-pot reaction maybe crucial and upon optimising this reaction it was noted that phosphonium salt $[C_{13}H_{27}PPh_3]^+[Br]^-$ is insoluble in PhMe therefore the one-pot procedure could not be carried out solely in PhMe. Initial attempts using PhMe as the solvent for the reduction and THF as the solvent for the deprotonation of the phosphonium salt, in a 1:1 (v/v) ratio gave olefins (*E*)-**157** and (*Z*)-**158** in 15% combined yield and ~57:43 dr. However, upon changing to a 2:1 (v/v) mixture of PhMe and THF, respectively, and increasing the concentration of the reaction olefins (*E*)-**157** and (*Z*)-**158** were isolated as an inseparable ~65:35 mixture in 31% combined yield. An impure sample of the olefins was also isolated in ~14% yield (27:73 dr). Reducing the amount of DIBAL-H from 1.5 to 1.05 equivalents increased the combined isolated yield of (*E*)-**157** and (*Z*)-**158** to 73% in 50:50 dr (Scheme 28).



156 **176+177** (*E*)-**157** (*Z*)-**158**

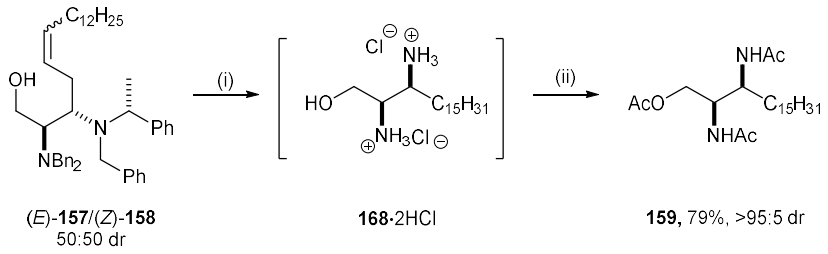
DIBAL-H / equiv	Time / h	Concentration / M	Solvent Ratio (PhMe/THF)	Combined yield of **157** and **158** / %
1.5	1	0.132	2:1	53[1]
1.5	1	0.05	1:1	15 (~57:43 dr)
1.5	1	0.103	2:1	31[a] (~65:35 dr)
1.05	1	0.108	2:1	73 (50:50 dr)

Scheme 28. *Reagents and Conditions*: (i) DIBAL-H, PhMe, –78 °C, 1 h; (ii) BuLi, **175**, THF, 80 °C, 1 h. {[a] An impure sample of (*E*)-**157** and (*Z*)-**158** was also isolated in ~14% yield and 27:73 dr [(*E*):(*Z*)]}.

The diastereomeric ratio was determined by integration of the C(α)*Me* proton resonances in the ^{1}H NMR spectrum. Peak overlap in the ^{1}H NMR spectrum of the isolated material did not allow ^{3}J coupling constant analysis although the ^{13}C NMR chemical shifts of the allylic carbon atoms [C(4) and C(7)] within (*E*)-**157** and (*Z*)-**158** were consistent with the presence of olefin isomers. The chemical shift values associated within (*Z*)-**158** were ~5 ppm lower than the corresponding resonances for (*E*)-**157**. This is consistent with the γ-steric effect which, due to the steric compression of γ-substituents, accounts for the deshielding of the ^{13}C NMR resonances of the allylic carbons (i.e. higher δ_C) in the (*E*)-isomer when compared to the (*Z*)-isomer.[4,5]

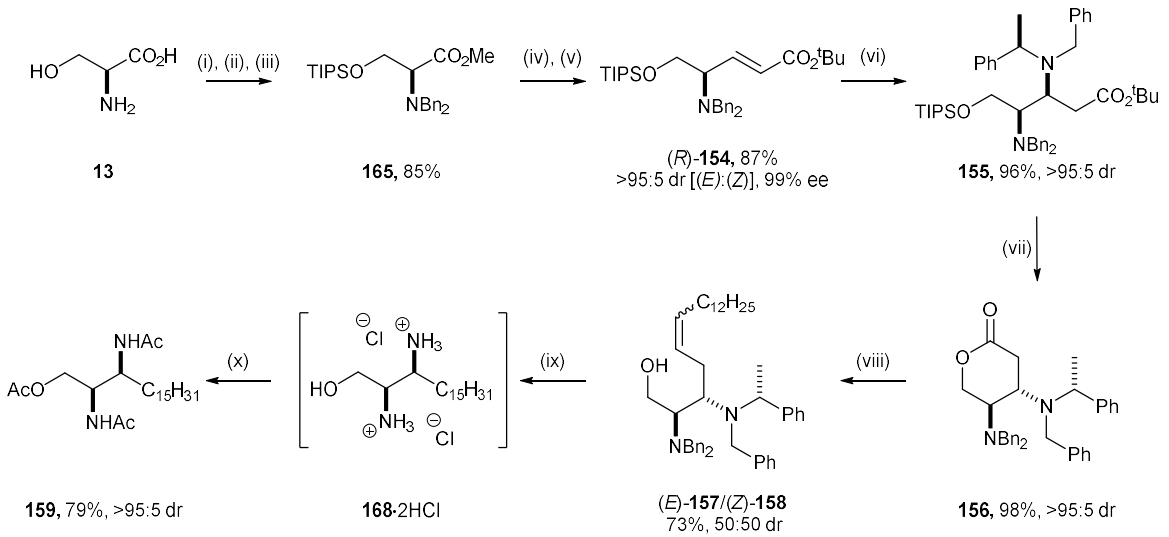
2.6.3 Deprotection

Increasing the time of the tandem hydrogenolysis/hydrogenation reaction from 48 to 72 h allowed for complete deprotection and gave a white solid with >500% mass return, which gave an uninterpretable ^{1}H NMR spectrum. Subsequent acetylation with Ac_2O and DMAP in pyridine for 72 h (increased by 18 h) gave *N*,*N*,*O*-triacetyl 3-deoxy-3-aminosafingol **159** in 79% yield [from (*E*)-**157** and (*Z*)-**158**] (Scheme 29). The convergence of the 50:50 mixture of (*E*)-**157** and (*Z*)-**158** into single compound **159** in 79% yield gives further support to the assignment of (*E*)-**157** and (*Z*)-**158** as olefin isomers.



Scheme 29. *Reagents and Conditions*: (i) $Pd(OH)_2/C$ (50% w/w), H_2 (5 atm), 1.25 M HCl in MeOH, rt, 72 h; (ii) Ac_2O, DMAP, py, rt, 72 h.

Peracetylated 3-deoxy-3-aminosafingol **159** was thus synthesised in 40% yield over 10 steps from commercially available L-serine (*S*)-**13** using the doubly diastereoselective 'matched' conjugate addition of lithium amide (*R*)-**163** to α,β-unsaturated ester (*R*)-**154** followed by lactonisation, one-pot reduction/olefination then global reductive deprotection/hydrogenation and peracetylation (Scheme 30).



Scheme 30. *Reagents and Conditions*: (i) AcCl, MeOH, 70 °C, 3 h; (ii) BnBr, K_2CO_3, MeCN, rt, 36 h; (iii) TIPSCl, imidazole, DMAP, CH_2Cl_2, rt, 36 h; (iv) DIBAL-H, PhMe, –78 °C, 1 h; (v) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 1 h then Et_3N, –78 °C, 20 min then rt, 20 min then $Ph_3PCHCO_2{}^tBu$ **167**, rt, 18 h; (vi) (*R*)-**163**, THF, –78 °C, 2 h; (vii) TBAF, THF, 0 °C to rt, 24 h; (viii) DIBAL-H, PhMe, –78 °C, 1 h then BuLi, **175**, THF, 80 °C, 1 h; (ix) $Pd(OH)_2/C$, H_2 (5 atm), 1.25 M HCl in MeOH, rt, 72 h ; (x) Ac_2O, DMAP, py, rt, 72 h.

2.7 Synthesis of Peracetylated 3-Deoxy-3-Aminophytosphingosine 169

After the successful synthesis of **159** it was envisaged the synthesis of 3-deoxy-3-aminophytosphingosine **169** could be achieved using an analogous synthetic route using the Davies aminohydroxylation procedure[6] to install the 3,4-*anti* amino alcohol moiety. Addition of lithium amide (*R*)-**163** to α,β-unsaturated ester (*R*)-**154** followed by oxidation with

camphorsulfonyloxaziridine (CSO) **182** would give **178** which could be *O*-silyl deprotected and lactonised to give lactone **179**. A one-pot reduction/olefination of **179** would give (*E*)**-180** and (*Z*)**-181** which could be converted to **169** under tandem hydrogenation/hydrogenolysis and peracetylation (Figure 12).

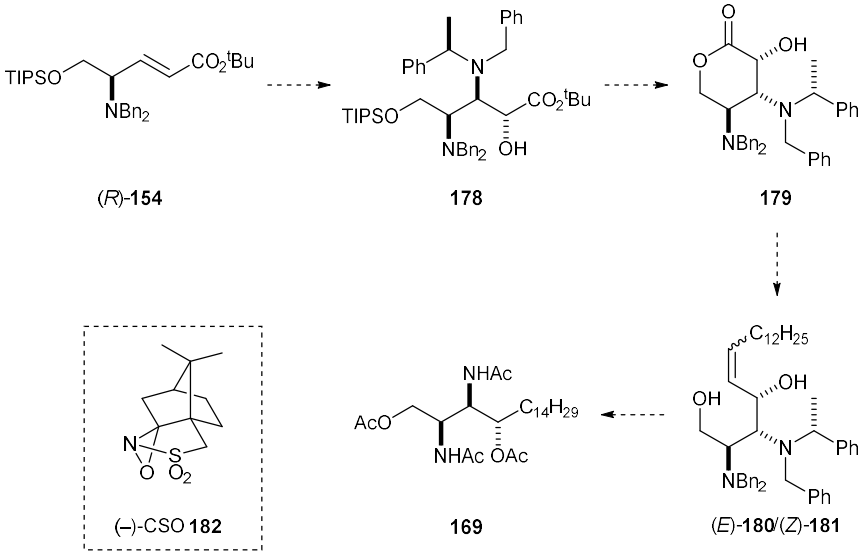
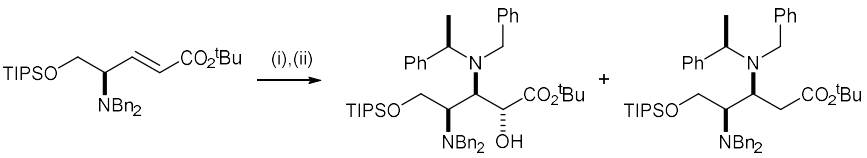


Figure 12. Proposed synthesis of peracetylated 3-deoxy-3-aminophytosphingosine **169**.

2.7.1 Previous Work

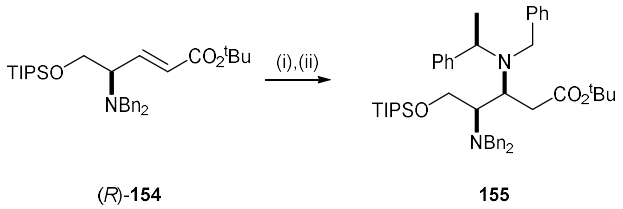
The aminohydroxylation of (*R*)**-154** had been probed previously and was shown to need a high concentration to allow for effective α-oxidation of the enolate that forms after addition (Scheme 31).[1]



Concentration of (–)-CSO **182** / M	Crude ratio (**178**:**155**)	Isolated Yield / % (**178**:**155**)
0.2	50:50	40:37
0.3	58:42	57:17
0.6	66:33	57:16
0.8	76:24	62:11

Scheme 31. *Reagents and Conditions*: (i) (*R*)**-163**, THF, –78 °C, 2 h; (ii) (–)-CSO **182**, –78 °C to rt, 18 h.

Furthermore it was discovered that using (+)-CSO **182** as the reagent for the enolate oxidation results in **155** only in the ^{1}H NMR spectrum of the crude reaction mixture, and no sign of **178** or its C(2)-epimer (Scheme 32).[1]

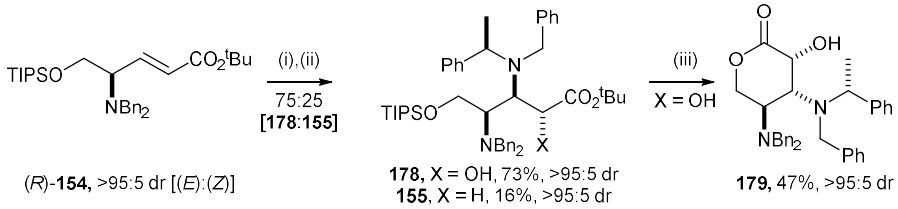


(*R*)-**154** **155**

Scheme 32. *Reagents and Conditions*: (i) (*R*)-**163**, THF, –78 °C, 2 h; (ii) (+)-CSO **182**, –78 °C to rt, 18 h.

2.7.2 Lactone/Wittig Protocol

Addition of lithium amide (*R*)-**163** upon (*R*)-**154** followed by oxidation of the resultant lithium (*Z*)-β,γ-diamino enolate[7] by (–)-CSO **182**[6] gave a 75:25 mixture of **178** and **155** (resulting from protonation of the enolate), respectively, from which **178** was isolated in 73% yield and >95:5 dr and **155** was isolated in 16% yield and >95:5 dr.[8] *O*-Desilylation with TBAF occurred with concomitant cyclisation to give **179** in a modest 47% yield as a single diastereoisomer (Scheme 33).

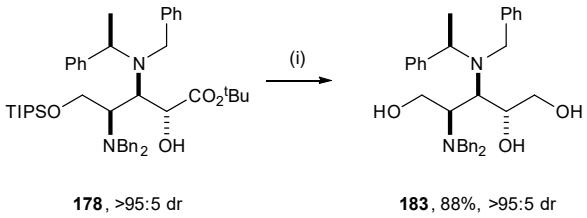


(*R*)-**154,** >95:5 dr [(*E*):(*Z*)] **178,** X = OH, 73%, >95:5 dr; **155**, X = H, 16%, >95:5 dr **179,** 47%, >95:5 dr

Scheme 33. *Reagents and Conditions*: (i) (*R*)-**163**, THF, –78 °C, 2 h; (ii) (–)-CSO **182**, –78 °C to rt, 18 h; (iii) TBAF, THF, 0 °C to rt, 18 h.

The relative configuration within **178** was established *via* single crystal X-ray diffraction analysis of a triol derivative **183**, which was synthesised by treating **178** with $LiAlH_4$ in THF and was isolated in 88% yield and >95:5 dr (Scheme 34).[9] The absolute (*R*,*R*,*R*,*R*)-configuration within **183** was assigned by reference to the known (*R*)-configuration of the α-methylbenzyl stereocentre. A Flack *x* parameter[10,11] of –0.1(3) for the crystal structure of **183** confirmed this assigned absolute (*R,R,R,R*)-configuration (Figure 13).[9] This also

unambiguously confirms the configuration within **155** as both **155** and **178** are derived from the same β,γ-diamino enolate upon either protonation or oxidation, respectively.



178, >95:5 dr **183**, 88%, >95:5 dr

Scheme 34. *Reagents and Conditions*: (i) $LiAlH_4$, THF, 0 °C to rt, 18 h.

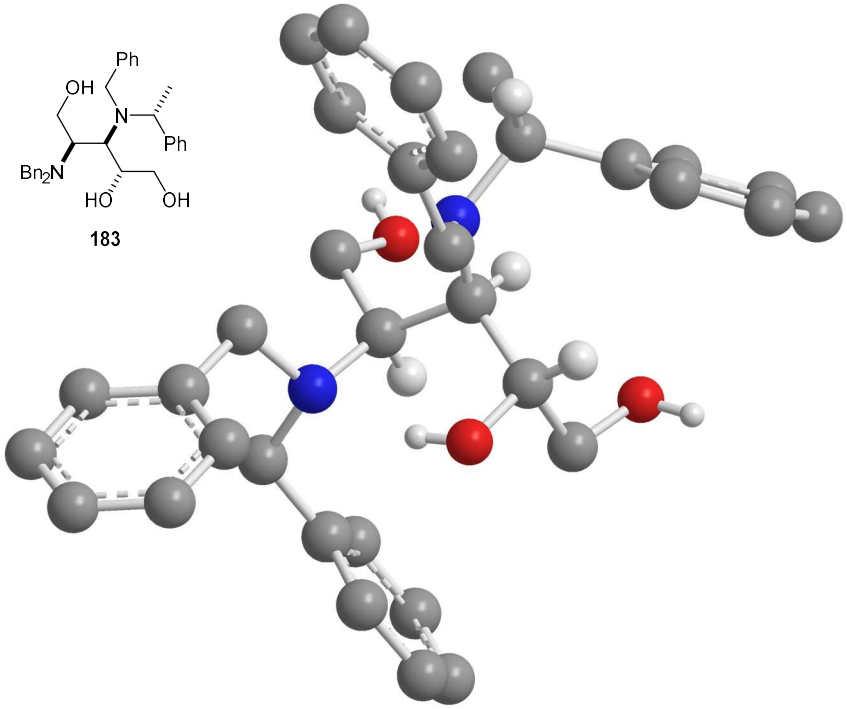
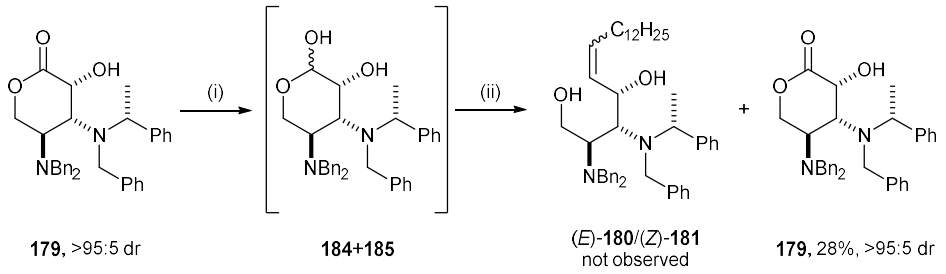


Figure 13. X-ray crystal structure of (*R*,*R*,*R*,*R*)-**183** (selected H atoms are omitted for clarity).

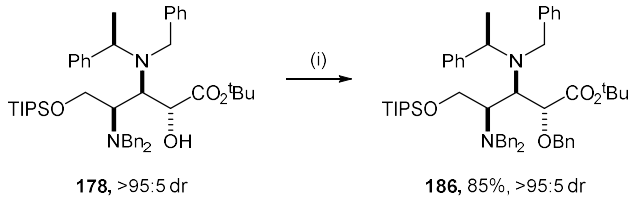
The one-pot reduction/Wittig olefination that was utilised in the synthesis of **159** was next attempted on lactone **179** to enable the synthesis of peracetylated 3-deoxy-3-aminophytosphingosine **169**. Attempts at a one-pot reduction/olefination procedure using DIBAL-H and the ylide derived from **175** based on the optimised conditions developed previously resulted in a complex mixture from which the starting lactone **179** was isolated in 28% yield and >95:5 dr. Attempts at varying DIBAL-H equivalents produced complex mixtures within which no olefin was observed by ^{1}H NMR spectroscopic analysis (Scheme 35).



Scheme 35. *Reagents and Conditions*: (i) DIBAL-H, PhMe, –78 °C, 1 h; (ii) BuLi, **175**, THF, 80 °C, 1 h.

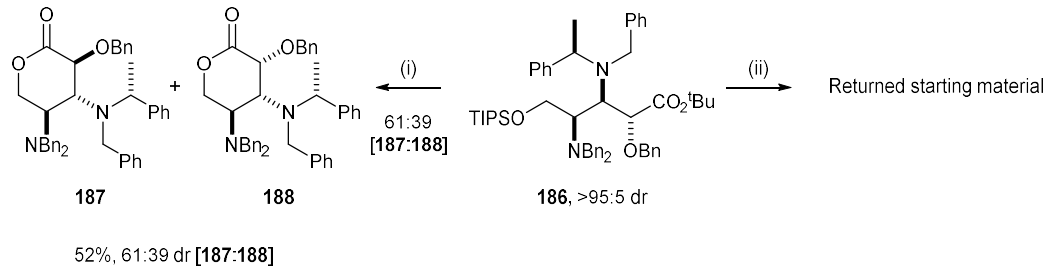
2.7.3 *O*-Benzyl Protected Lactone Synthesis

It was hypothesised that the failure of the one-pot reduction/Wittig reaction could be down to the chelation of metal ions between the oxygen atoms of the lactol, favouring the ring-closed lactol over the open-chain aldehyde, which is needed for olefination to occur. It was thought that *O*-benzylation would disfavour this chelate and so may allow olefination to occur. Therefore **178** was treated with NaH in THF and the subsequent anion was alkylated with BnBr to give *O*-benzylated diamino ester **186** in 85% yield and >95:5 dr (Scheme 36).



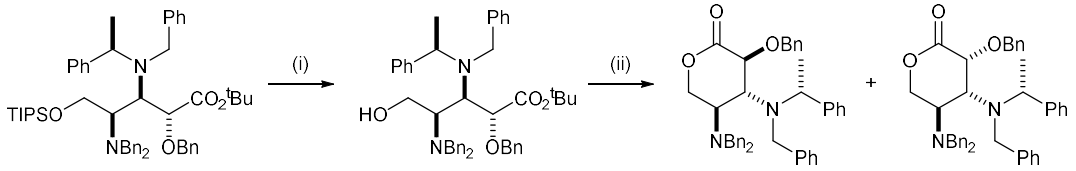
Scheme 36. *Reagents and Conditions*: (i) NaH, THF, 0 °C, 30 min then BnBr, 0 °C to rt, 24 h.

Using the same conditions for *O*-desilylation/lactonisation with TBAF gave a 61:39 mixture of lactone diastereoisomers **187** and **188**, respectively, which were isolated as an inseperable mixture in 52% yield and 61:39 dr. Attempts to supress the epimerisation using an AcOH-buffered TBAF procedure gave only starting material **186** (Scheme 37).



Scheme 37. *Reagents and Conditions*: (i) TBAF, THF, 0 °C to rt, 24 h; (ii) TBAF, AcOH, THF, 0 °C to rt, 24 h.

An alternative deprotection/lactonisation strategy was required to try to overcome the epimerisation. Treatment of **186** with HF·py complex gave complete *O*-desilylation with no lactonisation, to give alcohol **189** in 77% yield and >95:5 dr. A range of lactonisation procedures was then trialled under both acidic and basic conditions. Alcohol **189** was treated with HBF_4 in CH_2Cl_2 however this gave a complex mixture of products from which starting material **189** was isolated in 30% yield as a single diastereoisomer, and a 50:50 mixture of **188**:**189** was isolated in 34% combined yield. Subjection of alcohol **189** to the original TBAF conditions also promoted epimerisation, giving a 50:50 mixture of the two lactone diastereoisomers which were isolated as an inseparable mixture in 52% yield and 50:50 dr. Treatment of **189** with NaH in THF was also attempted to promote lactonisation however this gave an 81:19 mixture of **187** and **188**, respectively, which was isolated in 56% yield and 81:19 dr (Scheme 38).

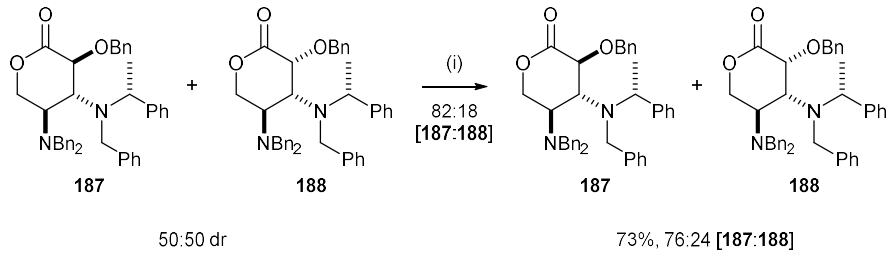


186, >95:5 dr **189**, 77%, >95:5 dr **187** **188**

Reagents	Conditions	Crude mixture	Yield
HBF_4, CH_2Cl_2	rt, 48 h	complex	**189**, 30%, >95:5 dr 34%, 50:50 (**188**:**189**)
TBAF, THF	0 °C to rt, 24 h	50:50 (**187**:**188**)	52%, 50:50 (**187**:**188**)
NaH, THF	0 °C to rt, 18 h	81:19 (**187**:**188**)	56%, 81:19 (**187**:**188**)

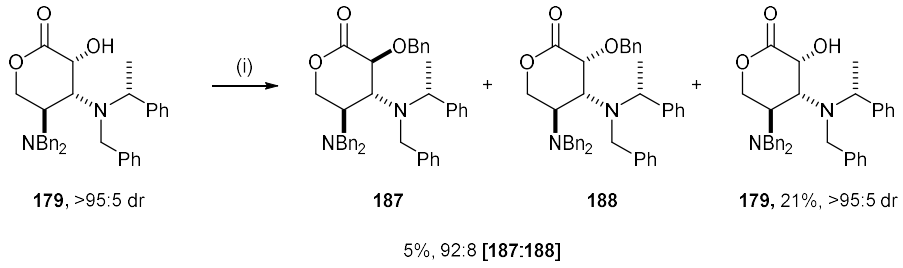
Scheme 38. *Reagents and Conditions*: (i) HF·py, THF, 0 °C to rt, 18 h; (ii) see table.

A 50:50 mixture of *O*-benzyl protected lactones **187** and **188**, respectively, was resubjected to the original TBAF conditions which resulted in an 82:18 mixture of **187** and **188**, respectively, which were isolated in 73% combined yield and 76:24 dr. This is consistent with a mechanism involving deprotection of **186**, subsequent cyclisation of the resultant δ-hydroxy ester, followed by epimerisation of lactone **188** into **187** under the original reaction conditions. It is on the basis of this mechanistic postulate that the configurations of both **187** and **188** were assigned (Scheme 39).



Scheme 39. *Reagents and Conditions*: (i) TBAF, THF, 0 °C to rt, 24 h.

Finally, *O*-benzylation of lactone **179** was attempted using NaH and BnBr. The alkylation was sluggish and the ^{1}H NMR spectrum of the crude mixture was complex. After exhaustive chromatographic purification, starting material **179** was isolated in 21% yield and >95:5 dr and a 92:8 mixture of **187** and **188**, respectively, was isolated in 5% yield (Scheme 40). This was also consistent with the proposition that the epimerisation was occurring at the lactone stage under various reaction conditions.



Scheme 40. *Reagents and Conditions*: (i) NaH, THF, 0 °C, 30 min then BnBr, 0 °C to rt, 18 h.

2.7.4 Synthesis of 169 *via* an Acyclic Procedure

Due to the inability to promote olefination of **179** and the reduced diastereomeric purity of the *O*-benzyl protected lactones, the lactone route was abandoned. A parallel synthetic route envisaged using a protocol involving olefination of the open-chain aldehyde **190** (Figure 14).

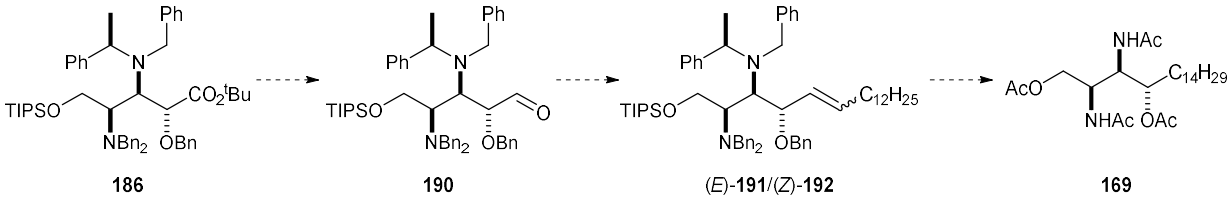
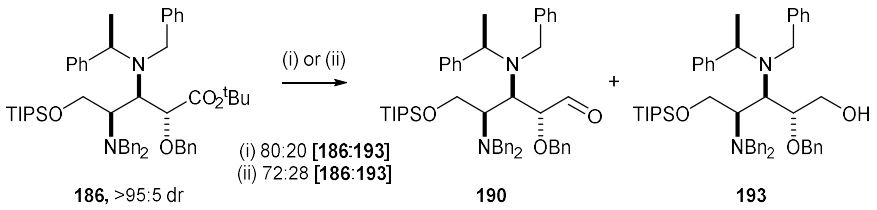


Figure 14. Alternative synthesis of peracetylated 3-deoxy-3-aminophytosphingosine **169**.

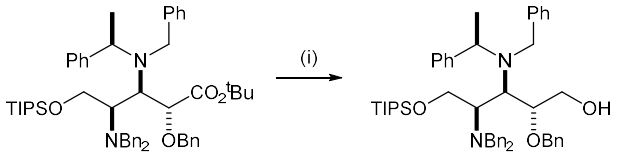
Despite β-amino aldehydes being potentially unstable with respect to polymerisation[12,13] it is known that α-*O*-substituted-β-amino aldehydes show greater stability. Attempts to reduce ester **186** to aldehyde **190** using DIBAL-H at –78 °C were unsuccessful under two sets of conditions, giving crude mixtures of starting material **186** and alcohol **193** in both cases (Scheme 41).



186, >95:5 dr **190** **193**

Scheme 41. *Reagents and Conditions*: (i) 1.1 equiv DIBAL-H, PhMe, –78 °C, 1 h then MeOH, –78 °C to rt; (ii) 3 equiv DIBAL-H, PhMe, –78 °C, 6 h, then MeOH, –78 °C to rt, then satd aq Rochelle salt, rt, 18 h.

A two-step reduction/oxidation procedure was pursued and, by increasing the temperature from –78 °C to rt, it was possible to reduce **186** fully to the corresponding alcohol **193** using DIBAL-H in PhMe. Following purification **193** was isolated in 87% yield as a single diastereoisomer (Scheme 42).

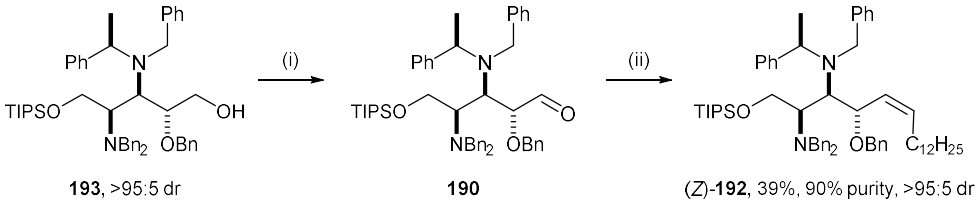


186, >95:5 dr **193**, 87%, >95:5 dr

Scheme 42. *Reagents and Conditions*: (i) DIBAL-H, PhMe, –78 °C to rt, 24 h.

Oxidation of alcohol **193** to aldehyde **190** was achieved with IBX in DMSO at rt. Purification of aldehyde **190** was not attempted, and it was subjected to Wittig olefination using the ylide derived from **175**. The conditions that were optimised for the formation of olefins (*E*)**-157** and (*Z*)**-158** were trialled although this resulted in formation of a complex mixture of products. When the reaction was run using THF as the only solvent, a complex mixture was also formed although this time a 90:10 ratio of olefin (*Z*)**-192** (^3J = 10.6 Hz) to starting material **190** was evident. Purification gave a sample of (*Z*)**-192** (~90% purity) in 39% isolated yield and

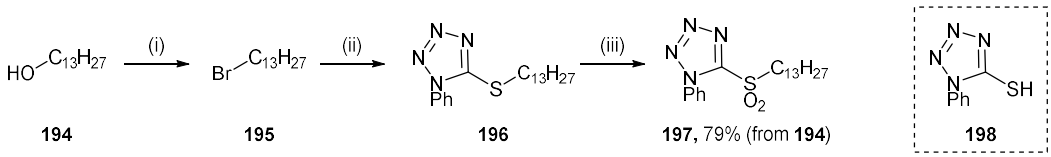
>95:5 dr. Allowing the reaction to stir at rt for 18 h gave a complex mixture with olefin (*Z*)-**192** as a minor component only (Scheme 43).



Scheme 43. *Reagents and Conditions*: (i) IBX, DMSO, rt, 18 h; (ii) BuLi, **175**, THF, 75 °C, 2 h.

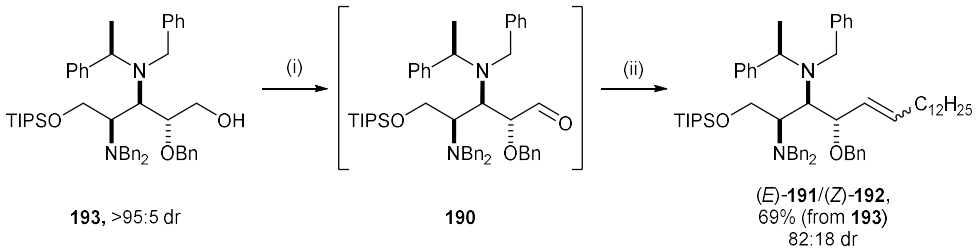
2.7.5 Julia-Kocienski Olefination

Next a Julia-Kocienski olefination procedure[14] was attempted. The requisite sulfone **197** was synthesised from tridecanol **194** in three steps: treatment of **194** with 48% aq HBr at 100 °C gave tridecyl bromide **195** which was treated with thiol **198** and K_2CO_3 in acetone to give sulfide **196**. Oxidation of sulfide **196** with H_2O_2 and catalytic ammonium molybdate gave sulfone **197** in 79% yield over 3 steps (Scheme 44).



Scheme 44. *Reagents and Conditions*: (i) 48% aq HBr, 100 °C, 18 h; (ii) **198**, K_2CO_3, acetone, 56 °C, 2.5 h; (iii) 30% aq H_2O_2, $(NH_4)_2Mo_7O_{24}{\cdot}4H_2O$, EtOH, 0 °C to rt, 18 h.

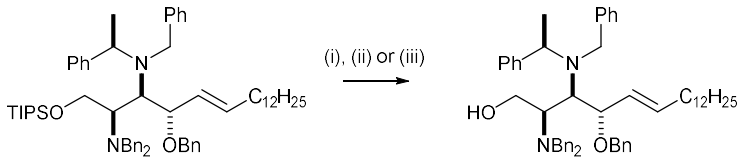
With sulfone **197** and aldehyde **190** in hand the Julia-Kocienski olefination was attempted. Treatment of **190** and **197** with LiHMDS in THF afforded a mixture of olefin isomers (*E*)-**191** and (*Z*)-**192** which were isolated in 69% combined yield (over two steps) and 82:18 dr (Scheme 45). It was not possible to identify the double bond geometry of either diastereoisomer due to overlapping signals however it was established *via* analysis of a derivative (*vide infra*).



Scheme 45. *Reagents and Conditions*: (i) IBX, DMSO, rt, 18 h; (ii) **197**, LiHMDS, 0 °C to rt, 18 h.

2.7.6 Deprotection

With olefin isomers in hand the final deprotection steps could be performed. Initially TBAF-mediated *O*-desilylation was sluggish. Standard conditions (TBAF, THF, 0 °C to rt, 18 h) gave incomplete conversion of starting material but gave alcohols (*E*)-**199** and (*Z*)-**200** in 61% combined yield as an 82:18 mixture [(*E*):(*Z*)] of geometric isomers and an 82:18 mixture of (*E*)-**191** and (*Z*)-**192** in 21% combined yield. A diastereomerically enriched sample of (*E*)-**199** and (*Z*)-**200** was also isolated in 7% yield and 98:2 dr [(*E*):(*Z*)]. Leaving the reaction for 84 h gave complete conversion although a mixture of (*E*)-**199** and (*Z*)-**200** was still only isolated in a modest 61% combined yield and 88:12 dr [(*E*):(*Z*)]. However, *O*-desilylation with HF·py in THF proved more successful and a mixture of (*E*)-**199** and (*Z*)-**200** was isolated in 86% combined yield and 82:18 dr [(*E*):(*Z*)] (Scheme 46). The configuration of (*E*)-**199** and (*Z*)-**200**, and therefore its precursors (*E*)-**191** and (*Z*)-**192**, was determined using three elements of NMR spectroscopy. Firstly, through ^{1}H NMR ^{3}J coupling constant analysis: the resonance corresponding to the C(5) proton of the major component has a large coupling constant of 15.5 Hz, indicating a *trans* olefin geometry within (*E*)-**199**. Secondly, using a ^{1}H NMR TOCSY experiment, decoupling of the allylic resonances of the minor component showed a triplet with a 10.9 Hz coupling constant indicating a *cis* olefin geometry within (*Z*)-**200**. Finally, using ^{13}C NMR analysis, the ^{13}C NMR resonances belonging to *C*(4) and *C*(7) (the allylic carbons) were found to be ~5 ppm upfield in the minor isomer [75.5 ppm compared to 80.3 ppm for *C*(4) and 27.9 ppm compared to 32.4 for *C*(7)], consistent with the previously discussed γ-effect.[4,5]

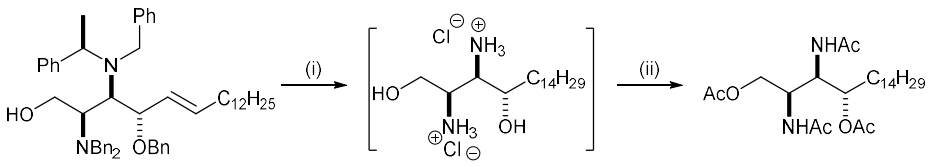


(*E*)-**191**/(*Z*)-**192**
82:18 dr

(*E*)-**199**/(*Z*)-**200**
(i) 61%,[a,b] 82:18 dr [(*E*):(*Z*)]
(ii) 61%, 88:12 dr [(*E*):(*Z*)]
(iii) 86%, 82:18 dr [(*E*):(*Z*)]

Scheme 46. *Reagents and Conditions*: (i) TBAF, THF, 0 °C to rt, 24 h; (ii) TBAF, THF, 0 °C to rt, 84 h; (iii) HF·py, THF, 0 °C to rt, 18 h. {[a] A sample of (*E*)**-191** and (*Z*)**-192** was also isolated in 21% and 82:18 dr [(*E*):(*Z*)]. [b] A sample (*E*)**-199** and (*Z*)**-200** was also isolated in 7% yield and 98:2 dr [(*E*):(*Z*)]}.

Optimised conditions from the tandem hydrogenation/hydrogenolysis from the synthesis of **159** were performed on (*E*)**-199** and (*Z*)**-200** to give **201**·2HCl which was followed by peracetylation with Ac_2O, pyridine and DMAP to give peracetylated 3-deoxy-3-aminophytosphingosine **169** in 72% yield and >95:5 dr over two steps (Scheme 47).



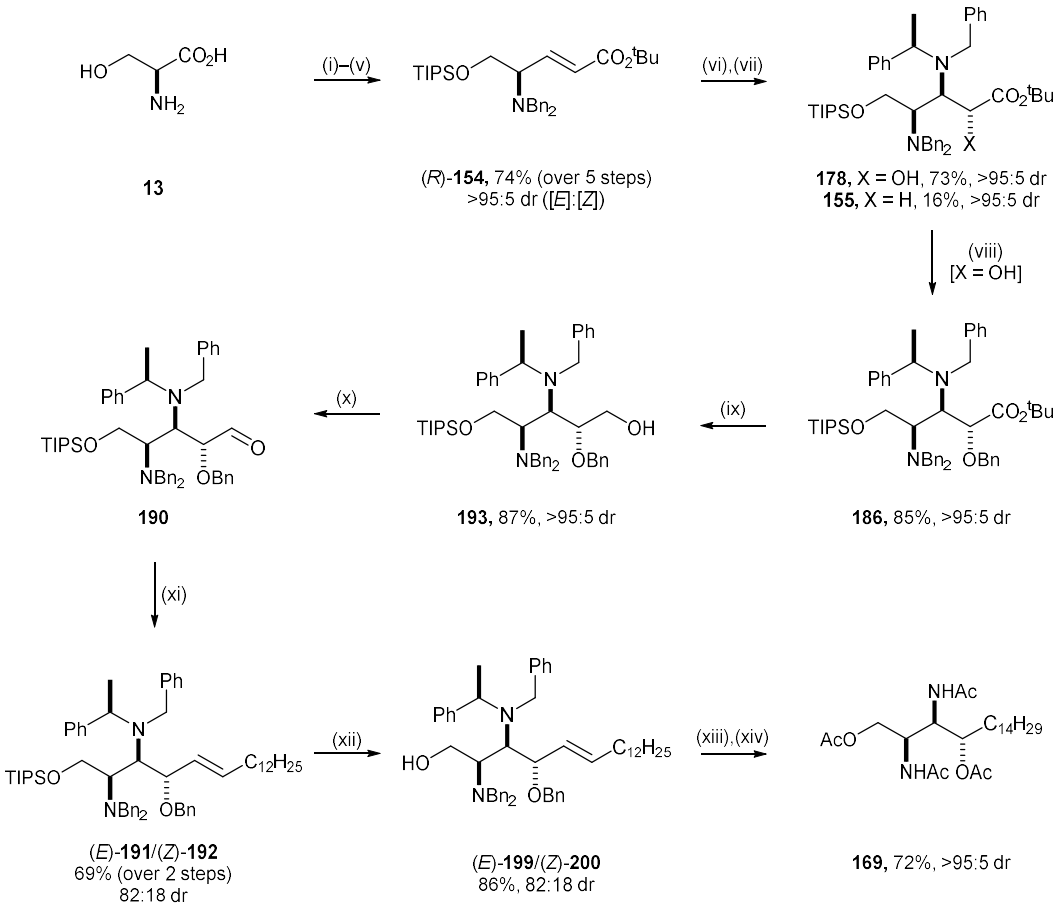
(*E*)-**199** and (*Z*)-**200**
82:18 dr ([*E*]:[*Z*])

201·2HCl

169, 72%, >95:5 dr

Scheme 47. *Reagents and Conditions*: (i) $Pd(OH)_2/C$ (50% w/w), H_2 (5 atm), 1.25 M HCl in MeOH, rt, 72 h; (ii) Ac_2O, DMAP, py, rt, 72 h.

Peracetylated 3-deoxy-3-aminophytosphingosine **169** was synthesised in 17% overall yield over 13 steps from L-serine (*S*)**-13** using aminohydroxylation and Julia-Kocienski olefination protocols as the key steps (Scheme 48).

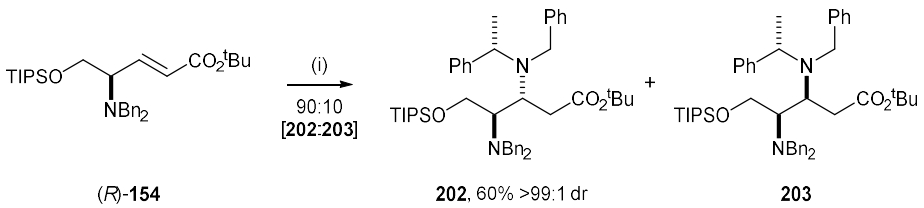


Scheme 48. *Reagents and Conditions*: (i) AcCl, MeOH, 70 °C, 3 h; (ii) BnBr, K_2CO_3, MeCN, rt, 36 h; (iii) TIPSCl, imidazole, DMAP, CH_2Cl_2, rt, 36 h; (iv) DIBAL-H, PhMe, –78 °C, 1 h; (v) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 1 h then Et_3N, –78 °C, 20 min then rt, 20 min then $Ph_3PCHCO_2{}^tBu$ **167**, –78 °C to rt , 18 h; (vi) (*R*)-**163**, THF, –78 °C, 2 h; (vii) (–)-CSO **182**, –78 °C to rt, 18 h; (viii) NaH, 0 °C, 30 min then BnBr, 0 °C to rt, 18 h; (ix) DIBAL-H, PhMe, –78 °C to rt, 18 h; (x) IBX, DMSO, rt, 18 h; (xi) **197**, LiHMDS, THF, rt, 18 h; (xii) HF (70% in py), THF, 0 °C to rt, 18 h; (xiii) H_2 (5 atm), $Pd(OH)_2/C$ (50% w/w), HCl (1.25 M in MeOH), rt 72 h; (xiv) Ac_2O, DMAP, py, rt, 72 h.

2.8 Synthesis of 3-Deoxy-3-Aminosphinganine

2.8.1 Previous Work

Previously, the addition of (*S*)-**163** to (*R*)-**154** was attempted and resulted in a 90:10 mixture of **202** and **203** from which, it was reported that, **202** was isolated in 60% yield and >99:1 dr after chromatographic purification (Scheme 49).[1]



Scheme 49. *Reagents and conditions*: (i) (*S*)-**163**, THF, –78 °C, 2 h.

Following the successful synthesis of **159** and **169** and the promising conjugate addition of (*S*)-**163** to (*R*)-**154** to give **202** it was envisaged that peracetylated 3-deoxy-3-aminosphinganine **170**, the C(3)-epimer of **159**, could be synthesised following the same route as described for **159**. Mismatched addition of (*S*)-**163** to α,β-unsaturated ester (*R*)-**154** gives **202** which could be *O*-silyl deprotected and lactonised to give lactone **204**. Reduction/olefination of **204** would give (*E*)-**205** and (*Z*)-**206** which upon subjection to a tandem hydrogenation/hydrogenolysis protocol followed by peracetylation would provide peracetylated 3-deoxy-3-aminosphinganine **170** (Figure 15).

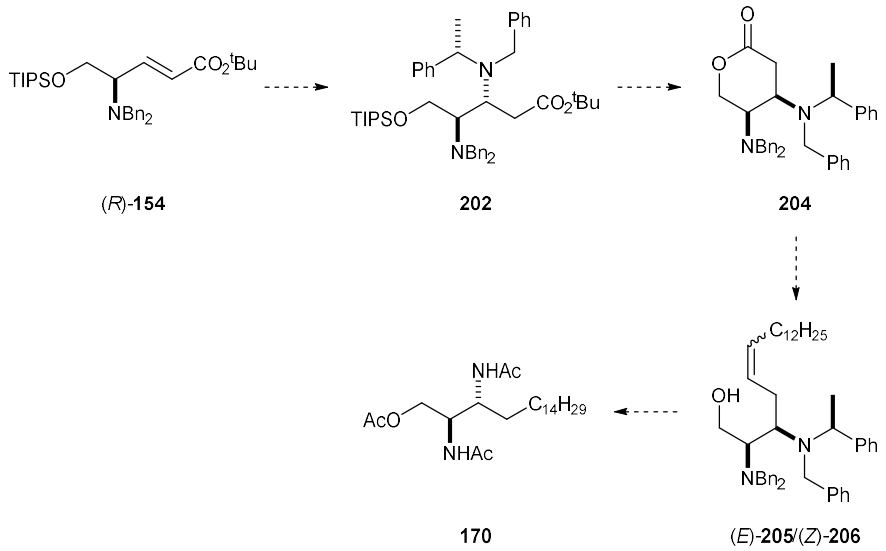
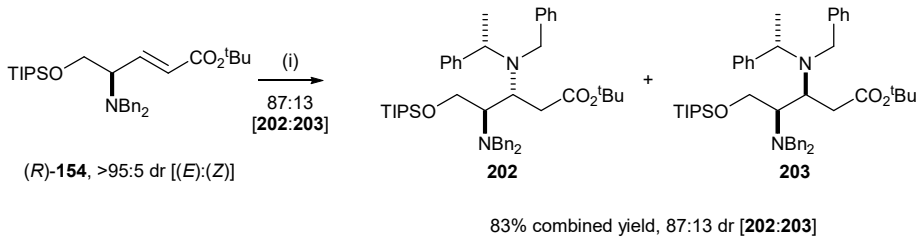


Figure 15. Proposed synthesis of peracetylated 3-deoxy-3-aminosphinganine **170**.

2.8.2 Doubly Diastereoselective 'Mismatched' Conjugate Addition

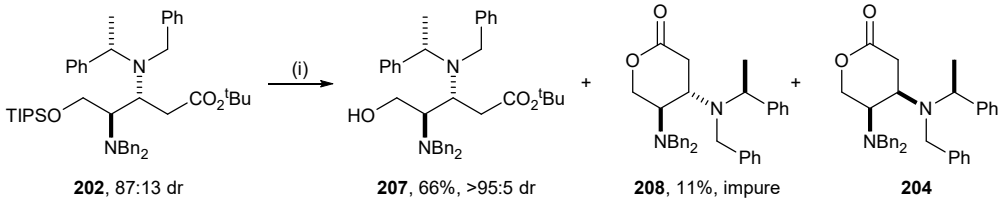
The addition of (*S*)-**162** (which was synthesised in an identical method to its enantiomer, in 68% yield and 98% ee)[15] to α,β-unsaturated ester (*R*)-**154** showed a lower level of diastereoselectivity, which was expected due to the envisaged 'mismatched' nature of the reaction. Addition of (*S*)-**163** to (*R*)-**154** gave an 87:13 mixture of **202** and **203**, respectively, which was isolated as an inseparable mixture in 83% yield and 87:13 dr (Scheme 50). The diastereoisomeric ratio was calculated from integration of the C(2)H_A and C(2)H_B resonances within **202** and **203** in the ^{1}H NMR spectra of the crude reaction mixture and isolated sample.



Scheme 50. *Reagents and Conditions*: (i) (*S*)-**163**, THF, –78 °C, 2 h.

2.8.3 Lactonisation Route

O-Desilylation with TBAF in THF did not, on this occasion, occur with concomitant lactonisation. Instead, alcohol **207** was isolated in 66% yield as a single diastereoisomer and an impure sample of lactone **208**, produced from the cyclisation of the minor diastereoisomer **203** was isolated in 11% yield (Scheme 51). The relative *anti*-configuration within **208** was determined by ^{1}H NMR ^{3}J coupling constant analysis in comparison with **156** (of known *anti*-configuration) (Table 1). It was theorised that lactonisation did not occur due to the significant steric influence of the two large dibenzylamino constituents, which would necessarily adopt a *syn*-configuration in the resulting lactone **204**.



Scheme 51. *Reagents and Conditions*: (i) TBAF, THF, 0 °C to rt, 24 h.

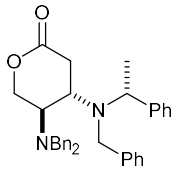
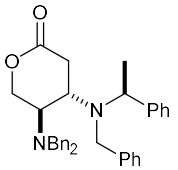
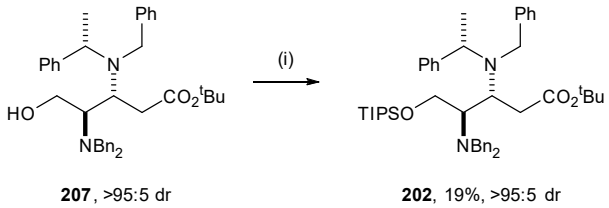
Resonance	 **156**	 **208**
C(3)H_A	dd, 15.3, 6.3	dd, 15.3, 6.6
C(3)H_B	dd, 15.3, 9.0	dd, 15.3, 8.3
C(4)*H*	m	m
C(5)*H*	q, 4.7	q, 4.9
C(6)H_A	dd, 12.4, 4.7	dd, 12.4, 4.9
C(6)H_B	dd, 12.4, 4.7	dd, 12.4, 4.9

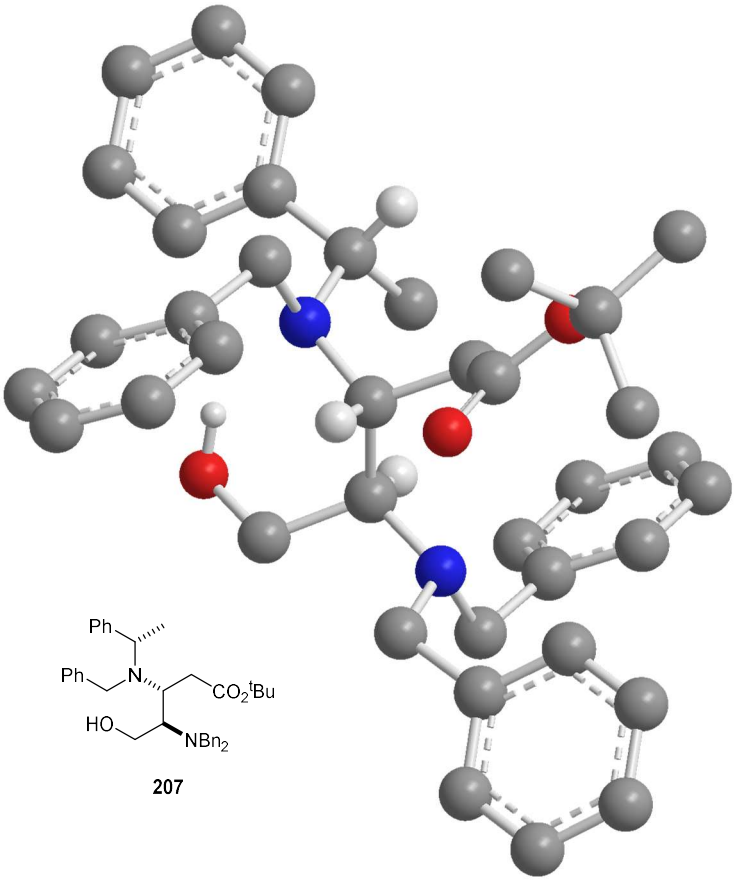
Table 1. ^{1}H NMR ^{3}J coupling constant analysis of lactones **156** and **208**.

The relative configuration within **207** was assigned by single crystal X-ray diffraction. Its absolute configuration was assigned from the known (*S*)-configuration of the α-methylbenzyl moiety (Figure 16).[9] A Flack *x* parameter[10,11] of +0.08(15) for the crystal structure of **207** confirmed this assigned absolute (3*R*,4*R*,α*S*)-configuration. This also establishes the configuration within **202**, the major product of the lithium amide conjugate addition reaction. The *O*-silylation of alcohol **207** with TIPSCl, imidazole and DMAP in CH_2Cl_2 allowed for the isolation of a diastereomerically pure sample of **202** in 19% yield providing further evidence for its relative and absolute configuration assignment (Scheme 52).



207, >95:5 dr **202**, 19%, >95:5 dr

Scheme 52. *Reagents and Conditions*: (i) TIPSCl, imidazole, DMAP, CH_2Cl_2, rt, 36 h.

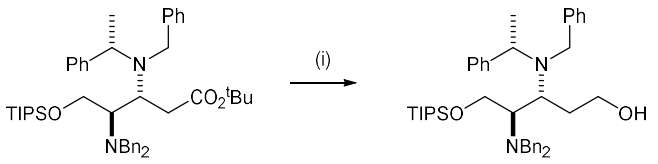


207

Figure 16. X-ray crystal structure of (3*R*,4*R*,α*S*)-**207** (selected H atoms are omitted for clarity).

2.8.4 Acyclic Route

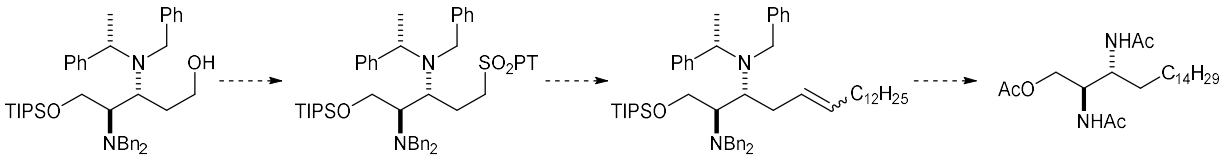
As lactone isolation proved difficult it was envisaged that the chain elongation could, once again, occur through an acyclic intermediate. The most obvious choice was to reduce the ester to the aldehyde which would easily undergo olefination. As with the reduction of ester **186**, a two stage reduction protocol to give aldehyde was attempted. Firstly, the reduction of an 87:13 mixture of **202** and **203**, respectively, with $LiAlH_4$ in THF gave alcohol **209** (from the reduction of the major component of the ester mixture) which was isolated in 64% yield and >95:5 dr (Scheme 53).



202, 87:13 dr **209**, 64%, >95:5 dr

Scheme 53. *Reagents and Conditions*: (i) $LiAlH_4$, THF, –78 °C to rt, 18 h.

Attempted oxidation of **209** proved unsuccessful under many conditions. The instability of β-amino aldehydes is well documented[12,13] and therefore an alternative approach was needed. As the electrophilic component of the olefination could not be made from the aminopolyol segment it was envisaged that employing a derivative of **209** as the nucleophilic component may be more successful. Therefore a Julia-Kocienski protocol was proposed (Figure 17).

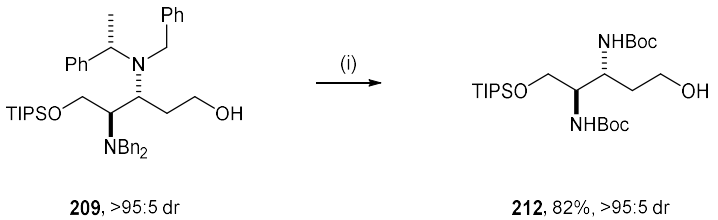


209 **210** **211** **170**

Figure 17. Proposed Julia-Kocienski procedure.

Attempts to synthesise sulfone **210**, *via* Mitsunobu chemistry,[16] to enable Julia-Kocienski olefination proved unsuccessful, giving a complex mixture of products thought to be from the nucleophilic nature of the dibenzylamino groups giving rise to 5-membered cyclic ammonium species. Attempted analysis of the crude mixture supported this assignment due to the

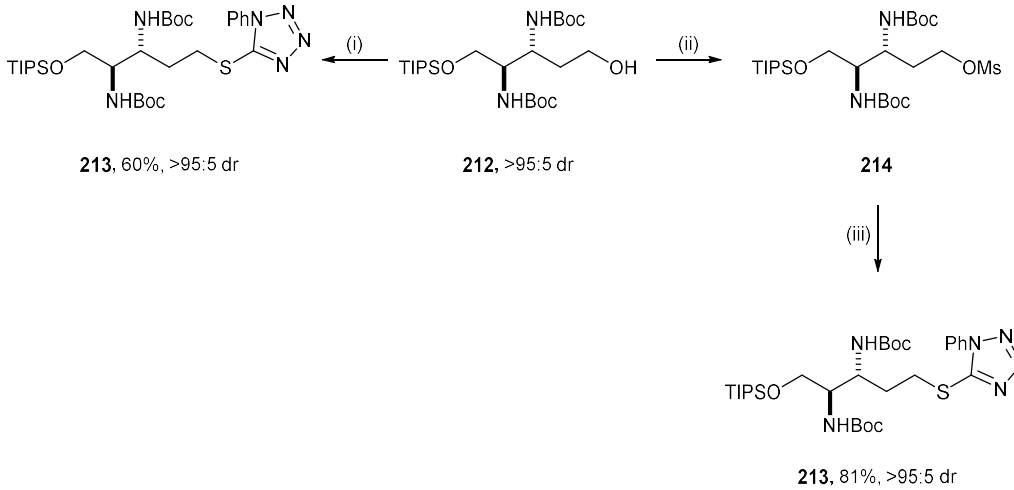
presence of deshielded, diastereotopic benzylic resonances in the ^{1}H NMR spectrum. It was thought that reducing the nucleophilic nature of the amino group, through protecting group manipulation, would allow successful preparation of a sulfide precursor for olefination. Therefore, **209** was submitted to 5 atm H_2 with Pearlman's catalyst (40% w/w) and Boc_2O in MeOH, which gave *N*,*N*-di-Boc-protected **212** in 82% yield and >95:5 dr (Scheme 54).



209, >95:5 dr **212**, 82%, >95:5 dr

Scheme 54. *Reagents and Conditions*: (i) H_2 (5 atm), $Pd(OH)_2/C$ (40% w/w), Boc_2O, MeOH, rt, 72 h.

Elaboration of alcohol **212** to the requisite sulfide **213** was first attempted by Mitsunobu reaction[16] with **198**, PPh_3 and DEAD, which gave sulfide **213** in 60% isolated yield and >95:5 dr. However, a two-step procedure involving activation of the hydroxyl functionality within **212** with MsCl, Et_3N and DMAP in CH_2Cl_2, to give mesylate **214**, followed by alkylation of **214** in acetone gave **213** in 81% yield as a single compound (>95:5 dr) (Scheme 55).

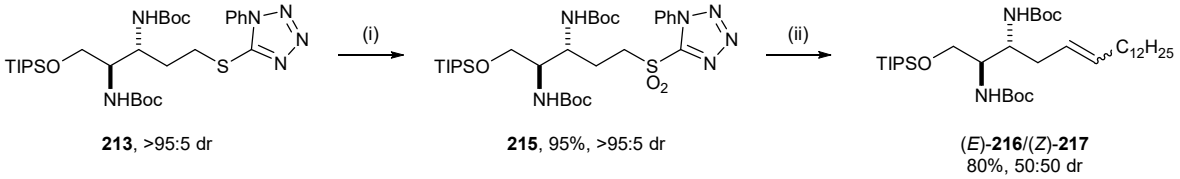


213, 60%, >95:5 dr **212**, >95:5 dr **214** **213**, 81%, >95:5 dr

Scheme 55. *Reagents and Conditions*: (i) PPh_3, DEAD, **198**, THF, 0 °C to rt, 18 h; (ii) MsCl, Et_3N, DMAP, CH_2Cl_2, rt, 3 h; (iii) **198**, K_2CO_3, acetone, 56 °C, 2.5 h.

Subsequent oxidation of **213** with H_2O_2 in EtOH with 20 mol% $(NH_4)_2Mo_7O_{24}.7H_2O$ as a catalyst gave sulfone **215** as the sole product which was isolated in 95% yield as a single

diastereoisomer. Treatment of sulfone **215** and tridecanal with LiHMDS in THF afforded olefin (*E*)-**216** and (*Z*)-**217** in 80% yield and 50:50 dr [(*E*):(*Z*)] (Scheme 56).

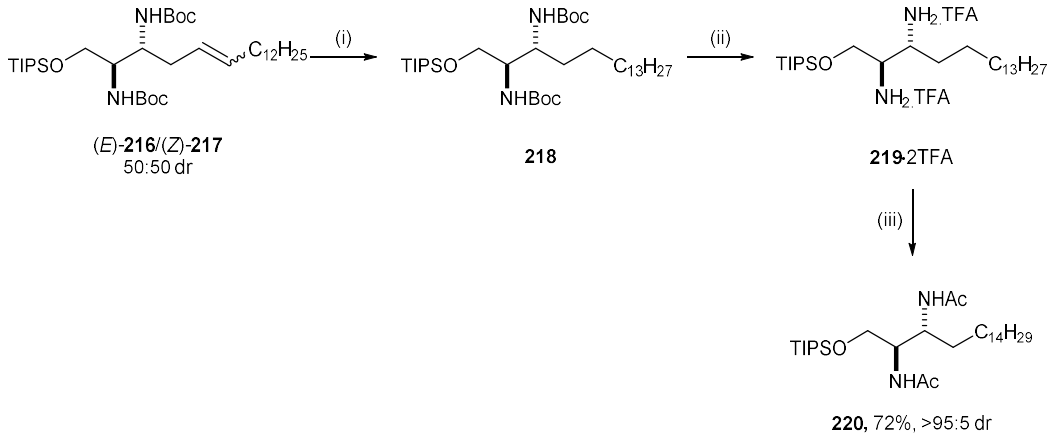


213, >95:5 dr **215**, 95%, >95:5 dr (*E*)-**216**/(*Z*)-**217** 80%, 50:50 dr

Scheme 56. *Reagents and Conditions*: (i) H_2O_2, $(NH_4)_2Mo_7O_{24}.7H_2O$, EtOH, 0 °C to rt, 18 h; (ii) LiHMDS, tridecanal, THF, 0 °C to rt, 18 h.

2.8.5 Deprotection

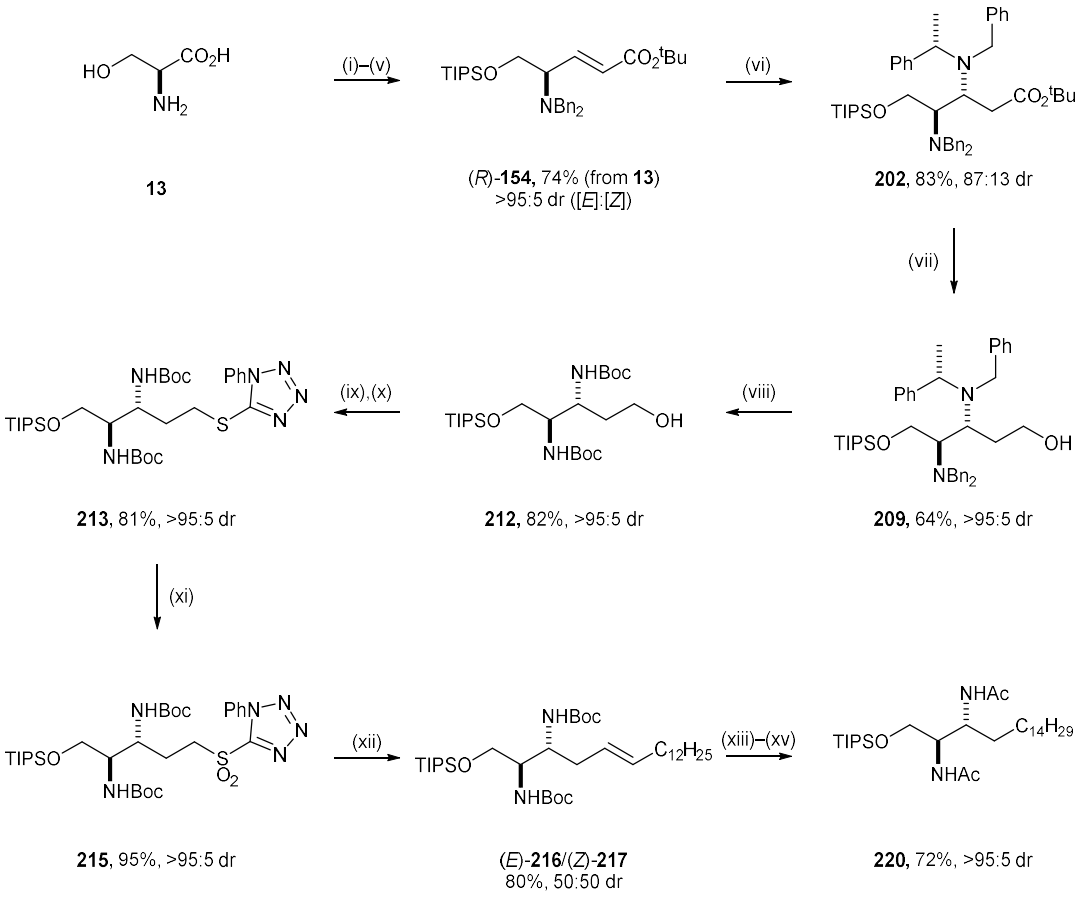
Hydrogenation of the 50:50 mixture of (*E*)-**216** and (*Z*)-**217** with H_2 (5 atm) and Pd/C in MeOH gave the saturated derivative **218**. Subsequent *N*-deprotection with TFA in CH_2Cl_2 gave the bis-trifluoroacetic acid salt, **219**·2TFA, which was acetylated (without purification) to give diacetate **220** which, after chromatographic purification, was isolated in 72% yield from a mixture of (*E*)-**216** and (*Z*)-**217**. Convergence of the 50:50 mixture of geometric isomers, (*E*)-**216** and (*Z*)-**217**, to a single diastereomer of **220** in greater than 50% yield gives further confirmation to the identity of the mixture being olefin isomers (Scheme 57).



(*E*)-**216**/(*Z*)-**217** 50:50 dr **218** **219**·2TFA **220**, 72%, >95:5 dr

Scheme 57. *Reagents and Conditions*: (i) H_2 (5 atm), Pd/C (20% w/w), MeOH, rt, 3 h; (ii) TFA, CH_2Cl_2, rt, 18 h; (iii) Ac_2O, DMAP, py, rt, 24 h.

Protected 3-deoxy-3-aminosphinganine **220** was synthesised in 14% yield over 15 steps with doubly diastereoselective lithium amide conjugate addition and Julia-Kocienski olefination as the key steps (Scheme 58).



Scheme 58. *Reagents and Conditions*: (i) AcCl, MeOH, 70 °C, 3 h; (ii) BnBr, K_2CO_3, MeCN, rt, 36 h; (iii) TIPSCl, imidazole, DMAP, CH_2Cl_2, rt, 36 h; (iv) DIBAL-H, PhMe, –78 °C, 1 h; (v) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 1 h then Et_3N, –78 °C, 20 min then rt, 20 min then $Ph_3PCHCO_2{}^tBu$ **167**, –78 °C to rt , 18 h; (vi) (*S*)-**163**, THF, –78 °C, 2 h; (vii) $LiAlH_4$, THF, –78 °C to rt, 18 h; (viii) H_2 (5 atm), $Pd(OH)_2/C$ (40% w/w), Boc_2O, MeOH, rt, 72 h; (ix) MsCl, Et_3N, DMAP, CH_2Cl_2, rt, 3 h; (x) **198**, acetone, 56 °C, 2.5 h; (xi) H_2O_2, $(NH_4)_2Mo_7O_{24}{\cdot}7H_2O$, EtOH, 0 °C to rt, 18 h; (xii) LiHMDS, tridecanal, THF, 0 °C to rt, 18 h; (xiii) H_2 (5 atm), Pd/C (20% w/w), MeOH, rt, 3 h; (xiv) TFA, CH_2Cl_2, rt, 18 h, (xv) Ac_2O, py, DMAP, rt, 24 h.

2.9 Summary

Three protected 3-deoxy-3-aminosphingoid bases, **159**, **169** and **220**, were synthesised in 14–40% overall yield from L-serine (*S*)-**13** in 10–15 steps.[17] Peracetylated 3-deoxy-3-aminosafingol **159** was synthesised in 10 steps and 40% overall yield using lithium amide conjugate addition, lactonisation and one-pot reduction/olefination as the key steps. Peracetylated 3-deoxy-3-aminophytosphingosine **169** was synthesised in 13 steps and 17% overall yield from L-serine using aminohydroxylation and Julia-Kocienski olefination as the key steps. Protected 3-deoxy-3-aminosphinganine **220** was synthesised in 15 steps and 14% overall yield from L-serine using lithium amide conjugate addition and Julia-Kocienski olefination as the key steps (Figure 18).

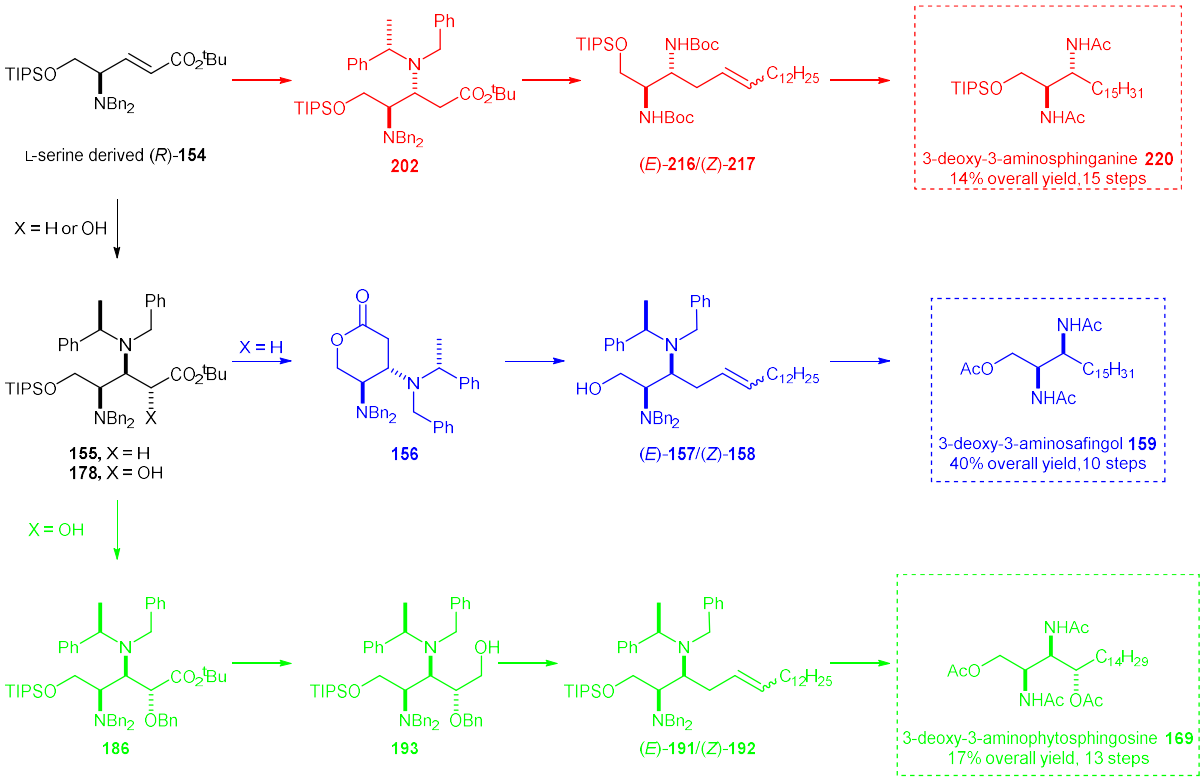


Figure 18. Successfully synthesised 3-deoxy-3-aminosphingoid bases **159**, **169** and **220**.

2.10 References

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(8) A PKR protocol for aminohydroxylation was attempted but was found to be low yielding and therefore was not pursued further.

(9) X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U. K.

(10) Flack, H. D. *Acta Crystallogr. Sect. A* **1983**, *39*, 876.

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(15) The enantiomeric excess of (*S*)-**162** was determined from ^{1}H NMR spectroscopic analysis in the presence of the chiral solvating agent (*S*)-*O*-acetylmandelic acid and comparison with an authentic racemic sample.

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Chapter 3: Asymmetric Synthesis of Fagomine and Three of its Diastereoisomers

3.1 Fagomine and its Stereoisomers

(+)-Fagomine **221** [(*R*,*R*,*R*)-3,4-dihydroxy-5-hydroxymethylpiperidine] is a piperidine iminosugar which was first isolated from Japanese buckwheat, *Fagopyrum esculentum*, in 1974 by Koyama and Sagamura,[1] and has more recently been isolated from a number of members of the *Morus* genus,[2,3] *Xanthocercis zambesiaca*[4] and the Moreton Bay chestnut *Castanospermum australe*.[5] Two of its diastereoisomers, 3-*epi*-fagomine **222** and 5-*epi*-fagomine **224**, have also been isolated from Nature[3,4,6,7] however the fourth diastereoisomer, 4-*epi*-fagomine **223**, has only been produced by chemical synthesis.[3,8–14] Fagomine **221**, along with other iminosugars including **222** and **9**, have been reported to show antiglycemic effects in streptozotocin-induced diabetic mice.[15] Inhibitory effects of **221** against α-glucosidase and β-galactosidases have been reported although **222** was found to be more potent against these enzymes. Furthermore, **222** has been shown to inhibit β-galactosidase whereas **221** shows no inhibitory effects. 5-*epi*-Fagomine **224** showed no significant inhibitory effects against any glycosidases studied.[4] 4-*epi*-Fagomine **223** has been shown to inhibit some α-galactosidases although its inhibitory potency was reduced over 6000-fold when compared to its 2-hydroxylated analogue, 1-deoxygalactonojirimycin (Figure 19).[16]

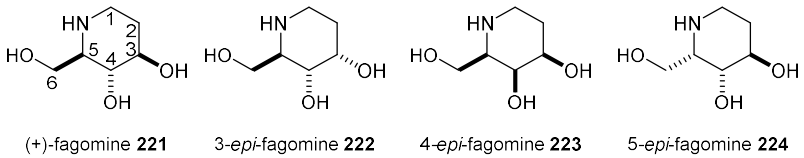


Figure 19. Structures of (+)-fagomine **221** and three of its diastereoisomers **222**–**224**.

3.2 Chapter Aims

It was envisaged that the syntheses of fagomine **221** and its diastereoisomers **222**, **223** and *ent*-**224** could be achieved *via* the reductive cyclisation of a polyhydroxylated

δ-amino aldehyde **148**, which could be made *via* oxidation of terminal olefin **225**. In turn, olefin **225** may be derived from the addition of an organometallic reagent to aldehyde **226**, itself derived from the aminohydroxylation[17] of α,β-unsaturated ester **227** (Figure 20).

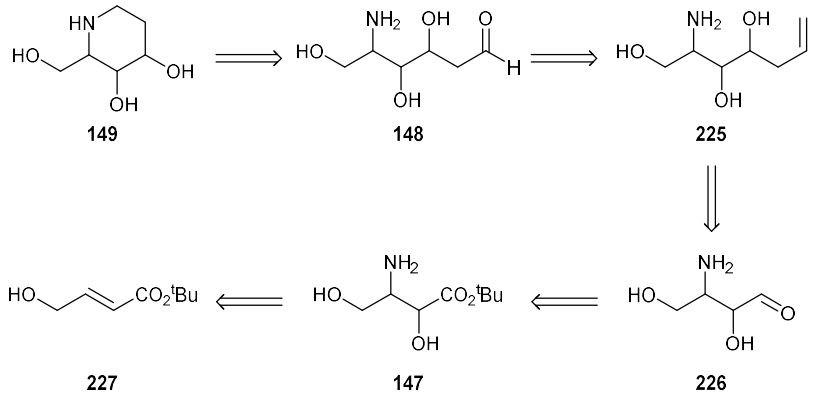
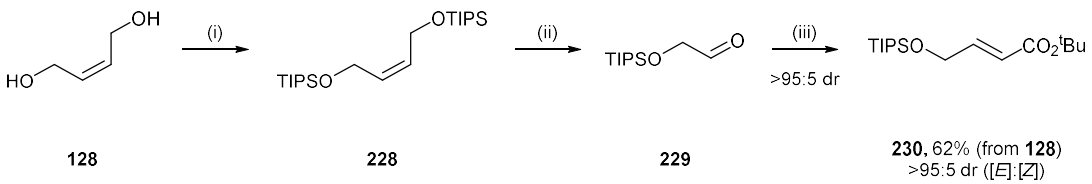


Figure 20. Retrosynthetic analysis for the synthesis of fagomine **221** and its diastereoisomers **222**, **223** and *ent*-**224**.

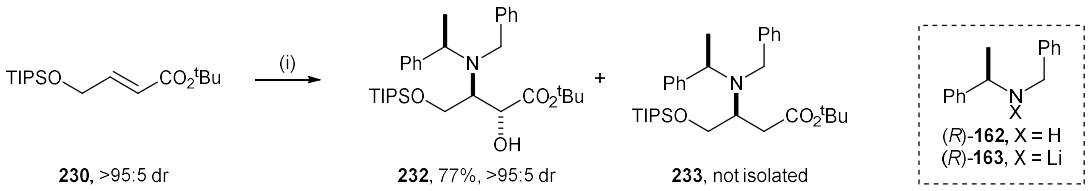
3.3 Synthesis of Alcohol 236

The synthesis of α,β-unsaturated ester **230** was achieved from *cis*-but-2-en-1,4-diol **128**, following a literature protocol[18] upon bis-*O*-silylation to give **228** followed by ozonolysis to give aldehyde **229**. Olefination of **229** under Masamune-Rousch conditions[19] with Hünig's base, LiCl and phosphonate **231** (made from the Arbusov reaction of triethyl phosphite and *tert*-butyl bromoacetate in quantitative yield) gave **230** in 62% yield and >95:5 dr [(*E*):(*Z*)] over 3 steps (Scheme 59).



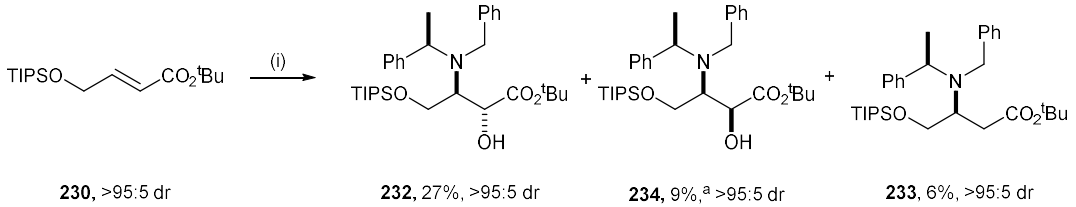
Scheme 59. *Reagents and Conditions*: (i) TIPSCl, imidazole, DMAP, CH_2Cl_2, rt, 18 h; (ii) O_3, MeOH, –78 °C then Me_2S, –78 °C to rt, 18 h; (iii) $^iPr_2NEt$, **231**, LiCl, MeCN, rt, 72 h.

Conjugate addition of (*R*)-**163** to α,β-unsaturated ester **230** gave a lithium (*Z*)-β-amino enolate[20] and then addition of (–)-CSO (–)-**182** gave diastereomerically pure α-hydroxy-β-amino ester **232** which was isolated in 77% yield and >95:5 dr (Scheme 60).[17]



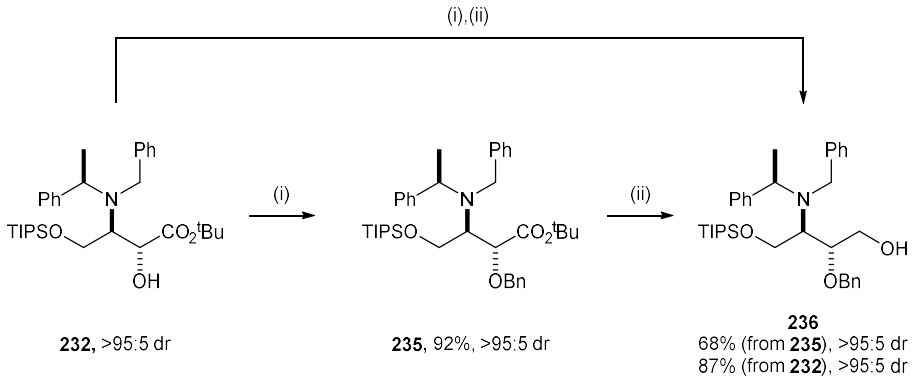
Scheme 60. *Reagents and Conditions*: (i) (*R*)-**163**, –78 °C, 2 h then (–)-**182**, –78 °C to rt, 18 h.

Replacement of (–)-CSO with its enantiomer (+)-CSO in the oxidation protocol resulted in a decrease in the diastereoselectivity of the oxidation step to give a complex mixture from which **232**, **234** and **233** were isolated in 27, 9 and 6% yield, respectively, as single diastereoisomers. An 89:11 mixture of **234** and **232**, respectively, was also isolated in 17% combined yield (Scheme 61).



Scheme 61. *Reagents and Conditions*: (i) (*R*)-**163**, –78 °C, 2 h then (+)-**182**, –78 °C to rt, 18 h. [[a] An 89:11 mixture of **234** and **232**, respectively, was also isolated in 17% yield].

Protection of the α-hydroxyl moiety within **232** upon treatment with NaH followed by BnBr gave α-benzyloxy-β-amino ester **235** in 92% yield and >95:5 dr, which could be reduced using DIBAL-H to give alcohol **236** in 68% yield and >95:5 dr. A higher yielding, telescoped procedure allowed the isolation of **236** in 87% yield and >95:5 dr over two steps and avoided the purification of intermediate **235** (Scheme 62).



Scheme 62. *Reagents and Conditions*: (i) NaH, 0 °C, 1 h then BnBr, 0 °C to rt, 18 h; (ii) DIBAL-H, CH_2Cl_2, –78 °C, 2 h.

3.4 Allylation of Aldehyde 237

As the ultimate goal of this investigation was to prepare all four diastereoisomers of fagomine it would be optimal to have a stereodivergent allylation allowing the synthesis of either diastereoisomer **238** or **239** preferentially, which could then be elaborated to two of the target compounds (Figure 21).

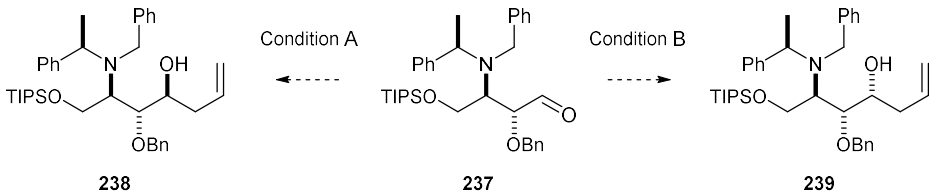
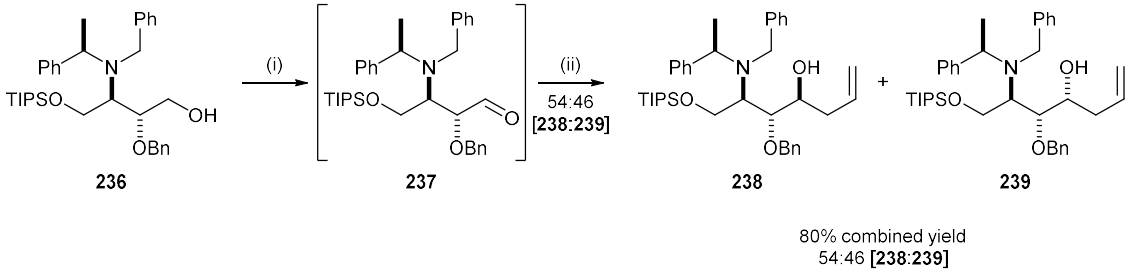


Figure 21. Proposed selective allylation of **237**.

Aldehyde **237** was synthesised from **236** using Swern conditions and then used immediately. Initially, allylmagnesium chloride was added to **237** in THF at 0 °C, to give a 54:46 mixture of **238** and **239**, respectively, which were isolated as an inseparable mixture in 80% combined yield and 54:46 dr. The configurations within **238** and **239** were later established by correlation to known compounds (*vide infra*) (Scheme 63).

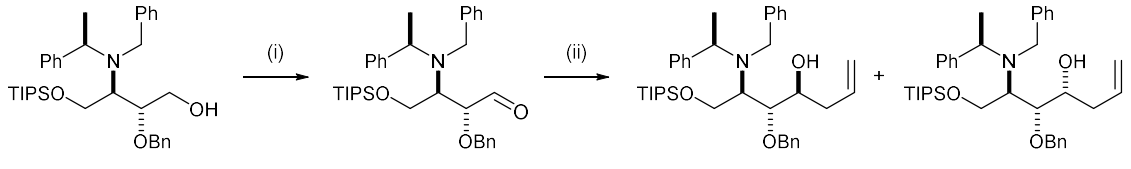


Scheme 63. *Reagents and Conditions*: (i) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 1 h then Et_3N, –78 °C, 20 min then rt, 20 min; (ii) allylmagnesium chloride, THF, 0 °C to rt, 18 h.

3.5 Optimisation of Allylation Protocol

A number of procedures were attempted to increase the diastereoselectivity of the allylation and/or provide access to each diastereoisomer selectively. Decreasing the temperature to –78 °C increased the diastereomeric ratio of **238** and **239** to 63:37, respectively, which were isolated as an inseparable mixture in 85% combined yield. Changing the solvent from THF to

Et_2O gave a diastereomeric ratio of 67:33 [**238** and **239**].[21] Forming the Grignard reagent *in situ* from allyl bromide and magnesium allowed for the incorporation of $MgBr_2$ as an additive (formed *in situ* from Mg and 1,2-dibromoethane) which, after addition to **237**, gave a 65:35 mixture of **238** and **239**, respectively (Scheme 64).

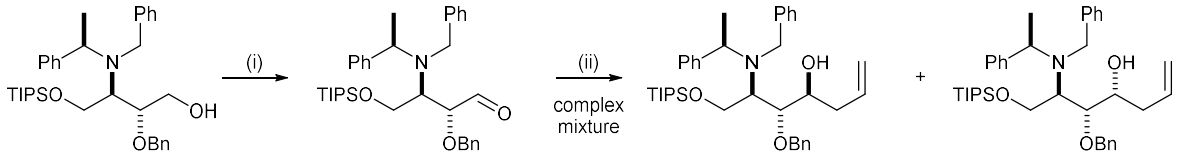


236 **237** **238** **239**

Reagent	Temperature / °C	Time	Solvent	Crude dr (**238**:**239**)	Yield / %
AllylMgCl	0 °C to rt	18 h	THF	54:46	80 (54:46 dr)
AllylMgCl	–78 °C to rt	18 h	THF	63:37	85 (63:37 dr)
AllylMgBr	–78 °C to rt	18 h	Et_2O	67:33	-
Allyl bromide, Mg, I_2, 1,2-dibromoethane	–78 °C to rt	18 h	Et_2O	65:35	-

Scheme 64. *Reagents and Conditions*: (i) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 1 h then Et_3N, –78 °C, 20 min then rt, 20 min; (ii) see table.

Alternative allylating agents were also employed: pinacol allylboronate was added to aldehyde **237** in CH_2Cl_2 giving a complex ^1H NMR spectrum of the crude reaction mixture from which no ratios could be obtained. After chromatographic purification, a 69:31 mixture of **238** and **239**, respectively, was isolated as an inseparable mixture in 57% combined yield. A sample of aldehyde **237** was also isolated in 20% yield and >95:5 dr (Scheme 65).



