The Asymmetric Synthesis of Amino Polyols

A thesis submitted in partial fulfilment of the requirement
for the degree of Doctor of Philosophy

by

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For my Nanny, Granny and Grandad

Declaration

The work described in this thesis was carried out in the Chemistry Research Laboratory, University of Oxford from September 2009 until December 2012, 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.

Emma Marie Foster

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Abstract

Emma Marie Foster D.Phil. Thesis

St. Catherine's College Michaelmas Term 2012

This thesis is concerned with the development of methodology for the asymmetric synthesis of a range of amino polyol containing compounds.

Chapter 1 highlights the abundance of the amino polyol motif in nature, the wide range of biological activities displayed by amino polyol containing compounds, and their occurrence in drug molecules. A variety of different methods for the synthesis of stereodefined amino polyols is then discussed.

Chapter 2 details a full investigation into the doubly diastereoselective conjugate addition reactions of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide to enantiopure α,β-unsaturated esters which contain a dioxolane unit. The "matched" conjugate addition reactions were further coupled with a highly diastereoselective *in situ* enolate oxidation using camphorsulfonyloxaziridine for the synthesis of key α-hydroxy-β-amino ester intermediates. Subsequent cyclisation and further elaboration allowed access to a range of amino polyol containing compounds including imino sugars, amino sugars, and amino acids.

Chapter 3 extends the investigation into the doubly diastereoselective lithium amide conjugate addition reaction to enantiopure α,β-unsaturated esters which contain two dioxolane units. A full assessment into the conjugate addition of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide to a series of D-pentose derived α,β-unsaturated esters is reported. Subsequent elaboration of the β-amino ester products of these conjugate addition reactions resulted in the synthesis of (2'*S*,3'*S*,4'*R*)-dihydroxyhomoproline and (2'*S*,3'*R*,4'*S*)-dihydroxyhomoproline.

Chapter 4 describes the asymmetric syntheses of protected forms of APTO and AETD, the 2,4,5-trihydroxy substituted β-amino acid residues found within the hexapeptide marine natural products microsclerodermins C, D and E. The optimised synthetic routes to APTO and AETD involved three key steps: a diastereoselective aminohydroxylation [via conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide to an achiral α,β-unsaturated ester followed by *in situ* enolate oxidation with camphorsulfonyloxaziridine], a diastereoselective dihydroxylation, and an olefination.

Chapter 5 contains full experimental procedures and characterisation data for all compounds synthesised in chapters 2, 3 and 4.

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To the Guernsey Crew: Kristína, thank you for all of your help, especially when I started working with OsO_4, and for teaching me the most useful Slovak word: čučoriedka! Michael, thank you for always having the time to listen, for making me laugh just by laughing yourself, and for your funny anecdotes (in fact, how is *Quant. Proc.* coming along?). And Anne, we did it! I too am so very glad that you took that year out…it meant that we could go through all the ups and downs together and I thank you so much for always being there for me. I certainly miss chatting to you as much as we used to but I know it won't be long before the elaborate dinner parties are back up and running!

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And finally, thank you to my family for always being there for me. This thesis represents the end of three years of hard work and it would not have been possible without the love and support you have all shown me. To Mum, Dad, Laura, Granny, Molly and Abby, I love you all so very much.

Abbreviations

~	Approximately
(±)	Racemic
$[\alpha]_D$	Specific rotation
Å	Angstroms
AA	Asymmetric aminohydroxylation
Ac	Acetyl
acac	Acetylacetonate
AD	Asymmetric dihydroxylation
AE	Asymmetric epoxidation
AETD	(2*S*,3*R*,4*S*,5*S*,*E*,*E*)-3-Amino-10-(4'-ethoxyphenyl)-2,4,5-trihydroxydeca-7,9-dienoic acid
app	Apparent
APTO	(2*S*,3*R*,4*S*,5*S*,*E*)-3-Amino-8-phenyl-2,4,5-trihydroxyoct-7-enoic acid
aq	Aqueous
Ar	Aryl
Atm	Atmosphere
ATP	Adenosine triphosphate
ATR	Attenuated total reflectance
BINAL	Lithium [(*S*)-1,1′-bi(2-naphthol)]methoxyaluminium hydride
Bn	Benzyl
Boc	*tert*-Butoxycarbonyl
br	Broad
BT	Benzothiazoyl
Bu	Butyl
Bz	Benzoyl
c	Concentration
C	Celsius
^{13}C	Carbon
ca.	Circa
CAN	Ceric ammonium nitrate
cat.	Catalytic
Cbz	Carboxylbenzyl
CI	Chemical ionisation
cm	Centimetres
cm^{-1}	Wavenumber
conc	Concentrated
COSY	Correlation spectroscopy
Cp	Cyclopentadienyl
CSA	Camphorsulfonic acid
CSI	Camphorsulfonimine
CSO	Camphorsulfonyloxaziridine
Cy	Cyclohexyl
d	Doublet
DEAD	Diethyl azodicarboxylate
dec	Decomposes
deg	Degrees
Dess-Martin periodinane	1,1,1-Tris(acetyloxy)-1,1-dihydro-1,2-benziodoxol-3-(1*H*)-one
DDQ	2,3-Dichloro-5,6-dicyano-1,4-benzoquinone
DGJNAc	2-Acetamido-1,2-dideoxy-D-*galacto*-nojirimicin
DHQ	Dihydroquinine

$(DHQ)_2PHAL$	Hydroquinine-1,4-phthalazinediyl diether
$(DHQD)_2PHAL$	Hydroquinidine-1,4-phthalazinediyl diether
DIAD	Diisopropyl azodicarboxylate
DIBAL-H	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
DMB	Dimethoxybenzyl
DME	Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DMP	2,2-Dimethoxypropane
DMSO	Dimethyl sulfoxide
DMSO-d_6	Deuterated dimethyl sulfoxide
dr	Diastereoisomeric ratio
δ_H	Proton (^{1}H) NMR chemical shift
δ_C	Carbon (^{13}C) NMR chemical shift
(*E*)	Entgegen
E1cB	Elimination, unimolecular, via conjugate base
ee	Enantiomeric excess
ent	Enantiomer
equiv	Equivalents
ESI	Electrospray ionisation
Et	Ethyl
FI	Field ionisation
FT	Fourier transform
g	Grams
GABOB	(*R*)-4-Amino-3-hydroxybutyric acid
GC	Gas chromatography
GCT, GCToF	Gas chromatography time of flight
Grubbs II	[1,3-Bis(2',4',6'-trimethylphenyl)-2-imidazolidinylidene]dichloro(phenylmethylene)(tricyclo-hexylphosphine)ruthenium
h	Hours
^{1}H	Proton
HCT-116	Human colorectal cancer cells
HMBC	Heteronuclear multiple bond correlation
HMDS	Hexamethyldisilazide
H-G II	[1,3-Bis-(2',4',6'-trimethylphenyl)-2-imidazolidinylidene]dichloro(*o*-isopropoxyphenylmethylene)ruthenium
HPLC	High performance liquid chromatography
HRMS	High resolution mass spectrometry
HSQC	Hetereonuclear single quantum correlation
Hz	Hertz
IND	Dihydroindole
i	Ipso
i	Iso
IR	Infrared
J	Coupling constant
^3J	Vicinal coupling constant
K	Kelvin
L	Litres
LC	Liquid chromatography
LCT	Liquid chromatography time of flight
LDA	Lithium diisopropylamide

lit.	Literature
m	Meta
m	Multiplet
M	Molar
$[M]^+$	Molecular ion
m-CPBA	*meta*-Chloroperbenzoic acid
Me	Methyl
MeOH-d_4	Deuterated methanol
mg	Milligrams
MHz	Megahertz
min	Minutes
Ms	Methanesulfonyl
MS	Mass spectrometry
µL	Microlitres
mL	Millilitres
µmol	Micromoles
mmol	Millimoles
mol	Moles
MOM	Methoxymethyl
mp	Melting point
m/z	Mass to charge ratio
n	Integer value
nm	Nanometre
Nu	Nucelophile
NMO	*N*-Methylmorpholine *N*-oxide
NMR	Nuclear magnetic resonance
NOE	Nuclear Overhauser effect
o	Ortho
p	Para
PCC	Pyridinium chlorochromate
Pf	9-Phenyl-9-fluorenyl
Ph	Phenyl
PhMe-d_8	Deuterated toluene
PMB	*para*-Methoxybenzyl
PMBz	*para*-Methoxybenzoyl
PMP	*para*-Methoxyphenyl
ppm	Parts per million
PPTS	Pyridinium *para*-toluenesulfonate
Pr	Propyl
PT	1-Phenyl-1*H*-tetrazol-5-yl
q	Quartet
QNO	Quinuclidine *N*-oxide
quant	Quantitative
R	Alkyl
(*R*)	Rectus
ROESY	Rotational nuclear Overhauser effect spectroscopy
*RS**	Undetermined absolute stereochemistry
rt	Room temperature
s	Singlet
(*S*)	Sinister
satd	Saturated
S_N1	Substitution, nucleophilic, unimolecular

S_N2	Substitution, nucleophilic, bimolecular
^{t}, *tert*	Tertiary
t	Triplet
T	Temperature
TBAF	Tetrabutylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TBDPS	*tert*-Butyldiphenylsilyl
TEMPO	2,2,6,6-Tetramethylpiperidine 1-oxyl
Tf	Trifluoromethanesulfonate
THF	Tetrahydrofuran
TIPS	Triisopropylsilyl
TMEDA	Tetramethylethylenediamine
ToF	Time of flight
TPAP	Tetrapropylammonium perruthenate
Ts	*para*-Toluenesulfonyl
U.K.	United Kingdom
UV	Ultra-violet
ν_{max}	Infra-red absorption
v	Volume
w	Weight
Wilkinson's catalyst	Tris(triphenylphosphine)rhodium(I) chloride
(*Z*)	Zusammen

Contents

Chapter 1: Introduction

1.1 The importance of amino polyols

The amino polyol motif is abundant in naturally occurring molecules, with many found to display potent biological activities.[1] Examples of amino polyol containing natural products include the actomyosin ATPase activator penaresidin A **1**,[2] the glycosidase inhibitor castanospermine **2**,[3] the amino sugar L-ristosamine **3** (a component of the antibiotic ristomycin A),[4] and the antifungal agent and immunosuppressant myriocin **4**[5] (Figure 1).

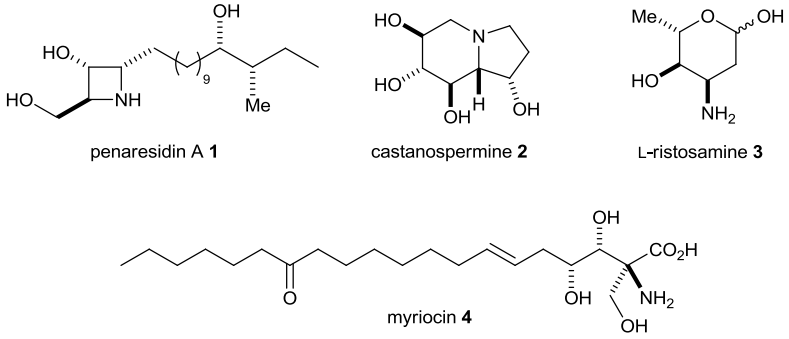


Figure 1. Amino polyol containing natural products **1**-**4**.

As a result of their biological activity, enantiopure amino polyols have been employed as key building blocks in organic synthesis[6] and have also been widely exploited by the pharmaceutical industry. For example, two leading drugs (which both contain amino sugar residues) are azithromycin **5** and nystatin **6**, and they are used as antibiotic[7] and antifungal[8] agents, respectively (Figure 2). Furthermore, amino polyols play important roles as chiral ligands for asymmetric catalysis,[9] as chiral auxiliaries for asymmetric synthesis,[10] and as metal-free organocatalysts.[11] As such, the stereocontrolled synthesis of amino polyols is still at the forefront of synthetic organic chemistry.[12]

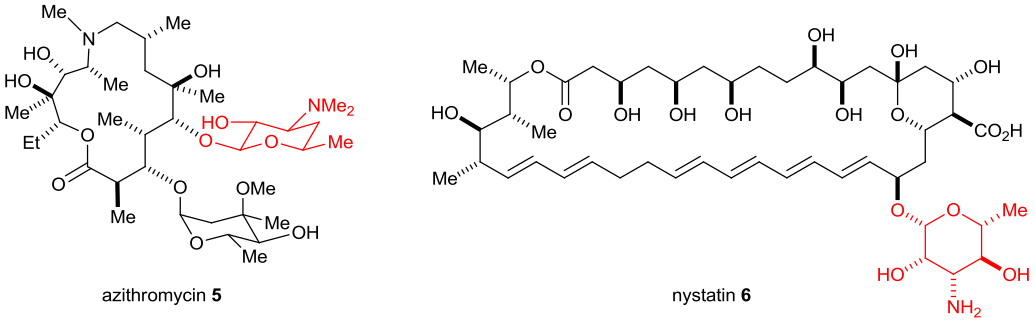


Figure 2. Amino polyol containing drugs azithromycin **5** and nystatin **6**.

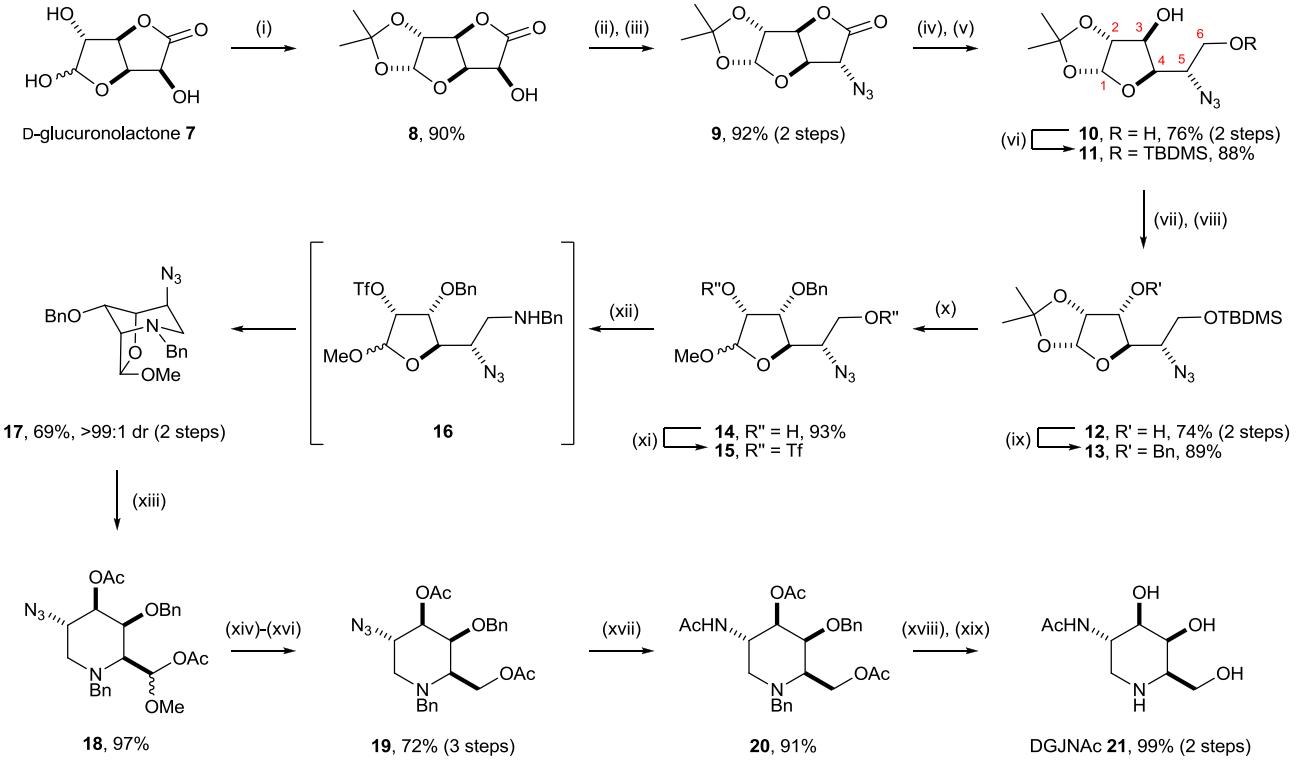
1.2 Synthesis of amino polyols

Many methodologies exist for the synthesis of amino polyols including olefin functionalisations,[5,13] cycloaddition reactions,[14] Mannich reactions,[15] Pinacol couplings,[16] aldol reactions,[17] and manipulation of the chiral pool.[18] Some of these methods will be discussed in more detail below.

1.2.1 Chiral pool syntheses

A useful method for the synthesis of amino polyols involves exploitation of the chiral pool. A number of naturally occurring enantiopure compounds (such as sugars and amino acids) are commercially available, and can therefore be used as the starting materials in the synthesis of amino polyols. A key advantage of this synthetic approach is that the starting materials already contain most, if not all, of the stereogenic centres required for the target products and so often syntheses mainly involve protecting group strategies and functional group interconversions. Fleet *et al.* have conducted a vast amount of work in this area, reporting the synthesis of many compounds containing the amino polyol motif.[19] For example, Fleet *et al.* recently reported the synthesis of the unnatural imino sugar 2-acetamido-1,2-dideoxy-D-*galacto*-nojirimicin (DGJNAc) **21** from D-glucuronolactone **7**, with subsequent biological evaluation resulting in the discovery that DGJNAc **21** is a sub-micromolar inhibitor of α-*N*-acetylgalactosaminidases.[20] D-Glucuronolactone **7** was first condensed with acetone in the presence of concentrated H_2SO_4 to give the corresponding acetonide **8** in 90% yield. Treatment of **8** with Tf_2O in pyridine gave the corresponding triflate, which was then subjected to an S_N2 reaction with NaN_3 to give azide **9** in 92% yield over the two steps. A two-step reduction of **9** was found to be the most efficient way to access diol **10**: azide-containing lactone **9** was therefore treated with DIBAL-H to give the corresponding lactol, which, upon subsequent treatment with $NaBH_4$ in MeOH gave diol **10** in 76% yield over the two steps. The primary alcohol moiety within **10** was then selectively *O*-silyl protected via treatment with TBDMSCl in pyridine. Inversion of configuration at the C(3)-position within **11** was achieved via an oxidation/diastereoselective reduction approach: oxidation of **11** using PCC gave the corresponding ketone, which was reduced completely diastereoselectively using $NaBH_4$ in EtOH to give **12** in 74% yield over the two steps. The hydroxyl group within **12** was then *O*-Bn protected using BnBr and NaH. Treatment of **13** with AcCl in MeOH served to effect both desilylation and removal of the acetonide functionality to give an anomeric mixture (α:β 88:12) of methyl furanosides **14** in 93% combined yield. Conversion of **14** into the corresponding ditriflate **15** via treatment with Tf_2O in pyridine proceeded cleanly, and **15** was then subjected to a double substitution reaction with $BnNH_2$. This reaction proceeded in a stepwise manner: initial substitution of the primary triflate group within **15** gave **16**, which then underwent an intramolecular substitution reaction involving the secondary triflate group. Interestingly, only the major α-anomer was found to undergo this second substitution reaction and so bicycle **17** was isolated as a single diastereoisomer in 69% yield over the two steps. Acetolysis of **17** using Ac_2O and $BF_3{\cdot}OEt_2$ gave a mixture of acetylated hemiacetals **18** in 97%

combined yield. Subsequent two-step reduction of **18** followed by acetylation of the resultant diol gave diacetate **19** in 72% yield over the three steps. Azide reduction (and subsequent *in situ N*-acetyl protection) of **19** was achieved using zinc and saturated aqueous $CuSO_4$ in the presence of AcOH and Ac_2O to give **20**, which was isolated in 91% yield. The final steps towards **21** involved the selective methanolysis of the acetate esters within **20** via treatment with NaOMe in MeOH, followed by hydrogenolysis in the presence of Pd/C to give imino sugar DGJNAc **21** in 99% yield over the two steps (Scheme 1).