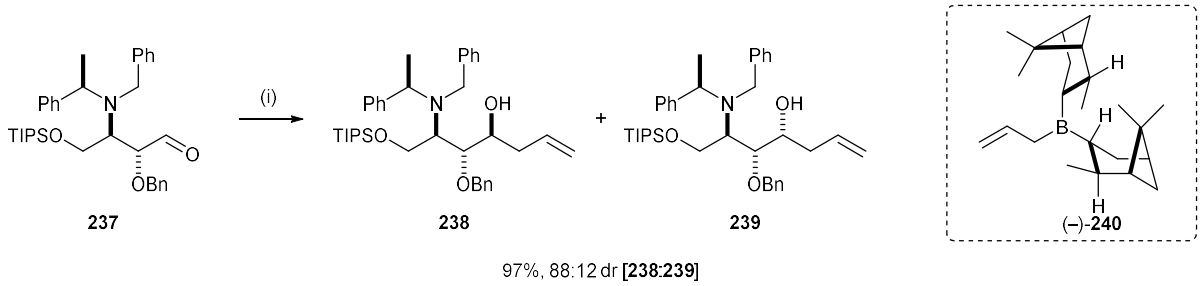
236 **237** **238** **239**

57%,[a] 69:31 dr [**238**:**239**]

Scheme 65. Reagents and Conditions: (i) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 1 h then Et_3N, –78 °C, 20 min then rt, 20 min; (ii) AllylBpin, THF, –78 °C to rt, 1 h then $N(CH_2CH_2OH)_3$, rt, 1 h. [[a] Starting material **237** was also recovered in 20% yield].

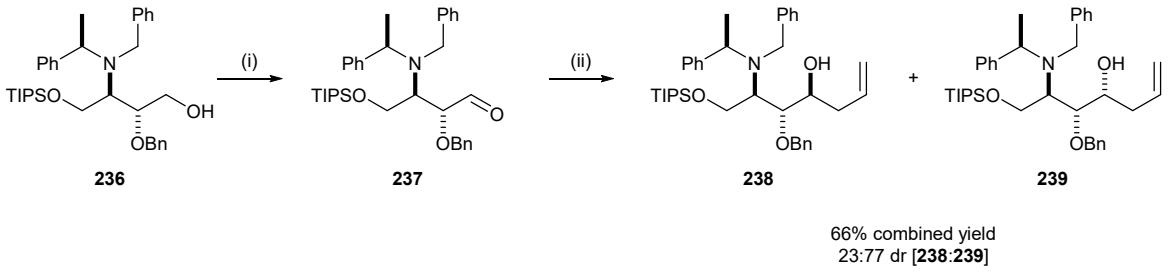
It was proposed that the use of chiral reagents to affect the allylation may exhibit a higher level of diastereoselectvity. A chiral borane, $Ipc_2B(Allyl)$ **240**, has been shown to allylate achiral aldehydes with high and predictable enantioselectivity.[22] Treatment of **237** with

(–)-Ipc$_2$B(allyl) gave a crude reaction mixture with an intractable ^{1}H NMR spectrum which precluded determination of a diastereomeric ratio. After chromatographic purification, an 88:12 mixture of **238** and **239**, respectively, was isolated in 97% combined yield (Scheme 66).



Scheme 66. *Reagents and Conditions*: (i) (–)-**240**, –78 °C, 2 h, then 3.0 M aq NaOH, 30% aq H_2O_2, –78 °C to rt, 18 h.

Addition of (+)-Ipc$_2$B(allyl) (+)-**240** to aldehyde **237** gave a 23:77 mixture of **238** and **239**, respectively, which were isolated in 66% combined yield (from **236**) (Scheme 67). The diastereocontrol of these reactions is consistent with the addition of enantiopure Ipc$_2$B(allyl) on achiral substrates.[23,24] Furthermore, the addition of enantiopure (–)-**240** and (+)-**240** shows high levels of reagent control when compared to the achiral model, pinacol allylboronate, and is therefore consistent with 'matched' and 'mismatched' reactions as defined by Masamune.[25]

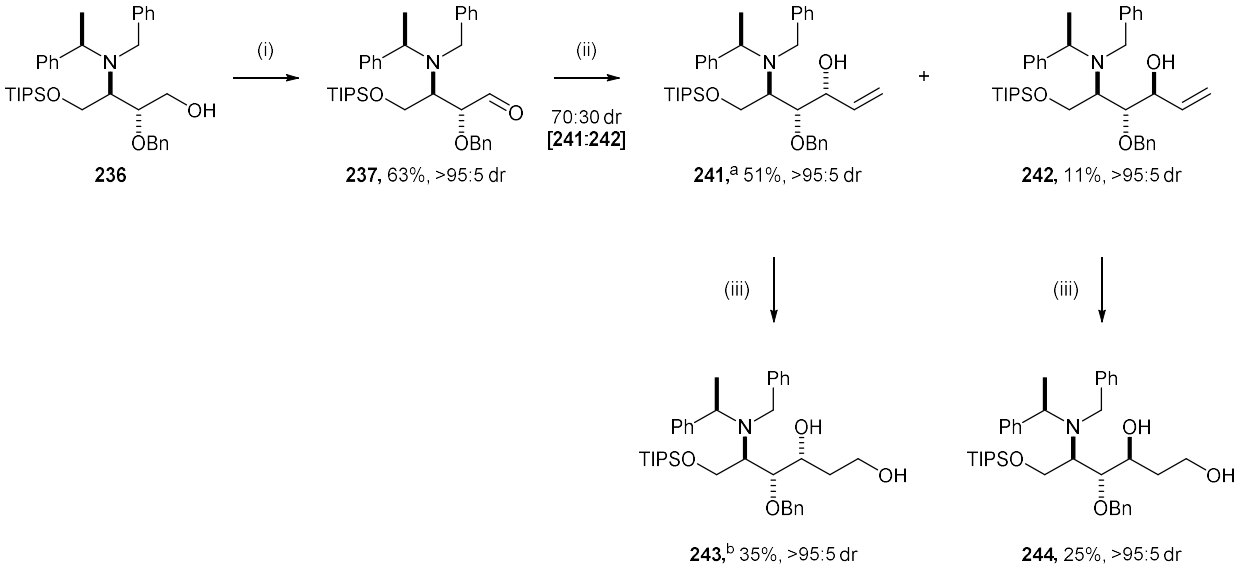


Scheme 67. *Reagents and Conditions*: (i) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 1 h then Et_3N, –78 °C, 20 min then rt, 20 min; (ii) (+)-**240**, Et_2O, –78 °C, 2 h, then 3.0 M aq NaOH, 30% aq H_2O_2, –78 °C to rt, 18 h.

3.6 Stereochemical Assignment

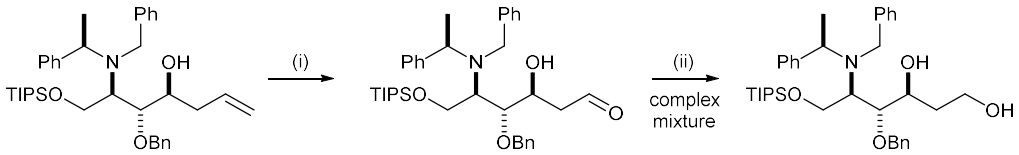
The configurations of **238** and **239** were next established by chemical correlation. As the addition of vinyl magnesium bromide had been performed previously, and the configurations of **241** and **242** were already established,[26] it was proposed that **241** and **242** could be correlated with **238** and **239**. The addition of vinylmagnesium bromide to **237** gave a 70:30

mixture of **241** and **242**, respectively, from which **241** was isolated in 51% yield and >95:5 dr, and **242** was isolated in 11% yield and >95:5 dr. Hydroboration[27] of **241** and **242** with $BH_3{\cdot}SMe_2$ gave diols **243** and **244** in 35% and 25% yield, respectively, as single diastereoisomers of known configuration (Scheme 68).



Scheme 68. *Reagents and Conditions*: (i) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 1 h then Et_3N, –78 °C, 20 min then rt, 20 min; (ii) Vinylmagnesium bromide, THF, 0°C to rt, 18 h; (iii) $BH_3{\cdot}SMe_2$, THF, rt, 2 h then MeOH/THF (1:1 v/v), 3.0 M aq NaOH, H_2O_2, rt, 2 h. [[a] A 95:5 mixture of **242** and **241**, respectively, was also isolated in 9% combined yield. [b] An impure sample of **241** was also isolated in ~30% yield].

Treatment of a 63:37 mixture of **238** and **239**, respectively, (derived upon addition of allylmagnesium chloride to **237**) with OsO_4 and $NaIO_4$ followed by reduction of the intermediate aldehydes **245** and **246** gave a complex mixture, from which a 63:37 mixture of **244** and **243**, respectively, was isolated in 42% combined yield (Scheme 69). The spectroscopic data of **243** and **244** are consistent with those of authentic samples prepared *via* hydroboration of **241** and **242**, respectively. This correlation establishes the configurations of **238** and **239**, *via* synthesis of derivatives **243** and **244**, to **241** and **242** of known stereochemistry.



63:37 dr
[238:239]

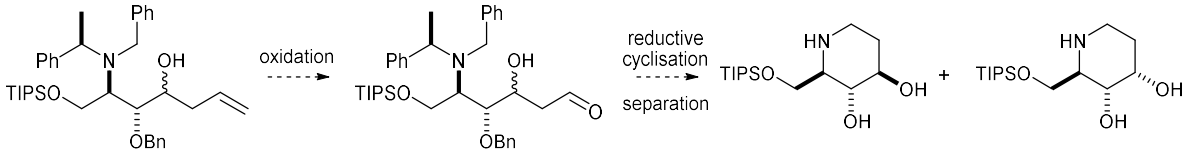
245+246

42%, 63:37 dr
[244:243]

Scheme 69. *Reagents and Conditions*: (i) OsO_4, $NaIO_4$, 2,6-lutidine, 1,4-dioxane/H_2O (3:1 v/v), rt, 1 h; (ii) $NaBH_4$, MeOH, rt, 30 min.

3.7 Attempted Cyclisation

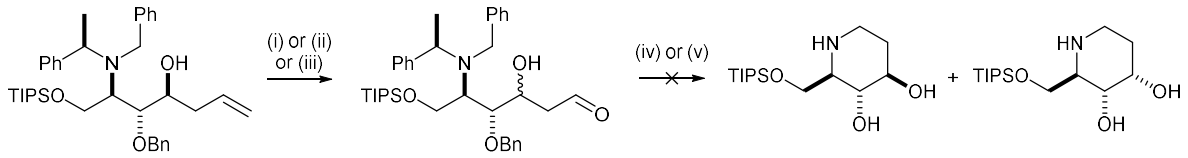
It was proposed to continue with a mixture of **238** and **239** to probe the oxidation of the double bond within **238** and **239** and cyclisation to give the required piperidine scaffolds in the hope that the formation of the cyclic derivatives would enable separation of the diastereomeric products (Figure 22).



238+239 245+246 247 248

Figure 22. Proposed synthesis of piperidines **247** and **248** *via* oxidation of **238** and **239** to give aldehydes **245** and **246** followed by reductive cyclisation.

A range of oxidation conditions were trialled. Firstly, a 63:37 mixture of **238** and **239**, respectively, was protected as the corresponding ammonium salt then subjected to ozonolysis conditions, using PPh_3 as a reducing agent, giving a complex mixture which was then treated with $Pd(OH)_2/C$ under H_2 in MeOH giving a complex mixture from which no product was isolated. Using polymer-supported PPh_3 for the reducing agent in the ozonolysis still gave a complex mixture. An alternative procedure using an $OsO_4/NaIO_4$ system, previously used for chemical correlation of **238** and **239** (*vide supra*), gave a complex mixture containing aldehydic species**,** which when subjected to two different hydrogenolysis conditions (in MeOH or MeOH/AcOH) gave complex mixtures in both cases (Scheme 70). Given the reduction with $NaBH_4$ had worked in modest yield and that no product had been observed after hydrogenolysis, another route was sought to effect formation of the piperidine scaffold.

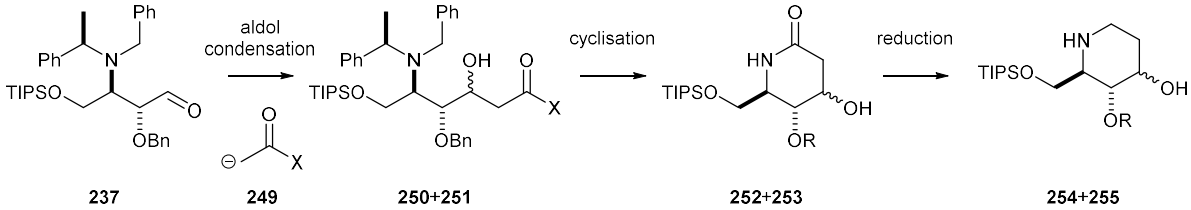


63:37 [**238**:**239**] **245+246** **247** **248**

Scheme 70. *Reagents and Conditions*: (i) HCl, Et_2O then O_3, CH_2Cl_2, –78 °C then PPh_3, –78 °C to rt, 2 h; (ii) HCl, Et_2O then O_3, CH_2Cl_2, –78 °C then polymer supported-PPh_3, –78 °C to rt, 2 h; (iii) OsO_4, $NaIO_4$, 2,6-lutidine, 1,4-dioxane/H_2O (3:1 v/v), rt, 1 h; (iv) $Pd(OH)_2/C$ (20% w/w), H_2 (5 atm), MeOH, rt, 18 h; (v) $Pd(OH)_2/C$ (20% w/w), H_2 (5 atm), MeOH/AcOH (10:1 v/v), rt, 18 h.

3.8 Increase in Oxidation State – Aldol Reaction

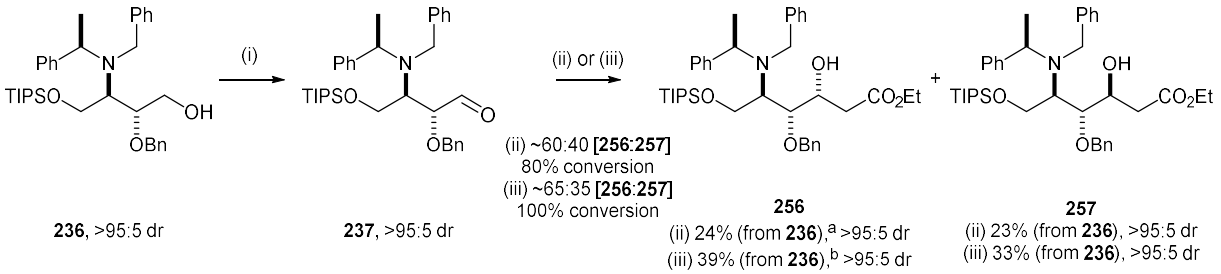
It was thought that an increase in oxidation state before the cyclisation may lead to a more efficient cyclisation producing lactams **252** and **253** from **250** and **251**, which could in turn be made from the aldol reaction of aldehyde **237** and an acetate enolate equivalent **249**. The reduction of lactams **252** and **253** would give piperdines **254** and **255** (Figure 23).



237 **249** **250+251** **252+253** **254+255**

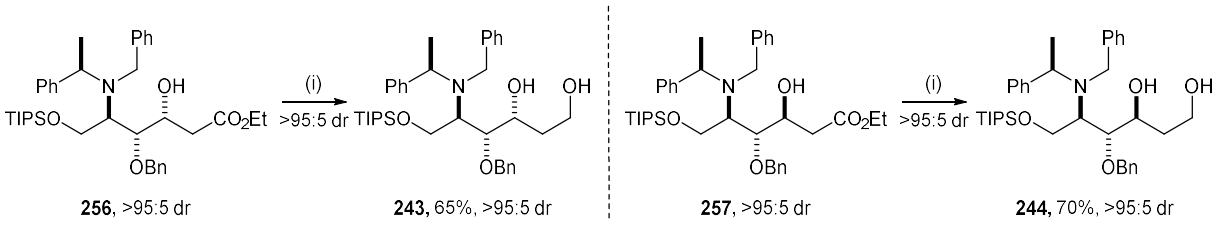
Figure 23. Proposed synthesis of piperidine scaffolds **254** and **255**: aldol condensation of aldehyde **237** with acetate enolate equivalent **249** to give **250** and **251**, followed by cyclisation to give lactams **252** and **253** then reduction to give **254** and **255**.

Aldehyde **237** was produced as before (from oxidation of alcohol **236**) then reacted with 0.9 equiv of the enolate of EtOAc (derived from the deprotonation of EtOAc with LDA) which gave 80% conversion to a 60:40 mixture of **256** and **257**, respectively. After chromatographic purification **257** was isolated in 23% yield (from **236**) and >95:5 dr, and **256** was isolated in 24% yield (from **236**) and >95:5 dr. A 74:26 mixture of **256** and **257**, respectively, was also isolated in combined 18% yield. Increasing the number of equivalents of the enolate from 0.9 to 1.4 resulted in 100% conversion to a 65:35 mixture of esters from which **256** and **257** were isolated in 39 and 33% yield, respectively, as single diastereoisomers in each case. A 74:26 mixture of **256** and **257**, respectively, was also isolated in 12% yield (Scheme 71).



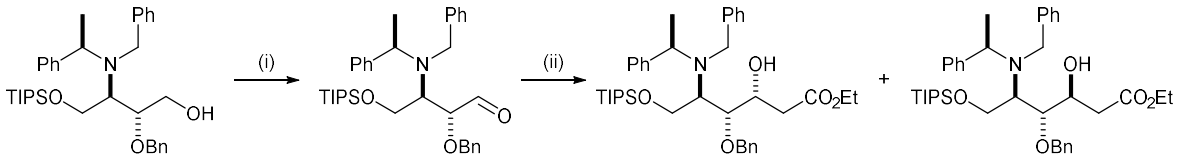
Scheme 71. *Reagents and Conditions*: (i) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 1 h then Et_3N, –78 °C, 20 min then rt, 20 min; (ii) BuLi, $^iPr_2NH$, 0.9 equiv EtOAc, –78 °C, 1 h then 0 °C, 2 h; (iii) BuLi, $^iPr_2NH$, 1.4 equiv EtOAc, –78 °C, 1 h then 0 °C, 2 h. [[a] A 74:26 mixture of **256** and **257**, respectively, was also isolated in 18% combined yield. [b] A 74:26 mixture of **256** and **257**, respectively, was also isolated in 12% combined yield].

The configuration of aldol adducts **256** and **257** were next established *via* chemical correlation to the corresponding alcohols **243** and **244**. Reduction of the ester functionalities within **256** and **257** using $LiAlH_4$ gave diols **243** and **244** in 65 and 70% yield, respectively. The spectroscopic data of **243** and **244** are consistent with those of authentic samples prepared *via* hydroboration of **241** and **242**. This establishes the stereochemistry of **256** and **257** and therefore the diastereocontrol of the aldol reaction of aldehyde **237** with the lithium enolate of EtOAc which favours 3,4-*syn*-**256** as the major product (Scheme 72).



Scheme 72. *Reagents and Conditions*: (i) $LiAlH_4$, THF, 0 °C to rt, 18 h.

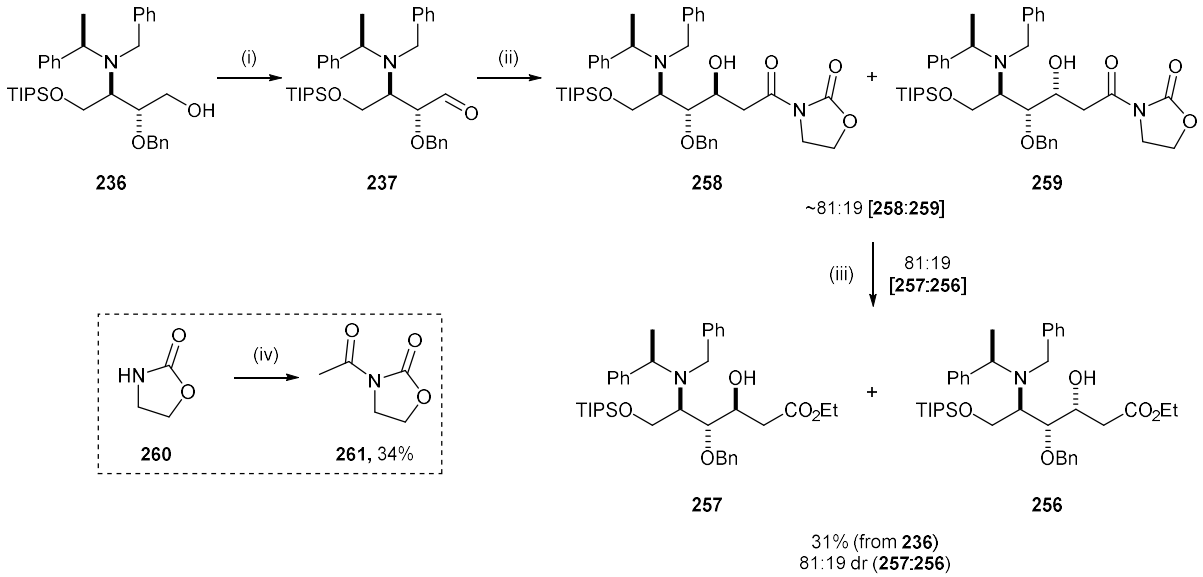
Boron enolates have been reported to give higher diastereoselectivity, which has been attributed to the shorter O–B bond length when compared to the O–Li bond length resulting in a tighter transition state.[28] The boron enolate of EtOAc was generated upon treatment with Bu_2BOTf and Et_3N in CH_2Cl_2, and upon addition to aldehyde **237** a complex mixture of products was isolated from which no ratios could be obtained. After chromatographic purification **256** was isolated in 9% yield and >95:5 dr, and **257** was isolated in 20% yield and >95:5 dr (Scheme 73). Although the ratio of isolated products would suggest a difference in selectivity for the addition, the low yield meant this was not investigated further.



236, >95:5 dr **237,** >95:5 dr **256,** 9%, >95:5 dr **257,** 20%, >95:5 dr

Scheme 73. *Reagents and Conditions*: (i) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 1 h then Et_3N, –78 °C, 20 min then rt, 20 min; (ii) EtOAc, Et_3N, Bu_2BOTf, CH_2Cl_2, –78 °C to rt, 18 h.

N-Acyl oxazolidinones (e.g., **261**) are known nucleophilic acetate equivalents which can be used in aldol condensations.[29] Addition of the boron enolate of **261** to aldehyde **237** gave a complex mixture from which an ~81:19 mixture of 3,4-*anti*-**258** and 3,4-*syn*-**259**, respectively, was isolated, although it was also contaminated with **261**. Treatment of the impure sample of **258** and **259** with $Ti(OEt)_4$ in EtOH gave an 81:19 mixture of the known esters 3,4-*anti*-**257** and 3,4-*syn*-**256**, respectively, which was isolated in 31% yield from alcohol **236**. This allowed for the configurations within **258** and **259** to be assigned (Scheme 74).

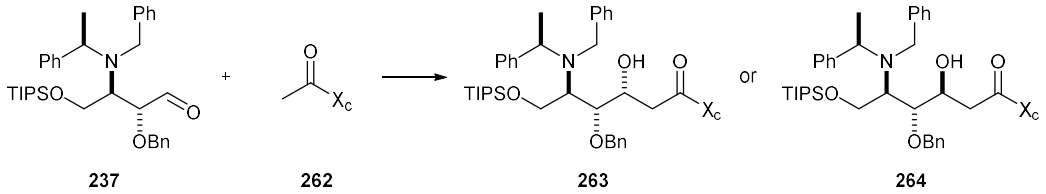


Scheme 74. *Reagents and Conditions*: (i) IBX, DMSO, rt, 2 h; (ii) **261**, BuBOTf, –78 °C to rt, 18 h; (iii) $Ti(OEt)_4$, EtOH, 78 °C, 18 h; (iv) BuLi, THF, –78 °C, 10 min then Ac_2O, –78 °C, 30 min then rt, 2 h.

3.9 Addition of Chiral Acetate Equivalents

Asymmetric acetate aldol reactions of achiral aldehydes are known to be less selective than examples where the enolate contains an α-substituent.[30] However, it was envisaged that the addition of a chiral acetate equivalent might show a greater propensity to add selectively to

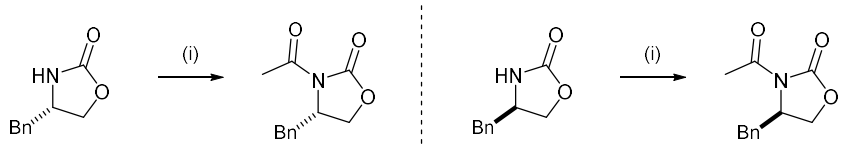
aldehyde **237**, particularly in the 'matched' case. Given that the addition of achiral oxazolidinone **261** to aldehyde **237** eventually resulted in an 81:19 mixture of esters **257** and **256**, respectively, it was hoped that if there was significant enantiorecognition the diastereoselectivity of the 'matched' addition[25] may be high (i.e., >81:19) (Figure 24).[25]



237 **262** **263** **264**

Figure 24. Proposed addition of chiral acetate **262** equivalent to aldehyde **237**.

Firstly, addition of *N*-acyl Evans auxillaries was attempted. Deprotonation of commercially available (*S*)-**265** followed by acetylation with Ac_2O gave (*S*)-**266** in 84% yield. An identical procedure with (*R*)-**265** gave (*R*)-**266** in 80% yield (Scheme 75).

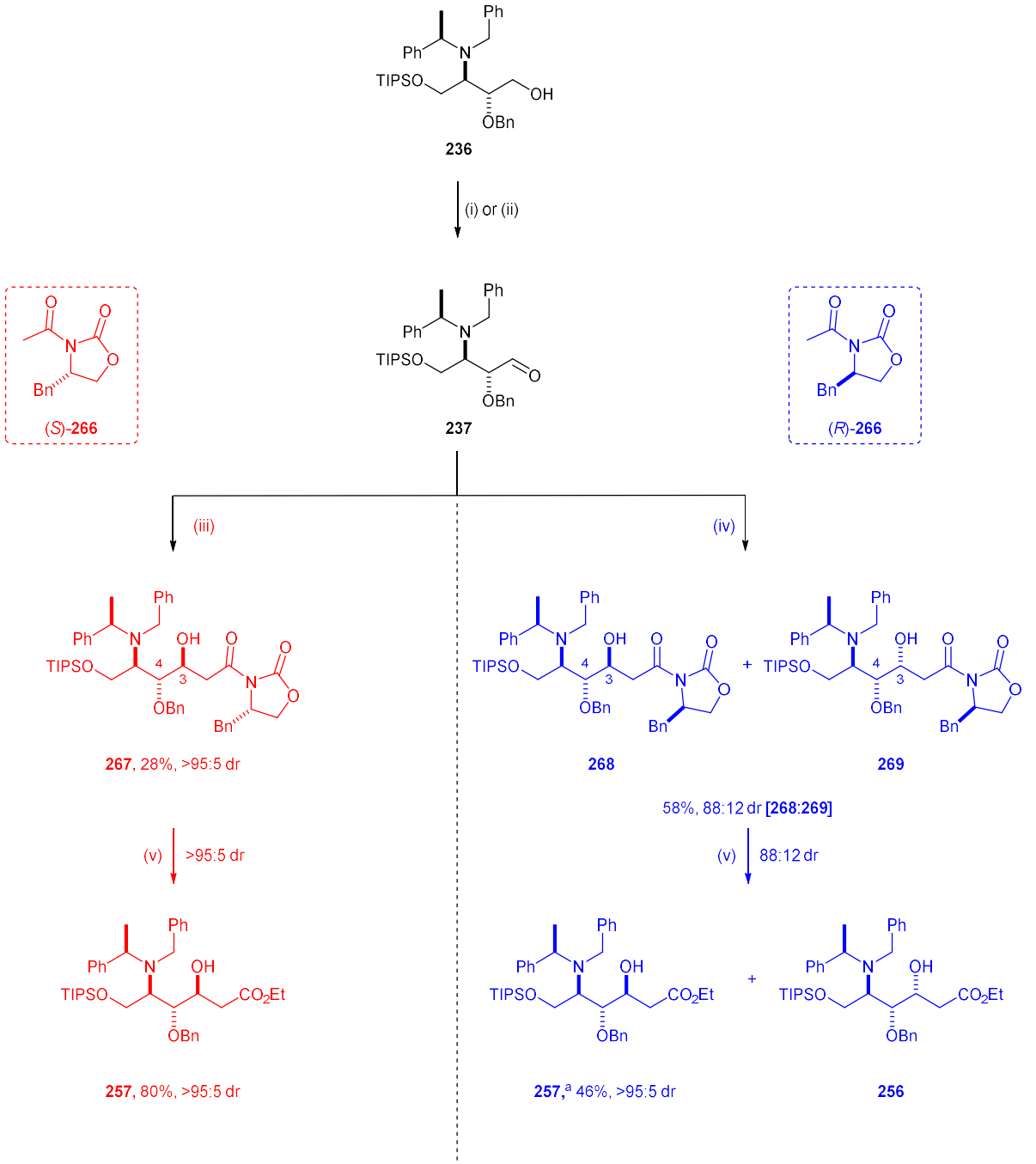


(*S*)-**265** (*S*)-**266**, 84% (*R*)-**265** (*R*)-**266**, 80%

Scheme 75. *Reagents and Conditions*: (i) BuLi, THF, –78 °C, 10 min then Ac_2O, –78 °C, 30 min then rt, 2 h.

Addition of the boron enolate of (*S*)-**266** to aldehyde **237** (generated upon oxidation of **236**) gave a complex mixture of 3,4-*anti*-**267** and aldehyde **237** from which 3,4-*anti*-**267** was isolated in 28% yield and >95:5 dr and **237** was isolated in 20% yield. Confirmation of the relative configurations within **267** was determined by chemical correlation: treatment of **267** with $Ti(OEt)_4$ in EtOH gave the known ester **257**, which was isolated in 80% yield and >95:5 dr. Following the same procedure, addition of (*R*)-**266** to aldehyde **237** gave a crude reaction mixture with an intractable ^1H NMR spectrum, which precluded determination of a diastereomeric ratio. Following purification of this mixture, an 88:12 mixture of 3,4-*anti*-**268** and 3,4-*syn*-**269**, respectively, was isolated in 58% combined yield. The relative configurations within 3,4-*anti*-**268** and 3,4-*syn*-**269** were again determined by correlation to

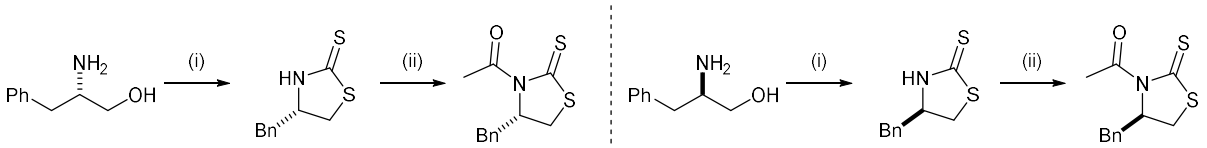
esters **257** and **256**: treatment of an 88:12 mixture of 3,4-*anti*-**268** and 3,4-*syn*-**269**, respectively, with $Ti(OEt)_4$ in EtOH gave an 88:12 mixture of **257** and **256**, respectively. After chromatographic purification **257** was isolated in 46% yield and >95:5 dr, and a 67:33 mixture of **257** and **256**, respectively, was also isolated in 23% combined yield (Scheme 76).



Scheme 76. *Reagents and Conditions*: (i) IBX, DMSO, rt, 2 h; (ii) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 1 h then Et_3N, –78 °C, 20 min then rt, 20 min; (iii) (*S*)-**266**, BuBOTf, Et_3N, CH_2Cl_2, –78 °C to rt, 18 h; (iv) (*R*)-**266**, BuBOTf, Et_3N, CH_2Cl_2, –78 °C to rt, 18 h; (v) $Ti(OEt)_4$, EtOH, 78 °C, 18 h. [[a] A 67:33 mixture of **257** and **256**, respectively, was also isolated in 23% combined yield].

The sense of diastereoselectivity upon addition of acyl oxazolidinones to enantiopure aldehyde **237** is the same for (*R*)-**266**, (*S*)-**266** and **261**, giving 3,4-*anti* as the major diastereoisomer in all three cases. This is consistent with the addition proceeding under substrate (i.e., **237**) control. However, for a system to show classical enantiorecognition it would be expected to see one enantiomer add with a lower diastereoselectivity when compared to the achiral model, defined as the 'mismatched' addition, and its antipode to show higher diastereoselectivity than the achiral model, defined as the 'matched' addition.[25] In this case both chiral auxiliaries present a higher diastereoselectivity of addition to **237** than **261** showing no obvious 'matched' or 'mismatched' combinations.[25]

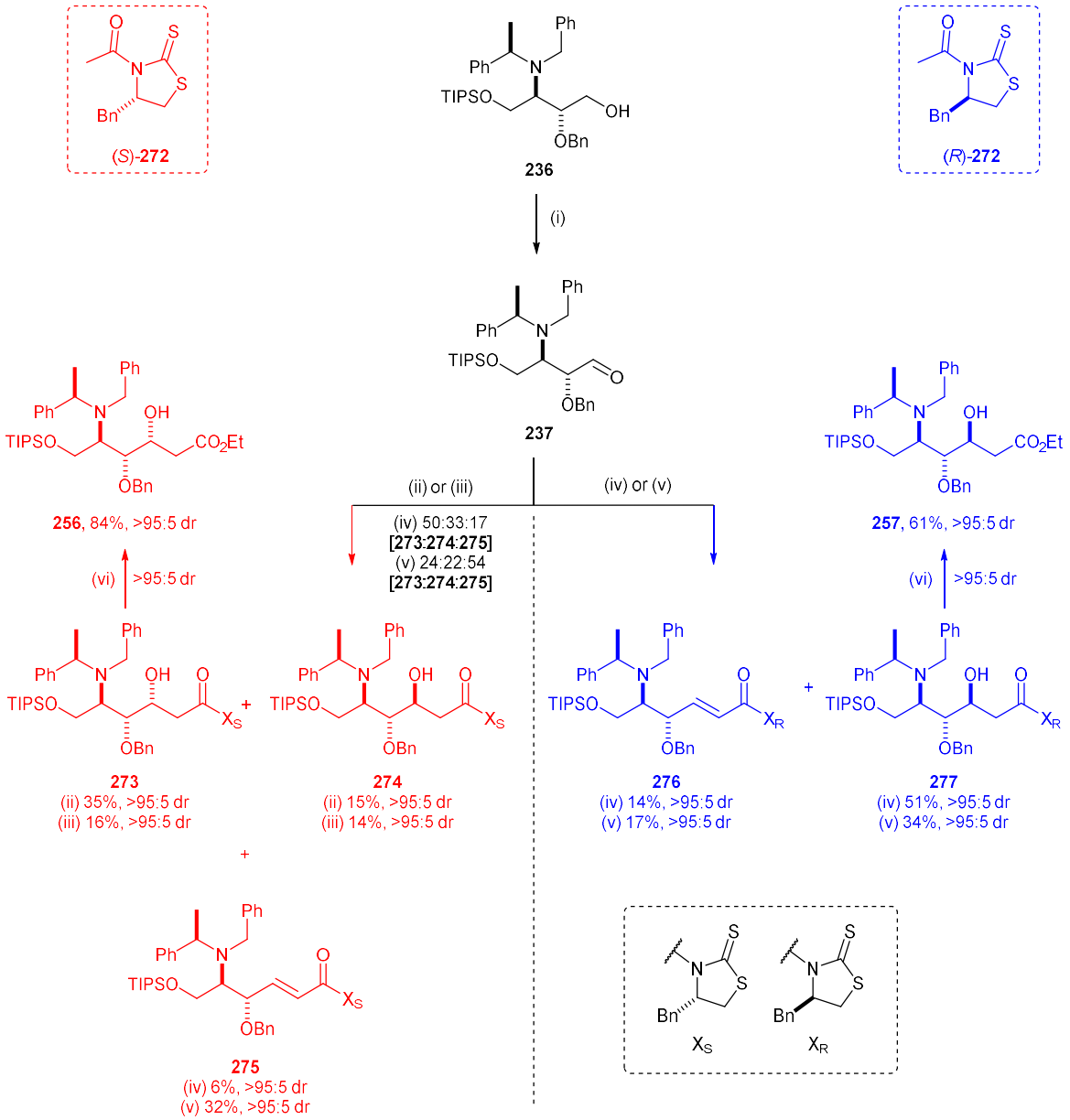
Crimmins *et al*. reported the aldol condensation of thiazolidinethiones to achiral aldehydes with high, tuneable diastereofacial selectivity dependent on the number of equivalents of (–)-sparteine used.[31] Therefore, chiral auxiliaries (*S*)-**272** and (*R*)-**272** were made by the reaction of CS_2 in 1.0 M aq KOH with L-phenylalaninol (*S*)-**270** and D-phenylalaninol (*R*)-**270**, respectively.[32] Deprotonation of crude (*S*)-**271** and (*R*)-**271** followed by acetylation with AcCl gave (*S*)-**272** in 65% yield and (*R*)-**272** in 73% yield, respectively (Scheme 77).



Scheme 77. *Reagents and Conditions*: (i) CS_2, 1.0 M aq KOH, 100 °C, 18 h; (ii) BuLi, THF, 0 °C, 30 min then AcCl, 0 °C, 1 h.

Addition of the titanium enolate of (*S*)-**272** [prepared by treatment of (*S*)-**272** with $TiCl_4$ and 1.0 equiv of (–)-sparteine] to enantiopure aldehyde **237** at –78 °C for 1 h gave a crude mixture containing returned aldehyde **237** and thiazolidinthione **272**. Increasing the temperature to –20 °C for 1 h still gave incomplete conversion from aldehyde **237** and therefore the reaction was left for 3.5 h, which gave a 50:33:17 mixture of **273**, **274** and **275**, respectively. After

chromatographic purification the aldol adducts **273** and **274** were isolated in 35 and 15% yield, respectively, and >95:5 dr in both cases. α,β-Unsaturated adduct (*E*)-**275** ($^3J_{2,3}$ = 15.4 Hz) (the product of *in situ* dehydration of **273** and/or **274**) was also isolated in 6% yield and >95:5 dr. When the number of equivalents of (–)-sparteine was increased to 2.0 the amount of dehydration increased giving a 24:22:54 mixture of **273**, **274** and **275**, respectively, from which desired products **273** and **274** were isolated in 16 and 14% yield, respectively, as single diastereoisomers in addition to the dehydrated product **275** which was isolated in 32% yield. The stereochemistry of addition was determined by correlation of **273** to ethyl ester **256** which was isolated in 84% yield and >95:5 dr. This confirms the 3,4-*syn* configuration within **273** and therefore **274** was assigned as the 3,4-*anti* diastereoisomer. Likewise, addition of the titanium enolate of (*R*)-**272** [prepared by treatment of (*R*)-**272** with $TiCl_4$ and 1.0 equiv (–)-sparteine] to enantiopure aldehyde **237** gave a complex mixture from which aldol adduct **277** was isolated in 51% yield and α,β-unsaturated adduct (*E*)-**276** ($^3J_{2,3}$ = 15.3 Hz) was isolated in 14% yield as single diastereoisomers (>95:5 dr) in both cases. When increasing the number of equivalents of (–)-sparteine to 2.0 a complex mixture was produced from which **276** was isolated in 17% yield and >95:5 dr, and **277** was isolated in 34% yield and >95:5 dr. The configuration within **277** was determined by chemical correlation: treatment of **277** with imidazole and EtOH in CH_2Cl_2 gave **257** in 61% isolated yield and >95:5 dr (Scheme 78).



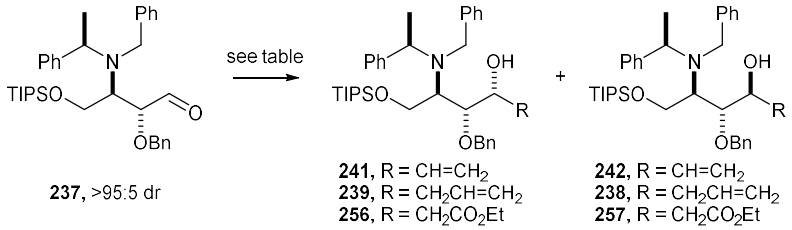
Scheme 78. *Reagents and Conditions*: (i) IBX, DMSO, rt, 2 h; (ii) (*S*)-**272**, $TiCl_4$, 1.0 equiv (–)-sparteine, –20 °C, 3.5 h; (iii) (*S*)-**272**, $TiCl_4$, 2.0 equiv (–)-sparteine, –20 °C, 3.5 h; (iv) (*R*)-**272**, $TiCl_4$, 1.0 equiv (–)-sparteine, –20 °C, 3.5 h; (v) (*R*)-**272**, $TiCl_4$, 2.0 equiv (–)-sparteine, –20 °C, 3.5 h; (vi) imidazole, EtOH, CH_2Cl_2, rt, 72 h.

As the source of the products of dehydration α,β-unsaturated adducts (*E*)-**275** and (*E*)-**276** are unknown (i.e., they could come from both or just one of the addition products) the crude ratios should be used as a guide only. However, unlike the addition of the oxazolidinone derivatives (*R*)-**266** and (*S*)-**266** (which proceeded *via* substrate control) the addition of the thiazolidinethiones (*R*)-**272** and (*S*)-**272** seem to proceed *via* reagent control as the major component of the addition differed depending on the absolute configuration of the auxiliary used. The main effect of increasing the number of equivalents of (–)-sparteine was to increase

the proportion of dehydration of **273**, **274** and **277** to give α,β-unsaturated adducts **275** and **276**. Using this method esters **256** and **257** were made in a partially selective manner in 29 and 31% yield from alcohol **236** *via* oxidation, chiral aldol addition and transesterification. Likewise, using chiral oxazolidinone, (*R*)-**266**, ester **257** is isolated in 27% yield from alcohol **236**. Neither of these methods show improvement on the aldol reaction of EtOAc and aldehyde **237** which give **256** and **257** in 39 and 33% yield, respectively, from alcohol **236**.

3.10 Stereocontrol in the Addition to Enantiopure Aldehyde 237

A variety of achiral nucleophiles have been added to aldehyde **237**, *viz*. vinyl- and allyl-magnesium bromide, the enolate of EtOAc and allylBpin with a range of stereocontrol (Figure 25).



237, >95:5 dr

241, R = $CH{=}CH_2$
239, R = $CH_2CH{=}CH_2$
256, R = CH_2CO_2Et

242, R = $CH{=}CH_2$
238, R = $CH_2CH{=}CH_2$
257, R = CH_2CO_2Et

Reagent	dr
VinylMgBr	70:30 [**241**:**242**]
AllylMgBr	33:67 [**239**:**238**]
allylBpin	31:69 [**239**:**238**]
EtOAc (Li)	65:35 [**256**:**257**]

Figure 25. Stereocontrolled addition of various nucleophiles to aldehyde **237**.

It was previously proposed that the addition of vinylmagnesium bromide to **237** is under Felkin-Anh control with a chelated model providing major diastereoisomer **241** and the electronegative model provides minor diastereoisomer **242**.[33] The stereochemical result of the addition of the lithium enolate of EtOAc is also consistent with a related transition state (Figure 26).[33]

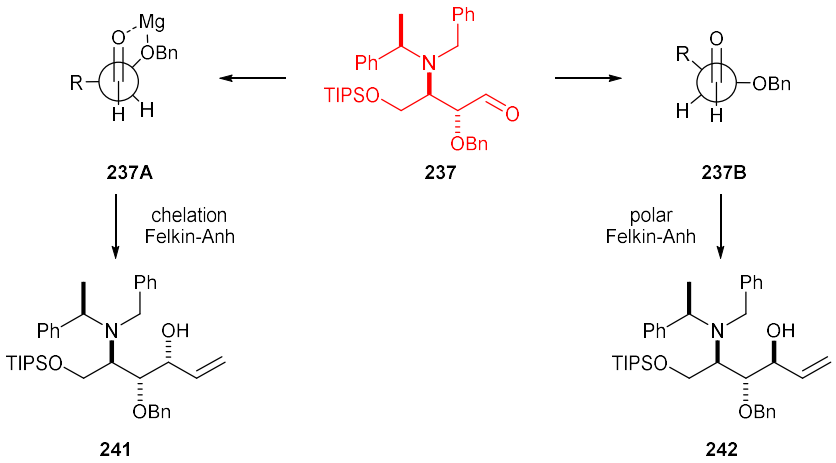


Figure 26. Felkin-Anh model describing the addition of vinylmagnesium bromide to **237**.

However, when allylmagnesium bromide was added a reversal in stereocontrol was observed. This would imply that there is a different mechanism of stereocontrol of addition for allylmagnesium bromide than previously seen for vinylmagensium bromide (*vide supra*). It has been reported that the structure of allylmagnesium bromide is either a rapidly equilibrating mixture of classical structures or a bridged magnesium compound[34] which could lead to two mechanisms of addition [through the α- or γ-carbons]. A model consistent with the preference for the 3,4-*anti* addition that is observed is *via* a cyclic transition state in which the C(2)-stereocentre within **237** controls the facial selectivity of addition to give major product **238**. The reactive conformation allows the minimisation of *syn*-pentane interactions between the C(2) and two ring C–H whereas the OBn component has only one *syn*-pentane interaction and the largest 'R' group has no *syn*-pentane interactions. This mechanism would also be appropriate for the addition of allylboron pinacol ester which shows near identical diastereoselectivity of addition (Figure 27).

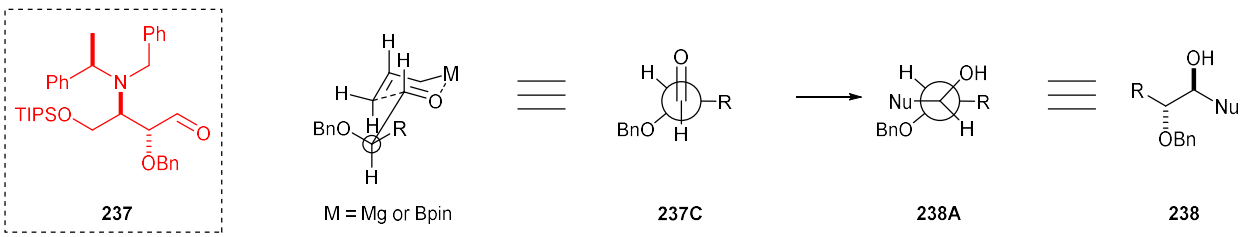
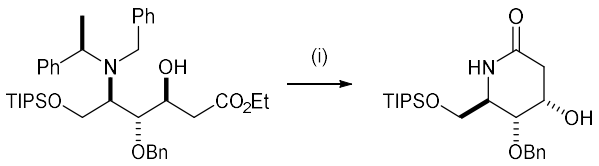


Figure 27. A model attempting to rationalise the stereocontrol in the addition of allylmagnesium bromide to **237**. [Nu = $CH_2CH{=}CH_2$].

3.11 Cyclisation of 257 and 256 to Lactams 278 and 281

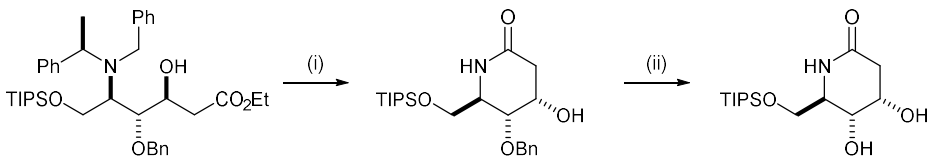
Cyclisation of the ethyl esters was expected to take place after hydrogenolysis of the *N*-protecting groups, which was also anticipated to deprotect the *O*-benzyl moiety to give a lactam. It was previously seen that δ-amino esters (similar to **256** and **257**) have been deprotected with 50% w/w $Pd(OH)_2/C$ under 5 atm H_2 in 16 h.[54] When these conditions were performed on **257**, *N*-deprotection and subsequent lactamisation occurred, although deprotection of the *O*-benzyl group did not occur and **278** was isolated in 47% yield and >95:5 dr (Scheme 79).



257, >95:5 dr **278**, 47%, >95:5 dr

Scheme 79. *Reagents and Conditions*: (i) $Pd(OH)_2/C$ (50% w/w), H_2 (5 atm), MeOH, rt, 18 h.

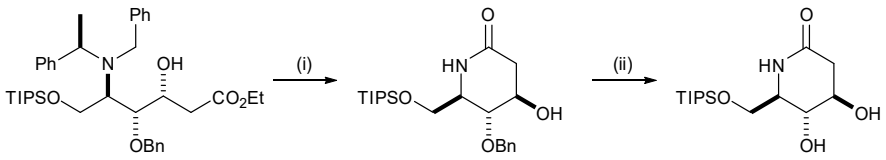
It was also shown that reaction with 20% w/w $Pd(OH)_2/C$ for 24 h was sufficient for *N*-deprotection and subsequent lactamisation giving **278**, which could then be *O*-debenzylated with sodium naphthalide in DME to give **279** in 76% yield (from **257**) and >95:5 dr (Scheme 80).



257, >95:5 dr **278** **279**, 76%, >95:5 dr

Scheme 80. *Reagents and Conditions*: (i) $Pd(OH)_2/C$ (20% w/w), H_2 (1 atm), MeOH, rt, 24 h; (ii) Na, naphthalene, DME, 0 °C to rt, 18 h.

The other diastereoisomer **256** could also be deprotected and cyclised in an analogous way giving lactam **281** in 56% yield as a single diastereoisomer (Scheme 81).



256, >95:5 dr **280** **281**, 56%, >95:5 dr

Scheme 81. *Reagents and Conditions*: (i) $Pd(OH)_2/C$ (20% w/w), H_2 (1 atm), MeOH, rt, 18 h; (ii) Na, naphthalene, DME, 0 °C to rt, 18 h.

The relative configuration within **281** was confirmed *via* single crystal X-ray diffraction analysis.[35] The absolute (*R*,*R*,*R*)-configuration was assigned from the known configurations of the C(5) and C(6) stereogenic centres which were established from the configuration within known aldehyde **237**.[26] A Flack *x* parameter[36,37] of –0.02(6) for the crystal structure of **281** was also consistent with its assigned absolute (*R*,*R*,*R*)-configuration. This also confirms the stereochemistry within ester **256** and therefore also ester **257** and lactam **279** (Figure 28).

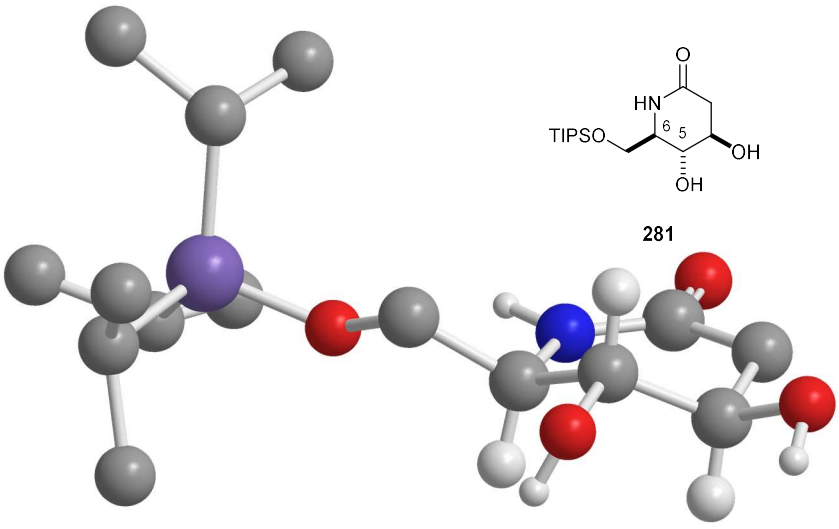
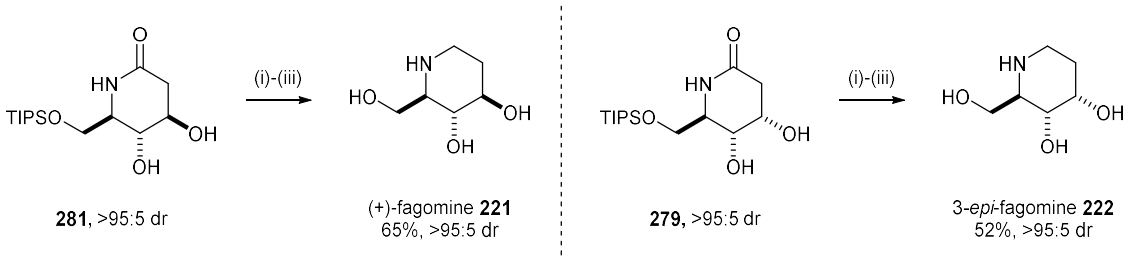


Figure 28. X-ray crystal structure of (*R*,*R*,*R*)-**281** (selected H atoms are omitted for clarity).

3.12 Elaboration of lactams 281 and 279 to fagomine 221 and 3-*epi*-fagomine 222

Following a protocol from Ham *et al*. reduction of lactams to piperidines and *O*-desilylation can be affected using $BH_3{\cdot}SMe_2$ followed by an oxidative work-up then treatment with HCl.[38] This procedure was applied to lactam **281** which gave (+)-fagomine **221** in 65% yield and >95:5 dr. Treatment of epimeric lactam **279** gave 3-*epi*-fagomine **222** in 52% yield and >95:5 dr (Scheme 82).



Scheme 82. *Reagents and Conditions*: (i) $BH_3{\cdot}SMe_2$, THF, 0 °C to rt, 2.5 h; (ii) 30% aq H_2O_2, 3.0 M aq NaOH, 85 °C, 1 h; (iii) 6.0 M aq HCl, 0 °C to rt, 18 h.

3.13 Proposed Synthetic Route to 223 and *ent*-224

After the successful syntheses of **221** and **222** it was envisaged that **223** and *ent*-**224** could be synthesised in an identical method beginning with epimerisation of *anti*-α-hydroxy-β-amino ester **232** at the C(2)-position *via* an oxidation/diastereoselective reduction pathway to give *syn*-**282** (Figure 29).

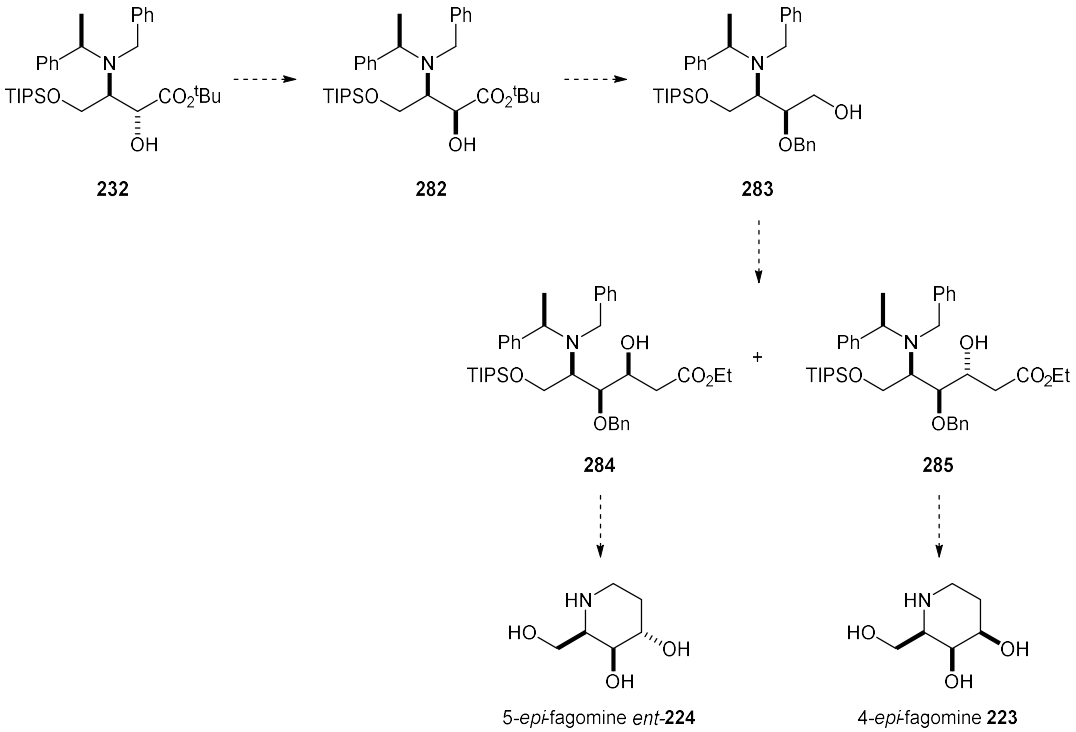
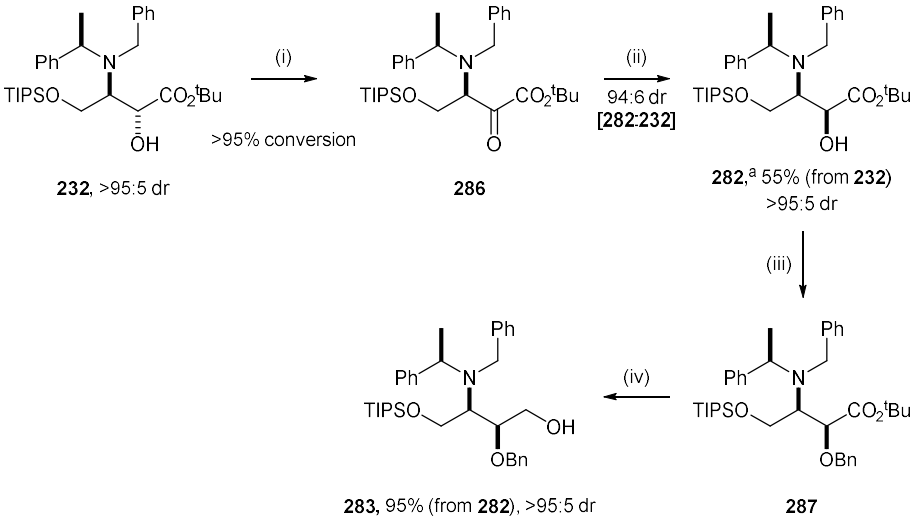


Figure 29. Proposed route to **223** and *ent*-**224**.

3.14 Synthesis of *syn*-283

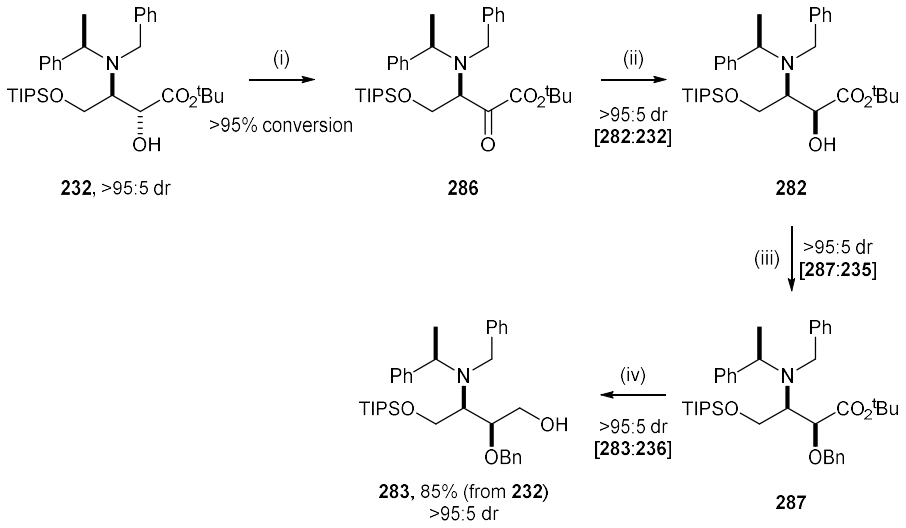
Following known procedures,[33] oxidation of *anti*-**232** using Swern conditions gave >95% conversion to α-ketoester **286**, which could be treated with $NaBH_4$ in MeOH at –20 °C to give a 94:6 mixture of *syn*-**282** and *anti*-**232**, respectively, from which *syn*-**282** was isolated in 55%

yield and >95:5 dr. An 88:12 mixture of *syn*-**282** and *anti*-**232**, respectively was also isolated in 32% yield. *O*-Benzylation of *syn*-**282** with NaH gave **287** which could be treated with DIBAL-H to give **283** which was isolated in 95% yield (over two steps) and >95:5 dr after purification (Scheme 83).



Scheme 83. *Reagents and Conditions*: (i) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 1 h then Et_3N, –78 °C, 20 min then rt, 20 min; (ii) $NaBH_4$, MeOH, –20 °C, 2 h; (iii) NaH, 0 °C, 1 h then BnBr, 0 °C to rt, 18 h; (iv) DIBAL-H, CH_2Cl_2, –78 °C, 2 h. [[a] An 88:12 mixture of *syn*-**282** and *anti*-**232**, respectively, was also isolated in 32% yield].

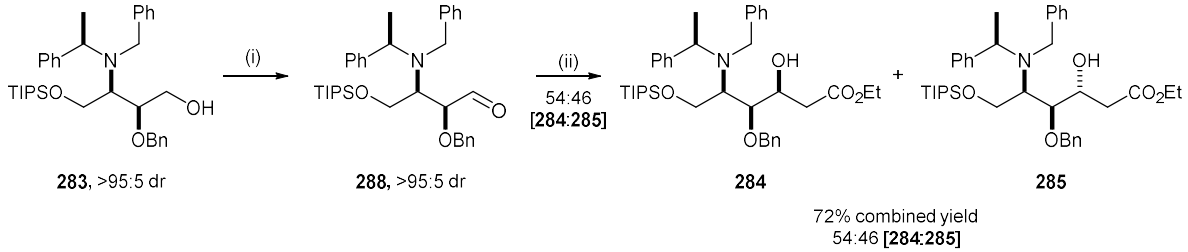
These four steps could also be telescoped allowing *syn*-**283** to be synthesised from *anti*-**232** in 85% yield and >95:5 dr, over four steps, from *anti*-**232** with only one chromatographic purification. This represents an improvement of 38% over the stepwise procedure as it obviates the separation of *syn*-**282** and *anti*-**232** (Scheme 84).



Scheme 84. *Reagents and Conditions*: (i) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 1 h then Et_3N, –78 °C, 20 min then rt, 20 min; (ii) $NaBH_4$, MeOH, –20 °C, 2 h; (iii) NaH, 0 °C, 1 h then BnBr, 0 °C to rt, 18 h; (iv) DIBAL-H, CH_2Cl_2, –78 °C, 2 h.

3.15 Aldol Condensation of *syn*-288 and EtOAc

The aldol condensation of **288** and EtOAc was next attempted. Oxidation of **283** was achieved *via* Swern conditions to give aldehyde **288** which was treated with the lithium enolate of EtOAc (formed after treatment of EtOAc with LDA) to give a 54:46 mixture of two diastereoisomers, **284** and **285**, respectively. The relative configurations within **284** and **285** were assigned using single crystal X-ray diffraction analysis of a derivative (*vide infra*). Purification *via* flash column chromatography gave an inseparable 54:46 mixture of **284** and **285**, respectively, in 72% combined yield (Scheme 85).

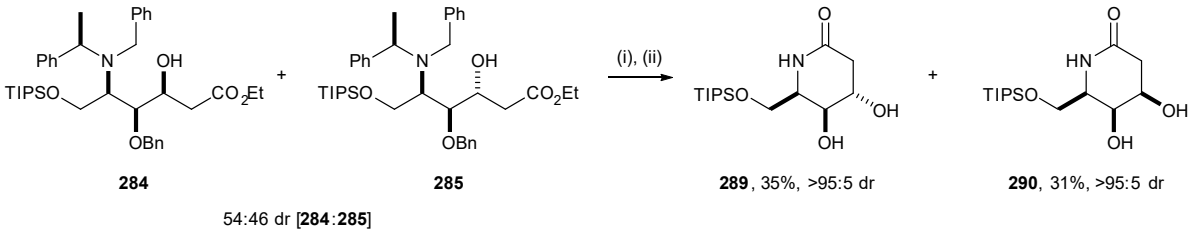


Scheme 85. *Reagents and Conditions*: (i) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 1 h then Et_3N, –78 °C, 20 min then rt, 20 min; (ii) BuLi, $^iPr_2NH$, 1.4 equiv EtOAc, –78 °C, 1 h then 0 °C, 2 h.

3.16 Cyclisation of 284 and 285

As previously, a two-step deprotection/cyclisation procedure was performed on a 54:46 mixture of **284** and **285**, respectively, using hydrogenolysis conditions followed by treatment

with Na and naphthalene to give a mixture of **289** and **290**. It was not possible to determine a crude ratio from the ^{1}H NMR spectrum due to excess naphthalene resonances. Purification *via* flash column chromatography allowed for the separation of the diastereoisomers and **289** was isolated in 35% yield and >95:5 dr, and **290** was isolated in 31% yield and >95:5 dr (Scheme 86).



Scheme 86. *Reagents and Conditions*: (i) $Pd(OH)_2/C$ (20% w/w), H_2 (1 atm), MeOH, rt, 24 h; (ii) Na, naphthalene, THF, 0 °C to rt, 18 h.

3.17 Stereochemical Assignment of 289 and 290

The relative configuration within **289** was established *via* single crystal X-ray diffraction analysis.[35] The absolute (4*S*,5*S*,6*R*)-configuration was assigned from the known configuration of the C(6) stereogenic centre which was established from the known configuration within **232** (*vide supra*). A Flack *x* parameter[36,37] of +0.10(8) for the crystal structure of **289** was also consistent with its assigned absolute (4*S*,5*S*,6*R*)-configuration. This also establishes the (4*R*,5*S*,6*R*)-configuration within lactam **290** (Figure 30).

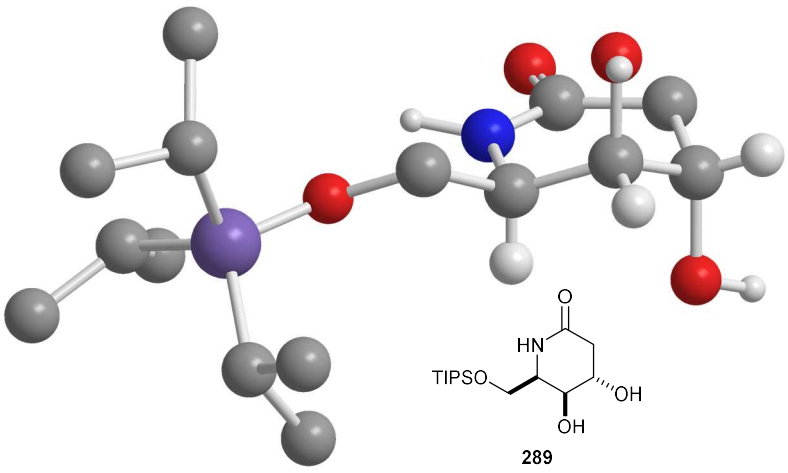
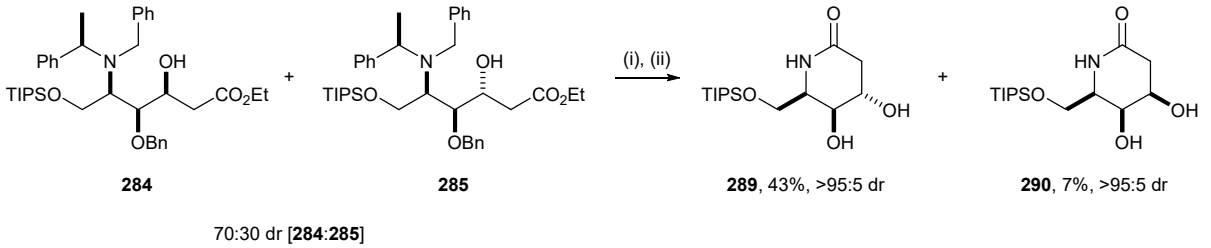


Figure 30. X-ray crystal structure of (4*S*,5*S*,6*R*)-**289** (selected H atoms are omitted for clarity).

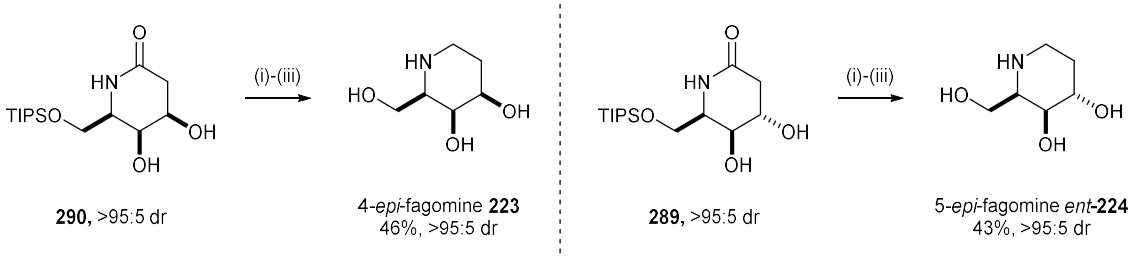
To be able to correlate the configurations within lactams **289** and **290** with their acyclic ester precursors, **284** and **285**, a 70:30 mixture of **284** and **285** was subjected to the lactamisation protocol which gave a ^{1}H NMR spectrum of the crude reaction mixture which was swamped with naphthalene and thus no diastereomeric ratio could be obtained. After chromatographic purification **289** was isolated in 43% yield and >95:5 dr, and **290** was isolated in 7% yield and >95:5 dr. As the yield of 43% for **289** is greater than the 30% of **285** in the starting material it can be confidently assigned that **289** is derived from **284** and **290** is derived from **285**. Thus, the relative configurations within the aldol adducts **284** and **285** were assigned as (3*S*,4*S*,5*R*,α*R*) and (3*R*,4*S*,5*R*,α*R*), respectively (Scheme 87).



Scheme 87. *Reagents and Conditions*: (i) $Pd(OH)_2/C$ (20% w/w), H_2 (1 atm), MeOH, rt, 24 h; (ii) Na, naphthalene, DME, 0 °C to rt, 18 h.

3.18 Elaboration of Lactams to 4-*epi*-Fagomine 223 and 5-*epi*-Fagomine *ent*-224

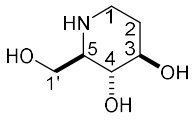
The deprotection procedure for the syntheses of **223** and *ent*-**224** was performed on lactams **290** and **289** to give 4-*epi*-fagomine **223** in 46% yield and >95:5 dr and 5-*epi*-fagomine *ent*-**224** in 43% yield and >95:5 dr (Scheme 88).



Scheme 88. *Reagents and Conditions*: (i) $BH_3{\cdot}SMe_2$, THF, 0 °C to rt, 2.5 h; (ii) 30% aq H_2O_2, 3.0 M aq NaOH, 85 °C, 1 h; (iii) 6.0 M aq HCl, 0 °C to rt, 18 h.

3.19 Spectroscopic Data for 221–223 and *ent*-224

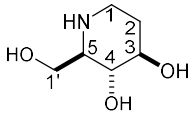
As a range of alkaloids are known to show variation in spectroscopic data depending on trace amounts of acid[39] it was decided to analyse spectra both after purification (DOWEX 50WX8-200 then silica/CH_2Cl_2/MeOH/NH_4OH) and after a base wash (KOH/$CHCl_3$/^{i}PrOH partition).[40] For this synthetic sample of (+)-fagomine **221** the spectroscopic data were compared only with the literature data where **221** was isolated from a natural source[1–6] due to the large number of previously reported syntheses. Asano *et al*. reported isolation of (+)-fagomine **221** from three different sources (*Morus bombycis*[2], *Morus alba*[3] and *Xanthocercis zambesiaca*[4]) with identical spectroscopic data. For the synthetic sample of **221** from this study the ^{1}H or ^{13}C NMR spectra were identical for pre- and post-base washed samples. The ^{1}H NMR chemical shifts[41] of synthetic **221** are well matched [$(-0.07 \leq \Delta\delta_H \leq -0.02)^1$ and $[(-0.04 \leq \Delta\delta_H \leq -0.01)^{2-4}]^{42}$ with the literature data of the sample isolated from Nature in both cases (Table 2). The ^{13}C NMR chemical shifts[41] show good comparison $[(-0.1 \leq \Delta\delta_C \leq 0.0)^{2-4}$ and $(+0.1 \leq \Delta\delta_C \leq +0.3)^5]^{43}$ with the literature data in all cases (Table 3). The specific rotation of synthetic **221** was determined as $[\alpha]_D^{25}$ +14.9 (*c* 1.0 in H_2O) which is comparable to literature values {$[\alpha]_D$ +19.5 (*c* 1 in H_2O);[2,3] $[\alpha]_D^{11}$ +23 (*c* 1 in H_2O)[1]. The melting point of synthetic **221** was recorded as 170–173 °C in comparison to reported values (mp 184–185 °C;[5] mp 186–188 °C)[1].



221

	This work	Isolation[a]		Isolation[b]	
	δ_H (400 MHz, D_2O)[41]	δ_H (220 MHz, D_2O)	$\Delta\delta_H$[42]	δ_H (400 MHz, D_2O)	$\Delta\delta_H$[42]
C(1)H_A	2.63 (td, *J* 12.8, 2.6)	2.58	–0.05	2.60 (dt, *J* 13.0, 2.6)	–0.03
C(1)H_B	3.04 (m)	2.98	–0.06	3.00 (dt, *J* 13.0, 4.5)	–0.04
C(2)H_A	1.46 (m)	1.43	–0.03	1.45 (ddt, *J* 13.0, 11.6, 4.5)	–0.01
C(2)H_B	2.01 (m)	1.97	–0.04	1.99 (dddd, *J* 13.0, 5.1, 2.6, 2.2)	–0.02
C(3)*H*	3.55 (ddd, *J* 11.5, 9.0, 5.0)	3.52	–0.03	3.54 (ddd, *J* 11.6, 9.2, 5.1)	–0.01
C(4)*H*	3.19 (t, *J* 9.7)	3.14	–0.05	3.17 (dd, *J* 9.5, 9.2)	–0.02
C(5)*H*	2.56 (ddd, *J* 9.7, 6.7, 3.0)	2.49	–0.07	2.52 (ddd, *J* 9.5, 6.6, 3.0)	–0.04
C(1')H_A	3.65 (dd, *J* 11.6, 6.7)	3.60	–0.05	3.63 (dd, *J* 11.7, 6.6)	–0.02
C(1')H_B	3.86 (dd, *J* 11.6, 3.0)	3.84	–0.02	3.85 (dd, *J* 11.7, 3.0)	–0.01

Table 2. Comparison of ^{1}H NMR spectroscopic data of (+)-fagomine **221**. [[a] Isolation from *Fagopyrum esculentum Moensch*.[1] [b] Isolation from *Morus bombycids*,[2] *Morus alba*[3] and *Xanthocercis zambesiaca*.[4]].



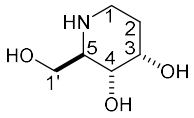
221

This work	Isolation[a]	Isolation[b]
δ_C (100 MHz, D_2O)[41]	δ_C (100 MHz, D_2O)[43]	δ_C (50.3 MHz, D_2O)[43]
35.5	35.6 (–0.1)	35.3 (+0.2)
45.4	45.4 (0.0)	45.3 (+0.1)
63.7	63.7 (0.0)	63.6 (+0.1)
64.5	64.5 (0.0)	64.2 (+0.3)
76.0	76.1 (–0.1)	75.8 (+0.2)
76.1	76.1 (0.0)	75.9 (+0.2)

Table 3. Comparison of ^{13}C NMR spectroscopic data of (+)-fagomine **221**. [[a] Isolation from *Morus bombycis*[2], *Morus alba*[3] and *Xanthocercis zambesiaca*.[4] [b] Isolation from *Castanospermum australe*[5]].

Again, due to the large number of synthetic samples reported the spectroscopic data from synthetic 3-*epi*-fagomine **222** was only compared with the literature data where **222** was isolated from a natural source.[3,4,6] Again, for the synthetic sample of 3-*epi*-fagomine the ^{1}H or ^{13}C NMR spectra were identical for pre- and post-base washed samples.[44] There is good agreement of the ^{1}H NMR spectroscopic data[41] of synthetic **222** with natural **222** ($-0.05 \leq \Delta\delta_H \leq +0.05$) (Table 4).[42] There is perfect agreement with the ^{13}C NMR spectroscopic data[41] ($\Delta\delta_C = 0.0$)[43] in all cases (Table 5). The specific rotation of synthetic **222** was determined as $[\alpha]_D^{25}$ +62.8 (*c* 1.0 in H_2O), which is comparable to literature values

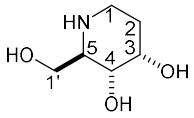
{$[\alpha]_D$ +69.0 (*c* 0.5 in H_2O)[3,4,6]}. No melting points are reported for **222** isolated from a natural source however it is described as a colourless powder.[6]



222

	This work	Isolation[a]	
	δ_H (400 MHz, D_2O)[41]	δ_H (400 MHz, D_2O)[6]	$\Delta\delta_H$[42]
C(1)H_A	2.82 (m)	2.77 (dddd, *J* 11.7, 5.9, 2.6)	–0.05
C(1)H_B	2.82 (m)	2.79 (dt, *J* 11.7, 2.6)	–0.03
C(2)H_A	1.72 (m)	1.73 (dddd, *J* 14.3, 11.7, 5.9, 2.6)	+0.01
C(2)H_B	1.84 (m)	1.85 (ddt, *J* 14.3, 3.3, 2.6)	+0.01
C(3)*H*	4.09 (app q, *J* 3.1)	4.09 (dt, *J* 3.3, 2.6)	0
C(4)*H*	3.47 (dd, *J* 10.1, 3.0)	3.48 (dd, *J* 9.9, 3.3)	+0.01
C(5)*H*	2.82 (m)	2.87 (dddd, *J* 9.9, 6.6, 3.3)	+0.05
C(1')H_A	3.62 (dd, *J* 11.5, 6.6)	3.63 (dd, *J* 11.7, 6.6)	+0.01
C(1')H_B	3.82(dd, *J* 11.5, 3.2)	3.82 (dd, *J* 11.7, 3.3)	0

Table 4. Comparison of ^{1}H NMR spectroscopic data of 3-*epi*-fagomine **222**. [[a] Isolation from *Morus alba*[3,6]].



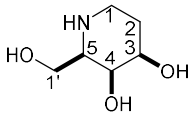
222

This work	Isolation[a]	Isolation[b]
δ_C (100 MHz, D_2O)[41]	δ_C (100 MHz, D_2O)[43]	δ_C (100 MHz, D_2O)[43]
33.8	33.8 (0.0)	33.8 (0.0)
41.2	41.2 (0.0)	41.2 (0.0)
58.6	58.6 (0.0)	58.6 (0.0)
64.9	64.9 (0.0)	64.9 (0.0)
70.7	70.7 (0.0)	70.7 (0.0)
72.4	72.4 (0.0)	72.4 (0.0)

Table 5. Comparison of ^{13}C NMR spectroscopic data of 3-*epi*-fagomine **222**. [[a] Isolation from *Morus alba*.[3,6] [b] Isolation from *Xanthocercis zambesiaca*[4]].

4-*epi*-(+)-Fagomine **223** has not been isolated from a natural source but has been the subject of a limited number of synthetic pursuits so a full comparison of all previous reported synthetic data was undertaken. The ^{1}H NMR spectroscopic data are inconsistent in the literature but the synthetic sample shows good agreement with the data of the sample synthesised by van den Berg and co-workers[13] ($+0.03 \leq \Delta\delta_H \leq +0.10$).[42] However, upon base-washing[45] to ensure the free base was being analysed a shift in ^{1}H NMR resonances was observed. Unfortunately the

free base sample included some unknown impurities although was deemed to be of sufficient quality for this analysis. The ^{1}H NMR chemical shifts of the free base showed good agreement with the data of the sample synthesised by Takahata and co-workers[11] ($+0.12 \leq \Delta\delta_H \leq +0.18$)[42] (Table 6). A variation in chemical shift was also noted in the pre- and post-base washed samples in the ^{13}C NMR spectra: the original spectrum of **223** was in good agreement with the synthetic samples from a number of sources [($+3.0 \leq \Delta\delta_C \leq +3.1$)[10] and ($+2.6 \leq \Delta\delta_C \leq +2.8$)[13]][43] and the free base spectrum also matched with the data of the synthetic samples from a number of sources [($-0.1 \leq \Delta\delta_C \leq +0.3$)[3] and ($+2.0 \leq \Delta\delta_C \leq +2.2$)[11,12]][43] (Table 8). A number of samples showed data that did not match either data set for **223** [for example:[8] ($-0.47 \leq \Delta\delta_H \leq -0.06$) and ($+2.5 \leq \Delta\delta_C \leq +3.0$) with pre-base washed **223** and ($-0.39 \leq \Delta\delta_H \leq +0.04$) and ($+1.8 \leq \Delta\delta_C \leq +6.0$) with the free base][42,43] (Tables 7 and 9). These data suggest that previously reported samples of this compound may be particularly prone to be contaminated with small amounts of acid, contributing to the inconsistency of data reported. The specific rotation of synthetic **223** was determined as $[\alpha]_D^{25}$ +13.9 (*c* 1.0 in H_2O), which is comparable to literature values {$[\alpha]_D^{25}$ +11.7 (*c* 1.8 in H_2O);[9] $[\alpha]_D^{25}$ +10.4 (*c* 1.4 in H_2O);[14] $[\alpha]_D^{22}$ +10.2 (*c* 1.42 in H_2O);[11] $[\alpha]_D$ +19 (*c* 0.46 in H_2O)[3]}.



223

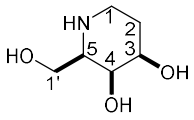
	This work	[13]		This work – Free base[46]	[11]	
	δ_H (400 MHz, D_2O)[41]	δ_H (500 MHz, D_2O)	$\Delta\delta_H$[42]	δ_H (400 MHz, D_2O)[41]	δ_H (300 MHz, D_2O)	$\Delta\delta_H$[42]
C(1)H_A	3.08 (td, *J* 13.2, 3.9)	3.16 (ddd, *J* 13.2, 13.2, 4.0)	+0.08	2.56 (td, *J* 12.5, 4.3)	2.44 (m)	+0.12
C(1)H_B	3.47 (ddd, *J* 13.2, 4.6, 2.4)	3.55 (ddd, *J* 13.1, 6.7, 2.3)	+0.08	3.04 (m)	2.91 (td, *J* 12.9, 3.3)	+0.13
C(2)H_A	2.01 (m)	2.05 (m)	+0.04	1.68 (m)	1.53 (m)	+0.15
C(2)H_B	2.01 (m)	2.05 (m)	+0.04	1.68 (m)	1.53 (m)	+0.15
C(3)*H*	3.87 (m)	None given	n/a	3.73 (m)	3.55 (m)	+0.18
C(4)*H*	4.09 (m)	4.17 (t, *J* 1.3)	+0.08	3.90 (m)	3.74 (br s)	+0.16
C(5)*H*	3.34 (ddd, *J* 8.5, 5.1, 1.2)	3.44 (ddd, *J* 8.6, 4.9, 1.3)	+0.10	2.68 (m)	2.57 (td, *J* 6.9, 5.2)	+0.11
C(1')H_A	3.87 (m)	3.90 (dd, *J* 12.1, 8.7)	+0.03	3.62 (m)	3.47 (dd, *J* 6.7, 3.4)	+0.15
C(1')H_B	3.87 (m)	3.95 (dd, *J* 12.1, 4.9)	+0.03	3.62 (m)	3.47 (dd, *J* 6.7, 3.4)	+0.15

Table 6. ^{1}H NMR spectroscopic data comparison of **223** and synthetic sample reported by van den Berg and co-workers.

	8		3		47	
	δ_H (500 MHz, D_2O)	$\Delta\delta_H$[42]	δ_H (400 MHz, D_2O)	$\Delta\delta_H$[42]	δ_H (400 MHz, D_2O)	$\Delta\delta_H$[42]
C(1)H_A	2.95	–0.13 –0.39	2.62 (ddd, *J* 13.0, 11.0, 4.4)	–0.46 –0.06	2.95	–0.13 –0.37
C(1)H_B	3.00	–0.47 +0.04	3.09 (ddd, *J* 13.0, 4.4, 2.6)	–0.38 –0.05	3.18	–0.29 –0.14
C(2)H_A	1.85	–0.16 –0.17	1.45 (m)	–0.56 –0.23	1.75	–0.26 –0.07
C(2)H_B	1.95	–0.06 –0.27	1.45 (m)	–0.56 –0.23	1.85	–0.16 –0.17
C(3)*H*	3.80	–0.07 –0.07	3.75 (ddd, *J* 10.5, 6.5, 3.0)	–0.12 –0.02	3.80	–0.07 –0.07
C(4)*H*	4.00	–0.09 –0.10	3.92 (dd, *J* 3.0, 1.5)	–0.17 –0.02	4.00	–0.09 –0.10
C(5)*H*	3.20	–0.14 –0.52	2.76 (dt, *J* 6.6, 1.5)	–0.58 –0.08	3.20	–0.14 –0.52
C(1')H_A	3.76	–0.11 –0.14	3.63 (dd, *J* 11.5, 6.6	–0.24 –0.01	3.72 (dd)	–0.15 –0.10
C(1')H_B	3.72	–0.15 –0.10	3.67 (dd, *J* 11.5, 6.6)	–0.24 –0.05	3.76 (dd)	–0.11 –0.14

	10		9	
	δ_H (600 MHz, D_2O)	$\Delta\delta_H$[42]	δ_H (700 MHz, D_2O)	$\Delta\delta_H$[42]
C(1)H_A	2.73 (m)	–0.35 –0.17	2.77 (m)	–0.31 –0.21
C(1)H_B	3.17 (dt, *J* 12.7, 3.6)	–0.30 –0.13	2.93 (t, *J* 6.6)	–0.54 –0.11
C(2)H_A	1.77 (m)	–0.24 –0.09	1.83 (m)	–0.18 –0.15
C(2)H_B	1.77 (m)	–0.24 –0.09	1.83 (m)	–0.18 –0.15
C(3)*H*	3.76 (ddd, *J* 10.5, 8.4, 2.8)	–0.11 –0.03	3.85 (m)	–0.02 –0.12
C(4)*H*	3.92 (br s)	–0.17 –0.02	4.01 (m)	–0.08 –0.11
C(5)*H*	2.92 (app t, *J* 7.1)	–0.42 –0.24	3.22 (m)	–0.12 –0.54
C(1')H_A	3.65 (dd, *J* 11.6, 7.6)	–0.22 –0.03	3.75 (m)	–0.12 –0.13
C(1')H_B	3.69 (dd, *J* 11.7, 5.8)	–0.18 –0.03	3.75 (m)	–0.12 –0.13

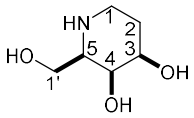
Table 7. ^{1}H NMR spectroscopic data of a number of synthetic samples of 4-*epi*-fagomine **223**. [$\Delta\delta_H$ indicated in RED are in reference to the pre-base washed sample of **223** and $\Delta\delta_H$ indicated in GREEN are in reference to the free base sample of **223**].



223

This work	10	13	This work - free base	3	11,12
δ_C[a,41]	δ_C[b,43]	δ_C[c,43]	δ_C[a,41,43]	δ_C[c,43]	δ_C[c,43]
27.0	**24.0** (+3.0)	**24.4** (+2.6)	30.5	**30.2** (+0.3)	**28.4** (+2.1)
45.2	**42.1** (+3.1)	**42.6** (+2.6)	45.7	**45.6** (+0.1)	**43.6** (+2.1)
62.5	**59.4** (+3.1)	**59.8** (+2.7)	61.7	**61.8** (–0.1)	**59.7** (+2.0)
63.0	**60.0** (+3.0)	**60.2** (+2.8)	64.7	**64.5** (+0.2)	**62.5** (+2.2)
68.9	**65.8** (+3.1)	**66.2** (+2.7)	70.6	**70.5** (+0.1)	**68.5** (+2.1)
70.4	**67.4** (+3.0)	**67.7** (+2.7)	72.9	**72.7** (+0.2)	**70.7** (+2.2)

Table 8. Comparison of ^{13}C NMR spectroscopic data of 4-*epi*-fagomine **223** and its free base with four synthetic samples. [[a] 100 MHz, D_2O. [b] 150 MHz, D_2O. [c] 125 MHz, D_2O]. [$\Delta\delta_C$ indicated in RED are in reference to the pre-base washed sample of **223** and $\Delta\delta_C$ indicated in GREEN are in reference to the free base sample of **223**].



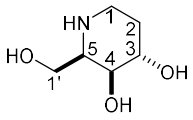
223

47	9	14	8
δ_C[a,43]	δ_C[a,43]	δ_C[a,43]	δ_C[a,43]
25.13 (+1.87) (+5.37)	**26.6** (+0.4) (+3.9)	**25.6** (+1.4) (+4.9)	**24.5** (+2.5) (+6.0)
42.40 (+2.8) (+3.3)	**42.6** (+2.6) (+3.1)	**46.8** (–1.6) (–1.1)	**42.2** (+3.0) (+3.5)
59.65 (+2.85) (+2.05)	**59.1** (+3.4) (+2.6)	**59.9** (+2.6) (+1.8)	**59.9** (+2.6) (+1.8)
60.17 (+2.83) (+4.53)	**61.1** (+1.9) (+3.6)	**62.8** (+0.2) (+1.9)	**60.3** (+2.7) (+4.4)
66.45 (+2.45) (+4.15)	**67.2** (+1.7) (+3.4)	**68.7** (+0.2) (+1.9)	**66.2** (+2.7) (+4.4)
68.26 (+2.14) (+4.64)	**69.3** (+1.1) (+3.6)	**69.3** (+1.1) (+3.6)	**67.6** (+2.8) (+5.3)

Table 9. ^{13}C NMR spectroscopic data of four synthetic samples of 4-*epi*-fagomine **223**. [[a] 125 MHz, D_2O. $\Delta\delta_C$ indicated in RED are in reference to the pre-base washed sample of **223** and $\Delta\delta_C$ indicated in GREEN are in reference to the free base sample of **223**].