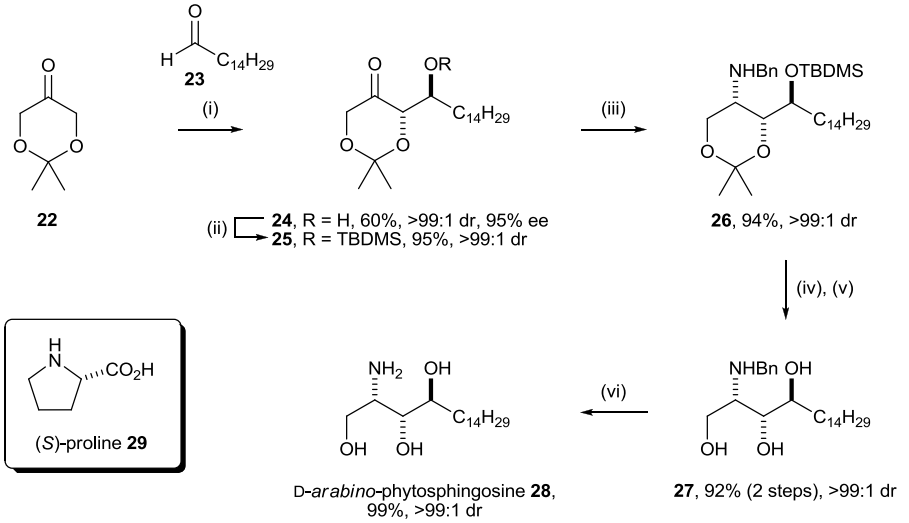


Scheme 1. *Reagents and conditions:* (i) conc H_2SO_4, acetone, rt, 4 h; (ii) Tf_2O, CH_2Cl_2, pyridine, –40 °C then –30 °C, 1 h; (iii) NaN_3, DMF, –30 °C, 1.5 h; (iv) DIBAL-H, CH_2Cl_2, –78 °C, 1.5 h; (v) $NaBH_4$, MeOH, –30 °C then –15 °C, 1.5 h; (vi) TBDMSCl, pyridine, rt, 18 h; (vii) PCC, CH_2Cl_2, 3 Å molecular sieves, rt, 18 h; (viii) $NaBH_4$, EtOH, H_2O, 0 °C to rt, 1.5 h; (ix) BnBr, NaH, DMF, 0 °C to rt, 1 h; (x) AcCl, MeOH, 55 °C, 2 h; (xi) Tf_2O, CH_2Cl_2, pyridine, –40 °C to –20 °C, 1 h; (xii) $BnNH_2$, THF, –30 °C to rt, 2 h; (xiii) $BF_3{\cdot}Et_2O$, Ac_2O, –30 °C to rt, 2.5 h; (xiv) DIBAL-H, CH_2Cl_2, –78 °C, 45 min; (xv) $NaBH_4$, MeOH, 0 °C to rt, 3 h; (xvi) Ac_2O, pyridine, rt, 16 h; (xvii) Zn powder, THF/AcOH/Ac_2O (v/v/v 3:2:1), satd aq $CuSO_4$, rt, 30 min; (xviii) MeONa, MeOH, rt, 16 h; (xix) Pd/C, H_2 (1 atm), H_2O/HCl (2.0 M, aq)/dioxane (v/v/v 10:2:1), rt, 24 h then DOWEX 50WX8.

1.2.2 Diastereoselective aldol reactions

Nucleophilic addition reactions to carbonyl compounds are often employed in organic synthesis for the formation of new C–C bonds.[21] The phytosphingosines (which consist of a 1,3,4-trihydroxy-2-amino unit connected to a long hydrocarbon chain) form the sub-units of sphingolipids, which are important components of eukaryotic cells[22] and also display significant biological activities.[23] Enders *et al.*[24] recently turned their attention to the synthesis of phytosphingosines via a direct organocatalytic aldol reaction using (*S*)-proline **29**, a widely used organocatalyst.[25] Thus, treatment of a 1:1 mixture of dioxanone **22** and pentadecanal **23** with (*S*)-proline **29** resulted in a highly diastereo-

and enantioselective aldol reaction to give **24**, which was isolated in 60% yield, >99:1 dr and 95% ee. Attempted reductive amination of **24** proved unselective; however, when **24** was first converted to its corresponding *O*-TBDMS protected derivative **25**, reductive amination of **25** using $BnNH_2$ and $NaBH(OAc)_3$ in the presence of AcOH proceeded to give the desired 1,3-*anti*-aminoalcohol **26** as a single diastereoisomer, which was isolated in 94% yield and >99:1 dr. Sequential treatment of **26** with TBAF and then F_3CCO_2H effected removal of the *O*-silyl and *O*-isopropylidine protecting groups, respectively, and **27** was isolated in 92% yield and >99:1 dr over the two steps. Hydrogenolysis of the *O*-Bn group within **27** revealed D-*arabino*-phytosphingosine **28**, which was isolated in 99% yield and >99:1 dr (Scheme 2).

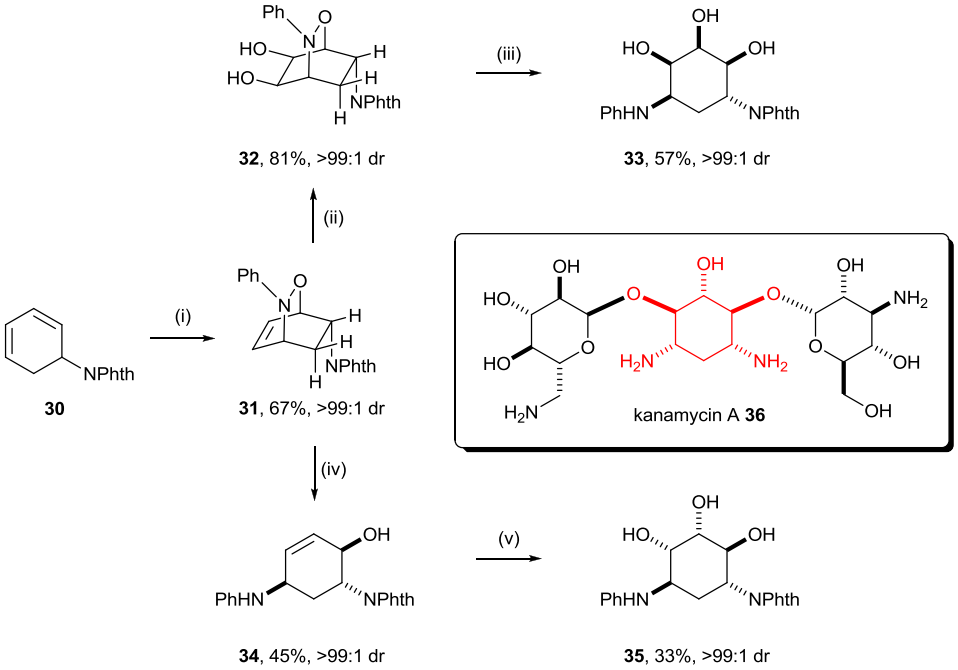


Scheme 2. *Reagents and conditions:* (i) **29** (30 mol%), $CHCl_3$, rt, 4 days; (ii) TBDMSOTf, 2,6-lutidine, CH_2Cl_2, –20 °C; (iii) $BnNH_2$, $NaBH(OAc)_3$, AcOH, CH_2Cl_2, 2 °C; (iv) TBAF, THF, $MgSO_4$, 50 °C; (v) F_3CCO_2H, THF, 50 °C; (vi) Pd/C, H_2 (1 atm), MeOH, rt.

1.2.3 Cycloaddition reactions

A cycloaddition reaction involves the combination of two unsaturated components to give a cyclic product.[26] Cycloadditions are widely employed in organic synthesis for the formation of new C–C bonds,[27] and so they are therefore used to form cyclic scaffolds which, upon further functionalisation, can allow access to amino polyol containing compounds. For example, Sar *et al.*[28] utilised a highly diastereoselective nitroso Diels-Alder reaction[29] as the key step in the synthesis of 4,5,6-trihydroxy-1,3-diaminocyclohexanes, an amino polyol subunit found in aminoglucoside antibiotics such as kanamycin A **36**.[30] Treatment of racemic **30** with nitrosobenzene resulted in the sole formation of bicycle **31**, which was isolated in 67% yield and >99:1 dr. Dihydroxylation of **31** using catalytic OsO_4 and NMO (Upjohn conditions[31]) gave *syn*-diol **32** as a single diastereoisomer, with oxidation found to occur on the face of the olefin opposite to the bulky phthalimide group. Diol **32** was then subjected to hydrogenolysis using Raney Ni to give the desired diamino triol **33** in 57% isolated yield and >99:1 dr. If **31** was instead treated with $Mo(CO)_6$, reductive N–O bond cleavage resulted to give

allylic alcohol **34** as the sole product, which was isolated in 45% yield. Subsequent Upjohn dihydroxylation of **34** then gave direct access to the alternative diamino triol **35** (Scheme 3).



Scheme 3. *Reagents and conditions:* (i) nitrosobenzene, CH_2Cl_2, rt, 2 h; (ii) OsO_4 (10 mol%) in PhMe, NMO in H_2O, acetone, rt, 10 h; (iii) Raney Ni (50% w/w in H_2O), H_2 (2.8 bar), MeOH, rt, 4 h; (iv) $Mo(CO)_6$, MeCN/H_2O (v/v 11:1), reflux, 1 h; (v) OsO_4 (10 mol%) in PhMe, NMO in H_2O, acetone, rt, 15 h.

1.2.4 Olefin functionalisation

The functionalisation of olefins is a popular method for the synthesis of the amino polyol motif, with the key transformations involving stereoselective dihydroxylation reactions, epoxidation reactions, and aminohydroxylation reactions.

1.2.4.1 Olefin dihydroxylation

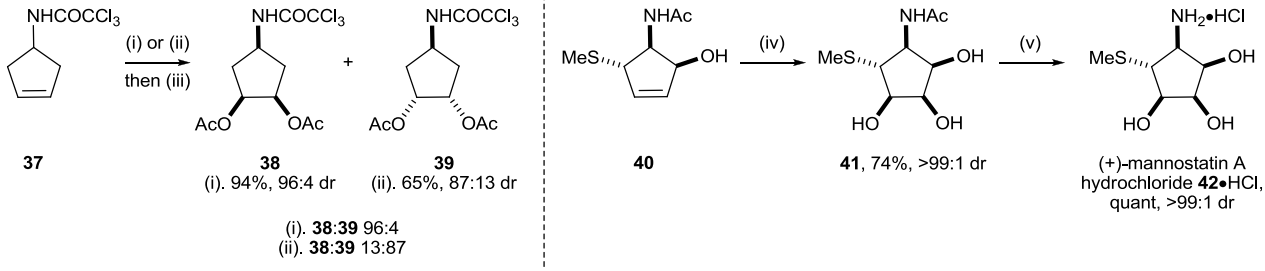
1.2.4.1.1 Dihydroxylation with OsO_4

In 1936, Criegee *et al*. first noted that the treatment of an olefin with a stoicheiometric amount of OsO_4 resulted in the selective formation of *syn*-1,2-diols.[32] Catalytic procedures [which make use of co-oxidants to regenerate the toxic and expensive osmium(VIII) reagent *in situ*] have also been developed.[33] A widely used procedure is the Upjohn dihydroxylation, developed by VanRheenan *et al.*, which makes use of a tertiary amine *N*-oxide [typically *N*-methylmorpholine *N*-oxide (NMO)] as the co-oxidant.[31]

1.2.4.1.2 Diastereoselective dihydroxylation with OsO_4

In 1983, Kishi *et al.* noted that the OsO_4-mediated dihydroxylation of chiral allylic alcohols often occurs preferentially on the opposite face of the olefin to the hydroxyl group.[34] In an attempt to

reverse this inherent diastereoselectivity, Donohoe *et al*. developed a procedure that involves treatment of unsaturated alcohols (or *N*-protected homoallylic amines) with stoicheiometric OsO_4 in the presence of TMEDA to give *syn*-directed dihydroxylation products.[35] The differing selectivities observed upon oxidation under Upjohn conditions (OsO_4/NMO) and Donohoe conditions (OsO_4/TMEDA) are thought to be a result of the occurrence of hydrogen-bonding in the latter case between the reagent and the hydroxyl (or amido) group in the substrate, which directs attack to the same face of the olefin as the hydroxyl (or amido) group. For example, treatment of homoallylic trichloroacetamide **37** under Upjohn conditions gave (after acetylation of the resultant 1,2-diols) a 13:87 mixture of diacetates **38** and **39**, respectively, whilst use of the OsO_4/TMEDA reagent instead gave a 96:4 mixture of **38** and **39**, respectively (Scheme 4).[36] Mariano *et al.*[37] later exploited this methodology in their synthesis of the amino triol (+)-mannostatin A (isolated as the corresponding hydrochloride salt **42**·HCl), which has been found to act as a potent α-mannosidase inhibitor.[38] The key step in this synthesis involved the diastereoselective directed dihydroxylation of **40** using OsO_4/TMEDA to give **41** in 74% yield as a single diastereoisomer (Scheme 4).

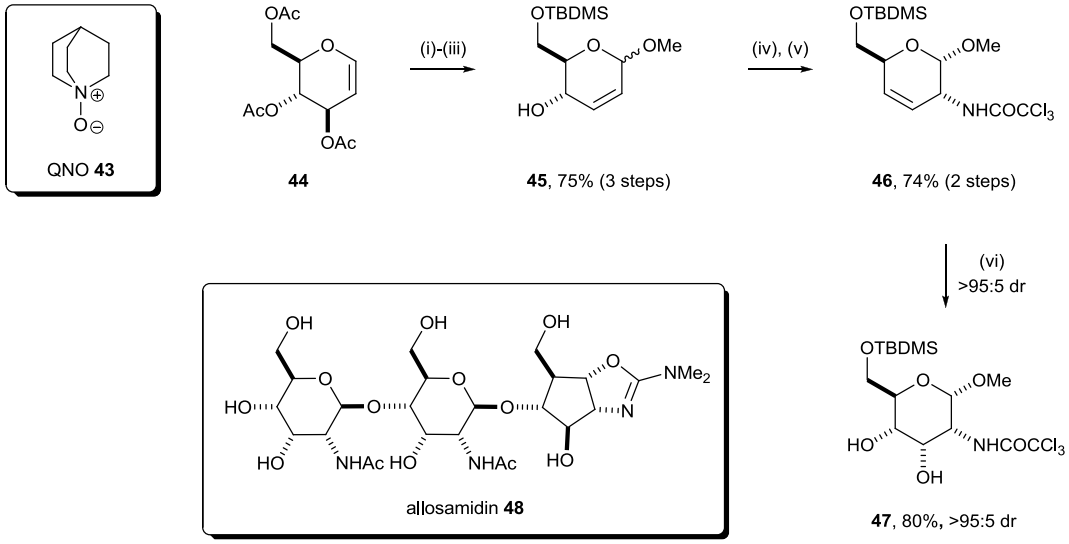


Scheme 4. *Reagents and conditions:* (i) OsO_4 (1.1 equiv), TMEDA (1.0 equiv), CH_2Cl_2, −78 °C, 30 min, then HCl, MeOH, rt, 30 min; (ii) OsO_4 (cat.), NMO, acetone/H_2O (v/v 4:1), rt, 4 h; (iii) Ac_2O, pyridine, DMAP, rt, 15 h; (iv) OsO_4 (1.1 equiv), TMEDA (1.0 equiv), CH_2Cl_2, −78 °C, 1.5 h, then Na_2SO_3, THF/H_2O (v/v 20:1), 65 °C, 5 h; (v) HCl (6.0 M, aq), 100 °C, 12 h.

1.2.4.1.3 Catalytic diastereoselective dihydroxylation with OsO_4

Donohoe *et al.* have also developed a diastereoselective OsO_4 directed dihydroxylation procedure that involves the use of catalytic (as opposed to stoicheiometric) OsO_4.[39] This procedure, which results in extremely high levels of diastereoselectivity for the dihydroxylation, involves treatment of an allylic amide with catalytic OsO_4 (5 mol%), two equivalents of quinuclidine *N*-oxide (QNO) **43** as a re-oxidant and four equivalents of H_2O. This protocol was applied in the synthesis of **47**, a protected form of the amino sugar D-allosamine.[40] *N*-Acetyl-D-allosamine is found as a repeating sugar unit in the chitinase inhibitor allosamidin **48**.[41] Commercially available tri-*O*-acetyl-D-glucal **44** was firstly transformed into allylic tricholoroacetamide **46** in five steps and 56% overall yield.

Treatment of **46** with catalytic OsO_4 in the presence of QNO **43** and H_2O gave **47** in >95:5 dr, which was subsequently isolated in 80% yield and >95:5 dr (Scheme 5).



Scheme 5. *Reagents and conditions:* (i) MeOH, $BF_3{\cdot}OEt_2$, PhMe, –20 °C to rt, 1 h; (ii) K_2CO_3, MeOH/H_2O (v/v 4:1), rt, 1 h; (iii) TBDMSCl, Et_3N, CH_2Cl_2, rt, 24 h; (iv) DBU, Cl_3CCN, CH_2Cl_2, –20 °C to rt, 1 h; (v) Ph_2O, K_2CO_3 (cat.), 195 °C, 3 h; (vi) QNO **43**, OsO_4 (5 mol%), CH_2Cl_2, –78 °C to rt, 1 h.