5-*epi*-Fagomine *ent*-**224** was isolated by Asano *et al*. in 1997 from *Xanthocercis zambesiaca* however no information about its absolute configuration was given.[4] It was also isolated by Kato and Fleet *et al*. in 2015 from *Castanospermum australe* however no spectroscopic data

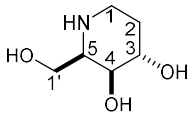
was given.[7] Once again, the ^{1}H NMR spectroscopic data were found to be variant upon its protonation level. Intially the ^{1}H NMR spectroscopic data of *ent*-**224** showed poor agreement with the sample isolated from *Xanthocercis zambesiaca*[4] ($+0.12 \leq \Delta\delta_H \leq +0.39$)[42] however upon basifying the data showed good agreement ($-0.02 \leq \Delta\delta_H \leq -0.08$)[42] (Table 10). The original ^{13}C NMR data from the synthetic sample of *ent*-**224** from this study showed poor agreement with the data from the sample isolated from *Xanthocercis zambesiaca*[4] ($-3.4 \leq \Delta\delta_C \leq +0.5$)[43] although upon base-washing it showed better agreement ($-0.7 \leq \Delta\delta_C \leq +0.1$)[43] (Table 11). Upon comparison of the synthetic spectroscopic data of *ent*-**224** from the literature with the pre-base washed data of *ent*-**224** from this study the ^{1}H NMR spectroscopic data shows excellent agreement with one source[13] ($-0.04 \leq \Delta\delta_H \leq -0.03$),[42] however upon basifying it shows excellent agreement with another source[11] ($+0.06 \leq \Delta\delta_H \leq +0.10$)[42] (Table 12). The ^{13}C NMR spectroscopic data initially showed excellent agreement with one source[13] ($+2.3 \leq \Delta\delta_C \leq +2.5$)[43] and, again, upon basifying showed good agreement with two other samples[11,48] [($+2.1 \leq \Delta\delta_C \leq +2.4$) and ($+2.03 \leq \Delta\delta_C \leq +2.32$)][43] (Table 13). A single sample showed data that did not match either data set for *ent*-**224** [($+0.21 \leq \Delta\delta_H \leq +0.33$) and ($-1.1 \leq \Delta\delta_C \leq +0.9$) for pre-base washed *ent*-**224** and [($-0.01 \leq \Delta\delta_H \leq +0.11$) and ($+0.3 \leq \Delta\delta_C \leq +3.0$) for the free base of *ent*-**224**][42,43] and (Tables 12 and 13).[49] The specific rotation of synthetic *ent*-**224** was determined as $[\alpha]_D^{25}$ +8.0 (*c* 1.0 in H_2O) which would infer that the absolute configuration of the sample isolated from *Xanthocercis zambesiaca* is (3*R*,4*R*,5*S*)-**224** {lit.[4] $[\alpha]_D$ –8.7 (*c* 0.3 in H_2O)}. This is consistent with the current data in the literature for (3*R*,4*R*,5*S*)-**224** {$[\alpha]_D^{25}$ –10.2 (*c* 0.5 in H_2O);[50] $[\alpha]_D^{21}$ –10.6 (*c* 0.32 in H_2O);[51] $[\alpha]_D^{25}$ –14 (*c* 1.96 in H_2O);[12] $[\alpha]_D$ –11.6 (*c* 0.94 in H_2O);[13] $[\alpha]_D^{20}$ –15 (*c* 0.5 in H_2O)[52]} and for (3*S*,4*S*,5*R*)-**224** [*ent*-**224**] {$[\alpha]_D^{25}$ +12.1 (*c* 0.33 in H_2O);[49] $[\alpha]_D^{25}$ +13.4 (*c* 0.32 in H_2O)[11]}.



ent-**224**

	This work	This work – free base	Isolation of **224**[a]	
	δ_H (400 MHz, D_2O)[41]	δ_H (400 MHz, D_2O)[41]	δ_H (400 MHz, D_2O)	$\Delta\delta_H$[42]
C(1)H_A	3.27 (m)	2.85 (m)	2.91 (m)	+0.36 –0.06
C(1)H_B	3.27 (m)	2.85 (m)	2.92 (m)	+0.25 –0.07
C(2)H_A	1.85 (m)	1.58 (dq, *J* 14.1, 4.2)	1.62 (ddt, *J* 13.0, 9.0, 3.4)	+0.23 –0.04
C(2)H_B	2.22 (m)	1.96 (m)	2.04 (m)	+0.18 –0.08
C(3)*H*	4.05 (m)	3.90 (app q, *J* 4.3)	3.93 (dt, *J* 4.6, 3.4)	+0.12 –0.03
C(4)*H*	3.95 (m)	3.71 (m)	3.75 (dd, *J* 4.6, 2.7)	+0.20 –0.04
C(5)*H*	3.55 (m)	3.10 (td, *J* 6.7, 2.6)	3.16 (ddd, *J* 7.3, 6.1, 2.7)	+0.39 –0.06
C(1')H_A	3.81 (dd, *J* 12.2, 8.7)	3.66 (m)	3.68 (dd, *J* 11.5, 7.3)	+0.13 –0.02
C(1')H_B	3.87 (dd, *J* 12.2, 5.0)	3.66 (m)	3.71 (dd, *J* 11.5, 6.1)	+0.16 –0.05

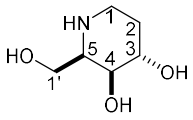
Table 10. Comparison of ^{1}H NMR spectroscopic data of 5-*epi*-fagomine *ent*-**224** with natural **224**. [[a] Isolated from *Xanthocercis zambesiaca*[4]].



ent-**224**

This work	This work – free base	Isolation of **224**[a]
δ_C (100 MHz, D_2O)[41]	δ_C (100 MHz, D_2O)[41]	δ_C (100 MHz, D_2O)[43]
26.5	30.6	29.9 (–3.4) (–0.7)
41.7	41.4	41.4 (+0.3) (+0.0)
58.7	58.1	58.2 (+0.5) (+0.1)
62.4	63.5	63.3 (–0.9) (–0.2)
67.7	70.5	70.0 (–2.3) (–0.5)
68.7	71.5	71.0 (–2.3) (–0.5)

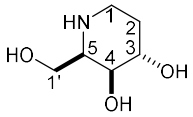
Table 11. Comparison of ^{13}C NMR spectroscopic data of 5-*epi*-fagomine *ent*-**224** with natural **224**. [[a] Isolated from *Xanthocercis zambesiaca*[4]].



ent-**224**

	This work	[13]		This work – free base	[11]		[49]	
	δ_H[a,41]	δ_H[a]	$\Delta\delta_H$[42]	δ_H[a,41]	δ_H[c]	$\Delta\delta_H$[42]	δ_H[b]	$\Delta\delta_H$[42]
C(1)H_A	3.27 (m)	3.30 (m)	–0.03	2.85 (m)	2.78 (m)	+0.07	2.96 (m)	+0.31 –0.11
C(1)H_B	3.27 (m)	3.30 (m)	–0.03	2.85 (m)	2.78 (m)	+0.07	2.96 (m)	+0.31 –0.11
C(2)H_A	1.85 (m)	1.88 (ddd, *J* 15.2, 2.4, 2.4)	–0.03	1.58 (dq, *J* 14.1, 4.2)	1.47 (m)	+0.09	1.59 (m)	+0.26 –0.01
C(2)H_B	2.22 (m)	2.25 (m)	–0.03	1.96 (m)	1.86 (m)	+0.10	1.97 (m)	+0.25 –0.01
C(3)*H*	4.05 (m)	4.07 (dd, *J* 6.8, 3.0)	–0.02	3.90 (app q, *J* 4.3)	3.80 (br s)	+0.10	3.84 (m)	+0.21 –0.06
C(4)*H*	3.95 (m)	3.98 (dt, *J* 4.3, 1.2)	–0.03	3.71 (m)	3.61 (br s)	+0.10	3.70 (m)	+0.25 +0.01
C(5)*H*	3.55 (m)	3.58 (ddd, *J* 8.4, 5.2, 2.0)	–0.03	3.10 (td, *J* 6.7, 2.6)	3.04 (m)	+0.06	3.22 (m)	+0.33 –0.12
C(1')H_A	3.81 (dd, *J* 12.2, 8.7)	3.85 (dd, *J* 12.2, 8.6)	–0.04	3.66 (m)	3.57 (m)	+0.09	3.62 (m)	+0.19 –0.04
C(1')H_B	3.87 (dd, *J* 12.2, 5.0)	3.90 (dd, *J* 12.2, 3.9)	–0.03	3.66 (m)	3.57 (m)	+0.09	3.62 (m)	+0.25 –0.04

Table 12. Comparison of ^{1}H NMR spectroscopic data of 5-*epi*-fagomine **224**. [[a] 400 MHz, D_2O. [b] 200 MHz, D_2O. [c] 500 MHz, D_2O]. [$\Delta\delta_H$ indicated in RED are in reference to the pre-base washed sample of **223** and $\Delta\delta_H$ indicated in GREEN are in reference to the free base sample of **223**].



ent-**224**

This work	[13]	This work – free base	[48]	[11]	[49]
δ_C[41,a]	δ_C[a,43]	δ_C[a,41,43]	δ_C[b,43,53]	δ_C[b,43]	δ_C[c,43]
26.5	**24.2** (+2.3)	30.6	**28.28** (+2.32)	**28.2** (+2.4)	**27.6** (–1.1) (+3.0)
41.7	**39.3** (+2.4)	41.4	**39.37** (+2.03)	**39.3** (+2.1)	**41.0** (+0.7) (+0.4)
58.7	**56.2** (+2.5)	58.1	**56.07** (+2.03)	**56.0** (+2.1)	**57.8** (+0.9) (+0.3)
62.4	**60.0** (+2.4)	63.5	**61.39** (+2.11)	**61.3** (+2.2)	**62.2** (+0.2) (+1.3)
67.7	**65.4** (+2.3)	70.5	**68.22** (+2.28)	**68.2** (+2.3)	**68.2** (–0.5) (+2.3)
68.7	**66.4** (+2.3)	71.5	**69.19** (+2.31)	**69.1** (+2.4)	**69.3** (–0.6) (+2.2)

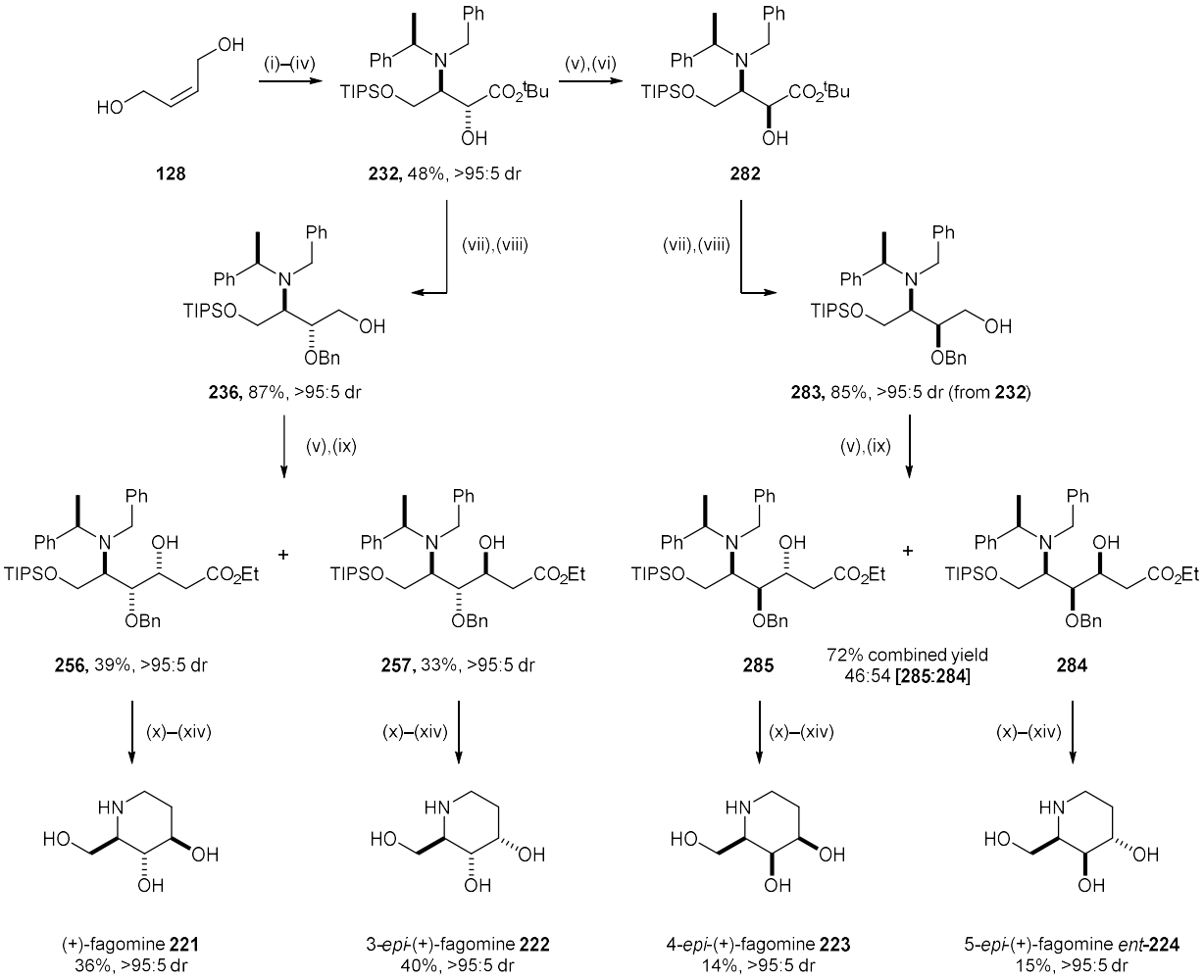
Table 13. Comparison of ^{13}C NMR spectroscopic data of 5-*epi*-fagomine **224**. [[a] 100 MHz, D_2O. [b] 125 MHz, D_2O. [c] 50 MHz, D_2O]. [$\Delta\delta_C$ indicated in RED are in reference to the pre-base washed sample of **223** and $\Delta\delta_C$ indicated in GREEN are in reference to the free base sample of **223**].

3.20 Summary

The syntheses of all four fagomine diastereoisomers have been achieved from *cis*-but-2-en-1,4-diol **128** using an aminohydroxylation reaction[17] and an aldol condensation as the key stereodefining steps.[55] An asymmetric aldol reaction was also explored to try to increase the diastereoselectivity of that transformation. Commercially available **128** was converted to α,β-unsaturated ester **230** *via O*-silylation, ozonolytic cleavage and Masamune-Rousche olefination.[19] Aminohydroxylation[17] of **230** with (*R*)-**163** followed by oxidation with (–)-CSO (–)-**182** gave **232** in 48% yield over 5 steps from commercially available **128**. *O*-Benzylation followed by reduction gave primary alcohol as **236** in 87% yield and >95:5 dr. Oxidation to aldehyde **237** allowed for an aldol reaction with EtOAc, which gave an ~65:35 mixture of **256** and **257** that were isolated in 39 and 33% yield, respectively, and >95:5 dr in both cases. Elaboration of **256**, *via* lactam **281**, to (+)-fagomine **221** occurred in 36% yield and >95:5 dr over five steps, corresponding to 5.9% overall yield from achiral starting materials over

13 steps. Elaboration of **257**, *via* lactam **279**, to 3-*epi*-fagomine **222** occurred in 40% yield and >95:5 dr, corresponding to 5.5% overall yield from achiral starting materials over 13 steps. 4-*epi*-Fagomine **223** and 5-*epi*-fagomine *ent*-**224** were synthesised using an analogous route. Epimerisation of *anti*-**232** *via* an oxidation-reduction strategy gave *syn*-**282**, which could be converted to primary alcohol using identical steps, and was isolated in 85% yield (from **232**) and >95:5 dr. Aldol reaction gave an inseparable mixture of **284** and **285** in 72% combined yield and 54:46 dr, which could be lactamised and deprotected to give 4-*epi*-fagomine **223** in 14% yield and >95:5 dr, and 5-*epi*-fagomine *ent*-**224** in 15% yield and >95:5 dr. The syntheses of **223** and *ent*-**224** were completed from **128** in 4.1 and 4.4% overall yield, respectively, over 15 steps (Scheme 89). The spectroscopic data and specific rotations of **221** and **222** were analysed and were found to be in accordance with the data from samples isolated from natural sources. The spectroscopic data for **223** and *ent*-**224** were found to be dependent on their level

of protonation and found to be in accordance with data from a number of sources in the literature.



Scheme 89. *Reagents and Conditions*: (i) TIPSCl, imidazole, DMAP, CH_2Cl_2, rt, 18 h; (ii) O_3, MeOH, rt then Me_2S, rt, 18 h; (iii) $^iPr_2NEt$, **231**, LiCl, MeCN, rt, 72 h; (iv) (*R*)-**163**, –78 °C, 2 h then (–)-**182**, –78 °C to rt, 18 h; (v) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 1 h then Et_3N, –78 °C, 20 min then rt, 20 min; (vi) $NaBH_4$, MeOH, –20 °C, 2 h (vii) NaH, 0 °C, 1 h then BnBr, 0 °C to rt, 18 h; (viii) DIBAL-H, CH_2Cl_2, –78 °C, 2 h; (ix) BuLi, $^iPr_2NH$, EtOAc, –78 °C, 1 h then 0 °C, 2 h; (x) $Pd(OH)_2$/C (20% w/w), H_2 (1 atm), MeOH, rt, 24 h; (xi) Na, naphthalene, DME, 0 °C to rt, 18 h; (xii) $BH_3{\cdot}SMe_2$, THF, 0 °C to rt, 2.5 h; (xiii) 30% aq H_2O_2, 3.0 M aq NaOH, 85 °C, 1 h; (xiv) 6.0 M aq HCl, 0 °C to rt, 18 h.

3.21 References

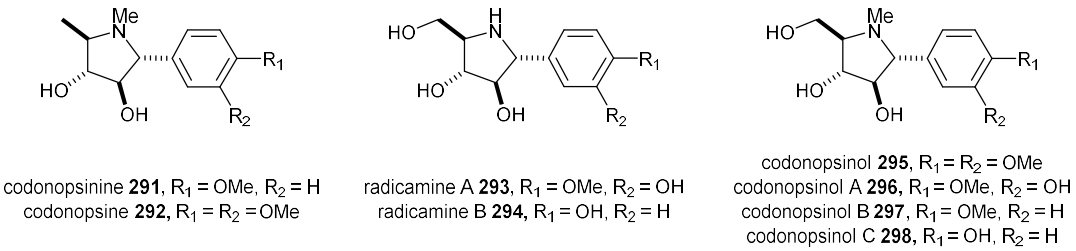
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(41) Chemical shifts were measured downfield from sodium 3-(trimethylsilyl)propanoate.
(42) $\Delta\delta_H$ is defined as the difference in the ^{1}H NMR spectroscopic resonances of the literature from the data from this study.
(43) $\Delta\delta_C$ is defined as the difference in the ^{13}C NMR spectroscopic resonances of the literature from the data from this study.
(44) To ensure the free-base of **222** was analysed a partition between NaOH (2.0 M aq) and $CHCl_3$/^{i}PrOH (3:1 v/v) was used to provide an analytical sample of **222**.
(45) Upon basifying the analytical sample of **223** reduced in purity however the impure sample was sufficient for this analysis.
(46) To ensure the free-base of **223** was analysed a partition between NaOH (2.0 M aq) and $CHCl_3$/^{i}PrOH (3:1 v/v) was used to provide an analytical sample of **223**.
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Chapter 4: Asymmetric Synthesis of Polyhydroxylated Pyrrolidines

There is a vast array of polyhydroxylated pyrrolidine natural products that have been widely investigated in synthetic and biological reports. A subclass of polyhydroxylated pyrrolidines are the 2-aryl substituted pyrrolidines which include 5-methyl-substituted codonopsinine **291** and codonopsine **292** and a number of 5-hydroxymethyl-substituted members **293**–**298** (Figure 31). Codonopsinine **291** $\{[\alpha]_D^{20}$ –8.8 (*c* 0.1 in MeOH)$\}$[1] and codonopsine **292** $\{[\alpha]_D^{20}$ –16 (*c* 0.84 in MeOH)$\}$[2] were first isolated in 1969 from *Codonopsis clematidea* however both the chemical structures were at first misassigned as various regioisomers[1,2] which were corrected in 1971.[3] The absolute configuration of **292** was established as (*R*,*R*,*R*,*R*) by Kibayashi and co-workers *via* single crystal X-ray diffraction analysis of an intermediate in a chemical synthesis[4,5] and in addition a number of syntheses of **291** and **292** have been published.[6–9]



codonopsinine **291**, R_1 = OMe, R_2 = H
codonopsine **292**, R_1 = R_2 = OMe

radicamine A **293**, R_1 = OMe, R_2 = OH
radicamine B **294**, R_1 = OH, R_2 = H

codonopsinol **295**, R_1 = R_2 = OMe
codonopsinol A **296**, R_1 = OMe, R_2 = OH
codonopsinol B **297**, R_1 = OMe, R_2 = H
codonopsinol C **298**, R_1 = OH, R_2 = H

Figure 31. Members of the 2-aryl polyhydroxylated pyrrolidine subclass of iminosugars.

More than 30 years later, in 2001, two 5-hydroxymethyl pyrrolidine iminosugars, radicamine A **293** $\{[a_D^{25}]$ +43.7 (*c* 0.13 in H_2O)$\}$ and radicamine B **294** $\{[a_D^{25}]$ +72.0 (*c* 0.10 in H_2O)$\}$ were isolated by Shibano *et al*. from *Lobelia chinensis* and their connectivity and relative configurations were assigned by NMR spectroscopic analyses.[10] Shibano *et al*. also assigned the absolute configurations of **293** and **294** as (*S*,*S*,*S*,*S*) after *N*-methylation of **293** and **294** to give **296** and **298**, respectively, and then comparison of the specific rotation of **296** $\{[\alpha]_D^{25}$ +6.3 (*c* 0.80 in MeOH)$\}$[10] and **298** $\{[\alpha]_D^{25}$ +8.3 (*c* 0.05 in MeOH)$\}$[10] with the specific rotations of synthetic[11] (*R*,*R*,*R*,*R*)-**291** $\{[\alpha]_D^{20}$ –11.8 (*c* 0.69 in MeOH)$\}$. After these

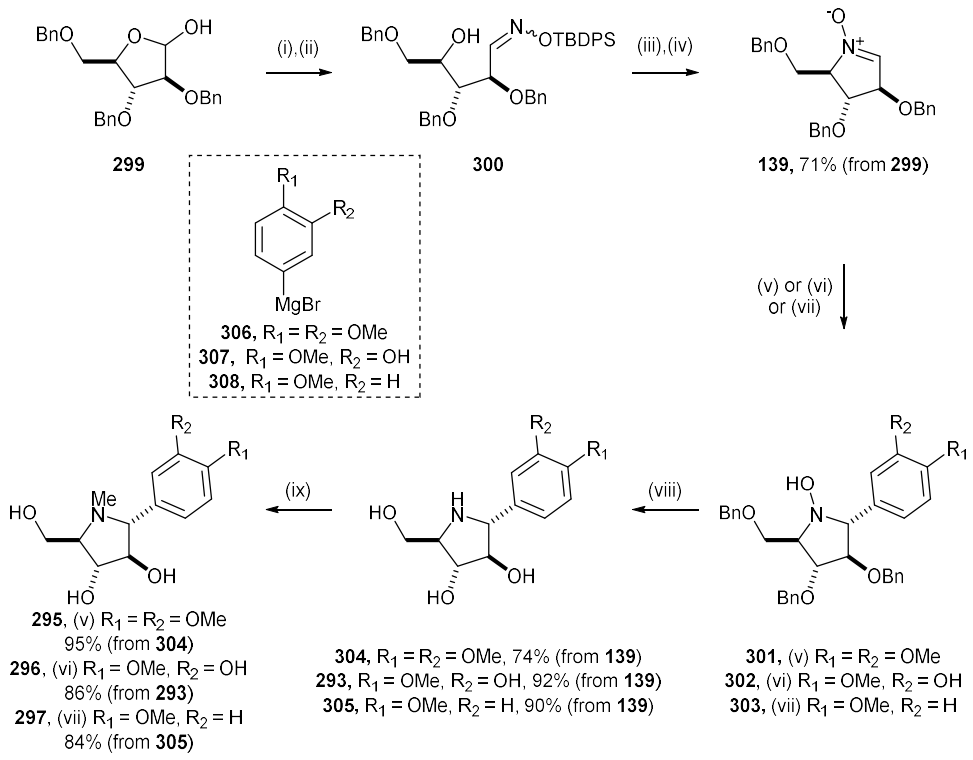
comparisons, it was concluded that **293** and **294** possessed the (*S*,*S*,*S*,*S*) absolute configuration. However, synthesis of authentic samples of (*S*,*S*,*S*,*S*)-**293** {$[\alpha]_D$ –44.4 (*c* 0.45 in H_2O)} and (*S*,*S*,*S*,*S*)-**294** {$[\alpha]_D^{30}$ –72.7 (*c* 0.17 in H_2O)} from D-xylose the absolute configurations of natural **293** and **294** were revised to be (*R*,*R*,*R*,*R*).[12] Subsequently to this, in 2008, codonopsinol **295** {$[\alpha]_D^{20}$ –15 (*c* 0.2 in MeOH)} was isolated from the aerial parts of *Codonopsis clematidea* by Takaishi and co-workers.[13] Its relative configuration was assigned by ^{1}H NMR nOe correlation[13] and its absolute configuration was initially assigned as (*S*,*S*,*S*,*S*) by comparison with synthetic *N*-methyl radicamine A {$[\alpha]_D^{25}$ +6.3 (*c* 0.80 in MeOH)}[10] (*vide supra*).[13] In 2008, a synthesis of (*R*,*R*,*R*,*R*)-**295** {$[\alpha]_D^{20}$ –15 (*c* 0.22 in MeOH)} was achieved from 2,3,5-tri-*O*-benzyl-D-arabinofuranose[14] and in 2009 Rao *et al*. also synthesised (*R*,*R*,*R*,*R*)-**295** from 1,5-D-gluconolactone {$[\alpha]_D^{20}$ –13 (*c* 0.22 in MeOH)}.[15] Thus the absolute configuration within **295** was reassigned to be (*R*,*R*,*R*,*R*).

In 2013, codonopsinols A–C **296**–**298** were isolated from the roots of *Codonopsis pilsoula* by Goda *et al*.[16] however they had previously been synthesised.[10,14] The absolute configurations within **296**–**298** were assigned by comparison of CD spectra with **295**. Although the specific rotation data for **297** were in agreement between isolated samples {$[\alpha]_D$ +5 (*c* 0.3 in MeOH)}[16] and synthetic samples {$[\alpha]_D^{25}$ +6.3 (*c* 0.8 in MeOH);[10] $[\alpha]_D^{20}$ +2 (*c* 0.69 in MeOH)}[14] there are conflicting data for **298** between the sample isolated from Nature {$[\alpha]_D$ –9 (*c* 0.60 in MeOH)}[16] and the only synthetic sample {$[\alpha]_D^{25}$ +8.3 (*c* 0.05 in MeOH)}[10] both of which were assigned the absolute (*R*,*R*,*R*,*R*)-configuration.

4.1 Previous Syntheses of Members of the Codonopsinol Family

Codonopsinol **295** has been the subject of three synthetic endeavours. Cheng, Cheng and co-workers developed a method for synthesising a range of 2-aryl polyhydroxylated pyrrolidines including codonopsinol **295** utilising the addition of Grignard reagents to a chiral nitrone.[14] This was also the first total synthesis of **296** and **297** before they were isolated from Nature.

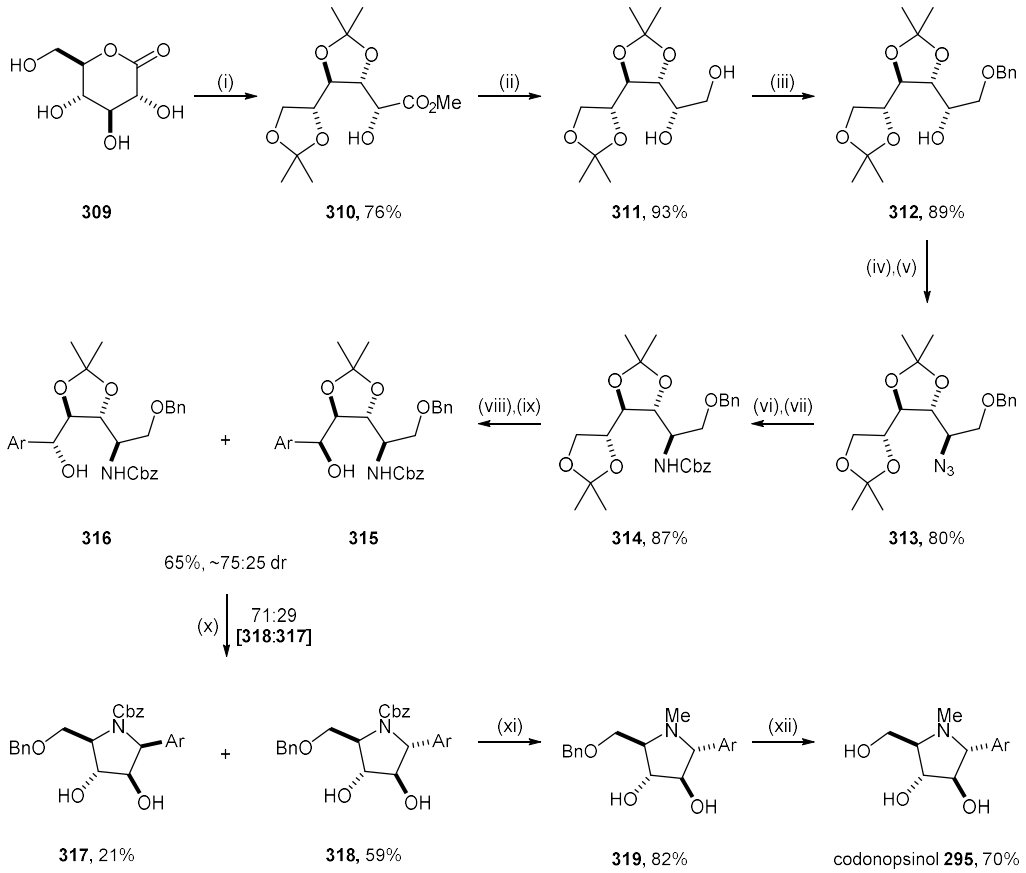
Synthesis of the chiral nitrone using literature procedures began with the condensation of hydroxylamine hydrochloride with **299** followed by *O*-silyl protection of the resultant oxime to give **300**. Treatment of **300** with I_2, PPh_3 and imidazole resulted in cyclisation to give nitrone **139** in 71% yield from **299**. Grignard reagents **306**–**308** were added to nitrone **139** giving **301**–**303**, respectively, which were subjected to hydrogenolysis conditions giving **304**, **293** and **305** in 74, 92 and 90% yield from nitrone **139**, respectively. *N*-Methylation of **304**, **293** and **305** occurred upon treatment with HCHO followed by $Pd(OH)_2$ and H_2 giving target compounds **295**–**297** in 95, 86 and 84% yield, respectively (Scheme 90).



Scheme 90. *Reagents and Conditions*: (i) $NH_2OH{\cdot}HCl$, NaOMe, MeOH, rt, 3 h; (ii) TBDPSCl, imidazole, CH_2Cl_2, rt, overnight; (iii) I_2, PPh_3, imidazole, PhMe, reflux, 2 h; (iv) TBAF, PhMe, reflux, 30 min; (v) **306**, THF, 0 °C, 1 h; (vi) **307**, THF, 0 °C, 1 h; (vii) **308**, THF, 0 °C, 1 h; (viii) $Pd(OH)_2$, H_2, conc HCl, THF, rt, 15 h; (ix) HCHO (37% in H_2O), MeOH, rt, 10 min then $Pd(OH)_2$, H_2, rt, overnight.

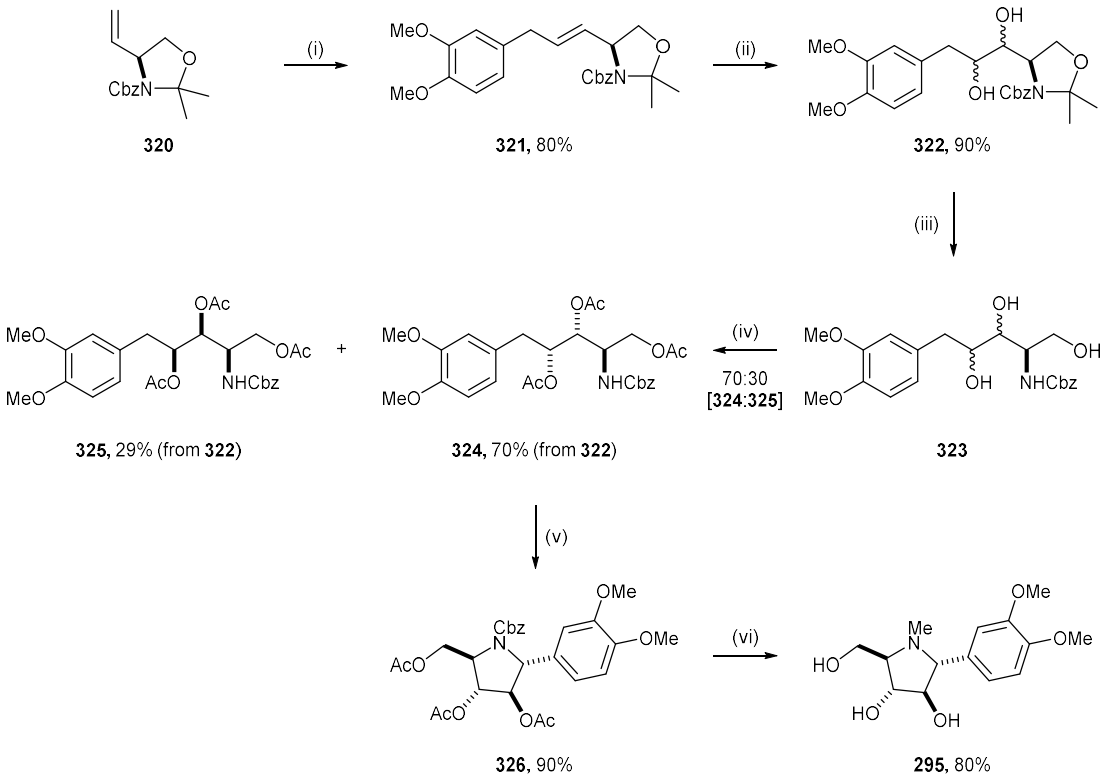
Rao and co-workers synthesised codonopsinol **295** from D-gluconolactone **309** using an acid catalysed amido cyclisation:[15] D-gluconolactone **309** was first protected as the bis-acetonide methyl ester giving **310** in 76% yield. The methyl ester within **310** was reduced using $LiAlH_4$ to give **311** in 93% yield which was selectively *O*-benzyl protected on the primary hydroxyl functionality using Bu_2SnO in PhMe followed by BnBr and TBAI giving **312** in 89% yield.

Activation of the free hydroxyl moiety within **312** was achieved with MsCl giving the secondary mesylate which was displaced, with inversion of configuration, by NaN_3 giving azide **313** in 80% yield. Reduction of the azide functionality within **313** with $LiAlH_4$ and protection of the resulting amine with CbzCl gave **314** in 87% yield. Treatment of **314** with periodic acid resulted in the regioselective deprotection of the terminal acetonide unit and concomitant diol cleavage to give the corresponding aldehyde, which was treated with Grignard reagent **306** to give alcohols **315** and **316** in 65% yield and ~75:25 dr. Treatment of the epimeric mixture of **315** and **316** with TFA in CH_2Cl_2 gave a 71:29 mixture of **318** and **317**, respectively, which were isolated in 59 and 21% yield, respectively. It was proposed that after acetonide deprotection, cleavage of the benzylic hydroxyl moiety occurred giving a benzylic carbocation, which was trapped intramolecularly to give a 71:29 mixture of pyrrolidines. Subjection of the major component of the starting material mixture to the reaction conditions resulted in the same diastereomeric ratio of pyrrolidines, which is consistent with this mechanistic proposal. Reduction of **318** with $LiAlH_4$ gave **319** in 82% yield which was deprotected in hydrogenolytic conditions with $PdCl_2$ giving codonopsinol **295** in 70% yield, equating to 9.6% overall yield from **309** (Scheme 91). An identical deprotection strategy of the *cis*-pyrrolidine diastereoisomer **317** was used to synthesise 2-*epi*-codonopsinol.



Scheme 91. *Reagents and Conditions*: (i) 2,2-dimethoxypropane, TsOH, acetone, MeOH, 0 °C to rt, 50 h; (ii) $LiAlH_4$, THF, 0 °C to rt, 4 h; (iii) Bu_2SnO, PhMe, reflux, 8 h then BnBr, TBAI, reflux, 16 h; (iv) MsCl, Et_3N, CH_2Cl_2, 0 °C to rt, 3 h; (v) NaN_3, DMF, 80 °C, 24 h; (vi) $LiAlH_4$, THF, 0 °C to rt, 5 h; (vii) CbzCl, Na_2CO_3, CH_2Cl_2, 0 °C to rt, 8 h; (viii) H_5IO_6, Et_2O, 0 °C to rt, 6 h; (ix) **306**, THF, 0 °C to rt, 16 h; (x) TFA, CH_2Cl_2, 0 °C to rt, 4 h; (xi) $LiAlH_4$, THF, 0°C to 60 °C, 5 h; (xii) $PdCl_2$, H_2, MeOH, rt, 12 h. [Ar = 3,4-dimethoxyphenyl].

Rao and co-workers reported a synthesis of **295** showcasing their DDQ-promoted C–H activation for the stereoselective intramolecular C–N bond formation.[17] Metathesis of **320** with 3,4-dimethoxyallylbenzene with Grubbs II catalyst gave olefin **321** in 80% yield. Dihydroxylation of **321** with catalytic OsO_4 with NMO as a stoichiometric reoxidant gave a mixture of diols in 90% yield. Hydrolysis of the *N*,*O*-acetal group within **322** with $CuCl_2$ gave a crude mixture of triols, which were acetylated with Ac_2O giving a 70:30 mixture of triacetates **324** and **325**, respectively, from which **324** was isolated in 70% yield (from **322**) and **325** (produced from opposite facial selectivity of dihydroxylation) was isolated in 29% yield (from **322**). DDQ-mediated cyclisation of **324** gave pyrrolidine **326** in 90% yield, which was fully deprotected upon treatment with $LiAlH_4$ to give codonopsinol **295** in 80% yield, corresponding to an overall yield of 36% from **320** (Scheme 92).

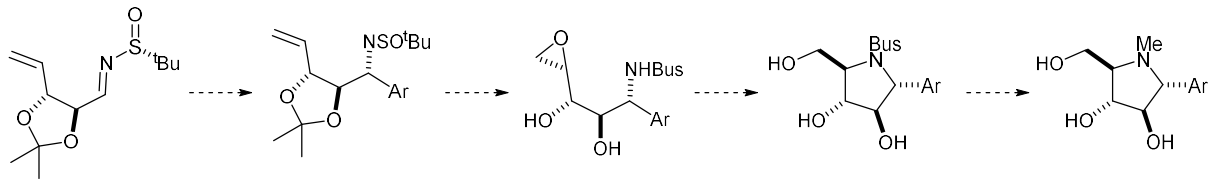


Scheme 92. *Reagents and Conditions*: (i) 3,4-dimethoxyallylbenzene, Grubbs II, CuI, CH_2Cl_2, reflux, 8 h; (ii) OsO_4, NMO, acetone/H_2O (4:1, v/v), rt, 8 h; (iii) $CuCl_2 \cdot 2H_2O$, MeCN, 0 °C to rt, 2 h; (iv) Ac_2O, Et_3N, DMAP, CH_2Cl_2, 0 °C to rt, 1 h; (v) DDQ, MeCN, reflux, 4 h; (vi) $LiAlH_4$, THF, reflux, 6 h.

4.2 Chapter Aims

Given the discrepancies between the specific rotation data in the literature and the intriguing history of the stereochemical assignment of a number of members of the 2-aryl pyrrolidine family, it was of interest to develop an independent route for preparation of all natural products with initial targets being **297** and **298**.

Therefore, this chapter outlines the exploration into a divergent route towards the codonopsinol family resulting in the synthesis of **297** and **298** and the analysis of their spectroscopic data thus confirming their assigned absolute configurations. It was envisaged that the addition of organometallic reagents to an enantiopure *N*-sulfinyl imine **150** would result in the synthesis of **151**. *O*-Deprotection and epoxidation would give epoxide **327** which could undergo cyclisation giving pyrrolidine **328**. *N*-Deprotection and *N*-methylation would then give members of the codonopsinol family **329** (Figure 32).

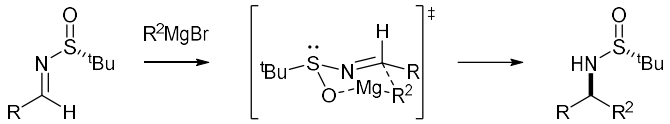


150 151 327 328 329

Figure 32. Proposed synthesis of members of the codonopsinol family **329** from enantiopure *N*-sulfinyl imine **150**.

4.3 Stereocontrol in the addition of Grignard reagents to *N*-sulfinyl imines

The use of enantiopure *N-tert*-butylsulfinyl imines in the syntheses of chiral amines has been extensively used in the synthesis of a number of natural products.[18,19] Ellman and co-workers have investigated the addition of organometallic reagents to a number of *N-tert*-butyl sulfinyl imines **330** (derived from achiral aldehydes) with a high diastereoselectivity of addition, controlled by the chiral sulfinyl moiety.[20] A chair-like transition state **331** was proposed, in which the *tert*-butyl group and non-hydrogen substituent on the imine carbon occupy pseudo-equatorial positions (Figure 33).



330 331 332

Figure 33. Observed stereocontrol in the addition of Grignard reagents to **330**.[20]

The addition of Grignard reagents to α-dioxolane *N-tert*-butyl sulfinyl imines has been reported by Babu and co-workers in the synthesis of cytoxazone and levetiracetam.[21] The stereochemical outcome of these additions was in conflict with the transition state proposed by Ellman. Given the similarity between the substrate from their work and this study the (*R*)-*tert*-butyl sulfinyl auxiliary was chosen, in anticipation that it would affect the desired stereocontrol in the Grignard addition step.

4.4 Synthesis of Enantiopure *N*-Sulfinyl Imine 150

It was envisaged that enantiopure *N*-sulfinyl imine **150** could be synthesised from D-ribose **333** using known procedures to give aldehyde **335**, which could be condensed with

(*R*)-*tert*-butylsulfinamine (*R*)-**338** to give *N*-*tert*-butylsulfinyl imine **336**. Epimerisation of either imine **336** or aldehyde **335** would allow for the synthesis of the requisite imine **150** with *trans*-configuration (Figure 34).

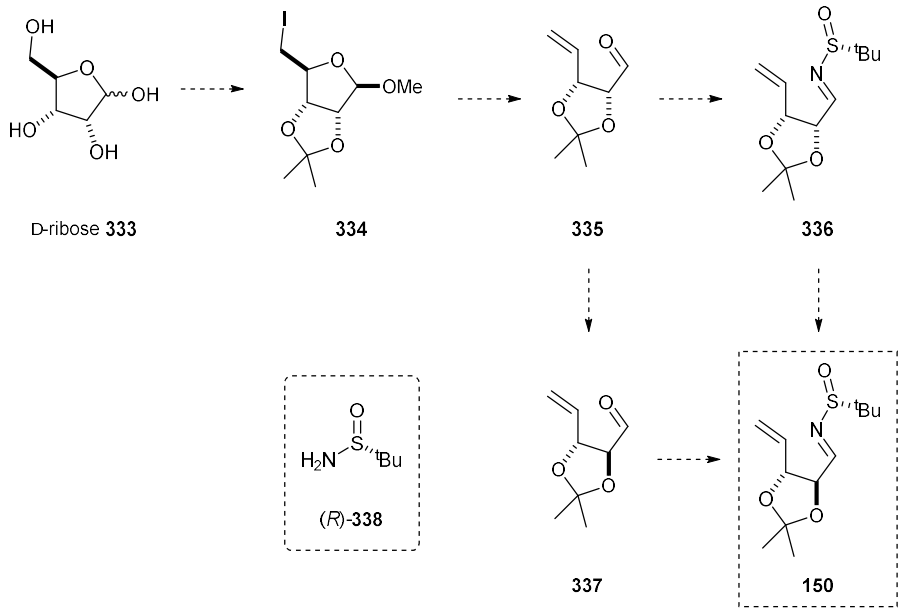
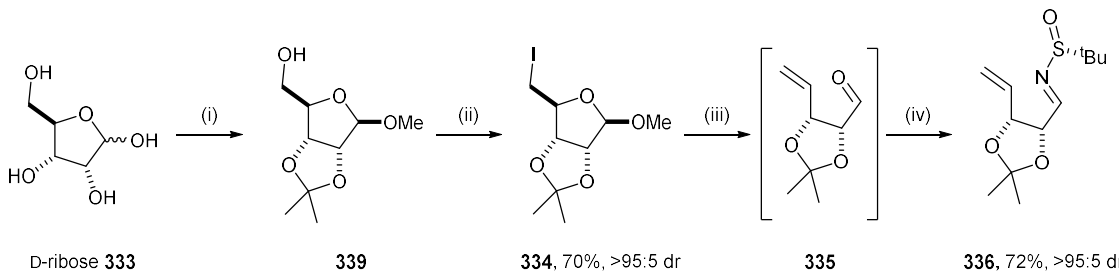


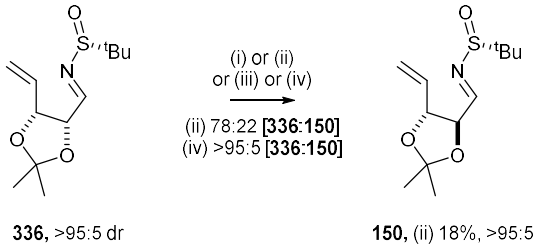
Figure 34. Proposed synthesis of enantiopure *N*-sulfinyl imine **150** from D-ribose **333**.

Using known procedures, the *cis*-diol moiety within D-ribose **333** was protected as the acetonide, as well as the anomeric hydroxyl group being transformed into methyl glycoside **339**, upon treatment with conc HCl in acetone/MeOH.[22] Substitution of the primary hydroxyl group within **339** with I_2, Ph_3P and imidazole gave iodide **334** in 70% yield and >95:5 dr from D-ribose **333**.[22] Treatment of **334** with BuLi in THF at –78 °C for 1 h gave aldehyde **335**, which was treated with sulfinamine (*R*)-**338** and $Ti(OEt)_4$ to give *N*-*tert*-butylsulfinyl imine **336** in 72% yield and >95:5 dr (Scheme 93).[23]



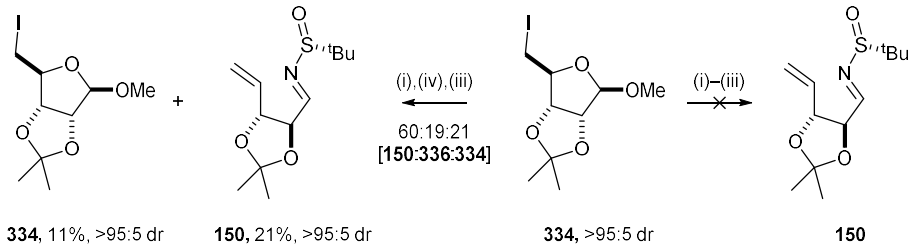
Scheme 93. *Reagents and Conditions*: (i) conc HCl, acetone/MeOH (1:1 v/v), 70 °C, 1 h; (ii) I_2, Ph_3P, imidazole, PhMe/MeCN (5:1 v/v), 60 °C, 1 h; (iii) BuLi, THF, –78 °C, 1 h; (iv) (*R*)-**338**, $Ti(OEt)_4$, –78 °C to rt, 1 h.

After the successful synthesis of *cis*-imine **336**, attention turned to epimerisation of **336** to afford the requisite *trans*-imine **150**. Firstly, treatment of **336** with K_2CO_3 in MeOH resulted in poor mass return with the starting *N*-sulfinamine (*R*)-**338** being the major component. Treatment of **336** with DBU in PhMe resulted in some epimerisation giving a 78:22 mixture of **336** and **150** from which *trans*-imine **150** was isolated in 18% yield and >95:5 dr. Attempted epimerisation using NaHMDS then aqueous workup resulted in a complex mixture and with Et_3N resulted in returned starting material **336** (Scheme 94).



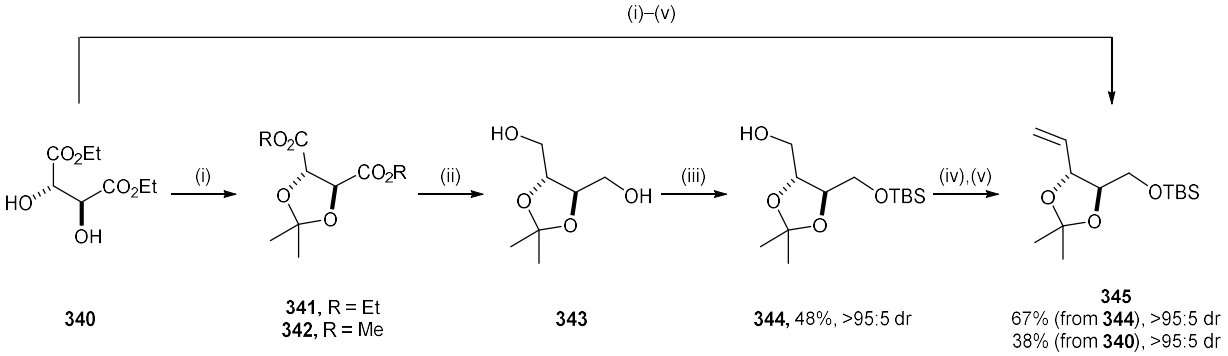
Scheme 94. *Reagents and Conditions*: (i) K_2CO_3, MeOH, rt, 18 h; (ii) DBU, PhMe, rt, 18 h; (iii) NaHMDS, THF, 0 °C, 1 h; (iv) Et_3N, CH_2Cl_2, rt, 18 h.

Epimerisation was also attempted on the intermediate aldehyde **335** under two conditions: treatment of the intermediate aldehyde **335** with K_2CO_3 in MeOH at rt for 18 h followed by condensation with (*R*)-**338** and $Ti(OEt)_4$ resulted in a crude reaction mixture that produced a complex ^1H NMR spectrum which contained (*R*)-**338** as the major component and **336** as the major diastereoisomer of the imine. Addition of DBU to **335** *in situ* followed by condensation with (*R*)-**338** and $Ti(OEt)_4$ resulted in a 60:19:21 mixture of **150**, **336** and **334**, respectively, from which starting material **334** was isolated in 11% yield and **150** was isolated in 21% yield and as single diastereoisomers in both cases (Scheme 95).



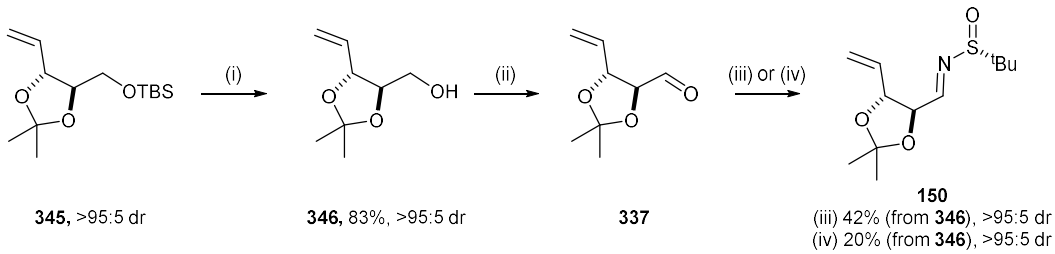
Scheme 95. *Reagents and Conditions*: (i) BuLi, THF, –78 °C, 1 h; (ii) K_2CO_3, MeOH, rt, 18 h; (iii) (*R*)-**338**, $Ti(OEt)_4$, –78 °C to rt, 1 h; (iv) DBU, rt, 2 h.

After the unsuccessful attempts at the epimerisation route another synthesis of *trans*-**150** was sought – starting from diethyl D-tartrate **340**. Protection of the diol unit within **340** as the acetonide gave a mixture of esters **341** and **342**, which were then reduced with $LiAlH_4$ to give **343.** Mono-*O*-silyl-protection of **343** with NaH and TBSCl gave **344** in 48% yield from diethyl D-tartrate.[24] Installation of the methylene moiety was achieved by Swern oxidation of the primary alcohol within **344** then Wittig olefination with the ylide derived from methyltriphenylphosphonium bromide giving **345** in 67% yield and >95:5 dr.[25] A telescoped procedure, with a single purification gave **345** in 38% yield and >95:5 dr over 5 steps from diethyl D-tartrate **340** (Scheme 96).[24]



Scheme 96. *Reagents and Conditions*: (i) 2,2-dimethoxypropane, TsOH, PhMe, 120 °C, 18 h; (ii) $LiAlH_4$, THF, 67 °C, 18 h; (iii) NaH, THF, 0 °C 45 min then TBSCl, 0 °C to rt, 18 h; (iv) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 1 h then Et_3N, –78 °C, 20 min then rt, 20 min; (v) $MePh_3P^+Br^-$, BuLi, THF, –78 °C to rt, 3 h.

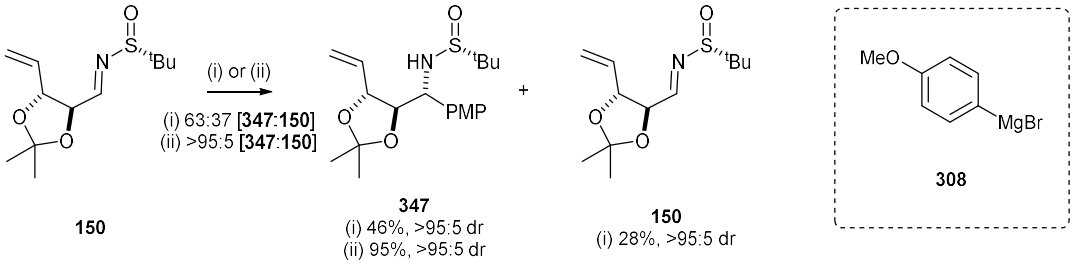
Facile *O*-silyl deprotection of **345** with TBAF in THF gave alcohol **346** in 83% yield and >95:5 dr. With **346** in hand, the synthesis of *N*-*tert*-butylsulfinyl imine **150** could be explored *via* condensation of *N*-*tert*-butylsulfinamine (*R*)-**338** with enantiopure aldehyde **337** (produced from oxidation of **346**). Oxidation of alcohol **346** under Swern conditions gave aldehyde **337** which has been reported to decompose rapidly during flash column chromatography or upon standing in $CDCl_3$,[26] and so was immediately treated with (*R*)-**338** and $Ti(OEt)_4$ to give *trans*-**150** with no sign of *cis*-**336**. After purification, **150** was isolated in a modest 42% yield from **346** and >95:5 dr. An alternative procedure for the condensation using 4 Å molecular sieves as the dehydrating agent was attempted, however this only resulted in the isolation of **150** in 20% yield from **346** and >95:5 dr (Scheme 97).



Scheme 97. *Reagents and Conditions*: (i) TBAF, THF, 0 °C to rt, 2.5 h; (ii) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 1 h then Et_3N, –78 °C, 20 min then rt, 20 min; (iii) (*R*)-**338**, $Ti(OEt)_4$, CH_2Cl_2, rt, 18 h; (iv) (*R*)-**338**, 4 Å MS, CH_2Cl_2, rt, 72 h.

4.5 Nucleophilic Addition to *N*-Sulfinyl Imine 150

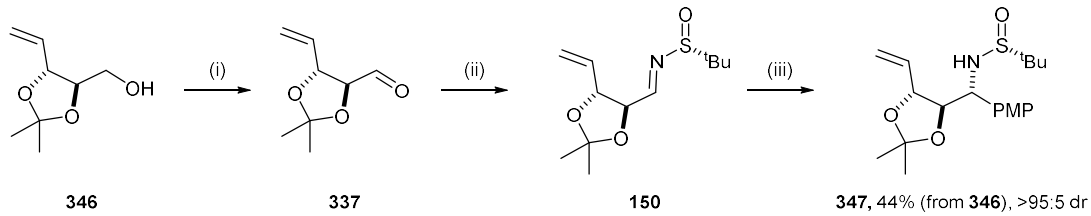
Following the procedure from Babu and co-workers,[21] addition of 1.2 equiv 4-methoxyphenylmagnesium bromide **308** to imine **150** in Et_2O gave a 37:63 mixture of **150** and **347** from which starting material **150** was isolated in 28% yield and >95:5 dr and sulfinamide **347** was isolated in 46% yield and >95:5 dr. To increase the conversion of starting material, 2.5 equiv of **308** were used, which resulted in a >95:5 mixture of **347** (>95:5 dr) and **150**, respectively, from which amine **347** was isolated in 95% yield as a single diastereoisomer. The configuration within **347** was determined by synthesis of a derivative (*vide infra*) (Scheme 98).



Scheme 98. *Reagents and Conditions*: (i) 1.2 equiv **308**, Et_2O, –78 °C, 5 h; (ii) 2.5 equiv **308**, Et_2O, –78 °C, 5 h.

It was proposed that the low yield of isolated *N*-*tert*-butylsulfinyl imine **150** was due to the instability upon silica column chromatography. Therefore it was decided to omit the purification of **150** and treat the crude reaction mixture with **308** to give **347** which could then be purified. Swern oxidation of **346** gave aldehyde **337** which was condensed with (*R*)-**338** to give *N*-sulfinyl imine **150** then treated with **308** in Et_2O to give **347** in 44% yield over 3 steps

from **346**. This shows a small improvement from 40% in the stepwise procedure. The synthesis of sulfinamide **347** was achieved in 13.9% overall yield over 9 steps from diethyl L-tartrate **340** with 3 chromatographic purifications. To proceed with the synthesis a more scalable route was sought, with the hope of being able to omit a large amount of powdered $LiAlH_4$ and the large excess of ylide required as well as increasing the overall yield (Scheme 99).

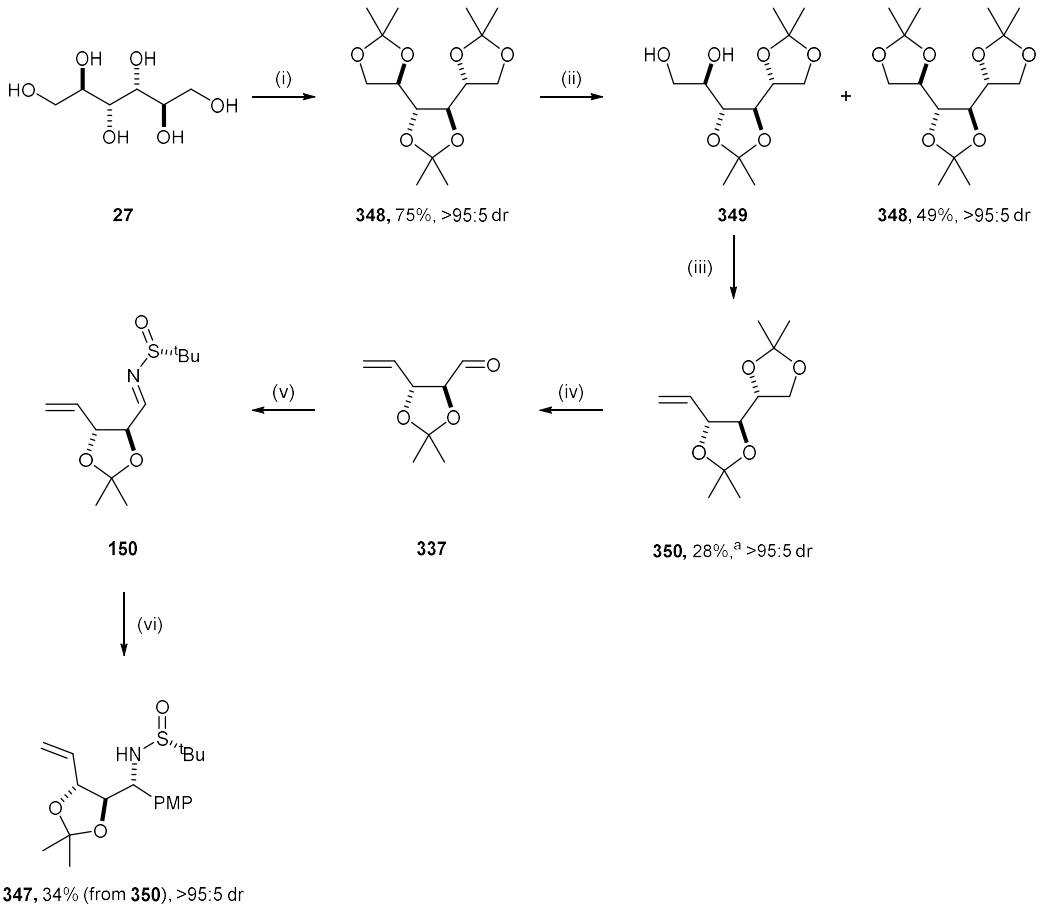


346 **337** **150** **347**, 44% (from **346**), >95:5 dr

Scheme 99. *Reagents and Conditions*: (i) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 1 h then Et_3N, –78 °C, 20 min then rt, 20 min; (ii) (*R*)-**338**, $Ti(OEt)_4$, CH_2Cl_2, rt, 18 h; (iii) 2.5 equiv **308**, Et_2O, –78 °C, 5 h.

An alternative procedure with a shorter step count for making amine **347** *via* imine **150** was also explored using D-mannitol **27** as a starting material and proceeding *via* aldehyde **337** using known procedures. Firstly D-mannitol **27** was protected as the triacetonide using H_2SO_4 in acetone giving **348** in 75% yield.[27] A partial hydrolysis of **348** was attempted with HCl in aqueous EtOH which gave a mixture of **349** and starting material **348** from which starting material **348** could be recovered *via* precipitation from H_2O in 49% yield.[27] Diol **349** was extracted from the aqueous filtrate without further purification and treated with Ph_3P, I_2 and imidazole in PhMe to give olefin **350** in 28% isolated yield over 2 steps from **348** (equivalent to 55% yield over two steps based on reclaimed starting material). Tandem regioselective acetonide hydrolysis and diol cleavage with H_5IO_6 in EtOAc[28] afforded aldehyde **337** which was, as before, condensed with (*R*)-**338** to give imine **150** which was treated with **308** to give sulfinamide **347** in 34% isolated yield from **350** (Scheme 100). This route achieved the synthesis of **347** in 7.1% yield from D-mannitol **27** (14.3% yield based on recovered starting material) over 6 steps with 3 chromatographic purifications. Although the overall yield is lower, this synthesis of **347** has a smaller step count (cf. 9 steps from diethyl D-tartrate **340**), is

more scalable and the reclaimed starting material from acetonide hydrolysis can be recycled to increase the overall yield.

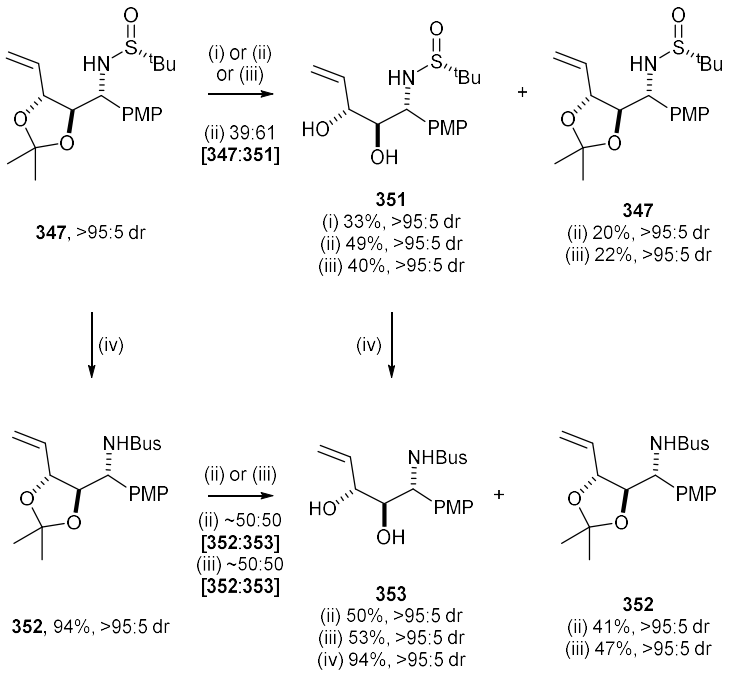


Scheme 100. *Reagents and Conditions*: (i) conc H_2SO_4, acetone, rt, 18 h; (ii) HCl, EtOH/H_2O (7:3 v/v), 45 °C, 1 h; (iii) I_2, Ph_3P, imidazole, PhMe, 110 °C, 3 h; (iv) H_5IO_6, EtOAc, rt, 30 min; (v) (*R*)-**338**, $Ti(OEt)_4$, CH_2Cl_2, rt, 18 h; (vi) **308**, Et_2O, –78 °C, 5 h. [[a] 55% yield based on reclaimed starting material.]

4.6 Elaboration of 347 to Pyrrolidines 356 and 357

The formation of the pyrrolidine scaffold would be dependent on removal of the acetonide protecting group in the presence of the acid-sensitive *N*-*tert*-butylsulfinyl moiety. Firstly, a procedure by Leclerc *et al*. was attempted:[29] treatment of **347** with TFA/H_2O (4:1 v/v) gave a crude reaction mixture with low mass return and which produced a ^{1}H NMR spectrum containing **351** as the major species from which only **351** was isolated in 33% yield and >95:5 dr. The acidic deprotection of an acetonide protecting group in the presence of an *N*-*tert*-butylsulfinyl moiety has also been reported by Linclau *et al*.[30] Treatment of **347** with 0.2 equiv of TsOH in MeOH gave a 39:61 mixture of starting material **347** and diol **351**,

respectively. After chromatographic purification **347** was isolated in 20% yield and **351** was isolated in 49% yield, as single diastereoisomers in both cases. Increasing the number of equivalents of TsOH to 0.5 had no benefit on the isolated yields of **347** and **351**, as a complex mixture was obtained from which **347** was isolated in 22% yield and >95:5 dr and **351** was isolated in 40% yield and >95:5 dr. Diol **351** was chemoselectively oxidised to sulfonamide **353** with 1.5 equiv of *m*-CPBA in 94% yield as a single diastereoisomer with no oxidation of the C=C bond. Due to the low yielding acetonide deprotection step it was envisaged that a rearrangement of the oxidation/deprotection steps was a potential way to increase the efficiency of the synthesis of **353**. Chemoselective oxidation of **347** with 1.5 equiv *m*-CPBA resulted in *S*-oxidation only to give sulfonamide **352** in 94% yield and >95:5 dr. Treatment of **352** with 0.2 equiv of TsOH in MeOH gave a ~50:50 mixture of **352** and **353** from which starting material **352** was isolated in 41% yield and diol **353** was isolated in 50% yield, both as single diastereoisomers. Once again, increasing the number of equivalents of TsOH to 0.5 had no effect on the product distribution (~50:50) and after purification starting material **352** was isolated in 47% yield and >95:5 dr, and diol **353** was isolated in 53% yield and >95:5 dr (Scheme 101). Acetonide hydrolysis of **347** followed by *S*-oxidation of **351** to give sulfonamide **353** occurred in 46% yield with 20% reclaimed starting material **347**. Conversely, oxidation of **347** to give **352** followed by acetonide hydrolysis gave sulfonamide **353** in 50% overall yield with 47% returned **352**, thus proving the more efficient route to **353**.



Scheme 101. *Reagents and Conditions*: (i) TFA/H_2O (4:1 v/v), rt, 3 h; (ii) 0.2 equiv TsOH, MeOH, rt, 18 h; (iii) 0.5 equiv TsOH, MeOH, rt, 18 h; (iv) 1.5 equiv *m*-CPBA, CH_2Cl_2, rt, 1 h.

The relative configuration within **351** was established *via* single crystal X-ray diffraction analysis.[31] The absolute (*R*,*R*,*R*,*R*)-configuration within **351** was assigned by reference to the known (*R*)-configuration of the sulfur atom. A Flack *x* parameter[32,33] of –0.013(14) for the crystal structure of **351** confirmed this assigned absolute (*R,R,R,R*)-configuration (Figure 35). This also establishes unambiguously the diastereoselectivity of addition of the Grignard reagent to **150** which was consistent with the selectivity reported by Babu and co-workers.[21]

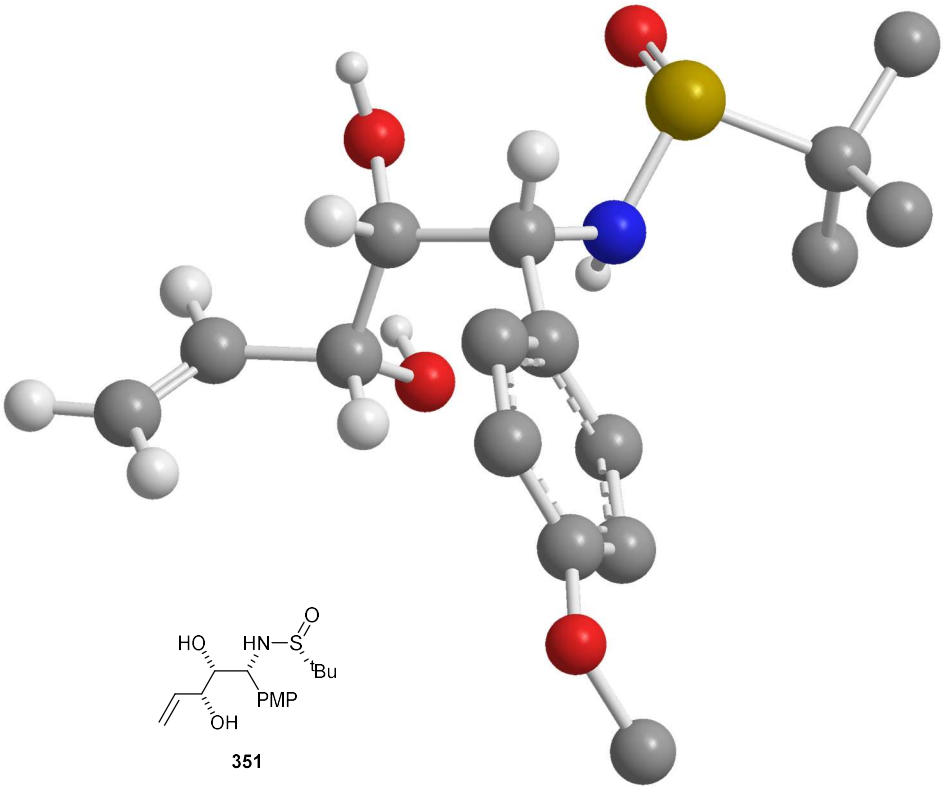
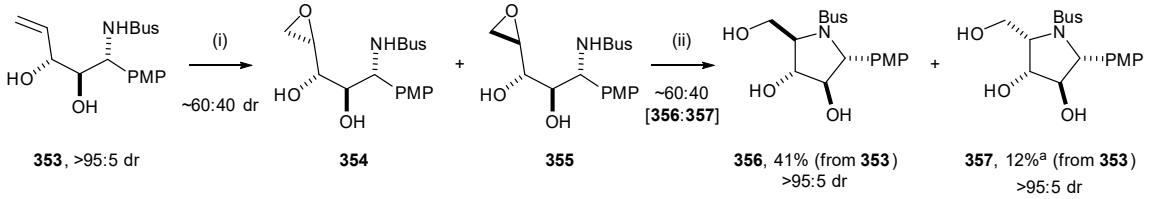


Figure 35. X-ray crystal structure of (*R*,*R*,*R*,*R*)-**351** (selected H atoms are omitted for clarity).

After the successful synthesis of **353** a cyclisation procedure was trialled: treatment of olefin **353** with 1.5 equivalents of *m*-CPBA in CH_2Cl_2 to give a ~60:40 mixture of epoxides which underwent cyclisation to a ~60:40 mixture of pyrrolidines **356** and **357**, respectively, using K_2CO_3 in MeOH. Exhaustive chromatography gave **356** in 41% yield and **357** in 12% yield and >95:5 dr in both cases. A 15:85 mixture of **356** and **357**, respectively, was also isolated in 11% yield (Scheme 102).

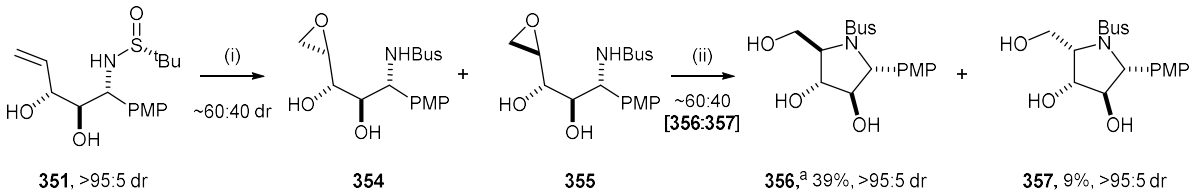


353, >95:5 dr | **354** | **355** | **356**, 41% (from **353**) >95:5 dr | **357**, 12%[a] (from **353**) >95:5 dr

Scheme 102. *Reagents and Conditions*: (i) 1.5 equiv *m*-CPBA, CH_2Cl_2, rt, 18 h; (ii) K_2CO_3, MeOH, rt, 18 h. [[a] An 85:15 mixture of **357** and **356**, respectively, was also isolated in 11% combined yield].

In an analogous manner, the treatment of olefin **351** with 3.0 equiv of *m*-CPBA in CH_2Cl_2 allowed for tandem *S*-oxidation and epoxidation to give a ~60:40 mixture of epoxides which underwent cyclisation to give a ~60:40 mixture of pyrrolidines **356** and **357**, respectively,

upon treatment with K_2CO_3 in MeOH. Exhaustive chromatography gave **356** in 39% yield and **357** in 9% yield as single diastereoisomers in both cases. A 70:30 mixture of **357** and **356**, respectively, was also isolated in 18% combined yield (Scheme 103). It was noted that the oxidation of **351** to **353** with a 1.5 equiv of *m*-CPBA occurred chemoselectively in 1 h, with no double bond oxidation, and that the diastereoselectivity of the epoxidation of **353** was similar to diastereoselectivity of the epoxidation of **351**. These results are consistent with *S*-oxidation of **351** to give **353** followed by epoxidation of the double bond moiety within **353** giving a mixture of epoxides. Stereospecific cyclisation of each epoxide diastereoisomer gives the corresponding pyrrolidine.



351, >95:5 dr **354** **355** **356**,[a] 39%, >95:5 dr **357**, 9%, >95:5 dr

Scheme 103. *Reagents and Conditions*: (i) 3.0 equiv *m*-CPBA, CH_2Cl_2, rt, 18 h; (ii) K_2CO_3, MeOH, rt, 18 h. [[a] A 70:30 mixture of **357** and **356**, respectively, was also isolated in 18% combined yield].

The relative configuration within **356** was established *via* single crystal X-ray diffraction analysis.[31] The absolute (*R*,*R*,*R*,*R*)-configuration within **356** was assigned by reference to the known (*R*,*R*,*R*)-configuration of the C(2), C(3) and C(4) stereocentres within **356** as they were previously established *via* single crystal X-ray diffraction analysis of precursor **351** (*vide supra*). A Flack *x* parameter[32,33] of –0.035(16) for the crystal structure of **356** confirmed this assigned absolute (*R*,*R*,*R*,*R*)-configuration (Figure 36).

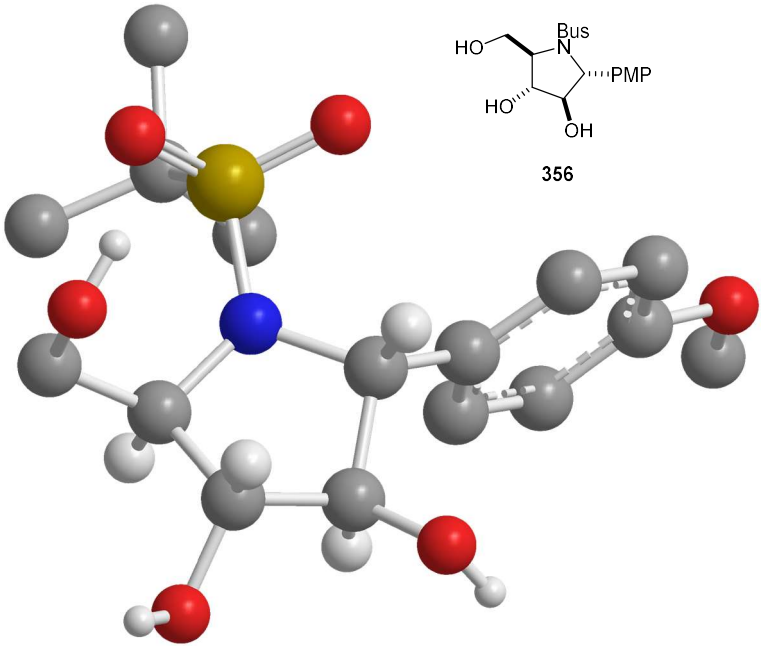
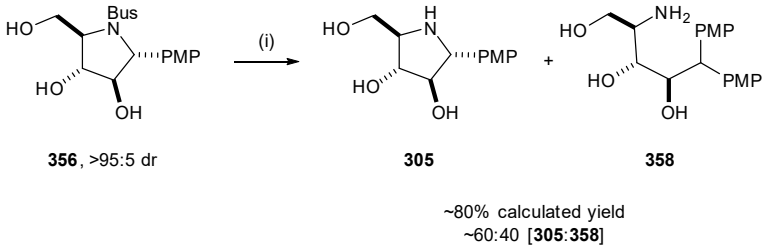


Figure 36. X-ray crystal structure of (*R*,*R*,*R*,*R*)-**356** (selected H atoms are omitted for clarity).

4.7 Attempted Deprotection of 356

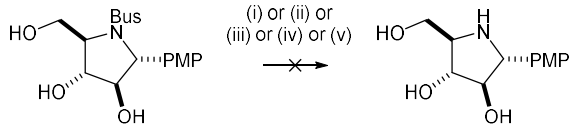
Deprotection of *N*-Bus protecting groups is known to occur readily upon treatment with TfOH and anisole: treatment of **356** with TfOH and anisole in CH_2Cl_2 for 2 h gave a ^1H NMR spectrum swamped with anisole and upon purification gave a ~60:40 mixture of two species which were tentatively assigned as **305** and **358**, respectively, based on mass spectrometric and NMR spectroscopic analyses, in ~80% calculated yield. The reaction was monitored by TLC and NMR analysis of the reaction mixture at various intervals which showed multiple species after 5 min (Scheme 104).



Scheme 104. *Reagents and Conditions*: (i) TfOH, anisole, CH_2Cl_2, rt, 2 h.

Alternative deprotection strategies that are known to deprotect sulfonamides were also trialled. Treatment of **356** with HCl at rt and 100 °C gave complex mixtures in both cases. Attempted reduction with $LiAlH_4$ in THF under reflux or Mg in MeOH in an ultrasonic bath gave

returned starting material in both cases. Finally, **356** was treated with sodium naphthalide (generated *in situ* from naphthalene and sodium metal) in THF which produced a ^{1}H NMR spectrum of the crude reaction mixture containing starting material **356** and naphthalene (Scheme 105).



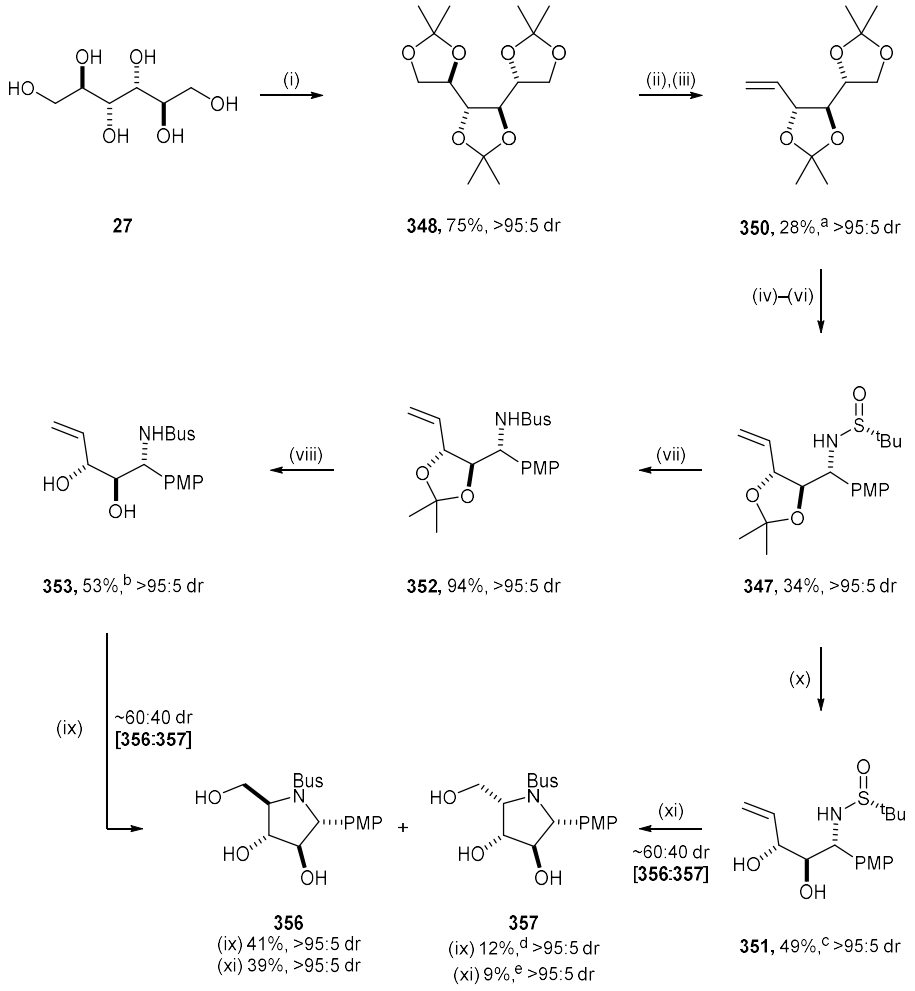
356 305

Scheme 105. *Reagents and Conditions*: (i) 3.0 M aq HCl, rt, 18 h; (ii) 3 M aq HCl, 100 °C, 3 h; (iii) $LiAlH_4$, THF, 67 °C, 18 h; (iv) Mg, MeOH, ultrasonic bath, rt, 24 h; (v) Na naphthalide, THF, –78 °C to rt, 18 h.

4.8 Summary

Although the final *N*-deprotection step was unsuccessful a synthetic route to *N*-protected pyrrolidine **356** was achieved from D-mannitol **27** or diethyl D-tartrate **340**. D-Mannitol **27** can be converted into its triacetonide **348** in 75% yield and >95:5 dr. Partial hydrolysis of a primary acetonide functionality within **348** with HCl in aqueous EtOH followed by treatment with Ph_3P, I_2 and imidazole afforded olefin **350** in 28% yield over 2 steps (with returned starting material **348** being isolated in 49% yield). Hydrolysis of the primary acetonide followed by diol cleavage with H_5IO_6 furnished aldehyde **337** which was condensed with *N*-*tert*-butylsulfinamine (*R*)-**338** to give imine **150**, which was treated with Grignard reagent **308** to give sulfinamide **347** in 34% yield and >95:5 dr. Sulfinamide **347** was chemoselectively oxidised with *m*-CPBA to give sulfonamide **352** in 94% yield which, when subjected to acidic conditions, underwent *O*-deprotection to give **353** in 53% yield as a single diastereoisomer. Treatment of **353** with *m*-CPBA gave a mixture of epoxides and cyclisation upon treatment with K_2CO_3 in MeOH gave a ~60:40 mixture of pyrrolidines **356** and **357**, which were isolated in 41 and 12% yield (from **353**), respectively, as single diastereoisomers in both cases. Pyrrolidines **356** and **357** were also synthesised from **351** *via* deprotection of **347** to give **351** in 49% yield and >95:5 dr followed by tandem *S*-oxidation/epoxidation with

m-CPBA to give a ~60:40 mixture of epoxides, which was subjected to the same cyclisation conditions to give a ~60:40 mixture of **356** and **357**. After chromatographic purification **356** was isolated in 39% yield and >95:5 dr, and **357** was isolated in 9% yield and >95:5 dr, over two steps from **351** (Scheme 106). After the unsuccessful deprotection of **356** another protecting group strategy was needed to allow for the synthesis of **305**.



Scheme 106. *Reagents and Conditions*: (i) H_2SO_4, acetone, rt, 18 h; (ii) HCl, EtOH/H_2O (7:3 v/v), 45 °C, 1 h; (iii) I_2, Ph_3P, imidazole, PhMe, 110 °C, 3 h; (iv) H_5IO_6, EtOAc, rt, 30 min; (v) (*R*)-**338**, $Ti(OEt)_4$, CH_2Cl_2, rt, 18 h; (vi) **308**, Et_2O, –78 °C, 5 h; (vii) 1.5 equiv *m*-CPBA, CH_2Cl_2, rt, 1 h; (viii) 0.5 equiv TsOH, MeOH, rt, 18 h; (ix) 1.5 equiv *m*-CPBA, CH_2Cl_2, rt, 18 h then K_2CO_3, MeOH, rt, 18 h; (ix) 0.2 equiv TsOH, MeOH, rt, 18 h; (xi) 3.0 equiv *m*-CPBA, CH_2Cl_2, rt, 18 h then K_2CO_3, MeOH, rt, 18 h. [[a] Starting material **348** was also isolated in 49% yield. [b] Starting material **352** was also isolated in 47% yield. [c] Starting material **347** was also isolated in 20% yield. [d] An 85:15 mixture of **357** and **356**, respectively, was also isolated in 11% combined yield. [e] A 70:30 mixture of **357** and **356**, respectively, was also isolated in 18% combined yield].

4.9 Alternative Protecting Group Strategy

Given treatment of **356** with Na naphthalide gave only returned staring material and showed no decomposition an *N*-tosyl protecting group strategy was proposed as they are known to be

cleaved with sodium naphthalide. It was envisaged that addition of **308** to *N*-tolylsulfinyl imine **359**, followed by oxidation, acetonide deprotection and cyclisation would give pyrrolidine **362** which could be deprotected under Na naphthalide conditions to give **305** (Figure 37).

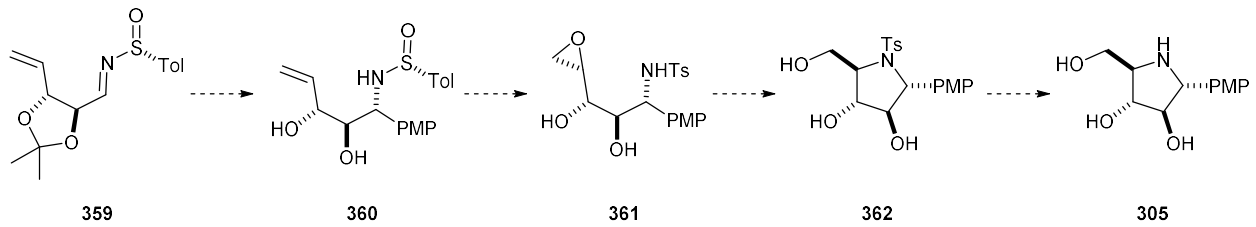
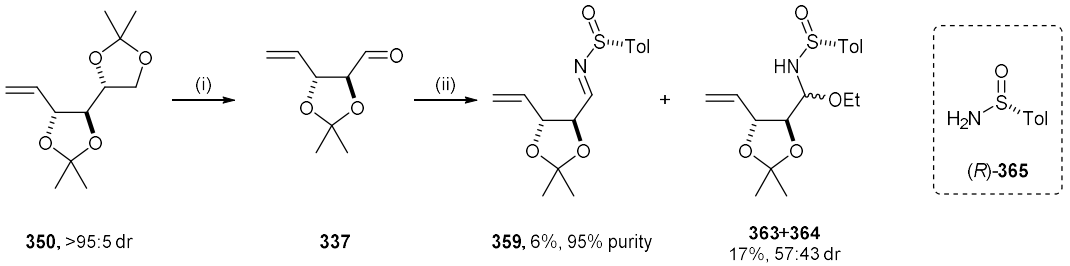


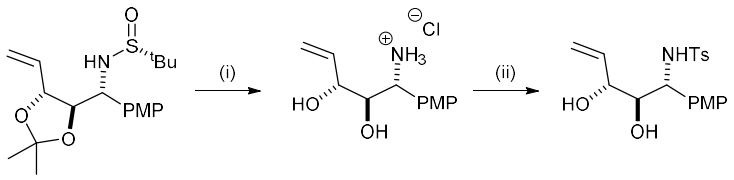
Figure 37. Proposed route to **305** using an alternative protecting group.