1.2.4.1.4 Catalytic asymmetric dihydroxylation (AD)

Sharpless *et al.*[42] have also developed a catalytic asymmetric variant of the OsO_4-promoted *cis*-dihydroxylation of olefins: treatment of an olefin with catalytic OsO_4, $K_3Fe(CN)_6$ (as the co-oxidant), K_2CO_3 and a cinchona alkaloid derived ligand in a 1:1 mixture of H_2O and ^tBuOH results in a highly enantioselective dihydroxylation. For ease of handling, commercially available mixtures of all the required reagents are often employed, whereby AD-mix-α contains a $(DHQ)_2PHAL$ **50** ligand whilst AD-mix-β contains a $(DHQD)_2PHAL$ **51** ligand. The mechanism of this reaction has been widely studied and the mnemonic device **49** is often used to predict the stereochemical outcome of the reaction (Figure 3).[43]

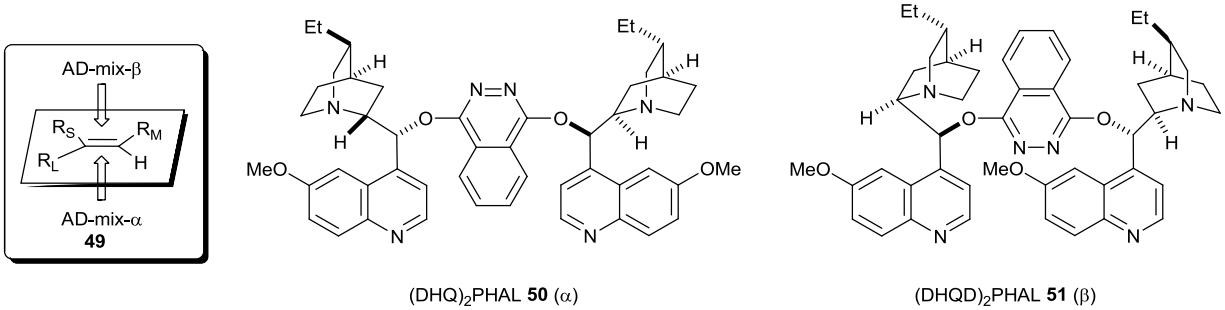
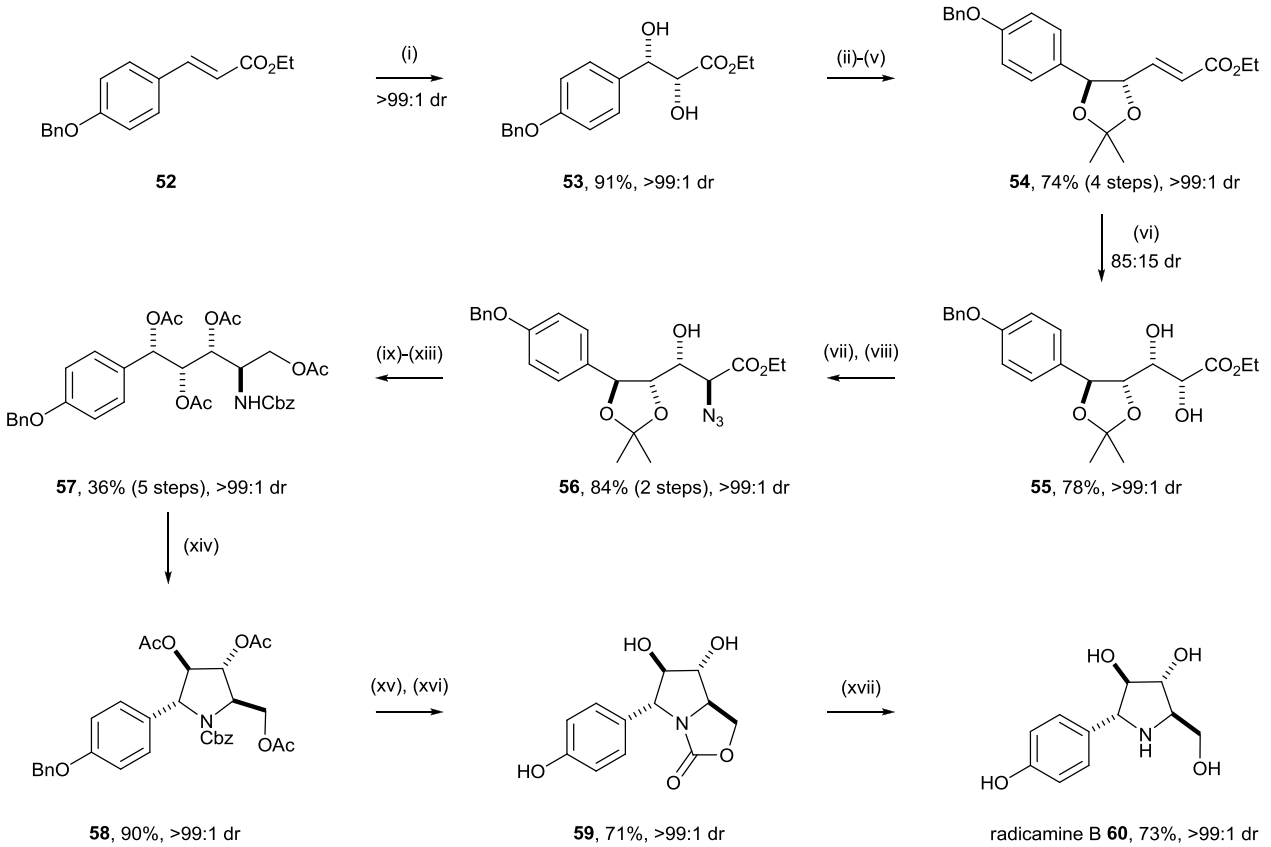


Figure 3. Structures of [$(DHQ)_2PHAL$] **50** and [$(DHQD)_2PHAL$] **51**, and mnemonic **49**, used to predict the enantiofacial selectivity of the AD reaction. [R_S = small, R_M = medium, R_L = large].

The Sharpless AD reaction has been applied extensively in synthesis.[42,44] For example, Rao *et al.*[45] utilised the Sharpless AD reaction twice in their synthesis of the naturally-occurring imino sugar radicamine B **60**, a known glycosidase inhibitor.[46] Treatment of α,β-unsaturated ester **52** with AD-mix-α gave diol **53** in >99:1 dr, which was isolated in 91% yield and >99:1 dr. The

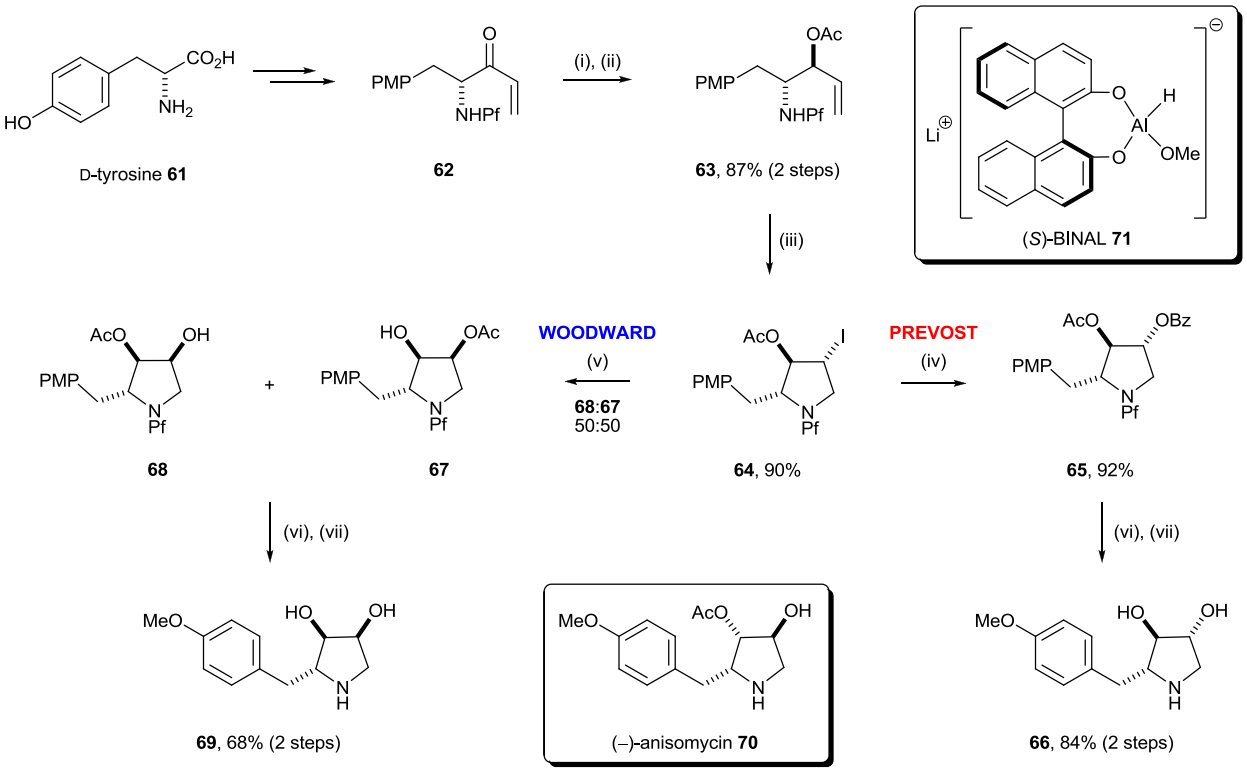
stereochemical outcome of this AD reaction is consistent with the outcome predicted by the mnemonic **49** (*vide supra*). Diol **53** was subsequently transformed into α,β-unsaturated ester **54** in four steps. It was predicted that a Sharpless AD reaction of **54** involving the use of AD-mix-α would again be required to obtain diol **55**; however, under the standard AD conditions, diol **55** was only produced in 60:40 dr.[47] When the reaction was repeated using excess $(DHQ)_2PHAL$ **50** ligand, these conditions were found to improve the diastereoselectivity of the dihydroxylation reaction and diol **55** was produced in 85:15 dr. Subsequent purification allowed the isolation of **55** in 78% yield and >99:1 dr. Treatment of **55** with $SOCl_2$ and Et_3N gave the corresponding cyclic sulfite, which, upon treatment with NaN_3, was opened regioselectively to give **56** in 84% yield and >99:1 dr over the two steps. Azido alcohol **56** was then converted into tetraacetate **57** in five steps, which involved azide reduction using PPh_3, ester reduction using $NaBH_4$, and protecting group manipulation. Treatment of **57** with F_3CCO_2H in CH_2Cl_2 gave pyrrolidine **58**, which was isolated in 90% yield and >99:1 dr. A series of deprotection steps then allowed access to radicamine B **60** as a single diastereoisomer (Scheme 6).



Scheme 6. *Reagents and conditions:* (i) AD-mix-α, $CH_3SO_2NH_2$, $^tBuOH/H_2O$ (v/v 1:1), 0 °C, 24 h; (ii) DMP, TsOH (cat.), CH_2Cl_2, rt, 12 h; (iii) $LiAlH_4$, THF, 0 °C to rt, 3 h; (iv) $(ClCO)_2$, DMSO, CH_2Cl_2, –78 °C, 1.5 h, then Et_3N, –78 °C, 10 min; (v) $Ph_3P{=}CHCO_2Et$, PhMe, reflux, 6 h; (vi) AD-mix-α, $CH_3SO_2NH_2$, $(DHQ)_2PHAL$ **50**, $^tBuOH/H_2O$ (v/v 1:1), 0 °C, 24 h; (vii) $SOCl_2$, Et_3N, CH_2Cl_2, 0 °C to rt, 30 min; (viii) NaN_3, DMF, 80 °C, 2 h; (ix) PPh_3, EtOH, 0 °C to rt, 6 h; (x) CbzCl, Na_2CO_3, EtOH, 0 °C to rt, 8 h; (xi) LiCl, $NaBH_4$, EtOH, THF, 0 °C to rt, 3 h; (xii) $AcOH/H_2O$ (v/v 5:4), rt, 8 h; (xiii) Ac_2O, Et_3N, CH_2Cl_2, DMAP (cat.), 0 °C to rt, 12 h; (xiv) F_3CCO_2H/CH_2Cl_2 (v/v 1:3), 0 °C to rt, 4 h; (xv) K_2CO_3, MeOH, 0 °C to rt, 1 h; (xvi) $PdCl_2$, H_2 (1 atm), MeOH, rt, 12 h; (xvii) MeOH, HCl (6.0 M, aq), reflux, 3 h then DOWEX 50WX8-200.

1.2.4.2 Woodward-Prévost methodology

Woodward[48]-Prévost[49] methodology refers to a complementary pair of stereospecific reactions that involve the generation of either *syn*- or *anti*-1,2-diols from the same olefin substrate by modification of the reaction conditions to include or exclude water. Kim *et al*. reported an application of this methodology towards the synthesis of analogues of the antifungal[50] and antitumor[51] agent (–)-anisomycin **70**.[52] α,β-Unsaturated ketone **62** (derived from D-tyrosine **61**) was initially reduced using (*S*)-BINAL **71** and then acetylated using Ac_2O to give protected allylic alcohol **63** in 87% yield over two steps. Treatment of **63** with I_2 generated β-acetoxy iodide **64** in 90% yield. Subjection of **64** to Prévost "dry" conditions (AgOBz) gave the *anti*-product **65** in 92% yield with subsequent reduction of **65** using $LiAlH_4$ followed by hydrogenolysis giving the anisomycin analogue **66** in 84% isolated yield over the two steps. Subjection of **64** to Woodward "wet" conditions ($AgBF_4$, H_2O) instead gave a 50:50 mixture of the two regioisomeric *syn*-β-hydroxy acetates **67** and **68**. Treatment of the mixture of **67** and **68** with $LiAlH_4$ followed by hydrogenolysis gave the alternative anisomycin analogue **69** in 68% isolated yield over two steps (Scheme 7).



Scheme 7. *Reagents and conditions:* (i) (*S*)-BINAL **71**, THF, –78 °C, 1 h then H_2O; (ii) Ac_2O, DMAP, CH_2Cl_2, rt, 2 h; (iii) I_2, satd aq $NaHCO_3$/THF/Et_2O (v/v/v 2:1:1), rt, 36 h then $Na_2S_2O_3$ (0.1 M, aq); (iv) AgOBz, PhMe, reflux, 12 h; (v) $AgBF_4$, PhMe/H_2O (v/v 9:1), rt, 12 h; (vi) $LiAlH_4$, THF, 0 °C, 30 min; (vii) Pd/C, H_2 (1 atm), EtOAc, rt, 6 h.

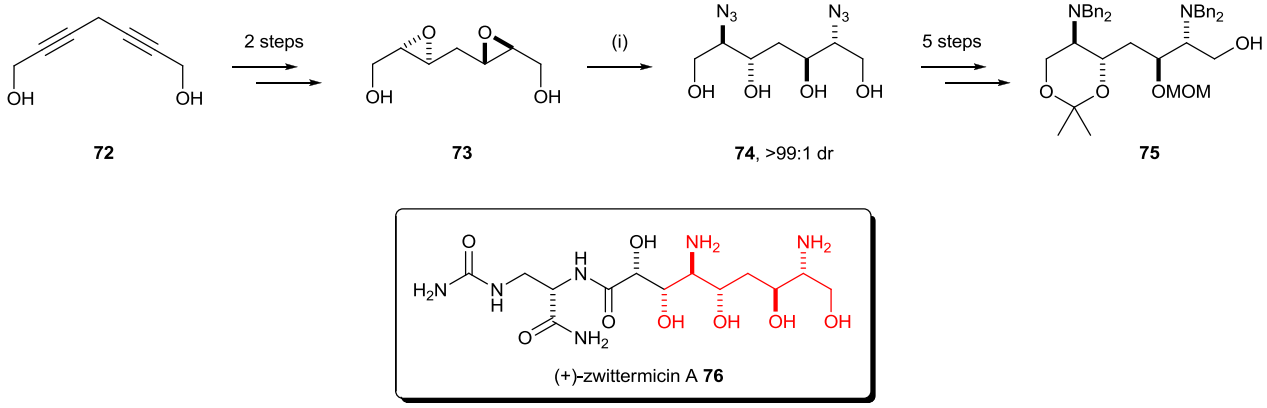
1.2.4.3 Olefin epoxidation

A wide range of oxidants can be employed for the epoxidation of olefins. Standard epoxidation procedures involve the use of reagents such as peroxides,[53] peracids,[54] and dioxiranes;[55] however, olefin epoxidation can also be achieved by the use of a peroxide (often ^tBuOOH) in the presence of a

catalytic metal species such as $VO(acac)_2$[56] or $Mo(CO)_6$.[57] The epoxidation of olefins remains a vibrant area of research; for example, Sharpless[58] and Shi[59] have each developed asymmetric epoxidation protocols.

1.2.4.3.1 Nucleophilic opening of epoxides

A popular method for the synthesis of amino alcohol units is the ring opening of an epoxide by an amine or the azide anion.[60] For example, Molinski *et al.*[61] applied this methodology to their synthesis of **75**, which represented a formal total synthesis of the natural product (+)-zwittermicin A **76**, an amino polyol antibiotic,[62] which has also recently received special attention for its potential use as a biopesticide.[61] Diepoxide **73** was first synthesised from diyne **72** according to a literature procedure[63] involving a double Sharpless asymmetric epoxidation (AE).[58] Treatment of **73** with two equivalents of NaN_3 in the presence of $B(OMe)_3$ gave the C_2 symmetric diazidotetraol **74**. Although **74** was initially isolated in 80% yield as a mixture of isomers after flash column chromatography, it was found that recrystallisation of the residue allowed isolation of **74** as a single diastereoisomer. Subsequent elaboration of **74** via protecting group manipulation and azide reduction allowed access to **75**, the desired fragment of zwittermicin A **76**, in five steps (Scheme 8).

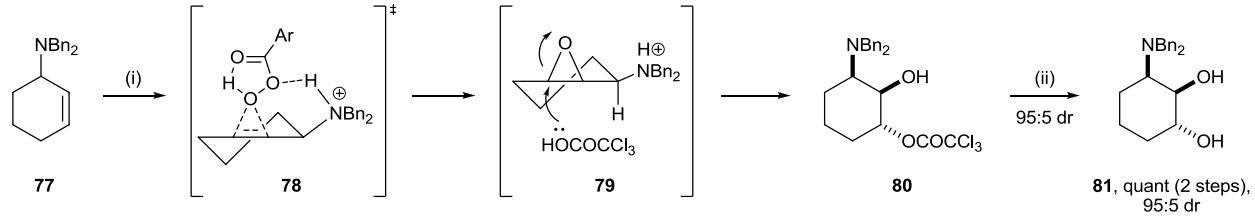


Scheme 8. *Reagents and conditions:* (i) $B(OMe)_3$, DMF, rt, 30 min then NaN_3, DMF, 40 °C, 4 h then 50 °C, 4 h.

1.2.4.3.2 Ammonium-directed epoxidation

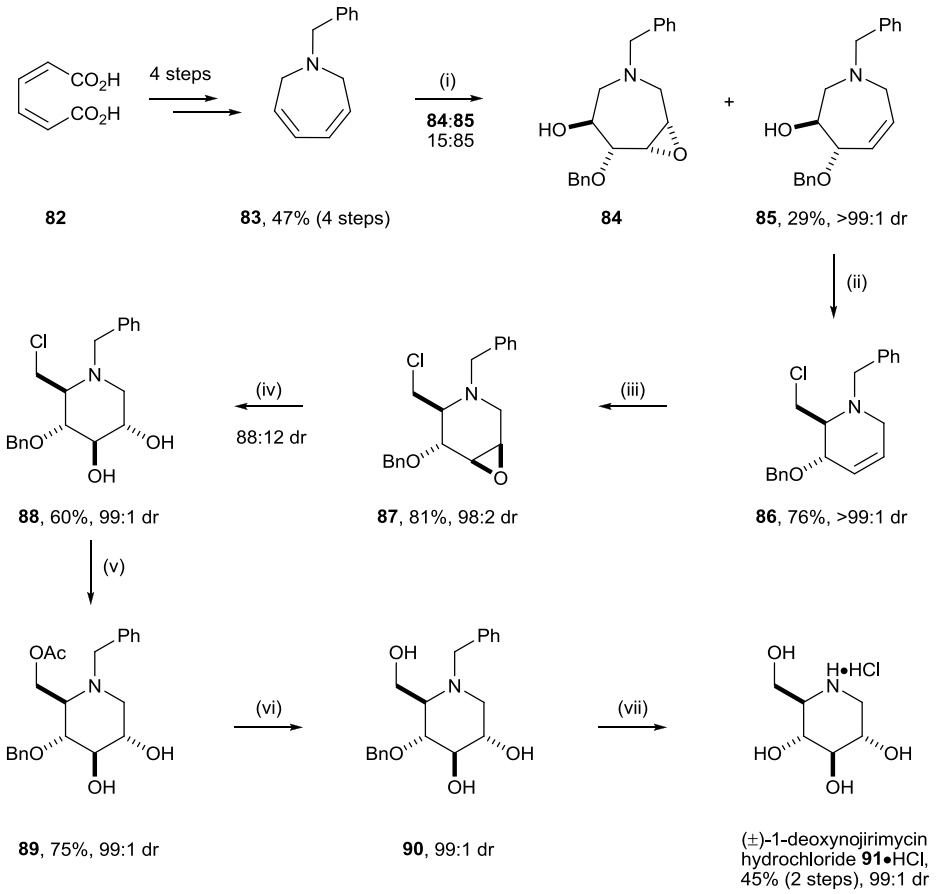
Davies *et al.* have developed an efficient procedure for the highly diastereoselective ammonium-directed oxidation of cyclic allylic and homoallylic amines.[64] For example, sequential treatment of 3-(*N*,*N*-dibenzylamino)cyclohex-1-ene **77** with Cl_3CCO_2H and *m*-CPBA resulted in formation of trichloroacetate ester **80**. It is proposed that the presence of Cl_3CCO_2H results in protonation of the *N*,*N*-dibenzylamino group, allowing hydrogen-bonded delivery of the oxidant to the olefin, via transition state **78**. Regioselective *in situ* ring-opening of the intermediate epoxide **79** by Cl_3CCO_2H

then occurs to give trichloroacetate ester **80**. Transesterification of **80** using K_2CO_3 and MeOH gave amino diol **81**, which was isolated in quantitative yield and 95:5 dr over the two steps (Scheme 9).



Scheme 9. *Reagents and conditions:* (i) Cl_3CCO_2H (5.0 equiv), *m*-CPBA (1.6 equiv), CH_2Cl_2, rt, 21 h, then $NaHCO_3$ (0.1 M, aq); (ii) K_2CO_3, MeOH, rt, 16 h.

This methodology has more recently been extended to the synthesis of polyhydroxylated pyrrolidines, including (±)-1-deoxynojirimycin **91**, via an oxidation/ring contraction approach.[65] Under optimised conditions, azepine **83** (prepared in four steps from *cis*,*cis*-muconic acid **82**) was treated with 1.5 equivalents of *m*-CPBA in the presence of HBF_4 and BnOH to give a 15:85 mixture of **84** and **85**, respectively. The major product **85** was subsequently isolated in 29% yield and >99:1 dr, with the low yield being attributed to the incompatibility of **85** with silica gel. The formation of **85** is consistent with a mechanism involving epoxidation of the double bond, followed by highly regioselective ring opening by BnOH. Excess *m*-CPBA can then further oxidise **85** to give epoxide **84** in a completely diastereoselective process. Subsequent treatment of tetrahydroazepine **85** with MsCl promoted ring contraction to give piperidine **86** in 76% yield as a single diastereoisomer. Oxidation of the olefin within **86** using a mixture of F_3CCO_3H and F_3CCO_2H gave epoxide **87** in 98:2 dr, which upon chromatographic purification was isolated in 81% yield and 98:2 dr. Regioselective ring-opening of epoxide **87** with Cl_3CCO_2H followed by hydrolysis of the resultant trichloroacetate ester with 2.0 M aqueous NaOH proceeded to give **88** in 88:12 dr, with subsequent purification via silica gel chromatography giving **88** in 60% yield and 99:1 dr. The primary chloride functionality within **88** was converted into the corresponding *O*-acetate ester **89** via treatment with AgOAc in DMF, and final transesterification and hydrogenolysis steps resulted in the formation of the hydrochloride salt of (±)-1-deoxynojirimycin **91**·HCl as a single diastereoisomer (Scheme 10). Further work involved resolution of the intermediate tetrahydroazepine **85** using preparative chiral HPLC, which allowed ultimate access to both enantiomers of **91**·HCl.[66]



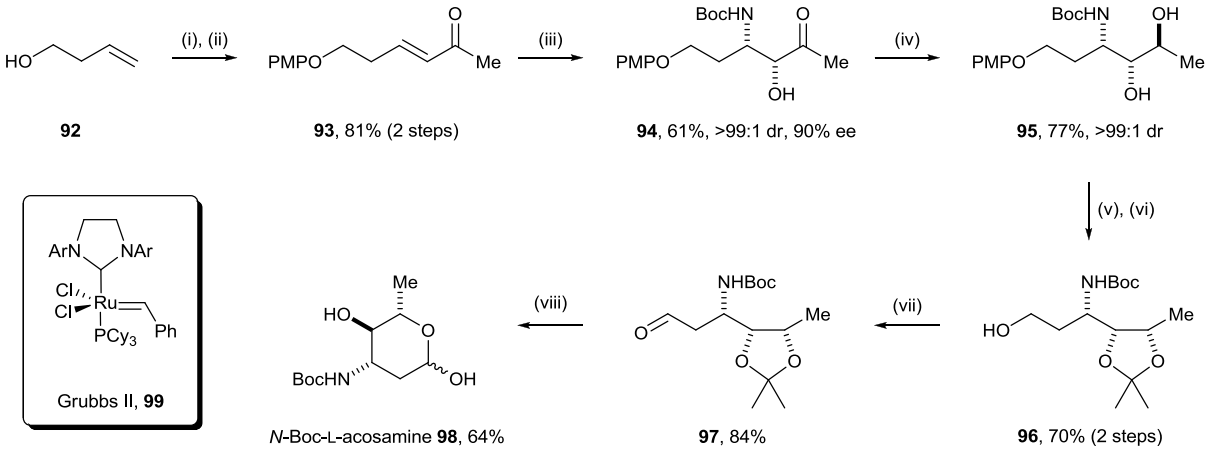
Scheme 10. *Reagents and conditions:* (i) *m*-CPBA (1.5 equiv), HBF_4, CH_2Cl_2, BnOH, rt, 24 h then NaOH (2.0 M, aq); (ii) MsCl, Et_3N, CH_2Cl_2, 0 °C, 1.5 h; (iii) F_3CCO_3H, F_3CCO_2H, CH_2Cl_2, 0 °C to rt, 6 h; (iv) Cl_3CCO_2H, CH_2Cl_2, rt, 16 h then NaOH (2.0 M, aq); (v) AgOAc, DMF, 65 °C, 24 h; (vi) K_2CO_3, MeOH, rt, 16 h; (vii) $Pd(OH)_2/C$, H_2 (1 atm), MeOH, rt, 72 h then HCl.

1.2.4.4 Olefin aminohydroxylation

1.2.4.4.1 Olefin asymmetric aminohydroxylation (AA)

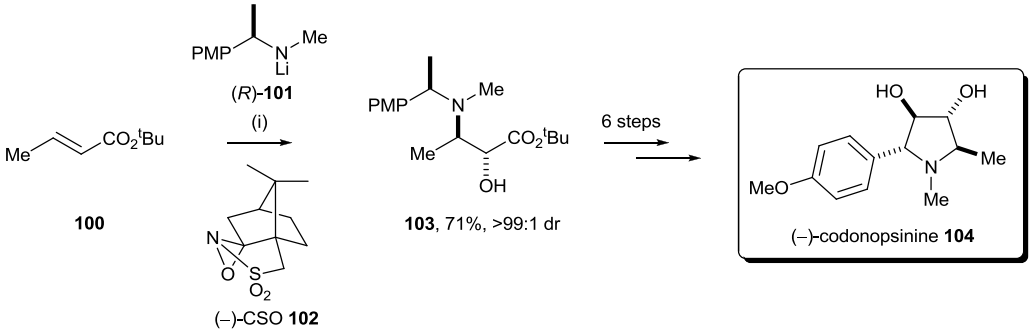
1,2-*syn*-Aminoalcohols can be synthesised directly via the Sharpless catalytic asymmetric aminohydroxylation of an olefin.[67] Under standard reaction conditions, the olefin is treated with a catalyst comprised of an osmium source [typically $K_2OsO_2(OH)_4$] coupled with either a $(DHQ)_2PHAL$ **50** ligand or a $(DHQD)_2PHAL$ **51** ligand, and a stoicheiometric nitrogen source. Unlike the analogous Sharpless AD reaction (*vide supra*), the Sharpless AA reaction can suffer problems of regioselectivity, and various optimised procedures have been developed.[68] For example, this asymmetric reaction was utilised by McLeod *et al.* as a key step in their synthesis of the protected amino sugar *N*-Boc-L-acosamine **98**.[69] 3-Butenol **92** was converted into ketone **93** in two sequential steps involving a Mitsunobu reaction (with *p*-methoxyphenol) and a cross metathesis reaction (using the Grubbs II catalyst **99**). Attempted Sharpless AA of **93** using the $(DHQ)_2PHAL$ **50** ligand under standard reaction conditions was found to result in very low yields of the desired product **94**; however, when the reaction was repeated under buffered conditions using $NaHCO_3$, a regioisomeric mixture of amino alcohol products (96:4 ratio) resulted, within which amino alcohol **94**

was identified as the major product. Subsequent purification allowed the isolation of **94** in 61% yield, >99:1 dr and 90% ee. Chelation-controlled reduction[70] of **94** using $Zn(BH_4)_2$ gave amino diol **95**, which was isolated in 77% yield and >99:1 dr. Acetonide protection of the diol unit within **95** using 2-methoxypropene and CSA followed by cleavage of the *O*-PMP ether using CAN gave alcohol **96** in 70% yield over the two steps. Oxidation of **96** using TEMPO and bis(acetoxy)iodobenzene gave the corresponding aldehyde **97** in 84% yield, which, upon treatment with DOWEX 50W acidic resin in aqueous dioxane, cyclised to give *N*-Boc-L-acosamine **98** in 64% yield (Scheme 11).



Scheme 11. *Reagents and conditions:* (i) *p*-methoxyphenol, PPh_3, DIAD, THF, reflux, 15 min; (ii) methyl vinyl ketone, Grubbs II **99** (5 mol%), CH_2Cl_2, reflux, 20 h; (iii) $(DHQ)_2PHAL$ **50** (5 mol%), $K_2OsO_2(OH)_4$ (5 mol%), $^tBuOCONH_2$, 1,3-dichloro-5,5-dimethylhydantoin, NaOH, $NaHCO_3$, $PrOH/H_2O$ (v/v 1:1), rt, 20 min; (iv) $Zn(BH_4)_2$ (0.2 M in Et_2O), Et_2O, rt, 20 min; (v) 2-methoxypropene, CSA, CH_2Cl_2, 0 °C, 5 h then 0 °C to rt, 14 h; (vi) CAN, $MeCN/H_2O$ (v/v 4:1), 0 °C, 25 min; (vii) TEMPO, bis(acetoxy)iodobenzene, CH_2Cl_2, rt, 4 h; (viii) DOWEX 50W, dioxane/H_2O (v/v 6:1), rt, 20 h. [Ar = 2,4,6-trimethylphenyl].

Davies *et al*. have established a highly diastereoselective method for the *anti*-aminohydroxylation of achiral α,β-unsaturated esters, involving the initial conjugate addition of an enantiopure lithium amide to an α,β-unsaturated ester, followed by *in situ* oxidation of the resultant enolate with the requisite antipode of camphorsulfonyloxaziridine (CSO) **102**.[71] This methodology has since been employed by Davies *et al.* in a wide range of syntheses,[72] including that of the naturally occurring pyrrolidine (–)-codonopsinine **104**.[73] In this synthetic route, conjugate addition of lithium amide (*R*)-**101** to *tert*-butyl crotonate **100** followed by *in situ* enolate oxidation using (–)-CSO **102** gave α-hydroxy-β-amino ester **103** as a single diastereoisomer, which was isolated in 71% yield and >99:1 dr. α-Hydroxy-β-amino ester **103** was then elaborated to (–)-codonopsinine **104** in six steps (Scheme 12).



Scheme 12. *Reagents and conditions:* (i) (*R*)-**101**, THF, –78 °C, 2 h, then (–)-CSO **102**, –78 °C to rt, 12 h.

1.3 Thesis aims

This thesis describes investigations towards the synthesis of a range of amino polyol containing compounds via synthetic routes that employ the conjugate addition of enantiopure lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **106** to an α,β-unsaturated ester as the key step. It was envisaged that conjugate addition of lithium amide **106** to a range of functionalised α,β-unsaturated esters **107** and **108** would result in the formation of either β-amino esters **105** (by reaction of the intermediate enolate with NH_4Cl) or α-hydroxy-β-amino esters **109** (by reaction of the intermediate enolate with the requisite antipode of CSO **102**). Subsequent elaboration of **105** and **109** was then anticipated to allow access to an array of amino polyols including amino sugars **110**-**113**, imino sugars **114**, and amino acids **115**-**117** (Figure 4).

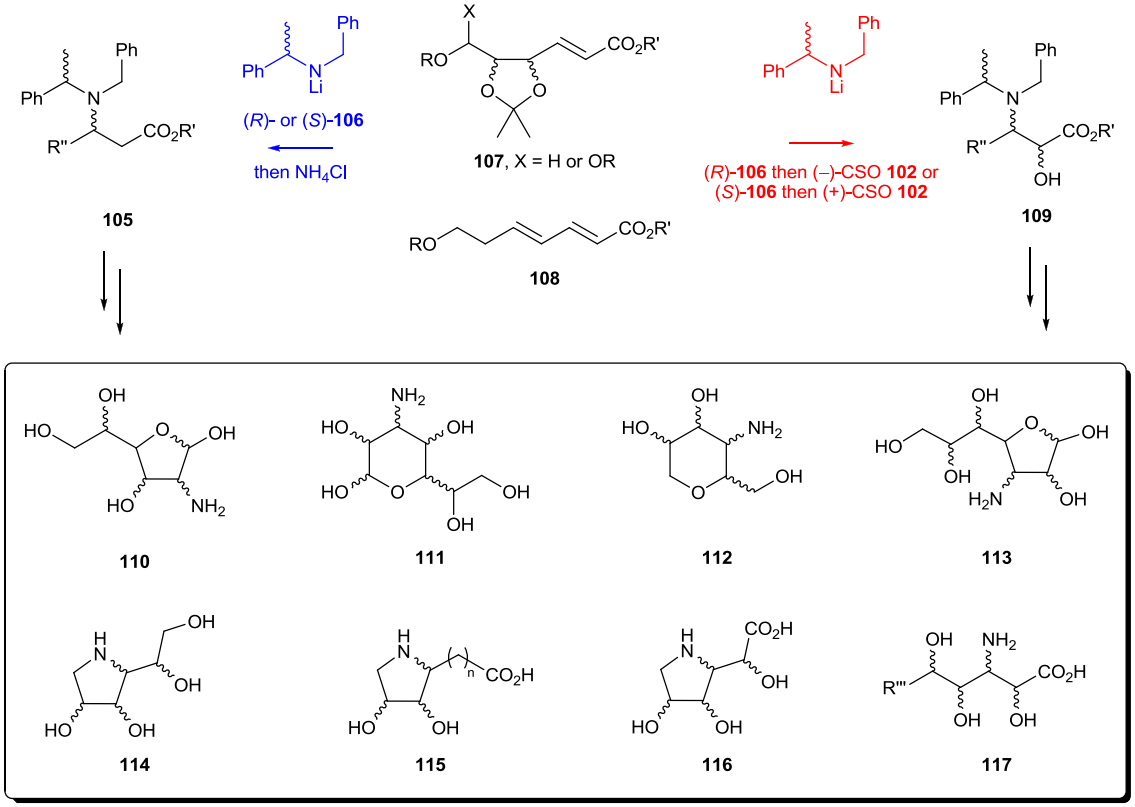


Figure 4. Lithium amide conjugate addition reactions of α,β-unsaturated esters as the key step in the synthesis of amino polyols.

1.4 References and notes for chapter 1

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Chapter 2: Asymmetric Syntheses of Polyhydroxylated Amino Acids, Imino Sugars and Amino Sugars

2.1 Introduction

Amino sugars result from the formal replacement of a sugar hydroxyl group with an amino group. Many such compounds occur naturally, both as discrete entities and as sub-structural units of more complex compounds, which have been found to display a wide range of useful biological activities. For example, the naturally-occurring antibiotics daunorubicin **118** and adriamycin **119** both contain an L-daunosamine amino sugar residue and are used in the treatment of acute leukaemia and to block tumour proliferation, respectively[1]. Meanwhile, epirubicin **120** contains an L-acosamine residue and is one of the leading synthetic drugs for the treatment of breast cancer[2] (Figure 5).

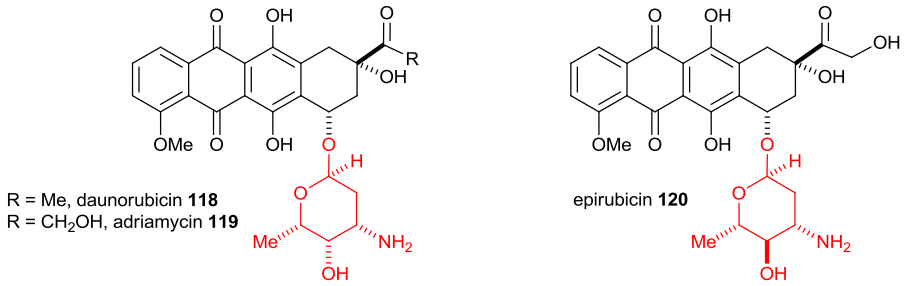
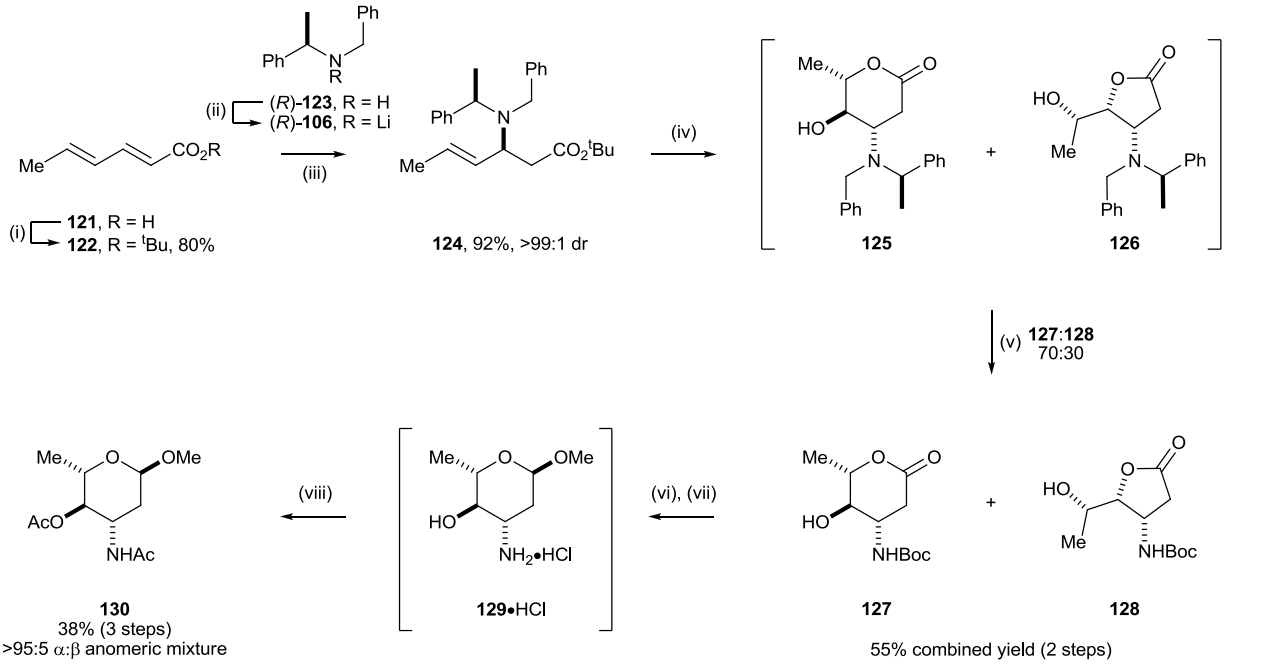


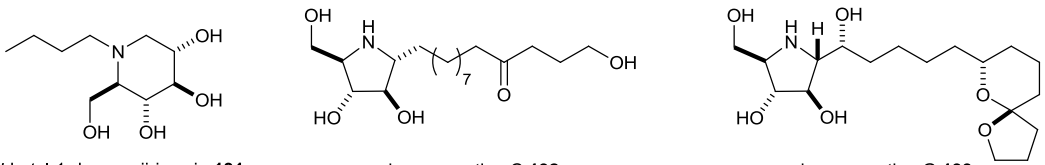
Figure 5. Amino sugar containing compounds daunorubicin **118**, adriamycin **119** and epirubicin **120**.