Synthesis of imine **359** was attempted in an analogous route to that of **150**: treatment of olefin **350** with H_5IO_6 gave aldehyde **337**, however upon condensation with commercially available, enantiopure (*R*)-**365** produced a ^{1}H NMR spectrum containing **359**, **363** and **364**, however no product ratios could be obtained. After chromatographic purification, imine **359** was isolated in only 6% yield and 95% purity. A 57:43 mixture of **363** and **364** was isolated in 17% combined yield presumably formed from nucleophilic attack of the ethoxide ion, present from hydrolysis of $Ti(OEt)_4$, upon imine **359** which has been previously noted (Scheme 107).[34]



Scheme 107. *Reagents and Conditions*: (i) H_5IO_6, EtOAc, rt, 30 min; (ii) (*R*)-**365**, $Ti(OEt)_4$, CH_2Cl_2, rt, 18 h.

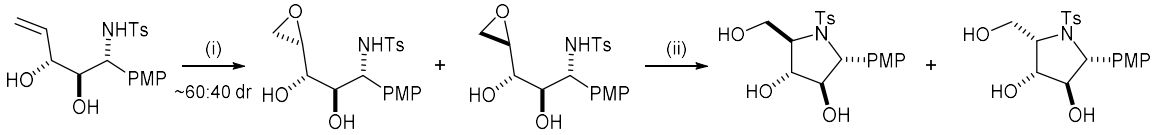
Given the unsuccessful synthesis of *N*-tolylsulfinyl imine **359** it was envisaged that the synthesis of **367** could be completed from **347** with established absolute configuration: treatment of **347** with HCl in MeOH allowed for global deprotection to give **366**·HCl which was followed by chemoselective *N*-protection with TsCl and Et_3N in CH_2Cl_2 to give **367** in 66% yield and >95:5 dr (Scheme 108).



347 **366**·HCl **367**, 66%, >95:5 dr

Scheme 108. *Reagents and Conditions*: (i) 1.25 M HCl in MeOH, rt, 18 h; (ii) TsCl, Et_3N, CH_2Cl_2, rt, 6 h.

After a successful synthesis of **367** the same epoxidation/cyclisation procedure was attempted: oxidation of **367** with *m*-CPBA gave a ~60:40 mixture of epoxides which was cyclised upon treatment with K_2CO_3 in MeOH giving a mixture of pyrrolidines **362** and **369**, which could not be quantified by ^{1}H NMR spectroscopic analysis of the crude reaction mixture. Exhaustive chromatography gave **362** in 30% yield as a single diastereoisomer. A 77:23 mixture of **369** and **362** was also isolated in 29% combined yield (Scheme 109).



367 **361** **368** **362**, 30%, >95:5 dr **369**, 29%, 77:23 dr

Scheme 109. *Reagents and Conditions*: (i) *m*-CPBA, CH_2Cl_2, rt, 18 h; (ii) K_2CO_3, MeOH, rt, 18 h.

The relative configuration within **362** was established *via* single crystal X-ray diffraction analysis.[31] The absolute (*R*,*R*,*R*,*R*)-configuration within **362** was assigned by reference to the known (*R*,*R*,*R*)-configuration of the C(2), C(3) and C(4) stereocentres within **362** as they were previously established *via* correlation to **351** for which a crystal structure was obtained (*vide supra*). A Flack *x* parameter[32,33] of –0.017(12) for the crystal structure of **362** confirmed this assigned absolute (*R*,*R*,*R*,*R*)-configuration (Figure 38).

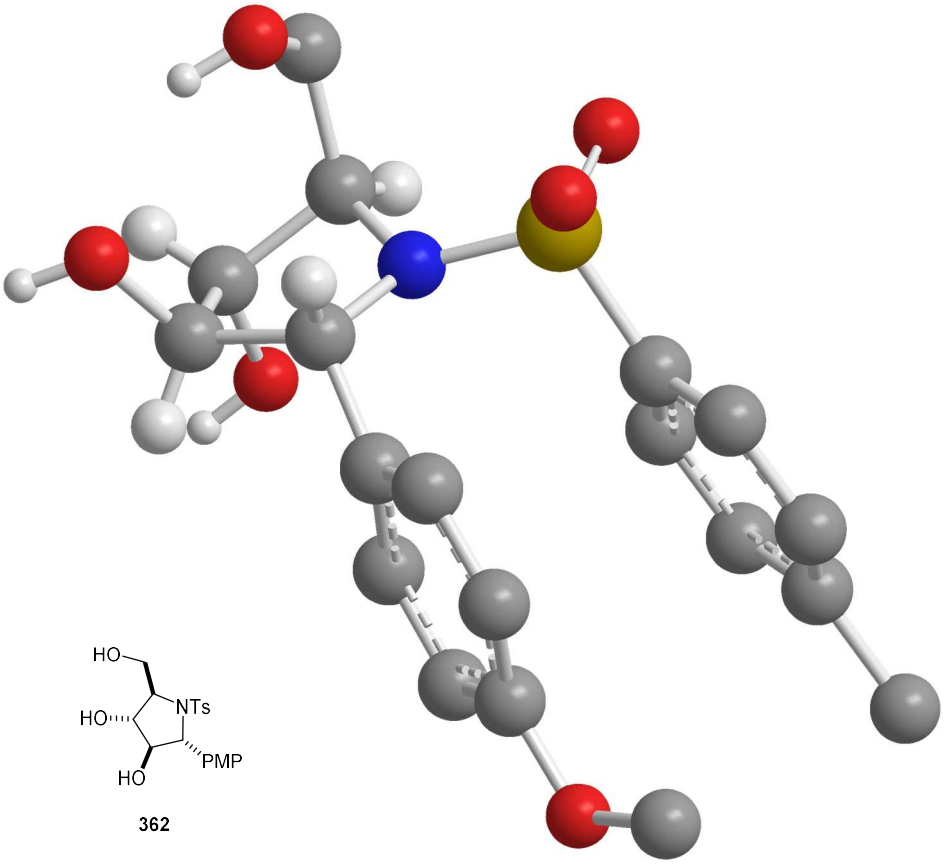
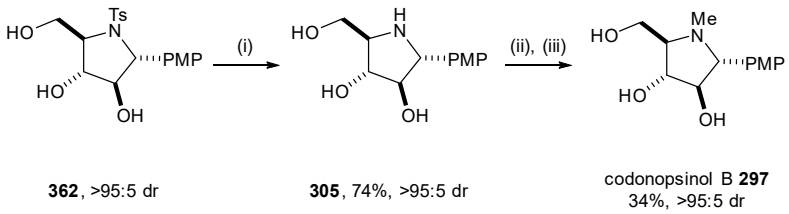


Figure 38. X-ray crystal structure of (*R*,*R*,*R*,*R*)-**362** (selected H atoms are omitted for clarity). [Within the crystal structure of **362** there were two distinct conformers in the asymmetric unit; for brevity only one is shown here].

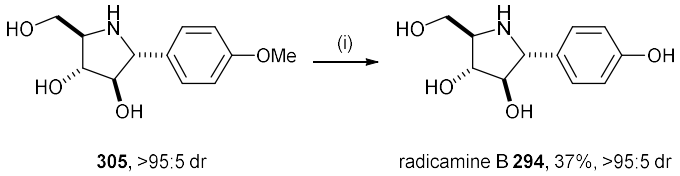
Pyrrolidine **362** was treated with sodium naphthalide (generated from the treatment of naphthalene in THF with sodium metal) to give a ^{1}H NMR of the crude reaction mixture that was swamped with excess naphthalene which upon chromatographic purification gave deprotected pyrrolidine **305** in 74% yield and >95:5 dr. Following a procedure by Cheng, Cheng and co-workers[14] **305** was treated with formaldehyde in MeOH then hydrogenated with Pearlman's catalyst giving codonopsinol B **297** in a modest 34% yield and >95:5 dr (Scheme 110).



362, >95:5 dr **305**, 74%, >95:5 dr codonopsinol B **297** 34%, >95:5 dr

Scheme 110. *Reagents and Conditions*: (i) Na, naphthalene, THF, 0 °C, 1 h; (ii) 37% aq HCHO, MeOH, rt, 10 min; (iii) $Pd(OH)_2/C$, H_2 (1 atm), rt, 24 h.

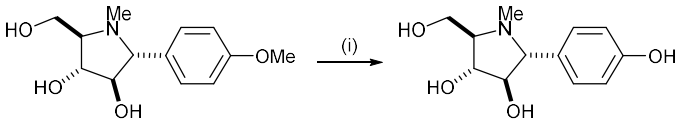
After the synthesis of pyrrolidines **305** and **297** an *O*-demethylation procedure was required to synthesise radicamine B **294** and codonopsinol C **298**.[35] Treatment of **305** with 5 equiv BBr_3 in CH_2Cl_2 only gave 51% conversion after 5 h so the mixture was resubjected to the same reaction conditions for a further 18 h. This still only gave 66% conversion however radicamine B **294** was eventually isolated in 37% yield and >95:5 dr (Scheme 111).



305, >95:5 dr radicamine B **294**, 37%, >95:5 dr

Scheme 111. *Reagents and Conditions*: (i) BBr_3, CH_2Cl_2, rt, 5 h then BBr_3, CH_2Cl_2, rt, 18 h.

In a similar manner: treatment of codonopsinol B **297** with BBr_3 in CH_2Cl_2 at rt for 18 h also gave incomplete conversion (~50%) however codonopsinol C **298** was isolated in 29% yield as a single diastereoisomer (Scheme 112).



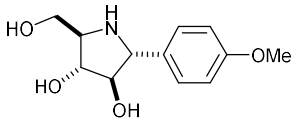
condonopsinol B **297**, >95:5 dr codonopsinol C **298** 29%, >95:5 dr

Scheme 112. *Reagents and Conditions*: (i) BBr_3, CH_2Cl_2, rt, 5 h.

4.10 Spectroscopic Data

The spectroscopic data and specific rotations of the four target pyrrolidines **294**, **297**, **298** and **305** were compared to the literature data for samples isolated from a natural source and synthetic samples. As previously it was noted that the spectroscopic data were variant on the trace amounts of acid it was imperative to ensure that analysis occurred on the pyrrolidines free bases. The ^1H and ^{13}C NMR spectroscopic data of **305**[36] were in excellent agreement with the synthetic sample reported by Cheng and Cheng [$(+0.02 \leq \Delta\delta_H \leq +0.05)$[33] and $(+2.7 \leq \Delta\delta_C \leq +3.0)$[37]] if the systematic referencing error in the ^{13}C NMR are ignored (Tables 14 and 15).[14] The specific rotation of **305** was determined to be $[\alpha]_D^{25}$ +44.4 (*c* 0.05 in H_2O)

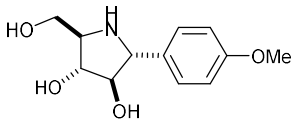
which shows good agreement with the value reported by Cheng and Cheng {$[\alpha]_D^{20}$ +42.5 (*c* 0.38 in H_2O)}.[14]



305

	This work	[14]	
	δ_H (400 MHz, D_2O)[39]	δ_H (600 MHz, D_2O)	$\Delta\delta_H$[38]
C(2)*H*	3.93 (d, *J* 9.2)	3.89 (d, *J* 9.1)	+0.04
C(3)*H*	4.12 (m)	4.08 (dd, J 7.6, 9.1)	+0.04
C(4)*H*	3.97 (t, *J* 7.4)	3.95 (t, 7.3, 7.3)	+0.02
C(5)*H*	3.27 (m)	3.24 (m)	+0.03
C(1')H_A	3.71 (dd, *J* 11.5, 6.5)	3.69 (dd, *J* 11.5, 6.5)	+0.02
C(1')H_B	3.77 (dd, *J* 11.5, 4.5)	3.75 (dd, *J* 11.5, 4.6)	+0.02
C(2")*H*/C(6")*H*	7.41 (d, *J* 8.7)	7.36 (d, *J* 8.7)	+0.05
C(3")*H*/C(5")*H*	7.04 (d, *J* 8.7)	7.00 (d, *J* 8.7)	+0.04
O*Me*	3.86 (s)	3.81 (s)	+0.05

Table 14. Comparison of ^{1}H NMR spectroscopic data of **305**.



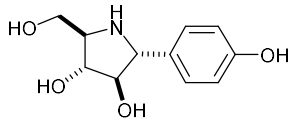
305

This work	[14]
δ_C (125 MHz, D_2O)[39]	δ_C (100 MHz, D_2O)[37]
58.3	55.3 (+3.0)
64.5	61.6 (+2.9)
65.4	62.5 (+2.9)
66.2	63.3 (+2.9)
80.2	77.4 (+2.8)
84.8	82.1 (+2.7)
117.2	114.2 (+3.0)
131.6	128.6 (+3.0)
134.9	132.2 (+2.7)
161.5	158.5 (+3.0)

Table 15. Comparison of ^{13}C NMR spectroscopic data of **305**.

The ^{1}H NMR spectroscopic data of radicamine B **294**[40] show excellent agreement with the sample isolated from Nature[10] ($+0.06 \leq \Delta\delta_H \leq +0.09$)[36] and a number of synthetic samples [($\Delta\delta_H = +0.09$),[41] and ($-0.03 \leq \Delta\delta_H \leq +0.02$)[42]].[36] Three other samples show poor agreement with the data resulting from this study [($+0.32 \leq \Delta\delta_H \leq +0.57$),[43] ($-0.18 \leq \Delta\delta_H \leq +0.38$)[44] and

($+0.29 \leq \Delta\delta_H \leq +0.72$)[45]][36] (Table 16). The ^{13}C NMR spectroscopic data of **294**[40] matched moderately well with the sample isolated from Nature[10] ($+0.08 \leq \Delta\delta_C \leq +0.52$)[37] and one synthetic sample[42] ($0.0 \leq \Delta\delta_C \leq +0.6$).[37] There is excellent agreement between the data from this study and the data for the synthetic sample reported by Rao ($+0.2 \leq \Delta\delta_C \leq +0.3$).[37,41] There is poor agreement between the data produced from this study and three literature samples [($-6.8 \leq \Delta\delta_C \leq +6.0$),[43] ($-6.9 \leq \Delta\delta_C \leq +6.0$)[45] and ($-1.2 \leq \Delta\delta_C \leq +10.3$)[44]] (Table 17).[37] The specific rotation was determined to be $[\alpha]_D^{25}$ +63.0 (*c* 0.1 in H_2O) which is in moderate agreement with those reported in the literature {$[\alpha]_D$ +72.7 (*c* 0.10 in H_2O);[10] $[\alpha]_D^{25}$ +70.6 (*c* 0.2 in H_2O);[46] $[\alpha]_D^{20}$ +74 (*c* 0.10 H_2O);[45] $[\alpha]_D^{25}$ +73.6 (*c* 0.10 in H_2O);[42] $[\alpha]_D^{25}$ +74 (*c* 0.10 in H_2O)[43]}.



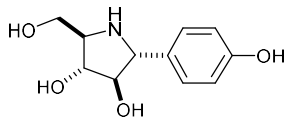
radicamine B **294**

	This work	Isolation[10]		41	
	δ_H (500 MHz, D_2O)	δ_H (D_2O)	$\Delta\delta_H$[38]	(500 MHz, D_2O)	$\Delta\delta_H$[38]
C(2)*H*	4.02 (m)	3.94 (d, *J* 9.0)	+0.08	3.93 (m)	+0.09
C(3)*H*	4.20 (m)	4.12 (dd, *J* 9.0, 7.6)	+0.08	4.11 (dd, *J* 9.0, 7.4)	+0.09
C(4)*H*	4.02 (m)	3.95 (t, *J* 7.6)	+0.07	3.93 (m)	+0.09
C(5)*H*	3.36 (m)	3.27 (m)	+0.09	3.27 (m)	+0.09
C(1')H_A	3.76 (dd, *J* 11.8, 6.4)	3.69 (dd, *J* 11.7, 6.4)	+0.07	3.67 (dd, *J* 12.1, 6.5)	+0.09
C(1')H_B	3.82 (dd, *J* 11.8, 4.3)	3.75 (dd, *J* 11.7, 4.4)	+0.07	3.73 (dd, *J* 12.1, 4.7)	+0.09
C(2")*H*/C(6")*H*	7.36 (d, *J* 8.5)	7.30 (d, *J* 8.7)	+0.06	7.27 (d, *J* 8.6)	+0.09
C(3")*H*/C(5")*H*	6.95 (d, *J* 8.5)	6.89 (d, *J* 8.7)	+0.06	6.86 (d, *J* 8.6)	+0.09

	42		43	
	δ_H (500 MHz, D_2O)	$\Delta\delta_H$[38]	δ_H (400 MHz, D_2O)	$\Delta\delta_H$[38]
C(2)*H*	4.00 (br d, *J* 9.0)	+0.02	3.50 (m)	+0.52
C(3)*H*	4.18 (dd, *J* 9.0, 7.5)	+0.02	3.75 (t, *J* 8.3)	+0.45
C(4)*H*	4.03 (t, *J* 7.5)	–0.01	3.50 (m)	+0.52
C(5)*H*	3.34 (ddd, *J* 7.5, 6.5, 4.5)	+0.02	2.89 (m)	+0.47
C(1')H_A	3.77 (dd, *J* 11.5, 6.5)	–0.01	3.36 (dd, *J* 11.1, 7.5)	+0.40
C(1')H_B	3.84 (dd, *J* 11.5, 4.5)	–0.02	3.50 (m)	+0.32
C(2")*H*/C(6")*H*	7.38 (app d, *J* 8.6)	–0.02	6.93 (d, *J* 8.4)	+0.43
C(3")*H*/C(5")*H*	6.98 (app d, *J* 8.6)	–0.03	6.38 (d, *J* 8.3)	+0.57

	44		45	
	δ_H (600 MHz, D_2O)	$\Delta\delta_H$[38]	δ_H (400 MHz, D_2O)	$\Delta\delta_H$[38]
C(2)*H*	3.64 (m)	+0.38	3.73 (pseudo t, *J* 7.8)	+0.29
C(3)*H*	4.30 (d, *J* 2.3)	–0.10	3.48 (m)	+0.72
C(4)*H*	4.12 (dd, *J* 2.2, 1.2)	–0.10	3.48 (m)	+0.55
C(5)*H*	3.54 (m)	–0.18	2.87 (m)	+0.49
C(1')H_A	3.85 (dd, *J* 12.1, 8.6)	–0.09	3.35 (pseudo t, *J* 9.9)	+0.41
C(1')H_B	3.95 (dd, *J* 12.1, 4.8)	–0.13	3.48 (m)	+0.34
C(2")*H*/C(6")*H*	7.30 (d, *J* 8.5)	–0.06	6.92 (d, *J* 8.0)	+0.44
C(3")*H*/C(5")*H*	6.86 (d, *J* 8.5)	–0.09	6.37 (d, *J* 8.0)	+0.61

Table 16. Comparison of ^{1}H NMR spectroscopic data of radicamine B **294**.

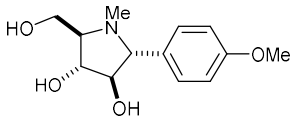


radicamine B **294**

This work	Isolation[10]	[41]	[42]	[43]	[45]	[44]
δ_C[a]	δ_C (D_2O)	δ_C[b]	δ_C[a]	δ_C[c]	δ_C[c]	δ_C[d]
64.4	64.12 (+0.28)	-	64.8 (+0.4)	62.3 (+2.1)	62.3 (+2.1)	59.2 (+5.2)
64.5	64.38 (+0.12)	64.2 (+0.3)	64.4 (+0.1)	63.5 (+1.0)	63.5 (+1.0)	64.5 (0.0)
66.1	65.86 (+0.24)	65.9 (+0.2)	66.1 (0.0)	63.8 (+2.3)	63.8 (+2.3)	67.3 (–1.2)
79.5	79.35 (+0.15)	79.3 (+0.2)	79.8 (+0.3)	78.4 (+1.1)	78.4 (+1.1)	76.0 (+3.5)
83.8	83.72 (+0.08)	83.6 (+0.2)	84.3 (+0.5)	82.9 (+0.9)	82.9 (+0.9)	76.5 (+7.3)
118.7	118.34 (+0.36)	118.4 (+0.3)	118.6 (+0.1)	118.7 (0.0)	116.7 (+2.0)	115.6 (+3.1)
132.1	131.68 (+0.42)	131.8 (+0.3)	131.8 (+0.3)	126.1 (+6.0)	126.1 (+6.0)	121.8 (+10.3)
132.3	131.78 (+0.52)	131.9 (+0.3)	133.2 (+0.1)	128.8 (+3.5)	128.8 (+3.5)	129.6 (+2.7)
158.8	158.30 (+0.50)	158.5 (+0.3)	158.2 (+0.6)	165.6 (–6.8)	165.7 (–6.9)	156.0 (+2.8)

Table 17. Comparison of ^{13}C NMR spectroscopic data of radicamine B **294**. [[a] 125 MHz, D_2O. [b] 75 MHz, D_2O. [c] 100 MHz, D_2O. [d] 151 MHz, D_2O].

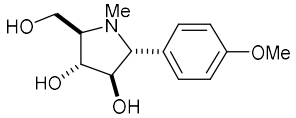
The spectroscopic data of the synthetic sample of codonopsinol B **297**[47] from this study was compared with the reported data from the isolation from Goda *et al.*[16] and the single synthetic sample.[14] The ^1H NMR spectroscopic data shows excellent agreement with the sample isolated from a natural source ($0.00 \leq \Delta\delta_H \leq +0.01$)[38] and good agreement with the synthetic sample ($-0.06 \leq \Delta\delta_H \leq 0.00$)[38] (Table 18). The ^{13}C NMR spectroscopic data of the sample of **297** from this study shows excellent agreement ($-0.1 \leq \Delta\delta_C \leq +0.2$)[37] with the reported data of the sample isolated from *Codonopsis pilsoula* and good comparison ($-0.3 \leq \Delta\delta_C \leq +0.2$)[37] with data from the synthetic sample[14] despite the missing ^{13}C NMR resonance belonging to C(1") (Table 19). The specific rotation was determined to be $[\alpha]_D^{25}$ –11.0 (*c* 0.47 in MeOH) which shows good agreement with the literature values {$[\alpha]_D^{20}$ –7.0 (*c* 0.16 in MeOH);[14] $[\alpha]_D$ –8 (*c* 0.45 in MeOH)[16]}.



codonopsinol B **297**

	This work	Isolation[16]		Synthetic[14]	
	δ_H (400 MHz, CD_3OD)	δ_H (CD_3OD)	$\Delta\delta_H$[38]	δ_H (600 MHz, CD_3OD)	$\Delta\delta_H$[38]
C(2)*H*	3.65 (d, *J* 6.6)	3.65 (d, *J* 6.5)	0.00	3.71 (d, *J* 6.7)	–0.06
C(3)*H*	3.93 (dd, *J* 6.6, 4.8)	3.92 (dd, *J* 6.5, 4.6)	+0.01	3.96 (dd, *J* 6.7, 5.0)	–0.03
C(4)*H*	4.01 (app t, *J* 4.6)	4.00 (t, *J* 4.6)	+0.01	4.02 (t, *J* 4.7)*	–0.01
C(5)*H*	3.07 (app q, *J* 4.3)	3.06 (td, *J* 4.6, 4.0)	+0.01	3.10 (dd, *J* 8.6, 4.3)	–0.03
C(1')H_A	3.81 (dd, *J* 11.6, 4.3)	3.80 (dd, *J* 11.5, 4.6)	+0.01	3.82 (dd, *J* 11.6, 4.3)	–0.01
C(1')H_B	3.85 (dd, *J* 11.6, 4.3)	3.84 (dd, *J* 11.5, 4.0)	+0.01	3.86 (dd, *J* 11.6, 4.1)	–0.01
C(2")*H*/C(6")*H*	7.28 (m)	7.27 (d, *J* 8.5)	+0.01	7.28 (d, *J* 8.6)	0.00
C(3")*H*/C(5")*H*	6.89 (m)	6.89 (d, *J* 8.5)	0.00	6.90 (d, *J* 8.6)	0.00
O*Me*	3.78 (s)	3.77 (s)	+0.01	3.78 (s)	0.00
N*Me*	2.17 (s)	2.16 (s)	+0.01	2.20 (s)	–0.03

Table 18. Comparison of ^{1}H NMR spectroscopic data of codonopsinol B **297**. [* Two ^3J values (4.7, 4.6 Hz) are reported].



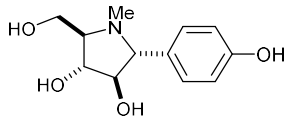
codonopsinol B **297**

This work	Isolation[16]	Synthetic[14]
δ_C (100 MHz, CD_3OD)	δ_C (150 MHz, CD_3OD)[37]	δ_C (150 MHz, CD_3OD)[37]
34.9	35.0 (–0.1)	35.2 (–0.3)
55.7	55.7 (0.0)	55.8 (–0.1)
60.9	60.8 (+0.1)	60.8 (+0.1)
71.0	71.0 (0.0)	71.2 (–0.2)
75.3	75.3 (0.0)	75.4 (–0.1)
80.0	79.9 (+0.1)	79.8 (+0.2)
85.7	85.6 (+0.1)	85.4 (–0.3)
114. 8	114.8 (0.0)	114.9 (–0.1)
130.6	130.6 (0.0)	130.8 (–0.2)
133.7	133.5 (+0.2)	-
160.7	160.7 (0.0)	160.9 (–0.2)

Table 19. Comparison of ^{13}C NMR spectroscopic data of codonopsinol B **297**.

The spectroscopic data of the synthetic sample of codonopsinol C **298** from this study was compared with the reported data from the isolation by Goda *et al.*[16] and the single synthetic sample of Kusano *et al.* (derived from radicamine B).[10] The ^{1}H and ^{13}C NMR spectroscopic data were in excellent agreement with the sample isolated from Nature[16] ($+0.01 \leq \Delta\delta_H \leq +0.04$)[38] and ($-0.4 \leq \Delta\delta_C \leq +0.1$) (Tables 20 and 21).[37] Kusano *et al.* only

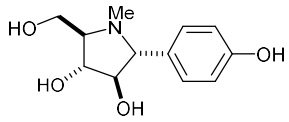
report ^{1}H NMR spectroscopic data in D_2O which do not match data collected from this study [$(-1.32 \leq \Delta\delta_H \leq -0.08)^{38}$] (Table 22).[10] The specific rotation of the sample of **298** was determined to be $[\alpha]_D^{25}$ +6.1 (*c* 0.2 in MeOH), which is consistent with the value reported by Kusano *et al.*[10] {$[\alpha]_D^{25}$ +8.3 (*c* 0.05 in MeOH)} and inconsistent with the value reported for the sample isolated from the natural source by Goda and co-workers[16] {$[\alpha]_D$ –9 (*c* 0.6 in MeOH)}. Upon the addition of 0.1 equiv TFA the specific rotation of **298** was determined to be $[\alpha]_D^{25}$ +26.2 (*c* 0.2 in MeOH). Given this relatively large variation with a small amount of acid from the free base, and the small magnitude of the measured rotation, these data are inconclusive to enable unambiguous assignment of the absolute configuration of the natural compound. However, given the related compounds (**293**, **294**, and **295**) have confirmed absolute (*R*,*R*,*R*,*R*)-configuration it would stand to reason that **298** also possesses this absolute configuration given a likely common biosynthetic origin.



codonopsinol C **298**

	This work	Isolation[16]	
	δ_H (500 MHz, CD_3OD)	δ_H (CD_3OD)	$\Delta\delta_H$[38]
C(2)*H*	3.65 (d, *J* 6.7)	3.61 (d, *J* 6.5)	+0.04
C(3)*H*	3.95 (dd, *J* 6.5, 5.0)	3.92 (dd, *J* 6.5, 4.8)	+0.03
C(4)*H*	4.01 (app t, *J* 4.7)	3.99 (t, *J* 4.8)	+0.02
C(5)*H*	3.07 (app q, *J* 4.3)	3.04 (td, *J* 4.8, 4.3)	+0.03
C(1')H_A	3.82 (dd, *J* 11.6, 4.3)	3.80 (dd, *J* 11.6, 4.3)	+0.02
C(1')H_B	3.85 (dd, *J* 11.6, 4.3)	3.84 (dd, *J* 11.6, 4.3)	+0.01
C(2")*H*/C(6")*H*	7.19 (d, *J* 8.5)	7.17 (d, *J* 8.5)	+0.02
C(3")*H*/C(5")*H*	6.77 (d, *J* 8.5)	6.75 (d, *J* 8.5)	+0.02
N*Me*	2.18 (s)	2.16 (s)	+0.02

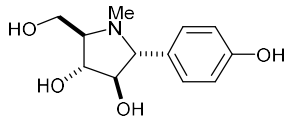
Table 20. ^{1}H NMR spectroscopic data of codonopsinol C **298**.



codonopsinol C **298**

This work	Isolation[16]
δ_H (125 MHz, CD_3OD)	δ_C (CD_3OD)
35.0	35.0 (0.0)
60.7	60.8 (–0.1)
71.0	71.0 (0.0)
75.3	75.3 (0.0)
79.7	79.9 (–0.2)
85.3	85.5 (–0.2)
116.1	116.1 (0.0)
130.8	130.7 (+0.1)
131.8	132.2 (–0.4)
158.2	158.1 (+0.1)

Table 21. ^{13}C NMR spectroscopic data of codonopsinol C **298**.



codonopsinol C **298**

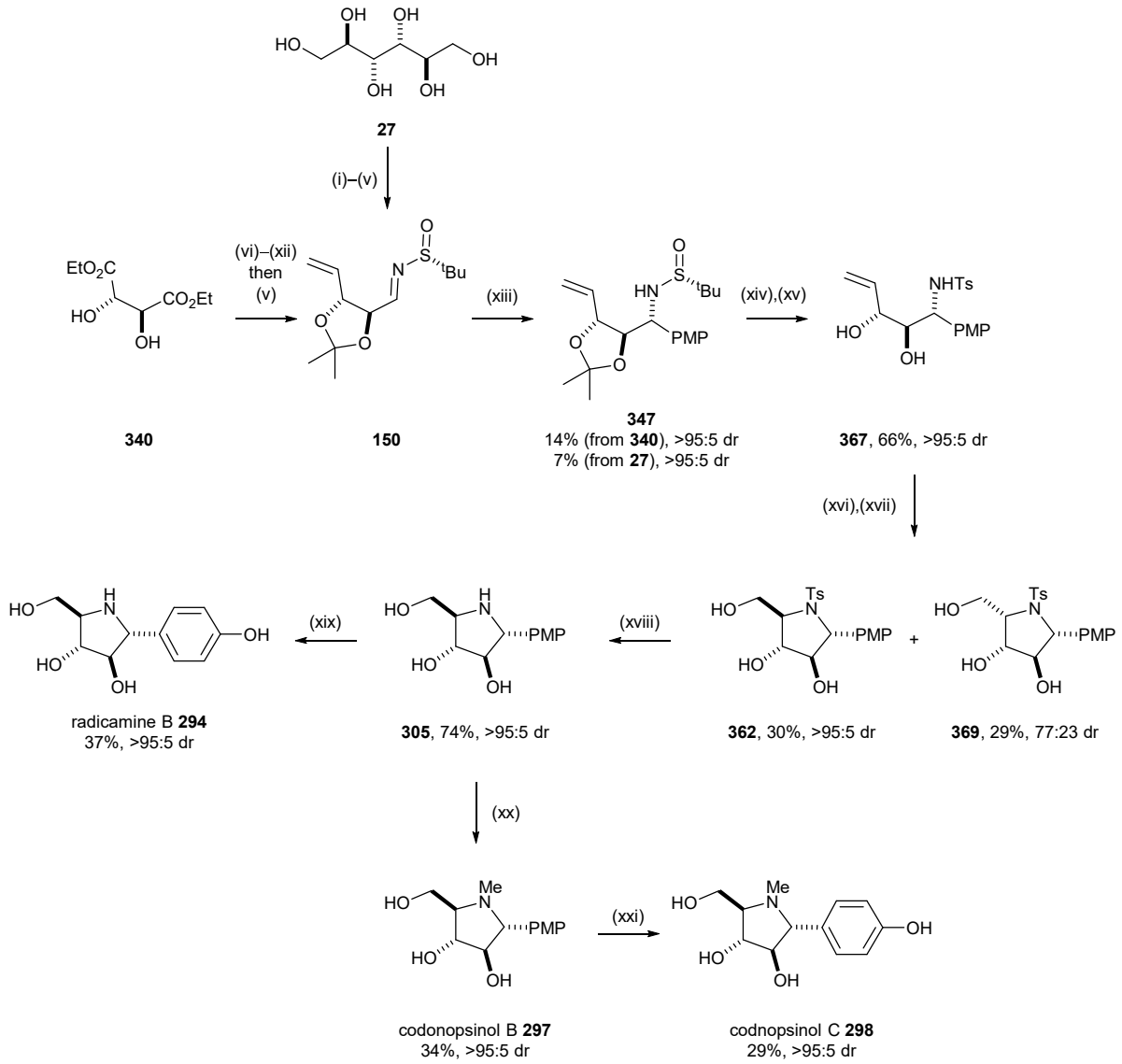
	This work	[10]	
	δ_H (400 MHz, D_2O)	δ_H (D_2O)	$\Delta\delta_H$[38]
C(2)*H*	3.74 (d, *J* 8.2)	4.36 (m)	–0.62
C(3)*H*	4.16 (dd, *J* 8.2, 6.0)	5.48 (dd, *J* 5.7, 5.5)	–1.32
C(4)*H*	4.08 (m)	4.36 (m)	–0.28
C(5)*H*	3.10 (app q, *J* 4.7)	3.55 (m)	–0.45
C(1')H_A	3.91 (m)	4.22 (m)	–0.31
C(1')H_B	3.91 (m)	4.22 (m)	–0.31
C(2")*H*/C(6")*H*	7.29 (d, *J* 8..6)	7.60 (d, *J* 8.0)	–0.31
C(3")*H*/C(5")*H*	6.94 (d, *J* 8.6)	7.02 (d, *J* 8.0)	–0.08
N*Me*	2.15 (s)	2.63 (s)	–0.48

Table 22. ^{1}H NMR spectroscopic data of codonopsinol C **298** in D_2O.

4.11 Conclusion

Four polyhydroxylated pyrrolidines; **305**, radicamine B **294**, codonopsinol B **297** and codonopsinol C **298** were synthesised from D-mannitol **27** or diethyl D-tartrate **340** giving an independant report of their relative and absolute configuration. Their spectroscopic and specific rotation data were compared against literature values. Diethyl D-tartrate **340** was converted into enantiopure *N*-sulfinyl imine **150** which, upon treatment with

4-methoxyphenylmagnesium bromide **308** gave enantiopure sulfinamide **347** in 14% yield from **340** (or in 7% yield, 14% based on recovered starting material, from **27**). Acidic global deprotection with HCl in MeOH followed by chemoselective *N*-tosylation gave **367** in 66% yield and >95:5 dr. Treatment of **367** with *m*-CPBA afforded a diastereomeric mixture of epoxides which underwent cyclisation to give a mixture of pyrrolidines **362** and **369** which after purification **362** was isolated in 30% yield and >95:5 dr and a 77:23 mixture of **369** and **362**, respectively, was isolated in 29% combined yield. *N*-Deprotection of **362** with sodium naphthalide gave known pyrrolidine **305** in 74% yield and >95:5 dr which was elaborated to radicamine B **294** upon treatment with BBr_3 in CH_2Cl_2 in 37% yield and >95:5 dr. The ^1H NMR spectroscopic data for radicamine B **294** from this study matches well with the sample isolated from Nature[10] and a number of synthetic samples.[41,42] The ^{13}C NMR spectroscopic data matches moderately well with the ^{13}C NMR data from the sample isolated from Nature.[10] The specific rotation was in agreement with those reported in the literature. Pyrrolidine **305** also underwent *N*-methylation with HCHO to give codonopsinol B **297** in 34% yield and >95:5 dr. The ^1H and ^{13}C NMR spectroscopic data and specific rotation for **297** were in excellent agreement with the sample isolated from Nature[16] and in good agreement with the data reported for the single synthetic sample.[14] Codonopsinol B **297** was converted into codonopsinol C **298** upon treatment with BBr_3 in 29% yield and >95:5 dr. The ^1H and ^{13}C NMR spectroscopic data show good agreement with the sample isolated from Nature.[16] The specific rotation data shows significant variance upon treatment with acid and is therefore inconclusive to enable unambiguous assignment of the absolute configuration of **298** (Scheme 113).



Scheme 113. *Reagents and Conditions*: (i) H_2SO_4, acetone, rt, 18 h; (ii) HCl, EtOH/H_2O (7:3 v/v), 45 °C, 1 h; (iii) I_2, Ph_3P, imidazole, PhMe, 110 °C, 3 h; (iv) H_5IO_6, EtOAc, rt, 30 min; (v) (*R*)-**338**, $Ti(OEt)_4$, CH_2Cl_2, rt, 18 h; (vi) 2,2-dimethoxypropane, TsOH, PhMe, 120 °C, 18 h; (vii) $LiAlH_4$, THF, 67 °C, 18 h; (viii) NaH, THF, 0 °C, 45 min then TBSCl, 0 °C to rt, 18 h; (ix) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 1 h then Et_3N, –78 °C, 20 min then rt, 20 min; (x) $MePh_3P^+Br^-$, BuLi, THF, –78 °C to rt, 3 h; (xi) TBAF, THF, 0 °C to rt, 2.5 h; (xii) DMSO, $(COCl)_2$, CH_2Cl_2, –78 °C, 1 h then Et_3N, –78 °C, 20 min then rt, 20 min (xiii) **308**, Et_2O, –78 °C, 5 h; (xiv) 1.25 M HCl in MeOH, rt, 18 h; (xv) TsCl, Et_3N, CH_2Cl_2, rt, 6 h; (xvi) *m*-CPBA, CH_2Cl_2, rt, 18 h; (xvii) K_2CO_3, MeOH, rt, 18 h; (xviii) Na, naphthalene, THF, 0 °C, 1 h; (xix) 37% aq HCHO, MeOH, rt, 10 min then $Pd(OH)_2/C$, H_2 (1 atm), rt, 24 h; (xx) BBr_3, CH_2Cl_2, rt, 5 h then BBr_3, CH_2Cl_2, rt, 18 h; (xxi) BBr_3, CH_2Cl_2, rt, 18 h.

4.12 Future Work

After the successful development of a synthetic route to **305**, radicamine B **294**, codonopsinol B **297** and codonopsinol C **298** future investigations will be in the synthesis of **304** and radicamine A **293** and the corresponding *N*-methyl analogues codonopsinol **295** and codonopsinol A **296** to allow the analysis of the spectroscopic data of all the members within

the codonopsinol family and provide an independent report into their absolute configuration (Figure 39).

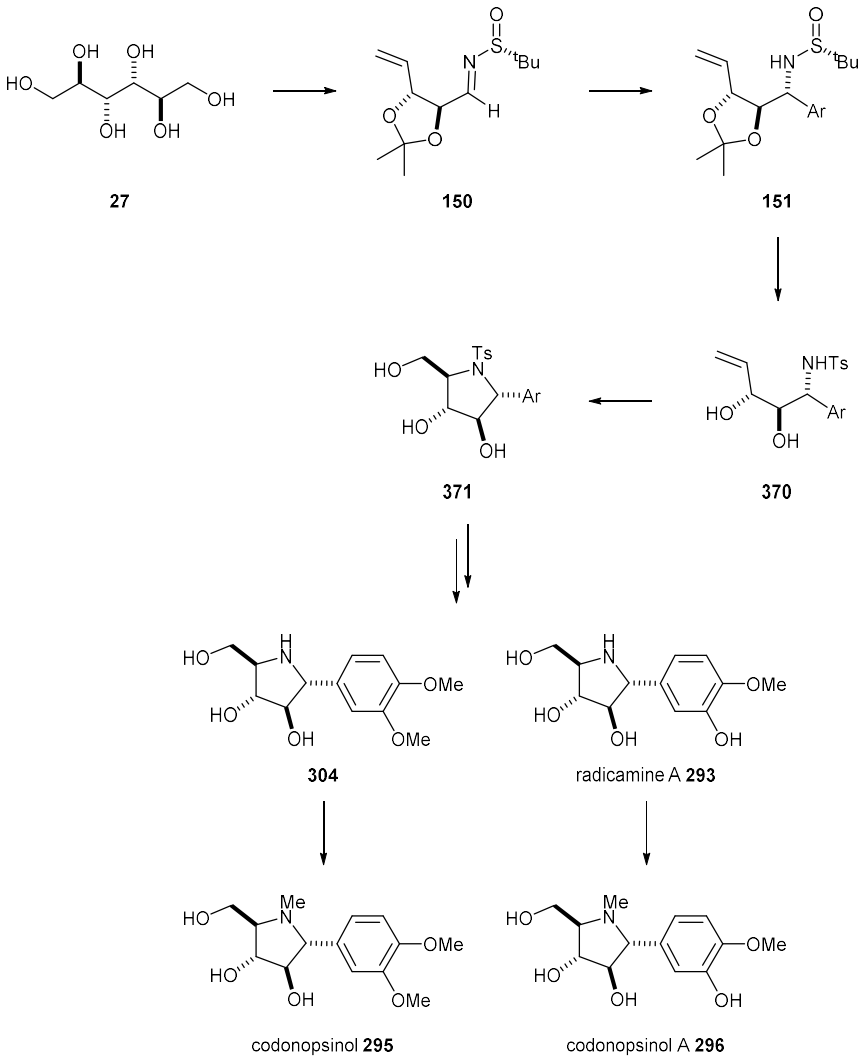


Figure 39. Future synthesis of **304**, radicamine A **293**, codonopsinol **295** and codonopsinol A **296**.

4.13 References

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(36) An analytical sample of the free base of **305** was obtained *via* a partition between 2.0 M aq KOH and $CHCl_3$/^{i}PrOH (3:1 v/v).
(37) $\Delta\delta_C$ is defined as the difference in the ^{13}C NMR spectroscopic resonances of the literature from the data from this study.
(38) $\Delta\delta_H$ is defined as the difference in the ^1H NMR spectroscopic resonances of the literature from the data from this study.
(39) Chemical shifts were measured downfield from sodium 3-(trimethylsilyl)propanoate.
(40) Ion exchange chromatography was performed on **294**·HCl to ensure the free base was analysed.
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(47) An analytical sample of the free base of **297** was obtained *via* a partition between 2.0 M aq KOH and $CHCl_3$/^{i}PrOH (3:1 v/v).

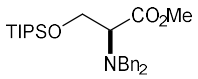
Chapter 5: Experimental

5.1 General Experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen atmosphere using standard vacuum line techniques and glassware that was flame dried and cooled under nitrogen before use. Solvents were dried according to the procedure outlined by Grubbs *et al.*[1] Water was purified by an Elix® UV-10 system. BuLi was supplied as a solution in hexanes and titrated against Ph_2CHCO_2H before use. All other solvents and reagents were used as supplied (analytical or HPLC grade) without prior purification. Organic layers were dried over $MgSO_4$ unless otherwise specified. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm) and 1% aq $KMnO_4$. Flash column chromatography was performed on Kieselgel 60 silica. For biphasic eluents, the aqueous phase was removed prior to flash column chromatography. Melting points were recorded on a Gallenkamp Hot Stage or Leica Gallen III apparatus and are uncorrected. Optical rotations were recorded on a Perkin-Elmer 241 or 341 polarimeter with a water-jacketed 10 cm cell. Specific rotations are reported in 10^{-1} deg cm^2 g^{-1} and concentrations in g 100^{-1} mL^{-1}. IR spectra were recorded on Bruker Tensor 27 FT-IR spectrometer on a diamond ATR module (ATR). Selected characteristic peaks are reported in cm^{-1}. NMR spectra were recorded on Bruker Avance spectrometers in the deuterated solvent stated and at rt unless otherwise specified. The field was locked by external referencing to the relevant deuteron resonance unless otherwise specified. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. Low-resolution mass spectra were recorded on either a Micromass LCT Premier or Agilent Quadrupole 6120 LC/MS spectrometer. Accurate mass measurements were run on a Bruker MicroToF internally calibrated with polyalanine.

5.2 Experimental Data for Chapter 2

Methyl (*S*)-2-(*N*,*N*-dibenzylamino)-3-(triisopropylsilyloxy)propanoate (*S*)-165

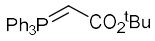


Step 1: AcCl (40.6 mL, 571 mmol) was added dropwise to MeOH (200 mL) at 0 °C. The resultant solution was stirred at 0 °C for 15 min then L-serine (*S*)-**13** (20.0 g, 190 mmol) was added portionwise. The resultant mixture was heated at reflux for 3 h, then allowed to cool to rt before being concentrated *in vacuo* to give **20**·HCl as a white solid.

Step 2: **20**·HCl was dissolved in MeCN (300 mL) and K_2CO_3 (131 g, 951 mmol) and BnBr (56.6 mL, 475 mmol) were added sequentially. The resultant mixture was stirred at rt for 36 h then H_2O (200 mL) was added and the aqueous layer was extracted with EtOAc (3 × 150 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **164** as an orange viscous oil.

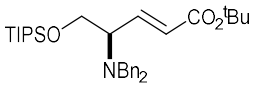
Step 3: The residue **164** was dissolved in CH_2Cl_2 (300 mL) and imidazole (25.9 g, 381 mmol), DMAP (5 mg) and TIPSCl (42.7 mL, 200 mmol) were added sequentially. The resultant mixture was stirred at rt for 36 h then concentrated *in vacuo*. The residue was dissolved in Et_2O (250 mL) and washed sequentially with 1 M aq HCl (150 mL) then satd aq $NaHCO_3$ (150 mL). The combined organic layers were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 30:1) gave **165** as colourless viscous oil (73.7 g, 85%);[2] $[\alpha]_D^{22}$ –42.9 (*c* 1.0 in $CHCl_3$); {lit.[2] $[\alpha]_D^{22}$ –44.2 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.99–1.15 (21H, m, Si(C*HMe*$_2$)$_3$), 3.57 (1H, app t, *J* 6.3, C(2)*H*), 3.70 (2H, *J* 14.3, N(CH_AH_BPh)$_2$), 3.75 (3H, s, O*Me*), 3.97 (2H, d, *J* 14.3, N(CH$_A$*H*$_B$Ph)$_2$), 3.91–4.01 (1H, m, C(3)H_A), 4.10 (1H, dd, *J* 9.8, 6.3, C(3)H_B), 7.20–7.25 (2H, m, *p-Ph*), 7.27–7.33 (4H, m, *Ph*), 7.37–7.43 (4H, m, *Ph*).

tert-Butyl (triphenylphosphoranylidene)acetate 167



tert-Butyl bromoacetate (50.0 g, 0.256 mmol) was added to a stirred solution of PPh_3 (67.2 g, 0.256 mmol) in EtOAc (400 mL) and was stirred at rt for 18 h. The resultant suspension was filtered, washed with Et_2O (100 mL) then partitioned between CH_2Cl_2 (500 mL) and 2.0 M aq NaOH (500 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 250 mL) and the combined organic layers were dried and concentrated *in vacuo* to give **167** as a pale yellow solid (85.8 g, 89%);[3] mp 150–154 °C {lit.[4] 154–155 °C}; δ_H (400 MHz, $CDCl_3$) 0.85−1.52 (9H, br s, C*Me*$_3$), 2.49−2.85 (1H, br s, C*H*$CO_2{}^t$Bu), 7.38−7.73 (15H, m, *Ph*).

tert-Butyl (*R*,*E*)-4-(*N*,*N*-dibenzylamino)-5-(triisopropylsilyloxy)penten-2-oate (*R*)-154

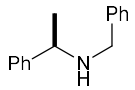


Step 1: DIBAL-H (1 M in PhMe, 100 mL, 100 mmol) was added to a stirred solution of **165** (18.2 g, 39.9 mmol) in PhMe (100 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. MeOH (10 mL) was added, the resultant mixture was allowed to warm to rt then satd aq Rochelle salt (150 mL) was added and the resultant mixture was left to stir at rt for 18 h. The aqueous layer was extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic layers were dried and concentrated *in vacuo* to give **166** (17.2 g).

Step 2: DMSO (11.4 mL, 160 mmol) was added to a stirred solution of $(COCl)_2$ (6.76 mL, 80.0 mmol) in CH_2Cl_2 (80 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min. Then the residue **166** (17.2 g) dissolved in CH_2Cl_2 (80 mL) was added at –78 °C, the resultant mixture was allowed to stir at –78 °C for 1 h then Et_3N (33.5 mL, 240 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 15 min then allowed to warm to rt before **167** (22.6 g, 60.0 mmol) was added. The resultant mixture was left to stir at rt for 18 h then washed with satd aq $NaHCO_3$ (150 mL). The aqueous layer was

extracted with CH_2Cl_2 (3 × 100 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (30–40 °C petroleum ether/Et_2O, 25:1) gave (*R*)-**154** as a colourless oil (18.2 g, 87%, >95:5 dr);[4] $[\alpha]_D^{22}$ –59.1 (*c* 1.0 in $CHCl_3$); {lit.[4] $[\alpha]_D^{22}$ –62.0 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.92–1.11 (21 H, m, Si(C*H*Me_2)$_3$), 1.51 (9H, s, CMe_3), 3.42 (1H, dd, *J* 12.3, 6.1, C(4)*H*), 3.64 (2H, d, *J* 13.8, N(C$H_A$$H_B$Ph)$_2$), 3.85 (2H, d, *J* 13.8, N(C$H_A$$H_B$Ph)$_2$), 3.88–3.92 (1H, m, C(5)H_A), 3.97 (1H, dd, *J* 10.1, 6.1, C(5)H_B), 5.92–5.99 (1H, m, C(2)*H*), 6.97 (1H, dd, *J* 16.0, 7.1, C(3)*H*), 7.19–7.25 (2H, m, *Ph*), 7.28–7.34 (4H, m, *Ph*), 7.37–7.43 (4H, m, *Ph*).

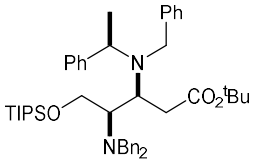
(*R*)-*N*-Benzyl-*N*-(α-methylbenzyl)amine (*R*)-162



Benzaldehyde (83.8 mL, 826 mmol) was added to a stirred solution of (*R*)-α-methylbenzylamine (*R*)-**171** (100 mL, 786 mmol, 98% ee) in EtOH (500 mL) at rt and the reaction mixture was heated at reflux for 3 h before being cooled to 0 °C. $NaBH_4$ (29.7 g, 786 mmol) was then added portionwise and the resultant suspension was stirred at rt for 48 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between H_2O (500 mL) and CH_2Cl_2 (750 mL). The organic layer was washed with brine (400 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 250 mL). The combined organic layers were dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (150 mL) and the resultant solution was added dropwise to a flask containing 10 M aq HCl (100 mL) and Et_2O (1.0 L) at 0 °C. The white precipitate was collected by filtration, washed with Et_2O (250 mL) and dissolved in CH_2Cl_2 (1.0 L). The resultant solution was dried and concentrated *in vacuo* to give (*R*)-**162**·HCl as a white solid (146 g, 75%). The free amine was regenerated by treatment of the hydrochloride salt with 2.0 M aq NaOH, followed by extraction with CH_2Cl_2 (3 × 300 mL). The combined organic layers were dried and concentrated *in vacuo* to give (*R*)-**162** as a pale yellow oil (121 g, 73%, 98% ee);[5] $[\alpha]_D^{22}$ +50.4 (*c* 1.0 in $CHCl_3$);

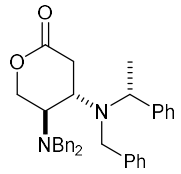
{lit.[5] $[\alpha]_D^{22}$ +46.4 (*c* 1.0 in $CHCl_3$)]}; δ_H (400 MHz, $CDCl_3$) 1.41 (3H, d, *J* 6.6, C(α)*Me*), 1.64 (1H, br s, N*H*), 3.64 (1H, d, *J* 13.2, NCH_AH$_B$Ph), 3.71 (1H, d, *J* 13.2, NCH$_A$$H_B$Ph), 3.86 (1H, q, *J* 6.6, C(α)*H*), 7.25−7.43 (10H, m, *Ph*).

***tert*-Butyl (3*S*,4*R*,*αR*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-5-(triisopropylsilyloxy)pentanoate 155**



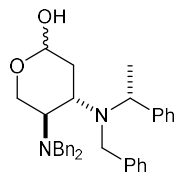
BuLi (2.2 M in hexanes, 5.08 mL, 11.2 mmol) was added dropwise to a stirred solution of (*R*)-**162** (2.42 g, 11.5 mmol, 98% ee) in THF (20 mL) at −78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of (*R*)-**154** (3.00 g, 5.73 mmol, >95:5 dr) in THF (20 mL) was then added *via* cannula and the reaction mixture was stirred at −78 °C for 2 h then was allowed to warm to rt. Satd aq NH_4Cl (5 mL) was added and the reaction mixture was stirred at rt for 5 min, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (100 mL) and 10% aq citric acid (50 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (150 mL) and brine (150 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent pentane/EtOAc, 25:1) gave **155** as a colourless viscous oil (4.03 g, 96%, >95:5 dr);[2] $[\alpha]_D^{22}$ –7.3 (*c* 1.0 in $CHCl_3$); {lit.[2] $[\alpha]_D^{22}$ –0.9 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.01−1.14 (21H, m, Si(C*HMe*$_2$)$_3$), 1.32 (9H, s, C*Me*$_3$), 1.34 (3H, d, *J* 7.0, C(α)*Me*), 1.77 (1H, dd, *J* 16.5, 2.8, C(2)H_A), 2.54 (1H, dd, *J* 16.5, 9.0, C(2)H_B), 2.95−3.01 (1H, m, C(4)*H*), 3.39 (1H, d, *J* 15.6, NCH_AH$_B$Ph), 3.56 (2H, d, *J* 13.9, N(CH_AH$_B$Ph)$_2$), 3.62−3.71 (2H, m, C(3)*H*, C(α)*H*), 3.82−3.95 (4H, m, N(CH$_A$$H_B$Ph)$_2$, NCH$_A$$H_B$Ph, C(5)$H_A$), 4.16 (1H, dd, *J* 10.4, 5.7, C(5)H_B), 6.89−6.94 (2H, m, *Ph*), 7.07−7.12 (3H, m, *Ph*), 7.18−7.30 (15H, m, *Ph*).

(4*S*,5*R*,α*R*)-4-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-5-(*N*,*N*-dibenzylamino)-tetrahydro-2*H*-pyran-2-one 156



TBAF (1.0 M in THF, 3.24 mL, 3.24 mmol) was added to a stirred solution of **155** (1.59 g, 2.16 mmol, >95:5 dr) in THF (40 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 24 h. Water (15 mL) and brine (15 mL) were added and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (50 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (30−40 °C petroleum ether/EtOAc, 5:1) gave **156** as a pale yellow viscous oil (1.07 g, 98%, >95:5 dr);[2] $[\alpha]_D^{22}$ +59.8 (*c* 1.0 in $CHCl_3$) {lit.[4] $[\alpha]_D^{22}$ +64.5 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, *J* 7.0, C(α)*H*), 2.14 (1H, dd, *J* 15.3, 6.3, C(3)H_A), 2.23 (1H, dd, *J* 15.3, 9.0, C(3)H_B), 3.27 (1H, q, *J* 4.7, C(5)*H*), 3.47 (2H, d, *J* 13.7, N(CH_AH$_B$Ph)$_2$), 3.56 (1H, d, *J* 14.5, NCH_AH$_B$Ph), 3.59−3.67 (2H, m, C(4)*H*, NCH$_A$$H_B$Ph), 3.78−3.89 (3H, m, C(α)*H*, N(CH$_A$$H_B$Ph)$_2$), 4.15 (1H, dd, *J* 12.4, 4.7, C(6)H_A), 4.45 (1H, dd, *J* 12.4, 4.7, C(6)H_B), 6.99−7.07 (2H, m, *Ph*), 7.19−7.41 (18H, m, *Ph*).

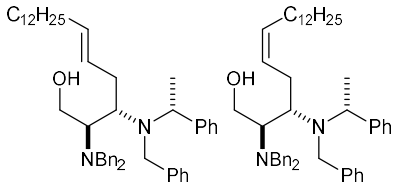
(2*R*,4*S*,5*R*,α*R*)- and (2*S*,4*S*,5*R*,α*R*)-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-(*N*,*N*-dibenzylamino)tetrahydro-2*H*-pyran-2-ol 176 and 177



DIBAL-H (1 M in CH_2Cl_2, 0.59 mL, 0.59 mmol) was added to a stirred solution of **156** (200 mg, 0.396 mmol, >95:5 dr) in CH_2Cl_2 (10 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. MeOH (2 mL) was added and the resultant mixture was allowed

to warm to rt then satd aq Rochelle salt (4 mL) was added and the resultant mixture was stirred at rt for 18 h. The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layers were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 50:1) gave a 53:47 mixture of **176** and **177**, respectively, as a colourless viscous oil (198 mg, 99%, 53:47 dr).[2] Selected data for **176**: δ_H (400 MHz, $CDCl_3$) 0.88–0.97 (1H, m, C(3)H_A), 1.46–1.60 (3H, m, C(α)*Me*), 1.67–1.73 (1H, m, C(3)H_B), 2.96–3.06 (2H, m, C(4)*H*, C(5)*H*), 3.39–3.61 (3H, m, N(CH_AH$_B$Ph)$_2$, NCH_AH$_B$Ph), 3.75–3.90 (4H, m, C(6)H_2, N(CH$_A$$H_B$Ph)$_2$), 3.90–4.02 (1H, m, C(α)*H*), 4.09–4.18 (1H, m, NCH$_A$$H_B$Ph), 4.34–4.40 (1H, m, C(2)*H*). Selected data for **177**: δ_H (400 MHz, $CDCl_3$) 0.70–0.78 (1H, m, C(3)H_A), 1.46–1.60 (4H, m, C(3)H_B, C(α)*Me*), 2.96–3.06 (1H, m, C(5)*H*), 3.29 (1H, dd, *J* 11.2, 8.4, C(6)H_A), 3.39–3.61 (4H, m, C(4)*H*, N(CH_AH$_B$Ph)$_2$, NCH_AH$_B$Ph), 3.75–3.90 (2H, m, N(CH$_A$$H_B$Ph)$_2$), 3.90–4.02 (1H, m, C(α)*H*), 4.09–4.18 (2H, m, C(6)H_A, NCH$_A$$H_B$Ph), 4.98–5.02 (1H, m, C(2)*H*).

(2*R*,3*S*,α*R*,*E*)-2-(*N*,*N*-dibenzylamino)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-octadec-5-en-1-ol (*E*)-157 and (2*R*,3*S*,α*R*,*Z*)-2-(*N*,*N*-dibenzylamino)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-octadec-5-en-1-ol (*Z*)-158



(*E*)-**157** (*Z*)-**158**

Method A: Step 1: DIBAL-H (1 M in CH_2Cl_2, 0.30 mL, 0.30 mmol) was added to a stirred solution of **156** (100 mg, 0.198 mmol, >95:5 dr) in CH_2Cl_2 (5 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. MeOH (1 mL) was added and the resultant mixture was allowed to warm to rt then satd aq Rochelle salt (2 mL) was added and the resultant mixture was stirred at rt for 18 h. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL)

and the combined organic layers were dried and concentrated *in vacuo* to give a mixture of **176** and **177**.

Step 2: DIBAL-H (1 M in THF, 0.24 mL, 0.240 mmol) was added to the residue from the previous step in THF (10 mL) at 0 °C and the resultant mixture was stirred at rt for 1 h. Meanwhile, BuLi (2.2 M in hexanes, 0.32 mL, 0.69 mmol) was added to a solution of **175** in THF (10 mL) at 0 °C and the resultant mixture was allowed to stir at rt for 45 min. The lactol solution was then cooled to 0 °C and the ylide solution was added and the resultant mixture was stirred at 67 °C for 1 h then allowed to cool to rt. H_2O (3 mL) and brine (3 mL) were added and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with satd aq $NaHCO_3$ (10 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 8:1) gave a 52:48 mixture of **176** and **177**, respectively, as a colourless viscous oil (67 mg, 67%, 52:48 dr).

Method B: DIBAL-H (1 M in THF, 0.59 mL, 0.59 mmol) was added to a stirred solution of 53:47 mixture of **176** and **177**, respectively, (198 mg, 0.391 mmol, 53:47 dr) in PhMe (2 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. Meanwhile, BuLi (2.2 M in hexanes, 0.26 mL, 0.57 mmol) was added to a solution of **175** in THF (2 mL) at 0 °C and the resultant mixture was allowed to stir at rt for 45 min. The lactol solution was then cooled to 0 °C and the ylide solution was added and the resultant mixture was stirred at 80 °C for 1 h then allowed to cool to rt. H_2O (3 mL) and brine (3 mL) were added and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with satd aq $NaHCO_3$ (10 mL) then dried and concentrated *in vacuo* to give a complex mixture.

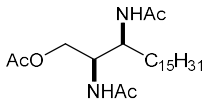
Method C: DIBAL-H (1 M in PhMe, 0.30 mL, 0.30 mmol) was added to a stirred solution of **156** (100 mg, 0.198 mmol, >95:5 dr) in PhMe (2 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h to give a mixture of lactols **176** and **177**. BuLi (2.2 M in hexanes, 0.14 mL, 0.30 mmol) was added to a solution of **175** (161 mg, 0.307 mmol) in THF (2 mL) at

0 °C and the resultant mixture was allowed to warm to rt and stirred at rt for 45 min then cooled to 0 °C. The freshly prepared solution of lactols in PhMe was added at 0 °C and the resultant mixture was heated at 80 °C for 1 h then was allowed to cool to rt before H_2O (5 mL) and brine (5 mL) were added. The aqueous layer was extracted with EtOAc (3 × 10 mL) then the combined organic extracts were washed with satd aq $NaHCO_3$ (30 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 12:1) gave a ~57:43 mixture of (*E*)-**157** and (*Z*)-**158**, respectively, as a colourless viscous oil (20 mg, 15%, ~57:43 dr {[*E*]:[*Z*]});[2] δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.8, C(18)H_3), 1.18–1.36 (20H, m, C(8)H_2–C(17)H_2), 1.40–1.48 (3H, m, C(α)*Me*), 1.83–2.43 (4H, m, C(4)H_2, C(7)H_2), 3.08 (1H, br s, O*H*). 3.14–3.27 (2H, m, C(2)*H*, C(3)*H*), 3.43–3.72 (7H, m, C(1)H_2, NCH_AH$_B$Ph, N(CH_2Ph)$_2$), 3.96–4.10 (2H, m, NCH$_A$$H_B$Ph, C(α)*Me*), 4.99–5.16 (1H, m, C(5)*H*), 5.18–5.32 (1H, m, C(6)*H*), 7.13–7.39 (20H, m, *Ph*).

Method D: DIBAL-H (1 M in PhMe, 0.59 mL, 0.59 mmol) was added to a stirred solution of **156** (200 g, 0.396 mmol, >95:5 dr) in PhMe (2 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h to give a mixture of lactols **176** and **177**. BuLi (2.2 M in hexanes, 0.26 mL, 0.57 mmol) was added to a solution of **175** (314 mg, 0.598 mmol) in THF (1 mL) at 0 °C and the resultant mixture was allowed to warm to rt and stirred at rt for 45 min then cooled to 0 °C. The freshly prepared solution of a mixture of lactols in PhMe was added at 0 °C and the resultant mixture was heated at 80 °C for 1 h then was allowed to cool to rt before H_2O (1 mL) and brine (1 mL) were added. The aqueous layer was extracted with EtOAc (3 × 5 mL) then the combined organic extracts were washed with satd aq $NaHCO_3$ (10 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 15:1) gave a ~65:35 mixture of (*E*)-**157** and (*Z*)-**158**, respectively, as a colourless viscous oil (81 mg, 31%, ~65:35 dr {[*E*]:[*Z*]}). Further elution gave an impure sample (37 mg, ~14%, 27:73 dr).

Method E: DIBAL-H (1 M in PhMe, 2.82 mL, 2.82 mmol) was added to a stirred solution of **156** (1.36 g, 2.69 mmol, >95:5 dr) in PhMe (13 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h to give a mixture of lactols. BuLi (2.2 M in hexanes, 1.78 mL, 3.91 mmol) was added to a solution of **175** (2.12 g, 4.03 mmol) in THF (6.5 mL) at 0 °C and the resultant mixture was allowed to warm to rt and stirred at rt for 45 min then cooled to 0 °C. The freshly prepared solution of a mixture of lactols in PhMe was added at 0 °C and the resultant mixture was heated at 80 °C for 1 h then was allowed to cool to rt before H_2O (5 mL) and brine (5 mL) were added. The aqueous layer was extracted with EtOAc (3 × 10 mL) then the combined organic extracts were washed with satd aq $NaHCO_3$ (30 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 12:1) gave a 50:50 mixture of (*E*)-**157** and (*Z*)-**158**, respectively, as a colourless viscous oil (1.32 g, 73%, 50:50 dr {[*E*]:[*Z*]}).

(2*R*,3*S*)-2,3-*N*,*N*-Diacetamidooctadecyl acetate 159

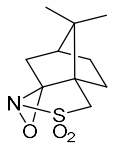


Step 1: $Pd(OH)_2/C$ (50% w/w of substrate, 100 mg) was added to a vigorously stirred suspension of (*E*)-**157** and (*Z*)-**158** (200 mg, 0.297 mmol, 50:50 dr) in degassed HCl (1.25 M in MeOH, 3 mL) at rt. The reaction mixture was stirred under hydrogen (5 atm) at rt for 72 h. The resultant mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo*.

Step 2: Ac_2O (0.22 mL, 2.37 mmol) and DMAP (2 mg) were added sequentially to a stirred solution of the residue in pyridine (0.83 mL, 10 mmol). The resultant solution was stirred at rt for 72 h then CH_2Cl_2 (5 mL) was added and the resultant solution was washed with satd aq $CuSO_4$ (5 mL) and the aqueous layer was extracted with EtOAc (3 × 5 mL). The combined organic layers were washed with satd aq $NaHCO_3$ (3 × 10 mL) and the aqueous layers extracted with EtOAc (3 × 10 mL). The combined organic layers were dried and concentrated *in vacuo*. Purification *via* recrystallisation (CH_2Cl_2/30–40 °C petroleum ether) gave **159** as a

pale orange solid (101 mg, 79%, >95:5 dr);[2] mp 115–116 °C {lit.[2] 99–100 °C}; $[\alpha]_D^{22}$ –16.0 (*c* 1.0 in $CHCl_3$) {lit.[2] $[\alpha]_D^{22}$ –17.7 (*c* 1.0 in $CHCl_3$)}; δ_H (500 MHz, $CDCl_3$) 0.88 (3H, t, *J* 7.0, C(18)H_3), 1.20−1.33 (26H, m, C(5)H_2–C(17)H_2), 1.36−1.45 (1H, m, C(4)H_A), 1.56−1.64 (1H, m, C(4)H_B), 1.97 (3H, s, NCO*Me*), 1.98 (3H, s, NCO*Me*), 2.10 (3H, s, OCO*Me*), 3.97 (1H, ddd, *J* 18.0, 9.0, 3.6, C(3)*H*), 4.05−4.11 (1H, m, C(2)*H*), 4.14 (1H, dd, *J* 11.7, 3.6, C(1)H_A), 4.20 (1H, dd, *J* 11.7, 5.0, C(1)H_B), 5.91 (1H, d, *J* 9.1, N*H*Ac), 6.46 (1H, d, *J* 8.5, N*H*Ac); δ_C (125 MHz, $CDCl_3$) 14.1 (*C*(18)), 20.8 (CO*Me*), 22.7 (*C*(17)), 23.3, 23.3 (CO*Me*), 25.6, 29.3, 29.4, 29.4, 29.5, 29.5, 29.6, 29.6, 29.7, 31.9 (*C*(5)−*C*(16)), 31.5 (*C*(4)), 50.5 (*C*(3)), 52.7 (*C*(2)), 63.7 (*C*(1)), 170.8, 171.0, 171.0 (*C*OMe); *m/z* (ESI^+) 876 ($[2M+Na]^+$, 100%); HRMS (ESI^+) $C_{24}H_{47}N_2O_4^+$ ($[M+H]^+$) requires 427.3530; found 427.3528.

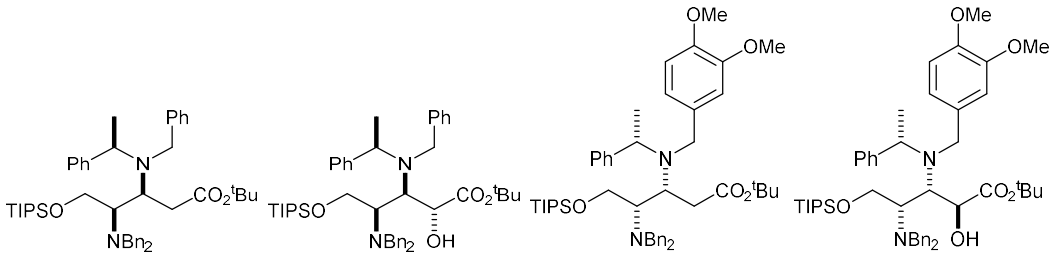
(–)-Camphorsulphonyloxaziridine [(−)-CSO] 182



Step 1: $SOCl_2$ (252 mL, 3.44 mol) was added dropwise to a stirred solution of (*R*)-10-camphorsulphonic acid (200 g, 0.861 mol) in $CHCl_3$ (1.0 L) and the resultant mixture was heated at reflux for 12 h. The reaction mixture was then concentrated *in vacuo*, the residue was dissolved in $CHCl_3$ (1.0 L) and the resultant solution was added dropwise to a stirred solution of 35% aq NH_3 (2.0 L) at 0 °C. The resultant mixture was stirred at 0 °C for 4 h then the aqueous layer was extracted with CH_2Cl_2 (2 × 800 mL) and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in PhMe (1.2 L) and Amberlyst 15 (wet) ion-exchange resin (12.0 g) was added to the resultant solution. A Dean-Stark apparatus was fitted to the reaction vessel and the reaction mixture was heated at reflux for 12 h. The reaction mixture was then allowed to cool to rt and filtered through Celite® (eluent $CHCl_3$). The filtrate was then concentrated *in vacuo*.

Step 2: The residue was dissolved in CH_2Cl_2 (1.5 L), the resultant solution was cooled to 0 °C and Aliquat 336 was added. 2 M aq K_2CO_3 (750 mL, 1.38 mol) was then added *via* a dropping funnel at such a rate as to maintain the reaction temperature below 5 °C. A solution of peracetic acid (32% in AcOH, 315 mL) was then added dropwise, whilst maintaining the reaction temperature below 5 °C, and the resultant mixture was allowed to warm to rt over 8 h. Na_2SO_3 (74.4 g, 0.590 mol) and 1.0 M aq NaOH (800 mL, 0.800 mol) were added and the resultant mixture was tested with starch-iodine paper, with further portions of Na_2SO_3 added as required, until no remaining oxidant was present. The aqueous layer was extracted with CH_2Cl_2 (3 × 500 mL) and the combined organic extracts were washed sequentially with H_2O (200 mL) and satd aq $NaHCO_3$ (400 mL), then dried and concentrated *in vacuo*. Purification *via* recrystallisation (CH_2Cl_2/30–40 °C petroleum ether) gave **182** as a white solid (79.2 g, 43%);[6] mp 168–171 °C {lit.[7] 163–165 °C}; $[\alpha]_D^{22}$ –41.6 (*c* 2.1 in $CHCl_3$) {lit.[8] $[\alpha]_D^{22}$ −43.6 (*c* 2.16 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.06 (3H, s, *Me*$_A$), 1.20 (3H, s, *Me*$_B$), 1.50–1.62 (1H, m, C*H*), 1.81 (1H, d, *J* 15.6, CH_ACN), 1.92–2.12 (4H, m, 2 × CH_2), 2.66 (1H, ddd, *J* 15.5, 4.5, 2.6, CH_BCN), 3.13 (1H, d, *J* 14.0, C$H_AH_BSO_2$), 3.31 (1H, d, *J* 14.0, $CH_AH_BSO_2$).

***tert*-Butyl (3*S*,4*R*,*αR*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-5-(triisopropylsilyloxy)pentanoate 155, *tert*-Butyl (*R*,*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-5-(triisopropylsilyloxy)pentanoate 178, *tert*-Butyl (3*R*,4S,*αS*)-3-[*N*-(3',4'-dimethoxybenzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-5-(triisopropylsilyloxy)pentanoate 372, *tert*-Butyl (*S*,*S*,*S*,*S*)-2-hydroxy-3-[*N*-(3',4'-dimethoxybenzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-5-(triisopropylsilyloxy)pentanoate 373**



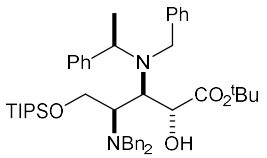
155 178 372 373

Parallel Kinetic Resolution: BuLi (2.2 M in hexanes, 0.69 mL, 1.5 mmol) was added dropwise to a stirred solution of (*R*)-**162** (161 mg, 0.764 mmol, 98% ee) and (*S*)-*N*-(3',4'-dimethoxybenzyl)-*N*-(α-methylbenzyl)amine (207 mg, 0.764 mmol, 98% ee) in THF (3 mL) at −78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of (*RS*)-**154** (200 mg, 0.382 mmol, >95:5 dr) in THF (1.5 mL) was then added *via* cannula and the reaction mixture was stirred at −78 °C for 2 h. (–)-CSO (–)-**182** (175 mg, 0.764 mmol) and (+)-CSO (+)-**182** (175 mg, 0.764 mmol) were added and the resultant mixture was allowed to warm to rt over 18 h. Satd aq NH_4Cl (1 mL) was added and the reaction mixture was stirred at rt for 5 min, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (30 mL) and brine (30 mL), then dried and concentrated *in vacuo.* The residue was dissolved in Et_2O (20 mL), filtered and the filtrate was concentrated *in vacuo* to give a complex mixture. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 25:1

to 10:1) gave **155** as a colourless viscous oil (42 mg, 15%, >95:5 dr). Further elution gave **178** as a colourless viscous oil (36 mg, 12%, >95:5 dr);[2] $[\alpha]_D^{22}$ –10.0 (*c* 1.0 in $CHCl_3$); {lit.[2] $[\alpha]_D^{22}$ –13.1 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.10−1.18 (21H, m, Si(C*H*Me$_2$)$_3$), 1.38 (3H, d, *J* 7.0, C(α)*Me*), 1.40 (9H, s, C*Me*$_3$), 3.36–3.42 (1H, m, C(4)*H*), 3.69–3.74 (1H, m, C(3)*H*), 3.75 (1H, d, *J* 14.0, N(CH_AH$_B$Ph)$_2$), 3.80 (1H, d, *J* 7.6, C(2)*H*), 3.87 (1H, d, *J* 16.5, NCH_ACH$_B$Ph), 3.95 (1H, q, *J* 7.0, C(α)*H*), 4.00 (2H, d, *J* 14.0, N(CH$_A$$H_B$Ph)$_2$), 4.06 (1H, dd, *J* 10.4, 7.1, C(5)H_A), 4.21 (1H, dd, *J* 10.4, 6.5, C(5)H_B), 4.48 (1H, d, *J* 16.5, NCH$_A$$H_B$Ph), 6.41 (1H, d, *J* 8.4, O*H*), 7.09–7.31 (20H, m, *Ph*). Further elution gave **372** as a colourless viscous oil (43 mg, 14%, >95:5 dr); $[\alpha]_D^{22}$ +5.8 (*c* 1.0 in $CHCl_3$) {lit.[2] $[\alpha]_D^{22}$ +3.0 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.06–1.16 (21H, m, Si(C*H*Me$_2$)$_3$), 1.31 (9H, s, C*Me*$_3$), 1.38 (3H, d, *J* 7.0, C(α)*Me*), 1.71 (1H, dd, *J* 16.6, 3.4, C(2)H_A), 2.46 (1H, dd, *J* 16.6, 8.0, C(2)H_B), 2.97–3.03 (1H, m, C(4)*H*), 3.41 (1H, d, *J* 15.8, NCH_AH$_B$Ph), 3.60–3.73 (7H, m, C(3)*H*, C(α)*H*, N(CH_AH$_B$Ph)$_2$, O*Me*), 3.78–3.95 (7H, m, C(5)H_A, NCH$_A$$H_B$Ph, N(CH$_A$$H_B$Ph)$_2$, O*Me*), 4.21 (1H, dd, *J* 10.5, 6.6, C(1)H_B), 6.54–6.59 (2H, m, *Ar*), 6.64 (1H, d, *J* 8.1, *Ar*), 7.14–7.20 (4H, m, *Ar*), 7.21–7.26 (8H, m , *Ar*), 7.28–7.33 (5H, m, *Ar*). Further elution gave **373** as a colourless viscous oil (13 mg, 4%, >95:5 dr); $[\alpha]_D^{22}$ +24.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3514 (O–H), 1722 (C=O); δ_H (500 MHz, $CDCl_3$) 1.15–1.22 (21H, m, Si(C*H*Me$_2$)$_3$), 1.30 (3H, d, *J* 6.7, C(α)*Me*), 1.51 (9H, s, C*Me*$_3$), 2.96 (1H, d, *J* 15.3, NCH_AH$_B$Ar), 3.21 (1H, br s, O*H*), 3.59–3.64 (1H, m, C(4)*H*), 3.76 (3H, s, C(4')O*Me*), 3.79 (3H, s, C(3')O*Me*), 3.89–3.91 (3H, m, NCH$_A$$H_B$Ar, N(C$H_AH_B$Ph)$_2$), 3.99 (1H, dd, *J* 6.4, 3.3, C(3)*H*), 4.05 (1H, q, *J* 6.7, C(α)*Me*), 4.11 (2H, d, *J* 14.0, N(CH$_A$$H_B$Ph)$_2$), 4.20 (1H, dd, *J* 11.4, 6.2, C(5)H_A), 4.38 (1H, dd, *J* 11.4, 3.1, C(5)H_B), 4.40–4.42 (1H, m, C(2)*H*), 6.11 (1H, dd, *J* 8.3, 1.7, C(6')*H*), 6.42–6.48 (2H, m, C(2')*H*, C(5')*H*), 6.92–6.98 (5H, m, *Ph*), 7.27–7.31 (2H, m, *Ph*), 7.37 (4H, t, *J* 7.6, *Ph*), 7.48 (4H, d, *J* 7.4, *Ph*); δ_C (125 MHz, $CDCl_3$) 12.2 (Si(*C*HMe$_2$)$_3$), 18.3 (Si(CH*Me*$_2$)$_3$), 22.0 (C(α)*Me*), 28.1 (C*Me*$_3$), 53.9 (N*C*H$_2$Ar), 55.6 (N(*C*H$_2$Ph)$_2$), 55.7 (C(3')O*Me*), 55.9 (C(4')O*Me*), 59.0 (*C*(2)), 59.4 (*C*(4)), 61.5 (*C*(5)), 62.7 (*C*(α)), 74.1 (*C*(2)),

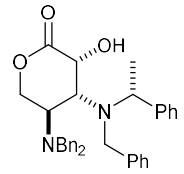
82.3 (*C*Me$_3$), 110.3 (*C*(5')), 111.4 (*C*(2')), 119.6 (*C*(6')), 126.4, 127.0, 127.3, 128.3, 128.4, 129.7 (*o*,*m*,*p*-*Ph*), 135.3 (*C*(1')), 140.0, 145.1 (*i*-*Ph*), 146.6 (*C*(4')), 148.1 (*C*(3')), 174.1 (*C*(1)); *m/z* (ESI$^+$) 814 ([M+2+H]$^+$, 22%), 813 ([M+H]$^+$, 69%), 812 ([M+H]$^+$, 100%), 755 ([M–C$_4$H$_8$]$^+$, 17%); HRMS (ESI$^+$) $C_{49}H_{71}O_6N_2Si^+$ ([M+H]$^+$) requires 811.5076; found 811.5067.

***tert*-Butyl (*R*,*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-5-(triisopropylsilyloxy)pentanoate 178**



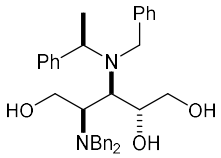
BuLi (2.2 M in hexanes, 6.77 mL, 14.9 mmol) was added dropwise to a stirred solution of (*R*)-**162** (3.23 g, 15.3 mmol, 98% ee) in THF (6.24 mL) at −78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of (*R*)-**154** (4.00 g, 7.64 mmol, >95:5 dr) in THF (6.24 mL) was then added *via* cannula and the reaction mixture was stirred at −78 °C for 2 h. (–)-CSO **182** (3.43 g, 15.0 mmol) was added and the resultant mixture was allowed to warm to rt over 18 h. Satd aq NH_4Cl (5 mL) was added and the reaction mixture was stirred at rt for 5 min, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (75 mL) and 10% aq citric acid (75 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (100 mL) and brine (100 mL), then dried and concentrated *in vacuo* to give a 75:25 mixture of **178**:**155**. The residue was dissolved in Et_2O (150 mL), filtered and the filtrate was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30−40 °C petroleum ether/acetone, 25:1) gave **155** as a pale yellow viscous oil (915 mg, 16%, >95:5 dr). Further elution gave **178** as a pale yellow viscous oil (4.17 g, 73%, >99:5 dr).

(3*R*,4*S*,5*R*,α*R*)-3-Hydroxy-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-(*N*,*N*-dibenzylamino)-tetrahydro-2*H*-pyran-2-one 179



TBAF (1.0 M in THF, 1.94 mL, 1.94 mmol) was added to a stirred solution of **178** (730 mg, 0.972 mmol, >95:5 dr) in THF (14 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 24 h. Water (5 mL) and brine (5 mL) were added and the aqueous layer was extracted with Et_2O (3 × 15 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (30 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30−40 °C petroleum ether/EtOAc, 4:1) gave **179** as a pale yellow viscous oil (238 mg, 47%, >95:5 dr);[2] $[\alpha]_D^{22}$ +13.2 (*c* 1.0 in $CHCl_3$) {lit.[2] –12.5 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.23 (3H, d, *J* 6.9, C(α)*Me*), 3.24–3.40 (5H, m, C(4)*H*, C(5)*H*, N(CH_AH$_B$Ph)$_2$, O*H*), 3.65–3.77 (4H, m, N(CH$_A$$H_B$Ph)$_2$, NC$H_2$Ph), 3.93 (1H, dd, *J* 13.1, 3.4, C(6)H_A), 4.23 (1H, q, *J* 6.9, C(α)*H*), 4.34 (1H, d, *J* 10.7, C(3)*H*), 4.67 (1H, d, *J* 13.1, C(6)H_B), 6.98–7.08 (2H, m, *Ph*), 7.15–7.43 (18H, m, *Ph*).

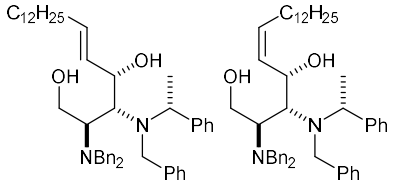
(*R*,*R*,*R*,*R*)-2-(*N*,*N*-Dibenzylamino)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]pentan-1,4,5-triol 183



$LiAlH_4$ (1 M in THF, 2.00 mL, 2.00 mmol) was added to a stirred solution of **178** (500 mg, 0.666 mmol, >95:5 dr) in THF (5 mL) at –78 °C and was stirred at rt for 18 h then cooled to 0 °C and 2.0 M aq NaOH (5 mL) was added and the resultant mixture was stirred at rt for 2 h before being filtered through Celite® (eluent EtOAc) and concentrated *in vacuo*. Purification

via flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 20:1) to give **183** as a pale yellow solid (309 mg, 88%, >95:5 dr); mp 80–83 °C; $[\alpha]_D^{22}$ +29.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3390 (O–H); δ_H (500 MHz, $CDCl_3$) 1.43 (3H, d, *J* 7.1. C(α)*Me*), 2.44 (1H, app t, *J* 9.4, C(5)H_A), 2.78 (1H, app d, *J* 7.6, C(5)H_B), 3.09–3.17 (2H, m, C(3)*H*, C(4)*H*), 3.22-3.27 (1H, m, C(2)*H*), 3.60 (2H, d, *J* 13.7, N(CH_AH$_B$Ph)$_2$), 3.82 (1H, br s, O*H*), 3.91 (1H, q, *J* 7.1, C(α)*H*), 4.03 (1H, d, *J* 16.1, NCH_AH$_B$Ph), 4.09–4.17 (3H, m, C(1)H_A, N(CH$_A$$H_B$Ph)$_2$), 4.32 (1H, dd, *J* 11.2, 5.0 (C(1)H_B), 4.62 (1H, d, *J* 16.1, NCH$_A$$H_B$Ph), 7.16–7.39 (20H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 19.5 (C(α)*Me*), 53.4 (N*C*H$_2$Ph), 56.0 (*C*(3)), 56.2 (N(*C*H$_2$Ph)$_2$), 58.2 (*C*(α)), 59.6 (*C*(1)), 60.5 (*C*(2)), 65.0 (*C*(5)), 72.8 (*C*(4)), 126.7, 127.4, 127.5, 127.8, 128.2, 128.3, 128.4, 128.5, 129.3 (*o*,*m*,*p*-*Ph*), 137.8, 139.8, 140.7 (*i*-*Ph*); *m/z* (ESI$^+$) 525 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{41}N_2O_3^+$ ([M+H]$^+$) requires 525.3112; found 525.3107.

(2*R*,3*R*,4*S*,*E*)-2-(*N*,*N*-dibenzylamino)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]octadec-5-en-1,4-diol (*E*)-180 and (2*R*,3*R*,4*S*,*Z*)-2-(*N*,*N*-dibenzylamino)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]octadec-5-en-1,4-diol (*Z*)-181



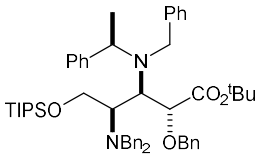
(*E*)-180 (*Z*)-181

Method A: DIBAL-H (1 M in PhMe, 0.24 mL, 0.24 mmol) was added to a stirred solution of **179** (119 mg, 0.229 mmol, >95:5 dr) in PhMe (1.1 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. BuLi (2.2 M in hexanes, 0.15 mL, 0.33 mmol) was added to a solution of **175** (180 mg, 0.343 mmol) in THF (0.55 mL) at 0 °C and the resultant mixture was allowed to warm to rt and stirred at rt for 45 min then cooled to 0 °C. The freshly prepared solution of lactols in PhMe was added at 0 °C and the resultant mixture was heated at 80 °C for 1 h then was allowed to cool to rt before H_2O (1 mL) and brine (1 mL) were added. The aqueous layer was extracted with EtOAc (3 × 2 mL) then the combined organic extracts were

washed with satd aq $NaHCO_3$ (4 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 10:1) to give **179** as a pale yellow viscous oil (33 mg, 28%, >95:5 dr).

Method B: DIBAL-H (1 M in PhMe, 0.67 mL, 0.67 mmol) was added to a stirred solution of **179** (100 mg, 0.192 mmol, >95:5 dr) in PhMe (0.44 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h to give a mixture of lactols. BuLi (2.2 M in hexanes, 0.17 mL, 0.37 mmol) was added to a solution of **175** (202 mg, 0.384 mmol) in THF (0.46 mL) at 0 °C and the resultant mixture was allowed to warm to rt and stirred at rt for 45 min then cooled to 0 °C. The freshly prepared solution of lactols in PhMe was added at 0 °C and the resultant mixture was heated at 80 °C for 1 h then was allowed to cool to rt before H_2O (1 mL) and brine (1 mL) were added. The aqueous layer was extracted with EtOAc (3 × 2 mL) then the combined organic extracts were washed with satd aq $NaHCO_3$ (4 mL) then dried and concentrated *in vacuo* to give a complex mixture.

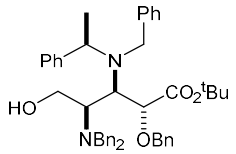
tert-Butyl (*R*,*R*,*R*,*R*)-2-benzyloxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-5-(triisopropylsilyloxy)pentanoate 186



NaH (60% dispersion in mineral oil, 83 mg, 2.1 mmol) was added to a stirred solution of **178** (910 mg, 1.21 mmol, >95:5 dr) in THF (10 mL) at 0 °C and was stirred at 0 °C for 30 min. BnBr (0.29 mL, 2.42 mmol) was added and the resultant mixture was allowed to warm to rt over 24 h then satd aq NH_4Cl (2 mL) was added. The organic layer was washed sequentially with brine (15 mL) and H_2O (15 mL) the combined aqueous layers were extracted with Et_2O (3 × 25 mL) then the combined organic layers were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30−40 °C petroleum ether/EtOAc, 1:0 to 20:1) gave **186** as a pale yellow viscous oil (863 mg, 85%, >95:5 dr); $[\alpha]_D^{22}$ +20.4 (*c* 1.0 in

$CHCl_3$); ν_{max} (ATR) 1735 (C=O); δ_H (400 MHz, $CDCl_3$) 0.97−1.12 (21H, m, Si(C*HMe*$_2$)$_3$), 1.37 (3H, d, *J* 6.7, C(α)*Me*), 1.52 (9H, s, C*Me*$_3$), 3.53−3.63 (2H, m, C(4)*H*, C(α)*H*), 3.67 (1H, d, *J* 15.3, NC*H*$_A$H$_B$Ph), 3.73−3.80 (2H, m, C(2)*H*, NCH$_A$*H*$_B$Ph), 3.81−3.89 (3H, m, C(3)*H*, N(C*H*$_A$H$_B$Ph)$_2$), 3.93−4.02 (3H, m, OC*H*$_A$H$_B$Ph, N(CH$_A$*H*$_B$Ph)$_2$), 4.02−4.12 (2H, m, C(5)*H*$_2$), 4.52 (1H, d, *J* 10.6, OCH$_A$*H*$_B$Ph), 6.98−7.13 (10H, m, *Ph*), 7.19−7.32 (11H, m, *Ph*), 7.36−7.42 (4H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.9 (Si(*C*HMe$_2$)$_3$), 18.2 (Si(CH*Me*$_2$)$_3$), 21.5 (C(α)*Me*), 28.1 (C*Me*$_3$), 53.0 (N*C*H$_2$Ph), 55.0 (N(*C*H$_2$Ph)$_2$), 59.1 (*C*(α)), 61.2 (*C*(4)), 61.8 (*C*(3)), 62.5 (*C*(5)), 72.1 (O*C*H$_2$Ph), 80.6 (*C*(2)), 81.6 (*C*Me$_3$), 125.8, 126.4, 126.6, 127.4, 127.6, 127.8, 127.8, 128.1, 128.3, 128.4, 129.7, 129.7 (*Ph*), 137.7 (*C*(1')), 141.0 (*C*(1'''')), 141.5 (*C*(1''')), 143.9 (*C*(1'')), 171.3 (*C*(1)); *m/z* (ESI$^+$) 841 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{54}H_{73}O_4N_2Si^+$ ([M+H]$^+$) requires 841.5345; found 841.5336.