The impressive biological activities of amino sugars have led to this class of compounds becoming highly desirable synthetic targets. For example, Davies *et al.* recently reported a highly selective synthesis of methyl *N*,*O*-diacetyl-α-L-acosaminide **130** (a protected form of the amino sugar L-acosamine) from commercially available sorbic acid **121**. Sorbic acid **121** was first converted into the corresponding *tert*-butyl ester **122** in 80% yield via treatment with isobutylene and catalytic H_2SO_4. Conjugate addition of lithium (*R*)-*N*-benzyl-*N*-(α-methylbenzyl)amide **106**[3] to **122** then gave β-amino ester **124** in 92% yield and >99:1 dr. A highly chemo- and diastereoselective ammonium-directed oxidation of **124** was next achieved by treatment of **124** with *m*-CPBA in the presence of aqueous HBF_4, which gave, after *in situ* lactonisation, a mixture of 6- and 5-membered ring lactones **125** and **126**, respectively. The lactone mixture was subjected to hydrogenolysis conditions in the presence of Boc_2O to give a 70:30 mixture of *N*-Boc protected lactones **127** and **128**, which were isolated in 55% combined yield. Reduction of the mixture of **127** and **128** using DIBAL-H followed by treatment of the resultant lactols with MeOH and concentrated HCl gave **129**·HCl, which was immediately peracetylated using Ac_2O in pyridine to give **130** in 38% yield over the three steps, and as a >95:5 α:β anomeric mixture. The asymmetric synthesis of protected amino sugar **130** was therefore achieved in seven steps and in 15% overall yield from **121** (Scheme 13).[4]



Scheme 13. *Reagents and conditions:* (i) isobutylene, conc H_2SO_4, CH_2Cl_2, 0 °C to rt, 48 h; (ii) (*R*)-**123**, BuLi, THF, −78 °C, 30 min; (iii) (*R*)-**106**, THF, −78 °C, 2 h; (iv) HBF_4 (40% w/w in H_2O), *m*-CPBA (4.0 equiv), CH_2Cl_2, rt, 48 h; (v) Boc_2O, $Pd(OH)_2/C$, H_2 (5 atm), EtOAc, rt, 48 h; (vi) DIBAL-H, CH_2Cl_2, −78 °C, 30 min; (vii) MeOH, conc HCl, rt, 16 h; (viii) Ac_2O, pyridine, DMAP, rt, 30 min.

Imino sugars are carbohydrate analogues containing a nitrogen atom in place of the endocyclic oxygen atom, and they have also become highly desirable synthetic targets[5] due to the wide range of biological activities that they exhibit.[6] Imino sugars comprise a vast family of natural products and many such compounds (and their derivatives) have already been exploited by the pharmaceutical industry. One such example is *N*-butyl-1-deoxynojirimycin **131**, which is used in the treatment of Gaucher's disease, a genetic lysosomal storage disorder.[7] Broussonetines C **132** and G **133** are members of a subgroup of iminosugars all containing a 2,3,4,5-tetrasubstituted pyrrolidine core unit. As well as being challenging targets for asymmetric synthesis,[8] these broussonetine alkaloids have been shown to be extremely effective glycosidase inhibitors and so have enormous potential as anti-tumour and anti-HIV agents[9] (Figure 6).



N-butyl-1-deoxynojirimycin **131** broussonetine C **132** broussonetine G **133**

Figure 6. *N*-Butyl-1-deoxynojirimycin **131** and broussonetines C **132** and G **133**.

2.2 Chapter aims

Davies *et al.* have shown that the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **106** exert very high levels of diastereocontrol upon conjugate addition reactions to achiral α,β-unsaturated esters, with the reactions found to typically proceed in >95:5 dr in >200 examples.[10] It was envisaged that if chiral α,β-unsaturated esters **134** and **136**, containing either *cis*- or *trans*-dioxolane units

respectively, were instead employed as substrates for this reaction then the conjugate addition reactions would become doubly diastereoselective, with the "matched" cases expected to proceed with complete diastereoselectivity. It was therefore anticipated that an initial investigation to establish the "matching" and "mismatching" effects of the conjugate addition reactions within these systems could be followed by application of this methodology to the analogous aminohydroxylation reactions of **134** and **136** [which would involve a lithium amide conjugate addition followed by *in situ* enolate oxidation using camphorsulfonyloxaziridine (CSO) **102**],[11] to give α-hydroxy-β-amino esters **135** and **137**. With **135** and **137** in hand, subsequent synthesis of a wide range of useful polyhydroxylated targets, including amino sugars **112**, imino sugars **114**, dihydroxyprolines **138**, and trihydroxyhomoprolines **116** was anticipated (Figure 7).

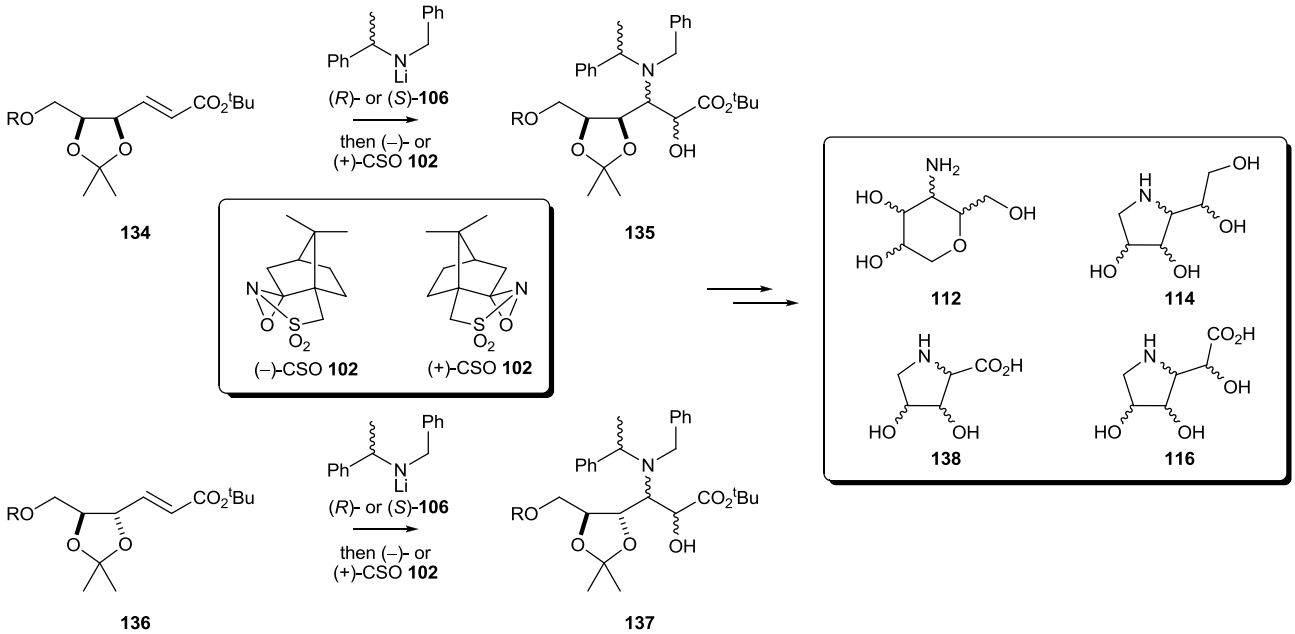
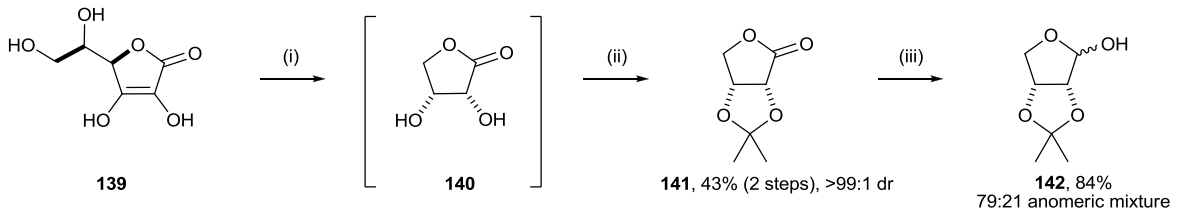


Figure 7. Doubly diastereoselective conjugate addition reactions of the antipodes of **106** to *cis*- and *trans*-dioxolane containing α,β-unsaturated esters **134** and **136**, and their application in target syntheses of amino sugars **112**, imino sugars **114**, dihydroxyprolines **138** and trihydroxyhomoprolines **116**.

2.3 Preparation of α,β-unsaturated esters containing *cis*-dioxolane units

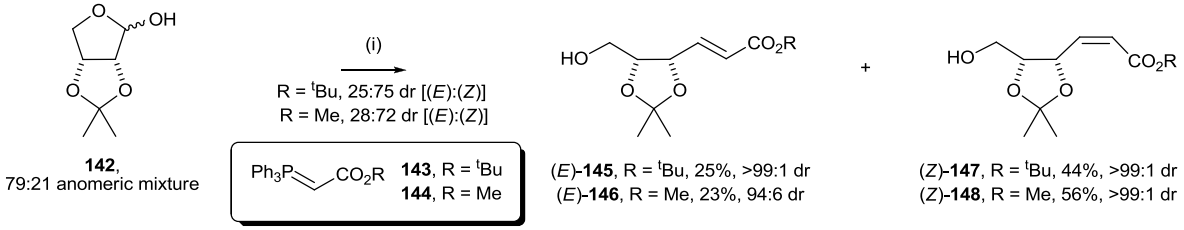
2.3.1 Attempted preparation of α,β-unsaturated esters from D-isoascorbic acid 139

In order to commence investigation towards the synthesis of these polyhydroxylated targets, α,β-unsaturated ester substrates containing a *cis*-dioxolane unit first had to be synthesised. Initial efforts concentrated on a synthetic route starting from D-isoascorbic acid **139**. Following a literature procedure,[12] treatment of **139** with basic aqueous H_2O_2 followed by acetonide protection of the resultant diol **140** gave 2,3-*O*-isopropylidene-D-erthyronolactone **141** in 43% isolated yield over two steps. Subsequent reduction of lactone **141** with DIBAL-H gave lactol **142** in 84% yield, and as a 79:21 mixture of anomers (Scheme 14).



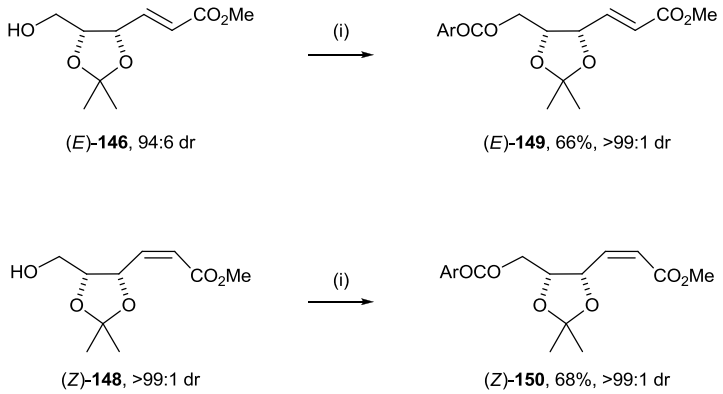
Scheme 14. *Reagents and conditions:* (i) H_2O_2 (30% w/w in H_2O), H_2O, Na_2CO_3, 0 °C, 30 min, then 40 °C, 1 h; (ii) DMP, acetone, TsOH, $MgSO_4$, rt, 16 h; (iii) DIBAL-H, CH_2Cl_2, –78 °C, 3 h.

In 1997, Scharf *et al*. reported that Wittig olefination of lactol **142** using methyl (triphenylphosphorylidene)acetate **144** gave a single diastereoisomeric product, which was assigned as having an (*E*)-configuration and was subsequently isolated in 60% yield.[13] Based on this precedent, lactol **142** (79:21 anomeric mixture) was treated with *tert*-butyl (triphenylphosphorylidene)acetate **143**[14] under identical conditions. Interestingly, a 25:75 mixture of olefin products (*E*)-**145** and (*Z*)-**147** resulted, from which (*E*)-**145** and (*Z*)-**147** were subsequently isolated in 25 and 44% yield, respectively, and in >99:1 dr in both cases. The relative configurations within **145** and **147** were assigned by comparison of the diagnostic ^{1}H NMR $^3J_{2,3}$ coupling constants between the olefinic protons: a $^3J_{2,3}$ value of 15.7 Hz was noted for (*E*)-**145** whereas a $^3J_{2,3}$ value of 11.6 Hz was recorded for (*Z*)-**147**. On this basis, repetition of the literature procedure using methyl (triphenylphosphorylidene)acetate **144**[15] was found to give a 28:72 mixture of (*E*)-**146** ($^3J_{2,3}$ = 15.6 Hz) and (*Z*)-**148** ($^3J_{2,3}$ = 11.6 Hz) respectively, with (*E*)-**146** being isolated in 23% yield and 94:6 dr and (*Z*)-**148** being isolated in 56% yield as a single diastereoisomer (Scheme 15).



Scheme 15. *Reagents and conditions:* (i) **143** or **144** (1.5 equiv), CH_2Cl_2, reflux, 3 days.

In the case of (*E*)-**146**, conversion to the *p*-nitrobenzoate ester derivative (*E*)-**149** ($^3J_{2,3}$ = 15.4 Hz) enabled the relative configuration within (*E*)-**149** [and therefore also the configurations within (*E*)-**146**, (*Z*)-**148** and (*Z*)-**150**] to be unambiguously confirmed via single crystal X-ray diffraction analysis,[16] with the absolute configurations being assigned relative to the known configuration of the D-isoascorbic acid derived dioxolane unit (Scheme 16 and Figure 8). This stereochemical outcome for the olefination procedure is therefore in contrast to that reported by Scharf *et al.*[17] {>99:1 dr [(*E*):(*Z*)]} and so a comparison of the two sets of product $^3J_{2,3}$ coupling constants was made. A $^3J_{2,3}$ value of 11.6 Hz was reported by Scharf *et al.* [a value indicative of a (*Z*)-configured double bond], indicating that their stereochemical assignment was made in error. An alternative olefination procedure was therefore sought.



Scheme 16. *Reagents and conditions:* (i) *p*-nitrobenzoyl chloride, pyridine, rt, 28 h. [Ar = *p*-$NO_2C_6H_4$].

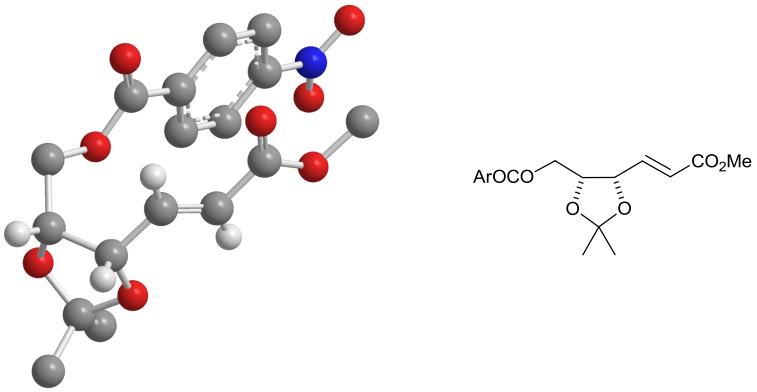
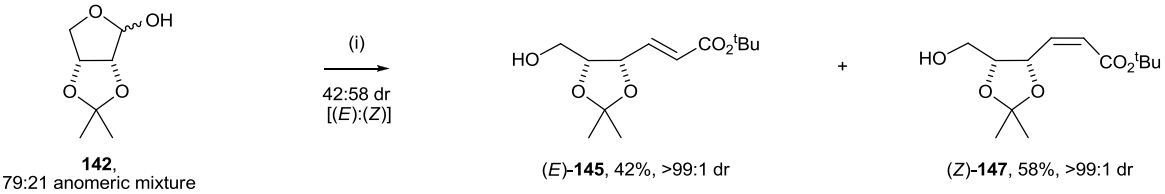


Figure 8. X-ray crystal structure of **149** (selected H atoms are omitted for clarity). [Ar = *p*-$NO_2C_6H_4$].

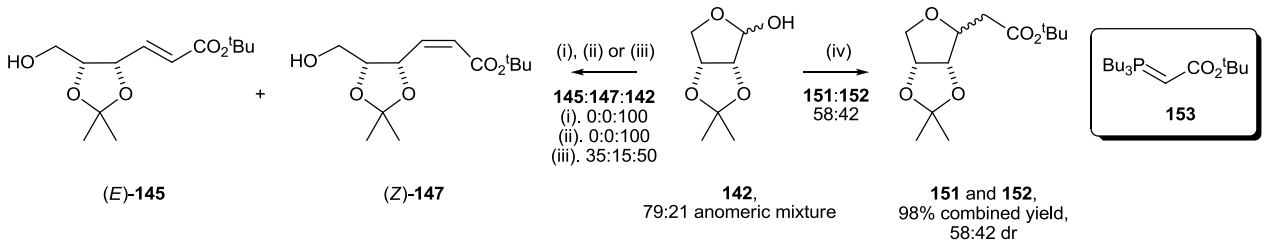
An alternative procedure[18] involving treatment of lactol **142** with ylid **143** in dioxane resulted in a 42:58 mixture of olefins (*E*)-**145** and (*Z*)-**147**, respectively. Upon column chromatography, (*E*)-**145** and (*Z*)-**147** were isolated in 42 and 58% yield, respectively, and in >99:1 dr in both cases. The predominance of the (*Z*)-configured olefin product meant that a more efficacious route to the desired (*E*)-configured α,β-unsaturated esters was still required (Scheme 17).



Scheme 17. *Reagents and conditions:* (i) **143** (1.5 equiv), dioxane, 90 °C, 6 h then 50 °C, 12 h.

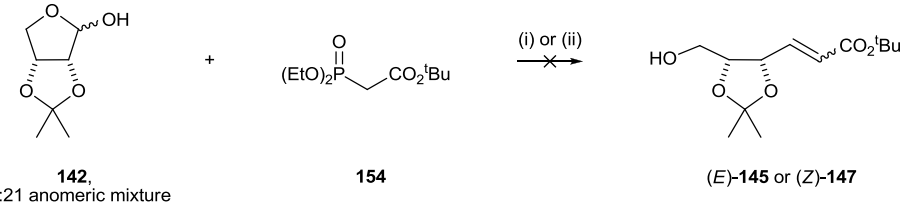
It has been reported that treatment of sugar-derived lactols with 1.25 equivalents of *tert*-butyl (tributylphosphorylidene)acetate **153** in PhMe in the presence of a catalytic amount of benzoic acid results in the corresponding (*E*)-α,β-unsaturated esters in high yields and diastereoselectivities.[19] In light of this, the olefination of **142** in refluxing CH_2Cl_2 (*vide supra*) was repeated using ylid **153** (both with and without catalytic benzoic acid); unfortunately, in both cases only starting material **142** was recovered. The reaction was next repeated using PhMe as the solvent and, under these conditions, a 35:15:50 mixture of olefins (*E*)-**145** and (*Z*)-**147**, and unreacted starting material **142**, respectively, resulted. Despite the (*E*)-diastereoisomer now being the major product, the reaction proceeded to only 50% conversion and so an attempt was made to force the reaction to conversion by increasing

the equivalents of **153**. In this case, treatment of **142** with 3.0 equivalents of **153** instead resulted in olefination followed by ring closure to give a mixture of **151** and **152**, which was isolated in 58:42 dr and 98% combined yield (Scheme 18).



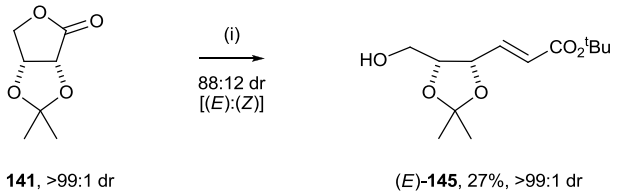
Scheme 18. *Reagents and conditions:* (i) **153** (1.25 equiv), CH_2Cl_2, reflux, 3 days; (ii) **153** (1.25 equiv), benzoic acid (0.2 equiv), CH_2Cl_2, reflux, 3 days; (iii) **153** (1.25 equiv), benzoic acid (0.2 equiv), PhMe, 90 °C, 10 min; (iv) **153** (3.0 equiv), benzoic acid (0.2 equiv), PhMe, 90 °C, 10 min.

Reaction of lactol **142** with stabilised ylids such as **143**, **144** and **153** was thus proving to be much less (*E*)-selective than was first anticipated. In an attempt to increase (*E*)-selectivity, a Wadsworth-Emmons olefination was carried out via treatment of lactol **142** with BuLi and *tert*-butyl diethylphosphonoacetate **154**; however, this gave only returned starting materials **142** and **154**. Similarly, the application of the highly (*E*)-selective MeMgBr-mediated Wadsworth-Emmons reaction developed by Davies *et al.*[20] also resulted in returned starting materials **142** and **154** (Scheme 19).



Scheme 19. *Reagents and conditions:* (i) BuLi, THF, –78 °C, 30 min, then –78 °C to rt, 2 h; (ii) MeMgBr, THF, reflux, 18 h.

A tandem DIBAL-H/Wadsworth-Emmons reaction of lactone **141** was also attempted. The reaction proceeded to be more (*E*)-selective [88:12 dr (*E*):(*Z*)], although unreacted **154** was present after work up (despite no evidence of lactone **141** or lactol **142**) and (*E*)-**145** was isolated in only 27% yield and in >99:1 dr (Scheme 20).

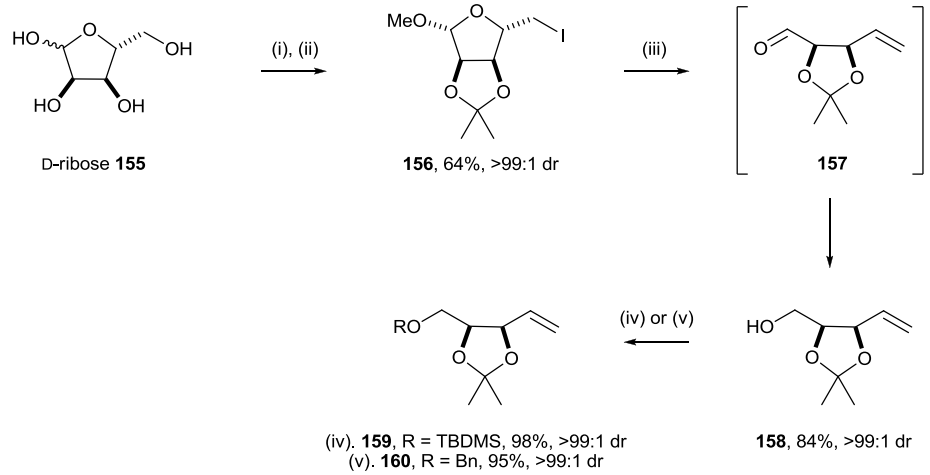


Scheme 20. *Reagents and conditions:* (i) BuLi, **154** (1.0 equiv), THF, –78 °C, 30 min then DIBAL-H, –78 °C to rt, 16 h.

2.3.2 Preparation of α,β-unsaturated esters from D-ribose 155

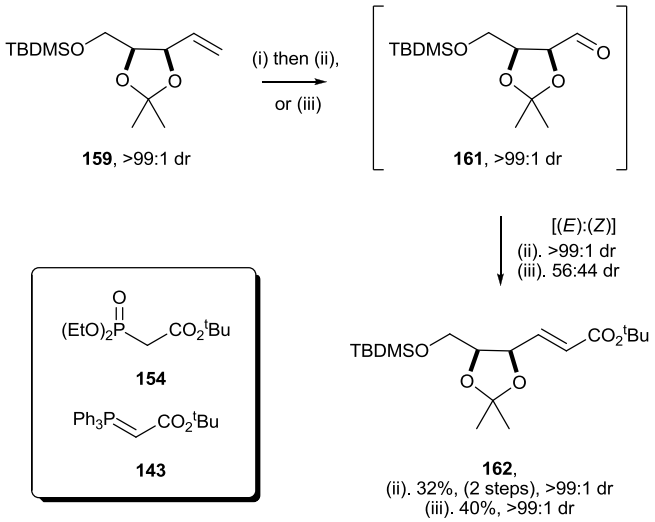
Due to the numerous problems encountered with the synthesis of the desired α,β-unsaturated esters from D-isoascorbic acid **139**, it was decided to investigate an alternative synthetic route, this time starting from the naturally occurring sugar D-ribose **155**. D-Ribose **155** was treated with acetone and

MeOH in the presence of concentrated HCl followed by Appel reaction with I_2 and PPh_3 to give iodide **156** in 64% yield over two steps. Iodide **156** was then subjected to a one-pot transmetallation/ring-opening/reduction procedure[21] which first involved treatment with BuLi to give intermediate aldehyde **157**, followed by addition of DIBAL-H to the reaction vessel to effect reduction to alcohol **158** which was isolated in 84% yield. *O*-Silyl and *O*-benzyl protection of the alcohol functionality within **158** gave **159** and **160** in 98 and 95% yield, respectively (Scheme 21).



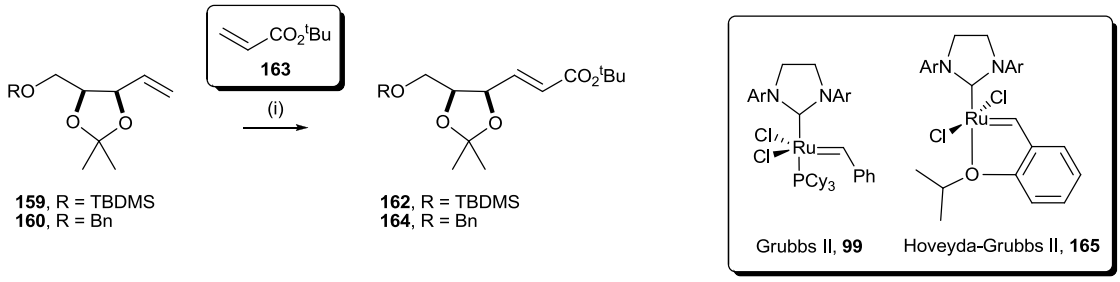
Scheme 21. *Reagents and conditions:* (i) conc HCl, acetone/MeOH (v/v 1:1), 60 °C, 1 h; (ii) imidazole, PPh_3, I_2, PhMe/MeCN (v/v 5:1), 60 °C, 1 h; (iii) BuLi, THF, –78 °C, 2 h then DIBAL-H, –78 °C to rt, 16 h; (iv) TBDMSCl, DMAP, imidazole, CH_2Cl_2, rt, 16 h; (v) NaH, THF, 0 °C, 45 min, then BnBr, rt, 16 h.

It was next decided to subject **159** to an ozonolysis reaction in the hope that the intermediate aldehyde **161** could be subjected to a Masamune-Roush olefination reaction.[22] Reaction of **159** with O_3 followed by treatment of the reaction mixture with Me_2S gave aldehyde **161**, which was immediately treated with phosphonoacetate **154**, $^{i}Pr_2NEt$ and LiCl to give **162** in >99:1 dr. Subsequent purification gave **162** in 32% isolated yield and >99:1 dr over the two steps. A one-pot ozonolysis/olefination reaction involving *in situ* treatment of aldehyde **161** with ylid **143** was also attempted. Unfortunately, this reaction proved to be much less (*E*)-selective [56:44 dr (*E*):(*Z*)], and (*E*)-**162** was isolated in 40% yield and >99:1 dr (Scheme 22).



Scheme 22. *Reagents and conditions:* (i) O_3, CH_2Cl_2, –78 °C then Me_2S, –78 °C to rt, 18 h; (ii) **154**, LiCl, $^{i}Pr_2NEt$, MeCN, rt, 48 h; (iii) O_3, CH_2Cl_2, –78 °C then PPh_3, –78 °C to rt, 1 h then **143**, rt, 12 h.

Due to the low yielding nature of the ozonolysis/olefination experiments, it was next anticipated that **159** and **160** could be coupled with *tert*-butyl acrylate **163** in a cross metathesis reaction using Grubbs II[23] **99** to give the desired α,β-unsaturated esters **162** and **164**. Thus, a mixture of **160**, *tert*-butyl acrylate **163** (2.0 equivalents) and Grubbs II **99** (0.2 mol%) was heated at reflux in CH_2Cl_2 for 12 h to give **164** in 15% conversion. Increasing the catalyst loading to 5 mol% did not change the product distribution; however, a 5 mol% catalyst loading coupled with an increase to 4.0 equivalents of *tert*-butyl acrylate **163** showed a slight increase in conversion (32% conversion to **164**). Increasing the catalyst loading further to 20 mol% still only gave a maximum of 43% conversion to **164** (Scheme 23). The more reactive Hoveyda-Grubbs 2nd generation catalyst **165** (H-GII)[24] was next employed and, after some optimisation studies, it was found that a 10 mol% catalyst loading, 3.0 equivalents of **163**, and heating at reflux for 22 h in CH_2Cl_2 was required to effect 100% conversion to the desired product **164** (in >99:1 dr), which was isolated in 78% yield and >99:1 dr. These conditions were also found to be optimal for *O*-silyl protected **159**, and in this case **162** was isolated in 68% yield and >99:1 dr (Scheme 23).



substrate	catalyst	catalyst loading mol%	time h	equiv of 163	conversion %	yield % (dr)
160	**99**	0.2	12	2.0	15	-
160	**99**	5.0	12	2.0	16	-
160	**99**	5.0	1	2.0	16	-
160	**99**	5.0	12	4.0	32	-
160	**99**	10.0	12	2.0	33	-
160	**99**	20.0	12	2.0	43	-
160	**165**	2.5	22	3.0	44	24 (>99:1)
160	**165**	**10.0**	**22**	**3.0**	**100**	**78 (>99:1)**
159	**99**	5.0	12	2.0	23	-
159	**165**	5.0	22	3.0	75	60 (>99:1)
159	**165**	**10.0**	**22**	**3.0**	**100**	**68 (>99:1)**

Scheme 23. *Reagents and conditions:* (i) **99** or **165**, *tert*-butyl acrylate **163**, CH_2Cl_2, 45 °C. For reaction times, see table. [Ar = 2,4,6-trimethylphenyl].

Thus, after extensive experimentation, a highly efficient five step route to *cis*-dioxolane containing α,β-unsaturated esters **162** and **164** from commercially available D-ribose **155** had been developed. With these substrates in hand, it was now possible to commence investigation into the doubly diastereoselective conjugate addition reactions of the antipodes of lithium amide **106**.

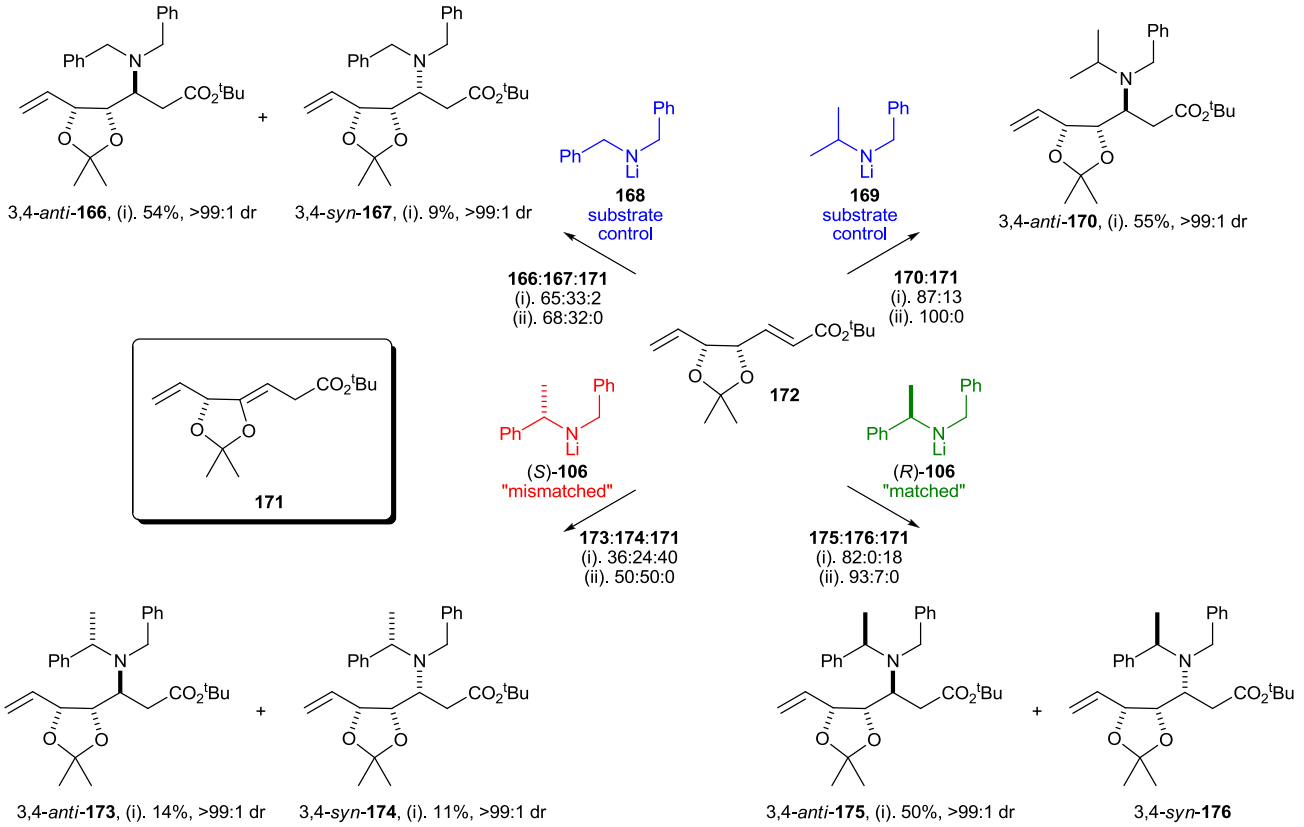
2.4 Double asymmetric induction

The phenomenon of double asymmetric induction occurs when two chiral species (e.g., a reagent and a substrate) are involved in a reaction. The individual stereochemical preferences of the two chiral species can either reinforce or oppose one another. When the two chiral species are working together to selectively produce the same stereochemical outcome, this is termed the "matched" reaction and very high levels of diastereoselectivity are often observed.[25] If, however, they are in competition and favour opposite stereochemical outcomes, this is termed "mismatched" and it is the agent with the greater directing ability that dominates the stereochemical outcome of the reaction, with diastereoisomeric mixtures of products usually being observed.[25] The interaction of the two chiral species will result in diastereoisomeric transition states. Of these, the lowest in energy will dictate the major stereochemical outcome of the reaction whilst the difference in energy between them will determine the degree of diastereoselectivity observed. In 1985, Masamune *et al*. first defined the concept of double asymmetric induction in the context of "matched" and "mismatched" reaction pairings,[25] and stated that "*the degree of asymmetric induction is approximated to be (a × b) for a matched pair and (a ÷ b) for a mismatched pair, where a and b are the diastereofacial selectivities of a substrate and a reagent, respectively*" although "*the multiplicativity will be valid only in a qualitative sense*" and that "*many secondary interactions which occur in the regions remote from the reaction site are entirely ignored [in this model]*." In addition to being a useful tool for mechanistic studies,[26] double asymmetric induction is often employed as a method for improving reaction diastereoselectivity and, as such, it has been exploited widely in many different classes of reactions.[27,28]

2.5 Previous work

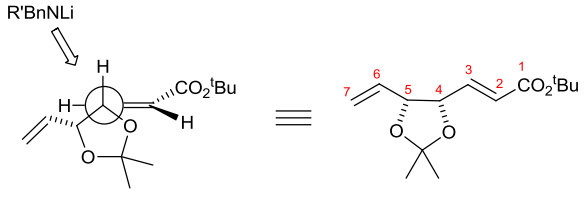
Previous studies into the conjugate addition reactions of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **106** to chiral α,β-unsaturated esters containing a *cis*-dioxolane unit have already been shown to be doubly diastereoselective, and were found to display "matching" and "mismatching" effects.[29] For example, in the case of the *cis*-dioxolane containing α,β-unsaturated ester **172**,[30] substrate control was first probed by the addition of achiral lithium amides. Lithium *N*-isopropyl-*N*-benzylamide **169**[31] and lithium dibenzylamide **168**[32] were chosen for this purpose, with **169** having already been shown to closely mimic the behaviour of chiral lithium amide **106**.[29,33] Thus, conjugate addition of lithium *N*-isopropyl-*N*-benzylamide **169** to **172** in THF at −78 °C gave 3,4-*anti*-**170** in >99:1 dr, providing evidence for high levels of substrate control. Under

these conditions, a competing γ-deprotonation pathway was observed which resulted in the production of (*Z*)-β,γ-unsaturated ester **171**. This pathway was found to be completely suppressed upon repetition of the reaction in Et_2O at −20 °C. The conjugate addition of lithium dibenzylamide **168** to **172** proceeded with much lower levels of diastereocontrol to give a 65:33:2 mixture of β-amino esters **166** and **167**, and (*Z*)-β,γ-unsaturated ester **171**, respectively, in THF at −78 °C. Following a series of rate studies, the reduced diastereoselectivity in this reaction was attributed to the fact that **168** is significantly more reactive than **169**, and so the conjugate addition reaction occurs much faster in the former case. This result indicates that **169** has the potential to act as a better mimic for the chiral lithium amide **106** than does **168**, and, as such, a series of rate studies were performed to subsequently confirm this suggestion.[29] The conjugate addition of (*R*)-**106** was therefore expected to represent the doubly diastereoselective "matched" reaction based upon the known diastereofacial selectivity elicited by this chiral lithium amide.[34] This was indeed found to be the case as the reaction proceeded to give 3,4-*anti*-**175** in >99:1 dr (in THF at −78 °C), which was subsequently isolated in 50% yield and >99:1 dr. The conjugate addition of (*S*)-**106** to **172** (in THF at −78 °C) gave a 60:40 mixture of **173** and **174**, respectively, and was therefore assigned as the "mismatched" pairing of chiral reagent and chiral substrate. In this "mismatched" reaction, it is the stereocontrol of the α,β-unsaturated ester **172** (substrate) that is dominant over that of the lithium amide (reagent),[34] resulting in a slight preference for the formation of 3,4-*anti*-**173**. In both cases, the conjugate addition reactions to **172** were accompanied by the competing pathway involving deprotonation of the α,β-unsaturated ester at the γ-position to give (*Z*)-β,γ-unsaturated ester **171** upon work-up. It was again found that this undesirable pathway could be completely suppressed by changing the reaction conditions from THF at −78 °C to Et_2O at −20 °C, which, in all cases, proceeded to give only the products of conjugate addition (Scheme 24).[29]



Scheme 24. *Reagents and conditions:* (i) lithium amide, THF, −78 °C, 2 h; (ii) lithium amide, Et_2O, −20 °C, 5 h.