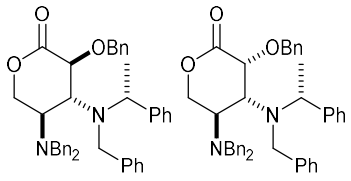
***tert*-Butyl (*R*,*R*,*R*,*R*)-2-benzyloxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-5-hydroxypentanoate 189**



HF (70% in pyridine, 0.46 mL, 18 mmol) was added to a stirred solution of **186** (500 mg, 0.594 mmol, >95:5 dr) in THF (10 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 18 h. Satd aq $NaHCO_3$ (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 15 mL) then the combined organic layers were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 8:1) gave **189** as a colourless viscous oil (313 mg, 77%, >95:5 dr); ν_{max} (ATR) 3527 (O–H), 1734 (C=O); $[\alpha]_D^{22}$ +2.6 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.50 (9H, s, C*Me*$_3$), 1.62 (3H, d, *J* 7.1, C(α)*Me*), 3.24 (1H, br s, O*H*), 3.39–3.47 (2H, m, C(4)*H*, C(5)*H*$_A$), 3.58–3.65 (2H, m, C(2)*H*, NC*H*$_A$H$_B$Ph), 3.66–3.76 (4H, m, C(5)H$_B$, N(C*H*$_A$H$_B$Ph)$_2$, OC*H*$_A$H$_B$Ph), 3.84 (2H, d, *J* 13.4, N(CH$_A$*H*$_B$Ph)$_2$), 4.02 (1H, d, *J* 7.2, C(3)*H*), 4.10 (1H, q, *J* 7.1, C(α)*H*), 4.40 (1H, d,

J 15.7, NCH_AH_BPh), 4.53 (1H, d, *J* 11.0, OCH_AH_BPh), 7.13–7.40 (25H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.5 (C(α)*Me*), 28.1 (CMe_3), 51.9 (NCH_2Ph), 54.4 ($N(CH_2Ph)_2$), 57.7 (*C*(α)), 58.9 (*C*(5)), 59.3 (*C*(3)), 60.9 (*C*(4)), 72.4 (OCH_2Ph), 79.1 (*C*(2)), 82.3 (CMe_3), 126.6, 126.9, 127.1, 127.5, 127.5, 128.1, 128.2, 128.2, 128.3, 128.3, 128.5, 129.2 (*o*,*m*,*p*-*Ph*), 137.7 (*C*(1')), 140.1 (*C*(1'''')), 140.5 (*C*(1''')), 142.5 (*C*(1'')), 171.6 (*C*(1)); *m/z* (ESI^+) 685 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{45}H_{53}N_2O_4^+$ ($[M+H]^+$) requires 685.4000; found 685.3994.

(3*S*,4*S*,5*R*,α*R*)-3-Benzyloxy-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-(*N*,*N*-dibenzylamino)-tetrahydro-2*H*-pyran-2-one 187 and (3*R*,4*S*,5*R*,α*R*)-3-benzyloxy-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-(*N*,*N*-dibenzylamino)-tetrahydro-2*H*-pyran-2-one 188



187 188

Method A: TBAF (1.0 M in THF, 0.24 mL, 0.24 mmol) was added to a stirred solution of **186** (100 mg, 0.119 mmol, >95:5 dr) in THF (2 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 24 h. Water (2 mL) and brine (2 mL) were added and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (15 mL) then dried and concentrated *in vacuo* to give a 61:39 mixture of **187** and **188**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 5:1) gave a 61:39 mixture of **187** and **188**, respectively, as a colourless viscous oil (38 mg, 52%, 61:39 dr); data for mixture: ν_{max} (ATR) 1753 (C=O); *m/z* (ESI^+) 611 ($[M+H]^+$, 100%), HRMS (ESI^+) $C_{41}H_{43}O_3N_2^+$ ($[M+H]^+$) requires 611.3268; found 611.3267. Selected data for **187**: δ_H (400 MHz, $CDCl_3$) 1.31 (3H, d, *J* 7.0, C(α)*Me*), 3.27–3.33 (1H, m, C(5)*H*), 3.57–3.64 (1H, m, C(3)*H*), 3.70–3.73 (1H, m, C(4)*H*), 3.97 (1H, q, *J* 7.0, C(α)*H*), 4.04 (1H, d, *J* 10.9, OCH_AH_BPh), 4.15–4.23 (1H, m, C(6)H_A), 4.55 (1H, d,

J 10.9, OCH_AH_BPh), 4.62 (1H, dd, *J* 11.4, 7.9, C(6)H_B); δ_C (100 MHz, $CDCl_3$) 21.1 (C(α)*Me*), 58.2 (*C*(5)), 58.9 (*C*(α)), 59.8 (*C*(4)), 64.4 (*C*(6)), 72.3 (OCH_2Ph), 76.9 (*C*(3)).

Method B: TBAF (1 M in THF, 0.24 mL, 0.24 mmol) was added to as stirred solution of **186** (100 mg, 0.119 mmol, >95:5 dr) and AcOH (10 μL, 0.16 mmol) in THF (1 mL) at 0 °C and allowed to warm to rt over 24 h. Water (1 mL) and brine (1 mL) were added and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (10 mL) then dried and concentrated *in vacuo* to give **186**.

Method C: HBF_4 (48% aq, 0.05 mL, 0.4 mmol) was added to as stirred solution of **189** (50 mg, 0.073 mmol, >95:5 dr) in CH_2Cl_2 (0.3 mL) and stirred at rt over 48 h. $CHCl_3$/^{i}PrOH (3:1 v/v, 3 mL) was added and the resultant mixture was washed with satd aq $NaHCO_3$ (2 mL) then dried and concentrated *in vacuo* to give a complex mixture. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 5:1) gave **189** as colourless viscous oil (15 mg, 30%, >95:5 dr). Further elution gave a 50:50 mixture of **188** and **189** as a colourless viscous oil (16 mg, 34%); selected data for **188**: δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 6.9, C(α)*Me*), 3.39–3.46 (3H, m, C(5)*H*, $N(CH_AH_BPh)_2$), 3.58–3.65 (1H, m, C(4)*H*), 3.66–3.74 (2H, m, $N(CH_AH_BPh)_2$), 3.76 (1H, d, *J* 4.7, C(3)*H*), 3.88–3.92 (2H, m, NCH_2Ph), 4.17–4.25 (2H, m, C(6)H_A, C(α)*H*), 4.36 (1H, d, *J* 11.6, OCH_AH_BPh), 4.49–4.57 (1H, m, C(6)H_B), 4.71 (1H, d, *J* 11.6, OCH_AH_BPh); δ_C (100 MHz, $CDCl_3$) 20.6 (C(α)*Me*), 52.2 (NCH_2Ph), 54.6 ($N(CH_2Ph)_2$), 56.9 (*C*(5)), 57.2 (*C*(4)), 59.7 (*C*(α)), 65.5 (*C*(6)), 72.7 (OCH_2Ph), 77.7 (*C*(3)).

Method D: TBAF (1.0 M in THF, 0.15 mL, 0.15 mmol) was added to a stirred solution of **189** (50 mg, 73 μmol, >95:5 dr) in THF (1.5 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 24 h. Water (1 mL) and brine (1 mL) were added and the aqueous layer was extracted with Et_2O (3 × 3 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (10 mL) then dried and concentrated *in vacuo* to give a 50:50 mixture of **187** and **188** respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum

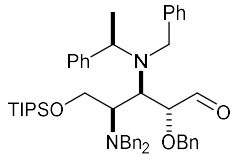
ether/EtOAc, 5:1) gave an 50:50 mixture of **187** and **188**, respectively, as colourless viscous oil (23 mg, 52%, 50:50 dr).

Method E: NaH (60% dispersion in mineral oil, 9 mg, 0.2 mmol) was added to a solution of **189** (125 mg, 0.183 mmol) in THF (2 mL) at 0 °C and allowed to warm to rt over 18 h then satd aq NH_4Cl (0.5 mL) was added. The aqueous layer was extracted with EtOAc (3 × 1 mL) then the combined organic layers were dried and concentrated *in vacuo* (81:19 dr, **187**:**188**). Purification *via* flash column chromatography gave an 81:19 mixture of **187** and **188**, respectively, as colourless viscous oil (63 mg, 56%, 81:19 dr).

Method F: NaH (60% dispersion in mineral oil, 20 mg, 0.50 mmol) was added to a stirred solution of **179** (238 mg, 0.457 mmol, >95:5 dr) in THF (5 mL) at 0 °C and was stirred at 0 °C for 30 min. BnBr (0.11 mL, 0.91 mmol) was added and the resultant mixture was allowed to warm to rt over 24 h then satd aq NH_4Cl (2 mL) was added. The organic layer was washed sequentially with brine (10 mL) and H_2O (10 mL) the combined aqueous layers were extracted with Et_2O (3 × 15 mL) then the combined organic layers were dried and concentrated *in vacuo* to give a complex mixture. Purification *via* flash column chromatography (eluent 30−40 °C petroleum ether/EtOAc, 5:1) gave **179** as a colourless viscous oil (49 mg, 21%, >95:5 dr). Exhaustive chromatography gave **187** as a colourless viscous oil (13 mg, 5%, 92:8 dr); data for **187**: δ_H (400 MHz, $(CD_3)_2CO$) 1.08 (3H, d, *J* 7.0, C(α)*Me*), 3.31 (1H, q, *J* 4.2, C(5)*H*), 3.47 (2H, d, *J* 13.7, N(C$H_A$$H_B$Ph)$_2$), 3.54 (1H, dd, *J* 8.1, 4.4, C(4)*H*), 3.66 (2H, d, *J* 13.7, N(C$H_A$$H_B$Ph)$_2$), 3.69 (1H, d, *J* 14.6, NC$H_A$$H_B$Ph), 3.80 (1H, d, *J* 14.6, NC$H_A$$H_B$Ph), 4.19 (1H, d, *J* 10.8, OC$H_A$$H_B$Ph), 4.26 (1H, q, *J* 7.0, C(α)*H*), 4.37 (1H, d, *J* 8.1, C(3)*H*), 4.45 (1H, dd, *J* 12.5, 4.1, C(6)H_A), 4.73 (1H, d, *J* 10.8, OC$H_A$$H_B$Ph), 4.73–4.79 (1H, m, C(6)H_B), 7.00–7.50 (25H, m, *Ph*); δ_C (125 MHz, $(CD_3)_2CO$) 22.6 (C(α)*Me*), 52.1 (N*C*H_2Ph), 55.3 (N(*C*H_2Ph)$_2$), 59.5 (*C*(5)), 60.8 (*C*(α)), 62.1 (*C*(4)), 65.0 (*C*(6)), 73.1 (O*C*H_2Ph), 77.5 (*C*(3)), 127.4, 127.9, 128.0, 128.7, 129.1, 129.2, 129.4, 130.1 (*o*,*m*,*p*-*Ph*), 139.0, 140.5, 142.6, 145.9 (*i*-*Ph*), 172.1 (*C*(2)).

Method G: TBAF (1 M in THF, 0.06 mL, 60 μmol) was added to a stirred solution of a mixture of **187** and **188** (18 mg, 30 μmol, 50:50 dr) in THF (0.5 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 24 h. Water (0.5 mL) and brine (0.5 mL) were added and the aqueous layer was extracted with Et_2O (3 × 2 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (5 mL) then dried and concentrated *in vacuo* to give a 82:18 mixture of **187** and **188** respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 10:1) gave a 76:24 mixture of **187** and **188**, respectively, as a pale yellow viscous oil (13 mg, 73%, 76:24 dr).

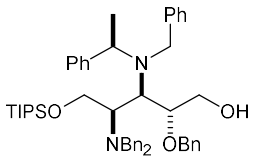
(*R*,*R*,*R*,*R*)-2-Benzyloxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-5-(triisopropylsilyloxy)pentanal 190



Method A: DIBAL-H (1 M in PhMe, 0.13 mL, 0.13 mmol) was added to a stirred solution of **186** (100 mg, 0.119 mmol) in PhMe (2 mL) at –78 °C and was stirred at –78 °C for 1 h then MeOH (1 mL) was added and the resultant mixture was allowed to warm to rt then concentrated *in vacuo* to give an 80:20 mixture of **186** and **193,** respectively.

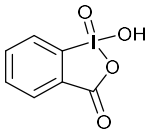
Method B: DIBAL-H (1 M in PhMe, 0.36 mL, 0.36 mmol) was added to a stirred solution of **186** (100 mg, 0.119 mmol) in PhMe (2 mL) at –78 °C and was stirred at –78 °C for 1 h then MeOH (1 mL) was added and the resultant mixture was allowed to warm to rt then concentrated *in vacuo* to give an 72:28 mixture of **186** and **193,** respectively.

(*R*,*R*,*R*,*R*)-2-Benzyloxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-5-(triisopropylsilyloxy)pentan-1-ol 193



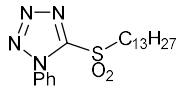
DIBAL-H (1 M in PhMe, 11.8 mL, 11.8 mmol) was added to a stirred solution of **186** (1.66 g, 1.97 mmol, >95:5 dr) in PhMe (33 mL) at –78 °C and was allowed to warm to rt over 24 h then cooled to 0 °C and satd aq NH_4Cl (10 mL) and satd aq Rochelle salt (20 mL) were added sequentially and the resultant mixture was left to stir at rt for 18 h then filtered through Celite® (eluent EtOAc) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30−40 °C petroleum ether/EtOAc, 10:1) gave **193** as colourless viscous oil (1.32 g, 87%, >95:5 dr); $[\alpha]_D^{22}$ +15.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3420 (O–H); δ_H (400 MHz, $CDCl_3$) 0.95 (3H, d, *J* 6.9, C(α)*Me*), 1.04–1.17 (21H, m, Si(C*HMe*$_2$)$_3$), 1.61 (1H, br s, O*H*), 3.24–3.29 (1H, m, C(2)*H*), 3.33 (1H, dd, *J* 6.6, 3.5, C(3)*H*), 3.44–3.61 (5H, m, C(1)H_2, C(4)*H*, C(α)*H*, NCH_AH_BPh), 3.72 (2H, d, *J* 13.0, N(CH_AH_BPh)$_2$), 3.74 (1H, d, *J* 14.8, NCH$_A$$H_B$Ph), 3.98 (1H, dd, *J* 10.7, 3.8, C(5)H_A), 4.15 (2H, d, *J* 13.0, N(CH$_A$$H_B$Ph)$_2$), 4.20 (1H, d, *J* 11.1, OCH_AH_BPh), 4.41 (1H, dd, *J* 10.7, 8.0, C(5)H_B), 4.60 (1H, d, *J* 11.1, OCH$_A$$H_B$Ph), 6.97 (2H, m, *Ph*), 7.15–7.21 (8H, m, *Ph*), 7.23–7.30 (7H, m, *Ph*), 7.35 (4H, t, *J* 7.4, *Ph*), 7.44 (4H, d, *J* 7.0, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 18.2 (C(α)*Me*), 18.3 (Si(CH*Me*$_2$)$_3$), 52.4 (N*C*H$_2$Ph), 55.6 (N(*C*H$_2$Ph)$_2$), 57.7 (*C*(α)), 62.0 (*C*(5)), 62.3 (*C*(1)), 63.1 (*C*(3)), 63.3 (*C*(4)), 71.1 (O*C*H$_2$Ph), 79.5 (*C*(2)), 126.5, 126.8, 127.0, 127.5, 127.5, 128.0, 128.1, 128.1, 128.1, 128.3, 128.3, 130.0 (*o*,*m*,*p*-*Ph*), 137.9, 140.3, 140.4, 143.1 (*i*-*Ph*); *m/z* (ESI^+) 771 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{50}H_{67}N_2O_3Si^+$ ($[M+H]^+$) requires 771.4916; found 771.4907.

2-Iodoxybenzoic acid [IBX]



2-Iodobenzoic acid (73.5 g, 296 mmol) was added to a mechanically stirred solution of Oxone® (551 g, 888 mmol) in H_2O (1.5 L) and the resultant mixture heated at 70 °C for 3 h. The reaction mixture was allowed to cool to rt and the precipitate was collected by filtration. The filter cake was washed with H_2O (2 × 250 mL), acetone (250 mL) and Et_2O (250 mL) before drying *in vacuo* to give IBX as a white solid (69.7 g, 84%); mp 235 °C (dec) {lit.[9] 232 °C (dec)}; δ_H (400 MHz, $(CD_3)_2CO$) 7.81–7.87 (1H, m, *Ar*), 7.97–8.06 (2H, m, *Ar*), 8.11–8.18 (1H, m, *Ar*).

1-(1'-phenyl-1*H*-tetrazol-5'-ylsulfonyl)tridecane 197



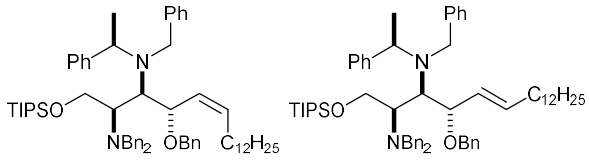
Step 1: Tridecanol **194** (1.50 g, 7.49 mmol) was dissolved in HBr (48% aq, 8 mL) and stirred at 100 °C for 18 h then, allowed to cool to rt and extracted with CH_2Cl_2 (3 × 15 mL) and the organic extracts were washed with satd aq $NaHCO_3$ (30 mL) then dried and concentrated *in vacuo* to give **195**; δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.8, C(13)H_3), 1.13–1.28 (18H, m, C(4)H_2–C(12)H_2), 1.38–1.48 (2H, m, C(3)H_2), 1.86 (2H, app quintet, *J* 7.1, C(2)H_2), 3.42 (2H, t, *J* 6.9, C(1)H_2).

Step 2: The residue **195** was dissolved in acetone (30 mL) and K_2CO_3 (2.07 g, 15.0 mmol) and **198** (1.47 g, 8.24 mmol) were added and the resultant mixture was stirred at 56 °C for 2.5 h then allowed to cool to rt. The suspension was filtered and concentrated *in vacuo* then partitioned between CH_2Cl_2 (20 mL) and H_2O (20 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) then the organic extracts were washed with H_2O (50 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **196** (2.40 g); δ_H (400 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.9, C(13)H_3), 1.20–1.35 (18H, m, C(4)H_2–C(12)H_2),

1.40–1.49 (2H, m, C(3)H_2), 1.82 (2H, app quintet, *J* 7.4, C(2)H_2), 3.40 (2H, t, J 7.4, C(1)H_2), 7.51–7.62 (5H, m, *Ph*).

Step 3: The residue **196** was dissolved in EtOH (100 mL) was added dropwise to a stirred solution of $(NH_4)_2Mo_7O_{24}{\cdot}4H_2O$ (1.85 g, 1.50 mmol) in 30% aq H_2O_2 (12.8 mL, 112 mmol) at 0 °C and the resultant mixture was left to warm to rt over 18 h. Brine (100 mL) was added and the aqueous layer was extracted with EtOAc (3 × 150 mL) and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in MeOH (30 mL) and stirred at rt for 1 h then at 0 °C for 1 h and filtered to give **197** as a white solid (2.33 g, 79%); mp 50–52 °C; ν_{max} (ATR) 1339 (S=O), 1151 (S=O); δ_H (400 MHz, $CDCl_3$) 0.88 (3H, t, *J* 6.7, C(13)H_3), 1.20–1.28 (18H, m, C(4)H_2–C(12)H_2), 1.44–1.54 (2H, m, C(3)H_2), 1.89–2.01 (2H, m, C(2)H_2), 3.68–3.77 (2H, m, C(1)H_2), 7.55–7.73 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(13)), 21.9 (*C*(2)), 22.6, 29.1, 29.3, 29.4, 29.5, 29.6 (*C*(4)–*C*(12)) 28.1 (*C*(3)), 56.0 (*C*(1)), 125.0, 129.7, 131.4 (*o*,*m*,*p*-*Ph*), 133.0 (*i*-*Ph*), 153.4 (*C*(1')); *m/z* (ESI^+) 415 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{20}H_{32}O_2N_4NaS^+$ ($[M+Na]^+$) requires 415.2138; found 415.2142.

(2*R*,3*R*,4*S*,*Z*)-1-(Triisopropylsilyloxy)-2-(*N*,*N*-dibenzylamino)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-benzyloxyoctadec-5-ene (*Z*)-192 and (2*R*,3*R*,4*S*,*E*)-1-(Triisopropylsilyloxy)-2-(*N*,*N*-dibenzylamino)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-benzyloxyoctadec-5-ene (*E*)-191



Method A: *Step 1*: IBX (109 mg, 0.389 mmol) was added to a stirred solution of **193** (100 mg, 0.130 mmol) in DMSO (2 mL) at rt and stirred at rt for 18 h. Et_2O (2 mL) was added and the organic layer was washed with H_2O (5 × 2 mL) then dried and concentrated *in vacuo*.

Step 2: BuLi (2.2 M in hexanes, 0.17 mL, 0.38 mmol) was added to a stirred solution of **175** (204 mg, 0.389 mmol) in THF (2.5 mL) at 0 °C and stirred at 0 °C for 30 min. The residue from the previous step was dissolved in THF (2.5 mL), the two solutions were combined and the resultant mixture was stirred at rt for 18 h before being concentrated *in vacuo* to give ~80:20 mixture of **190** and (*Z*)-**192**, respectively.

Method B: *Step 1*: IBX (54 mg, 0.19 mmol) was added to a stirred solution of **193** (50 mg, 65 μmol) in DMSO (1 mL) at rt and stirred at rt for 18 h. Et_2O (2 mL) was added and the organic layer was washed with H_2O (5 × 2 mL) then dried and concentrated *in vacuo*.

Step 2: BuLi (2.2 M in hexanes, 0.09 mL, 0.2 mmol) was added to a stirred solution of **175** (102 mg, 0.195 mmol) in THF (1.2 mL) at 0 °C and stirred at 0 °C for 30 min. The residue from the previous step was dissolved in THF (1.2 mL), the two solutions were combined and the resultant mixture was heated at 75 °C for 2 h before being concentrated *in vacuo* to give a complex mixture containing a ~10:90 mixture of **190** and (*Z*)-**192**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 50:1) gave (*Z*)-**192** as a colourless viscous oil (24 mg, 39%, >95:5 dr, ~90% pure); ν_{max} (ATR) 1602 (C=C); δ_H (500 MHz, $CDCl_3$) 0.87 (3H, t, *J* 6.9, C(18)H_3), 1.01–1.12 (24H, m, C(α)*Me*, Si(C*HMe*$_2$)$_3$)), 1.22–1.31 (20H, m, C(8)H_2–C(17)H_2), 1.84–1.93 (1H, m, C(7)H_A), 1.97–2.06 (1H, m, C(7)H_B), 3.20 (1H, dd, *J* 6.9, 3.8, C(3)*H*), 3.54 (2H, d, *J* 13.9, (N(CH_AH$_B$Ph)$_2$), 3.49–3.56 (1H, m C(2)*H*), 3.69 (1H, d, *J* 15.3, NCH_AH$_B$Ph), 3.79 (1H, d, *J* 11.2, OCH_AH$_B$Ph), 3.92 (1H, q, *J* 6.8, C(α)*H*), 3.93–4.00 (3H, m, N(CH$_A$$H_B$Ph)$_2$, NCH$_A$$H_B$Ph), 4.16 (1H, dd, *J* 10.6, 6.0, C(1)H_A), 4.21 (1H, dd, *J* 10.6, 5.8, C(1)H_B), 4.31–4.38 (2H, m, C(4)*H*, OCH$_A$$H_B$Ph), 5.23 (1H, t, *J* 10.6, C(5)*H*), 5.49–5.56 (1H, m, C(6)*H*), 7.00–7.28 (25H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 14.1 (*C*(18)), 18.2 (Si(CH*Me*$_2$)$_3$), 20.3 (C(α)*Me*), 22.7 (*C*(17)), 29.4, 29.5, 29.6, 29.6–29.7, 31.9 (*C*(8)–*C*(16)), 27.9 (*C*(7)), 51.8 (N*C*H$_2$Ph), 55.1 (N(*C*H$_2$Ph)$_2$), 58.3 (*C*(α)), 61.1 (*C*(1)), 62.9 (*C*(2)), 64.6 (*C*(3)), 69.2 (O*C*H$_2$Ph), 74.7 (*C*(4)),

125.9, 126.3, 126.5, 126.9, 127.2, 127.7, 127.7, 127.9, 128.0, 128.0, 128.4, 128.4 (*o*,*m*,*p*-*Ph*), 129.4 (*C*(5)), 133.6 (*C*(6)), 138.8, 141.0, 142.1, 145.3 (*i*-*Ph*).

Method C: *Step 1*: IBX (54 mg, 0.19 mmol) was added to a stirred solution of **193** (50 mg, 65 μmol) in DMSO (1 mL) at rt and stirred at rt for 18 h. Et_2O (2 mL) was added and the organic layer was washed with H_2O (5 × 2 mL) then dried and concentrated *in vacuo*.

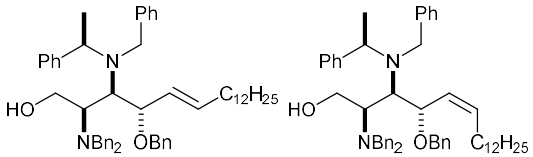
Step 2: BuLi (2.2 M in hexanes, 0.09 mL, 0.2 mmol) was added to a stirred solution of **175** (102 mg, 0.195 mmol) in THF (0.8 mL) at 0 °C and stirred at 0 °C for 30 min. The residue from the previous step was dissolved in PhMe (1.6 mL), the two solutions were combined and the resultant mixture was heated at 70 °C for 2 h before being concentrated *in vacuo* to give a complex mixture.

Method D: Step 1: IBX (411 mg, 1.47 mmol) was added to a stirred solution of **193** (372 mg, 0.482 mmol) in DMSO (7.5 mL) at rt and stirred at rt for 18 h. Et_2O (20 mL) was added and the organic layer was washed with H_2O (5 × 30 mL) then dried and concentrated *in vacuo.*

Step 2: LiHMDS (1 M in THF, 0.89 mL, 0.89 mmol) was added to a solution of the resiudue from the previous step and **197** (175 mg, 0.445 mmol) in THF (1.5 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 18 h then cooled to 0 °C then satd aq NH_4Cl (1 mL) and brine (3 mL) were added. The aqueous layer was extracted with Et_2O (3 × 5 mL) and then the combined organic layers were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 40:1) gave an 82:18 mixture of (*E*)-**191** and (*Z*)-**192**, respectively, as pale yellow viscous oil (312 mg, 69%, 82:18 dr {[*E*]:[*Z*]}); data for mixture: ν_{max} (ATR) 1603 (C=C); *m/z* (ESI$^+$) 938 ([M+4H]$^+$, 13%), 937 ([M+3H]$^+$, 53%), 936 ([M+2H]$^+$, 70%), 935 ([M+H]$^+$, 56%), 831 ([M+H-αMeBn]$^+$, 100%); HRMS (ESI$^+$) $C_{63}H_{91}O_2N_2Si^+$ requires 935.6844; found 935.6833; δ_C (100 MHz, $CDCl_3$) 29.3, 29.4, 29.5, 29.6, 29.6–29.8, 30.3, 30.9, 32.0 (*C*(8)–*C*(17)). Data for (*E*)-**191**: δ_H (400 MHz, $CDCl_3$) 0.87–0.93 (3H, m, C(18)*H*$_3$), 1.02 (3H, d, *J* 7.1, C(α)*Me*), 1.05–1.17 (21H, m, Si(C*HMe*$_2$)$_3$), 1.27–1.38 (20H, m, C(8)*H*$_2$–C(17)*H*$_2$), 1.83–2.07 (4H, m, C(7)*H*$_2$), 3.17–3.26

(1H, m, C(3)*H*), 3.49–3.60 (1H, m, C(2)*H*), 3.63–3.76 (4H, m, C(4)*H*, N(CH_AH_BPh)$_2$, NCH_AH_BPh), 3.78–3.84 (1H, m, C(α)*H*), 3.87 (1H, d, *J* 11.6, OCH_AH_BPh), 3.91–3.99 (1H, m, NCH$_A$$H_B$Ph), 4.04–4.12 (3H, m, C(1)H_A, N(CH$_A$$H_B$Ph)$_2$), 4.30–4.42 (2H, m, C(1)H_B, OCH$_A$$H_B$Ph), 5.15–5.32 (2H, C(5)*H*, C(6)*H*), 7.08–7.40 (25H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 14.2 (*C*(18)), 18.3 (Si(CH*Me*$_2$)$_3$), 19.1 (C(α)*Me*), 22.7 (*C*(17), 32.3 (*C*(7)), 51.8 (N*C*H$_2$Ph), 55.3 (N(*C*H$_2$Ph)$_2$), 57.4 (*C*(α)), 61.7 (*C*(1)), 63.5 (*C*(2)), 64.2 (*C*(3)), 69.5 (O*C*H$_2$Ph), 81.6 (*C*(4)), 126.1, 126.3, 126.4, 127.0, 127.4, 127.7, 127.8, 127.9, 128.0, 128.2, 128.3 (*o*,*m*,*p*-*Ph*), 130.3 (*C*(5)), 134.2 (*C*(6)), 138.9, 141.2, 141.7, 144.4 (*i*-*Ph*).

(2*R*,3*R*,4*S*,*E*)-2-(*N*,*N*-Dibenzylamino)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-benzyloxyoctadec-5-en-1-ol (*E*)-199 and (2*R*,3*R*,4*S*,*Z*)-2-(*N*,*N*-dibenzylamino)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-benzyloxyoctadec-5-en-1-ol (*Z*)-200



(*E*)-**199** (*Z*)-**200**

Method A: TBAF (1.0 M in THF, 0.42 mL, 0.42 mmol) was added to a stirred solution of a mixture of (*E*)-**191** and (*Z*)-**192** (195 mg, 0.207 mmol, 82:18 dr {[*E*]:[*Z*]}) in THF (4 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 24 h. Water (2 mL) and brine (2 mL) were added and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (15 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 30:1 to 5:1) gave an 82:18 mixture of (*E*)-**191** and (*Z*)-**192**, respectively, as a pale yellow viscous oil (40 mg, 21%, 82:18 dr {[*E*]:[*Z*]}). Further elution gave an 82:18 mixture of (*E*)-**199** and (*Z*)-**200**, respectively, as a colourless viscous oil (99 mg, 61%, 82:18 dr {[*E*]:[*Z*]}). Further elution gave a 98:2 mixture of (*E*)-**199** and (*Z*)-**200**, respectively, as a colourless viscous oil (12 mg, 7%, 98:2 dr {[*E*]:[*Z*]}). Data for mixture:

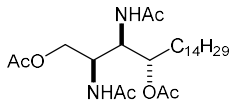
ν_{max} (ATR) 3453 (O–H), 1602 (C=C); *m/z* (ESI$^+$) 782 ([M+4H]$^+$, 9%), 781 ([M+3H]$^+$, 44%), 780 ([M+2H]$^+$, 100%), 779 ([M+H]$^+$, 98%); HRMS (ESI$^+$) $C_{63}H_{91}O_2N_2Si^+$ ([M+H]$^+$) requires 779.5510; found 779.5495. Data for (*E*)-**199:** δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 6.9, C(18)H_3), 1.24–1.30 (20H, m, C(8)H_2–C(17)H_2), 1.33 (3H, d, *J* 7.0, C(α)*Me*), 1.91–2.06 (2H, m, C(7)H_2), 3.26 (1H, dd, *J* 6.2, 3.4, C(3)*H*), 3.41 (1H, q, *J* 6.0, C(2)*H*), 3.57 (2H, d, *J* 14.0, N(CH_AH$_B$Ph)$_2$), 3.64–3.83 (7H, m, C(1)H_2, C(4)*H*, N(CH$_A$$H_B$Ph)$_2$, NC$H_AH_BPh, OCH_AH_B$Ph), 3.96 (1H, q, *J* 7.0, C(α)*H*), 4.25 (1H, d, *J* 15.4, NCH$_A$$H_B$Ph), 4.33 (1H, d, *J* 11.2, OCH$_A$$H_B$Ph), 5.30 (1H, dd, *J* 15.7, 7.7, C(5)*H*), 5.36–5.44 (1H, m, C(6)*H*), 7.11–7.36 (25H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 14.2 (*C*(18)), 21.7 (C(α)*Me*), 22.7 (*C*(17)), 29.2, 29.3, 29.4, 29.5, 29.6–29.7, 30.3, 31.9 (*C*(8)–*C*(17)), 32.4 (*C*(7)), 52.0 (N*C*H$_2$Ph), 54.5 (N(*C*H$_2$Ph)$_2$), 58.1 (*C*(α)), 60.0 (*C*(1)), 62.8 (*C*(3)), 62.9 (*C*(2)), 69.8 (O*C*H$_2$Ph), 80.3 (*C*(4)), 125.5, 126.5, 126.8, 127.5, 127.7, 128.0, 128.2, 128.3, 128.3, 128.5, 129.2 (*o*,*m*,*p*-*Ph*), 129.8 (*C*(5)), 134.5 (*C*(6)), 138.0, 140.3, 141.4, 144.4 (*i*-*Ph*). Selected data for (*Z*)-**200**: δ_H (500 MHz, $CDCl_3$) 0.86–0.93 (3H, m, C(18)H_3), 1.24–1.30 (20H, m, C(8)H_2–C(17)H_2), 1.98–2.06 (1H, m, C(7)H_A), 1.96–1.98 (1H, m, C(7)H_B), 3.16 (1H, dd, *J* 6.2, 3.2, C(3)*H*), 3.39–3.50 (3H, m, C(3)*H*, N(CH_AH$_B$Ph)$_2$), 3.55–3.61 (1H, m, OCH_AH$_B$Ph), 3.65–3.85 (2H, m, N(CH$_A$$H_B$Ph)$_2$), 4.02 (1H, q, *J* 7.2, C(α)*H*), 4.30 (1H, d, *J* 11.2, OCH$_A$$H_B$Ph), 4.40 (1H, dd, *J* 10.0, 3.0, C(4)*H*), 5.35–5.45 (1H, m, C(5)*H*), 5.53–5.63 (1H, m, C(6)*H*); δ_C (125 MHz, $CDCl_3$) 14.2 (*C*(18)), 22.7 (*C*(17)), 27.9 (*C*(7)), 54.2 (N(*C*H$_2$Ph)$_2$), 58.5 (*C*(α)), 62.2 (*C*(2)), 63.7 (*C*(3)), 69.6 (O*C*H$_2$Ph), 75.5 (*C*(4)), 129.5 (*C*(5)), 134.2 (*C*(6)).

Method B: TBAF (1.0 M in THF, 3.62 mL, 3.62 mmol) was added to a stirred solution of a mixture of (*E*)-**191** and (*Z*)-**192** (847 mg, 0.905 mmol, 82:18 dr {[*E*]:[*Z*]}) in THF (17 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 84 h. Water (10 mL) and brine (10 mL) were added and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (30 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C

petroleum ether/Et_2O/NH_4OH, 87:13:1) gave an 88:12 mixture of (*E*)-**199** and (*Z*)-**200**, respectively, as a colourless viscous oil (429 mg, 61%, 88:12 dr {[*E*]:[*Z*]}).

Method C: HF (70% in pyridine, 0.17 mL, 6.6 mmol) was added to a stirred solution of a mixture of (*E*)-**191** and (*Z*)-**192** (207 mg, 0.221 mmol, 82:18 dr {[*E*]:[*Z*]}) in THF (4 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 18 h. Satd aq $NaHCO_3$ (15 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL) then the combined organic layers were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc/NH_4OH, 90:10:1) gave an 82:18 mixture of **(*E*)-199** and **(*Z*)-200**, respectively, as a colourless viscous oil (149 mg, 86%, 82:18 dr {[*E*]:[*Z*]}).

(2*R*,3*S*,4*S*)-1,4-*O*,*O*-Diacetoxy-2,3-*N*,*N*-diacetamidooctadecane 169

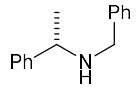


Step 1: $Pd(OH)_2/C$ (50% w/w of substrate, 122 mg) was added to a vigorously stirred suspension of a mixture of (*E*)-**191** and (*Z*)-**192** (243 mg, 0.312 mmol, 82:18 dr) in degassed HCl (1.25 M in MeOH, 3 mL) at rt. The reaction mixture was stirred under hydrogen (5 atm) at rt for 72 h. The resultant mixture was filtered through Celite® (eluent MeOH) and concentrated *in vacuo* to give **201**·2HCl (340 mg).

Step 2: Ac_2O (0.59 mL, 6.2 mmol) and DMAP (4 mg) were added sequentially to a stirred solution of the residue in pyridine (4 mL). The resultant solution was stirred at rt for 72 h then EtOAc (5 mL) was added and the resultant solution was washed with satd aq $CuSO_4$ (10 mL) and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layers were washed with satd aq $NaHCO_3$ (3 × 50 mL) and the aqueous layers extracted with EtOAc (3 × 50 mL). The combined organic layers were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent PhMe/^{i}PrOH, 4:1) gave **169** as pale orange solid

(109 mg, 72%, >95:5 dr); mp 73–75 °C; $[\alpha]_D^{22}$ –28.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3292 (N–H), 1740 (C=O, ester), 1657 (C=O, amide); δ_H (400 MHz, $CDCl_3$) 0.87 (3H, t, *J* 6.8, C(18)*Me*), 1.18–1.33 (24H, m, C(6)H_2–C(17)H_2), 1.53–1.61 (2H, m, C(5)H_2), 1.95 (3H, s, C(2)NHCO*Me*), 1.99 (3H, s, C(3)NHCO*Me*), 2.05 (3H, s, C(4)OCO*Me*), 2.09 (3H, s, C(1)OCO*Me*), 4.08–4.27 (4H, m, C(1)H_2, C(2)*H*, C(3)*H*), 4.91 (1H, app q, *J* 5.9, C(4)*H*), 6.47–6.62 (2H, m, C(2)N*H*, C(3)N*H*); δ_C (100 MHz, $CDCl_3$) 14.1 (*C*(18)), 20.8 (C(1)OCO*Me*), 21.0 (C(4)OCO*Me*), 23.2 (C(2)NHCO*Me*), 23.2 (C(3)NHCO*Me*), 22.6, 25.4, 29.3, 29.4, 29.5, 29.5, 29.6, 29.6, 29.6, 29.6, 31.9 (*C*(6)–*C*(17)), 49.2 (*C*(2)), 52.4 (*C*(3)), 63.4 (*C*(1)), 72.6 (*C*(4)), 171.0 (4 × *C*=O); δ_H (400 MHz, C_6D_6) 0.92 (3H, t, *J* 6.8, C(18)H_3), 1.24–1.38 (24H, m, C(6)H_2–C(17)H_2), 1.66–1.73 (2H, m, C(5)H_2), 1.76 (3H, s, NHCO*Me*), 1.78 (3H, s, NHCO*Me*), 1.84 (3H, s, C(1)OCO*Me*), 1.92 (3H, s, C(4)OCO*Me*), 4.20 (1H, dd, *J* 11.4, 5.7, C(1)H_A), 4.31 (1H, dd, *J* 11.4, 4.4, C(1)H_B), 4.46–4.54 (2H, m, C(2)*H*, C(3)*H*), 5.21 (1H, q, *J* 6.0, C(4)*H*), 6.74–6.82 (2H, m, 2 × N*H*); δ_C (100 MHz, C_6D_6) 14.7 (*C*(18)), 20.9 (C)(1)OCO*Me*), 21.3 (C(3)OCO*Me*), 23.3, 23.5 (2 × NHCO*Me*), 26.2, 30.2, 30.4, 30.5–30.6, 32.7 (*C*(6)–*C*(17)), 49.8 (*C*(2)), 53.0, (*C*(3)), 64.1 (*C*(1)), 72.9 (*C*(4)), 171.0, 171.1, 171.1, 171.2 (4 × *C*=O); *m/z* (ESI^+) 507 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{26}H_{48}O_6N_2Na^+$ ($[M+Na]^+$) requires 507.3405; found 507.3398.

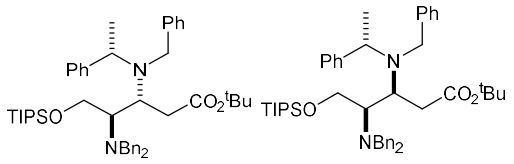
(*S*)-*N*-Benzyl-*N*-(α-methylbenzyl)amine (*S*)-162



Benzaldehyde (83.8 mL, 826 mmol) was added to a stirred solution of (*S*)-α-methylbenzylamine (*S*)-**171** (100 mL, 786 mmol, 98% ee) in EtOH (500 mL) at rt and the reaction mixture was heated at reflux for 3 h before being cooled to 0 °C. $NaBH_4$ (29.7 g, 786 mmol) was then added portionwise and the resultant suspension was stirred at rt for 48 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between H_2O (500 mL) and CH_2Cl_2 (750 mL). The organic layer was washed with brine (400 mL) and the

combined aqueous layers were extracted with CH_2Cl_2 (2 × 250 mL). The combined organic layers were dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (150 mL) and the resultant solution was added dropwise to a flask containing 10 M aq HCl (100 mL) and Et_2O (1.0 L) at 0 °C. The white precipitate was collected by filtration, washed with Et_2O (250 mL) and dissolved in CH_2Cl_2 (1.0 L). The resultant solution was dried and concentrated *in vacuo* to give (*S*)-**162**·HCl as a white solid. The free amine was regenerated quantitatively by treatment of the hydrochloride salt with 2.0 M aq NaOH, followed by extraction with CH_2Cl_2 (3 × 300 mL). The combined organic layers were dried and concentrated *in vacuo* to give (*S*)-**162** as a colourless viscous oil (114 g, 68%, 98% ee);[10] $[\alpha]_D^{22}$ –55.3 (*c* 1.0 in $CHCl_3$) {lit.[10] $[\alpha]_D^{20}$ −49.7 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.6, C(α)*Me*), 1.60 (1H, br s, N*H*), 3.61 (1H, d, *J* 13.2, NCH_AH$_B$Ph), 3.68 (1H, d, *J* 13.2, NCH$_A$$H_B$Ph), 3.83 (1H, q, *J* 6.6, C(α)*H*), 7.23–7.41 (10H, m, *Ph*).

***tert*-Butyl (3*R*,4*R*,*αS*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-5-(triisopropylsilyloxy)pentanoate 202 and *tert*-Butyl (3*S*,4*R*,*αS*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-5-(triisopropylsilyloxy)pentanoate 203**



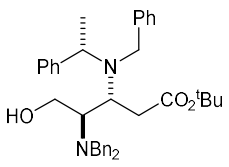
202 203

Method 1: BuLi (2.2 M in hexanes, 8.46 mL, 18.6 mmol) was added dropwise to a stirred solution of (*S*)-**162** (4.03 g, 19.1 mmol, 98% ee) in THF (50 mL) at −78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of (*R*)-**154** (5.00 g, 9.55 mmol, >95:5 dr) in THF (25 mL) was then added *via* cannula and the reaction mixture was stirred at −78 °C for 2 h then was allowed to warm to rt. Satd aq NH_4Cl (5 mL) was added and the reaction mixture was stirred at rt for 5 min, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (100 mL) and 10% aq citric acid (100 mL), and the aqueous layer was extracted with

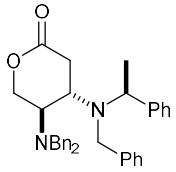
CH_2Cl_2 (3 × 100 mL). The combined organic extracts were washed sequentially with satd aq $NaHCO_3$ (200 mL) and brine (200 mL), then dried and concentrated *in vacuo* to give an 87:13 mixture of **202** and **203**, respectively. Purification *via* flash column chromatography (30–40 °C petroleum ether/EtOAc, 25:1) gave an 87:13 mixture of **202** and **203**, respectively, as yellow viscous oil [83%, 87:13 dr (**202**:**203**)]. Selected data for **203**: δ_H (400 MHz, $CDCl_3$) 2.57 (1H, dd, *J* 16.1, 3.5, C(2)H_A), 2.81 (1H, dd, *J* 16.1, 8.7, C(2)H_B).

Method 2: TIPSCl (40 μL, 0.19 mmol) was added to a stirred solution of **207** (100 mg, 0.196 mmol, >95:5 dr), DMAP (cat) and imidazole (24 mg, 0.35 mmol) in CH_2Cl_2 (2 mL) and stirred and rt for 36 h then concentrated *in vacuo*. The residue was partitioned between Et_2O (5 mL) and 1 M aq HCl (2 mL) and the aqueous layer was extracted with Et_2O (3 × 3 mL) then the combined organic layers were washed with satd aq $NaHCO_3$ (5 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C/EtOAc, 20:1) gave **202** as a pale yellow viscous oil (24 mg, 19%, >95:5 dr);[2] $[\alpha]_D^{22}$ –7.8 (*c* 1.0 in $CHCl_3$); {lit.[2] –8.6 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.18 (3H, d, *J* 7.0, C(α)*Me*), 1.19–1.30 (21H, m, Si(C*HMe*$_2$)$_3$), 1.42 (9H, s, C*Me*$_3$), 1.78–1.90 (1H, m, C(2)H_A), 2.71 (1H, dd, *J* 17.0, 5.0, C(2)H_B), 2.94–3.03 (1H, m, C(4)*H*), 3.06–3.21 (1H, m, NCH_AH$_B$Ph), 3.29 (1H, d, *J* 15.0, NCH$_A$$H_B$Ph), 3.36–3.43 (1H, m, C(3)*H*), 3.67 (1H, q, *J* 7.0, C(α)*H*), 3.71–3.79 (2H, m, N(CH_AH$_B$Ph)$_2$), 3.83–3.97 (3H, m, C(5)H_A, N(CH$_A$$H_B$Ph)$_2$), 4.50 (1H, dd, *J* 10.7, 3.8, C(5)H_B), 7.12–7.34 (20H, m, *Ph*).

tert-Butyl (3*R*,4*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-5-hydroxypentanoate 207 and (4*S*,5*R*,α*S*)-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-5-(*N*,*N*-dibenzylamino)-tetrahydro-2*H*-pyran-2-one 208



207

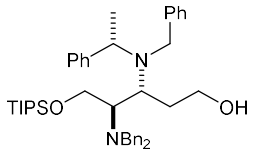


208

TBAF (1.0 M in THF, 1.02 mL, 1.02 mmol) was added to a stirred solution of **202** (500 mg, 0.680 mmol, 87:13 dr) in THF (12 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 24 h. Water (5 mL) and brine (5 mL) were added and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were washed with satd aq $NaHCO_3$ (30 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 5:1) gave **207** as a pale yellow viscous oil (260 mg, 66%, >95:5 dr); $[\alpha]_D^{22}$ –26.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3424 (O–H), 1724 (C=O); δ_H (500 MHz, CD_3OD) 1.16 (3H, d, *J* 6.8, C(α)*Me*), 1.41 (9H, s, C*Me*$_3$), 1.94–2.03 (1H, m, C(2)H_A), 2.74 (1H, dd, *J* 16.5, 3.0, C(2)H_B), 2.86–2.93 (1H, m, C(4)*H*), 3.26–3.31 (2H, m, NCH_2Ph), 3.54 (2H, d, *J* 11.7, N(CH_AH$_B$Ph)$_2$), 3.62–3.72 (3H, m, C(3)*H*, N(CH$_A$$H_B$Ph)$_2$), 3.73 (1H, q, *J* 6.8, C(α)*H*), 3.80–3.87 (1H, m, C(5)H_A), 3.90–4.05 (1H, m, C(5)H_B), 7.15–7.30 (20H, m, *Ph*); δ_C (125 MHz, CD_3OD) 22.4 (C(α)*Me*), 28.7 (C*Me*$_3$), 34.3 (*C*(2)), 53.7 (N*C*H$_2$Ph), 55.6 (N(*C*H$_2$Ph)$_2$), 56.6 (*C*(3)), 61.3 (*C*(5)), 61.5 (*C*(4)), 63.1 (*C*(α)), 81.7 (*C*Me$_3$), 128.0, 128.1, 128.4, 129.2, 129.3, 129.6, 130.0, 130.0, 130.8 (*o*,*m*,*p*-*Ph*), 141.5, 142.0, 145.5 (*i*-*Ph*), 175.2 (*C*(1)); *m/z* (ESI$^+$) 579 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{38}H_{47}N_2O_3^+$ ([M+H]$^+$) requires 579.3581; found 579.3572. Further elution gave **208** as colourless viscous oil (37 mg, 11%, impure); ν_{max} (ATR) 1748 (C=O); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 6.9, C(α)*Me*), 2.72 (1H, dd, *J* 15.3, 6.6, C(3)H_A), 2.82 (1H, dd, *J* 15.3, 8.5, C(3)H_B), 3.25 (1H, q, *J* 4.9, C(5)*H*), 3.28 (2H, d, *J* 13.7, N(CH_AH$_B$Ph)$_2$), 3.50 (2H, d, *J* 13.7,

N($CH_AH_BPh)_2$), 3.53–3.56 (1H, m, C(4)*H*), 3.59 (1H, d, *J* 13.6, NCH_AH_BPh), 3.65 (1H, d, *J* 13.6, NCH_AH_BPh), 3.90 (1H, q, *J* 6.9, C(α)*H*), 4.15 (1H, dd, *J* 12.4, 4.9, C(6)H_A), 4.43 (1H, dd, *J* 12.4, 4.9, C(6)H_B), 6.95–7.05 (5H, m, *Ph*), 7.20−7.43 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.9 (C(α)*Me*), 34.4 (*C*(3)), 50.4 (N*C*H_2Ph), 53.3 (*C*(4)), 54.7 (N(*C*H_2Ph)$_2$), 56.5 (*C*(α)), 58.1 (*C*(5)), 66.0 (*C*(6)), 127.0, 127.1, 128.2, 128.2, 128.2, 128.3, 128.8, 129.0, 129.0 (*o*,*m*,*p*-*Ph*), 139.1, 139.5, 143.4 (*i*-*Ph*), 173.1 (*C*(2)); *m/z* (ESI^+) 505 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{34}H_{37}N_2O_2^+$ ($[M+H]^+$) requires 505.2850; found 505.2846.

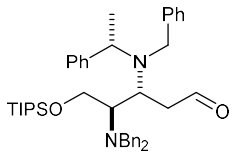
(3*R*,4*R*,*αS*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-5-(triisopropylsilyloxy)pentan-1-ol 209



$LiAlH_4$ (1 M in THF, 1.08 mL, 1.08 mmol) was added to a stirred solution of a mixture of **202** and **203** (200 mg, 0.272 mmol, 87:13 dr) in THF (13 mL) at –78 °C and allowed to warm to rt over 18 h then cooled to 0 °C. 1.0 M aq NaOH (1 mL) was added and the resultant mixture was heated at 67 °C for 1 h, allowed to cool to rt then filtered through Celite® (eluent EtOAc) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (30−40 °C petroleum ether/EtOAc, 5:1) gave **209** as a colourless viscous oil (115 mg, 64%, >95:5 dr); $[\alpha]_D^{22}$ +24.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3410 (O–H); δ_H (400 MHz, C_6D_6) 1.13 (3H, d, *J* 6.8, C(α)*Me*), 1.22–1.28 (21H, m, Si(C*HMe*$_2$)$_3$), 1.50–1.57 (1H, m, C(2)H_A), 1.60–1.67 (1H, m, C(2)H_B), 2.24 (1H, br s, O*H*), 2.82–2.88 (1H, m, C(3)*H*), 3.26–3.34 (1H, m, C(4)*H*), 3.35–3.42 (1H, m, NCH_AH_BPh), 3.45–3.55 (3H, m, C(1)H_2, NCH_AH_BPh), 3.66 (1H, q, *J* 6.8, C(α)*H*), 3.80–3.88 (2H, m, N(CH_AH_BPh)$_2$), 3.93–4.13 (3H, m, C(5)H_A, N(CH_AH_BPh)$_2$), 4.58 (1H, dd, *J* 10.9, 3.9, C(5)H_B), 7.05–7.09 (4H, m, *Ph*), 7.17–7.27 (10H, m, *Ph*), 7.34 (2H, d, *J* 7.3, *Ph*), 7.49 (4H, d, *J* 7.3, *Ph*); δ_C (100 MHz, C_6D_6) 12.8 (Si(*C*HMe$_2$)$_3$), 18.9 (Si(CH*Me*$_2$)$_3$), 23.0 (C(α)*Me*), 32.4 (*C*(2)), 53.2 (N*C*H_2Ph), 55.9

(N($CH_2Ph)_2$), 56.3 (*C*(1)), 56.9 (*C*(3)), 61.3 (*C*(α)), 62.5 (*C*(4)), 66.3 (*C*(5)), 127.2, 127.6, 127.8–129.5, 131.0 (*o*,*m*,*p-Ph*), 140.7, 142.7, 146.4 (*i-Ph*); *m/z* (ESI^+) 665 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{43}H_{61}N_2O_2Si^+$ ($[M+H]^+$) requires 665.4497; found 665.4492.

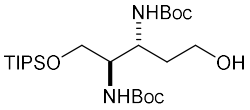
(3*R*,4*R*,*αS*)-3-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-4-(*N*,*N*-dibenzylamino)-5-(triisopropylsilyloxy)pentanal



Method A: DMSO (0.04 mL, 0.6 mmol) was added to a stirred solution of $(COCl)_2$ (0.02 mL, 0.3 mmol) in CH_2Cl_2 (2 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min. A solution of **209** (100 mg, 0.150 mmol, >95:5 dr) in CH_2Cl_2 (2 mL) was added at –78 °C, the resultant mixture was allowed to stir at –78 °C for 1 h then Et_3N (0.13 mL, 0.90 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 15 min then allowed to warm to rt. H_2O (2 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL) then the combined organic layers were dried and concentrated *in vacuo* to give a complex mixture.

Method B: IBX (126 mg, 0.451 mmol) was added to a stirred solution of **209** (100 mg, 0.150 mmol) in DMSO (2 mL) at rt and stirred at rt for 18 h. Et_2O (2 mL) was added and the organic layer was washed with H_2O (5 × 2 mL) then dried and concentrated *in vacuo* to give a complex mixture.

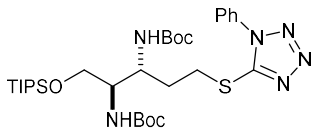
(*R*,*R*)-1-Triisopropylsilyloxy-2,3-di-(*N*-*tert*-butoxycarbonylamino)pentan-5-ol 212



$Pd(OH)_2$/C (40% w/w of substrate, 400 mg) was added to a vigorously stirred suspension of **209** (1.00 g, 1.50 mmol, >95:5 dr) and Boc_2O (985 mg, 4.51 mmol) in degassed MeOH

(5 mL) at rt. The reaction mixture was stirred under hydrogen (5 atm) at rt for 72 h. The resultant mixture was filtered through a small plug of Celite® (eluent MeOH) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 3:1 to 1:1) gave **212** as a pale yellow viscous oil (606 mg, 82%, >95:5 dr); $[\alpha]_D^{22}$ +19.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3355 (N–H, O–H), 1684 (C=O); δ_H (400 MHz, $CDCl_3$) 1.02–1.19 (21H, m, Si(C*H*Me_2)$_3$), 1.44 (18H, s, 2 × CMe_3), 1.38–1.51 (1H, m, C(4)H_A), 1.77–1.87 (1H, m, C(4)H_B), 3.56–3.74 (3H, m, C(2)*H*, C(5)H_2), 3.88 (1H, d, *J* 13.0, C(1)H_A), 3.93–4.04 (3H, m, C(1)H_B, C(3)*H*), 5.12 (1H, d, *J* 8.5, C(2)N*H*), 5.94 (1H, d, *J* 9.2, C(3)N*H*); δ_C (100 MHz, $CDCl_3$) 11.7 (Si(*C*HMe_2)$_3$), 17.9 (Si(CH*Me*$_2$)$_3$), 28.3, 28.4 (2 × CMe_3), 36.3 (*C*(4)), 50.0 (*C*(3)), 53.1 (*C*(2)), 58.4 (*C*(5)), 63.5 (*C*(1)), 79.7, 79.8 (2 × *C*Me_3), 155.4, 157.5 (2 × *C*=O); *m/z* (ESI$^+$) 513 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{50}N_2NaO_6Si^+$ ([M+Na]$^+$) requires 513.3330; found 513.3341.

(*R*,*R*)-1-Triisopropylsilyloxy-2,3-di-(*N*-*tert*-butoxycarbonylamino)-5-(1'-phenyl-1*H*-tetrazol-5'-ylthio)pentane 213



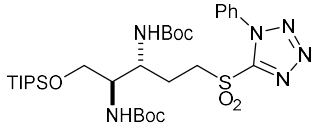
Method A: DEAD (0.04 mL, 0.3 mmol) was added to a stirred solution of **212** (100 mg, 0.204 mmol, >95:5 dr), PPh_3 (64 mg, 0.25 mmol) and **198** (182 mg, 1.02 mmol) in THF (1.5 mL) at 0 °C and allowed to warm to rt over 18 h. EtOAc (2 mL) was added and the resultant solution was washed with brine (2 mL) then H_2O (2 mL) and the organic layer was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/^{i}PrOH, 30:1) gave **213** as a colourless viscous oil (80 mg, 60%, >95:5 dr); $[\alpha]_D^{22}$ +25.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3357 (N–H), 1687 (C=O); δ_H (400 MHz, $CDCl_3$) 1.10–1.15 (21H, m, Si(C*H*Me_2)$_3$), 1.43 (18H, s, 2 × CMe_3), 1.96–2.07 (1H, m, C(4)H_A), 2.10–2.27 (1H, m, C(4)H_B), 3.26–3.35 (1H, m, C(5)H_A), 3.55–3.70 (2H, m, C(5)H_B, C(2)*H*), 3.85 (1H, d,

J 10.6, C(1)H_A), 3.99 (1H, dd, *J* 10.6, 2.1, C(1)H_B), 4.01–4.06 (1H, m, C(3)*H*), 5.11 (1H, d, *J* 8.5, C(2)N*H*), 5.75 (1H, d, *J* 9.5, C(3)N*H*), 7.50–7.62 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.7 (Si(*C*HMe_2)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 28.3, 28.3 (2 × C*Me*$_3$), 30.3 (*C*(5)), 33.7 (*C*(4)), 52.2 (*C*(2)), 52.8 (*C*(3)), 63.5 (*C*(1)), 79.3, 79.6 (2 × *C*Me$_3$), 123.9, 129.8, 130.0 (*o*,*m*,*p*-*Ph*), 133.7 (*i*-*Ph*), 154.4 (*C*(5')), 155.4, 156.3 (2 × *C*=O); *m/z* (ESI$^+$) 673 ([M+Na]$^+$, 100%), 651 ([M+H]$^+$, 47%); HRMS (ESI$^+$) $C_{31}H_{55}N_6O_5SiS^+$ ([M+H]$^+$) requires 651.3718; found 651.3716.

Method B: *Step 1*: MsCl (0.13 mL, 1.7 mmol) was added to a stirred solution of **212** (427 mg, 0.870 mmol, >95:5 dr), Et_3N (0.61 mL, 4.4 mmol) and DMAP (3 mg) in CH_2Cl_2 (26 mL) at rt and allowed to stir at rt for 3 h then H_2O was added (15 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) then the combined organic layers were extracted sequentially with 1 M aq HCl (50 mL), satd aq $NaHCO_3$ (50 mL) and brine (50 mL) then dried and concentrated *in vacuo* to give **214** as a colourless viscous oil.

Step 2: The residue was dissolved in acetone (8 mL) and **198** (171 mg, 0.957 mmol) and K_2CO_3 (240 mg, 1.74 mmol) were added and the resultant mixture was stirred at 56 °C for 2.5 h then allowed to cool to rt and filtered. CH_2Cl_2 (10 mL) and H_2O (10 mL) were added to the filtrate and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) then the combined organic layers were washed with H_2O then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 6:1) gave **213** as a pale yellow viscous oil (458 mg, 81%, >95:5 dr).

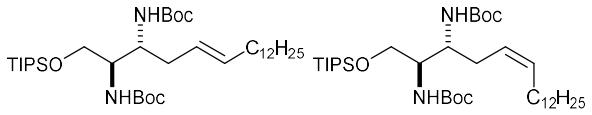
(*R*,*R*)-1-Triisopropylsilyloxy-2,3-di-(*N*-*tert*-butoxycarbonylamino)-5-(1'-phenyl-1*H*-tetrazol-5'-ylsulfonyl)pentane 215



A solution of **213** (632 mg, 0.971 mmol, >95:5 dr) in EtOH (15 ml) was added dropwise to a stirred solution of $(NH_4)_2Mo_7O_{24}\cdot 4H_2O$ (240 mg, 0.194 mmol) in 30% aq H_2O_2 (1.65 mL,

14.6 mmol) at 0°C and the resultant mixture was left to warm to rt over 18 h. Brine (10 mL) was added and the aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30−40 °C petroleum ether/EtOAc, 5:1) gave **215** as a white solid (632 mg, 95%, >95:5 dr); mp 95–97 °C; $[\alpha]_D^{22}$ –1.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3355 (N–H), 1684 (C=O), 1164 (S=O); δ_H (400 MHz, $CDCl_3$) 1.00–1.18 (21H, m, Si(C*HMe*$_2$)$_3$), 1.41–1.46 (18H, m, 2 × C*Me*$_3$), 2.04–2.15 (1H, m, C(4)H_A), 2.19–2.30 (1H, m, C(4)H_B), 3.64–3.72 (1H, m, C(2)*H*), 3.76–3.91 (3H, m, C(1)H_A, C(5)H_2), 3.91–4.01 (2H, m, C(1)H_B, C(3)*H*), 5.07 (1H, d, *J* 8.4, C(2)N*H*), 5.66 (1H, d, *J* 9.0, C(3)N*H*), 7.50–7.65 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.6 (Si(*C*HMe$_2$)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 29.7 (*C*(4)), 28.2 (2 × C*Me*$_3$), 51.7 (*C*(3)), 53.0 (*C*(2)), 53.7 (*C*(5)), 63.2 (*C*(1)), 79.7, 79.9 (2 × *C*Me$_3$), 125.0, 129.6, 131.4 (*o*,*m*,*p*-*Ph*), 132.9 (*i*-*Ph*), 153.2, 155.4, 156.0 (*C*(5'), 2 × *C*=O); *m/z* (ESI$^+$) 705 ([M+Na]$^+$, 100%), 583 ([M+H-Boc]$^+$, 27%), 527 ([M+H-TIPS]$^+$, 66%); HRMS (ESI$^+$) $C_{31}H_{54}O_7N_6NaSSi^+$ ([M+Na]$^+$) requires 705.3436; found 705.3442.

(*R*,*R*,*E*)-1-Triisopropylsilyloxy-2,3-di-(*N*-*tert*-butoxycarbonylamino)octadec-5-ene (*E*)-216 and (*R*,*R*,*Z*)-1-triisopropylsilyloxy-2,3-di-(*N*-*tert*-butoxycarbonylamino)octadec-5-ene (*Z*)-217

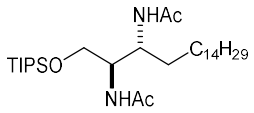


(*E*)-**216** (*Z*)-**216**

LiHMDS (1 M in THF, 2.36 mL, 2.36 mmol) was added to a solution of **215** (400 mg, 0.586 mmol, >95:5 dr) and tridecanal (0.13 mL, 0.56 mmol) in THF (2 mL) at –10 °C and the resultant mixture was allowed to warm to rt over 18 h then cooled to 0 °C then satd aq NH_4Cl (1 mL) and brine (5 mL) were added. The aqueous layer was extracted with Et_2O (3 × 5 mL) and then the combined organic layers were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 10:1)

gave a 50:50 mixture of (*E*)-**216** and (*Z*)-**217**, respectively, as a colourless oil (291 mg, 80%, ~50:50 dr). Data for mixture: ν_{max} (ATR) 3365 (N–H), 1687 (C=O, C=C); δ_H (500 MHz, $CDCl_3$) 0.85–0.90 (6H, m, C(18)H_3(**216**), C(18)H_3(**217**), 1.03–1.14 (42H, m, Si(CHMe_2)$_3$(**216**), Si(CHMe_2)$_3$(**217**)), 1.21–1.31 (40H, m, C(8)H_2–C(17)H_2(**216**), C(8)H_2–C(17)H_2(**217**)), 1.39–1.47 (36H, m, 2 × CMe_3 (**216**) 2 × CMe_3 (**217**)), 1.92–1.98 (2H, m, C(7)H_2(**216**)), 1.98–2.05 (2H, m, C(7)H_2(**217**)), 2.17–2.27 (2H, m, C(4)H_A(**216**), C(4)H_A(**217**)), 2.29–2.43 (2H, m, C(4)H_B(**216**), C(4)H_B(**217**)), 3.62–3.68 (2H, m, C(2)*H*(**216**), C(2)*H*(**217**)), 3.76–3.92 (4H, m, C(1)H_A(**216**), C(1)H_A(**217**), C(3)*H*(**216**), C(3)*H*(**217**)), 3.93–3.99 (2H, m, C(1)H_B(**216**), C(1)H_B(**217**)), 5.09–5.14 (2H, m, C(2)N*H*(**216**), C(2)N*H*(**217**)), 5.32–5.40 (2H, m, C(5)*H*(**216**), C(5)*H*(**217**)), 5.43–5.51 (2H, m, C(6)*H*(**216**), C(6)*H*(**217**)), 5.54–5.64 (2H, m, C(3)N*H*(**216**), C(3)N*H*(**217**)); δ_C (125 MHz, $CDCl_3$) [selected data] 11.7 (Si(*C*HMe_2)$_3$(**216**), Si(*C*HMe_2)$_3$(**217**)), 14.1 ((*C*(18)(**216**), *C*(18)(**217**)), 18.0 (Si(CHMe_2)$_3$(**216**)), 18.0 (Si(CHMe_2)$_3$(**217**)), 22.7 (C(17)(**216**), C(17)(**217**), 27.6 (C(7)(**217**)), 28.4, 28.4 (2 × CMe_3(**216**), 2 × CMe_3(**217**)), 31.2 (*C*(4)(**217**)), 32.6 (*C*(7)(**216**), 36.7 (*C*(4)(**216**)), 51.5, 51.6 (*C*(2)(**216**), *C*(2)(**217**)), 53.1, 53.4 (*C*(3)(**216**), *C*(3)(**217**)), 63.2, 63.3 (*C*(1)(**216**), *C*(1)(**217**)), 124.8 (*C*(5)(**217**)), 125.4 (*C*(5)(**216**)), 132.7 (*C*(6)(**217**)), 134.0 (*C*(6)(**216**)), 155.3, 155.9 (2 × *C*=O(**216**), 2 × *C*=O(**217**)); *m/z* (ESI$^+$) 677 ([M+Na]$^+$, 100%), 499 ([M+H-TIPS]$^+$, 59%); HRMS (ESI$^+$) $C_{37}H_{74}O_5N_2NaSi^+$ requires 677.5259; found 677.5250.

(*R*,*R*)-1-Triisopropylsilyloxy-2,3-diacetamido-octadecane 220



Step 1: Pd/C (20% w/w of substrate, 12 mg) was added to a vigorously stirred suspension of a mixture of (*E*)-**216** and (*Z*)-**217** (59 mg, 0.09 mmol, 50:50 dr) in degassed MeOH (1.5 mL) at rt. The reaction mixture was stirred under hydrogen (5 atm) at rt for 3 h. The resultant mixture

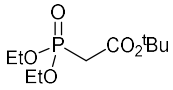
was filtered through Celite®, (eluent MeOH) and concentrated *in vacuo* to give **218** as a pale yellow viscous oil (53 mg).

Step 2: TFA (0.07 mL, 0.9 mmol) was added to a stirred solution of the residue (53 mg) in CH_2Cl_2 (1.5 mL) and stirred at rt for 18 then concentrated *in vacuo* to give **219**·2TFA (93 mg).

Step 3: Ac_2O (0.13 mL, 1.4 mmol) was added to a stirred solution of the residue (93 mg) and DMAP (1 mg, cat) in pyridine (2 mL) and stirred at rt for 18 h then diluted with EtOAc (10 mL) and washed with satd aq $CuSO_4$ (2 × 5 mL) and the aqueous layer was extracted with EtOAc (2 × 5 mL). The combined organic fractions were washed with satd aq $NaHCO_3$ (15 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/^{i}PrOH/ NH_4OH, 90:3:1) gave **220** as a white solid (35 mg, 72%, >95:5 dr); mp 146–149 °C; ν_{max} (ATR) 3270 (N–H), 1643 (C=O); $[\alpha]_D^{22}$ +45.7 (*c* 1.0 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 0.89 (3H, t, *J* 7.0, C(18)H_3), 1.06–1.14 (21H, m, Si(C*HMe*$_2$)$_3$), 1.22–1.33 (26H, m, C(5)H_2–C(17)H_2), 1.46–1.56 (2H, m, C(4)H_2), 1.99 (3H, s, C(2)NHCO*Me*), 2.00 (3H, s, C(3)NHCO*Me*), 3.85 (1H , dd, *J* 10.4, 3.9, C(1)H_A), 3.93–3.99 (2H, m, C(1)H_B, C(2)*H*), 4.06–4.13 (1H, m, C(3)*H*), 6.16 (1H, d, *J* 7.6, C(2)N*H*), 6.50 (1H, d, *J* 9.2, C(3)N*H*); δ_C (125 MHz, $CDCl_3$) 11.7 (Si(*C*HMe$_2$)$_3$), 14.1 (*C*(18)), 17.9 (Si(CH*Me*$_2$)$_3$), 22.7, 26.2, 29.3, 29.4, 29.5, 29.5, 29.6–29.7 32.0 (*C*(5)–*C*(17)), 23.4, 23.5 (2 × CO*Me*), 33.2 (*C*(4)), 52.1 (*C*(2)), 52.3 (*C*(3)), 63.1 (*C*(1)), 169.9 (C(2)NH*C*OMe), 170.3 (C(3)NH*C*OMe); *m/z* (ESI$^+$) 542 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{65}O_3N_2Si^+$ ([M+H]$^+$) requires 541.4759; found 541.4753.

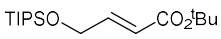
5.3 Experimental Data for Chapter 3

tert-Butyl diethylphosphonoacetate 231



A stirred mixture of $P(OEt)_3$ (44.0 mL, 256 mmol) and *tert*-butyl bromoacetate (37.9 mL, 256 mmol) was heated at 50 °C for 72 h then allowed to cool to rt and concentrated *in vacuo* to give **231** as a colourless viscous oil (65.5 g, quant);[11] δ_H (400 MHz, $CDCl_3$) 1.37 (6H, t, *J* 7.1, $P(OCH_2\mathit{Me})_2$), 1.49 (9H, s, $C\mathit{Me}_3$), 2.90 (2H, d, *J* 21.4, $PC\mathit{H}_2$), 4.14–4.23 (4H, m, $P(OC\mathit{H}_2Me)_2$).

tert-Butyl (*E*)-4-(triisopropylsilyloxy)but-2-enoate 230



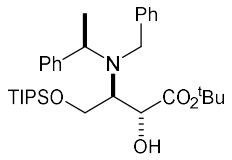
Step 1: TIPSCl (61.2 mL, 286 mmol) was added to a stirred solution of **128** (12.0 g, 136 mmol), imidazole (27.8 g, 409 mmol) and DMAP (50 mg, cat.) in CH_2Cl_2 (300 mL) at rt and the resultant mixture was stirred at rt for 18 h then concentrated *in vacuo*. The residue was dissolved in Et_2O (400 mL) and the resultant solution was washed with 1.0 M aq HCl (200 mL), then dried and concentrated *in vacuo* to give **228**.

Step 2: O_3 was bubbled through a stirred, degassed solution of the residue of **228** in CH_2Cl_2 (500 mL) at –78 ºC until a blue colouration was apparent then the reaction mixture was purged with O_2 until it became colourless. Me_2S (10 mL) was added dropwise and the resultant mixture was warmed to rt over 18 h. The reaction mixture was concentrated *in vacuo*, the residue was dissolved in Et_2O (300 mL) and the resultant solution was washed with H_2O (200 mL), then dried and concentrated *in vacuo* to give **229**.

Step 3: **231** (82.2 g, 326 mmol), LiCl (69.2 g, 1.63 mol) and $^iPr_2NEt$ (52.1 mL, 299 mmol) were added to a stirred solution of the residue of **229** in MeCN (500 mL) and the resultant

mixture was stirred at rt for 72 h and then H_2O (300 mL) was added. The aqueous layer was extracted with EtOAc (3 × 300 mL) and the combined organic layers were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 50:1) gave **230** as colourless viscous oil (52.7 g, 62%, >95:5 dr);[12] δ_H (400 MHz, $CDCl_3$) 1.04–1.10 (21H, m, Si(C*H*Me_2)$_3$), 1.50 (9H, s, CMe_3), 4.41 (2H, dd, *J* 3.4, 2.2, C(4)H_2), 6.06 (1H, dt, *J* 15.4, 2.3, C(2)*H*), 6.90 (1H, dt, *J* 15.4, 3.4, C(3)*H*).

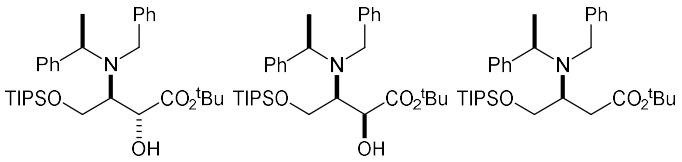
***tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino-4-(triisopropylsilyloxy)butanoate 232**



BuLi (2.2 M in hexanes, 46.1 mL, 101 mmol) was added dropwise to a stirred solution of (*R*)-**162** (22.1 g, 105 mmol, 98% ee) in THF (170 mL) at −78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **230** (20.6 g, 65.4 mmol, >95:5 dr) in THF (170 mL) was then added and the resultant mixture was stirred at −78 °C for 2 h. (–)-CSO (–)-**182** (30.0 g, 131 mmol) was added then the resultant mixture was allowed to warm to rt over 18 h. Satd aq NH_4Cl (30 mL) was added and the reaction mixture was stirred at rt for 5 min, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (400 mL) and 10% aq citric acid (400 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 200 mL). The combined organic layers were washed sequentially with satd aq $NaHCO_3$ (300 mL) and brine (300 mL), then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (200 mL), filtered and the filtrate was concentrated *in vacuo* to give a complex mixture. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 30:1) gave **232** as a colourless viscous oil (27.9 g, 77%, >95:5 dr);[13] $[\alpha]_D^{25}$ –35.7 (*c* 1.0 in $CHCl_3$) {lit.[13] for *ent*-**232** $[\alpha]_D^{20}$ +37.4 (*c* 1.1 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.02–1.10 (21H, m, Si(C*H*Me_2)$_3$), 1.35 (1H, d, *J* 7.1, C(α)*Me*), 1.42 (9H, s, CMe_3), 3.03 (1H, d, *J* 6.6, O*H*),

3.49–3.54 (1H, m, C(3)*H*), 3.80 (1H, d, *J* 15.0, NCH_AH_BPh), 3.84–3.89 (2H, m, C(4)H_2), 3.99 (1H, dd, *J* 6.6, 1.7, C(2)*H*), 4.02 (1H, q, *J* 7.1, C(α)*H*), 4.20 (1H, d, *J* 15.0, NCH_AH_BPh), 7.21–7.47 (10H, m, *Ph*).

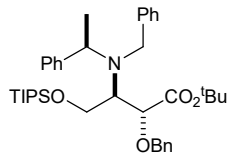
***tert*-Butyl (*R*,*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino-4-(triisopropylsilyloxy)butanoate 233, *tert*-Butyl (*R*,*R*,*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino-4-(triisopropylsilyloxy)butanoate 232 and *tert*-Butyl (2*S*,3*R*,*αR*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino-4-(triisopropylsilyloxy)butanoate 234**



BuLi (2.2 M in hexanes, 0.45 mL, 0.99 mmol) was added dropwise to a stirred solution of (*R*)-**162** (215 mg, 1.02 mmol, 98% ee) in THF (1.6 mL) at −78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **230** (200 mg, 0.636 mmol, >95:5 dr) in THF (1.6 mL) was then added *via* cannula and the reaction mixture was stirred at −78 °C for 2 h. (+)-CSO (292 mg, 1.27 mmol) was added then the resultant mixture was allowed to warm to rt over 18 h. Satd aq NH_4Cl (1 mL) was added and the reaction mixture was stirred at rt for 5 min, then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 (10 mL) and 10% aq citric acid (10 mL), and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were washed sequentially with satd aq $NaHCO_3$ (25 mL) and brine (25 mL), then dried and concentrated *in vacuo*. The residue was dissolved in Et_2O (20 mL), filtered and the filtrate was concentrated *in vacuo* to give a complex mixture. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 15:1) gave **233** as a colourless viscous oil (19 mg, 6%, >95:5 dr); $[\alpha]_D^{25}$ –5.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.02–1.18 (21H, m, Si(C*H*Me_2)$_3$), 1.41 (3H, d, *J* 6.9, C(α)*Me*), 1.44 (9H, s, CMe_3), 2.08 (1H, dd, *J* 15.3, 4.9, C(2)H_A), 2.32 (1H, dd, *J* 15.3, 8.0, C(2)H_B), 3.54–3.61 (1H, m, C(3)*H*), 3.67–3.74 (2H, m, C(4)H_A, NCH_AH_BPh), 3.79–3.86

(1H, m, C(4)H_B), 3.93 (1H, d, *J* 15.3, NCH$_A$$H_B$Ph), 3.97 (1H, q, *J* 6.9, C(α)*H*), 7.20–7.47 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.9 (Si(*C*HMe$_2$)$_3$), 18.0 (Si(CH*Me*$_2$)$_3$), 19.6 (C(α)*Me*), 28.0 (C*Me*$_3$), 35.2 (*C*(2)), 50.7 (N*C*H$_2$Ph), 55.8 (*C*(3)), 58.5 (*C*(α)), 65.2 (*C*(4)), 79.9 (*C*Me$_3$), 126.4, 126.6 127.8, 128.0, 128.2 (*o*,*m*,*p-Ph*), 142.0, 143.8 (*i-Ph*), 171.9 (*C*(1)); *m/z* (ESI$^+$) 526 ([M+H]$^+$, 100%), HRMS (ESI$^+$) $C_{32}H_{52}NO_3Si^+$ ([M+H]$^+$) requires 526.3711; found 526.3707. Further elution gave **232** as a colourless viscous oil (93 mg, 27%, >95:5 dr). Further elution gave a 89:11 mixture of **234** and **232**, respectively, as a colourless viscous oil (57 mg, 17%, 89:11 dr). Further elution gave **234** as a colourless viscous oil (31 mg, 9%, >95:5 dr);[14] $[\alpha]_D^{25}$ –26.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3510 (O–H), 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 1.06–1.14 (21H, m, Si(C*HMe*$_2$)$_3$), 1.41 (9H, s, C*Me*$_3$), 1.46 (3H, d, *J* 7.0, C(α)*Me*), 3.29 (1H, q, *J* 6.4, C(3)*H*), 3.74 (1H, d, *J* 3.4, O*H*), 3.86–3.99 (4H, m, C(2)*H*, C(4)H_2, NCH_AH$_B$Ph), 4.04 (1H, d, *J* 13.9, NCH$_A$$H_B$Ph), 4.18 (1H, q, *J* 7.0, C(α)*H*), 7.18–7.32 (10H, m, *Ph*); δ_C (400 MHz, $CDCl_3$) 11.9 (Si(*C*HMe$_2$)$_3$), 17.4 (C(α)*Me*), 18.1 (Si(CH*Me*$_2$)$_3$), 27.9 (C*Me*$_3$), 51.0 (N*C*H$_2$Ph), 58.8 (*C*(α)), 61.5 (*C*(3)), 61.7 (*C*(4)), 70.1 (*C*(2)), 81.5 (*C*Me$_3$), 126.8, 126.9, 127.9, 128.2, 128.7 (*o*,*m*,*p-Ph*), 140.7, 143.7 (*i-Ph*), 172.9 (*C*(1)); *m/z* (ESI$^+$) 542 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{52}NO_4Si^+$ ([M+H]$^+$) requires 542.3660; found 542.3650.

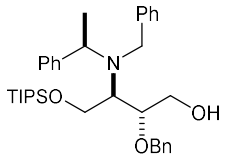
***tert*-Butyl (*R*,*R*,*R*)-2-benzyloxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino-4-(triisopropylsilyloxy)butanoate 235**



A solution of **232** (13.1 g, 24.2 mmol, >95:5 dr) in THF (290 mL) was added to a stirred solution of NaH (60% in mineral oil, 1.93 g, 48.4 mmol) in THF (290 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 1 h. BnBr (5.76 mL, 48.4 mmol) was added and the resultant mixture was allowed to warm to rt over 18 h then satd aq NH_4Cl (50 mL) and Et_2O (300 mL) were added. The resultant mixture was washed with brine (300 mL) and the aqueous layers were extracted with Et_2O (3 × 200 mL) then the combined organic layers were dried

and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 1:0 increased to 30:1) gave **235** as a colourless viscous oil (14.0 g, 92%, >95:5 dr);[13] $[\alpha]_D^{25}$ +24.1 (*c* 1.0 in $CHCl_3$) {lit.[13] for *ent*-**235** $[\alpha]_D^{25}$ –33.1 (*c* 0.7 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.04–1.14 (21H, m, Si(C*H*Me_2)$_3$), 1.35 (3H, d, *J* 6.9, C(α)*Me*), 1.42 (9H, s, C*Me*$_3$), 3.48–3.53 (1H, m, C(3)*H*), 3.65 (1H, d, *J* 15.2, NC$H_A$$H_B$Ph), 3.75 (1H, d, *J* 2.7, C(2)*H*), 3.83 (1H, dd, *J* 11.0, 3.7, C(4)H_A), 3.94–4.06 (2H, m, C(4)H_B, C(α)*H*), 4.18 (1H, d, *J* 11.2, OC$H_A$$H_B$Ph), 4.26 (1H, d, *J* 15.2, NCH$_A$$H_B$Ph), 4.54 (1H, d, *J* 11.2, OCH$_A$$H_B$Ph), 7.17–7.31 (11H, m, Ph), 7.36 (2H, d, *J* 7.1, *Ph*), 7.44 (2H, d, *J* 7.3, *Ph*).

(*R*,*R*,*R*)-2-Benzyloxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino-4-(triisopropylsilyloxy)butan-1-ol 236



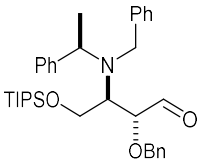
Method A: DIBAL-H (1 M in CH_2Cl_2, 29.9 mL, 29.9 mmol) was added to a stirred solution of **235** (4.72 g, 7.47 mmol, >95:5 dr) in CH_2Cl_2 (125 mL) at –78 °C then stirred at rt for 2 h. Satd aq NH_4Cl (30 mL) was added and the resultant mixture was filtered through Celite® (eluent CH_2Cl_2) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 15:1) gave **236** as a pale yellow viscous oil (2.78 g, 68%, >95:5 dr);[14] $[\alpha]_D^{25}$ +18.1 (*c* 1.0 in $CHCl_3$) {lit.[14] $[\alpha]_D^{20}$ +8.9 (*c* 1.1 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.05–1.18 (21H, m, Si(C*H*Me_2)$_3$), 1.43 (3H, d, *J* 6.9, C(α)*Me*), 3.03 (1H, br s, O*H*), 3.18 (1H, q, *J* 5.7, C(3)*H*), 3.41–3.50 (3H, m, C(1)H_2, C(2)*H*), 3.94–4.09 (4H, m, C(4)H_A, C(α)*H*, NCH_2Ph), 4.16 (1H, dd, *J* 10.2, 5.2, C(4)H_B), 4.36 (1H, d, *J* 11.5, OCH$_A$$H_B$Ph), 4.55 (1H, d, *J* 11.5, OCH$_A$$H_B$Ph), 7.22–7.33 (15H, m, *Ph*).

Method B: *Step A*: A solution of **232** (15.0 g, 27.6 mmol, >95:5 dr) in THF (250 mL) was added to a stirred solution of NaH (60% in mineral oil, 2.21 g, 55.2 mmol) in THF (250 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 1 h. BnBr (6.56 mL, 55.2 mmol) was

added and the resultant mixture was allowed to warm to rt over 18 h then satd aq NH_4Cl (50 mL) and Et_2O (300 mL) were added. The resultant mixture was washed with brine (300 mL) and the aqueous layers were extracted with Et_2O (3 × 200 mL) then the combined organic layers were dried and concentrated *in vacuo*.

Step B: DIBAL-H (1 M in CH_2Cl_2, 110 mL, 110 mmol) was added to a stirred solution of the residue from the previous step in CH_2Cl_2 (500 mL) at –78 °C then stirred at rt for 2 h. Satd aq NH_4Cl (30 mL) and satd aq Rochelle salt (100 mL) were added at 0 °C and the resultant mixture was allowed to warm to rt over 18 h, then filtered through Celite® (eluent CH_2Cl_2), dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 15:1) gave **236** as a pale yellow viscous oil (13.4 g, 87%, >95:5 dr).

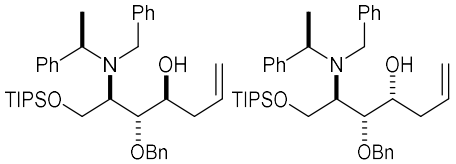
(*R*,*R*,*R*)-2-Benzyloxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino-4-(triisopropylsilyloxy)butanal 237



DMSO (0.70 mL, 9.9 mmol) was added to a stirred solution of $(COCl)_2$ (0.42 mL, 5.0 mmol) in CH_2Cl_2 (14 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then **236** (1.39 g, 2.48 mmol, >95:5 dr) in CH_2Cl_2 (14 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et_3N (2.07 mL, 14.9 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 20 min then at rt for 20 min. The organic layer was washed with H_2O (2 × 5 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 5 mL) then the combined organic layers were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 40:1) gave **237** as a pale yellow viscous oil (872 mg, 63%, >95:5 dr); $[\alpha]_D^{25}$ +30.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2866 (C–H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$)

1.01–1.10 (21H, m, Si(C*H*Me$_2$)$_3$), 1.38 (3H, d, *J* 7.0, C(α)*Me*), 3.46–3.52 (1H, m, C(3)*H*), 3.55 (1H, dd, *J* 4.2, 2.5, C(2)*H*), 3.77 (1H, d, *J* 14.7, NC*H*$_A$H$_B$Ph), 3.81–3.91 (2H, m, C(4)*H*$_A$, C(α)*H*), 4.06 (1H, dd, *J* 9.6, 7.6, C(4)*H*$_B$), 4.12 (1H, d, *J* 14.7, NCH$_A$*H*$_B$Ph), 4.34 (1H, d, *J* 11.3, OC*H*$_A$H$_B$Ph), 4.48 (1H, d, *J* 11.3, OCH$_A$*H*$_B$Ph), 7.20–7.38 (15H, m, *Ar*), 9.19 (1H, d, *J* 2.5, C*H*O); δ_C (100 MHz, $CDCl_3$) 11.9 (Si(*C*HMe$_2$)$_3$), 17.1 (C(α)*Me*), 18.0 (Si(CH*Me*$_2$)$_3$), 51.9 (N*C*H$_2$Ph), 57.1 (*C*(α)), 59.6 (*C*(3)), 62.0 (*C*(4)), 72.6 (O*C*H$_2$Ph), 83.2 (*C*(2)), 126.7, 127.1, 127.8, 128.1, 128.2, 128.2, 128.3, 128.3, 128.4 (*o*,*m*,*p*-*Ph*), 137.2, 141.2, 142.2 (*i*-*Ph*), 202.9 (*C*HO); *m/z* (ESI$^+$) 592 ([M+CH_5O]$^+$, 100%); HRMS (ESI$^+$) $C_{36}H_{54N}O_4Si^+$ ([M+CH_5O]$^+$) requires 592.3807; found 592.3817.

(2*R*,3*R*,4*S*,*αR*)-1-(Triisopropylsilyloxy)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-benzyloxyhept-6-en-4-ol 238 and (*R*,*R*,*R*,*R*)-1-(triisopropylsilyloxy)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-benzyloxyhept-6-en-4-ol 239



238 **239**

Method A: Step 1: DMSO (0.25 mL, 3.6 mmol) was added to a stirred solution of $(COCl)_2$ (0.15 mL, 1.8 mmol) in CH_2Cl_2 (3.5 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then **236** (500 mg, 0.890 mmol, >95:5 dr) in CH_2Cl_2 (3.5 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et_3N (0.74 mL, 5.3 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 20 min then at rt for 20 min. The organic layer was washed with H_2O (2 × 5 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 5 mL) then the combined organic layers were dried and concentrated *in vacuo* to give **237** as a pale yellow viscous oil.

Step 2: Allylmagnesium chloride (1.27 M in THF, 0.84 mL, 1.1 mmol) was added to the residue **237** from the previous step in THF (15 mL) at 0 °C and allowed to warm to rt over 18 h. The resultant mixture was cooled to 0 °C then satd aq NH_4Cl (1 mL) was added and

resultant mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc (10 mL) and H_2O (10 mL) and the aqueous layer was extracted with EtOAc (3 × 10 mL) then the combined organic layers were washed with brine (25 mL) then dried and concentrated *in vacuo* to give a 54:46 mixture of **238** and **239**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 25:1) gave a 54:46 mixture of **238** and **239**, respectively (429 mg, 80%, 54:46 dr); data for mixture: ν_{max} (ATR) 3398 (O–H), 1640 (C=C); *m/z* (ESI^+) 602 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{38}H_{56}O_3NSi^+$ ($[M+H]^+$) requires 602.4024; found 602.4012. Selected data for **238**: δ_H (400 MHz, $CDCl_3$) 1.05–1.20 (21H, m, Si(C*H*Me_2)$_3$), 1.44 (3H, d, *J* 6.5, C(α)*Me*), 1.85–2.00 (2H, m, C(5)H_2), 3.28 (1H, app q, *J* 6.0, C(2)*H*), 3.43 (1H, app t, *J* 5.4, C(3)*H*), 3.71–3.78 (1H, m, C(4)*H*), 4.61 (1H, d, *J* 11.2, OCH_AH_BPh), 4.92–5.06 (2H, m, C(7)H_2), 5.63–5.78 (1H, m, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 18.0 (C(α)*Me*), 37.5 (*C*(5)), 59.5 (*C*(2)), 71.9 (*C*(4)), 72.4 (O*C*H_2Ph), 81.7 (*C*(3)), 116.6 (*C*(7)), 135.9 (*C*(6)). Selected data for **239**: 1.05–1.20 (21H, m, Si(C*H*Me_2)$_3$), 1.47 (3H, d, *J* 6.5, C(α)*Me*), 1.73–1.83 (1H, m, C(5)H_A), 1.85–2.00 (1H, m, C(5)H_B), 3.31–3.39 (2H, m, C(2)*H*), C(3)*H*), 3.82–3.89 (1H, m, C(4)*H*), 4.45 (1H, d, *J* 11.4, O*C*H_AH_BPh), 4.52 (1H, d, *J* 11.4, OCH_AH_BPh), 4.92–5.06 (2H, m, C(7)H_2), 5.63–5.78 (1H, m, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 18.0 (C(α)*Me*), 38.1 (*C*(5)), 59.2 (*C*(2)), 71.4 (*C*(4)), 73.9 (O*C*H_2Ph), 80.4 (*C*(3)), 116.4 (*C*(7)), 136.0 (*C*(6)).

Method B: Step 1: DMSO (0.92 mL, 13 mmol) was added to a stirred solution of $(COCl)_2$ (0.55 mL, 6.6 mmol) in CH_2Cl_2 (12 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then **236** (1.85 g, 3.28 mmol, >95:5 dr) in CH_2Cl_2 (12 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et_3N (2.74 mL, 19.7 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 20 min then at rt for 20 min. The organic layer was washed with H_2O (2 × 15 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 15 mL) then the combined organic layers were dried and concentrated *in vacuo* to give **237** as a pale yellow viscous oil.

Step 2: Allylmagnesium chloride (1.27 M in THF, 3.10 mL, 3.94 mmol) was added to the residue **237** from the previous step in THF (55 mL) at –78 °C and allowed to warm to rt over 18 h. The resultant mixture was cooled to 0 °C then satd aq NH_4Cl (5 mL) was added and resultant mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc (25 mL) and H_2O (25 mL) and the aqueous layer was extracted with EtOAc (3 × 20 mL) then the combined organic layers were washed with brine (50 mL) then dried and concentrated *in vacuo* to give a 63:37 mixture of **238** and **239**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 25:1) gave a 63:37 mixture of **238** and **239**, respectively, as a colourless viscous oil (1.69 g, 85%, 63:37 dr).

Method C: Step 1: DMSO (0.10 mL, 1.4 mmol) was added to a stirred solution of $(COCl)_2$ (0.06 mL, 0.7 mmol) in CH_2Cl_2 (1.5 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then **236** (200 mg, 0.356 mmol, >95:5 dr) in CH_2Cl_2 (1.5 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et_3N (0.30 mL, 2.1 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 20 min then at rt for 20 min. The organic layer was washed with H_2O (2 × 5 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 5 mL) then the combined organic layers were dried and concentrated *in vacuo* to give **237** as a pale yellow viscous oil.

Step 2: Allylmagnesium bromide (0.6 M in Et_2O, 0.71 mL, 0.43 mmol) was added to the residue **237** in Et_2O (6 mL) at –78 °C and allowed to warm to rt over 18 h then cooled to 0 °C and satd aq NH_4Cl (1 mL) and H_2O (5 mL) were added. The aqueous layer was extracted with Et_2O (3 × 10 mL) then dried and concentrated *in vacuo* to give a 67:33 mixture of **238** and **239**, respectively.

Method D: Step 1: DMSO (0.10 mL, 1.4 mmol) was added to a stirred solution of $(COCl)_2$ (0.06 mL, 0.71 mmol) in CH_2Cl_2 (1.5 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then **236** (200 mg, 0.356 mmol, >95:5 dr) in CH_2Cl_2 (1.5 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et_3N

(0.30 mL, 2.1 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 20 min then at rt for 20 min. The organic layer was washed with H_2O (2 × 5 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 5 mL) then the combined organic layers were dried and concentrated *in vacuo* to give **237** as a pale yellow viscous oil.

Step 2: A solution of allyl bromide (0.15 mL, 1.8 mmol) and 1,2-dibromoethane (0.77 mL, 8.9 mmol) in Et_2O (5 mL) were added *via* a dropping funnel to a stirred solution of magnesium turnings (649 mg, 26.7 mmol) and I_2 (50 mg) in Et_2O (5 mL) at 35 °C. The resultant mixture was heated at 40 °C for 1 h. An aliquot (2.14 mL) was added to a stirred solution of the residue from the previous step in Et_2O (6 mL) at –78 °C and allowed to warm to rt over 18 h then satd aq NH_4Cl (1 mL) and H_2O (5 mL) were added. The aqueous layer was extracted with Et_2O (3 × 10 mL) then dried and concentrated *in vacuo* to give a 65:35 mixture of **238** and **239**, respectively.

Method E: Step 1: DMSO (0.05 mL, 0.7 mmol) was added to a stirred solution of $(COCl)_2$ (0.03 mL, 0.4 mmol) in CH_2Cl_2 (0.7 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then **236** (100 mg, 0.178 mmol, >95:5 dr) in CH_2Cl_2 (0.7 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et_3N (0.15 mL, 1.1 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 20 min then at rt for 20 min. The organic layer was washed with H_2O (2 × 15 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 15 mL) then the combined organic layers were dried and concentrated *in vacuo* to give **237** as a pale yellow viscous oil.

Step 2: Pinacol allylboronate (0.04 mL, 0.2 mmol) was added to a stirred solution of the residue from the previous step in CH_2Cl_2 (1 mL) at –78 °C and the resultant mixture was stirred for 1 h then warmed to rt. Triethanolamine (0.03 mL, 0.2 mmol) was added and the resultant mixture was stirred for 1 h, filtered through silica (eluent Et_2O) and concentrated *in vacuo* to give a complex mixture. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 25:1) gave **237** as a colourless viscous oil (20 mg,

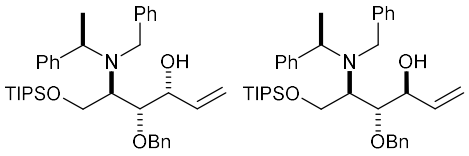
20%, >95:5 dr). Further elution gave a 69:31 mixture of **238** and **239**, respectively, as a colourless viscous oil (61 mg, 57%, 69:31 dr).

Method F: (–)-*B*-allyl-*B*-IPC borane (–)-**240** (1 M in pentane, 0.40 mL, 0.40 mmol) was added to a stirred solution of **237** in Et_2O (2 mL) at –78 °C and stirred at –78 °C for 2 h then 3.0 M aq NaOH (0.29 mL) and 30% aq H_2O_2 (0.30 mL) were added. The resultant mixture was allowed to warm to rt over 18 h then the aqueous layer was extracted with EtOAc (3 × 2 mL). The combined organic layers were washed with H_2O (5 mL) and brine (5 mL) then dried and concentrated *in vacuo* to give a complex mixture. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 25:1) gave a 88:12 mixture of **238** and **239** as a colourless viscous oil (156 mg, 97%, 88:12 dr).

Method G: Step 1: DMSO (0.10 mL, 1.4 mmol) was added to a stirred solution of $(COCl)_2$ (0.06 mL, 0.71 mmol) in CH_2Cl_2 (1 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then **236** (200 mg, 0.356 mmol, >95:5 dr) in CH_2Cl_2 (1 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et_3N (0.30 mL, 2.1 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 20 min then at rt for 20 min. The organic layer was washed with H_2O (2 × 2 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 3 mL) then the combined organic layers were dried and concentrated *in vacuo* to give **237** as a pale yellow viscous oil.

Step 2: (+)-*B*-allyl-*B*-IPC borane (+)-**240** (1 M in pentane, 0.53 mL, 0.53 mmol) was added to a stirred solution of **237** in Et_2O (2.6 mL) at –78 °C and stirred at –78 °C for 2 h then 3.0 M aq NaOH (0.40 mL) and 30% aq H_2O_2 (0.40 mL) were added and the resultant was allowed to warm to rt over 18 h. The aqueous layer was extracted with EtOAc (3 × 2 mL) then the combined organic layers were washed with H_2O (5 mL) then brine (5 mL) then dried and concentrated *in vacuo* to give a 23:77 mixture of **238** and **239**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 25:1) gave a 23:67 mixture of **238** and **239** as a colourless viscous oil (141 mg, 66%, 23:77 dr).

(*R*,*R*,*R*,*R*)-1-(Triisopropylsilyloxy)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-benzyloxyhex-5-en-4-ol 241 and (2*R*,3*R*,4*S*,*αR*)-1-(triisopropylsilyloxy)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-benzyloxyhex-5-en-4-ol 242

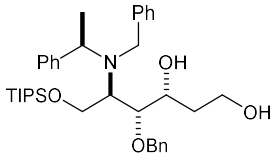


241 **242**

Vinylmagnesium bromide (1 M in THF, 0.54 mL, 0.54 mmol) was added to **237** (250 mg, 0.447 mmol, >95:5 dr) in THF (5 mL) at 0 °C and allowed to warm to rt over 18 h then cooled to 0 °C. Satd aq NH_4Cl (1 mL) was added and the resultant mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc (10 mL) and H_2O (10 mL) and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layers were washed with brine (25 mL) then dried and concentrated *in vacuo* to give a 70:30 mixture of **241** and **242**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 25:1) gave **241** as a colourless viscous oil (133 mg, 51%, >95:5 dr);[14] $[\alpha]_D^{25}$ +38.2 (*c* 1.0 in $CHCl_3$) {lit.[14] +36.5 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.06–1.15 (21H, m, Si(C*H*Me_2)$_3$), 1.39 (3H, d, *J* 6.8, C(α)*Me*), 3.18 (1H, d, *J* 6.9, O*H*), 3.22 (1H, dd, *J* 7.8, 2.4, C(3)*H*), 3.43 (1H, app dt, *J* 7.8, 4.8, C(2)*H*), 3.96 (2H, app s, NCH_2Ph), 4.02 (1H, dd, *J* 10.4, 7.8, C(1)H_A), 4.06–4.18 (2H, m, C(1)H_B, C(α)*H*), 4.29 (1H, d, *J* 11.3, OC$H_A$$H_B$Ph), 4.46 (1H, br s, C(4)*H*), 4.51 (1H, d, *J* 11.3, OC$H_A$$H_B$Ph), 5.03 (1H, app dt, *J* 10.5, 1.8, C(6)H_A), 5.23 (1H, app dt, *J* 17.2, 1.8, C(6)H_B), 5.58 (1H, ddd, *J* 17.2, 10.5, 4.7, C(5)*H*), 7.15–7.41 (15H, m, *Ph*). Further elution gave a 95:5 mixture of **242** and **241** as a colourless viscous oil (23 mg, 9%, 95:5 dr). Further elution gave **242** as a colourless viscous oil (29 mg, 11%, >95:5 dr);[14] $[\alpha]_D^{22}$ +1.6 (*c* 1.0 in $CHCl_3$) {lit.[14] +2.4 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.06–1.17 (21H, m, Si(C*H*Me_2)$_3$), 1.35 (3H, d, *J* 6.8, C(α)*Me*), 3.21–3.26 (1H, m, C(2)*H*), 3.53 (1H, app t, *J* 4.5, C(3)*H*), 3.90 (1H, d, *J* 14.3, NC$H_A$$H_B$Ph), 3.94 (1H, obscured dd, *J* 9.5, 5.6, C(1)H_A), 4.00 (1H, d, *J* 14.3, NC$H_A$$H_B$Ph), 4.07 (1H, q, *J* 6.8, C(α)*H*), 4.17 (1H,

dd, *J* 9.5, 7.2, C(1)H_B), 4.22–4.29 (1H, m, C(4)*H*), 4.39 (1H, d, *J* 11.2, OCH_AH$_B$Ph), 4.68 (1H, d, *J* 11.2, OCH$_A$$H_B$Ph), 4.96 (1H, app dt, *J* 10.4, 1.8, C(6)H_A), 5.03 (1H, d, *J* 5.2, O*H*), 5.19 (1H, app dt, *J* 17.1, 1.8, C(6)H_B), 5.49 (1H, ddd, *J* 17.1, 10.4, 5.2, C(5)*H*), 7.19–7.37 (15H, m, *Ph*).

(*R*,*R*,*R*,*R*)-1-(Triisopropylsilyoxy)-2-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-3-benzyloxyhexa-4,6-diol 243

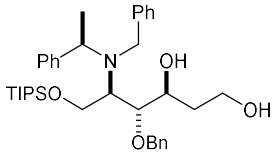


Method A:[15] BH_3·Me_2S (2 M in THF, 0.26 mL, 0.53 mmol) was added to a stirred solution of **241** (100 mg, 0.170 mmol, >95:5 dr) in THF (1.6 mL) at 0 °C and the resultant mixture was stirred at rt for 2 h then cooled to 0 °C. MeOH/THF (1:1 v/v, 1.8 mL), 3.0 M aq NaOH (1.73 mL) and 30% aq H_2O_2 (0.58 mL, 5.10 mmol) were added sequentially and the resultant mixture was left to stir at rt for 2 h. EtOAc (5 mL) and H_2O (5 mL) were added and the aqueous layer was extracted with EtOAc (3 × 5 mL) then the combined organic layers were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 15:1 increased to 2:1) gave an impure sample of **241** as colourless viscous oil (30 mg). Further elution gave **243** as a colourless viscous oil (36 mg, 35%, >95:5 dr); $[\alpha]_D^{25}$ +19.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3407 (O–H); δ_H (500 MHz, $CDCl_3$) 1.08–1.15 (21H, m, Si(C*HMe*$_2$)$_3$), 1.19–1.28 (2H, m, C(5)H_2), 1.48 (3H, d, *J* 6.9, C(α)*Me*), 2.63 (1H, br s, O*H*), 3.31–3.35 (2H, m, C(2)*H*, C(3)*H*), 3.50–3.65 (2H, m, C(6)H_2), 3.76 (1H, br s, O*H*), 3.97–4.16 (6H, m, C(1)H_2, C(4)*H*, NCH_2Ph, C(α)*H*), 4.46 (1H, d, *J* 11.4, OCH_AH$_B$Ph), 4.52 (1H, d, *J* 11.4, OCH$_A$$H_B$Ph), 7.21–7.35 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 17.5 (C(α)*Me*), 18.1 (Si(CH*Me*$_2$)$_3$), 34.7 (*C*(5)), 52.1 (N*C*H$_2$Ph), 58.7 (*C*(α)), 58.9 (*C*(2)), 62.1 (*C*(6)), 62.7 (*C*(1)), 72.0 (*C*(4)), 73.9 (O*C*H$_2$Ph), 80.3 (*C*(3)), 127.0, 127.0, 127.6, 128.0, 128.3, 128.4, 129.1 (*o*,*m*,*p*-*Ph*), 138.1, 140.7, 144.5 (*i*-*Ph*);

m/z (ESI$^+$) 606 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{37}H_{56}NO_4Si^+$ ([M+H]$^+$) requires 606.3973; found 606.3972.

Method B: $LiAlH_4$ (2.4 M in THF, 0.10 mL, 0.23 mmol) was added to a stirred solution of **256** (100 mg, 0.154 mmol, >95:5 dr) in THF at 0 °C and allowed to warm to rt over 18 h. 2.0 M aq NaOH (2 mL) was added and the resultant mixture was stirred at rt for 2 h then filtered and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 40–60 °C petroleum ether/EtOAc/35% aq NH_4OH, 66:33:1) gave **243** as a colourless viscous oil (61 mg, 65%, >95:5 dr).

(2*R*,3*R*,4*S*,*αR*)-1-(Triisopropylsilyoxy)-2-[*N*-Benzyl-*N*-(α-methylbenzyl)amino]-3-benzyloxyhexa-4,6-diol 244



Method A:[15] $BH_3{\cdot}Me_2S$ (2 M in THF, 0.46 mL, 0.92 mmol) was added to a stirred solution of **242** (175 mg, 0.298 mmol, >95:5 dr) in THF (2.8 mL) at 0 °C and the resultant mixture was stirred at rt for 2 h then cooled to 0 °C. MeOH/THF (1:1 v/v, 3.2 mL), 3.0 M aq NaOH (3.04 mL) and 30% aq H_2O_2 (1.01 mL, 10.2 mmol) were added sequentially and the resultant mixture was left to stir at rt for 2 h. EtOAc (5 mL) and H_2O (5 mL) were added and the aqueous layer was extracted with EtOAc (3 × 5 mL) then the combined organic layers were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc/35% aq NH_4OH, 75:25:1) gave **244** as colourless viscous oil (45 mg, 25%, >95:5 dr); $[\alpha]_D^{25}$ +12.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3377 (O–H); δ_H (400 MHz, $CDCl_3$) 1.06–1.19 (21H, m, Si(C*H*Me_2)$_3$), 1.30–1.41 (2H, m, C(5)H_2), 1.44 (3H, d, *J* 6.9, C(α)*Me*), 3.06 (1H, br s, O*H*), 3.29 (1H, app q, *J* 6.0, C(2)*H*), 3.39 (1H, app t, *J* 5.6, C(3)*H*), 3.63–3.68 (2H, m, C(6)H_2), 3.76–3.73 (1H, m, C(4)*H*), 4.00 (2H, app s, NCH_2Ph), 4.07 (1H, dd, *J* 10.0, 6.2, C(1)H_A), 4.14 (1H, q, *J* 6.9, C(α)*H*), 4.21 (1H, dd, *J* 10.0, 6.0,

C(1)H_B), 4.42 (1H, d, *J* 11.2, OC$H_A$$H_B$Ph), 4.60 (1H, d, *J* 11.2, OCH$_A$$H_B$Ph), 5.31 (1H, br s, O*H*), 7.21–7.36 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 17.5 (C(α)*Me*), 18.1 (Si(CH*Me*$_2$)$_3$), 34.3 (*C*(5)), 51.9 (N*C*H$_2$Ph), 58.7 (*C*(α)), 59.9 (*C*(2)), 62.0 (*C*(1)), 62.1 (*C*(6)), 72.5 (O*C*H$_2$Ph), 73.4 (*C*(4)), 81.6 (*C*(3)), 126.9, 127.0, 127.5, 127.6, 127.9, 128.2, 128.3, 129.0 (*o*,*m*,*p*-*Ph*), 138.1, 140.5, 144.4 (*i*-*Ph*); *m/z* (ESI^+) 606 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{37}H_{56}NO_4Si^+$ ($[M+H]^+$) requires 606.3973; found 606.3966.

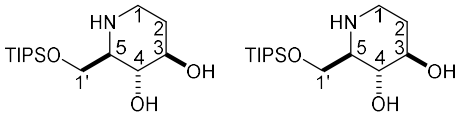
Method B: $LiAlH_4$ (2.4 M in THF, 0.10 mL, 0.231 mmol) was added to a stirred solution of **257** (100 mg, 0.154 mmol, >95:5 dr) in THF at 0 °C and allowed to warm to rt over 18 h. 2.0 M aq NaOH (2 mL) was added and the resultant mixture was stirred at rt for 2 h then filtered and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc/35% aq NH_4OH, 66:33:1) gave **244** as a colourless viscous oil (65 mg, 70%, >95:5 dr).

Method C: Step 1: OsO_4 (3 mg, 13 μmol) was added to a stirred solution of a 63:37 mixture of **238** and **239**, respectively (200 mg, 0.332 mmol, 63:37 dr), $NaIO_4$ (284 mg, 1.33 mmol) and 2,6-lutidine (0.08 mL, 0.7 mmol) in 1,4-dioxane/H_2O (3:1 v/v , 15 mL) at rt and stirred at rt for 1 h. Satd aq citric acid (5 mL) and CH_2Cl_2 (10 mL) were added and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with satd aq $NaHCO_3$ (10 mL) and brine (10 mL) then dried and concentrated *in vacuo*.

Step 2: $NaBH_4$ (25 mg, 0.664 mmol) was added to a stirred solution of the residue from the previous step in MeOH (5 mL) and the resultant mixture was stirred at rt for 30 min then concentrated *in vacuo*. The residue was partitioned between H_2O (5 mL) and CH_2Cl_2 (5 mL) and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with brine (10 mL) then dried and concentrated *in vacuo* to give a complex mixture. Purification *via* flash column chromatography (eluent 40–60 °C petroleum ether/EtOAc/35% aq NH_4OH, 66:33:1) gave a 63:37 mixture of **244** and **243**, respectively, as a colourless viscous oil (84 mg, 42%, 63:37 dr).

Method D: A 63:37 mixture of **238** and **239**, respectively (200 mg, 0.332 mmol, 63:37 dr) was coevaporated with HCl (2 M in Et_2O, 3 × 5 mL) then dissolved in CH_2Cl_2 (10 mL) and the solution was degassed with N_2. O_3 was bubbled through the solution at –78 ºC until a blue colouration was apparent then the reaction mixture was purged with O_2 until it became colourless. $NaBH_4$ (25 mg, 0.66 mmol) was added and the resultant mixture was stirred at rt for 18 h then H_2O (5 mL) was added. The aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL) then the combined organic layers were dried and concentrated *in vacuo* to give a complex mixture.

(3*S*,4*R*,5*R*)-3,4-Dihydroxy-5-(triisopropylsilyloxymethyl)piperidine 247 and (*R*,*R*,*R*)-3,4-dihydroxy-5-(triisopropylsilyloxymethyl)piperidine 248



247 **248**

Method A: Step 1: A 63:37 mixture of **238** and **239**, respectively, (200 mg, 0.332 mmol, 63:37 dr) was coevaporated with HCl (2 M in Et_2O, 3 × 5 mL) then dissolved in CH_2Cl_2 (10 mL) and the solution was degassed with N_2. O_3 was bubbled through the solution at –78 ºC until a blue colouration was apparent then the reaction mixture was purged with O_2 until it became colourless. Polymer-supported-PPh_3 (3 mmol/g, 332 mg, 0.996 mmol) was added and the resultant mixture was left to warm to rt over 2 h then filtered through Celite® (eluent CH_2Cl_2) and concentrated *in vacuo*.

Step 2: $Pd(OH)_2/C$ (40 mg, 20% w/w) was added to a vigorously stirred solution of the residue from the previous step in degassed MeOH (2 mL). The reaction mixture was stirred under H_2 (5 atm) for 18 h then filtered through Celite® and concentrated *in vacuo* to give a complex mixture.

Method B: Step 1: A 63:37 mixture of **238** and **239**, respectively, (200 mg, 0.332 mmol, 63:37 dr) was coevaporated with HCl (2 M in Et_2O, 3 × 5 mL) then dissolved in CH_2Cl_2

(10 mL) and the solution was degassed with N_2. O_3 was bubbled through the solution at –78 ºC until a blue colouration was apparent then the reaction mixture was purged with O_2 until it became colourless. PPh_3 (130 mg, 0.498 mmol) was added and the resultant mixture was left to warm to rt over 2 h then filtered through Celite® (eluent CH_2Cl_2) and concentrated *in vacuo*.

Step 2: $Pd(OH)_2/C$ (40 mg, 20% w/w) was added to a vigorously stirred solution of the residue from the previous step in degassed MeOH (2 mL). The reaction mixture was stirred under H_2 (5 atm) for 18 h then filtered through Celite® and concentrated *in vacuo* to give a complex mixture.

Method C: Step 1: OsO_4 (5 mg, 20 μmol) was added to a stirred solution of a 63:37 mixture of **238** and **239**, respectively, (300 mg, 0.498 mmol, 63:37 dr), $NaIO_4$ (426 mg, 1.99 mmol) and 2,6-lutidine (0.12 mL, 1.0 mmol) in 1,4-dioxane/H_2O (20 mL, 3:1 v/v) at rt and stirred at rt for 1 h. Satd aq citric acid (5 mL) and CH_2Cl_2 (10 mL) were added and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with satd aq $NaHCO_3$ (10 mL) and brine (10 mL) then dried and concentrated *in vacuo* to give an aldehydic species.

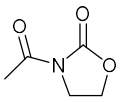
Step 2: $Pd(OH)_2/C$ (60 mg, 20% w/w) was added to a vigorously stirred solution of the residue from the previous step in degassed MeOH (3 mL). The reaction mixture was stirred under H_2 (5 atm) for 18 h then filtered through Celite® and concentrated *in vacuo* to give a complex mixture.

Method D: Step 1: OsO_4 (5 mg, 20 μmol) was added to a stirred solution of a 63:37 mixture of **238** and **239**, respectively, (300 mg, 0.498 mmol, 63:37 dr), $NaIO_4$ (426 mg, 1.99 mmol) and 2,6-lutidine (0.12 mL, 1.0 mmol) in 1,4-dioxane/H_2O (3:1 v/v, 20 mL) at rt and stirred at rt for 1 h. Satd aq citric acid (5 mL) and CH_2Cl_2 (10 mL) were added and the aqueous layer was extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were washed with satd aq

$NaHCO_3$ (10 mL) and brine (10 mL) then dried and concentrated *in vacuo* to give an aldehydic species.

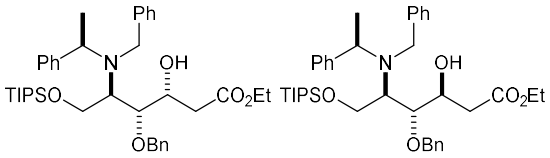
Step 2: $Pd(OH)_2/C$ (60 mg, 20% w/w) was added to a vigorously stirred solution of the residue from the previous step in degassed MeOH/AcOH (10:1 v/v, 3 mL). The reaction mixture was stirred under H_2 (5 atm) for 18 h then filtered through Celite® and concentrated *in vacuo* to give a complex mixture.

(*R*)-*N*(3)-Acetyloxazolidin-2-one 261



BuLi (2.2 M in hexanes, 31.5 mL, 69.3 mmol) was added to a stirred solution of **260** (5.03 g, 57.8 mmol) in THF (170 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 10 min. Ac_2O (8.20 mL, 86.7 mmol) was added at –78 °C and the resultant mixture was allowed at –78 °C for 30 min and at rt for 2 h then satd aq NH_4Cl (20 mL) and H_2O (20 mL) and the aqueous layer was extracted with EtOAc (3 × 80 mL). The combined organic layers were washed with brine (100 mL) then dried and concentrated *in vacuo*. Purification *via* recrystallisation (EtOAc/heptane) gave **261** as an orange solid (2.53 g, 34%);[16] mp 59–61 °C (lit.[17] mp 70 °C); δ_H (400 MHz, $CDCl_3$) 2.54 (3H, s, CO*Me*), 4.00–4.06 (2H, m, C(4)H_2), 4.40–4.46 (2H, m, C(5)H_2).

Ethyl (*R*,*R*,*R*,*R*)-3-hydroxy-4-benzyloxy-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6-(triisoproylsilyloxy)hexanoate 256 and ethyl (3*S*,4*R*,5*R*,α*R*)-3-hydroxy-4-benzyloxy-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6-(triisoproylsilyloxy)hexanoate 257



256 **257**

Method A: Step 1: DMSO (0.76 mL, 11 mmol) was added to a stirred solution of $(COCl)_2$ (0.45 mL, 5.3 mmol) in CH_2Cl_2 (15 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then **236** (1.50 g, 2.67 mmol, >95:5 dr) in CH_2Cl_2 (15 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et_3N (2.23 mL, 16.0 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 20 min then at rt for 20 min. The organic layer was washed with H_2O (2 × 15 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 15 mL) then the combined organic layers were dried and concentrated *in vacuo* to give **237** as a pale yellow viscous oil.

Step 2: BuLi (2.2 M in hexanes, 1.10 mL, 2.42 mmol) was added to a stirred solution of $^{i}Pr_2NH$ (0.34 mL, 2.4 mmol) in THF (5 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 20 min then EtOAc (0.24 mL, 2.4 mmol) was added at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of **237** in THF (10 mL) was added at –78 °C and the resultant mixture was allowed to stir at –78 °C for 1 h then at 0 °C for 2 h before satd aq NH_4Cl (2 mL) and Et_2O (10 mL) was added. The aqueous layer was extracted with Et_2O (3 × 10 mL) then the combined organic layers were washed with brine (25 mL) then dried and concentrated *in vacuo* to give a 32:48:20 mixture of **257**, **256** and **237**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 10:1) gave **257** as a pale yellow viscous oil (396 mg, 23% from **236**, >95:5 dr); $[\alpha]_D^{25}$ +8.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3519 (broad, O–H), 1731 (C=O); δ_H (500 MHz, $CDCl_3$) 1.08–1.20 (21H,

m, Si(C*H*Me$_2$)$_3$), 1.28 (3H, t, *J* 7.2, OCH$_2$*Me*), 1.48 (3H, d, *J* 6.9, C(α)*Me*), 1.79 (1H, dd, *J* 16.3, 3.6, C(2)H_A), 2.22 (1H, dd, *J* 16.3, 8.9, C(2)H_B), 3.04–3.08 (1H, m, C(5)*H*), 3.61 (1H, dd, *J* 7.2, 3.4, C(4)*H*), 3.99 (1H, d, *J* 14.1, NCH_AH$_B$Ph), 4.03 (1H, d, *J* 14.1, NCH$_A$$H_B$Ph), 4.06 (1H, dd, *J* 10.1, 6.6, C(6)H_A), 4.09–4.16 (3H, m, OCH_2Me, C(α)*H*), 4.18–4.23 (2H, m, C(6)H_B, O*H*), 4.28–4.33 (1H, m, C(3)*H*), 4.48 (1H, d, *J* 11.5, OCH_AH$_B$Ph), 4.76 (1H, d, *J* 11.5, OCH$_A$$H_B$Ph), 7.21–7.38 (15H, m, *Ph*); δ_C (125 MHz, CDCl$_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 14.1 (OCH$_2$*Me*), 17.1 (C(α)*Me*), 18.1 (Si(CH*Me*$_2$)$_3$), 36.4 (*C*(2)), 51.8 (N*C*H$_2$Ph), 57.7 (*C*(α)), 59.0 (*C*(5)), 60.3 (O*C*H$_2$Me), 62.5 (*C*(6)), 69.3 (*C*(3)), 73.0 (O*C*H$_2$Ph), 81.3 (*C*(4)), 126.7, 126.8, 127.3, 127.5, 127.9, 128.1, 128.2, 128.2, 129.0 (*o*,*m*,*p*-*Ph*), 138.5, 140.9, 144.6 (*i*-*Ph*), 173.0 (*C*(1)); *m/z* (ESI$^+$) 544 ([M+2H-αMeBn]$^+$, 9%), 648 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{39}H_{58}NO_5Si^+$ ([M+H]$^+$) requires 648.4079; found 648.4062. Further elution gave a 26:74 mixture of **257** and **256**, respectively, as a pale yellow viscous oil (318 mg, 18% (from **236**), 76:24 dr). Further elution gave **256** as a pale yellow viscous oil (422 mg, 24% (from **236**), >95:5 dr); $[\alpha]_D^{25}$ +13.1 (*c* 1.0 in CHCl$_3$); ν_{max} (ATR) 3505 (O–H), 1735 (C=O); δ_H (500 MHz, CDCl$_3$) 1.08–1.18 (21H, m, Si(C*H*Me$_2$)$_3$), 1.28 (3H, t, *J* 14.3, OCH$_2$*Me*), 1.50 (3H, d, *J* 6.9, C(α)*Me*), 1.89 (1H, dd, *J* 15.4, 9.5, C(2)H_A), 2.08 (1H, dd, *J* 15.4, 3.9, C(2)H_B), 3.36–3.43 (2H, m, C(4)*H*, C(5)*H*), 3.72 (1H, br s, O*H*), 4.01 (1H, d, *J* 14.3, NCH_AH$_B$Ph), 4.09 (1H, d, *J* 14.3, NCH$_A$$H_B$Ph), 4.10–4.18 (5H, m, C(6)H_2, C(α)*H*, OCH_2Me), 4.43 (1H, d, *J* 11.4, OCH$_A$$H_B$Ph), 4.46 (1H, br s, C(3)*H*), 4.51 (1H, d, *J* 11.4, OCH$_A$$H_B$Ph), 7.20–7.38 (15H, m, *Ph*); δ_C (125 MHz, CDCl$_3$) 12.1 (Si(*C*HMe$_2$)$_3$), 14.2 (OCH$_2$*Me*), 17.6 (C(α)*Me*), 18.2 (Si(CH*Me*$_2$)$_3$), 38.3 (*C*(2)), 52.2 (N*C*H$_2$Ph), 58.7 (*C*(5)), 59.0 (*C*(α)), 60.2 (O*C*H$_2$Me), 62.7 (*C*(6)), 68.4 (*C*(3)), 73.6 (O*C*H$_2$Ph), 78.9 (*C*(4)), 127.0, 127.1, 127.5, 127.6, 128.1, 128.2, 128.4, 128.4, 129.1 (*o*,*m*,*p*-*Ph*), 138.0, 140.7, 144.6 (*i*-*Ph*), 172.1 (*C*(1)); *m/z* (ESI$^+$) 544 ([M+2H-αMeBn]$^+$, 100%); HRMS (ESI$^+$) $C_{39}H_{58}NO_5Si^+$ ([M+H]$^+$) requires 648.4079; found 648.4070.

Method B: Step 1: DMSO (0.76 mL, 11 mmol) was added to a stirred solution of $(COCl)_2$ (0.45 mL, 5.3 mmol) in CH_2Cl_2 (15 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then **236** (1.50 g, 2.67 mmol, >95:5 dr) in CH_2Cl_2 (15 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et_3N (2.23 mL, 16.0 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 20 min then at rt for 20 min. The organic layer was washed with H_2O (2 × 15 mL) then the combined aqueous layers were extracted with CH_2Cl_2 (2 × 15 mL) then the combined organic layers were dried and concentrated *in vacuo* to give **237** as a pale yellow viscous oil.

Step 2: BuLi (2.2 M in hexanes, 1.70 mL, 3.74 mmol) was added to a stirred solution of $^{i}Pr_2NH$ (0.52 mL, 3.7 mmol) in THF (5 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 20 min then EtOAc (0.37 mL, 3.7 mmol) was added at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of the residue from the previous step in THF (10 mL) was added at –78 °C and the resultant mixture was allowed to stir at –78 °C for 1 h then at 0 °C for 2 h before satd aq NH_4Cl (2 mL) and Et_2O (10 mL) was added. The aqueous layer was extracted with Et_2O (3 × 10 mL) then the combined organic layers were washed with brine (25 mL) then dried and concentrated *in vacuo* to give a ~65:35 mixture of **256** and **257**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 10:1) gave **257** as a pale yellow viscous oil (566 mg, 33% from **236**, >95:5 dr). Further elution gave a 26:74 mixture of **257** and **256**, respectively, as a pale yellow viscous oil (210 mg, 12% (from **236**), 26:74 dr). Further elution gave **256** as a pale yellow viscous oil (675 mg, 39% (from **236**), >95:5 dr).

Method C: *Step 1*: DMSO (0.10 mL, 1.4 mmol) was added to a stirred solution of $(COCl)_2$ (0.06 mL, 0.7 mmol) in CH_2Cl_2 (2 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then **236** (200 mg, 0.356 mmol, >95:5 dr) in CH_2Cl_2 (2 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et_3N (0.30 mL, 2.14 mmol) was added and the resultant mixture was allowed to stir at –78 °C for

20 min then at rt for 20 min. The organic layer was washed with H_2O (2 × 5 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 5 mL) then the combined organic layers were dried and concentrated *in vacuo* to give **237** as a pale yellow viscous oil.

Step 2: Bu_2BOTf (1 M in CH_2Cl_2, 0.71 mL, 0.71 mmol) and Et_3N (0.11 mL, 0.819 mmol) were added to a mixture of EtOAc (0.05 mL, 0.5 mmol) and CH_2Cl_2 (2 mL) at –78 °C and stirred at –78 °C for 1 h. A solution of the residue from the previous step in CH_2Cl_2 (2 mL) was added at –78 °C and allowed to warm to rt over 18 h. Triethanolamine (0.14 mL) was added at rt and the resultant mixture was allowed to stir at rt for 1 h, then filtered through silica (eluent CH_2Cl_2) and concentrated *in vacuo* to give a complex mixture. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 10:1) gave **257** as a colourless viscous oil (46 mg, 20%, >95:5 dr). Further elution gave **256** as a colourless viscous oil (21 mg, 9%, >95:5 dr).

Method D: *Step 1*: IBX (150 mg, 0.534 mmol) was added to a stirred solution of **236** (200 mg, 0.356 mmol, >95:5 dr) in DMSO (2 mL) at rt and stirred at rt for 2 h. Et_2O (10 mL) and H_2O (10 mL) were added and the organic layer was washed with H_2O (5 × 10 mL) then dried and concentrated *in vacuo* to give **237** as a pale yellow viscous oil.

Step 2: Bu_2BOTf (1 M in CH_2Cl_2, 0.71 mL, 0.71 mmol) and Et_3N (0.11 mL, 0.82 mmol) were added to a stirred solution of **261** (69 mg, 0.53 mmol) in CH_2Cl_2 (1 mL) at –78 °C and stirred at –78 °C for 1 h. A solution of the residue from the previous step in CH_2Cl_2 (1 mL) was added at –78 °C and allowed to warm to rt over 18 h. Triethanolamine (0.14 mL, 1.07 mmol) was added at rt and the resultant mixture was allowed to stir at rt for 1 h, then filtered through silica (eluent CH_2Cl_2) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc/35% aq NH_4OH, 50:50:1) gave an ~81:19 mixture of **258** and **259** contaminated with **261** (117 mg).

Step 3: $Ti(OEt)_4$ (0.11 mL, 0.51 mmol) was added to a stirred solution of the residue from the previous step in EtOH (0.5 mL) and heated at 78 °C for 18 h then concentrated *in vacuo*. The

residue was dissolved in EtOAc/H_2O (10:1 v/v, 1.1 mL) and stirred at rt for 30 min then the resultant suspension was filtered, dried and concentrated *in vacuo* to a 81:19 mixture of **257** and **256**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 10:1) gave an 81:19 mixture of **257** and **256**, respectively, as a colourless viscous oil (73 mg, 31%, 81:19 dr).

Method E: $Ti(OEt)_4$ (0.06 mL, 0.3 mmol) was added to a stirred solution of **273** (78 mg, 0.10 mmol, >95:5 dr) in EtOH (0.5 mL) and heated at 78 °C for 18 h then concentrated *in vacuo*. The residue was dissolved in EtOAc/H_2O (10:1 v/v, 1.1 mL) and stirred at rt for 30 min then the resultant suspension was filtered, dried and concentrated *in vacuo* to give a >95:5 mixture of **257** and **256**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 10:1) gave **257** as a colourless viscous oil (52 mg, 80%, >95:5 dr).

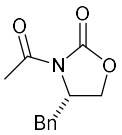
Method F: $Ti(OEt)_4$ (0.09 mL, 0.4 mmol) was added to a stirred solution of **268** (113 mg, 0.145 mmol, 88:12 dr) in EtOH (0.5 mL) and heated at 78 °C for 18 h then concentrated *in vacuo*. The residue was dissolved in EtOAc/H_2O (10:1 v/v, 1.1 mL) and stirred at rt for 30 min then the resultant suspension was filtered, dried and concentrated *in vacuo* to give an 88:12 mixture of **257** and **256**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 10:1) gave **257** as a colourless viscous oil (43 mg, 46%, >95:5 dr). Further elution gave a 67:33 mixture of **257** and **256**, respectively, as a colourless viscous oil (22 mg, 23%, 67:33 dr).

Method G: Imidazole (12 mg, 0.18 mmol) and EtOH (0.07 mL, 1 mmol) were added to a stirred solution of **273** (96 mg, 0.12 mmol, >95:5 dr) in CH_2Cl_2 (1.8 mL) at rt and stirred at rt for 72 h then concentrated *in vacuo* to give a >95:5 mixture of **256** and **257**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 7:2) gave **256** as a colourless viscous oil (65 mg, 84%, >95:5 dr).

Method H: Imidazole (26 mg, 0.38 mmol) and EtOH (0.15 mL, 2.6 mmol) were added to a stirred solution of **277** (208 mg, 0.256 mmol, >95:5 dr) in CH_2Cl_2 (4 mL) at rt and stirred at rt

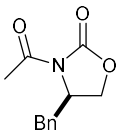
for 72 h then concentrated *in vacuo* to give a complex mixture containing a >95:5 mixture of **257** and **256**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 5:1) gave **257** as a colourless viscous oil (101 mg, 61%, >95:5 dr).

(*S*)-*N*(3)-Acetyl-4-benzyloxazolidin-2-one (*S*)-266



BuLi (2.2 M in hexanes, 15.4 mL, 33.8 mmol) was added to a stirred solution of (*S*)-**265** (5.00 g, 28.2 mmol) in THF (82 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 10 min. Ac_2O (4.00 mL, 42.3 mmol) was added at –78 °C and the resultant mixture was allowed to stir at –78 °C for 30 min and at rt for 2 h then satd aq NH_4Cl (10 mL) and H_2O (10 mL) were added and the aqueous layer was extracted with EtOAc (3 × 25 mL). The combined organic layers were washed with brine (100 mL) then dried and concentrated *in vacuo*. Purification *via* recrystallisation (EtOAc/heptane) gave (*S*)-**266** as a pale orange solid (5.19 g, 84%);[18] $[\alpha]_D^{25}$ +71.6 (*c* 1.0 in $CHCl_3$) {lit.[19] $[\alpha]_D^{rt}$ +63.0 (*c* 1.2 in $CHCl_3$)}; mp 105–106 °C (lit.[18] 109 °C); δ_H (400 MHz, $CDCl_3$) 2.57 (3H, s, CO*Me*), 2.79 (1H, dd, *J* 13.5, 9.6, C$H_A$$H_B$Ph), 3.32 (1H, dd, *J* 13.5, 3.2, CH$_A$$H_B$Ph), 4.16–4.25 (2H, m, C(5)H_2), 4.65–4.72 (1H, m, C(4)*H*), 7.20–7.38 (5H, m, *Ph*).

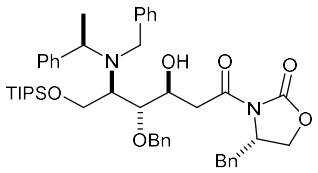
(*R*)-*N*(3)-Acetyl-4-benzyloxazolidin-2-one (*R*)-266



BuLi (2.2 M in hexanes, 15.4 mL, 33.8 mmol) was added to a stirred solution of (*R*)-**265** (5.00 g, 28.2 mmol) in THF (82 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 10 min. Ac_2O (4.00 mL, 42.3 mmol) was added at –78 °C and the resultant mixture was allowed to stir at –78 °C for 30 min and at rt for 2 h then satd aq NH_4Cl (10 mL) and H_2O (10 mL) were added and the aqueous layer was extracted with EtOAc (3 × 25 mL). The

combined organic layers were washed with brine (100 mL) then dried and concentrated *in vacuo*. Purification *via* recrystallisation (EtOAc/heptane) gave (*R*)-**266** as a white solid (4.93 g, 80%);[20] mp 106–108 °C (lit.[21] mp 101–102 °C); $[\alpha]_D^{rt}$ –68.9 (*c* 1.0 in $CHCl_3$) {lit.[19] for (*S*)-**266** $[\alpha]_D^{25}$ +63.0 (*c* 1.2 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 2.57 (3H, s, CO*Me*), 2.79 (1H, dd, *J* 13.5, 9.6, CH_AH$_B$Ph), 3.32 (1H, dd, *J* 13.5, 3.2, CH$_A$$H_B$Ph), 4.16–4.24 (2H, m, C(5)H_2), 4.65–4.72 (1H, m, C(4)*H*), 7.20–7.38 (5H, m, *Ph*).

(*S*)-4'-Benzyloxazolidin-2'-onyl (3*S*,4*R*,5*R*,α*R*)-3-hydroxy-4-benzyloxy-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6-(triisoproylsilyloxy)hexanamide 267

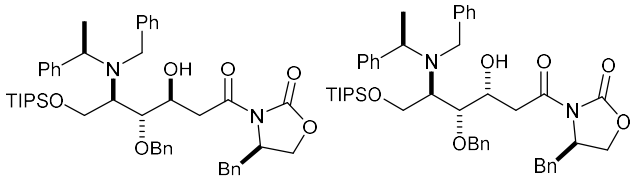


Step 1: IBX (150 mg, 0.534 mmol) was added to a stirred solution of **236** (200 mg, 0.356 mmol, >95:5 dr) in DMSO (2 mL) at rt and stirred at rt for 2 h. Et_2O (10 mL) and H_2O (10 mL) were added and the organic layer was washed with H_2O (5 × 10 mL) then dried and concentrated *in vacuo* to give **237** as a pale yellow viscous oil.

Step 2: Bu_2BOTf (1 M in CH_2Cl_2, 0.71 mL, 0.71 mmol) and Et_3N (0.11 mL, 0.82 mmol) were added to (*S*)-**266** (117 mg, 0.534 mmol) in CH_2Cl_2 (1 mL) at –78 °C and stirred at –78 °C for 1 h. A solution of the residue from the previous step in CH_2Cl_2 (1 mL) was added at –78 °C and allowed to warm to rt over 18 h. Triethanolamine (0.14 mL, 1.1 mmol) was added at rt and the resultant mixture was allowed to stir at rt for 1 h, then filtered through silica (eluent CH_2Cl_2) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 1:1) gave **237** as a pale yellow viscous oil (41 mg, 20%, >95:5 dr). Further elution gave **267** as a pale yellow viscous oil (77 mg, 28%, >95:5 dr); ν_{max} (ATR) 3470 (O–H), 1788 (C=O), 1688 (C=O); $[\alpha]_D^{25}$ +9.5 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.01–1.12 (21H, m, Si(C*HMe*$_2$)$_3$), 1.47 (3H, d, *J* 6.8, C(α)*Me*), 2.28 (1H, dd, *J* 17.5, 2.5, C(2)H_A), 2.71 (1H, dd, *J* 13.4, 9.7, C(4')CH_AH$_B$Ph), 2.84

(1H, dd, *J* 17.5, 9.6, C(2)H_B), 3.06–3.09 (1H, m, C(5)*H*), 3.29 (1H, dd, *J* 13.4, 3.2, C(4')CH_AH_BPh), 3.70 (1H, dd, *J* 7.7, 3.2, C(4)*H*), 3.97–4.25 (8H, m, C(6)H_2, C(5')H_2, C(α)*H*, NCH_2Ph, O*H*), 4.39–4.47 (1H, m, C(3)*H*), 4.52 (1H, d, *J* 11.6, OCH_AH_BPh), 4.56–4.65 (1H, m, C(4')*H*), 4.81 (1H, d, *J* 11.6, OCH_AH_BPh), 7.13–7.39 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe_2)$_3$), 16.3 (C(α)*Me*), 18.1 (Si(CH*Me*$_2$)$_3$), 37.7 (*C*(2)), 37.8 (C(4')*C*H_2Ph), 52.0 (NCH_2Ph), 55.0 (*C*(4')), 57.2 (*C*(α)), 58.6 (*C*(5)), 62.7 (*C*(6)), 66.0 (*C*(5')), 69.1 (*C*(3)), 73.0 (OCH_2Ph), 81.1 (*C*(4)), 126.4, 126.5, 127.2, 127.3, 127.4, 128.1, 128.2, 128.2, 128.9, 129.2, 129.4 (*o*,*m*,*p*-*Ph*), 135.3, 138.7, 141.1, 144.6 (*i*-*Ph*), 152.9 (*C*(2')), 172.7 (*C*(1)); *m/z* (ESI^+) 675 ($[M–C_8H_8]^+$, 23%), 779 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{47}H_{63}N_2O_6Si^+$ ($[M+H]^+$) requires 779.4450; found 779.4436.

(*R*)-4'-Benzyloxazolidin-2'-onyl (3*S*,4*R*,5*R*,α*R*)-3-hydroxy-4-benzyloxy-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6-(triisoproylsilyloxy)hexanamide 268 and (*R*)-4'-Benzyloxazolidin-2'-onyl (*R*,*R*,*R*,*R*)-3-hydroxy-4-benzyloxy-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6-(triisoproylsilyloxy)hexanamide 269

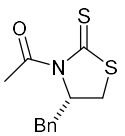


268 **269**

Step 1: DMSO (0.10 mL, 1.4 mmol) was added to a stirred solution of $(COCl)_2$ (0.06 mL, 0.7 mmol) in CH_2Cl_2 (2 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then **236** (200 mg, 0.356 mmol, >95:5 dr) in CH_2Cl_2 (2 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et_3N (0.30 mL, 2.1 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 20 min then at rt for 20 min. The organic layer was washed with H_2O (2 × 15 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 15 mL) then the combined organic layers were dried and concentrated *in vacuo* to give **237** as a pale yellow viscous oil.

Step 2: Bu_2BOTf (1 M in CH_2Cl_2, 0.62 mL, 0.62 mmol) and Et_3N (0.10 mL, 0.71 mmol) were added to (*R*)-**266** (102 mg, 0.464 mmol) in CH_2Cl_2 (2 mL) at –78 °C and stirred at –78 °C for 1 h. A solution of **237** in CH_2Cl_2 (2 mL) was added at –78 °C and allowed to warm to rt over 18 h. Triethanolamine (0.12 mL) was added at rt and the resultant mixture was allowed to stir at rt for 1 h, then filtered through silica (eluent CH_2Cl_2) and concentrated *in vacuo* to give a complex mixture. Purification *via* flash column chromatography (eluent 40–60 °C petroleum ether/Et_2O/35% aq NH_4OH, 33:66:1) gave an 88:12 mixture of **268** and **269**, respectively, as pale yellow viscous oil (139 mg, 58%, 88:12 dr). Data for mixture: ν_{max} (ATR) 3546 (O–H), 1785 (C=O), 1696 (C=O); *m/z* (ESI^+) 779 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{47}H_{63}N_2O_6Si^+$ ($[M+H]^+$) requires 779.4450; found 779.4434. Data for **268**: δ_H (400 MHz, $CDCl_3$) 1.03–1.23 (21H, m, Si(C*H*Me_2)$_3$), 1.50 (3H, d, *J* 7.0, C(α)*Me*), 2.38 (1H, dd, *J* 16.8, 3.0, C(2)H_A), 2.70 (1H, dd, *J* 13.2, 10.1, C(4')C$H_A$$H_B$Ph), 2.96 (1H, dd, *J* 16.8, 8.7, C(2)H_B), 3.19–3.26 (1H, m, C(5)*H*), 3.35 (1H, qd, *J* 13.7, 3.2, C(4')C$H_A$$H_B$Ph), 3.62 (1H, dd, *J* 7.4, 3.7, C(4)*H*), 3.99–4.21 (6H, m, C(6)H_A, C(5')H_2, C(α)*H*, NCH_2Ph), 4.25 (1H, dd, *J* 10.2, 4.9, C(6)H_B), 4.38–4.54 (3H, m, C(3)*H*, C(4')*H*, OC$H_A$$H_B$Ph), 4.71 (1H, d, *J* 11.4, OC$H_A$$H_B$Ph), 7.20–7.42 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe_2)$_3$), 17.1 (C(α)*Me*), 18.1 (Si(CH*Me*$_2$)$_3$), 37.2 (*C*(2)), 37.9 (C(4')*C*H_2Ph), 52.0 (N*C*H_2Ph), 55.0 (*C*(4')), 58.1 (*C*(α)), 58.9 (*C*(5)), 62.6 (*C*(6)), 66.0 (*C*(5')), 69.6 (*C*(3)), 73.2 (O*C*H_2Ph), 81.5 (*C*(4)), 126.7, 127.2, 127.3, 127.6, 128.0, 128.1, 128.2, 128.3, 128.9, 129.1, 129.4 (*o*,*m*,*p*-*Ph*), 135.4, 138.5, 141.0, 144.6 (*i*-*Ph*), 153.0 (*C*(2')), 172.7 (*C*(1)). Selected data for **269**: δ_H (400 MHz, $CDCl_3$) 1.55 (3H, d, *J* 7.2, C(α)*Me*).

(*S*)-*N*(3)-Acetyl-4-benzylthiazolidin-2-thione (*S*)-272

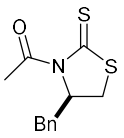


Step 1: CS_2 (9.94 mL, 165 mmol) was added to a stirred solution of L-phenylalaninol (*S*)-**270** (5.00 g, 165 mmol) in 1 M aq KOH (165 mL) and the resultant mixture was heated at 100 °C

for 18 h then cooled to rt and the aqueous layer extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried and concentrated *in vacuo*.

Step 2: BuLi (2.2 M in hexanes, 18.0 mL, 39.7 mmol) was added to a stirred solution of the residue from the previous step in THF (75 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 30 min. AcCl (3.53 mL, 49.7 mmol) was added at 0 °C and the resultant mixture was allowed to stir at 0 °C for 1 h then satd aq NH_4Cl (20 mL) was added and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 20:1) gave (*S*)-**272** as a yellow solid;[22] mp 109–111 °C (lit.[22] mp 111–115 °C); $[\alpha]_D^{25}$ +224 (*c* 1.0 in $CHCl_3$) {lit.[23] $[\alpha]_D^{20}$ +211 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 2.81 (3H, s, CO*Me*), 2.90 (1H, d, *J* 11.5, C(5)H_A), 3.05 (1H, dd, *J* 13.2, 10.5, CH_AH$_B$Ph), 3.23 (1H, dd, *J* 13.2, 3.7, CH$_A$$H_B$Ph), 3.39 (1H, ddd, *J* 11.5, 7.3, 1.0, C(5)H_B), 5.35–5.43 (1H, m, C(4)*H*), 7.26–7.38 (5H, m, *Ph*).

(*R*)-*N*(3)-Acetyl-4-benzylthiazolidin-2-thione (*R*)-272

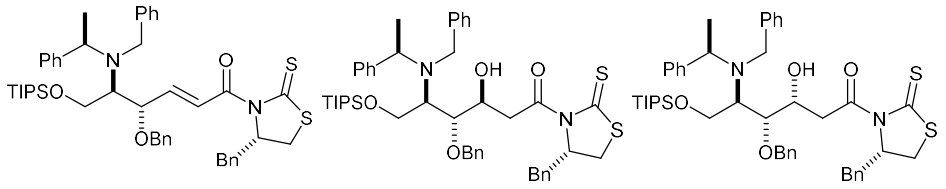


Step 1: CS_2 (9.94 mL, 165 mmol) was added to a stirred solution of L-phenylalaninol (*R*)-**270** (5.00 g, 165 mmol) in 1 M aq KOH (165 mL) and the resultant mixture was heated at 100 °C for 18 h then cooled to rt and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic layers were dried and concentrated *in vacuo*.

Step 2: BuLi (2.2 M in hexanes, 18.0 mL, 39.7 mmol) was added to a stirred solution of the residue from the previous step in THF (75 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 30 min. AcCl (3.53 mL, 49.7 mmol) was added at 0 °C and the resultant mixture was allowed to stir at 0 °C for 1 h then satd aq NH_4Cl (20 mL) was added and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic layers were washed with H_2O (50 mL) and brine (50 mL) then dried and concentrated *in vacuo*. Purification *via* flash column

chromatography (eluent 30–40 °C petroleum ether/Et_2O, 7:1) gave (*S*)-**272** as a yellow solid (6.10 g, 73%);[22] mp 104–105 °C (lit.[22] mp 87–89 °C); $[\alpha]_D^{25}$ –192 (*c* 1.0 in $CHCl_3$) {lit.[24] $[\alpha]_D^{25}$ –210 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 2.81 (3H, s, CO*Me*), 2.90 (1H, d, *J* 11.5, C(5)H_A), 3.05 (1H, dd, *J* 13.2, 10.5, CH_AH$_B$Ph), 3.23 (1H, dd, *J* 13.2, 3.7, CH$_A$$H_B$Ph), 3.39 (1H, ddd, *J* 11.5, 7.3, 1.0, C(5)H_B), 5.35–5.43 (1H, m, C(4)*H*), 7.26–7.38 (5H, m, *Ph*).

(*S*)-4'-Benzylthiazolidithi-2'-onyl (4*R*,5*R*,α*R*,*E*)-4-benzyloxy-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6-(triisoproylsilyloxy)hex-2-enamide 275, (*S*)-4'-benzylthiazolidithi-2'-onyl (3*S*,4*R*,5*R*,α*R*)-3-hydroxy-4-benzyloxy-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6-(triisoproylsilyloxy)hexanamide 274 and (*S*)-4'-benzylthiazolidithi-2'-onyl (3*R*,4*R*,5*R*,α*R*)-3-hydroxy-4-benzyloxy-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6-(triisoproylsilyloxy)hexanamide 273



275 274 273

Method A: Step 1: IBX (150 mg, 0.534 mmol) was added to a stirred solution of **236** (200 mg, 0.356 mmol, >95:5 dr) in DMSO (2 mL) at rt and stirred at rt for 2 h. Et_2O (10 mL) and H_2O (10 mL) were added and the organic layer was washed with H_2O (5 × 10 mL) then dried and concentrated *in vacuo* to give **237** as a pale yellow viscous oil.

Step 2: $TiCl_4$ (1 M in CH_2Cl_2, 0.36 mL, 0.36 mmol) was added to (*S*)-**272** (90 mg, 0.36 mmol) in CH_2Cl_2 (4 mL) at 0 °C and stirred at 0 °C for 5 min and the resultant mixture was cooled to –40 °C. A solution of (–)-sparteine (0.08 mL, 0.4 mmol) in CH_2Cl_2 (1 mL) was added and the resultant mixture was stirred at –78 °C for 35 min. A solution of the residue from the previous step in CH_2Cl_2 (1 mL) was added and the resultant mixture was stirred at –78 °C for 1 h then half satd aq NH_4Cl (2 mL) and CH_2Cl_2 (5 mL) were added and the resultant mixture was allowed to warm to rt. The organic layer was washed with half satd aq

NH_4Cl (3 × 3 mL), the combined aqueous layers were extracted with CH_2Cl_2 (3 × 5 mL) then the combined organic layer were dried with Na_2SO_4 and concentrated *in vacuo* to give a mixture of (*S*)-**272** and **237**.

Method B: Step 1: IBX (150 mg, 0.534 mmol) was added to a stirred solution of **236** (200 mg, 0.356 mmol, >95:5 dr) in DMSO (2 mL) at rt and stirred at rt for 2 h. Et_2O (10 mL) and H_2O (10 mL) were added and the organic layer was washed with H_2O (5 × 10 mL) then dried and concentrated *in vacuo* to give **237** as a pale yellow viscous oil.

Step 2: $TiCl_4$ (1 M in CH_2Cl_2, 0.36 mL, 0.36 mmol) was added to (*S*)-**272** (90 mg, 0.36 mmol) in CH_2Cl_2 (4 mL) at 0 °C and stirred at 0 °C for 5 min and the resultant mixture was cooled to –40 °C. A solution of (–)-sparteine (0.08 mL, 0.4 mmol) in CH_2Cl_2 (1 mL) was added and the resultant mixture was stirred at –78 °C for 35 min then warmed to –20 °C. A solution of the residue from the previous step in CH_2Cl_2 (1 mL) was added and the resultant mixture was stirred at –20 °C for 1 h then half satd aq NH_4Cl (2 mL) and CH_2Cl_2 (5 mL) were added then left to warm to rt. The organic layer was washed with half satd aq NH_4Cl (3 × 3 mL) then the combined aqueous layers were extracted with CH_2Cl_2 (3 × 5 mL) and the combined organic layer were dried with Na_2SO_4 and concentrated *in vacuo* to give a complex mixture. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 6:1 increased to 3:1) to give **237** as a colourless viscous oil (22 mg, 11%, >95:5 dr). Further elution gave **275** as a yellow viscous oil (33 mg, 12%, >95:5 dr); $[\alpha]_D^{25}$ +54.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1680 (C=O), 1632 (C=C); δ_H (400 MHz, $CDCl_3$) 1.02–1.15 (21H, m, Si(C*HMe*$_2$)$_3$), 1.39 (3H, d, *J* 6.9, C(α)*Me*), 2.96 (1H, d, *J* 11.4, C(5')H_A), 3.09 (1H, dd *J* 13.1, 10.8, C(4')CH_AH$_B$Ph), 3.18–3.24 (1H, m, C(5)*H*), 3.35–3.44 (2H, m, C(5')H_B, C(4')CH$_A$$H_B$Ph), 3.83 (1H, d, *J* 14.9, NCH_AH$_B$Ph), 3.86–3.90 (1H, m, C(4)*H*), 3.91–4.06 (3H, m, C(6)H_2, C(α)*H*), 4.13–4.22 (2H, m, NCH$_A$$H_BPh, OCH_AH_B$Ph), 4.53 (1H, d, *J* 11.4, OCH$_A$$H_B$Ph), 5.14–5.22 (1H, m, C(4')*H*), 6.97 (1H, dd, *J* 15.4, 5.5, C(3)*H*), 7.20–7.48 (21H, m, C(2)*H*, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 18.1 (Si(CH*Me*$_2$)$_3$), 18.2 (C(α)*Me*),

32.7 (*C*(5')), 36.6 (C(4')*C*H$_2$Ph), 51.7 (N*C*H$_2$Ph), 57.8 (*C*(α)), 61.7 (*C*(6)), 62.0 (*C*(5)), 68.8 (*C*(4')), 71.7 (O*C*H$_2$Ph), 79.4 (*C*(4)), 122.3 (*C*(2)), 126.5, 126.8, 127.2, 127.5, 127.9, 128.1, 128.1, 128.2, 128.2, 128.4, 128.9, 129.5 (*o*,*m*,*p-Ph*), 136.6, 137.9, 141.9, 143.9 (*i-Ph*), 148.8 (*C*(3)), 165.8 (*C*(1)), 200.6 (*C*(2')); *m/z* (ESI$^+$) 793 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{47}H_{61}N_2O_3S_2Si^+$ ([M+H]$^+$) requires 793.3887; found 793.3884. Further elution gave (*S*)-**272** as a yellow solid (15 mg). Further elution gave a 50:50 mixture of **274** and (*S*)-**272** as a yellow solid (38 mg). Further elution gave an impure sample of **274** as a yellow viscous oil (19 mg). Further elution gave an impure sample of **273** as yellow viscous oil (94 mg).

Method C: Step 1: IBX (150 mg, 0.534 mmol) was added to a stirred solution of **236** (200 mg, 0.356 mmol, >95:5 dr) in DMSO (2 mL) at rt and stirred at rt for 2 h. Et$_2$O (10 mL) and H$_2$O (10 mL) were added and the organic layer was washed with H$_2$O (5 × 10 mL) then dried and concentrated *in vacuo*.

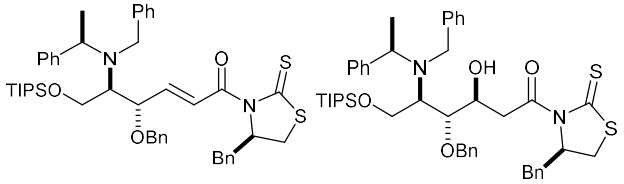
Step 2: TiCl$_4$ (1 M in CH$_2$Cl$_2$, 0.36 mL, 0.36 mmol) was added to (*S*)-**272** (90 mg, 0.36 mmol) in CH$_2$Cl$_2$ (4 mL) at 0 °C and stirred at 0 °C for 5 min and the resultant mixture was cooled to –40 °C. A solution of (–)-sparteine (0.08 mL, 0.4 mmol) in CH$_2$Cl$_2$ (1 mL) was added and the resultant mixture was stirred at –78 °C for 35 min. A solution of the residue from the previous step in CH$_2$Cl$_2$ (1 mL) was added and the resultant mixture was stirred at –20 °C for 3.5 h then ½ satd aq NH$_4$Cl (2 mL) and CH$_2$Cl$_2$ (5 mL) were added then left to warm to rt. The organic layer was washed with ½ satd aq NH$_4$Cl (3 × 3 mL) then the combined aqueous layers were extracted with CH$_2$Cl$_2$ (3 × 5 mL) and the combined organic layer were dried with Na$_2$SO$_4$ and concentrated *in vacuo* to give a 17:33:50 mixture of **275**, **274** and **273**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et$_2$O, 6:1 increased to 2:1) to give **273** as a yellow viscous oil (18 mg, 6%, >95:5 dr). Further elution gave (*S*)-**272** as a yellow solid (14 mg). Further elution gave **274** as yellow viscous oil (42 mg, 15%, >95:5 dr); $[\alpha]_D^{25}$ +33.5 (*c* 1.0 in CHCl$_3$); ν_{max} (ATR) 3562 (O–H), 1679 (C=O), 1494 (C=S); δ_H (400 MHz, CDCl$_3$) 1.05–1.15 (21H, m,

Si(C*H*Me$_2$)$_3$), 1.47 (3H, d, *J* 6.9, C(α)*Me*), 2.55 (1H, dd, *J* 17.8, 2.3, C(2)H_A), 2.90 (1H, d, *J* 11.6, C(5')H_A), 2.95–3.04 (2H, m, C(5)*H*, C(4')CH_AH$_B$Ph), 3.19 (1H, dd, *J* 13.5, 3.8, C(4')CH$_A$$H_B$Ph), 3.25 (1H, dd, *J* 17.8, 5.7, C(2)H_B), 3.38 (1H, dd, *J* 11.6, 7.1, C(5')H_B), 3.70 (1H, dd, *J* 7.8, 3.0, C(4)*H*), 3.99–4.13 (5H, m, C(6)H_A, C(α)*H*, NCH_2Ph, O*H*), 4.20 (1H, dd, *J* 10.3, 4.4, C(6)H_B), 4.34–4.41 (1H, m, C(3)*H*), 4.50 (1H, d, *J* 11.7, OCH_AH$_B$Ph), 4.83 (1H, d, *J* 11.7, OCH$_A$$H_B$Ph), 5.32–5.40 (1H, m, C(4')*H*), 7.14–7.40 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.1 (Si(*C*HMe$_2$)$_3$), 16.2 (C(α)*Me*), 18.2 (Si(CH*Me*$_2$)$_3$), 31.7 (*C*(5')), 36.9 (C(4')*C*H$_2$Ph), 40.8 (*C*(2)), 51.9 (N*C*H$_2$Ph), 57.0 (*C*(α)), 58.7 (*C*(5)), 62.7 (*C*(6)), 68.2 (*C*(4')), 69.4 (*C*(3)), 73.1 (O*C*H$_2$Ph), 81.1 (*C*(4)), 126.6, 127.2, 127.4, 128.1, 128.1, 128.2, 128.9, 129.2, 129.5 (*o*,*m*,*p*-*Ph*), 136.6, 138.8, 141.2, 144.6 (*i*-*Ph*), 173.6 (*C*(1)), 200.5 (*C*(2')); *m/z* (ESI$^+$) 811 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{47}H_{63}N_2O_4S_2Si^+$ ([M+H]$^+$) requires 811.3993; found 811.3986. Further elution gave **273** as yellow viscous oil (100 mg, 35%, >95:5 dr); $[\alpha]_D^{25}$ +81.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3560 (O–H), 1698 (C=O); δ_H (400 MHz, $CDCl_3$) 1.10–1.17 (21H, m, Si(C*H*Me$_2$)$_3$), 1.52 (3H, d, *J* 6.9, C(α)*Me*), 2.83–2.91 (2H, m, C(2)H_A, C(5')H_A), 3.05 (1H, dd, *J* 13.8, 10.2, C(4')CH_AH$_B$Ph), 3.16 (1H, dd, *J* 17.4, 2.2, C(2)H_B), 3.28 (1H, dd, *J* 13.3, 3.5, C(4')CH$_A$$H_B$Ph), 3.33 (1H, dd, *J* 11.5, 7.2, C(5')H_B), 3.44–3.47 (2H, m, C(4)*H*, C(5)*H*), 4.03 (1H, d, *J* 14.0, NCH_AH$_B$Ph), 4.11 (1H, d, *J* 14.0, NCH$_A$$H_B$Ph), 4.14–4.24 (3H, m, C(6)H_2, C(α)*H*), 4.43 (1H, d, *J* 11.4, OCH_AH$_B$Ph), 4.56 (1H, d, *J* 11.4, OCH$_A$$H_B$Ph), 4.66 (1H, d, *J* 10.0, C(3)*H*), 5.31–5.38 (1H, m, C(4')*H*), 7.22–7.42 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.1 (Si(*C*HMe$_2$)$_3$), 17.6 (C(α)*Me*), 18.2 (Si(CH*Me*$_2$)$_3$), 31.9 (*C*(5')), 36.5 (C(4')*C*H$_2$Ph), 42.6 (*C*(2)), 52.2 (N*C*H$_2$Ph), 58.9 (*C*(5)), 58.9 (*C*(α)), 62.7 (*C*(6)), 67.6 (*C*(3)), 68.7 (*C*(4')), 73.5 (O*C*H$_2$Ph), 78.7 (*C*(4)), 126.8, 126.9, 127.1, 127.5, 127.7, 128.1, 128.2, 128.4, 128.5, 129.2, 129.4 (*o*,*m*,*p*-*Ph*), 136.7, 138.0, 140.5, 144.5 (*i*-*Ph*), 172.2 (*C*(1)), 200.7 (*C*(2')); *m/z* (ESI$^+$) 811 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{47}H_{63}N_2O_4S_2Si^+$ ([M+H]$^+$) requires 811.3993; found 811.3977.

Method D: Step 1: IBX (319 mg, 1.14 mmol) was added to a stirred solution of **236** (427 mg, 0.759 mmol, >95:5 dr) in DMSO (3 mL) at rt and stirred at rt for 2 h. Et_2O (10 mL) and H_2O (10 mL) were added and the organic layer was washed with H_2O (5 × 10 mL) then dried and concentrated *in vacuo* to give **237** as a pale yellow viscous oil.

Step 2: $TiCl_4$ (1 M in CH_2Cl_2, 0.76 mL, 0.76 mmol) was added to (*S*)-**272** (191 mg, 0.759 mmol) in CH_2Cl_2 (8.2 mL) at 0 °C and stirred at 0 °C for 5 min and the resultant mixture was cooled to –40 °C. A solution of (–)-sparteine (0.35 mL, 1.5 mmol) in CH_2Cl_2 (2.1 mL) was added and the resultant mixture was stirred at –78 °C for 35 min. A solution of the residue from the previous step in CH_2Cl_2 (2.1 mL) was added and the resultant mixture was stirred at –20 °C for 3.5 h then half satd aq NH_4Cl (4 mL) and CH_2Cl_2 (10 mL) were added then left to warm to rt. The organic layer was washed with half satd aq NH_4Cl (3 × 5 mL) then the combined aqueous layers were extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic layer were dried with Na_2SO_4 and concentrated *in vacuo* to give a 54:22:24 mixture of **275**, **274** and **273**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 6:1 increased to 2:1) gave **275** as a yellow viscous oil (193 mg, 32%, >95:5 dr). Further elution gave **274** as a yellow viscous oil (84 mg, 14%, >95:5 dr). Further elution gave **273** as a yellow viscous oil (100 mg, 16%, >95:5 dr).

(*R*)-4'-Benzylthiazolidithi-2'-onyl (4*R*,5*R*,α*R*,*E*)-4-benzyloxy-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6-(triisoproylsilyloxy)hex-2-enamide 276, (*R*)-4'-benzylthiazolidithi-2'-onyl (3*S*,4*R*,5*R*,α*R*)-3-hydroxy-4-benzyloxy-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6-(triisoproylsilyloxy)hexanamide 277



276 **277**

Method A: Step 1: IBX (150 mg, 0.534 mmol) was added to a stirred solution of **236** (200 mg, 0.356 mmol, >95:5 dr) in DMSO (2 mL) at rt and stirred at rt for 2 h. Et_2O (10 mL) and H_2O (10 mL) were added and the organic layer was washed with H_2O (5 × 10 mL) then dried and concentrated *in vacuo* to give **237** as a pale yellow viscous oil.

Step 2: $TiCl_4$ (1 M in CH_2Cl_2, 0.36 mL, 0.36 mmol) was added to (*R*)-**272** (90 mg, 0.36 mmol) in CH_2Cl_2 (4 mL) at 0 °C and stirred at 0 °C for 5 min and the resultant mixture was cooled to –40 °C. A solution of (–)-sparteine (0.08 mL, 0.4 mmol) in CH_2Cl_2 (1 mL) was added and the resultant mixture was stirred at –78 °C for 35 min. A solution of the residue from the previous step in CH_2Cl_2 (1 mL) was added at –20 °C and the resultant mixture was stirred at –20 °C for 3.5 h then half satd aq NH_4Cl (2 mL) and CH_2Cl_2 (5 mL) were added and the organic layer was washed with half satd aq NH_4Cl (3 × 3 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 × 5 mL) then the combined organic layer were dried with Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 6:1 increased to 2:1) gave **276** as a yellow viscous oil (39 mg, 14%, >95:5 dr); $[\alpha]_D^{25}$ +6.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1681 (C=O), 1632 (C=C), 1494 (C=S); δ_H (400 MHz, $CDCl_3$) 1.05–1.16 (21H, m, Si(C*HMe*$_2$)$_3$), 1.39 (1H, d, *J* 6.9, C(α)*Me*), 2.97 (1H, d, *J* 11.5, C(5')H_A), 3.08 (1H, dd, *J* 13.1, 10.8, C(4')CH_AH$_B$Ph), 3.13–3.19

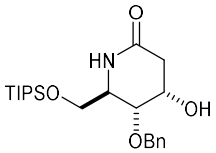
(1H, m, C(5)*H*), 3.38 (1H, obsc dd, *J* 13.1, 10.8, C(4')CH$_A$*H*$_B$Ph), 3.42 (1H, obsc dd, *J* 11.5, 7.1, C(5')H$_B$), 3.80 (1H, d, *J* 14.9, NC*H*$_A$H$_B$Ph), 3.84–3.89 (1H, m, C(4)*H*), 3.95–4.08 (3H, m, C(6)*H*$_2$, C(α)*H*), 4.15–4.22 (2H, m, NCH$_A$*H*$_B$Ph, OC*H*$_A$H$_B$Ph), 4.49 (1H, d *J* 11.6, OCH$_A$*H*$_B$Ph), 5.17–5.27 (1H, m, C(4')*H*), 6.85 (1H, dd, *J* 15.3, 5.8, C(3)*H*), 7.10 (1H, d, *J* 15.3, C(2)*H*), 7.20–7.48 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$)12.0 (Si(*C*HMe$_2$)$_3$), 18.2 (Si(CH*Me*$_2$)$_3$), 18.3 (C(α)*Me*), 32.6 (*C*(5')), 36.6 (C(4')*C*H$_2$Ph), 51.7 (N*C*H$_2$Ph), 57.5 (*C*(α)), 61.8 (*C*(6)), 61.9 (*C*(5)), 68.7 (*C*(4')), 71.2 (O*C*H$_2$Ph), 79.2 (*C*(4)), 123.8 (*C*(2)), 126.5, 126.7, 127.2, 127.5, 127.8, 128.0, 128.1, 128.1, 128.2, 128.5, 128.9, 129.4 (*o*,*m*,*p*-*Ph*), 136.6, 137.9, 141.8, 144.2 (*i*-*Ph*), 147.8 (*C*(3)), 165.8 (*C*(1)), 200.6 (*C*(2')); *m/z* (ESI$^+$) 793 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{47}H_{61}N_2O_3S_2Si^+$ ([M+H]$^+$) requires 793.3887; found 793.3880. Further elution gave (*R*)-**272** as a yellow solid (20 mg). Further elution gave **277** as yellow solid (147 mg, 51%, >95:5 dr); mp 46–48 °C; $[\alpha]_D^{25}$ –103 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3567 (O–H), 1683 (C=O); δ_H (400 MHz, $CDCl_3$) 1.06–1.17 (21H, m, Si(C*HMe*$_2$)$_3$), 1.48 (3H, d, *J* 6.8, C(α)*Me*), 2.76–2.84 (2H, m, C(2)*H*$_A$, C(5')*H*$_A$), 3.02 (1H, dd, *J* 13.1, 11.0, C(4')C*H*$_A$H$_B$Ph), 3.14–3.28 (4H, m, C(2)*H*$_B$, C(5)*H*, C(5')*H*$_B$, C(4')H$_A$*H*$_B$Ph), 3.50–3.56 (1H, m, C(4)*H*), 3.96–4.03 (2H, m, NC*H*$_2$Ph), 4.07 (1H, dd, *J* 10.3, 6.8, C(6)*H*$_A$), 4.16 (1H, q, *J* 6.8, C(α)*H*), 4.21 (1H, dd, *J* 10.3, 4.9, C(6)*H*$_B$), 4.40–4.47 (3H, m, C(3)*H*, OC*H*$_A$H$_B$Ph, O*H*), 4.69 (1H, d, *J* 11.4, OCH$_A$*H*$_B$Ph), 5.21–5.29 (1H, m, C(4')*H*), 7.17–7.40 (20H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.1 (Si(*C*HMe$_2$)$_3$), 17.3 (C(α)*Me*), 18.2 (Si(CH*Me*$_2$)$_3$), 31.8 (*C*(5')), 36.6 (C(4')*C*H$_2$Ph), 41.5 (*C*(2)), 52.0 (N*C*H$_2$Ph), 58.2 (*C*(α)), 59.6 (*C*(5)), 62.5 (*C*(6)), 68.6 (*C*(4')), 69.4 (*C*(3)), 73.2 (O*C*H$_2$Ph), 81.2 (*C*(4)), 126.8, 126.9, 127.2, 127.4, 127.7, 127.9, 128.2, 128.4, 128.4, 129.0, 129.1, 129.5 (*o*,*m*,*p*-*Ph*), 136.7, 138.5, 140.9, 144.6 (*i*-*Ph*), 173.0 (*C*(1)), 200.6 (*C*(2')); *m/z* (ESI$^+$) 811 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{47}H_{61}N_2O_3S_2Si^+$ ([M+H]$^+$) requires 811.3993; found 811.3982.

Method B: Step 1: IBX (321 mg, 1.15 mmol) was added to a stirred solution of **236** (430 mg, 0.765 mmol, >95:5 dr) in DMSO (3 mL) at rt and stirred at rt for 2 h. Et_2O (10 mL) and H_2O

(10 mL) were added and the organic layer was washed with H_2O (5 × 10 mL) then dried and concentrated *in vacuo* to give **237** as a pale yellow viscous oil.

Step 2: $TiCl_4$ (1 M in CH_2Cl_2, 0.77 mL, 0.77 mmol) was added to (*R*)-**272** (192 mg, 0.77 mmol) in CH_2Cl_2 (8.2 mL) at 0 °C and stirred at 0 °C for 5 min and the resultant mixture was cooled to –40 °C. A solution of (–)-sparteine (0.35 mL, 1.5 mmol) in CH_2Cl_2 (2.1 mL) was added and the resultant mixture was stirred at –78 °C for 35 min. A solution of the residue from the previous step in CH_2Cl_2 (2.1 mL) was added at –20 °C and the resultant mixture was stirred at –20 °C for 3.5 h then ½ satd aq NH_4Cl (4 mL) and CH_2Cl_2 (10 mL) were added and the organic layer was washed with ½ satd aq NH_4Cl (3 × 5 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 × 10 mL) then the combined organic layer were dried with Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 6:1 increased to 2:1) gave **276** as a yellow viscous oil (102 mg, 17%, >95:5 dr). Further elution gave **277** as a yellow solid (210 mg, 34%, >95:5 dr).

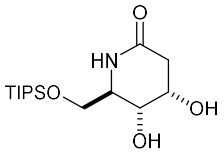
(4*S*,5*R*,6*R*)-4-Hydroxy-5-benzyloxy-6-(triisopropylsilyloxymethyl)piperidin-2-one 278



$Pd(OH)_2/C$ (27 mg, 50% w/w) was added to a vigorously stirred solution of **257** (54 mg, 0.083 mmol, >95:5 dr) in degassed MeOH (1 mL). The reaction mixture was stirred under H_2 (5 atm) for 18 h then filtered through Celite® and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent EtOAc/35% aq NH_4OH, 100:1) gave **278** as a colourless viscous oil (16 mg, 47%, >95:5 dr); $[\alpha]_D^{25}$ +48.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3400 (O–H), 1666 (C=O); δ_H (500 MHz, $CDCl_3$) 0.98–1.14 (21H, m, Si(C*H*Me_2)$_3$), 2.50 (1H, dd, *J* 17.9, 4.1, C(3)H_A), 2.54 (1H, br s, O*H*), 2.66 (1H, dd, *J* 17.9, 3.8, C(3)H_B), 3.44–3.50 (2H, m, C(5)*H*, CH_AH$_B$OTIPS), 3.72 (1H, td, *J* 8.3, 3.5, C(6)*H*), 3.89 (1H, dd, *J* 9.7, 3.5,

CH_AH_BOTIPS), 4.25–4.29 (1H, m, C(4)*H*), 4.52 (1H, d, *J* 11.8, OCH_AH_BPh), 4.68 (1H, d, *J* 11.8, OCH_AH_BPh), 6.03 (1H, s, N*H*), 7.30–7.40 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 11.8 ($Si(CHMe_2)_3$), 17.9 ($Si(CHMe_2)_3$), 36.3 (*C*(3)), 53.4 (*C*(6)), 63.8 (*C*(4)), 64.9 (*C*(1')), 71.5 (OCH_2Ph), 75.0 (*C*(5)), 127.9, 128.3, 128.7 (*o*,*m*,*p*-*Ph*), 137.1 (*i*-*Ph*), 169.1 (*C*(2)); *m/z* (ESI^+) 408 ($[M+H]^+$, 71%), 430 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{22}H_{38}NO_4Si^+$ ($[M+H]^+$) requires 408.2565; found 408.2566.

(4*S*,5*R*,6*R*)-4,5-Dihydroxy-6-(triisopropylsilyloxymethyl)piperidin-2-one 279

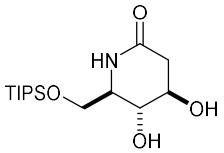


Method A: *Step 1*: $Pd(OH)_2/C$ (20 mg, 20% w/w) was added to a vigorously stirred solution of **257** (100 mg, 0.154 mmol, >95:5 dr) in degassed MeOH (2 mL). The reaction mixture was stirred under H_2 (1 atm) for 24 h then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*.

Step 2: Na (35 mg, 1.5 mmol) was added to a stirred solution of naphthalene (237 mg, 1.85 mmol) in DME (2 mL) at rt and stirred at rt for 2 h then cooled to –78 °C. The residue from the previous step was dissolved in DME (4 mL) and added at –78 °C and the resultant mixture was allowed to warm to rt over 18 h. Satd aq NH_4Cl (5 mL) was added and the aqueous layer was extracted with Et_2O (3 × 5 mL). The combined organic layers were washed with brine (10 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3/^iPrOH$/35% aq NH_4OH, 86:14:1) to give **279** as a pale orange solid (37 mg, 76%, >95:5 dr); mp 50–53 °C; $[\alpha]_D^{25}$ +31.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3399 (O–H, N–H), 1651 (C=O); δ_H (500 MHz, $CDCl_3$, 18.9 mM)[25] 1.05–1.11 (21H, m, $Si(CHMe_2)_3$), 2.57 (1H, dd, *J* 18.1, 4.1, C(3)H_A), 2.63 (1H, dd, *J* 18.1, 3.2, C(3)H_B), 2.88 (1H, br s, O*H*), 3.14 (1H, br s, O*H*), 3.63–3.75 (3H, m, C(5)*H*, C(6)*H*, C(1')H_A), 3.97 (1H, dd, *J* 9.6, 5.2, C(1')H_B), 4.18 (1H, dd, *J* 5.9, 3.5, C(4)*H*), 5.92 (1H, br s, N*H*); δ_C (125 MHz,

$CDCl_3$, 18.9 mM)[25] 11.7 (Si(*C*HMe$_2$)$_3$), 17.9 (Si(CH*Me*$_2$)$_3$), 36.9 (*C*(3)), 54.3 (*C*(6)), 66.0 (*C*(1')), 67.4 (*C*(4)), 69.7 (*C*(5)), 169.5 (*C*(2)); δ_H (500 MHz, $CDCl_3$, 139 mM)[25] 1.03–1.09 (21H, m, Si(C*HMe*$_2$)$_3$), 2.53 (1H, dd, *J* 17.9, 3.9, C(3)H_A), 2.59 (1H, dd, *J* 17.9, 3.5, C(3)H_B), 3.58–3.72 (3H, m, C(5)*H*, C(6)*H*, C(1')H_A), 3.83 (1H, br s, OH), 3.97 (1H, dd, *J* 9.6, 4.4, C(1')H_B), 4.05 (1H, br s, O*H*), 4.11–4.16 (1H, m, C(4)*H*), 6.29 (1H, brs, N*H*); δ_C (125 MHz, $CDCl_3$, 139 mM)[25] 11.7 (Si(*C*HMe$_2$)$_3$), 17.9 (Si(CH*Me*$_2$)$_3$), 37.0 (*C*(3)), 54.9 (*C*(6)), 65.4 (*C*(1')), 67.1 (*C*(4)), 69.0 (*C*(5)), 170.4 (*C*(2)); δ_H [400 MHz, $(CD_3)_2CO$] 1.06–1.11 (21H, m, Si(C*HMe*$_2$)$_3$), 2.35 (1H, dd, *J* 17.2, 4.5, C(3)H_A), 2.45 (1H, dd, *J* 17.2, 4.1, C(3)H_B), 3.56–3.62 (1H, m, C(6)*H*), 3.80 (1H, obsc dd, *J* 9.9, 6.0, C(1')H_A), 3.81–3.84 (1H, m, C(5)*H*), 4.00 (1H, dd, *J* 9.9, 4.2, C(1')H_B), 4.09–4.14 (1H, m, C(4)*H*), 4.19 (1H, d, *J* 5.9, O*H*), 4.26 (1H, d, *J* 3.6, O*H*), 6.32 (1H, br s, N*H*); δ_C (125 MHz, $(CD_3)_2CO$) 12.6 (Si(*C*HMe$_2$)$_3$), 18.3 (Si(CH*Me*$_2$)$_3$), 38.1 (*C*(3)), 56.6 (*C*(6)), 65.8 (*C*(1')), 68.1 (*C*(4)), 68.8 (*C*(5)), 169.9 (*C*(2)); *m/z* (ESI^+) 318 ($[M+H]^+$, 100%), 340 ($[M+Na]^+$, 25%); HRMS (ESI^+) $C_{15}H_{32}NO_4Si^+$ ($[M+H]^+$) requires 318.2095; found 318.2096.

(*R*,*R*,*R*)-4,5-Dihydroxy-6-(triisopropylsilyloxymethyl)piperidin-2-one 281

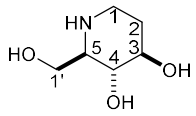


Step 1: $Pd(OH)_2$/C (160 mg, 20% w/w) was added to a vigorously stirred solution of **256** (802 mg, 1.24 mmol, >95:5 dr) in degassed MeOH (10 mL). The reaction mixture was stirred under H_2 (1 atm) for 24 h then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*.