In order to rationalise the inherent substrate control, Davies *et al.* proposed that the conjugate addition of lithium amides to **172** could be occurring with the substrates adopting a conformation **177**, whereby the hydrogen atom at C(4) lies perpendicular to the α,β-unsaturated ester. In this conformation, any substrate control would direct the approach of the lithium amide reagent to the *Si* face of the α,β-unsaturated ester **172**, opposite to the large alkoxyalkyl substituent and *syn* to the hydrogen atom at C(4) to preferentially give the corresponding 3,4-*anti*-configured conjugate addition products. Coupled with the known diastereofacial selectivity of lithium amide (*R*)-**106**, it was expected that the conjugate addition of this chiral lithium amide would therefore represent the doubly diastereoselective "matched" reaction and so the experimental results are consistent with the proposed reactive conformation. Conformation **177** was also used to explain the observation of the detritic γ-deprotonation pathway to give (*Z*)-β,γ-unsaturated ester **171**: in this conformation, the hydrogen atom at C(4) is well positioned for deprotonation by the basic lithium amide reagent. It was postulated that the observed differences in diastereoselectivity and product distribution upon changing the reaction conditions from THF at −78 °C to Et_2O at −20 °C could be explained by a change in the aggregation state of the lithium amide with solvent, although the active species involved in both the conjugate addition and γ-deprotonation pathways are still unknown (Figure 9).[29]



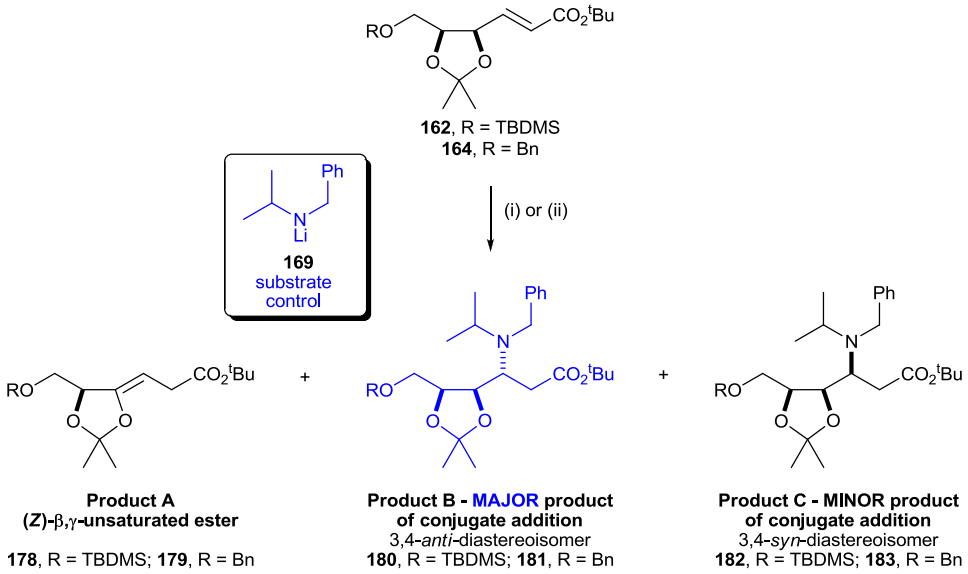
177 **172**

Figure 9. Suggested favoured conformation **177** for the conjugate addition reaction and γ-deprotonation pathway of **172**.

It was envisaged that a similar strategy could be applied to the more complex *cis*-dioxolane containing α,β-unsaturated esters **162** and **164**, for application in the ultimate synthesis of a wide range of polyhydroxylated products.

2.6 Evaluation of substrate control in the conjugate addition of achiral lithium amides to D-ribose derived α,β-unsaturated esters containing *cis*-dioxolane units

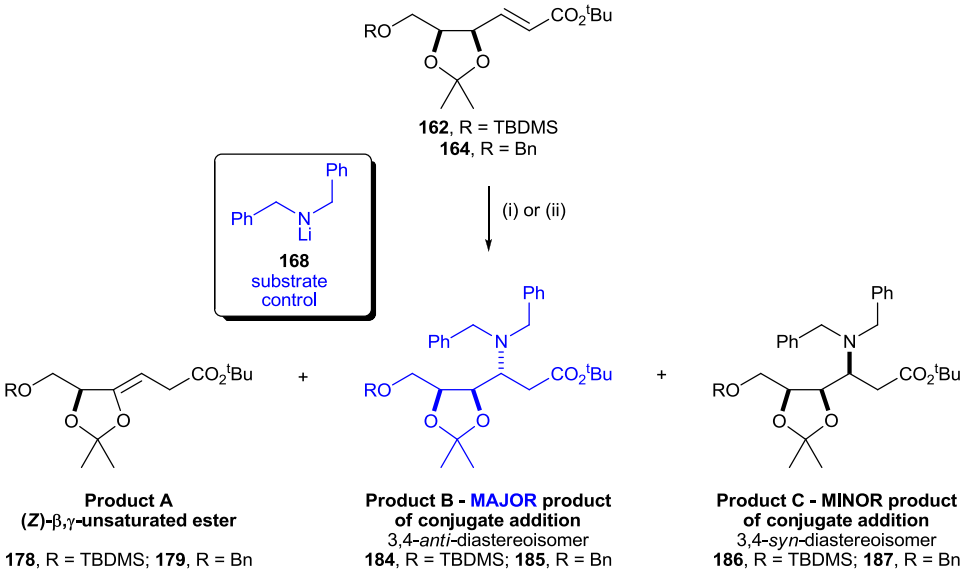
The conjugate additions of lithium *N*-benzyl-*N*-isopropylamide **169** to α,β-unsaturated esters **162** and **164** were first examined in order to determine the inherent substrate control. When carried out in THF at −78 °C, these reactions proceeded to give the 3,4-*anti* β-amino esters **180** and **181**, respectively, as the only products of conjugate addition. Unfortunately, the conjugate addition reactions were accompanied by the formation of γ-deprotonation products **178** and **179**:[35] in the case of **162**, an 88:12 mixture of β-amino ester **180** and (*Z*)-β,γ-unsaturated ester **178** was isolated, whilst for **164**, an 85:15 mixture of β-amino ester **181** and (*Z*)-β,γ-unsaturated ester **179** was isolated. As expected, when the reactions were instead carried out in Et_2O at −20 °C, this γ-deprotonation pathway was completed suppressed and the high diastereoselectivity of the conjugate addition reactions was maintained. Subsequent purification via flash column chromatography allowed the isolation of 3,4-*anti*-**180** in 82% yield and >99:1 dr, and also of 3,4-*anti*-**181** in 64% yield and >99:1 dr (Scheme 25). The configurations at the newly formed C(3)-stereogenic centres within **180** and **181** were later established via chemical correlation (*vide infra*).



R	conditions	product ratio A:B:C	dr B:C	yield B % (dr)
TBDMS	(i)	12:88:0	>99:1	-
TBDMS	(ii)	0:100:0	>99:1	82 (>99:1)
Bn	(i)	15:85:0	>99:1	-
Bn	(ii)	0:95:5	95:5	64 (>99:1)

Scheme 25. *Reagents and conditions:* (i) **169**, THF, –78 °C, 2 h; (ii) **169**, Et_2O, –20 °C, 5 h.

The conjugate additions of lithium dibenzylamide **168** to **162** and **164** were next considered. When the reactions were carried out in THF at –78 °C, it was interesting to note that no γ-deprotonation was observed. The addition of **168** to **162** in THF at –78 °C gave a 61:39 mixture of 3,4-*anti*-**184** and 3,4-*syn*-**186**, respectively, whilst conditions of Et_2O at –20 °C instead gave a slight enhancement of diastereoselectivity, with an 80:20 mixture of 3,4-*anti*-**184** and 3,4-*syn*-**186**, respectively, being recovered upon workup. After purification via flash column chromatography, 3,4-*anti*-**184** was isolated in 41% yield and 83:17 dr. On the other hand, the conjugate addition of **168** to **164** in THF at –78 °C gave a 75:25 mixture of β-amino esters 3,4-*anti*-**185** and 3,4-*syn*-**187**, respectively; upon changing the reaction conditions to Et_2O at –20 °C, a slightly higher preference for the formation of 3,4-*anti*-**185** (83:17 dr) was observed; 3,4-*anti*-**185** was subsequently isolated from this reaction mixture in 45% yield and 83:17 dr (Scheme 26). The configurations at the newly formed C(3)-stereogenic centres within **184**-**187** were again later assigned via chemical correlation (*vide infra*).



R	conditions	product ratio A:B:C	dr B:C	yield B % (dr)
TBDMS	(i)	0:61:39	61:39	-
TBDMS	(ii)	0:80:20	80:20	41 (83:17)
Bn	(i)	0:75:25	75:25	-
Bn	(ii)	0:83:17	83:17	45 (83:17)

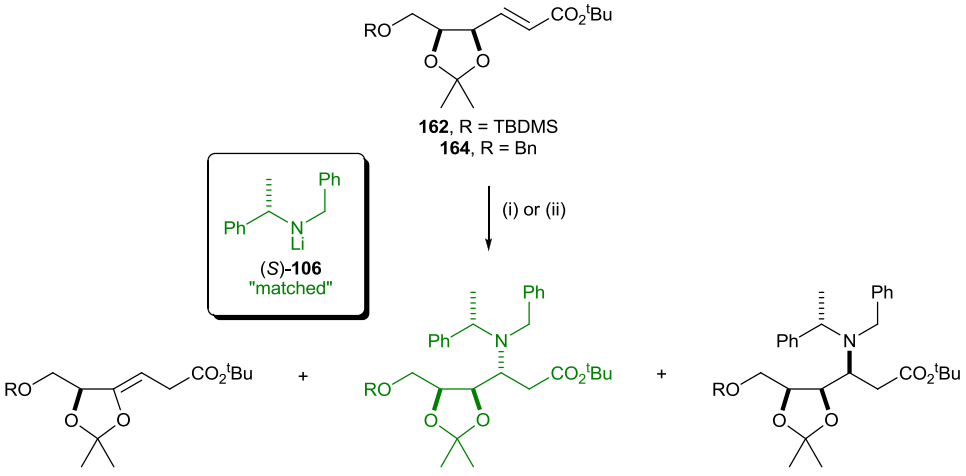
Scheme 26. *Reagents and conditions:* (i) **168**, THF, –78 °C, 2 h; (ii) **168**, Et_2O, –20 °C, 5 h.

It is clear from these results that the conjugate addition of lithium dibenzylamide **168** to both **162** and **164** proceeds with much lower levels of diastereocontrol than the conjugate addition of lithium *N*-benzyl-*N*-isopropylamide **169** to **162** and **164**, an observation that may be related to the difference in reactivity between these two lithium amides.[29] Nonetheless, the major products of conjugate addition were the corresponding 3,4-*anti* diastereoisomers in all cases, thereby confirming that the substrate control provided by **162** and **164** directs addition of the lithium amides **168** and **169** to the *Re* face of the α,β-unsaturated esters.

2.7 Evaluation of "matching" and "mismatching" effects in the conjugate addition of chiral lithium amides to D-ribose derived α,β-unsaturated esters containing *cis*-dioxolane units

With the substrate control provided by **162** and **164** now established, it was predicted that the conjugate addition of (*S*)-**106**[36] to **162** and **164** would represent the doubly diastereoselective "matched" reactions, as these pairings would result in both reagent and substrate favouring conjugate addition to the *Re* face of the α,β-unsaturated ester, based also upon the established diastereofacial selectivity of chiral lithium amide (*S*)-**106**.[34] Thus, the conjugate addition reactions of (*S*)-**106** to **162** and **164** were first attempted. These conjugate addition reactions again showed a tendency for the formation of (*Z*)-β,γ-unsaturated esters **178** and **179** when the reactions were carried out in THF at –78 °C: in the case of **162**, a 75:25 mixture of β-amino ester **188** and (*Z*)-β,γ-unsaturated ester **178** was observed, whilst for **164**, an 80:6:14 mixture of β-amino esters **189** and **191**, and (*Z*)-β,γ-unsaturated ester **179**, respectively, resulted. Changing the reaction conditions to Et_2O at

–20 °C was found to completely suppress the γ-deprotonation reaction pathway, with no erosion of diastereoselectivity for the conjugate addition reaction being observed. In these cases, the corresponding 3,4-*anti* diastereoisomers **188** and **189** were produced in >99:1 and 93:7 dr, respectively. Upon column chromatography of the crude reaction mixtures, 3,4-*anti*-**188** was isolated in 90% yield and >99:1 dr and 3,4-*anti*-**189** was isolated in 79% yield and 93:7 dr (Scheme 27). The configurations of the newly formed stereogenic centres at C(3) within **188** and **189** were later unambiguously established by chemical correlation (*vide infra*). The very high levels of diastereoselectivity observed in these systems support the proposal that the addition of (*S*)-**106** to **162** and **164** represents the doubly diastereoselective "matched" pairing of reagent and substrate in both cases. It is, however, interesting to note that the diastereoselectivity observed for the addition of (*S*)-**106** to α,β-unsaturated ester **164** (93:7 dr) is not as high as would be predicted for a doubly diastereoselective "matched" conjugate addition reaction, especially considering the very high levels of stereocontrol exerted by **106** in its conjugate addition reactions to achiral α,β-unsaturated esters (>95:5 dr in >200 examples).[10] This may imply that the normal mode of action of (*S*)-**106** may be disrupted to some degree during this reaction, potentially due to chelation by the polyoxygenated α,β-unsaturated ester **164**.

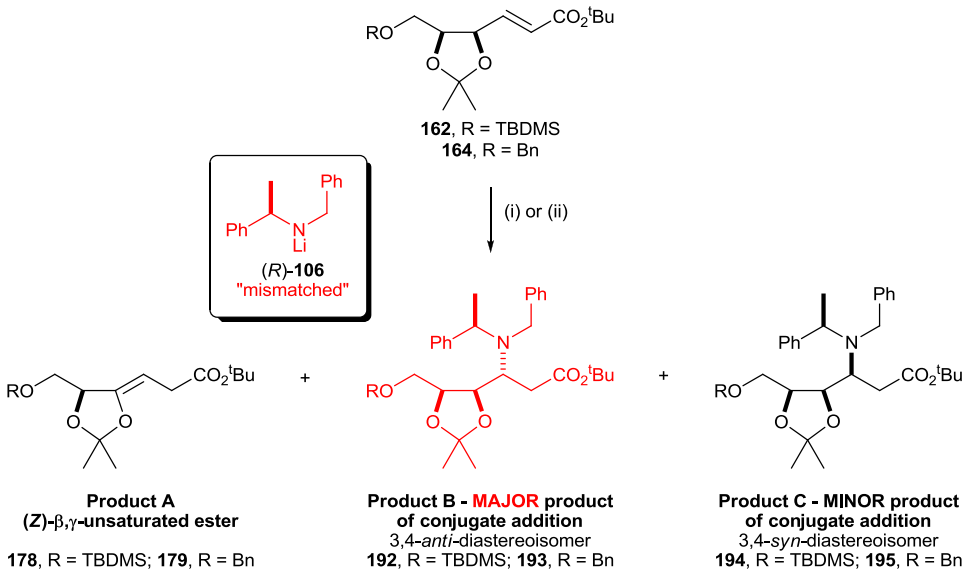


R	conditions	product ratio A:B:C	dr B:C	yield B % (dr)
TBDMS	(i)	25:75:0	>99:1	-
TBDMS	(ii)	0:100:0	>99:1	90 (>99:1)
Bn	(i)	14:80:6	93:7	-
Bn	(ii)	0:93:7	93:7	79 (93:7)

Scheme 27. *Reagents and conditions:* (i) (*S*)-**106**, THF, –78 °C, 2 h; (ii) (*S*)-**106**, Et_2O, –20 °C, 5 h.

Following these results, it was assumed that the conjugate addition of (*R*)-**106** to **162** and **164** would demonstrate the doubly diastereoselective "mismatched" pairings. The conjugate addition reactions were first conducted in THF at –78 °C and, in contrast to earlier results from the conjugate addition studies to **172** [where the corresponding (*Z*)-β,γ-unsaturated ester **171** featured as a side product],[29]

(*Z*)-β,γ-unsaturated esters **178** and **179** were formed as the major products in both instances. In the case of **162**, conjugate addition of (*R*)-**106** was found to give **178** exclusively, and **178** was subsequently isolated in 72% yield and >99:1 dr. Upon conjugate addition of (*R*)-**106** to **164**, a 37:17:46 mixture of **193**, **195** and **179** was produced from which 3,4-*anti*-**193** was isolated in 29% yield and >99:1 dr. Upon changing the reaction solvent and temperature to Et_2O at –20 °C, complete suppression of the γ-deprotonation pathway was observed: the conjugate addition of (*R*)-**106** to **164** gave an 83:17 mixture of β-amino esters **193** and **195**, respectively, from which major product 3,4-*anti*-**193** and minor product 3,4-*syn*-**195** were isolated in 44 and 7% yield, respectively, and in >99:1 dr in each case. The addition of (*R*)-**106** to **162** under identical conditions gave an 82:18 mixture of β-amino esters **192** and **194**, respectively, from which the major product 3,4-*anti*-**192** was isolated in 58% yield and >99:1 dr and the minor product 3,4-*syn*-**194** was isolated in 12% yield and >99:1 dr (Scheme 28). The relative configuration within β-amino ester 3,4-*syn*-**195** was determined unambiguously by single crystal X-ray diffraction analysis,[16] allowing the absolute configuration within **195** to be assigned relative to the known (*R*)-configuration of the α-methylbenzyl group, and also relative to the D-ribose derived dioxolane unit (Figure 10). The X-ray crystal structure of **195** therefore also allowed unambiguous assignment of the absolute configuration within 3,4-*anti*-**193**, the corresponding major product from the conjugate addition of (*R*)-**106** to **164**. The configurations within **192** and **194** were initially assigned by analogy and were later unambiguously established by chemical correlation (*vide infra*). The diastereoisomeric mixtures obtained from these reactions therefore support the prediction that these reactions involving lithium amide (*R*)-**106** represent the doubly diastereoselective "mismatched" reagent and substrate pairings. In addition, the observation that the major products formed during the conjugate addition of (*R*)-**106** to **162** and **164** are the 3,4-*anti* products **192** and **193**, suggests that the "mismatched" reactions are proceeding under the dominant stereocontrol of the substrates **162** and **164**.



R	conditions	product ratio A:B:C	dr B:C	yield A % (dr)	yield B % (dr)	yield C % (dr)
TBDMS	(i)	100:0:0	-	72 (>99:1)	-	-
TBDMS	(ii)	0:82:18	82:18	-	58 (>99:1)	12 (>99:1)
Bn	(i)	46:37:17	69:31	-	29 (>99:1)	-
Bn	(ii)	0:83:17	83:17	-	44 (>99:1)	7 (>99:1)

Scheme 28. *Reagents and conditions:* (i) (*R*)-**106**, THF, –78 °C, 2 h; (ii) (*R*)-**106**, Et_2O, –20 °C, 5 h.