Step 2: Na (285 mg, 12.4 mmol) was added to a stirred solution of naphthalene (1.91 g, 14.9 mmol) in DME (14 mL) at rt and stirred at rt for 2 h then cooled to –78 °C. The residue from the previous step was dissolved in DME (33 mL) and added at –78 °C and the resultant mixture was allowed to warm to rt over 18 h. Satd aq NH_4Cl (5 mL) was added and the aqueous layer was extracted with Et_2O (3 × 25 mL). The combined organic layers were

washed with brine (40 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/^{i}PrOH/35% aq NH_4OH, 78:12:1) to give **281** as an off-white solid (220 mg, 56%, >95:5 dr); mp 109–111 °C; $[\alpha]_D^{25}$ +16.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3398 (O–H, N–H), 1651 (C=O); δ_H (500 MHz, $CDCl_3$, 18.9 mM)[25] 1.04–1.09 (21H, m, Si(C*HMe*$_2$)$_3$), 2.37 (1H, dd, *J* 17.4, 11.0, C(3)H_A), 2.68 (1H, d, *J* 3.5, O*H*), 2.82 (1H, dd, *J* 17.4, 5.7, C(3)H_B), 3.09 (1H, d, *J* 2.7, O*H*), 3.36 (1H, app td, *J* 8.5, 4.5, C(6)*H*), 3.47 (1H, td, *J* 9.1, 2.5, C(5)*H*), 3.67 (1H, dd, *J* 9.7, 8.2, C(1')H_A), 3.89–3.96 (1H, m, C(4)*H*), 4.04 (1H, dd, *J* 9.7, 4.5, C(1')H_B), 5.95 (1H, br s, N*H*); δ_C (125 MHz, $CDCl_3$, 18.9 mM)[25] 11.8 (Si(*C*HMe$_2$)$_3$), 17.9 (Si(CH*Me*$_2$)$_3$), 37.8 (*C*(3)), 56.3 (*C*(6)), 65.6 (*C*(1')), 69.0 (*C*(4)), 72.5 (*C*(5)), 169.3 (*C*(2)); δ_H (500 MHz, $CDCl_3$, 139 mM)[25] 1.00–1.16 (21H, m, Si(C*HMe*$_2$)$_3$), 2.34 (1H, dd, *J* 17.5, 10.8, C(3)H_A), 2.78 (1H, dd, *J* 17.5, 6.0, C(3)H_B), 3.31–3.36 (1H, m, C(6)*H*), 3.42 (1H, t, *J* 9.0, C(5)*H*), 3.63 (1H, dd, *J* 9.6, 8.5, C(1')H_A), 3.83 (1H, q, *J* 8.6, C(4)*H*), 4.06 (1H, dd, *J* 9.8, 3.9, C(1')H_B), 6.25 (1H, br s, N*H*); δ_C (125 MHz, $CDCl_3$, 139 mM)[25] 11.7 (Si(*C*HMe$_2$)$_3$), 17.9 (Si(CH*Me*$_2$)$_3$), 37.7 (*C*(3)), 56.7 (*C*(6)), 65.2 (*C*(1')), 68.8 (*C*(4)), 71.9 (*C*(5)), 170.3 (*C*(2)); *m/z* (ESI$^+$) 318 ([M+H]$^+$, 100%), 340 ([M+Na]$^+$, 63%); HRMS (ESI$^+$) $C_{15}H_{32}NO_4Si^+$ ([M+H]$^+$) requires 318.2095; found 318.2096.

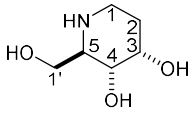
(*R*,*R*,*R*)-3,4-Dihydroxy-5-hydroxymethylpiperidine [(+)-fagomine] 221



BH_3·DMS (2.0 M in THF, 1.10 mL, 2.20 mmol) was added to a solution of **281** (100 mg, 0.315 mmol, >95:5 dr) in THF (6 mL) at 0 °C and stirred at 0 °C for 30 min then warmed to rt over 2 h. 3.0 M aq NaOH (2 mL) and 30% aq H_2O_2 (2 mL) were added and the resultant mixture was heated at 85 °C for 1 h then cooled to 0 °C. 6 M HCl (5 mL) was added and the resultant mixture was allowed to warm to rt over 18 h then the volatiles were removed *in vacuo* and the aqueous layer subjected to ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH). Purification *via* flash column

chromatography (eluent CH_2Cl_2/MeOH/35% aq NH_4OH, 25:25:1) gave **221** as a white solid (30 mg, 65%, >95:5 dr);[26] mp 170–173 °C (lit.[27] mp 184–185 °C, lit.[26] mp 186–188 °C); $[\alpha]_D^{25}$ +14.9 (*c* 1.0 in H_2O) {lit.[28,29] $[\alpha]_D$ +19.5 (*c* 1.0 in H_2O); lit.[26] $[\alpha]_D^{11}$ +23.0 (*c* 1.0 in H_2O); lit.[27] $[\alpha]_D^{20}$ +24.7 (*c* 0.4 in H_2O)}; δ_H (400 MHz, D_2O)[30] 1.40–1.52 (1H, m, C(2)H_A), 1.97–2.04 (1H, m, C(2)H_B), 2.56 (1H, ddd, *J* 9.7, 6.7, 3.0, C(5)*H*), 2.63 (1H, td, *J* 12.8, 2.6, C(1)H_A), 3.00–3.07 (1H, m, C(1)H_B), 3.19 (1H, t, *J* 9.7, C(4)*H*), 3.55 (1H, ddd, *J* 11.5, 9.0, 5.0, C(3)*H*), 3.65 (1H, dd, *J* 11.6, 6.7, C(1')H_A), 3.86 (1H, dd, *J* 11.6, 3.0, C(1')H_B); δ_C (100 MHz, D_2O)[30] 35.5 (*C*(2)), 45.4 (*C*(1)), 63.7 (*C*(5)), 64.5 (*C*(1')), 76.0 (*C*(4)), 76.1 (*C*(3)); *m/z* (ESI^+) 148 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_6H_{14}NO_3^+$ ($[M+H]^+$) requires 148.0968; found 148.0968. A sample of **221** was dissolved in $CHCl_3$/^{i}PrOH (3:1 v/v) and 2.0 M aq NaOH and the aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1 v/v). The ^1H and ^{13}C NMR spectroscopic data was identical with reported that above.

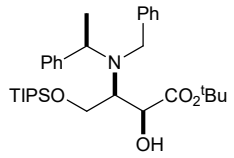
(3*S*,4*R*,5*R*)-3,4-Dihydroxy-5-hydroxymethylpiperidine [3-*epi*-fagomine] 222



BH_3·DMS (2.0 M in THF, 1.66 mL, 3.31 mmol) was added to a solution of **279** (150 mg, 0.472 mmol, >95:5 dr) in THF (6 mL) at 0 °C and stirred at 0 °C for 30 min then warmed to rt over 2 h. 3.0 M aq NaOH (2 mL) and 30% aq H_2O_2 (2 mL) were added and the resultant mixture was heated at 85 °C for 1 h then cooled to 0 °C. 6 M HCl (5 mL) was added and the resultant mixture was allowed to warm to rt over 18 h then the volatiles were removed *in vacuo* and the aqueous layer subjected to ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH). Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH/35% aq NH_4OH, 25:25:1) gave **222** as a white solid (36 mg, 52%, >95:5 dr);[29] mp 188–191 °C; $[\alpha]_D^{25}$ +62.8 (*c* 1.0 in H_2O) {lit.[29,31,32] $[\alpha]_D$ +69.0 (*c* 0.5 in H_2O)}; δ_H (400 MHz, D_2O)[30] 1.67–1.77 (1H, m, C(2)H_A), 1.80–1.88 (1H, m, C(2)H_B), 2.73–2.91 (3H, m, C(5)*H*, C(1)H_2), 3.47 (1H, dd, *J* 10.1, 3.0, C(4)*H*), 3.62 (1H, dd,

J 11.5, 6.6, C(1')H_A), 3.82 (1H, dd, *J* 11.5, 3.2, C(1')H_B), 4.09 (1H, app q, *J* 3.1, C(3)*H*); δ_C (100 MHz, D_2O)[30] 33.8 (*C*(2)), 41.2 (*C*(1)), 58.6 (*C*(5)), 64.9 (*C*(1')), 70.7 (*C*(3)), 72.4 (*C*(4)); *m/z* (ESI^+) 148 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_6H_{14}NO_3^+$ ($[M+H]^+$) requires 148.0968; found 148.0968. A sample of **222** was dissolved in $CHCl_3$/^{i}PrOH (3:1 v/v) and 2.0 M aq NaOH and the aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1 v/v). The ^{1}H and ^{13}C NMR spectroscopic data was identical with reported that above.

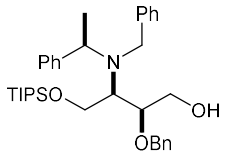
tert-Butyl (2*S*,3*R*,α*R*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino-4-(triisopropylsilyloxy)butanoate 282



Step 1: DMSO (2.62 mL, 36.9 mmol) was added to a stirred solution of $(COCl)_2$ (1.56 mL, 18.5 mmol) in CH_2Cl_2 (23 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then **232** (5.00 g, 9.23 mmol, >95:5 dr) in CH_2Cl_2 (23 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et_3N (7.72 mL, 55.4 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 20 min then at rt for 20 min. The organic layer was washed with H_2O (2 × 20 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 20 mL) then the combined organic layers were dried and concentrated *in vacuo* to give **286** (>95% conversion) as a yellow viscous oil.

Step 2: $NaBH_4$ (349 mg, 9.23 mmol) was added to a stirred solution of the residue in MeOH (307 mL) at –20 °C and the resultant mixture was stirred at –20 °C for 2 h then concentrated *in vacuo* to give a 94:6 mixture of **282** and **232**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 25:1) gave a 88:12 mixture of **282** and **232**, respectively, as pale yellow viscous oil (1.58 g, 32%, 88:12 dr). Further elution gave **282** as a pale yellow viscous oil (2.76 g, 55%, >95:5 dr).

(2*S*,3*R*,*αR*)-2-Benzyloxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino-4-(triisopropylsilyloxy)butan-1-ol 283



Method A: Step 1: A solution of **282** (2.76 g, 5.09 mmol, >95:5 dr) in THF (45 mL) was added to a stirred suspension of NaH (60% in mineral oil, 408 mg, 10.2 mmol) in THF (45 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 1 h. BnBr (1.21 mL, 10.2 mmol) was added and the resultant mixture was allowed to warm to rt over 18 h then satd aq NH_4Cl (10 mL) and Et_2O (50 mL) were added. The resultant mixture was washed with brine (300 mL) and the aqueous layers were extracted with Et_2O (3 × 50 mL) then the combined organic layers were dried and concentrated *in vacuo*.

Step 2: DIBAL-H (1 M in CH_2Cl_2, 20.4 mL, 20.4 mmol) was added to a stirred solution of the residue from the previous step in CH_2Cl_2 (80 mL) at –78 °C then stirred at rt for 2 h. Satd aq NH_4Cl (10 mL) was added and the resultant mixture was filtered through Celite® (eluent CH_2Cl_2) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 12:1) gave **283** as a pale yellow viscous oil (2.73 g, 95%, >95:5 dr);[14] $[\alpha]_D^{25}$ –9.1 (*c* 1.0 in $CHCl_3$); $\nu_{max\ (ATR)}$ 3591 (O–H); δ_H (400 MHz, $CDCl_3$) 1.04–1.18 (21H, m, Si(C*H*Me$_2$)$_3$), 1.44 (3H, d, *J* 6.9, C(α)*Me*), 2.39 (1H, br s, O*H*), 2.95–3.01 (1H, m, C(3)*H*), 3.20–3.29 (1H, m, C(1)H_A), 3.56–3.63 (2H, m, C(1)H_B, C(2)*H*), 3.72 (1H, d, *J* 13.2, NCH_AH$_B$Ph), 4.05 (1H, dd, *J* 9.5, 5.1, C(4)H_A), 4.09–4.16 (1H, m, C(4)H_B), 4.19 (1H, q, *J* 6.9, C(α)*H*), 4.35 (1H, d, *J* 13.2, NCH$_A$$H_B$Ph), 4.43 (1H, d, *J* 11.7, OCH_AH$_B$Ph), 4.61 (1H, d, *J* 11.7, OCH$_A$$H_B$Ph), 7.21–7.39 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 13.7 (C(α)*Me*), 18.1, 18.1 (Si(CH*Me*$_2$)$_3$), 52.0 (N*C*H$_2$Ph), 56.4 (*C*(α)), 59.3 (*C*(3)), 61.3 (*C*(4)), 61.9 (*C*(1)), 72.3 (O*C*H$_2$Ph), 79.6 (*C*(2)), 126.9, 127.2, 127.3, 128.1, 128.2, 128.2, 128.3, 129.2 (*o*,*m*,*p*-*Ph*), 139.0, 141.0, 143.9 (*i*-*Ph*);

m/z (ESI$^+$) 562 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{52}NO_3Si$+ ([M+H]$^+$) requires 562.3711; found 562.3709.

Method B: *Step 1*: DMSO (14.1 mL, 199 mmol) was added to a stirred solution of $(COCl)_2$ (8.42 mL, 99.5 mmol) in CH_2Cl_2 (125 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then **232** (27.0 g, 49.8 mmol, >95:5 dr) in CH_2Cl_2 (125 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et_3N (41.7 mL, 299 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 20 min then at rt for 20 min. The organic layer was washed with H_2O (2 × 150 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 200 mL) then the combined organic layers were dried and concentrated *in vacuo* to give **286** (>95% conversion) as a yellow viscous oil.

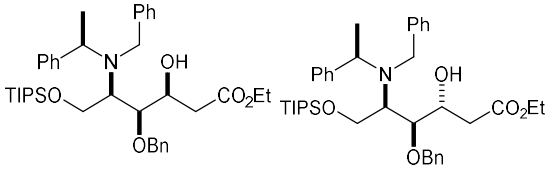
Step 2: $NaBH_4$ (1.88 g, 49.8 mmol) was added to a stirred solution of the residue in MeOH (1.60 L) at –20 °C and the resultant mixture was stirred at –20 °C for 2 h then concentrated *in vacuo* to give a >95:5 mixture of *syn*-**282** and *anti*-**232**, respectively.

Step 3: A solution of the residue from the previous in THF (300 mL) was added to a stirred suspension of NaH (60% in mineral oil, 3.98 g, 99.6 mmol) in THF (300 mL) at 0 °C and the resultant mixture was stirred at 0 °C for 1 h. BnBr (11.9 mL, 99.6 mmol) was added and the resultant mixture was allowed to warm to rt over 18 h then satd aq NH_4Cl (20 mL) and Et_2O (100 mL) were added. The resultant mixture was washed with brine (100 mL) and the aqueous layers were extracted with Et_2O (3 × 150 mL) then the combined organic layers were dried and concentrated *in vacuo* to give an >95:5 mixture of *syn*-**287** and *anti*-**235**, respectively.

Step 4: DIBAL-H (1 M in CH_2Cl_2, 200 mL, 200 mmol) was added to a stirred solution of the residue from the previous step in CH_2Cl_2 (600 mL) at –78 °C then stirred at rt for 2 h. Satd aq NH_4Cl (50 mL) was added and the resultant mixture was filtered through Celite® (eluent CH_2Cl_2) then dried and concentrated *in vacuo* to give an >95:5 mixture of *syn*-**283** and

anti-**236**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 12:1) gave **283** as a pale yellow viscous oil (23.9 g, 85%, >95:5 dr).

Ethyl (3*S*,4*S*,5*R*,α*R*)-3-hydroxy-4-benzyloxy-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6-(triisoproylsilyloxy)hexanoate 284 and ethyl (3*R*,4*S*,5*R*,α*R*)-3-hydroxy-4-benzyloxy-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6-(triisoproylsilyloxy)hexanoate 285



284 **285**

Step 1: DMSO (0.51 mL, 7.1 mmol) was added to a stirred solution of $(COCl)_2$ (0.30 mL, 3.6 mmol) in CH_2Cl_2 (10 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then **283** (1.00 g, 1.78 mmol, >95:5 dr) in CH_2Cl_2 (10 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et_3N (1.49 mL, 10.7 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 20 min then at rt for 20 min. The organic layer was washed with H_2O (2 × 15 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (2 × 15 mL) then the combined organic layers were dried and concentrated *in vacuo* to give **288** as a pale yellow viscous oil.

Step 2: BuLi (2.2 M in hexanes, 1.13 mL, 2.49 mmol) was added to a stirred solution of $^{i}Pr_2NH$ (0.35 mL, 2.5 mmol) in THF (5 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 20 min then EtOAc (0.24 mL, 2.49 mmol) was added at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of the residue from the previous step in THF (5 mL) was added at –78 °C and the resultant mixture was allowed to stir at –78 °C for 1 h then at 0 °C for 2 h before satd aq NH_4Cl (2 mL) and Et_2O (10 mL) was added. The aqueous layer was extracted with Et_2O (3 × 10 mL) then the combined organic layers were washed with brine (25 mL) then were dried and concentrated *in vacuo* to give a 54:46 mixture of **284** and **285**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 10:1) gave a 54:46 mixture of **284** and **285**, respectively, as a

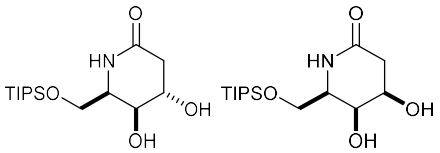
colourless viscous oil (902 mg, 72%, 54:46 dr). Data for mixture: ν_{max} (ATR) 3587 (O–H), 1733 (C=O); *m/z* (ESI$^+$) 544 ([M–C_8H_8]$^+$, 29%), 648 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{39}H_{58}NO_5Si^+$ ([M+H]$^+$) requires 648.4079; found 648.4076. Data for **284**: δ_H (400 MHz, $CDCl_3$) 1.07–1.16 (21H, m, Si(C*HMe*$_2$)$_3$), 1.20–1.26 (3H, m, OCH$_2$*Me*), 1.40–1.46 (3H, m, C(α)*Me*), 1.99 (1H, dd, *J* 15.4, 5.0, C(2)H_A), 2.24 (1H, dd, *J* 15.4, 8.3, C(2)H_B), 3.02 (1H, td, *J* 6.8, 3.4, C(5)*H*), 3.50 (1H, t, *J* 3.4, C(4)*H*), 3.74 (1H, d, *J* 13.4, NCH_AH$_B$Ph), 3.84–3.91 (1H, m, C(3)*H*), 4.00–4.30 (5H, m, C(6)H_2, C(α)*H*, OCH_2Me), 4.41 (1H, d, *J* 13.4, NCH$_A$$H_B$Ph), 4.46–4.53 (1H, m, OCH_AH$_B$Ph), 4.63 (1H, d, *J* 11.6, OCH$_A$$H_B$Ph), 7.19–7.42 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) [selected data] 12.0 (Si(*C*HMe$_2$)$_3$), 14.2 (OCH$_2$*Me*), 18.2 (Si(CH*Me*$_2$)$_3$), 38.9 (*C*(2)), 51.9 (N*C*H$_2$Ph), 55.6 (*C*(α)), 60.0 (*C*(5)), 60.9 (*C*(6)), 69.8 (*C*(3)), 75.2 (O*C*H$_2$Ph), 81.0 (*C*(4)). Data for **285**: δ_H (400 MHz, $CDCl_3$) 1.07–1.16 (21H, m, Si(C*HMe*$_2$)$_3$), 1.20–1.26 (3H, m, OCH$_2$*Me*), 1.40–1.46 (3H, m, C(α)*Me*), 1.87 (1H, dd, *J* 15.7, 8.8, C(2)H_A), 2.11 (1H, dd, *J* 15.7, 4.4, C(2)H_B), 3.07–3.13 (1H, m, C(5)*H*), 3.55 (1H, dd, *J* 5.9, 2.5, C(4)*H*), 3.61–3.68 (1H, m, NCH_AH$_B$Ph), 4.00–4.30 (5H, m, C(6)H_2, C(α)*H*, OCH_2Me), 4.31–4.37 (1H, m, C(3)*H*), 4.46–4.53 (1H, m, NCH$_A$$H_B$Ph), 4.57 (1H, d, *J* 11.7, OCH_AH$_B$Ph), 4.69 (1H, d, *J* 11.7, OCH$_A$$H_B$Ph), 7.19–7.42 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) [selected data] 12.0 (Si(*C*HMe$_2$)$_3$), 14.2 (OCH$_2$*Me*), 18.2 (Si(CH*Me*$_2$)$_3$), 38.7 (*C*(2)), 52.0 (N*C*H$_2$Ph), 55.6 (*C*(α)), 57.8 (*C*(5)), 60.9 (*C*(6)), 68.2 (*C*(3)), 73.6 (O*C*H$_2$Ph), 81.0 (*C*(4)).

Method B: Step 1: DMSO (0.74 mL, 10.4 mmol) was added to a stirred solution of $(COCl)_2$ (0.44 mL, 5.2 mmol) in CH_2Cl_2 (15 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then **283** (1.43 g, 2.60 mmol, >95:5 dr) in CH_2Cl_2 (15 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et_3N (2.18 mL, 15.6 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 20 min then at rt for 20 min. The organic layer was washed with H_2O (2 × 20 mL) and the combined

aqueous layers were extracted with CH_2Cl_2 (2 × 20 mL) then the combined organic layers were dried and concentrated *in vacuo* to give **288** as a pale yellow viscous oil.

Step 2: BuLi (2.2 M in hexanes, 1.65 mL, 3.64 mmol) was added to a stirred solution of $^{i}Pr_2NH$ (0.51 mL, 3.6 mmol) in THF (7 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 20 min then EtOAc (0.35 mL, 3.6 mmol) was added at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. A solution of the residue from the previous step in THF (8 mL) was added at –78 °C and the resultant mixture was allowed to stir at –78 °C for 1 h then at 0 °C for 2 h before satd aq NH_4Cl (2 mL) and Et_2O (10 mL) was added. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic layers were washed with brine (25 mL) then were dried and concentrated *in vacuo* to give a 56:44 mixture of **284** and **285**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/acetone, 25:1) gave a 95:5 mixture of **284** and **285**, respectively, as a colourless viscous oil (329 mg, 20%, 95:5 dr). Further elution gave a 70:30 mixture of **284** and **285**, respectively, as a colourless viscous oil (885 mg, 53%, 70:30 dr). Further elution gave **284** as a colourless viscous oil (141 mg, 8%, >95:5 dr).

(4*S*,5*S*,6*R*)-4,5-dihydroxy-6-(triisopropylsilyloxymethyl)piperidin-2-one 289 and (4*R*,5*S*,6*R*)-4,5-Dihydroxy-6-(triisopropylsilyloxymethyl)piperidin-2-one 290



289 290

Method A: *Step 1*: $Pd(OH)_2/C$ (134 mg, 20% w/w) was added to a vigorously stirred solution of a 70:30 mixture of **284** and **285**, respectively, (670 mg, 1.03 mmol, 70:30 dr) in degassed MeOH (4 mL). The reaction mixture was stirred under H_2 (5 atm) for 24 h then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*.

Step 2: Na (237 mg, 10.3 mmol) was added to a stirred solution of naphthalene (1.58 g, 12.4 mmol) in DME (11 mL) at rt and stirred at rt for 2 h then cooled to –78 °C. The residue

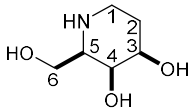
from the previous step was dissolved in DME (25 mL) and added at –78 °C and the resultant mixture was allowed to warm to rt over 18 h. Satd aq NH_4Cl (10 mL) was added and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (25 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/^{i}PrOH/35% aq NH_4OH, 89:11:1) to give **290** as colourless viscous oil (24 mg, 7%, >95:5 dr); $[\alpha]_D^{25}$ +27.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3402 (O–H), 1646 (C=O); δ_H (500 MHz, $CDCl_3$, 18.9 mM)[25] 1.04–1.18 (21H, m, Si(C*H*Me$_2$)$_3$), 2.61 (1H, dd, *J* 17.2, 10.2, C(3)H_A), 2.67 (1H, dd, *J* 17.2, 6.6, C(3)H_B), 2.79 (1H, br s, O*H*), 2.98 (1H, br s, O*H*), 3.50–3.55 (1H, m, C(6)*H*), 3.91 (1H, dd, *J* 10.1, 4.4, C(1')H_A), 3.91 (1H, dd, *J* 10.1, 8.0, C(1')H_B), 4.04–4.12 (2H, m, C(4)*H*, C(5)*H*), 5.95 (1H, br s, N*H*); δ_C (125 MHz, $CDCl_3$, 18.9 mM)[25] 11.8 (Si(*C*HMe$_2$)$_3$), 17.9 (Si(CH*Me*$_2$)$_3$), 35.5 (*C*(3)), 55.2 (*C*(6)), 63.9 (*C*(1')), 67.7 (*C*(4)), 67.7 (*C*(5)), 170.3 (*C*(2)); δ_H (500 MHz, $CDCl_3$, 139 mM)[25] 1.01–1.14 (21H, m, Si(C*H*Me$_2$)$_3$), 2.55–2.67 (2H, m, C(3)H_2), 3.47–3.52 (1H, m, C(6)*H*), 3.79 (1H, br s, O*H*), 3.85–3.91 (2H, m, C(1')H_2), 4.00–4.07 (2H, m, C(4)*H*, C(5)*H*), 4.19 (1H, br s, O*H*),5.95 (1H, br s, N*H*); δ_C (125 MHz, $CDCl_3$, 139 mM)[25] 11.8 (Si(*C*HMe$_2$)$_3$), 17.9 (Si(CH*Me*$_2$)$_3$), 35.3 (*C*(3)), 55.7 (*C*(6)), 63.8 (*C*(1')), 67.3 (*C*(5)), 67.6 (*C*(4)), 171.2 (*C*(2)); *m/z* (ESI$^+$) 318 ([M+H]$^+$, 100%), 340 ([M+Na]$^+$, 74%); HRMS (ESI$^+$) $C_{15}H_{32}NO_4Si^+$ ([M+H]$^+$) requires 318.2095; found 318.2088. Further elution gave **289** as a pale orange solid (142 mg, 43%, >95:5 dr); mp 140–141 °C; $[\alpha]_D^{25}$ +29.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3398 (O–H), 1644 (C=O); δ_H (500 MHz, $CDCl_3$, 18.9 mM)[25] 1.04–1.11 (21H, m, Si(C*H*Me$_2$)$_3$), 2.39 (1H, dd, *J* 17.9, 3.4, C(3)H_A), 2.80 (1H, brs, O*H*), 2.86 (1H, dd, *J* 17.9, 4.6, C(3)H_B), 3.49 (1H, br s, O*H*), 3.78–3.82 (1H, m, C(6)*H*), 3.92–3.99 (2H, m, C(1')H_2), 3.99–4.03 (1H, m, C(5)*H*), 4.15–4.20 (1H, m, C(4)*H*), 5.93 (1H, br s, N*H*); δ_C (125 MHz, $CDCl_3$, 18.9 mM)[25] 11.7 (Si(*C*HMe$_2$)$_3$), 17.9 (Si(CH*Me*$_2$)$_3$), 36.1 (*C*(3)), 52.9 (*C*(6)), 64.5 (*C*(1')), 67.1 (*C*(4)), 69.1 (*C*(5)), 170.8 (*C*(2)); δ_H (500 MHz, $CDCl_3$, 139 mM)[25] 1.00–1.19 (21H, m, Si(C*H*Me$_2$)$_3$), 2.35 (1H, d, *J* 17.5, C(3)H_A), 2.81 (1H, d, *J* 17.5, C(3)H_B), 3.75–3.80 (1H, m, C(6)*H*), 3.89–3.98

(3H, m, C(5)*H*, C(1')H_2), 4.09–4.14 (1H, m, C(4)*H*), 4.17 (1H, br s, O*H*), 4.23 (1H, br s, O*H*), 6.28 (1H, br s, N*H*); δ_C (125 MHz, $CDCl_3$, 139 mM)[25] 11.7 (Si(*C*HMe$_2$)$_3$), 17.9 (Si(CH*Me*$_2$)$_3$), 35.8 (*C*(3)), 53.3 (*C*(6)), 64.2 (*C*(1')), 66.9 (*C*(4)), 68.1 (*C*(5)), 171.6 (*C*(2)); *m/z* (ESI^+) 318 ($[M+H]^+$, 72%), 340 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{15}H_{32}NO_4Si^+$ ($[M+H]^+$) requires 318.2095; found 318.2090.

Method B: *Step 1*: $Pd(OH)_2$/C (100 mg, 20% w/w) was added to a vigorously stirred solution of a 54:46 mixture of **284** and **285**, respectively, (500 mg, 0.772 mmol, 54:46 dr) in degassed MeOH (4 mL). The reaction mixture was stirred under H_2 (5 atm) for 24 h then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*.

Step 2: Na (177 mg, 7.72 mmol) was added to a stirred solution of naphthalene (1.19 g, 9.26 mmol) in THF (10 mL) at rt and stirred at rt for 2 h then cooled to –78 °C. The residue from the previous step was dissolved in THF (10 mL) and added at –78 °C and the resultant mixture was allowed to warm to 0 °C over 3 h. Satd aq NH_4Cl (10 mL) was added and the aqueous layer was extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with brine (25 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/^{i}PrOH/35% aq NH_4OH, 89:11:1) to give **290** as colourless viscous oil (76 mg, 31%, >95:5 dr). Further elution gave **289** as a pale orange solid (85 mg, 35%, >95:5 dr).

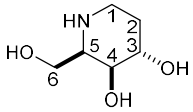
(3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-hydroxymethylpiperidine [4-*epi*-fagomine] 223



BH_3·DMS (2.0 M in THF, 1.14 mL, 2.27 mmol) was added to a solution of **290** (103 mg, 0.324 mmol, >95:5 dr) in THF (4 mL) at 0 °C and stirred at 0 °C for 30 min then warmed to rt over 2 h. 3.0 M aq NaOH (2 mL) and 30% aq H_2O_2 (2 mL) were added and the resultant mixture was heated at 85 °C for 1 h then cooled to 0 °C. 6 M aq HCl (5 mL) was added and the resultant mixture was allowed to warm to rt over 18 h then the volatiles were removed *in*

vacuo and the aqueous layer subjected to ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH). Purification *via* flash column chromatography (eluent CH_2Cl_2/MeOH/35% aq NH_4OH, 50:50:1) gave **223** as colourless viscous oi (22 mg, 46%, >95:5 dr);[33] $[\alpha]_D^{25}$ +13.9 (*c* 1.0 in $CHCl_3$) {lit.[34] $[\alpha]_D^{25}$ +11.7 (*c* 1.8 in H_2O); lit.[35] $[\alpha]_D^{25}$ +10.4 (*c* 1.4 in H_2O); lit.[36] $[\alpha]_D^{22}$ +10.2 (*c* 1.42 in H_2O); lit.[29] $[\alpha]_D$ +19 (*c* 0.46 in H_2O)}; δ_H (400 MHz, D_2O)[30] 1.92–2.10 (2H, m, C(2)H_2), 3.08 (1H, td, *J* 13.2, 3.9, C(1)H_A), 3.34 (1H, ddd, *J* 8.5, 5.1, 1.2, C(5)*H*), 3.47 (1H, ddd, *J* 13.2, 4.6, 2.4, C(1)H_B), 3.79–3.94 (3H, m, C(3)*H*, C(1')H_2), 4.08–4.10 (1H, m, C(4)*H*); δ_C (100 MHz, D_2O)[30] 27.0 (*C*(2)), 45.2 (*C*(1)), 62.5 (*C*(1')), 63.0 (*C*(5)), 68.9 (*C*(4)), 70.4 (*C*(3)); *m/z* (ESI^+) 148 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_6H_{14}NO_3^+$ ($[M+H]^+$) requires 148.0968; found 148.0969. A sample of **223** was dissolved in $CHCl_3$/^{i}PrOH (3:1 v/v) and 2.0 M aq NaOH and the aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1 v/v). The ^1H and ^{13}C NMR spectroscopic data was different with reported that above: δ_H (400 MHz, D_2O) 1.64–1.72 (2H, m, C(2)H_2), 2.56 (1H, td, *J* 12.5, 4.3, C(1)H_A), 2.65–2.71 (1H, m, C(5)*H*), 3.00–3.08 (1H, m, C(1)H_B), 3.60–3.64 (2H, m, C(1')H_2), 3.70–3.76 (1H, m, C(3)*H*), 3.88–3.92 (1H, m, C(4)*H*); δ_C (100 MHz, D_2O) 30.5 (*C*(2)), 45.7 (*C*(1)), 61.7 (*C*(5)), 64.7 (*C*(1'), 70.6 (*C*(4)), 72.9 (*C*(3)).

(3*S*,4*S*,5*R*)-3,4-Dihydroxy-5-hydroxymethylpiperidine [5-*epi*-fagomine] *ent*-224

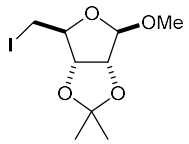


BH_3·DMS (2.0 M in THF, 1.38 mL, 2.76 mmol) was added to a solution of **289** (125 mg, 0.394 mmol, >95:5 dr) in THF (4 mL) at 0 °C and stirred at 0 °C for 30 min then warmed to rt over 2 h. 3.0 M aq NaOH (2 mL) and 30% aq H_2O_2 (2 mL) were added and the resultant mixture was heated at 85 °C for 1 h then cooled to 0 °C. 6 M aq HCl (5 mL) was added and the resultant mixture was allowed to warm to rt over 18 h then the volatiles were removed *in vacuo* and the aqueous layer subjected to ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH). Purification *via* flash column

chromatography (eluent CH_2Cl_2/MeOH/35% aq NH_4OH, 25:25:1) gave *ent*-**224** as colourless viscous oil (25 mg, 43%, >95:5 dr);[31] $[\alpha]_D^{25}$ +8.0 (*c* 1.0 in $CHCl_3$) {lit.[31] for **224** $[\alpha]_D$ –8.7 (*c* 0.3 in H_2O); lit.[37] for **224** $[\alpha]_D^{25}$ –10.2 (*c* 0.5 in H_2O); lit.[38] for **224** $[\alpha]_D^{21}$ –10.6 (*c* 0.32 in H_2O); lit.[39] for **224** $[\alpha]_D^{25}$ –14 (*c* 1.96 in H_2O); lit.[40] for **224** $[\alpha]_D$ –11.6 (*c* 0.94 in H_2O); lit.[41] for **224** $[\alpha]_D^{20}$ –15 (*c* 0.5 in H_2O); lit.[42] for *ent*-**224** $[\alpha]_D^{25}$ +12.1 (*c* 0.33 in H_2O); lit.[36] for *ent*-**224** $[\alpha]_D$ +13.4 (*c* 0.32 in H_2O)}; δ_H (400 MHz, D_2O)[30] 1.81–1.89 (1H, m, C(2)H_A), 2.15–2.28 (1H, m, C(2)H_B), 3.21–3.32 (2H, m, C(1)H_2), 3.51–3.59 (1H, m, C(5)*H*), 3.81 (1H, dd, *J* 12.2, 8.7, C(1')H_A), 3.87 (1H, dd, *J* 12.2, 5.0, C(1')H_B), 3.93–3.97 (1H, m, C(4)*H*), 4.01–4.07 (1H, m, C(3)*H*); δ_C (100 MHz, D_2O)[30] 26.5 (C(2)), 41.7 (*C*(1)), 58.7 (*C*(5)), 62.4 (*C*(1')), 67.7 (*C*(3)), 68.7 (*C*(4)); *m/z* (ESI^+) 148 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_6H_{14}NO_3^+$ ($[M+H]^+$) requires 148.0968; found 148.0967. A sample of **223** was dissolved in $CHCl_3$/^{i}PrOH (3:1 v/v) and 2.0 M aq NaOH and the aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1 v/v). The ^1H and ^{13}C NMR spectroscopic data was different with reported that above: δ_H (400 MHz, D_2O) 1.58 (1H, dq, *J* 14.1, 4.2, C(2)H_A), 1.91–2.01 (1H, m, C(2)H_B), 2.81–2.88 (2H, m, C(1)H_2). 3.10 (td, *J* 6.7, 2.6, C(5)*H*), 3.62–3.69 (2H, m, C(1')H_2), 3.69–3.73 (1H, m, C(4)*H*), 3.90 (1H, app q, *J* 4.3, C(3)*H*); δ_C (125 MHz, D_2O) 30.6 (*C*(2)), 41.4 (*C*(1)), 58.1 (*C*(5)), 63.5 (*C*(1')), 70.5 (*C*(4)), 71.5 (*C*(3)).

5.4 Experimental Data for Chapter 4

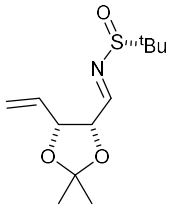
(2*R*,3*R*,4*S*,5*S*)-2-Methoxy-3,4-dihydroxy-3,4-*O*-isopropylidene-4-iodomethyltetrahydrofuran 334



Step 1: 37% aq HCl (2.1 mL, 26 mmol) was added to a stirred solution of D-ribose **333** (15.0 g, 99.9 mmol) in acetone/MeOH (1:1 v/v, 168 mL) and the resultant mixture was heated at 70 °C for 1 h then allowed to cool to rt. Pyridine was added until pH 7 was achieved then H_2O (100 mL) and Et_2O (100 mL) were added. The aqueous layer was extracted with EtOAc (3 × 100 mL) then the combined organic layers were washed sequentially with satd aq $CuSO_4$ (200 mL), H_2O (200 mL) and brine (100 mL) then dried and concentrated *in vacuo*.

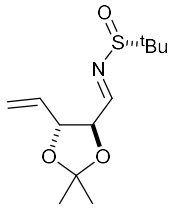
Step 2: I_2 (30.4 g, 120 mmol) was added to a stirred solution of the residue from the previous step, imidazole (10.2 g, 150 mmol) and PPh_3 (31.5 g, 120 mmol) in PhMe/MeCN (5:1 v/v, 450 mL) and the resultant mixture was heated at 60 °C for 1 h then cooled to rt. Et_2O (200 mL) was added and the resultant mixture was washed sequentially with satd aq $Na_2S_2O_3$ (100 mL), H_2O (100 mL) and brine (100 mL) then the organic layer was dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/Et_2O, 19:1) gave **334** as colourless viscous oil (21.8 g, 70%, >95:5 dr);[43] $[\alpha]_D^{25}$ –70.5 (*c* 1.0 in $CHCl_3$) {lit.[44] $[\alpha]_D^{25}$ –79.8 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, s, *Me*CMe), 1.49 (3H, s, MeC*Me*), 3.17 (1H, t, *J* 10.0, C(1')H_A), 3.30 (1H, dd, *J* 9.9, 6.0, (C(1')H_B), 3.38 (3H, s, O*Me*), 4.45 (1H, ddd, *J* 10.1, 6.0, 0.7, C(5)*H*), 4.64 (1H, d, *J* 5.9, C(4)*H*), 4.77 (1H, d, *J* 5.9, C(3)*H*), 5.06 (1H, s, C(2)*H*).

(2*S*,3*R*,*R*S,*E*)-*N*-[2,3-Dihydroxy-2,3-*O*-isopropylidinepentylidine]-*tert*-butylsulfinimine 336



BuLi (2.2 M in hexanes, 1.55 mL, 3.41 mmol) was added to a stirred solution of **334** (1.07 g, 3.41 mmol, >95:5 dr) in THF (10 mL) at –78 °C and was stirred at –78 °C for 1 h. (*R*)-**338** (825 mg, 6.81 mmol) and $Ti(OEt)_4$ (1.43 mL, 6.81 mmol) were added, the resultant mixture was allowed to warm to rt then stirred at rt for 1 h. H_2O (5 mL) was added and the resultant suspension was filtered through Celite (eluent EtOAc) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 5:1) gave **336** as a pale yellow viscous oil (634 mg, 72%, >95:5 dr); ν_{max} (ATR) 1609 (C=N), 1378, 1216, 1081; $[\alpha]_D^{25}$ –198 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.22 (9H, s, C*Me*$_3$), 1.46 (3H, s, *Me*CMe), 1.61 (3H, s, MeC*Me*), 4.86–4.90 (1H, m, C(3)*H*), 4.94 (1H, dd, *J* 6.9, 5.1, C(2)*H*), 5.32 (1H, dt, *J* 10.4, 1.1, C(5)H_A), 5.46 (1H, dt, *J* 17.1, 1.2, C(5)H_B), 5.76 (1H, ddd, *J* 17.1, 10.4, 6.9, C(4)*H*), 7.92 (1H, d, *J* 5.1, C(1)*H*); δ_C (100 MHz, $CDCl_3$) 22.5 (C*Me*$_3$), 25.5 (*Me*CMe), 27.7 (MeC*Me*), 57.2 (*C*Me$_3$), 79.5 (*C*(2)), 79.5 (*C*(3)), 110.7 (Me*C*Me), 119.9 (*C*(5)), 131.6 (*C*(4)), 166.2 (*C*(1)); *m/z* (ESI$^+$) 260 ([M+H]$^+$, 100%), 282 ([M+Na]$^+$, 86%); HRMS (ESI$^+$) $C_{12}H_{21}NNaO_3S^+$ ([M+Na]$^+$) requires 282.1134; found 282.1132.

(*R*,*R*,*R*S,*E*)-*N*-[2,3-Dihydroxy-2,3-*O*-isopropylidinepentylidine]-*tert*-butylsulfinimine 150



Method A: K_2CO_3 (1.07 g, 7.71 mmol) was added to a stirred solution of **336** (200 mg, 0.771 mmol, >95:5 dr) in MeOH (10 mL) at rt and the resultant mixture was stirred at rt for 18 h then concentrated *in vacuo*. The residue was partitioned between Et_2O (5 mL) and H_2O (5 mL) and the aqueous layer was extracted with Et_2O (3 × 5 mL) then the combined organic layers were dried and concentrated *in vacuo* to give a complex mixture containing (*R*)-**338**.

Method B: DBU (0.32 mL, 2.3 mmol) was added to a stirred solution of **336** (200 mg, 0.77 mmol, >95:5 dr) in PhMe (2 mL) at rt and the resultant mixture was stirred at rt for 18 h then H_2O (2 mL) was added. The aqueous layer was extracted with EtOAc (3 × 2 mL) then the combined organic layers were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 7:1) gave **150** as a colourless viscous oil (35 mg, 18%, >95:5 dr); ν_{max} (ATR) 1625 (C=N), 1459, 1372, 1072; $[\alpha]_D^{25}$ –143 (*c* 1.0 in $CHCl_3$); δ_H (400 MHz, $CDCl_3$) 1.18 (9H, s, C*Me*$_3$), 1.47 (3H, s, *Me*CMe), 1.49 (3H, s, MeC*Me*), 4.40 (1H,dd, *J* 8.0, 7.0, C(3)*H*), 4.48 (1H, dd, *J* 8.0, 5.0, C(2)*H*), 5.31 (1H, dt, *J* 10.3, 1.0, C(5)H_A), 5.38 (1H, dt, *J* 17.1, 1.1, C(5)H_B), 5.89 (1H, ddd, *J* 17.1, 10.3, 7.0, C(4)*H*), 8.06 (1H, d, *J* 5.0, C(1)*H*); δ_C (100 MHz, $CDCl_3$) 22.3 (C*Me*$_3$), 26.5 (*Me*CMe), 26.9 (MeC*Me*), 56.8 (*C*Me$_3$), 80.2 (*C*(3)), 81.7 (*C*(2)), 111.1 (Me*C*Me), 119.8 (*C*(5)), 133.7 (*C*(4)), 166.2 (*C*(1)); *m/z* (ESI$^+$) 260 ([M+H]$^+$, 16%), 282 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{12}H_{22}NO_3S^+$ ([M+H]$^+$) requires 260.1315; found 260.1317.

Method C: NaHMDS (1 M in THF, 0.58 mL, 0.58 mmol) was added to a stirred solution of **336** (100 mg, 0.386 mmol, >95:5 dr) in THF (1 mL) at 0 °C and the resultant mixture was

stirred at rt for 1 h then NH_4Cl (0.5 mL) was added and the aqueous layer was extracted with EtOAc (3 × 1 mL). The combined organic layers were dried and concentrated *in vacuo* to give a complex mixture.

Method D: Et_3N (0.16 mL, 1.2 mmol) was added to a stirred solution of **336** (100 mg, 0.386 mmol, >95:5 dr) in CH_2Cl_2 (1 mL) at rt and the resultant mixture was stirred at rt for 18 h then concentrated *in vacuo* to give returned starting material **336**.

Method E: *Step 1*: BuLi (2.2 M in hexanes, 13.4 mL, 29.6 mmol) was added to a stirred solution of **334** (6.17 g, 19.7 mmol, >95:5 dr) in THF (88 mL) at –78 °C and was stirred at –78 °C for 1 h then NH_4Cl (500 mg) was added and the resultant mixture was allowed to warm to rt. H_2O (50 mL) was added and the aqueous layer was extracted with Et_2O (3 × 50 mL) then the combined organic layers were dried and concentrated *in vacuo*.

Step 2: K_2CO_3 (27.2 g, 196 mmol) was added to a stirred solution of the residue from the previous step in MeOH (80 mL) at rt and the resultant mixture was allowed to stir at rt for 18 h. AcOH (11.2 mL, 196 mmol) and CH_2Cl_2 (100 mL) were added and washed with H_2O (2 × 50 mL). The combined aqueous layers were extracted with CH_2Cl_2 (3 × 50 mL) and the combined organic layers were dried and concentrated *in vacuo*.

Step 3: $Ti(OEt)_4$ (20.7 mL, 98.5 mmol) was added to a stirred solution of the residue from the previous step and (*R*)-**338** (2.51 g, 20.7 mmol) in CH_2Cl_2 (150 mL) at rt and allowed to stir at rt for 18 h then H_2O (20 mL) was added. The resultant suspension was filtered through Celite® (eluent CH_2Cl_2) then concentrated *in vacuo* to give a complex mixture containing (*R*)-**338** as the major component and **336** as the major imine diastereoisomer.

Method F: BuLi (2.2 M in hexanes, 13.4 mL, 29.6 mmol) was added to a stirred solution of **334** (6.17 g, 19.7 mmol, >95:5 dr) in THF (88 mL) at –78 °C and was stirred at –78 °C for 1 h then DBU (0.48 mL, 3.2 mmol) was added at –78 °C and the resultant mixture was stirred at –78 °C for 1 h then allowed to warm to rt. The resultant mixture was stirred at rt for 20 min then (*R*)-**338** (825 mg, 6.81 mmol) and $Ti(OEt)_4$ (1.43 mL, 6.81 mmol) were added and the resultant mixture was stirred at rt for 1 h. H_2O (5 mL) was added and the resultant suspension was filtered through Celite (eluent EtOAc) and concentrated *in vacuo* to give a 60:19:21 mixture of **150**, **336** and **334**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 7:1) gave **334** as a colourless viscous oil (53 mg, 11%, >95:5 dr). Further elution gave **150** as a colourless viscous oil (86 mg, 21%, >95:5 dr).

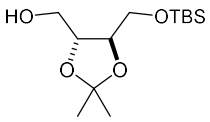
Method G: *Step 1*: DMSO (0.36 mL, 5.1 mmol) was added to a stirred solution of $(COCl)_2$ (0.21 mL, 2.5 mmol) in CH_2Cl_2 (3 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then **346** (200 mg, 1.26 mmol, >95:5 dr) in CH_2Cl_2 (3 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et_3N (1.05 mL, 7.56 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 20 min then at rt for 20 min. The organic layer was washed with H_2O (2 × 5 mL) then the combined aqueous layers were extracted with CH_2Cl_2 (3 × 5 mL) then the combined organic layers were dried and concentrated *in vacuo* to give **337** as a yellow viscous oil.

Step 2: $Ti(OEt)_4$ (0.53 mL, 2.5 mmol) was added to a stirred solution of the residue from the previous step and (*R*)-**338** (305 mg, 2.52 mmol) in CH_2Cl_2 (10 mL) at rt and allowed to stir at rt for 18 h then H_2O (3 mL) was added. The resultant suspension was filtered through Celite® (eluent CH_2Cl_2) then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 7:1) gave **150** as a colourless viscous oil (137 mg, 42%, >95:5 dr).

Method H: *Step 1*: DMSO (0.25 mL, 3.5 mmol) was added to a stirred solution of $(COCl)_2$ (0.15 mL, 1.8 mmol) in CH_2Cl_2 (2 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then **346** (140 mg, 0.885 mmol, >95:5 dr) in CH_2Cl_2 (2 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et_3N (0.74 mL, 5.3 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 20 min then at rt for 20 min. The organic layer was washed with H_2O (2 × 5 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (3 × 5 mL) then the combined organic layers were dried and concentrated *in vacuo* to give **337** as a yellow viscous oil.

Step 2: 4 Å MS (825 mg) were added to a stirred solution of the residue from the previous step and (*R*)-**338** (107 mg, 0.885 mmol) in CH_2Cl_2 (5 mL) at rt and allowed to stir at rt for 72 h then filtered through Celite® (eluent CH_2Cl_2) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 7:1) gave **150** as a colourless viscous oil (45 mg, 20%, >95:5 dr).

(*R*,*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,3,4-trihydroxy-2,3-*O*-isopropylidinebutane 344

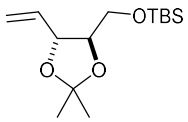


Step 1: TsOH (501 mg, 2.64 mmol) was added to a stirred solution of diethyl D-tartrate **340** (54.3 g, 264 mmol) and 2,2-dimethoxypropane (48.6 mL, 395 mmol) in PhMe (300 mL) at rt and the resultant mixture was heated at 120 °C, with azeotropic removal of MeOH by means of Dean-Stark apparatus, for 18 h then allowed to cool to rt. Satd aq $NaHCO_3$ (50 mL) was added and the resultant mixture was stirred at rt for 15 min. The aqueous layer was extracted with EtOAc (3 × 100 mL) and the combined organic layers were washed sequentially with H_2O (200 mL) and brine (200 mL) then dried and concentrated *in vacuo* to give a mixture of esters **341** and **342** as colourless viscous oil.

Step 2: A solution of the residue from the previous step in THF (280 mL) was added to a stirred suspension of $LiAlH_4$ (25.0 g, 660 mmol) in THF (280 mL) at 0 °C and the resultant mixture was heated at 67 °C for 18 h then cooled to rt. 2.0 M aq NaOH (100 mL) was added and the resultant mixture was stirred at rt for 2 h then filtered through Celite® (eluent EtOAc), dried and concentrated *in vacuo* to give **343** as a colourless viscous oil.

Step 3: NaH (60% in mineral oil, 10.6 g, 264 mmol) was stirred in THF (200 mL) for 15 min at 0 °C then a solution of the residue from the previous step in THF (210 mL) was added and the resultant mixture was stirred at 0 °C for 45 min. TBDMSCl (39.8 g, 264 mmol) was added and the resultant mixture was allowed to warm to rt over 18 h. Et_2O (200 mL) and satd aq $NaHCO_3$ (150 mL) were added and the aqueous layer was extracted with Et_2O (3 × 100 mL) then the combined organic layers were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 7:1) gave **344** as a colourless viscous oil (35.3 g, 48%, >95:5 dr);[45] $[\alpha]_D^{25}$ –17.6 (*c* 1.0 in $CHCl_3$) {lit.[46] $[\alpha]_D^{20}$ –18 (*c* 1.02 in $CHCl_3$)]}; δ_H (400 MHz, $CDCl_3$) 0.09 (6H, s, Si*Me*$_2$) 0.91 (9H, s, SiC*Me*$_3$), 1.41 (3H, s, *Me*CMe), 1.42 (3H, s, MeC*Me*), 2.40 (1H, br s, O*H*), 3.64–3.70 (1H, m, C(1)H_A), 3.71–3.76 (1H, m, C(4)H_A), 3.78 (1H, dd, *J* 11.4, 4.8, C(4)H_B), 3.85–3.92 (2H, m, C(1)H_B, C(2)*H*), 3.96–4.03 (1H, m, C(3)*H*).

(*R*,*R*)-1-(*tert*-Butyldimethylsilyloxy)-2,3-dihydroxy-2,3-*O*-isopropylidinepent-4-ene 345



Method A: Step *1*: DMSO (15.4 mL, 217 mmol) was added to a stirred solution of $(COCl)_2$ (9.22 mL, 109 mmol) in CH_2Cl_2 (135 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then **344** (15.0 g, 54.3 mmol, >95:5 dr) in CH_2Cl_2 (135 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et_3N

(45.4 mL, 326 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 20 min then at rt for 20 min. The organic layer was washed with H_2O (2 × 100 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (3 × 150 mL) then the combined organic layers were dried and concentrated *in vacuo*.

Step 2: BuLi (2.2 M in hexanes, 69.0 mL, 152 mmol) was added to a stirred solution of $MePh_3P^+Br^-$ (58.2 g, 163 mmol) in THF (264 mL) at 0 °C then allowed to warm to rt over 3 h before the precipitate was allowed to settle. The liquid was added *via* cannula to a stirred solution of the residue from the previous step in THF (150 mL) at –78 °C and allowed to warm to rt over 3 h then H_2O (100 mL) was added. The aqueous layer was extracted with EtOAc (3 × 100 mL) then the combined organic layers were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 50:1) gave **345** as colourless viscous oil (7.33 g, 67%, >95:5 dr); $[\alpha]_D^{25}$ –2.9 (*c* 0.5 in $CHCl_3$) {lit.[46] $[\alpha]_D^{25}$ –4.5 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.07 (3H, s, *Me*SiMe), 0.08 (3H, s, MeSi*Me*), 0.90 (9H, s, SiC*Me*$_3$), 1.42 (3H, s, *Me*CMe), 1.44 (3H, s, MeC*Me*), 3.70–3.80 (3H, m, C(1)*H*$_2$, C(2)*H*), 4.31–4.39 (1H, m, C(3)*H*), 5.21–5.26 (1H, m, C(5)H_A), 5.37 (1H, dt, *J* 17.2, 1.3, C(5)H_B), 5.87 (1H, ddd, *J* 17.2, 10.3, 6.9, C(4)*H*).

Method B: *Step 1*: TsOH (138 mg, 0.727 mmol) was added to a stirred solution of diethyl D-tartrate **340** (14.5 g, 70.3 mmol, >95:5 dr) and 2,2-dimethoxypropane (13.0 mL, 105 mmol) in PhMe (100 mL) at rt and the resultant mixture was heated at 120 °C, with azeotropic removal of MeOH by means of Dean-Stark apparatus, for 18 h then allowed to cool to rt. Satd aq $NaHCO_3$ (20 mL) was added and the resultant mixture was stirred at rt for 15 min. The aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic layers were washed sequentially with H_2O (100 mL) and brine (100 mL) then dried and concentrated *in vacuo* to give a mixture of esters **341** and **342** as a colourless viscous oil.

Step 2: $LiAlH_4$ (2.4 M in THF, 73.2 mL, 176 mmol) was added to a stirred solution of the residue from the previous step in THF (150 mL) at 0 °C and the resultant mixture was heated at 67 °C for 18 h then cooled to rt. 2.0 M aq NaOH (20 mL) was added and the resultant mixture was filtered through Celite® (eluent EtOAc), dried and concentrated *in vacuo* to give **343** as a colourless viscous oil.

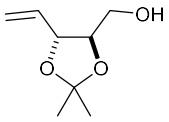
Step 3: NaH (60% in mineral oil, 2.81 g, 70.3 mmol) was stirred in THF (55 mL) for 15 min at 0 °C then a solution of the residue from the previous step in THF (55 mL) was added and the resultant mixture was stirred at 0 °C for 45 min. TBDMSCl (10.6 g, 70.3 mmol) was added and the resultant mixture was allowed to warm to rt over 18 h. Et_2O (50 mL) and satd aq $NaHCO_3$ (50 mL) were added and the aqueous layer was extracted with Et_2O (3 × 50 mL) then the combined organic layers were dried and concentrated *in vacuo* to give **344** as a colourless viscous oil.

Step 4: DMSO (20.0 mL, 281 mmol) was added to a stirred solution of $(COCl)_2$ (11.9 mL, 141 mmol) in CH_2Cl_2 (175 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then a solution of the residue from the previous step in CH_2Cl_2 (175 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et_3N (58.8 mL, 422 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 20 min then at rt for 20 min. The organic layer was washed with H_2O (2 × 50 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (3 × 100 mL) then the combined organic layers were dried and concentrated *in vacuo*.

Step 5: BuLi (2.2 M in hexanes, 64.1 mL, 141 mmol) was added to a stirred solution of $MePh_3P^+Br^-$ (62.8 g, 176 mmol) in THF (344 mL) at 0 °C then allowed to warm to rt over 3 h before the precipitate was allowed to settle. The liquid was added *via* cannula to a stirred solution of the residue from the previous step in THF (200 mL) at –78 °C and allowed to warm to rt over 3 h then H_2O (50 mL) was added. The aqueous layer was extracted with

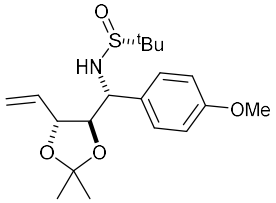
EtOAc (3 × 50 mL) then the combined organic layers were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 50:1) gave **345** as colourless viscous oil (7.33 g, 38%, >95:5 dr).

(*R*,*R*)-1,2,3-Trihydroxy-2,3-*O*-isopropylidinepent-4-ene 346



TBAF (1 M in THF, 13.1 mL, 13.1 mmol) was added to a stirred solution of **345** (2.97 g, 10.9 mmol) in THF (50 mL) at 0 °C and was stirred at 0 °C for 2.5 h then satd aq NH_4Cl (10 mL), H_2O (20 mL) and Et_2O (50 mL) were added. The aqueous layer was extracted with Et_2O (3 × 50 mL) then the combined organic layers were washed with brine (50 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 5:1) gave **346** as colourless viscous oil (1.43 g, 83%, >95:5 dr); $[\alpha]_D^{25}$ +1.9 (*c* 1.0 in $CHCl_3$) {lit.[47] for *ent*-**346** $[\alpha]_D^{20}$ −3.6 (*c* 1.1 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.45 (6H, s, *Me*C*Me*), 2.00 (1H, br s, O*H*), 3.57–3.65 (1H, m, C(1)H_A), 3.78–3.88 (2H, m, C(1)H_B, C(2)*H*), 4.33 (1H, app t, *J* 8.0, C(3)*H*), 5.28 (1H, dt, *J* 10.3, 0.9, C(5)H_A), 5.40 (1H, dt, *J* 17.1, 1.1, C(5)H_B). 5.87 (1H, ddd, *J* 17.1, 10.3, 7.2, C(4)*H*).

(*R*,*R*,*R*,*R*s)-1-(4'-methoxyphenyl)-1-(*N*-*tert*-butylsulfinamido)-2,3-dihydroxy-2,3-*O*-isopropylidinepent-4-ene 347



Method A:[48] 4-Methoxyphenylmagnesium bromide **308** (0.5 M in THF, 0.80 mL, 0.40 mmol) was added to a stirred solution of **150** (86 mg, 0.33 mmol, >95:5 dr) in Et_2O (2 mL) at

–78 °C and stirred at –78 °C for 5 h then satd aq NH_4Cl (0.5 mL) was added and the resultant mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 2 mL) then the combined organic layers were dried and concentrated *in vacuo* to give a 37:63 mixture of **150** and **347**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 5:1 increased to 1:1) gave **150** as colourless viscous oil (24 mg, 28%, >95:5 dr). Further elution gave **347** as a colourless viscous oil (56 mg, 46%, >95:5 dr); $[\alpha]_D^{25}$ –80.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1613, 1514, 1249, 1173, 1057 (S=O); δ_H (400 MHz, $CDCl_3$) 1.23 (9H, s, C*Me*$_3$), 1.34 (3H, s, *Me*CMe), 1.37 (3H, s, MeC*Me*), 3.79 (3H, s, O*Me*), 3.98–4.05 (2H, m, C(2)*H*, N*H*), 4.23–4.31 (1H, m, C(3)*H*), 4.63–4.67 (1H, m, C(1)*H*), 5.07 (1H, app d, *J* 10.4, C(5)H_A), 5.19 (1H, app d, *J* 17.1, C(5)H_B), 5.44 (1H, ddd, *J* 17.1, 10.4, 6.6, C(4)*H*), 6.86 (2H, d, *J* 8.7, C(3')*H*, C(5')*H*), 7.24 (2H, d, *J* 8.7, C(2')*H*, C(6')*H*); δ_C (100 MHz, $CDCl_3$) 22.6 (C*Me*$_3$), 26.7 (MeC*Me*), 26.9 (*Me*CMe), 55.1 (O*Me*), 55.7 (*C*Me$_3$), 57.1 (*C*(1)), 78.0 (*C*(3)), 83.4 (*C*(2)), 109.3 (Me*C*Me), 113.6 (*C*(3'), *C*(5')), 118.4 (*C*(5)), 128.6 (*C*(1')), 129.6 (*C*(2'), *C*(6')), 135.4 (*C*(4)), 159.4 (*C*(4')); *m/z* (ESI^+) 368 ($[M+H]^+$, 42%), 390 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{19}H_{30}NO_4S^+$ ($[M+H]^+$) requires 368.1890; found 368.1891.

Method B: 4-Methoxyphenylmagnesium bromide **308** (0.5 M in THF, 2.38 mL, 1.19 mmol) was added to a stirred solution of **150** (123 mg, 0.474 mmol, >95:5 dr) in Et_2O (3 mL) at –78 °C and stirred at –78 °C for 5 h then satd aq NH_4Cl (0.5 mL) was added and the resultant mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 2 mL) then the combined organic layers were dried and concentrated *in vacuo* to give a >95:5 mixture of **347** (>95:5 dr) and **150**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 1:1) gave **347** as a colourless viscous oil (165 mg, 95%, >95:5 dr).

Method C: *Step 1*: DMSO (2.54 mL, 35.7 mmol) was added to a stirred solution of $(COCl)_2$ (1.51 mL, 17.8 mmol) in CH_2Cl_2 (20 mL) at –78 °C and the resultant mixture was allowed to stir at –78 °C for 10 min then **346** (1.41 g, 8.91 mmol, >95:5 dr) in CH_2Cl_2 (20 mL) was added at –78 °C. The resultant mixture was allowed to stir at –78 °C for 1 h then Et_3N (7.46 mL, 53.5 mmol) was added and the resultant mixture was allowed to stir at –78 °C for 20 min then at rt for 20 min. The organic layer was washed with H_2O (2 × 20 mL) and the combined aqueous layers were extracted with CH_2Cl_2 (3 × 20 mL) then the combined organic layers were dried and concentrated *in vacuo* to give **337** as a yellow viscous oil.

Step 2: $Ti(OEt)_4$ (3.74 mL, 17.8 mmol) was added to a stirred solution of the residue from the previous step and (*R*)-**338** (1.08 g, 17.8 mmol) in CH_2Cl_2 (14 mL) at rt and allowed to stir at rt for 18 h then H_2O (5 mL) was added. The resultant mixture was filtered through Celite® (eluent CH_2Cl_2) then concentrated *in vacuo* to give **150** as a pale yellow viscous oil.

Step 3: 4-Methoxyphenylmagnesium bromide **308** (0.5 M in THF, 44.5 mL, 22.3 mmol) was added to a stirred solution of the residue from the previous step in Et_2O (56 mL) at –78 °C and stirred at –78 °C for 5 h then satd aq NH_4Cl (20 mL) was added and the resultant mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 50 mL) then the combined organic layers were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 1:1) gave **347** as a colourless viscous oil (1.50 g, 44%, >95:5 dr).

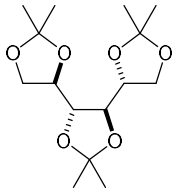
Method D: H_5IO_6 (272 mg, 1.19 mmol) was added to a stirred solution of **350** (136 mg, 0.596 mmol, >95:5 dr) in EtOAc (9 mL) at rt and allowed to stir at rt for 30 min then satd aq $NaHCO_3$ (5 mL) was added. The resultant mixture was filtered through Celite® (eluent EtOAc) then dried and concentrated *in vacuo* to give **337** as a pale yellow viscous oil.

Step 2: $Ti(OEt)_4$ (0.25 mL, 1.2 mmol) was added to a stirred solution of the residue from the previous step and (*R*)-**338** (72 mg, 0.60 mmol) in CH_2Cl_2 (1 mL) and rt and allowed to stir at

rt for 18 h. H_2O (0.5 mL) was added and the resultant suspension was filtered through Celite® (eluent CH_2Cl_2) then dried and concentrated *in vacuo* to give **150** as a pale yellow viscous oil.

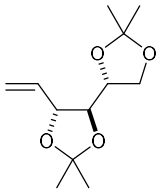
Step 3: 4-Methoxyphenylmagnesium bromide **308** (0.5 M in THF, 2.98 mL, 1.49 mmol) was added to a stirred solution of the residue from the previous step in Et_2O (4 mL) at –78 °C and stirred at –78 °C for 5 h then satd aq NH_4Cl (1 mL) was added and the resultant mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 5 mL) then the combined organic layers were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 1:1) gave **347** as a colourless viscous oil (74 mg, 34%, >95:5 dr).

(*R*,*R*,*R*,*R*)-1,2,3,4,5,6-Tris-*O*-isopropylidinehexan-1,2,3,4,5,6-hexaol 348



H_2SO_4 (3 mL) was added to a stirred solution of D-mannitol **27** (10.0 g, 54.9 mmol, >95:5 dr) in acetone (500 mL) at rt and the resultant mixture was allowed to stir at rt for 18 h. 6.0 M aq NaOH was added until pH 7 was reached then the resultant mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc (250 mL) and H_2O (150 mL) and the aqueous was extracted with EtOAc (3 × 100 mL) then the combined organic layers were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 2:1) gave **348** as a pale yellow solid (12.4 g, 75%, >95:5 dr);[49] mp 66–67 °C (lit.[50] mp 70–71 °C); $[\alpha]_D^{25}$ +14.6 (*c* 1.0 in $CHCl_3$); {lit.[50] $[\alpha]_D^{20}$+13.8 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.36 (6H, s, *Me*C*Me*), 1.40 (6H, s, *Me*C*Me*), 1.44 (6H, s, *Me*C*Me*), 3.93–4.02 (4H, m, C(1)H_A, C(3)*H*, C(4)*H*, C(6)H_A), 4.09 (2H, dd, *J* 8.4, 6.4, C(1)H_B, C(6)H_B), 4.18–4.23 (2H, m, C(2)*H*, C(5)*H*).

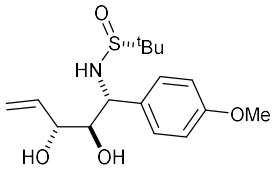
(3*R*,4*S*,5*R*)-3,4,5,6-Bis-*O*-isopropylidinehex-1-en-3,4,5,6-tetraol 350



Step 1: HCl (conc, 0.80 mL) was added in 10 portions at 5 min intervals to a stirred solution of **348** (11.4 g, 37.7 mmol) in EtOH/H_2O (7:3 v/v, 260 mL) at 45 °C. K_2CO_3 (3.80 g, 27.5 mmol) was added upon completion of the addition of HCl and the resultant mixture was extracted with EtOAc (3 × 200 mL) then the combined organic layers were dried concentrated *in vacuo*. The residue was dissolved in cold water, then filtered to give **348** (5.60 g, 49%). The aqueous layer was extracted with EtOAc (3 × 100 mL) then the combined organic layers were dried and concentrated *in vacuo* to give **349**.

Step 2: PPh_3 (14.5 g, 55.2 mmol), imidazole (3.76 g, 55.2 mmol) and I_2 (10.4 g, 41.4 mmol) were added to a stirred solution of the residue from the previous step in PhMe (280 mL) at rt then the resultant mixture was heated at 110 °C for 3 h then allowed to cool to rt. Satd aq $Na_2S_2O_3$ (50 mL) and satd aq $NaHCO_3$ (25 mL) were added then the aqueous layer was extracted with EtOAc (3 × 80 mL). The combined organic layers were dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 20:1) gave **350** as a white viscous oil (2.37 g, 28% from **348**);[49] $[\alpha]_D^{25}$ –3.2 (*c* 1.0 in $CHCl_3$); {lit.[50] $[\alpha]_D^{26}$ –3.1 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.36 (3H, s, *Me*CMe), 1.42 (3H, s, MeC*Me*), 1.42 (6H, m, *Me*C*Me*), 3.69–3.74 (1H, m, C(6)H_A), 3.93–4.00 (1H, m, C(6)H_B), 4.07–4.17 (2H, m, C(4)*H*, C(5)*H*), 4.35–4.40 (1H, m, C(3)*H*), 5.22 (1H, dt, *J* 10.5, 1.4, C(1)H_A), 5.43 (1H, dt, *J* 17.2, 1.4, C(1)H_B), 5.90 (1H, ddd, *J* 17.2, 10.5, 6.1, C(2)*H*).

(*R*,*R*,*R*)-1-(4'-Methoxyphenyl)-1-(*N*-*tert*-butylsulfinamido)-pent-4-en-2,3-diol 351



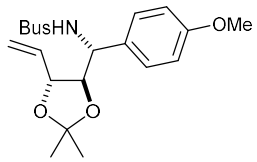
Method A:[47] A solution of **347** (100 mg, 0.272 mmol, >95:5 dr) in TFA/H_2O (4:1 v/v, 0.30 mL) was stirred at rt for 3 h then satd aq $NaHCO_3$ (0.25 mL) was added. The aqueous layer was extracted with EtOAc (3 × 1 mL) then the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent EtOAc) gave **351** as a white solid (29 mg, 33%, >95:5 dr); mp 156–158 °C; $[\alpha]_D^{25}$ –81.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3275 (O–H), 1612 (C=C), 1513, 1249, 1176, 1033 (S=O); δ_H (400 MHz, $CDCl_3$) 1.29 (9H, s, C*Me*$_3$), 2.25 (1H, d, *J* 7.6, C(3)O*H*), 3.80–3.85 (4H, m, C(2)*H*, O*Me*), 3.98–4.04 (1H, m, C(3)*H*), 4.39 (1H, d, *J* 8.3, C(2)O*H*), 4.67 (1H, dd, *J* 8.3, 4.1, C(1)*H*), 5.15–5.21 (2H, m, C(5)H_2), 5.35 (1H, d, *J* 8.7, N*H*), 5.85–5.96 (1H, m, C(4)*H*), 6.88–6.94 (2H, m, C(3')*H*, C(5')*H*), 7.25–7.30 (2H, m, C(2')*H*, C(6')*H*); δ_C (100 MHz, $CDCl_3$) 22.8 (C*Me*$_3$), 55.3 (O*Me*), 55.9 (*C*Me$_3$), 64.5 (*C*(1)), 71.9 (*C*(3)), 74.9 (*C*(2)), 114.0 (*C*(3'), *C*(5')), 116.5 (*C*(5)), 128.0 (*C*(2'), *C*(6')), 131.4 (*C*(1')), 138.0 (*C*(4)), 158.9 (*C*(4')); *m/z* (ESI^+) 350 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{16}H_{26}NO_4S^+$ ($[M+H]^+$) requires 328.1577; found 328.1577.

Method B:[51] $TsOH{\cdot}H_2O$ (15 mg, 0.079 mmol) was added to a stirred solution of **347** (145 mg, 0.394 mmol, >95:5 dr) in MeOH (4 mL) at rt and the resultant mixture was stirred at rt for 18 h. Satd aq $NaHCO_3$ (1 mL) was added and the resultant mixture was concentrated *in vacuo*. The residue was partitioned between H_2O (2 mL) and EtOAc (2 mL) and the aqueous layer was extracted with EtOAc (3 × 2 mL) then the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to give a 39:61 mixture of **347** and **351**, respectively. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 1:2

increased to 0:1) gave **347** (29 mg, 20%, >95:5 dr). Further elution gave **351** as a white solid (64 mg, 49%, >95:5 dr).

Method C: TsOH·H_2O (46 mg, 0.24 mmol) was added to a stirred solution of **347** (179 mg, 0.485 mmol, >95:5 dr) in MeOH (4.6 mL) at rt and the resultant mixture was stirred at rt for 18 h. Satd aq $NaHCO_3$ (1 mL) was added and the resultant mixture was concentrated *in vacuo*. The residue was partitioned between H_2O (2 mL) and EtOAc (2 mL) and the aqueous layer was extracted with EtOAc (3 × 2 mL) then the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to give a complex mixture. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 1:2 increased to 0:1) gave **347** (39 mg, 22%, >95:5 dr). Further elution gave **351** as a white solid (63 mg, 40%, >95:5 dr).

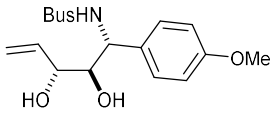
(*R*,*R*,*R*)-1-(4'-Methoxyphenyl)-1-(*N*-*tert*-butylsulfonamido)-2,3-dihydroxy-2,3-*O*-isopropylidinepent-4-ene 352



m-CPBA (70%, 56 mg, 0.23 mmol) was added to a stirred solution of **347** (56 mg, 0.15 mmol, >95:5 dr) in CH_2Cl_2 (1.6 mL) at 0 °C and the resultant mixture was stirred at rt for 1 h then satd aq Na_2SO_3 was added until there was no sign of oxidant left. The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were washed with brine (5 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 5:1) gave **352** as colourless viscous oil (55 mg, 94%, >95:5 dr); $[\alpha]_D^{25}$ –18.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3297 (N–H), 1613 (C=C), 1308 (S=O), 1129 (S=O); δ_H (400 MHz, $CDCl_3$) 1.17 (3H, s, *Me*CMe), 1.22 (9H, s, C*Me*$_3$), 1.40 (3H, s, MeC*Me*), 3.75–3.83 (4H, m, C(3)*H*, O*Me*), 4.09 (1H, dd, *J* 8.6, 3.6, C(2)*H*), 4.53 (1H, dd, *J* 9.1, 3.6, C(1)*H*), 4.91 (1H, d, *J* 9.1, N*H*), 5.26–5.38 (2H, m, C(5)*H*$_2$), 5.81 (1H,

ddd, *J* 17.7, 10.3, 7.4, C(4)*H*), 6.85–6.90 (2H, m, C(3')*H*, C(5')*H*), 7.17–7.22 (2H, m, C(2')*H*, C(6')*H*); δ_C (100 MHz, $CDCl_3$) 24.0 (C*Me*$_3$), 26.7 (*Me*CMe), 27.0 (MeC*Me*), 55.2 (O*Me*), 57.6 (*C*(1)), 59.7 (*C*Me$_3$), 79.3 (*C*(3)), 83.8 (*C*(2)), 109.4 (Me*C*Me), 113.6 (*C*(3'), *C*(5')), 119.9 (*C*(5)), 129.5 (*C*(2'), *C*(6')), 129.8 (*C*(1')), 134.2 (*C*(4)), 159.3 (*C*(4')); *m/z* (ESI^+) 401 ($[M+NH_4]^+$, 100%); HRMS (ESI^+) $C_{19}H_{29}NNaO_5S^+$ ($[M+Na]^+$) requires 406.1659; found 406.1658.

(*R*,*R*,*R*)-1-(4'-Methoxyphenyl)-1-(*N*-*tert*-butylsulfonamido)-pent-4-en-2,3-diol 353



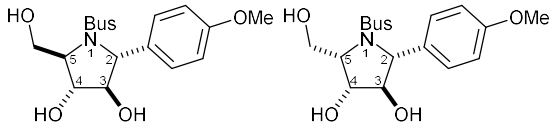
Method A:[51] TsOH·H_2O (10 mg, 52 μmol) was added to a stirred solution of **352** (100 mg, 0.261 mmol, >95:5 dr) in MeOH (2.6 mL) at rt and the resultant mixture was stirred at rt for 18 h then satd aq $NaHCO_3$ (1 mL) was added and the resultant mixture was concentrated *in vacuo*. The residue was partitioned between H_2O (2 mL) and EtOAc (2 mL) and the aqueous layer was extracted with EtOAc (3 × 2 mL) then the combined organic layers were dried and concentrated *in vacuo* to give a ~50:50 mixture of **352** and **353**, respectively. Purification *via* flash column chromatography (eluent 40–60 °C petroleum ether/EtOAc, 2:1 increased to 0:1) gave **352** as a colourless viscous oil (41 mg, 41%, >95:5 dr). Further elution gave **353** as white foam (45 mg, 50%, >95:5 dr); $[\alpha]_D^{25}$ –33.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3476, 3300, 1613, 1514, 1301, 1125; δ_H (400 MHz, $CDCl_3$) 1.27 (9H, s, C*Me*$_3$), 2.63 (1H, br s, O*H*), 3.00 (1H, br s, O*H*), 3.75–3.80 (1H, m, C(2)*H*), 3.82 (3H, s, O*Me*), 4.00–4.07 (1H, m, C(3)*H*), 4.62 (1H, dd, *J* 9.6, 5.0, C(1)*H*), 5.21–5.33 (2H, m, C(5)*H*$_2$), 5.67 (1H, d, *J* 9.6, N*H*), 5.91 (1H, ddd, *J* 17.2, 10.5, 5.9, C(4)*H*), 6.88–6.94 (2H, m, C(3')*H*, C(5')*H*), 7.24–7.30 (2H, m, C(2')*H*, C(6')*H*); δ_C (100 MHz, $CDCl_3$) 24.1 (C*Me*$_3$), 55.2 (O*Me*), 59.8 (*C*Me$_3$), 60.4 (*C*(1)), 71.9 (*C*(3)), 76.2 (*C*(2)), 114.1 (*C*(3'), *C*(5')), 117.5 (*C*(5)), 128.6 (*C*(2'), *C*(6')), 130.4 (*C*(1')), 137.0

(*C*(4)), 159.1 (*C*(4')); *m/z* (ESI$^+$) 366 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{25}NNaO_5S^+$ ([M+Na]$^+$) requires 366.1346; found 366.1344.

Method B: TsOH·H_2O (79 mg, 0.42 mmol) was added to a stirred solution of **352** (319 mg, 0.832 mmol, >95:5 dr) in MeOH (8 mL) at rt and the resultant mixture was stirred at rt for 18 h. Satd aq $NaHCO_3$ (3 mL) was added and the resultant mixture was concentrated *in vacuo*. The residue was partitioned between H_2O (5 mL) and EtOAc (5 mL) and the aqueous layer was extracted with EtOAc (3 × 10 mL) then the combined organic layers were dried and concentrated *in vacuo* to give a ~50:50 mixture of **352** and **353**, respectively. Purification *via* flash column chromatography (eluent 40–60 °C petroleum ether/EtOAc, 2:1 increased to 0:1) gave **352** as a colourless viscous oil (150 mg, 47%, >95:5 dr). Further elution gave **353** as a white foam (152 mg, 53%, >95:5 dr).

Method C: *m*-CPBA (70%, 113 mg, 0.458 mmol) was added to a stirred solution of **351** (100 mg, 0.305 mmol, >95:5 dr) in CH_2Cl_2 (3.2 mL) at 0 °C and the resultant mixture was stirred at rt for 1 h then satd aq Na_2SO_3 was added until there was no sign of oxidant left. The aqueous layer was extracted with CH_2Cl_2 (3 × 2 mL). The combined organic layers were washed with brine (5 mL) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 1:2) gave **353** as a white foam (98 mg, 94%, >95:5 dr).

(*R*,*R*,*R*,*R*)-*N*(1)-(te*rt*-Butylsulfonamido)-2-(4''-methoxyphenyl)-3,4-hydroxy-5-hydroxymethylpyrrolidine 356 and (2*R*,3*R*,4*R*,5*S*)-*N*(1)-(te*rt*-butylsulfonamido)-2-(4''-methoxyphenyl)-3,4-hydroxy-5-hydroxymethylpyrrolidine 357



356 **357**

Method A: *Step 1*: *m*-CPBA (70%, 222 mg, 0.904 mmol) was added to a stirred solution of **353** (207 mg, 0.603 mmol, >95:5 dr) in CH_2Cl_2 (12 mL) at rt and was stirred at rt for 18 h then satd aq Na_2SO_3 was added until there was no sign of oxidant left. Satd aq $NaHCO_3$ (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) then the combined organic layers were dried with Na_2SO_4 then concentrated *in vacuo* to give a ~60:40 mixture of **354** and **355**, respectively.

Step 2: K_2CO_3 (167 mg, 1.21 mmol) was added to a stirred solution of the residue from the previous step in MeOH (15 mL) at rt and was stirred at rt for 18 h then satd aq NH_4Cl (1 mL) was added and the resultant mixture was concentrated *in vacuo*. The residue was partitioned between $CHCl_3$/^{i}PrOH (3:1 v/v, 5 mL) and H_2O (2 mL) and the aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1 v/v, 3 × 10 mL) then the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to give a ~60:40 mixture of **356** and **357**, respectively. Purification *via* exhaustive flash chromatography (eluent $CHCl_3$/^{i}PrOH/aq NH_4OH, 89:11:1) gave **356** as a white solid (88 mg, 41%, >95:5 dr); mp 191–194 °C; $[\alpha]_D^{25}$ –10.2 (*c* 1.0 in MeOH); ν_{max} (ATR) 3387 (O–H), 1302 (S=O), 1123 (S=O); δ_H (400 MHz, CD_3OD) 1.09 (9H, s, C*Me*$_3$), 3.77 (3H, s, O*Me*), 3.91–3.96 (1H, m, C(5)*H*), 4.00 (1H, dd, *J* 10.9, 3.2, C(1')H_A), 4.09–4.17 (2H, m, C(3)*H*, C(1')H_B), 4.23–4.27 (1H, m, C(4)*H*), 4.73 (1H, d, *J* 2.2, C(2)*H*), 6.82–6.86 (2H, m, C(3")*H*, C(5")*H*), 7.46–7.50 (2H, m, C(2")*H*, C(6")*H*); δ_C (100 MHz, CD_3OD) 23.7 (C*Me*$_3$), 54.3 (O*Me*), 61.7 (*C*(1')), 62.2 (*C*Me$_3$), 72.4 (*C*(5)), 73.9 (*C*(2)), 79.1

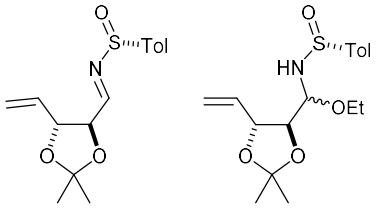
(*C*(4)), 83.4 (*C*(3)), 112.7 (*C*(3"), *C*(5")), 131.3 (*C*(2"), *C*(6")), 133.0 (*C*(1")), 159.3 (*C*(4")); *m/z* (ESI$^+$) 382 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{16}H_{25}NNaO_6S^+$ ([M+Na]$^+$) requires 382.1295; found 382.1293. Further elution gave an 85:15 mixture of **357** and **356**, respectively (25 mg, 11%, 85:15 dr). Further elution gave **357** as a colourless viscous oil (26 mg, 12%, >95:5 dr); $[\alpha]_D^{25}$ –7.8 (*c* 1.0 in MeOH); ν_{max} (ATR) 3415 (O–H), 1306 (S=O), 1117 (S=O); δ_H (400 MHz, CD_3OD) 1.16 (9H, s, C*Me*$_3$), 3.73 (3H, s, O*Me*), 3.91 (1H, dd, *J* 11.1, 4.0, C(1')H_A), 3.96 (1H, dd, *J* 11.1, 5.2, C(1')H_B), 4.12–4.22 (3H, m, C(3)*H*, C(4)*H*, C(5)*H*), 4.64–4.68 (1H, m, C(2)*H*), 6.82 (2H, d, *J* 8.8, C(3")*H*, C(5")*H*), 7.40 (2H, d, *J* 8.8, C(2")*H*, C(6")*H*); δ_C (100 MHz, CD_3OD) 25.2 (C*Me*$_3$), 62.2 (*C*(1')), 62.8 (*C*Me$_3$), 64.7 (*C*(5)), 69.9 (*C*(2)), 77.1 (*C*(4)), 83.5 (*C*(3)), 114.5 (*C*(3"), *C*(5")), 130.6 (*C*(2"), *C*(6")), 134.5 (*C*(1")), 160.6 (*C*(4")); *m/z* (ESI$^+$) 262 ([M–C_4H_8SO+Na]$^+$, 100%), 382 ([M+Na]$^+$, 71%); HRMS (ESI$^+$) $C_{16}H_{25}NNaO_6S^+$ ([M+Na]$^+$) requires 382.1295; found 382.1293.

Method B: *Step 1*: *m*-CPBA (70%, 450 mg, 1.83 mmol) was added to a stirred solution of **351** (200 mg, 0.610 mmol, >95:5 dr) in CH_2Cl_2 (12 mL) at rt and was stirred at rt for 18 h then satd aq Na_2SO_3 was added until there was no sign of oxidant left. Satd aq $NaHCO_3$ (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) then the combined organic layers were dried with Na_2SO_4 then concentrated *in vacuo* to give a ~60:40 mixture of **354:355**, respectively as a white solid.

Step 2: K_2CO_3 (169 mg, 1.22 mmol) was added to a stirred solution of the residue from the previous step in MeOH (9 mL) at rt and was stirred at rt for 18 h then satd aq NH_4Cl (1 mL) was added and the resultant mixture was concentrated *in vacuo*. The residue was partitioned between $CHCl_3$/^{i}PrOH (3:1, v/v, 5 mL) and H_2O (2 mL) and the aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1, v/v, 3 × 10 mL) then the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to give a ~60:40 mixture of **356** and **357**, respectively. Purification *via* exhaustive flash chromatography (eluent $CHCl_3$/^{i}PrOH/aq NH_4OH, 89:11:1)

gave **356** as a white solid (85 mg, 39%, >95:5 dr). Further elution gave a 70:30 mixture of **357** and **356**, respectively (40 mg, 18%, 70:30 dr). Further elution gave **357** as a colourless viscous oil (19 mg, 9%, >95:5 dr).

(2*S*,3*R*,*R*S,*E*)-*N*-[2,3-Dihydroxy-2,3-*O*-isopropylidinepentylidine]-tolylsulfinamide 357 and (*R*,*R*,*R*,*R*S)-1-ethoxy-1-*N*-tolylsulfinamido-2,3-dihydroxy-2,3-*O*-isopropylidinepent-4-ene and (1*S*,2*R*,3*R*,*R*S)-1-ethoxy-1-tolylsulfinamido-2,3-dihydroxy-2,3-*O*-isopropylidinepent-4-ene 363 and 364



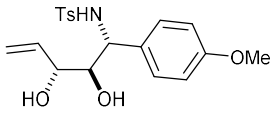
359 363+364

Step 1: H_5IO_6 (635 mg, 2.91 mmol) was added to a stirred solution of **350** (382 mg, 1.46 mmol, >95:5 dr) in EtOAc (21 mL) at rt and allowed to stir at rt for 30 min then satd aq $NaHCO_3$ (5 mL) was added. The resultant mixture was filtered through Celite® (eluent EtOAc) then dried and concentrated *in vacuo* to give **337** as a yellow viscous oil.

Step 2: $Ti(OEt)_4$ (0.61 mL, 2.9 mmol) was added to a stirred solution of the residue from the previous step and (*R*)-**365** (226 mg, 1.46 mmol) in CH_2Cl_2 (3.5 mL) and rt and allowed to stir at rt for 18 h. H_2O (2 mL) was added and the resultant suspension was filtered through Celite® (eluent CH_2Cl_2) then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 5:1) gave **359** as an orange viscous oil (24 mg, 6%, >95:5 dr, 95% purity); $[\alpha]_D^{25}$ +34.8 (*c* 0.1 in $CHCl_3$); ν_{max} (ATR) 1654 (C=C), 1461, 1381, 1260, 1080 (S=O); δ_H (400 MHz, $CDCl_3$) 1.44 (3H, s, *Me*CMe), 1.48 (3H, s, MeC*Me*), 2.41 (3H, s, Ar*Me*), 4.29–4.34 (1H, m, C(3)*H*), 4.44 (1H, dd, *J* 8.0, 4.7, C(2)*H*), 5.13–5.15 (1H, m, C(5)H_A), 5.17–5.19 (1H, m, C(5)H_B), 5.78 (1H, ddd, *J* 17.4, 10.5, 6.8, C(4)*H*), 7.29 (2H, d, *J* 8.1, C(3')*H*, C(5')*H*), 7.53 (2H, d, *J* 8.1, C(2')*H*, C(6')*H*), 8.22 (1H, d, *J*

4.6, C(1)*H*); δ_C (100 MHz, $CDCl_3$) 21.4 (Ar*Me*), 26.5 (*Me*CMe), 26.9 (MeC*Me*), 80.0 (*C*(3)), 81.4 (*C*(2)), 111.1 (Me*C*Me), 119.3 (*C*(5)), 124.5 (*C*(2'), *C*(6')), 129.8 (*C*(3'), *C*(5')), 133.5 (*C*(4)), 141.2 (*C*(1')), 142.0 (*C*(4')), 163.3 (*C*(1)); *m/z* (ESI^+) 294 ($[M+H]^+$, 23%), 609 ($[2M+Na]^+$, 100%); HRMS (ESI^+) $C_{15}H_{20}NO_3S^+$ ($[M+H]^+$) requires 294.1158; found 294.1160. Further elution gave a 57:43 mixture of **363** and **364** as colourless viscous oil (83 mg, 17%, 53:47 dr). Data for mixture: ν_{max} (ATR) 3194 (N–H), 1626 (C=C); *m/z* (ESI^+) 362 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{17}H_{25}NNaO_4S^+$ ($[M+Na]^+$) requires 362.1397; found 362.1398. Data for **363**: δ_H (400 MHz, $CDCl_3$) [selected data] 1.15 (3H, t, *J* 7.0, OCH_2*Me*), 2.42 (3H, s, Ar*Me*), 3.35 (1H, dq, *J* 9.5, 7.0, OC$H_A$$H_B$Me), 3.80 (1H, dq, *J* 9.5, 7.0, $OCH_A$$H_B$Me), 3.89 (1H, dd, *J* 8.0, 3.1, C(2)*H*), 4.40–4.48 (1H, m, C(3)*H*), 4.59 (1H, dd, *J* 10.0, 3.1, C(1)*H*), 4.81 (1H, d, *J* 10.0, N*H*), 5.30 (1H, dt, *J* 10.3, 1.1, C(5)H_A), 5.47 (1H, dt, *J* 17.1, 1.2, C(5)H_B), 5.91 (1H, ddd, *J* 17.1, 10.3, 7.3, C(4)*H*); δ_C (100 MHz, $CDCl_3$) [selected data] 14.8 (OCH_2*Me*), 21.3 (Ar*Me*), 63.9 (O*C*H_2Me), 79.9 (*C*(3)), 82.6 (*C*(2)), 85.5 (*C*(1)), 119.0 (*C*(5)), 135.5 (*C*(4)). Data for **364**: δ_H (400 MHz, $CDCl_3$) [selected data] 1.26 (3H, t, *J* 7.0, OCH_2*Me*), 2.42 (3H, s, Ar*Me*), 3.55 (1H, dq, *J* 9.5, 7.0, OC$H_A$$H_B$Me), 3.75 (1H, dd, *J* 8.0, 3.1, C(2)*H*), 3.96 (1H, dq, *J* 9.5, 7.0, $OCH_A$$H_B$Me), 4.40–4.48 (1H, m, C(3)*H*), 4.54 (1H, dd, *J* 9.6, 3.4, C(1)*H*), 4.89 (1H, d, *J* 9.6, N*H*), 5.24 (1H, dt, *J* 10.3, 1.1, C(5)H_A), 5.37 (1H, dt, *J* 17.2, 1.2, C(5)H_B), 5.80 (1H, ddd, *J* 17.2, 10.3, 7.2, C(4)*H*); δ_C (100 MHz, $CDCl_3$) [selected data] 14.8 (OCH_2*Me*), 21.3 (Ar*Me*), 63.5 (O*C*H_2Me), 78.3 (*C*(3)), 83.3 (*C*(2)), 83.7 (*C*(1)), 119.3 (*C*(5)), 135.2 (*C*(4)).

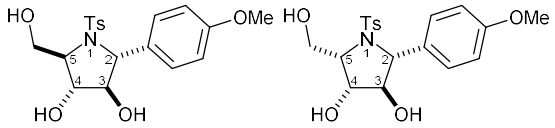
(*R*,*R*,*R*)-1-(4'-Methoxyphenyl)-1-*N*-tosylamino-pent-4-en-2,3-diol 367



Step 1: A solution of **347** (200 mg, 0.544 mmol, >95:5 dr) in HCl (1.25 M in MeOH, 2.18 mL, 2.72 mmol) was stirred at rt for 18 h then concentrated *in vacuo* to give **366**·HCl as a pale orange solid.

Step 2: Et_3N (0.19 mL, 1.4 mmol) and TsCl (114 mg, 0.598 mmol) were added to a stirred solution of the residue from the previous step in CH_2Cl_2 (2 mL) at rt and the resultant mixture was stirred at rt for 6 h then concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30–40 °C petroleum ether/EtOAc, 1:1) gave **367** as a pale yellow solid (136 mg, 66%, >95:5 dr); mp 132–134 °C; $[\alpha]_D^{25}$ –49.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 1476, 3288, 1612, 1513, 1181; δ_H (400 MHz, $CDCl_3$) 2.26 (1H, br s, O*H*), 2.36 (3H, s, Ar*Me*), 2.51 (1H, br s, O*H*), 3.71–3.77 (4H, m, C(2)*H*, O*Me*), 4.06–4.11 (1H, m, C(3)*H*), 4.46 (1H, dd, *J* 8.7, 5.6, C(1)*H*), 5.25 (1H, app dt, *J* 10.5, 1.3, C(5)H_A), 5.27 (1H, app dt, *J* 17.2, 1.3, C(5)H_B), 5.67 (1H, d, *J* 8.7, N*H*), 5.87 (1H, ddd, *J* 17.2, 10.5, 6.1, C(4)*H*), 6.66–6.71 (2H, m, C(3')*H*, C(5')*H*), 6.95–7.00 (2H, m, C(2')*H*, C(6')*H*), 7.12 (2H, d, *J* 8.0, C(3")*H*, C(5")*H*), 7.50–7.55 (2H, m, C(2")*H*, C(6")*H*); δ_C (100 MHz, $CDCl_3$) 21.4 (Ar*Me*), 55.2 (O*Me*), 59.3 (*C*(1)), 71.9 (*C*(3)), 75.6 (*C*(2)), 113.9 (*C*(3'), *C*(5')), 117.8 (*C*(5)), 127.0 (*C*(2"), *C*(6")), 128.7 (*C*(2'), *C*(6')), 129.1 (*C*(1')), 129.3 (*C*(3"), *C*(5")), 137.5 (*C*(1"), 136.7 (*C*(4)), 143.1 (*C*(4"), 159.2 (*C*(4')); *m/z* (ESI^+) 777 ($[2M+Na]^+$, 100%); HRMS (ESI^+) $C_{38}H_{46}N_2NaO_{10}S_2^+$ ($[2M+Na]^+$) requires 777.2486; found 777.2485.

(*R*,*R*,*R*,*R*)-*N*(1)-Tosyl-2-(4''-methoxyphenyl)-3,4-hydroxy-5-hydroxymethylpyrrolidine 362 and (2*R*,3*R*,4*R*,5*S*)-*N*(1)-tosyl-2-(4''-methoxyphenyl)-3,4-hydroxy-5-hydroxymethylpyrrolidine 369



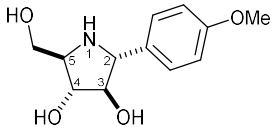
362 **369**

Step 1: *m*-CPBA (70%, 341 mg, 1.39 mmol) was added to a stirred solution of **367** (252 mg, 0.693 mmol, >95:5 dr) in CH_2Cl_2 (14 mL) at rt and was stirred at rt for 18 h then satd aq Na_2SO_3 was added until there was no sign of oxidant left. Satd aq $NaHCO_3$ (5 mL) was added and the aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) then the combined organic layers were dried with Na_2SO_4 then concentrated *in vacuo* to give a ~60:40 mixture of **361** and **368**, respectively as a white solid.

Step 2: K_2CO_3 (192 mg, 1.39 mmol) was added to a stirred solution of the residue from the previous step in MeOH (17 mL) at rt and was stirred at rt for 18 h then satd aq NH_4Cl (1 mL) was added and the resultant mixture was concentrated *in vacuo*. The residue was partitioned between $CHCl_3$/^{i}PrOH (3:1, v/v, 5 mL) and H_2O (2 mL) and the aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1, v/v, 3 × 10 mL) then the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo* to give a mixture of **362** and **369**. Purification *via* exhaustive flash chromatography (eluent PhMe/^{i}PrOH, 8:1) gave **362** as a white solid (82 mg, 30%, >95:5 dr); mp 143–146 °C; ν_{max} (ATR) 3409 (O–H), 1326 (S=O), 1178 (S=O); $[\alpha]_D^{25}$ +16.0 (*c* 1.0 in MeOH); δ_H (400 MHz, CD_3OD) 2.33 (3H, s, Ar*Me*), 3.72 (3H, s, O*Me*), 3.96–3.98 (1H, m, C(3)*H*), 4.01 (1H, dd, *J* 9.8, 2.5, C(1')H_A), 4.04–4.08 (1H, m, C(5)*H*), 4.11 (1H, dd, *J* 9.8, 6.6, C(1')H_B), 4.24 (1H, app t, *J* 1.4, C(4)*H*), 4.61 (1H, d, *J* 2.5, C(2)*H*), 6.53 (2H, d, *J* 8.7, C(3'')*H*, (5'')*H*), 7.03 (2H, d, *J* 8.2, C(3''')*H*, C(5''')*H*), 7.08 (2H, d, *J* 8.7, C(2'')*H*, C(6'')*H*), 7.18 (2H, d, *J* 8.2, C(2''')*H*, C(6''')*H*); δ_C (100 MHz, CD_3OD) 21.4 (Ar*Me*), 55.7

(O*Me*), 63.3 (*C*(1')), 72.8 (*C*(5)), 74.5 (*C*(2)), 80.1 (*C*(4)), 85.8 (*C*(3)), 114.1 (*C*(3''), *C*(5'')), 127.9 (*C*(2'''), *C*(6''')), 129.9 (*C*(3'''), *C*(5''')), 131.4 (*C*(1'')), 131.9 (*C*(2''), *C*(6'')), 140.4 (*C*(1''')), 143.8 (*C*(4''')), 160.5 (*C*(4'')); *m/z* (ESI^+) 809 ($[2M+Na]^+$, 100%); HRMS (ESI^+) $C_{19}H_{24}NO_6S^+$ ($[M+H]^+$) requires 394.1319; found 394.1320. Further elution gave a 77:23 mixture of **369** and **362**, respectively, as a colourless viscous oil (77 mg, 29%, 77:23 dr). Data for **369**: δ_H (400 MHz, CD_3OD) [selected data] 2.42 (3H, s, N*Me*), 3.77 (3H, s, O*Me*), 6.80–6.86 (2H, m, *Ar*), 7.32–7.40 (4H, m, *Ar*), 7.63–7.67 (2H, m, *Ar*); δ_C (100 MHz, CD_3OD) [selected data] 21.5 (N*Me*), 55.7 (O*Me*), 63.0 (C(1'), 63.3, 68.7, 75.9, 83.2 (*C*(2), *C*(3), *C*(4), *C*(5)).

(*R*,*R*,*R*,*R*)-2-(4''-Methoxyphenyl)-3,4-hydroxy-5-hydroxymethylpyrrolidine 305



Method A: TfOH (0.15 mL, 1.67 mmol) was added to a stirred solution of **356** (100 mg, 0.278 mmol, >95:5 dr) and anisole (0.60 mL, 5.6 mmol) in CH_2Cl_2 (9 mL) at rt and the resultant mixture was stirred at rt for 2 h then 1 M aq NaOH (5 mL) was added. The aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1 v/v, 3 × 5 mL) then the combined organic layers were dried with K_2CO_3 and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/^{i}PrOH/35% aq NH_4OH, 75:25:1 increased to 67:33:1) gave a ~60:40 mixture of species tentatively assigned as **305** and **358**, respectively (63 mg, ~80% calculated yield). Data for mixture: δ_H (400 MHz, D_2O) [selected data] 6.72–6.83 (4H [**358**], m), 6.89 (2H [**305**], d, *J* 8.7), 7.16–7.23 (2H [**305**] and 2H [**358**], m), 7.28 (2H [**358**], d, *J* 8.9); δ_C (100 MHz, D_2O) [selected data] 158.1, 157.5, 157.4, 135.2, 134.8, 129.3, 129.2, 129.2, 128.7, 114.4, 114.2, 113.9; *m/z* (ESI^+) 240 ([**305**+H]$^+$, 70%), 348 ([**358**+H]$^+$, 100%), 370 ([**358**+Na]$^+$, 80%).

Method B: A stirred solution of **356** (50 mg, 0.14 mmol, >95:5 dr) in 3 M aq HCl (1 mL) was allowed to stir at rt for 18 h then concentrated *in vacuo* to give a complex mixture.

Method C: A stirred solution of **356** (50 mg, 0.14 mmol, >95:5 dr) in 3 M aq HCl (1 mL) was heated at 100 °C for 3 h then cooled to rt and concentrated *in vacuo* to give a complex mixture.

Method D: $LiAlH_4$ (2.4 M in THF, 0.25 mL, 0.60 mmol) was added to a stirred solution of **356** (72 mg, 0.20 mmol, >95:5 dr) in THF and the resultant mixture was heated at 67 °C for 18 h then cooled to rt. 2 M NaOH (1 mL) was added and the resultant mixture was stirred at rt for 2 h then filtered thorough Celite® (eluent EtOAc) and concentrated *in vacuo* to give starting material **356**.

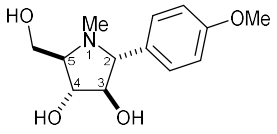
Method E: Mg (28 mg, 1.2 mmol) was added to a solution of **356** (28 mg, 78 μmol, >95:5 dr) in MeOH (2.2 mL) and the resultant mixture was left in an ultrasonic bath for 24 h then filtered and concentrated *in vacuo* to give starting material **356**.

Method F: Na (22 mg, 1.0 mmol) was added to a stirred solution of naphthalene (153 mg, 1.20 mmol) in THF (5 mL) at rt and stirred at rt for 18 h. A portion of the solution was added to a stirred solution of **356** (28 mg, 78 μmol, >95:5 dr) in THF (1 mL) at –78 °C until a green colour persisted and the resultant mixture was allowed to warm to rt over 18 h. EtOH (2 mL) was added and the resultant mixture was concentrated *in vacuo* to give a mixture of naphthalene and starting material **356**.

Method G: Na (230 mg, 10.0 mmol) was added to a stirred solution of naphthalene (1.41 g, 11.0 mmol) in THF (10 mL) at rt and stirred at rt for 18 h. A portion of the solution was added to a stirred solution of **362** (61 mg, 0.15 mmol, >95:5 dr) in THF (1.5 mL) at 0 °C until a green colour persisted and the resultant mixture was allowed to stir at rt for 1 h. EtOH (2 mL) was added and the resultant mixture was concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/^{i}PrOH/35% aq NH_4OH, 75:25:1 increased to 66:33:1) gave

305 as pale yellow viscous oil (27 mg, 74%, >95:5 dr). To ensure the free base of **305** was analysed an analytical sample was prepared: a sample of **305** was dissolved in $CHCl_3$/^{i}PrOH (3:1 v/v) and 2.0 M aq NaOH and the aqueous layer was extracted with $CHCl_3$/^{i}PrOH (3:1 v/v);[52] $[\alpha]_D^{25}$ +44.4 (*c* 0.05 in H_2O) {lit.[52] $[\alpha]_D^{20}$ +42.5 (*c* 0.38 in H_2O)}; δ_H (500 MHz, CD_3OD) 3.15–3.21 (1H, m, C(5)*H*), 3.63 (1H, dd, *J* 11.2, 6.3, C(1')H_A), 3.71 (1H, dd, *J* 11.2, 4.2, C(1')H_B), 3.78 (3H, s, O*Me*), 3.84–3.89 (2H, m, C(2)*H*, C(4)*H*), 3.91–3.95 (1H, m (C(3)*H*), 6.90 (2H, d, *J* 8.7, C(3")*H*, C(5")*H*), 7.37–7.43 (2H, d, *J* 8.7, C(2")*H*, C(6")*H*); δ_C (125 MHz, CD_3OD) 55.7 (O*Me*), 63.8 (*C*(1')), 64.5 (*C*(5)), 66.1 (*C*(2)), 79.4 (*C*(4)), 85.0 (*C*(3)), 114.9 (*C*(3"), *C*(5")), 129.5 (*C*(2"), *C*(6")), 131.8 (*C*(1"), 160.7 (*C*(4")); δ_H (500 MHz, D_2O) 3.24–3.29 (1H, m, C(5)*H*), 3.71 (1H, dd, *J* 11.5, 6.5, C(1')H_A), 3.77 (1H, dd, *J* 11.5, 4.5, C(1')H_B), 3.86 (3H, s, O*Me*), 3.93 (1H, d, *J* 9.2, C(2)*H*), 3.97 (1H, t, *J* 7.4, C(4)*H*), 4.09–4.14 (1H, m, C(3)*H*), 7.04 (2H, d, *J* 8.7, C(3")*H*, C(5")*H*), 7.41 (2H, d, *J* 8.7, C(2")*H*, C(6")*H*); δ_C (125 MHz, D_2O) 58.3 (O*Me*), 64.5 (*C*(5)), 65.4 (*C*(1')), 66.2 (*C*(2)), 80.2 (*C*(4)), 84.8 (*C*(3)), 117.2 (*C*(3"), *C*(5")), 131.6 (*C*(2"), *C*(6")), 134.9 (*C*(1')), 161.5 (*C*(4')); *m/z* (ESI^+) 501 ($[2M+Na]^+$, 100%) ; HRMS (ESI^+) $C_{12}H_{18}NO_4$+ ($[M+H]^+$) requires 240.1230; found 240.1230.

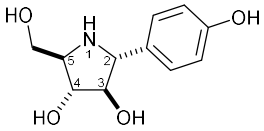
(*R*,*R*,*R*,*R*)-*N*(1)-Methyl-2-(4''-methoxyphenyl)-3,4-hydroxy-5-hydroxymethylpyrrolidine [codonopsinol B] 297



HCHO (37% aq, 0.18 mL, 1.6 mmol) was added to a solution of **305** (36 mg, 0.15 mmol, >95:5 dr) in degassed MeOH at rt and stirred at rt for 10 min. $Pd(OH)_2$/C (18 mg, 50% w/w) was added and the resultant mixture was stirred under H_2 (1 atm) for 24 h then filtered through Celite® (eluent MeOH) and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent $CHCl_3$/MeOH/35% aq NH_4OH, 83:17:1) gave **297** as a colourless

viscous oil (13 mg, 34%, >95:5 dr);[53] $[\alpha]_D^{25}$ –11.0 (*c* 0.47 in MeOH) {lit.[52] $[\alpha]_D^{20}$ –7.0 (*c* 0.16 in MeOH); lit.[53] $[\alpha]_D$ –8 (*c* 0.45 in MeOH}; δ_H (400 MHz, CD_3OD) 2.17 (3H, s, N*Me*), 3.07 (1H, app q, *J* 4.3, C(5)*H*), 3.65 (1H, d, *J* 6.6, C(2)*H*), 3.78 (1H, s, O*Me*), 3.81 (1H, dd, *J* 11.6, 4.3, C(1')H_A), 3.85 (1H, dd, *J* 11.6, 4.3, C(1')H_B), 3.93 (1H, dd, *J* 6.6, 4.8, C(3)*H*), 4.01 (1H, app t, *J* 4.6, C(4)*H*), 6.87–6.91 (2H, m, C(3")*H*, C(5")*H*), 7.25–7.30 (2H, m, C(2")*H*, C(6")*H*); δ_C (100 MHz, CD_3OD) 34.9 (N*Me*), 55.7 (O*Me*), 60.9 (*C*(1')), 71.0 (*C*(5)), 75.3 (*C*(2)), 80.0 (*C*(4)), 85.7 (*C*(3)), 114.8 (*C*(3"), *C*(5")), 130.6 (*C*(2"), *C*(6")), 133.7 (*C*(1")), 160.7 (*C*(4")); *m/z* (ESI^+) 254 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{20}NO_4^+$ ($[M+H]^+$) requires 254.1387; found 254.1386.

(*R*,*R*,*R*,*R*)-2-(4''-Hydroxyphenyl)-3,4-hydroxy-5-hydroxymethylpyrrolidine [radicamine B] 294

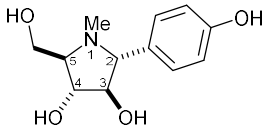


Step 1: BBr_3 (0.31 mL, 0.31 mmol) was added to a stirred solution of **305** (15 mg, 53 μmol, >95:5 dr) in CH_2Cl_2 (1.25 mL) at 0 °C and was allowed to stir at rt for 5 h. MeOH (1 mL) was added and the resultant mixture was concentrated *in vacuo* to give 51:49 of **294** and **305**, respectively.

Step 2: BBr_3 (0.31 mL, 0.31 mmol) was added to a stirred solution of the residue from the previous step in CH_2Cl_2 (1.25 mL) at 0 °C and was allowed to stir at rt for 18 h. MeOH (1 mL) was added and the resultant mixture was concentrated *in vacuo* to give 34:66 of **305** and **294**, respectively. Purification *via* flash column chromatography (eluent Et_2O/MeOH/35% aq NH_4OH, 83:17:1) followed by purification *via* ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH) gave **294** as colourless viscous oil (5 mg, 37%, >95:5 dr);[54] $[\alpha]_D^{25}$ +57.1 (*c* 0.2 in H_2O) {lit.[54] $[\alpha]_D$ +72.7 (*c* 0.10 in H_2O); lit.[55] $[\alpha]_D^{25}$ +70.6 (*c* 0.2 in H_2O); lit.[56] $[\alpha]_D^{20}$ +74 (*c* 0.10 H_2O); lit.[57] $[\alpha]_D^{25}$ +73.6 (*c* 0.10 in H_2O); lit.[58] $[\alpha]_D^{25}$ +74 (*c* 0.10

in H_2O)}; δ_H (500 MHz, D_2O) 3.33–3.38 (1H, m, C(5)*H*), 3.76 (1H, dd, *J* 11.8, 6.4, C(1')H_A), 3.81 (1H, dd, *J* 11.8, 4.3, C(1')H_B), 4.00–4.04 (2H, m, C(2)*H*, C(4)*H*), 4.17–4.22 (1H, m, C(3)*H*), 6.95 (2H, d, *J* 8.5, C(3")*H*, C(5")*H*), 7.36 (2H, d, *J* 8.5, C(2")*H*, C(6")*H*); δ_C (125 MHz, D_2O) 64.4 (*C*(5)), 64.5 (*C*(1')), 66.1 (*C*(2)), 79.5 (*C*(4)), 83.8 (*C*(3)), 118.7 (*C*(3"), *C*(5")), 132.1 (*C*(2"), *C*(6")), 132.3 (*C*(1")), 158.8 (*C*(4")); *m/z* (ESI^+) 226 ($[M+H]^+$, 100%), 248 ($[M+Na]^+$, 25%); HRMS (ESI^+) $C_{11}H_{16}NO_4^+$ ($[M+H]^+$) requires 226.1074; found 226.1076.

(*R*,*R*,*R*,*R*)-*N*(1)-Methyl-2-(4''-hydroxyphenyl)-3,4-hydroxy-5-hydroxymethylpyrrolidine [codonopsinol C] 298



BBr_3 (0.43 mL, 0.43 mmol) was added to a stirred solution of **297** in CH_2Cl_2 (1 mL) at 0 °C and was allowed to stir at rt for 18 h. MeOH (1 mL) was added and the resultant mixture was concentrated *in vacuo* to give an ~50:50 mixture of **298** and **297**, respectively. Purification *via* flash column chromatography (eluent Et_2O/MeOH/35% aq NH_4OH, 89:11:1) followed by purification *via* ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH) gave **298** as colourless viscous oil (3 mg, 29%, >95:5 dr);[53] $[\alpha]_D^{25}$ +6.1 (*c* 0.2 in H_2O) {lit.[10] $[\alpha]_D^{25}$ +8.3 (*c* 0.05 in MeOH); lit.[16] $\{[\alpha]_D$ –9 (*c* 0.6 in MeOH)}. Data for **298**·0.1TFA $[\alpha]_D^{25}$ +26.2 (*c* 0.2 in MeOH) δ_H (500 MHz, CD_3OD) 2.18 (3H, s, N*Me*), 3.07 (1H, app q, *J* 4.3, C(5)*H*), 3.65 (1H, d, *J* 6.7, C(2)*H*), 3.82 (1H, dd, *J* 11.6, 4.3, C(1')H_A), 3.85 (1H, dd, *J* 11.6, 4.3, C(1')H_B), 3.95 (1H, dd, *J* 6.5, 5.0, C(3)*H*), 4.01 (1H, app t, *J* 4.7, C(4)*H*), 6.77 (2H, d, *J* 8.5, C(3")*H*, C(5")*H*), 7.19 (2H, d, *J* 8.5, C(2")*H*, C(6")*H*); δ_C (125 MHz, CD_3OD), 35.0 (N*Me*), 60.7 (*C*(1')), 71.0 (*C*(5)), 75.3 (*C*(2)), 79.7 (*C*(4)), 85.3 (*C*(3)), 116.1 (*C*(3"), *C*(5")), 130.8 116.1 (*C*(3"), *C*(5")), 131.8 (*C*(1")), 158.2 (*C*(4")); δ_H (400 MHz, D_2O)[54] 3.15 (3H, s, N*Me*), 3.10 (1H, app q, *J* 4.7, C(5)H), 3.74 (1H, d, *J* 8.2, C(2)*H*), 3.87–3.95 (2H, m, C(1')H_2),

4.06–4.10 (1H, m, C(4)*H*), 4.16 (1H, dd, *J* 8.2, 6.0, C(3)*H*), 6.94 (2H, d, *J* 8.6, C(3")*H*, C(5")*H*), 7.29 (2H, d, *J* 8.6, C(2")*H*, C(6")*H*); *m/z* (ESI^+) 240 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{12}H_{18}NO_4^+$ ($[M+H]^+$) requires 240.1230; found 240.1231.

5.5 References

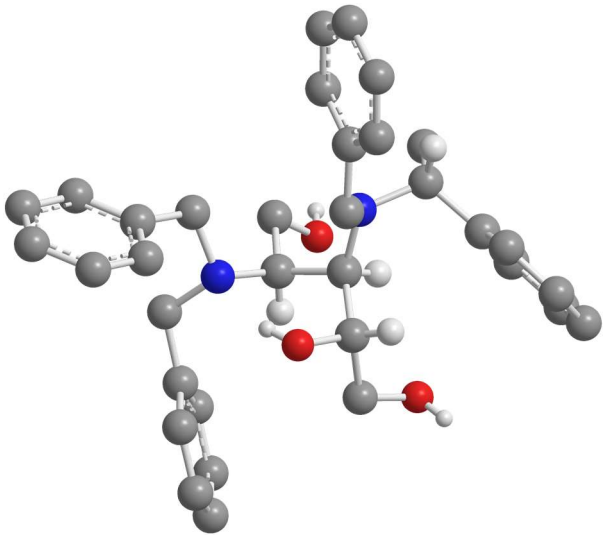
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Appendix 1: X-ray Crystal Structure Data

X-Ray crystal structure data for (*R*,*R*,*R*,*R*)-183

(selected H atoms are omitted for clarity)



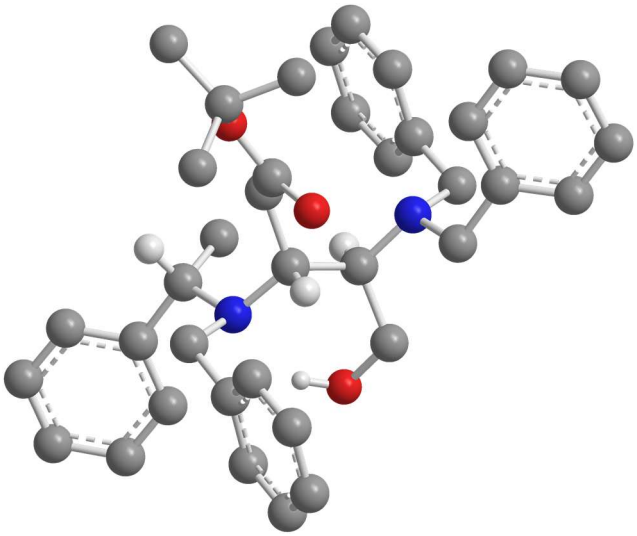
X-ray crystal structure determination for 183

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **183** [$C_{35}H_{46}N_2O_5$]: M = 574.76, orthorhombic, space group $P\,2_1\,2_1\,2_1$, a = 7.59159(19) Å, b = 20.3087(3) Å, c = 21.5684(4) Å, V = 3325.31(12) Å^3, Z = 4, μ = 0.607 mm^{-1}, colourless block, crystal dimensions = 0.29 × 0.32 × 0.35 mm^3. A total of 6897 unique reflections were measured for $4 < \theta < 76$ and 6261 reflections were used in the refinement. The final parameters were wR_2 = 0.182 and R_1 = 0.066 [$I > -3.0\sigma(I)$], with Flack enantiopole = –0.1(3).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (3*R*,4*R*,α*S*)-207

(selected H atoms are omitted for clarity)



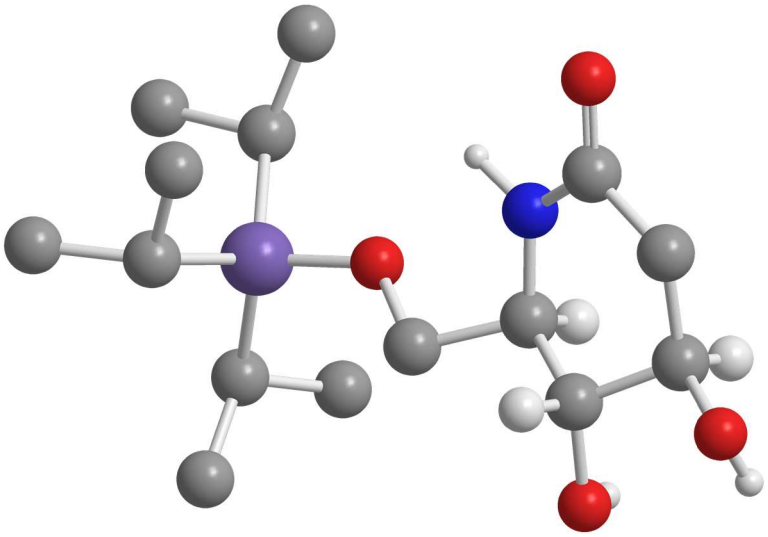
X-ray crystal structure determination for 207

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **207** [$C_{38}H_{46}N_2O_3$]: M = 578.79, triclinic, space group *P 1*, a = 7.10434(19) Å, b = 10.6840(3) Å, c = 11.6324(4) Å, α = 82.814(3)°, β = 75.572(2)°, γ = 76.583(2)°, V = 829.63(4) Å^3, Z = 1, μ = 0.567 mm^{-1}, colourless block, crystal dimensions = 0.15 × 0.16 × 0.18 mm^3. A total of 6075 unique reflections were measured for 4 < θ < 74 and 6047 reflections were used in the refinement. The final parameters were wR_2 = 0.096 and R_1 = 0.037 [$I > -3.0\sigma(I)$], with Flack enantiopole = 0.08(15).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (*R*,*R*,*R*)-281

(selected H atoms are omitted for clarity)



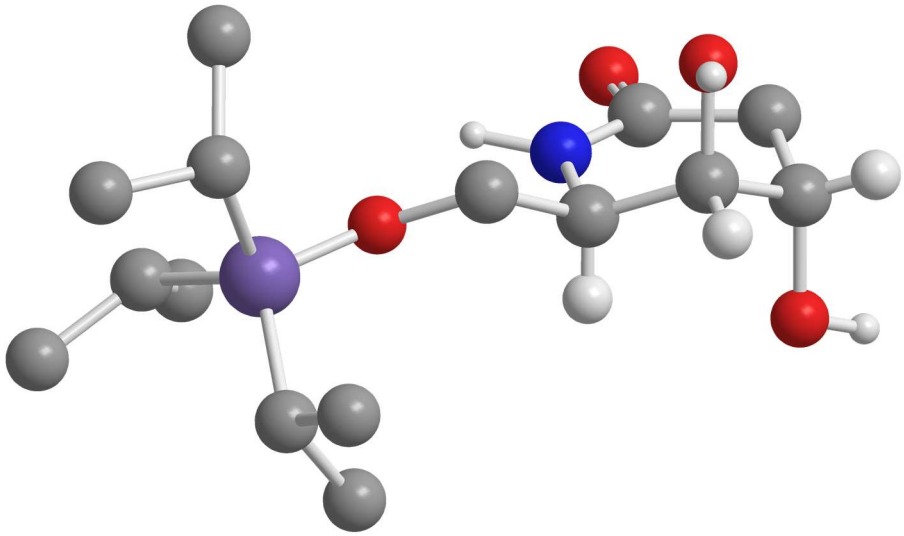
X-ray crystal structure determination for 281

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 250 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **281** [$C_{15}H_{31}NO_4Si$]: $M = 317.50$, monoclinic, space group $P\,2_1$, $a = 14.0713(7)$ Å, $b = 8.2150(4)$ Å, $c = 16.8488(8)$ Å, $\beta = 107.330(5)°$, $V = 1859.12(17)$ Å^3, $Z = 4$, $\mu = 0.1.232$ mm^{-1}, colourless prism, crystal dimensions = 0.12 × 0.13 × 0.25 mm^3. A total of 7686 unique reflections were measured for $5 < \theta < 76$ and 7655 reflections were used in the refinement. The final parameters were $wR_2 = 0.257$ and $R_1 = 0.096$ [$I > -3.0\sigma(I)$], with Flack enantiopole = –0.02(6).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (4*S*,5*S*,6*R*)-289

(selected H atoms are omitted for clarity)



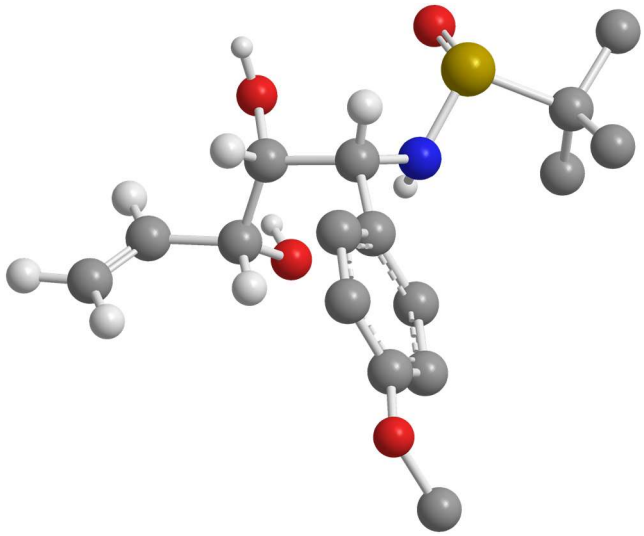
X-ray crystal structure determination for 289

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 250 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **289** [$C_{15}H_{31}NO_4Si$]: M = 317.50, orthorhombic, space group $P\ 2_1\ 2_1\ 2$, a = 32.2727(12) Å, b = 11.3243(4) Å, c = 10.2112(4) Å, V = 3731.8(2) Å^3, Z = 8, μ = 0.1.228 mm^{-1}, colourless block, crystal dimensions = 0.14 × 0.16 × 0.21 mm^3. A total of 6959 unique reflections were measured for $4 < \theta < 76$ and 6933 reflections were used in the refinement. The final parameters were wR_2 = 0.277 and R_1 = 0.105 [$I > -3.0\sigma(I)$], with Flack enantiopole = 0.10(8).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (*R*,*R*,*R*,*R*)-351

(selected H atoms are omitted for clarity)



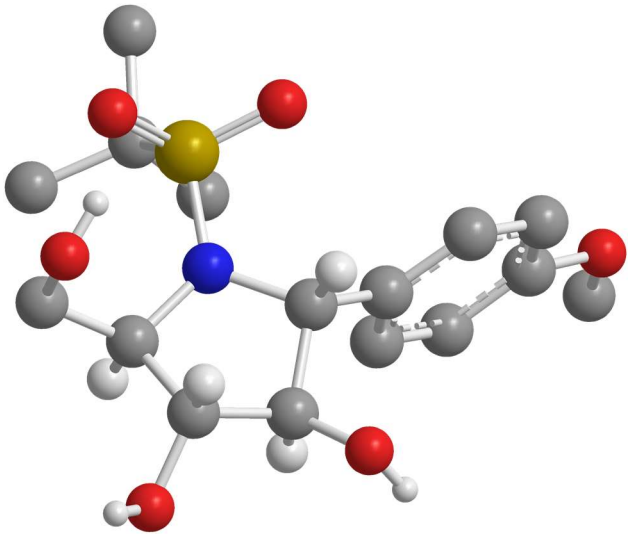
X-ray crystal structure determination for 351

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **351** [$C_{16}H_{25}NO_4S$]: M = 327.44, monoclinic, space group $P\,2_1$, a = 11.7741(4) Å, b = 5.9385(3) Å, c = 12.5384(5) Å, β = 104.495(4)°, V = 848.78(6) Å^3, Z = 2, μ = 0.1.841 mm^{-1}, colourless block, crystal dimensions = 0.08 × 0.12 × 0.19 mm^3. A total of 3153 unique reflections were measured for $4 < \theta < 73$ and 2621 reflections were used in the refinement. The final parameters were wR_2 = 0.064 and R_1 = 0.026 [$I > -3.0\sigma(I)$], with Flack enantiopole = –0.013(14).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (*R*,*R*,*R*,*R*)-356

(selected H atoms are omitted for clarity)



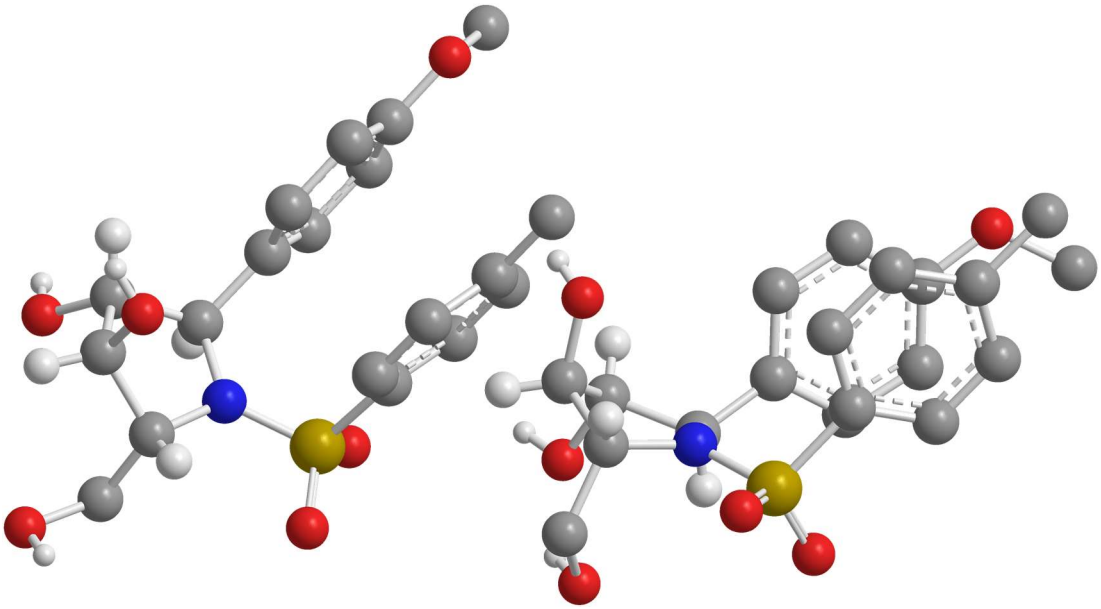
X-ray crystal structure determination for 356

Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **356** [$C_{16}H_{25}NO_6S$]: M = 359.44, monoclinic, space group $P\,2_1$, a = 9.1659(3) Å, b = 5.7096(2) Å, c = 16.7254(6) Å, β = 99.801(3)°, V = 862.52(5) Å^3, Z = 2, μ = 1.953 mm^{-1}, colourless prism, crystal dimensions = 0.04 × 0.05 × 0.19 mm^3. A total of 3467 unique reflections were measured for $5 < \theta < 76$ and 3226 reflections were used in the refinement. The final parameters were wR_2 = 0.090 and R_1 = 0.034 [$I > -3.0\sigma(I)$], with Flack enantiopole = –0.035(16).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (*R*,*R*,*R*,*R*)-362

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 362

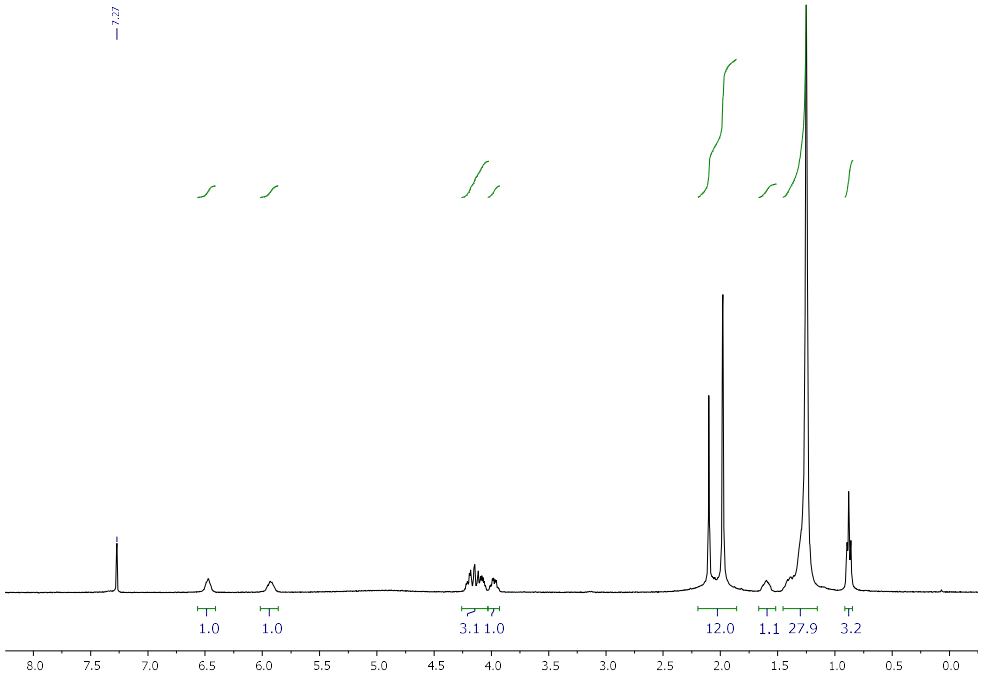
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **362** [$C_{19}H_{23}NO_6S$]: M = 393.46, orthorhombic, space group $P\,2_1\,2_1\,2_1$, a = 7.41026(13) Å, b = 12.3737(2) Å, c = 40.8802(6) Å, V = 3748.39(11) Å^3, Z = 8, μ = 1.855 mm^{-1}, colourless block, crystal dimensions = 0.22 × 0.25 × 0.26 mm^3. A total of 7818 unique reflections were measured for $2 < \theta < 76$ and 6816 reflections were used in the refinement. The final parameters were wR_2 = 0.084 and R_1 = 0.036 [$I > -3.0\sigma(I)$], with Flack enantiopole = –0.017(12).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Dr A. M. Fletcher, Chemistry Research Laboratory, University of Oxford, U.K.

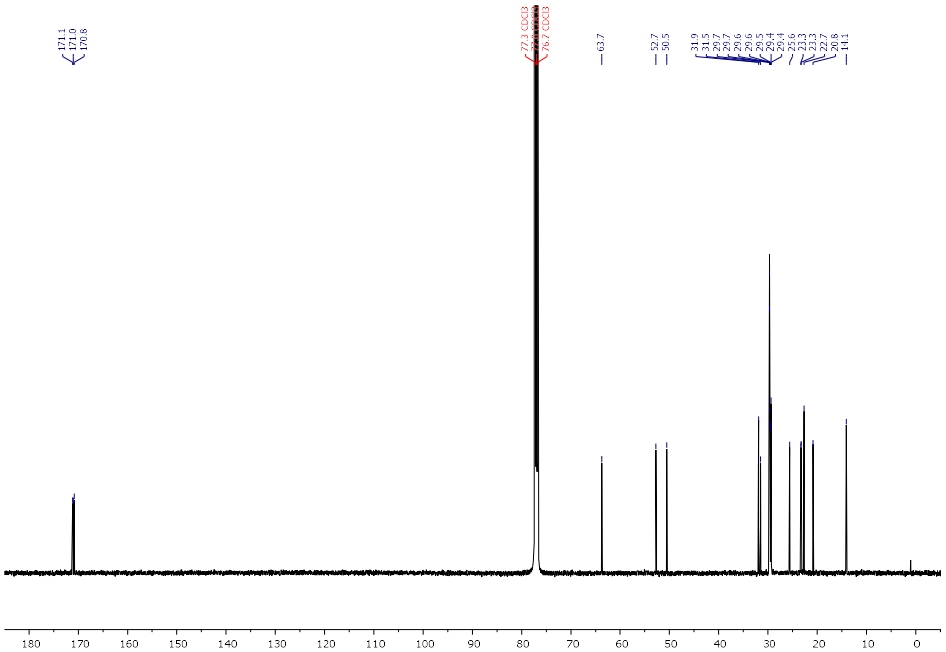
(1) Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.
(2) Flack, H. D.; Bernardinelli, G. *Acta Crystallogr. Sect. A* **1999**, *55*, 908.

Appendix 2: NMR Spectra of Final Compounds

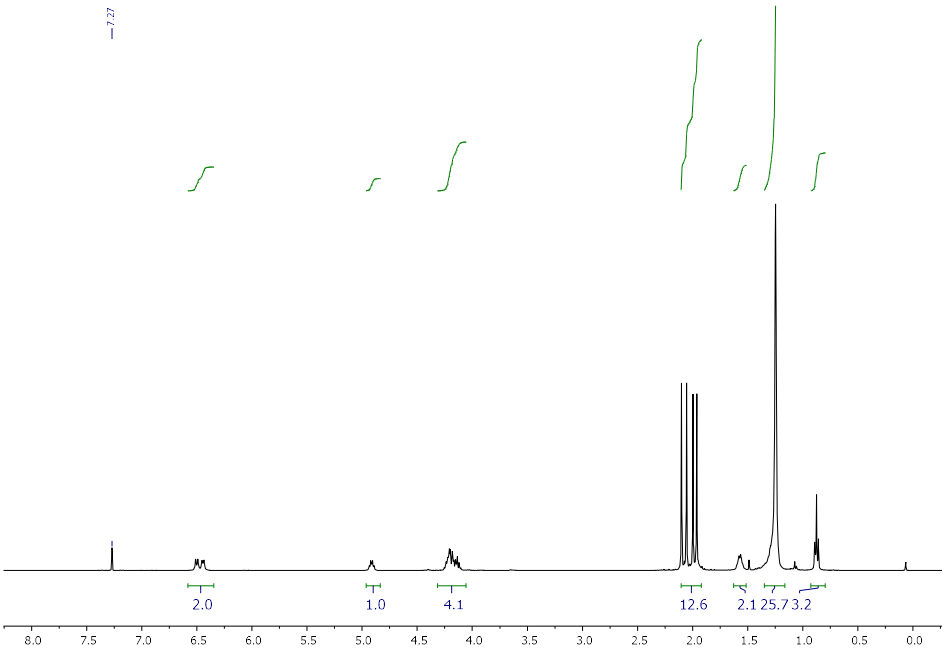
(2*R*,3*S*)-2,3-*N*,*N*-Diacetamidooctadecyl acetate 159 (^{1}H, 400 MHz, $CDCl_3$)



(2*R*,3*S*)-2,3-*N*,*N*-Diacetamidooctadecyl acetate 159 (^{13}C, 125 MHz, $CDCl_3$)

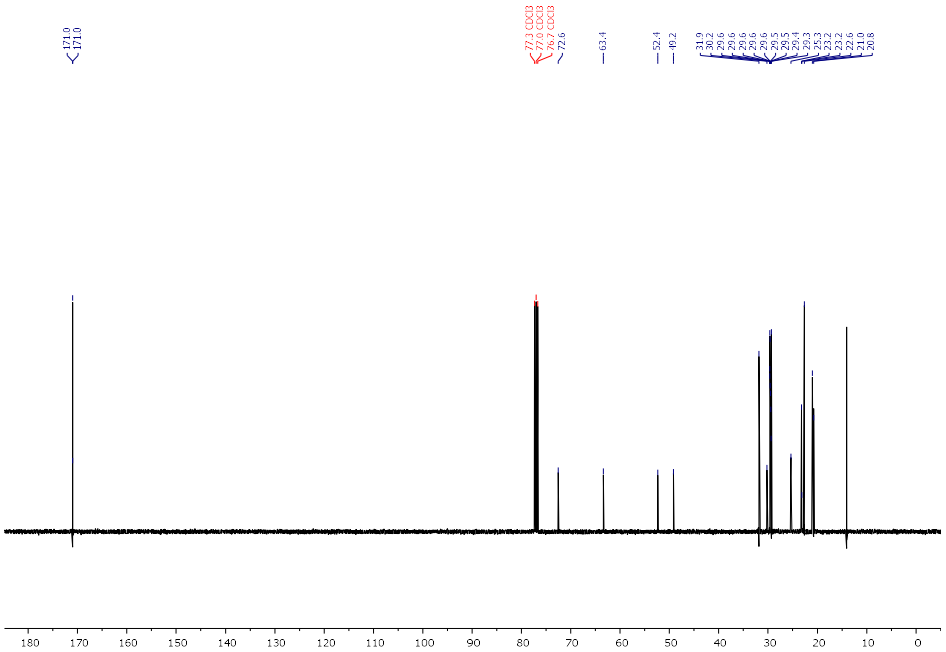


(2*R*,3*S*,4*S*)-1,4-*O*,*O*-Diacetoxy-2,3-*N*,*N*-diacetamidooctadecane 169 (^{1}H, 400 MHz, $CDCl_3$)

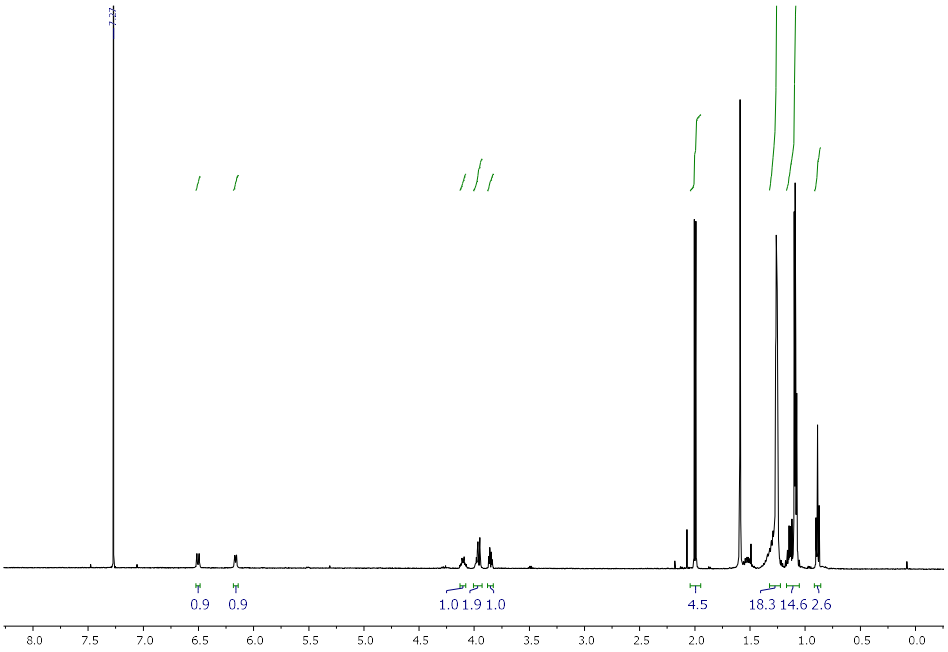


(2*R*,3*S*,4*S*)-1,4-*O*,*O*-Diacetoxy-2,3-*N*,*N*-diacetamidooctadecane 169

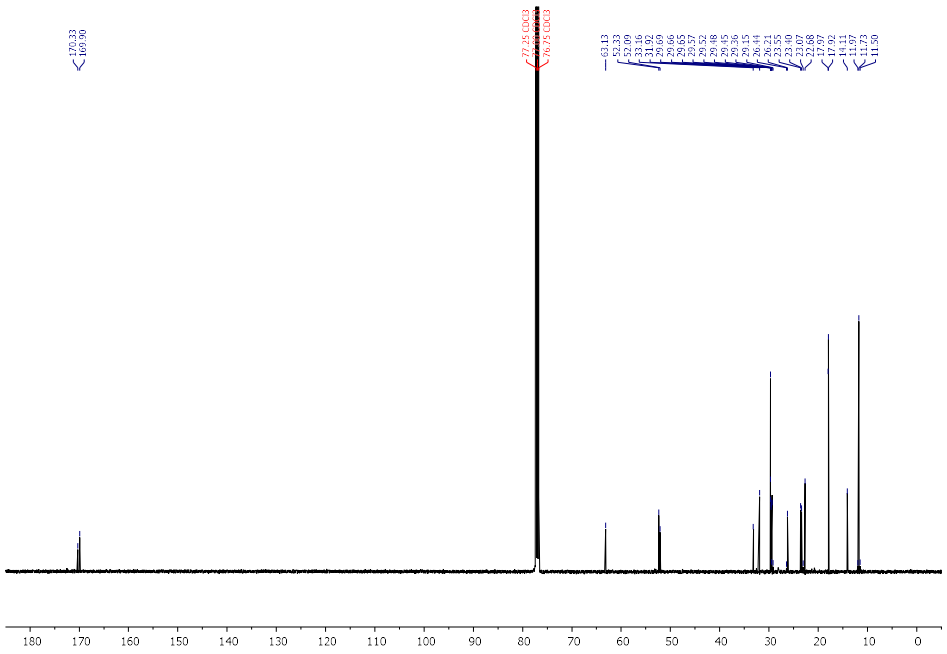
(^{13}C, 100 MHz, $CDCl_3$)



(*R*,*R*)-1-Triisopropylsilyloxy-2,3-diacetamido-octadecane 220 (^{1}H, 500 MHz, $CDCl_3$)

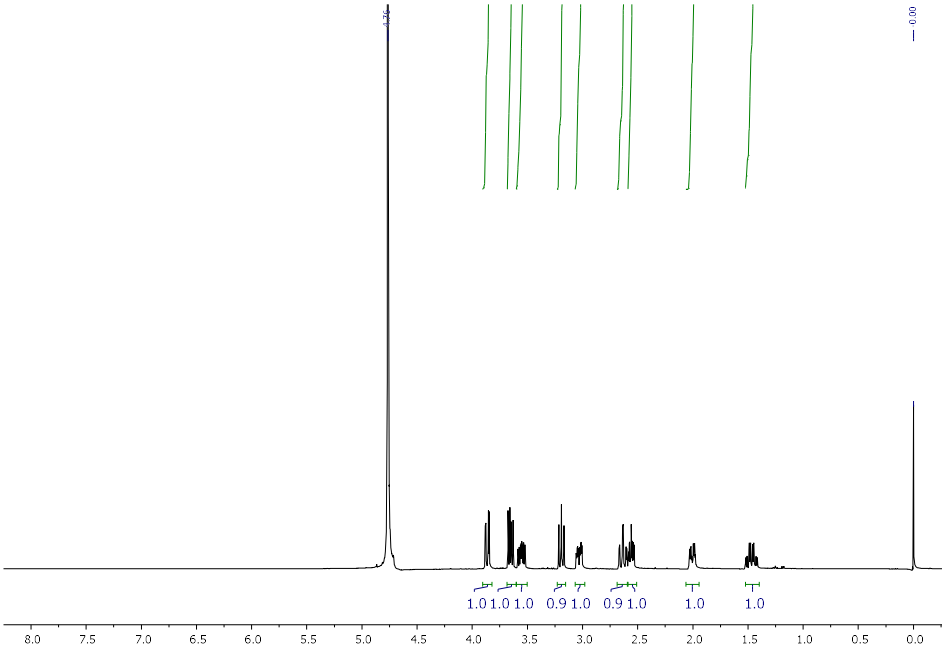


(*R*,*R*)-1-Triisopropylsilyloxy-2,3-diacetamido-octadecane 220 (^{13}C, 125 MHz, $CDCl_3$)



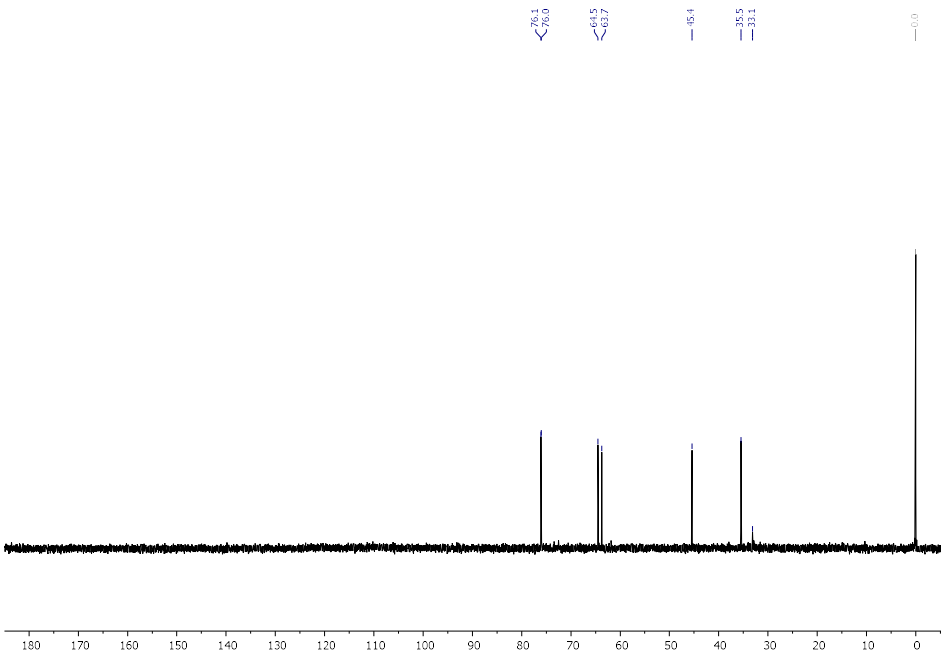
(*R*,*R*,*R*)-3,4-Dihydroxy-5-hydroxymethylpiperidine [(+)-fagomine] 221

(^{1}H, 400 MHz, D_2O)

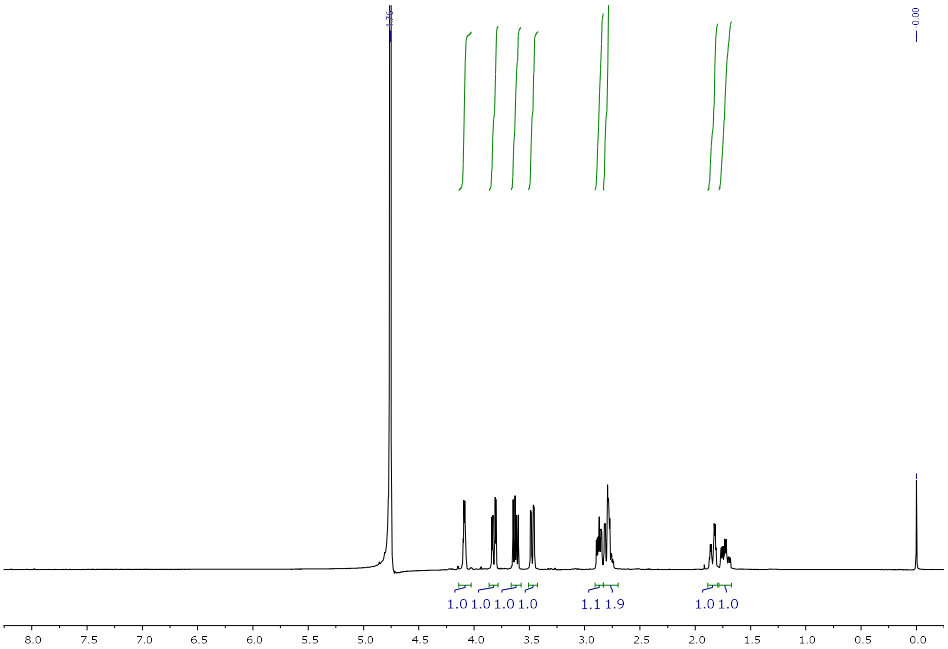


(*R*,*R*,*R*)-3,4-Dihydroxy-5-hydroxymethylpiperidine [(+)-fagomine] 221

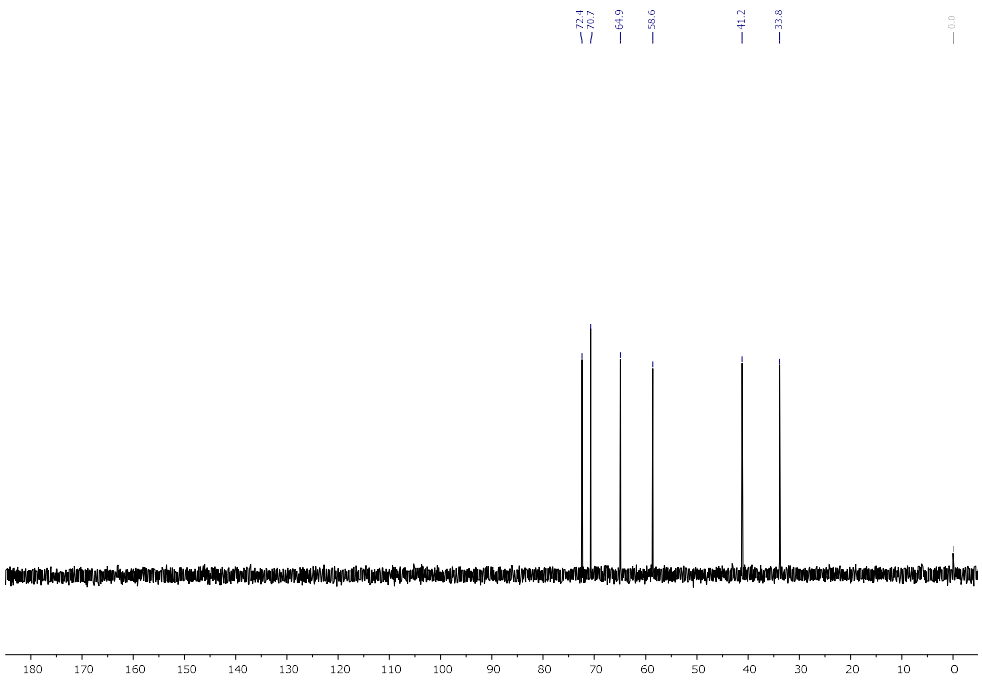
(^{13}C, 100 MHz, D_2O)



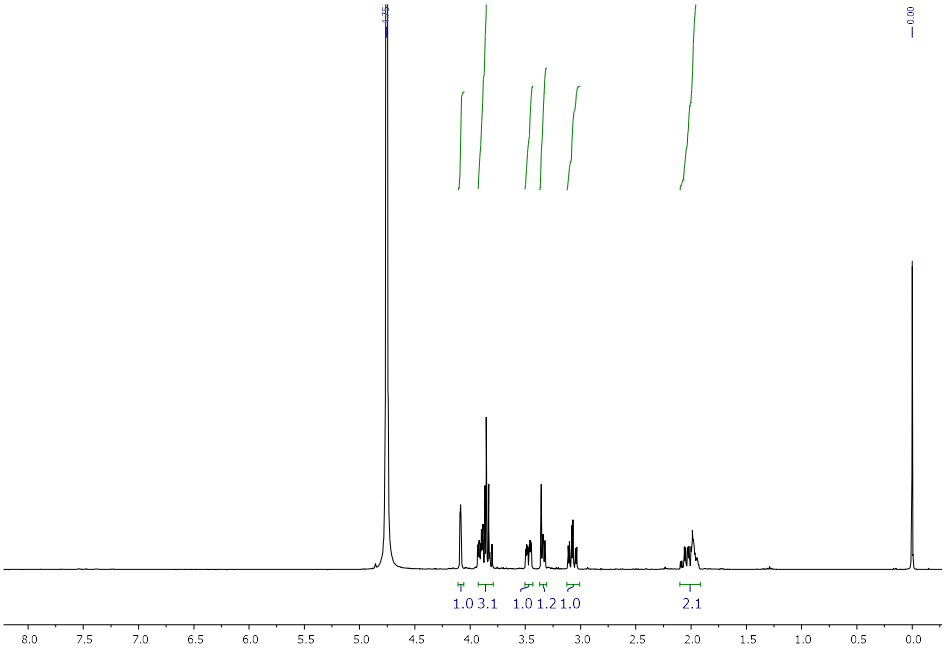
(3*S*,4*R*,5*R*)-3,4-Dihydroxy-5-hydroxymethylpiperidine [3-*epi*-fagomine] 222 (^{1}H, 400 MHz, D_2O)



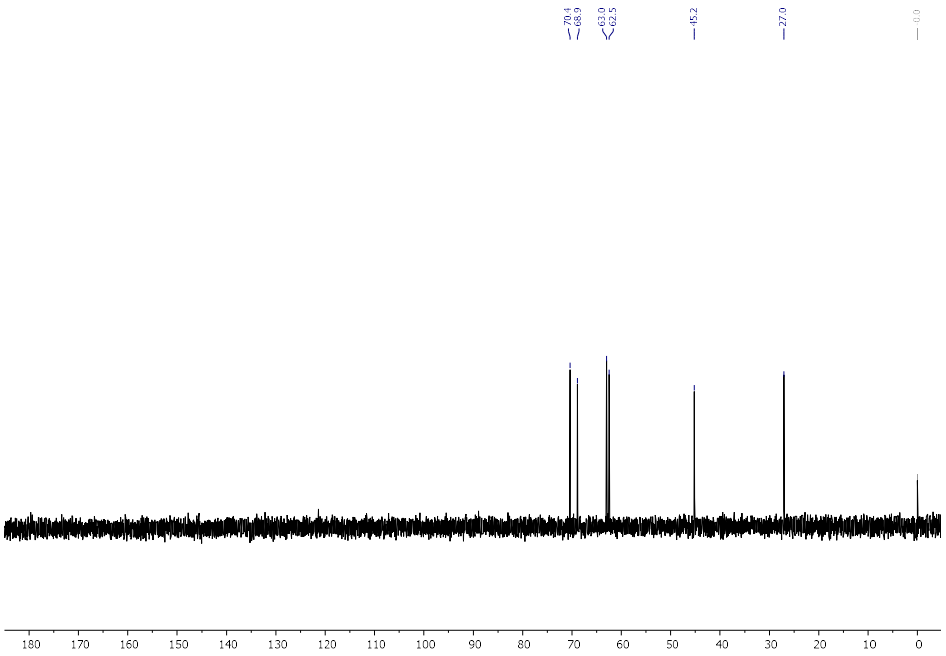
(3*S*,4*R*,5*R*)-3,4-Dihydroxy-5-hydroxymethylpiperidine [3-*epi*-fagomine] 222 (^{13}C, 100 MHz, D_2O)



(3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-hydroxymethylpiperidine [4-*epi*-fagomine] 223 (^{1}H, 400 MHz, D_2O)[1]

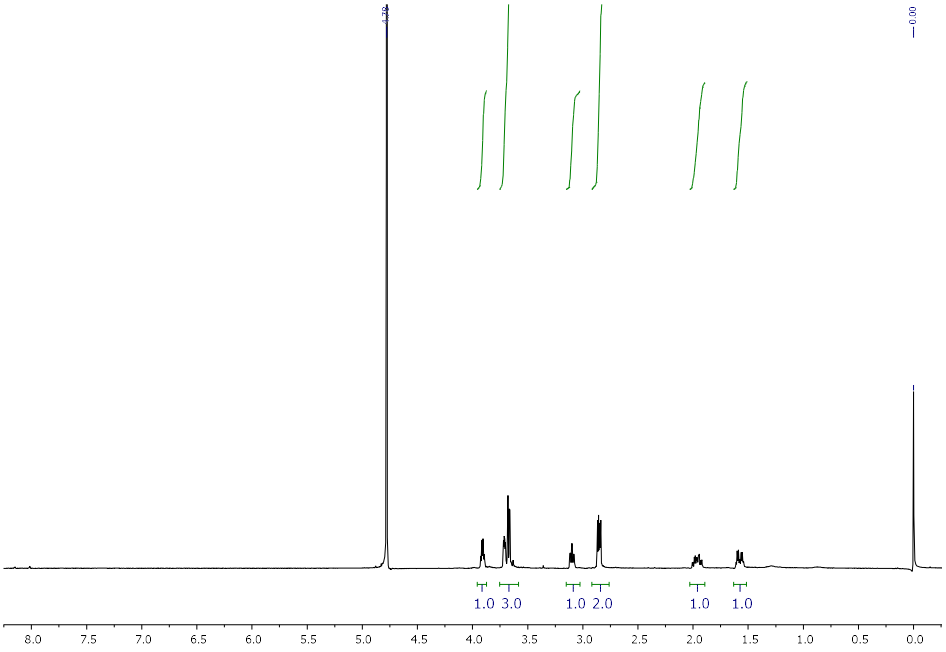


(3*R*,4*S*,5*R*)-3,4-Dihydroxy-5-hydroxymethylpiperidine [4-*epi*-fagomine] 223 (^{13}C, 100 MHz, D_2O)[1]

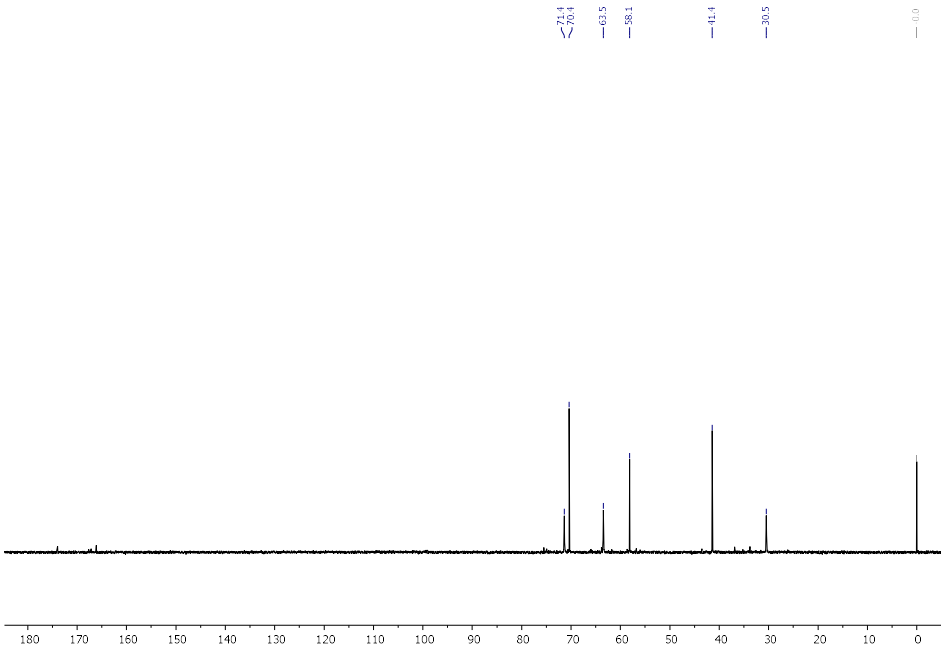


[1] Upon base-washing the samples of **223** became contaminated with unknown impurities. Although they were of sufficient quality for the requisite analysis, these spectra of **223** are prior to basifying.

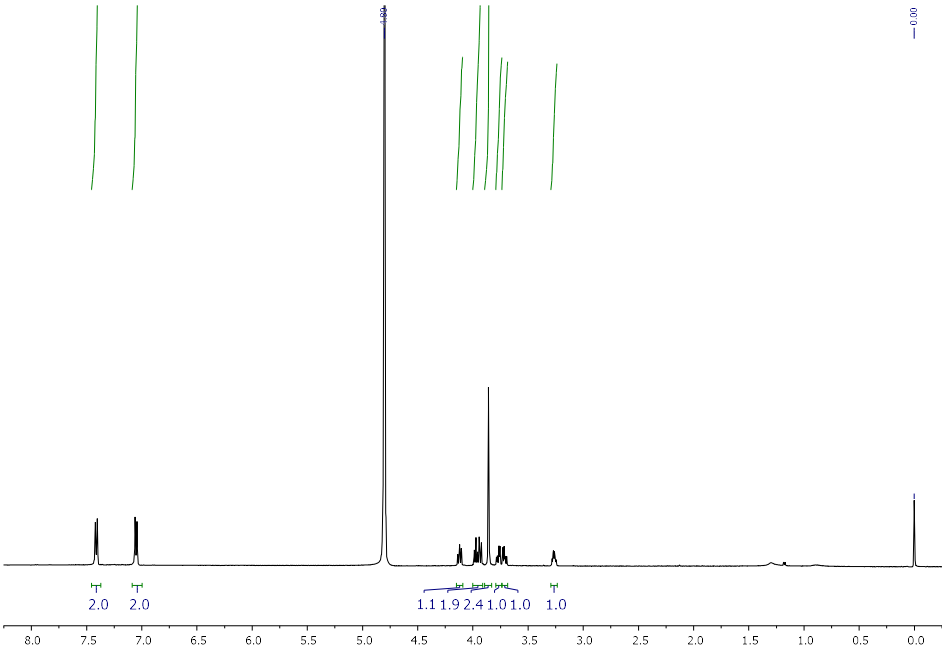
(3*S*,4*S*,5*R*)-3,4-Dihydroxy-5-hydroxymethylpiperidine [5-*epi*-fagomine] *ent*-224 (^{1}H, 400 MHz, D_2O)



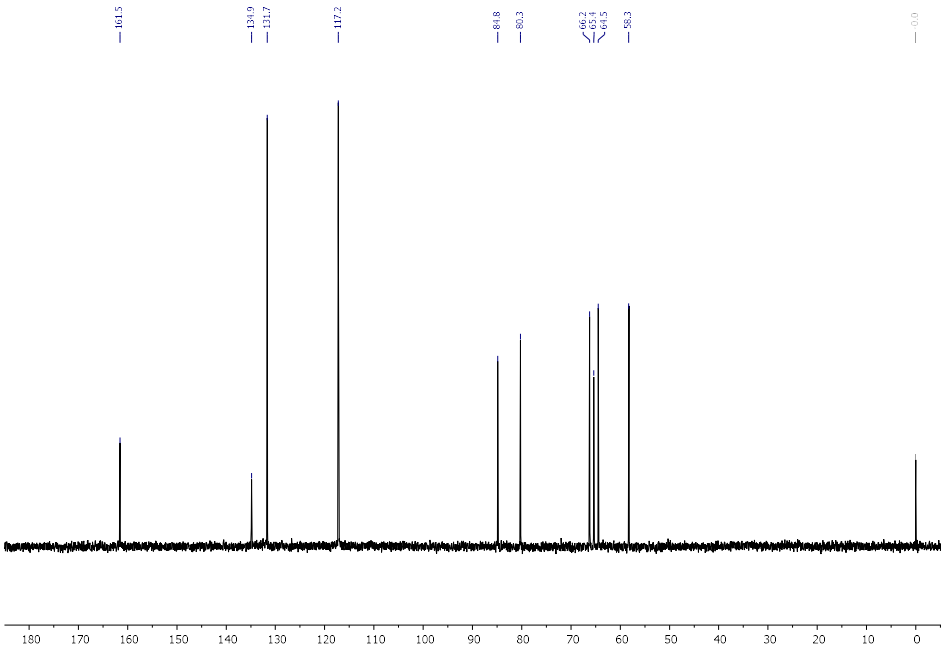
(3*S*,4*S*,5*R*)-3,4-Dihydroxy-5-hydroxymethylpiperidine [5-*epi*-fagomine] *ent*-224 (^{13}C, 125 MHz, D_2O)



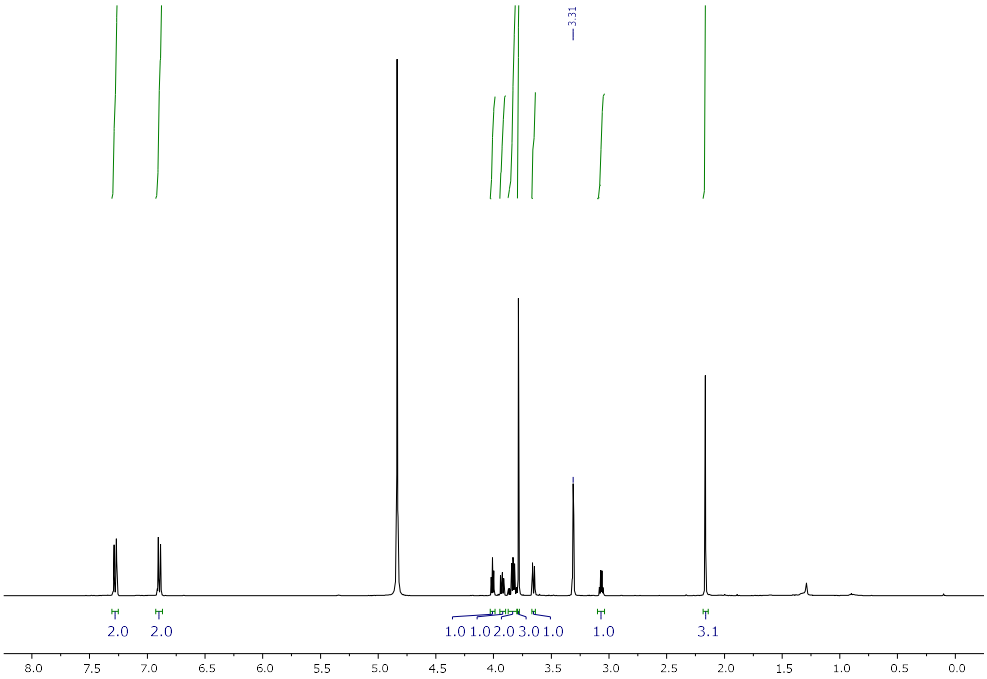
(*R*,*R*,*R*,*R*)-2-(4''-Methoxyphenyl)-3,4-hydroxy-5-hydroxymethylpyrrolidine 305 (^{1}H, 500 MHz, D_2O)



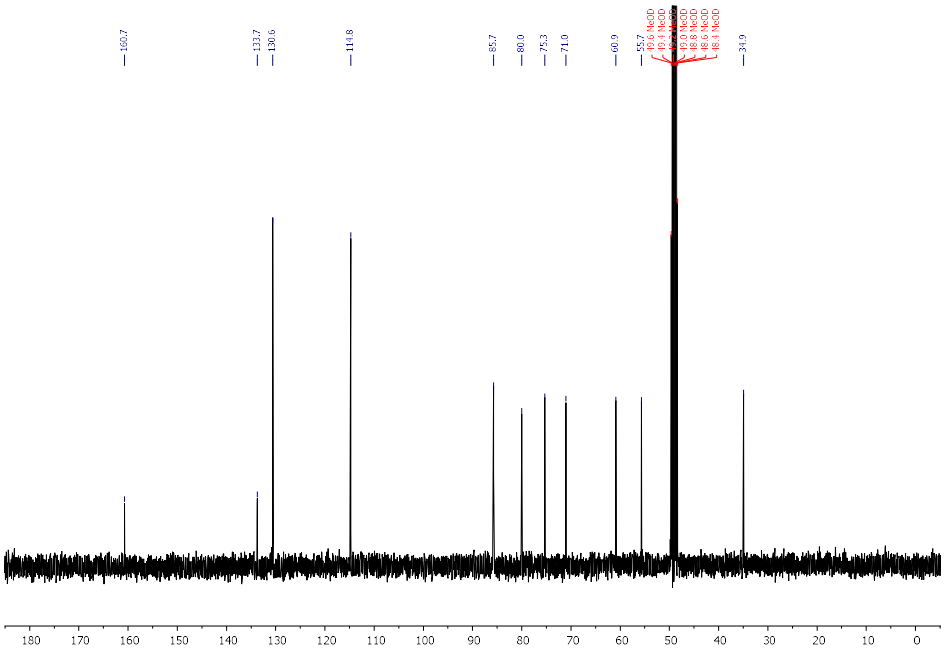
(*R*,*R*,*R*,*R*)-2-(4''-Methoxyphenyl)-3,4-hydroxy-5-hydroxymethylpyrrolidine 305 (^{13}C, 125 MHz, D_2O)



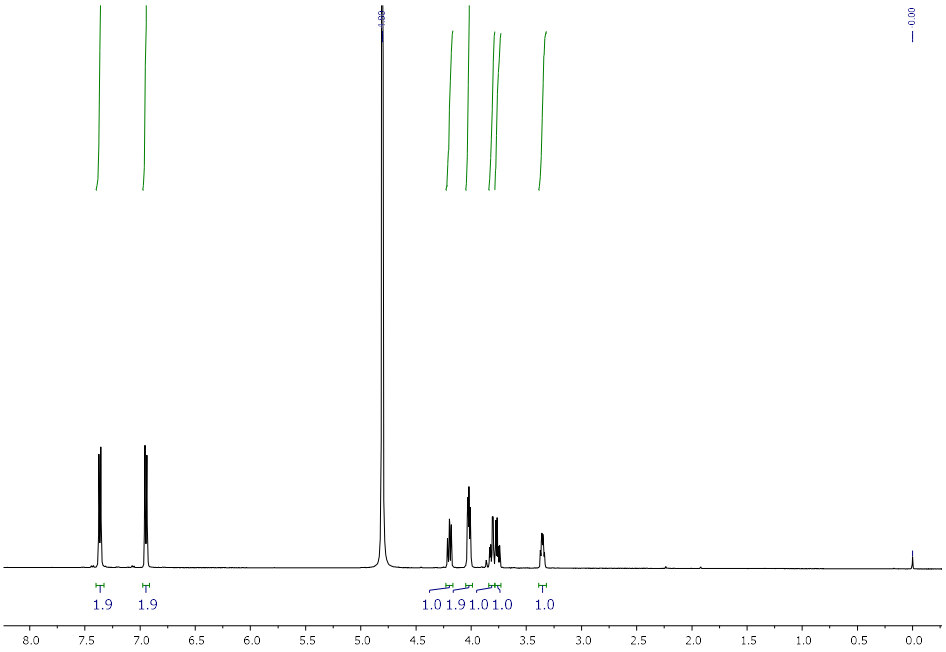
(*R*,*R*,*R*,*R*)-*N*(1)-Methyl-2-(4''-methoxyphenyl)-3,4-hydroxy-5-hydroxymethylpyrrolidine [codonopsinol B] 297 (^{1}H, 400 MHz, CD_3OD)



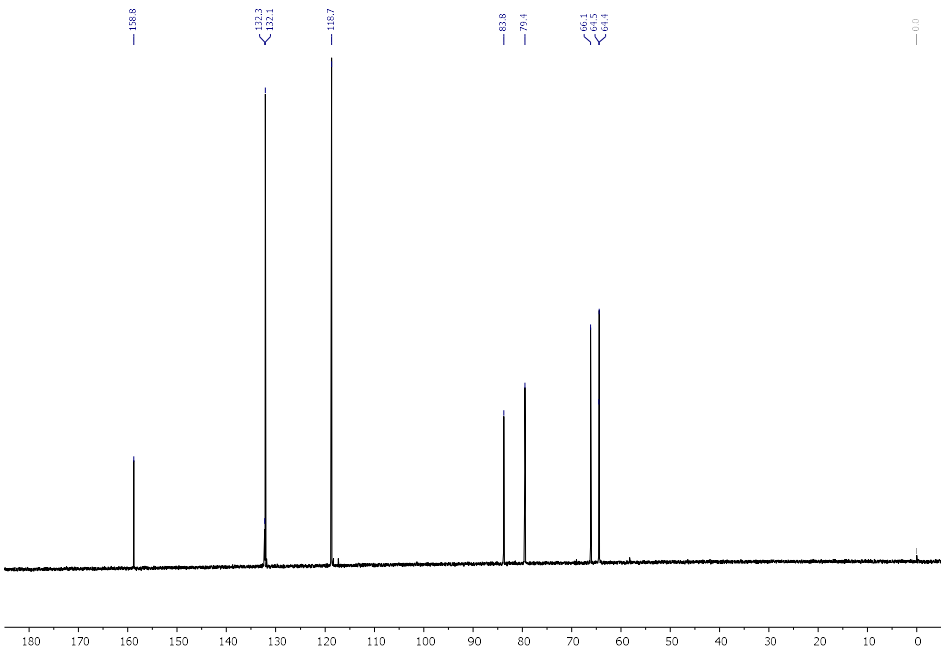
(*R*,*R*,*R*,*R*)-*N*(1)-Methyl-2-(4''-methoxyphenyl)-3,4-hydroxy-5-hydroxymethylpyrrolidine [codonopsinol B] 297 (^{13}C, 100 MHz, CD_3OD)



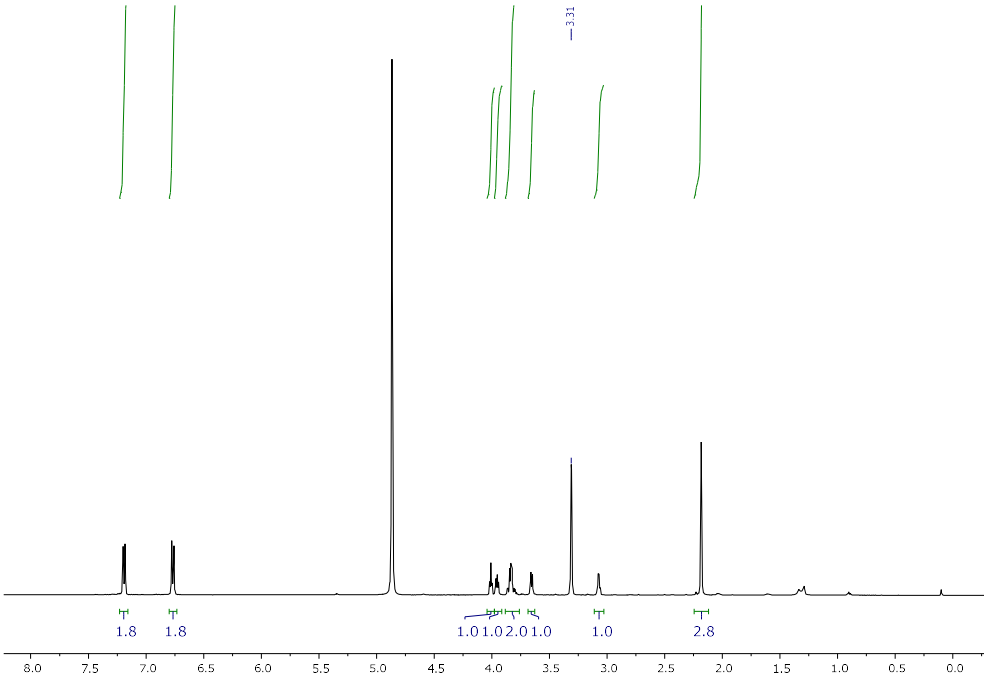
(*R*,*R*,*R*,*R*)-2-(4''-Hydroxyphenyl)-3,4-hydroxy-5-hydroxymethylpyrrolidine [radicamine B] 294 (^{1}H, 500 MHz D_2O)



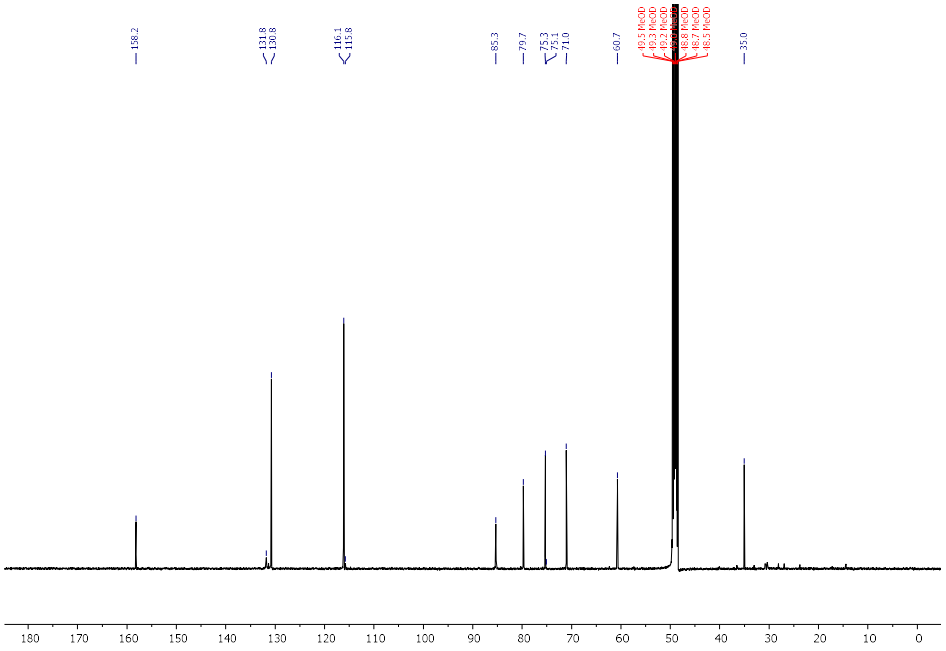
(*R*,*R*,*R*,*R*)-2-(4''-Hydroxyphenyl)-3,4-hydroxy-5-hydroxymethylpyrrolidine [radicamine B] 294 (^{13}C, 125 MHz D_2O)



(*R*,*R*,*R*,*R*)-*N*(1)-Methyl-2-(4''-hydroxyphenyl)-3,4-hydroxy-5-hydroxymethylpyrrolidine [codonopsinol C] 298 (^{1}H, 500 MHz CD_3OD)



(*R*,*R*,*R*,*R*)-*N*(1)-Methyl-2-(4''-hydroxyphenyl)-3,4-hydroxy-5-hydroxymethylpyrrolidine [codonopsinol C] 298 (^{13}C, 125 MHz CD_3OD)



(*R*,*R*,*R*,*R*)-*N*(1)-Methyl-2-(4''-hydroxyphenyl)-3,4-hydroxy-5-hydroxymethylpyrrolidine [codonopsinol C] 298 (^{1}H, 400 MHz D_2O)