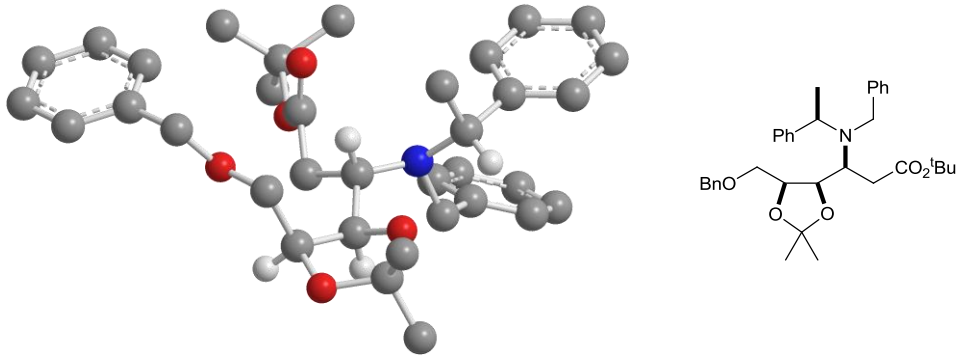
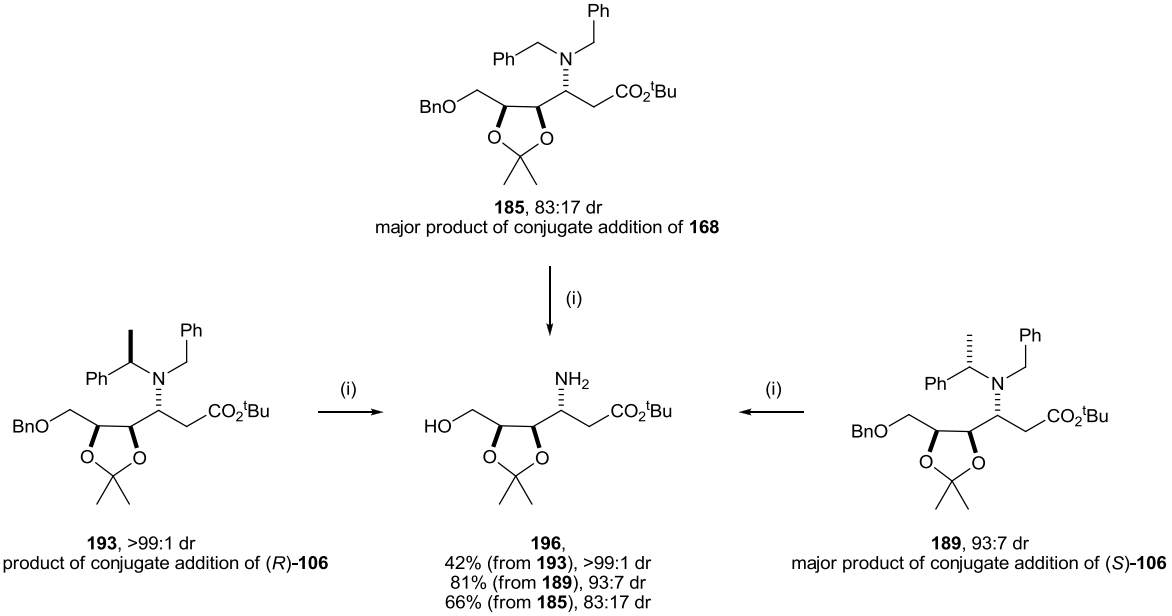


Figure 10. X-ray crystal structure of 3,4-*syn*-**195** (selected H atoms are omitted for clarity).

2.8 Correlation experiments

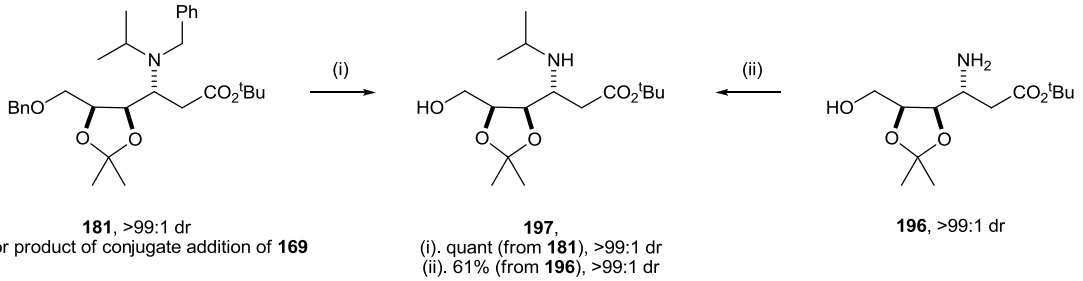
As 3,4-*syn*-**195** proved to be crystalline the absolute configuration within 3,4-*syn*-**195** (and therefore also that within 3,4-*anti*-**193**) had already been unambiguously confirmed. A series of hydrogenolytic/reductive alkylation correlation experiments were next conducted in order to unambiguously establish the configurations within all other β-amino ester products from this series of conjugate addition reactions. Hydrogenolysis of a sample of known absolute configuration of 3,4-*anti*-**193** (>99:1 dr) using $Pd(OH)_2/C$ gave an authentic sample of primary β-amino ester 3,4-*anti*-**196** in 42% yield and >99:1 dr. Similar treatment of a 93:7 dr sample of 3,4-*anti*-**189** [the major product from the addition of (*S*)-**106** to **164**] gave **196** in 81% yield and 93:7 dr. Subjection of an 83:17 dr sample of 3,4-*anti*-**185** to the same hydrogenolysis conditions gave **196** in 66% yield and 83:17 dr. The ^{1}H NMR spectra of the samples of **196** obtained from hydrogenolysis of **185** and **189**

were found to be identical to that of the authentic sample formed from hydrogenolysis of **193**, thus establishing the absolute configurations within **185** and **189** (Scheme 29).



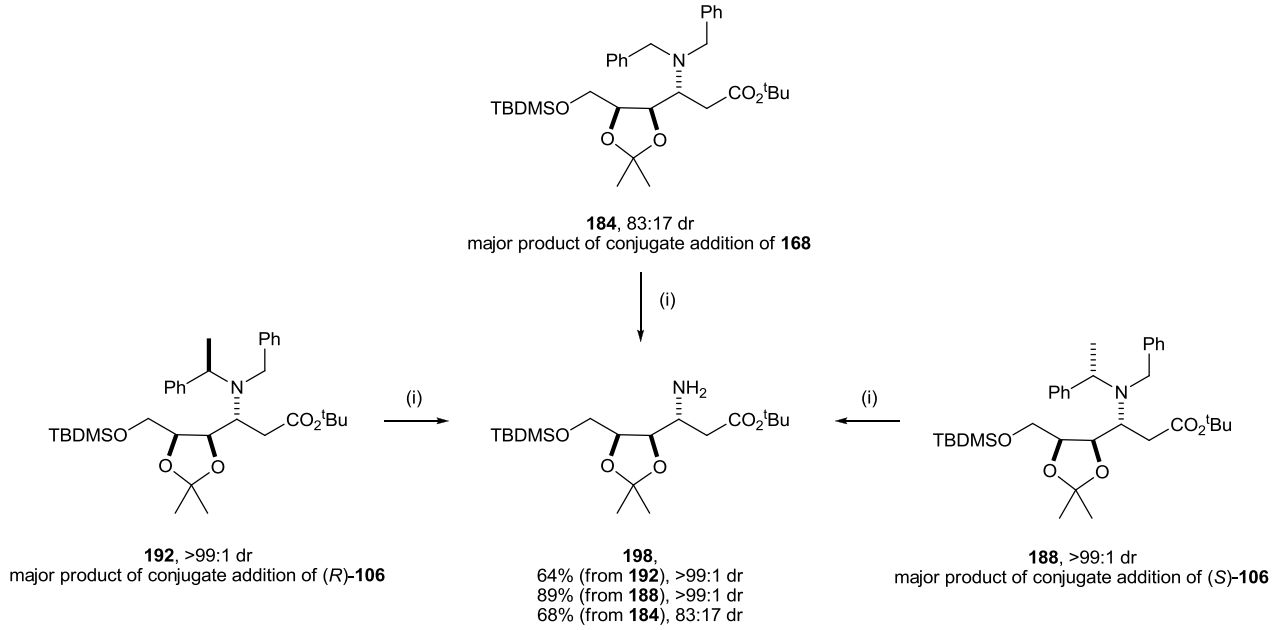
Scheme 29. *Reagents and conditions:* (i) $Pd(OH)_2/C$, H_2 (1 atm), EtOAc, 18 h, rt.

Hydrogenolysis of 3,4-*anti*-**181** (obtained as the major product from conjugate addition of **169** to **164**) gave *N*-isopropyl substituted β-amino ester 3,4-*anti*-**197** in quantitative yield and >99:1 dr. In order to correlate this result with results from earlier hydrogenolysis reactions, primary β-amino ester **196** (>99:1 dr) was subjected to a reductive alkylation reaction using $NaBH_3CN$ and acetone to give an authentic sample of **197** in 61% yield and >99:1 dr. The ^{1}H NMR spectra of the two samples of 3,4-*anti*-**197** were found to be in complete agreement, thus establishing the absolute configuration within **181** (Scheme 30).



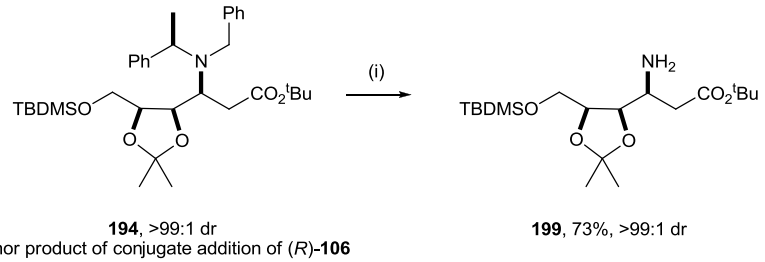
Scheme 30. *Reagents and conditions:* (i) $Pd(OH)_2/C$, H_2 (1 atm), EtOAc, rt, 18 h; (ii) $NaBH_3CN$, acetone, MeOH, rt, 18 h.

The major products from the conjugate addition of lithium amides (*S*)-**106** and (*R*)-**106** to *O*-TBDMS protected α,β-unsaturated ester **162** (3,4-*anti*-**188** and 3,4-*anti*-**192**, respectively), were next subjected to hydrogenolysis in the presence of $Pd(OH)_2/C$ to give the same primary β-amino ester **198** in 89 and 64% yield, respectively. Similar treatment of an 83:17 dr sample of 3,4-*anti*-**184** gave **198** in 68% yield and 83:17 dr. Comparison of the ^{1}H NMR spectra of all samples of 3,4-*anti*-**198** were found to be in full agreement thereby establishing the homochirality of these species at C(3) (Scheme 31).



Scheme 31. *Reagents and conditions:* (i) $Pd(OH)_2/C$, H_2 (1 atm), EtOAc, 18 h, rt.

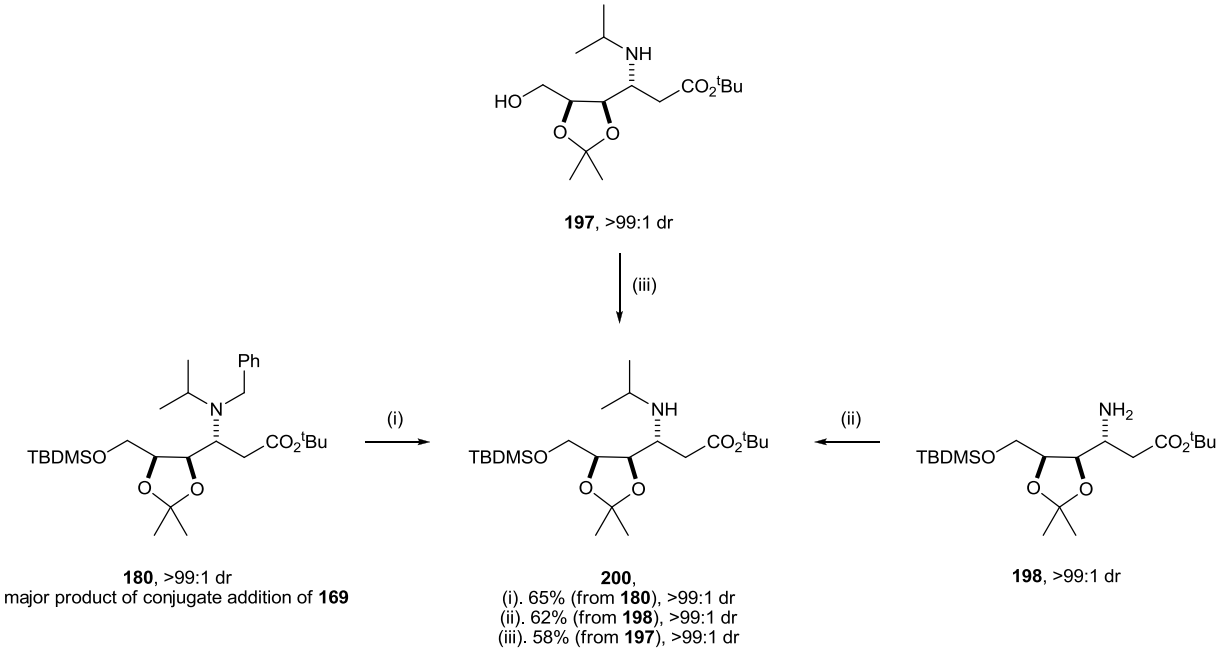
Subjection of a diastereoisomerically pure sample of 3,4-*syn*-**194** [the minor product from conjugate addition of (*R*)-**106** to **162**] to the hydrogenolysis conditions gave 3,4-*syn*-**199** in 73% yield and >99:1 dr. The ^{1}H NMR spectrum of **199** was found to be very different from that of **198**, thereby serving to confirm the opposite C(3)-configurations within the primary β-amino esters **198** and **199**. In addition, the ^{1}H NMR spectrum of **199** was found to correspond to the peaks for the minor component in the ^{1}H NMR spectrum of the 83:17 dr sample of **198** (obtained from hydrogenolysis of an 83:17 dr sample of **184**), providing further evidence for the opposite C(3)-configurations within **198** and **199** (Scheme 32).



Scheme 32. *Reagents and conditions:* (i) $Pd(OH)_2/C$, H_2 (1 atm), EtOAc, 18 h, rt.

Hydrogenolysis of 3,4-*anti*-**180**, obtained as the major product from conjugate addition of **169** to **162**, gave a sample of *N*-isopropyl substituted β-amino ester 3,4-*anti*-**200** in 65% yield and >99:1 dr. Reductive alkylation of primary β-amino ester **198** (>99:1 dr) using $NaBH_3CN$ and acetone gave 3,4-*anti*-**200** in 62% yield and >99:1 dr. The ^{1}H NMR spectra of the two samples of 3,4-*anti*-**200** were found to be in complete agreement. This series of reactions had therefore served to confirm that all the major products of lithium amide conjugate addition to α,β-unsaturated ester **162** are homochiral at C(3). Due to the absence of an X-ray crystal structure within the series of conjugate additions to α,β-unsaturated ester **162**, a cross correlation experiment was necessary to allow the configurations within the remaining β-amino esters to be unambiguously established. Therefore,

N-isopropyl substituted β-amino ester 3,4-*anti*-**197** (>99:1 dr) was *O*-TBDMS protected by treatment with TBDMSCl, imidazole and catalytic DMAP to give 3,4-*anti*-**200** in 58% yield and >99:1 dr. The ^{1}H NMR spectra of the samples of 3,4-*anti*-**200** derived from **180** and **198** were found to match completely with the data for the authentic sample of **200** derived from **197** (Scheme 33).



Scheme 33. *Reagents and conditions:* (i) $Pd(OH)_2/C$, H_2 (1 atm), EtOAc, rt, 18 h; (ii) $NaBH_3CN$, acetone, MeOH, rt, 18 h; (iii) TBDMSCl, DMAP, imidazole, CH_2Cl_2, rt, 16 h.

The X-ray crystal structure of **195** and the subsequent series of chemical correlation experiments therefore allowed the configurations of all β-amino ester products from the conjugate additions of (*R*)-**106**, (*S*)-**106**, **168** and **169** to both α,β-unsaturated esters **162** and **164** to be unambiguously established. The results from this investigation showed that within these doubly diastereoselective conjugate addition reactions, the substrate control conferred by both **162** and **164** was to direct the lithium amides to the *Re* face of the *cis*-dioxolane containing α,β-unsaturated ester substrates to give the corresponding 3,4-*anti* diastereoisomeric products. As a result, the prediction that the conjugate addition of (*S*)-**106** to both **162** and **164** would be the "matched" case pairings of reagent and substrate was correct, and these reactions resulted in the production of the corresponding 3,4-*anti* products as single diastereoisomers in each case. The "mismatched" reactions of (*R*)-**106** to both **162** and **164** gave mixtures of 3,4-*anti* and 3,4-*syn* β-amino ester products in each case, with the substrates **162** and **164** found to be the chiral agents that displayed the dominant stereocontrol during the conjugate addition reactions, due to the 3,4-*anti* configured β-amino ester products being the major components of these mixtures.

2.9 The origins of diastereoselectivity observed upon conjugate addition and the competitive γ-deprotonation pathway

The stereochemical outcomes of the doubly diastereoselective lithium amide conjugate addition reactions of the antipodes of **106** to **162** and **164** were found to be consistent with previous results reported by Davies *et al.* for analogous α,β-unsaturated ester systems.[29,35b] Also in line with previous results,[29,35b] the conjugate addition reactions to α,β-unsaturated esters **162** and **164** in THF at −78 °C were found to be accompanied by the formation of the corresponding (*Z*)-β,γ-unsaturated esters **178** and **179**. Upon changing the reaction conditions from THF at −78 °C to Et_2O at −20 °C, the γ-deprotonation pathways of **162** and **164** were found to be completely suppressed, suggesting that the conjugate addition reactions are very sensitive to the reaction conditions.[37] In addition, it has previously been noted that this change of solvent is often accompanied by a change in reaction diastereoselectivity,[29,35b] which was also observed for some of the lithium amide conjugate addition reactions to **162** and **164**. The conjugate addition reactions of chiral lithium amides such as (*R*)-**106** and (*S*)-**106** to achiral α,β-unsaturated esters are renowned for being highly diastereoselective.[10] As such, Davies *et al.* have reported a transition state mnemonic[34] to reliably predict the stereochemical outcome of this class of reaction. However, many different factors have the potential to contribute to the reaction outcomes, including the known tendency of lithium amides to exist as aggregates in different solvents,[37,38] meaning that the true origin of the diastereoselectivity in these reactions is still unclear. In the case of **162** and **164**, the observed changes in reactivity of the lithium amide reagents (*R*)-**106**, (*S*)-**106**, **168** and **169** upon a change in the conjugate addition reaction solvent may therefore potentially originate in an alteration of the aggregation state of the lithium amide reagent with solvent. The observation of undesired (*Z*)-β,γ-unsaturated ester products in the ^{1}H NMR spectra of the crude reaction mixtures of the conjugate addition reactions of (*R*)-**106**, (*S*)-**106**, **168** and **169** to *cis*-dioxolane containing α,β-unsaturated esters has led Davies *et al.* to previously postulate that this is consistent with a γ-deprotonation pathway involving reactive conformation **201C**[29,35b] and so it may therefore be assumed that any conjugate addition reaction occurs via a similar reactive conformation of the *cis*-dioxolane containing α,β-unsaturated ester. The conjugate addition reactions to *cis*-dioxolane containing α,β-unsaturated esters **162** and **164** were found to display very high levels of substrate control (*vide supra*) with a clear diastereofacial preference for either γ-deprotonation or the generation of the corresponding 3,4-*anti* β-amino ester products being noted. As such, these results are consistent with a preferential approach of the lithium amide reagent on the *Re* face of the α,β-unsaturated ester in any of the conformations **201A**, **201B** or **201C** [all related by rotation about

the C(3)–C(4) bond]: in all three conformations the *Si* face of the α,β-unsaturated ester is sterically blocked by the C(5)-substituent (as shown explicitly for conformation **201C**), thereby demonstrating the overwhelming effect of substrate control (Figure 11).[35b] In fact, the X-ray crystal structure obtained earlier for the *p*-nitrobenzoate α,β-unsaturated ester derivative **149**[39] displays a dihedral angle of 62.6° between the C(3)*H* and C(4)*H* atoms indicating that, in the solid phase at least, a conformation similar to **201B** is adopted. This observation therefore supports the suggestion that for α,β-unsaturated esters such as **149** there is a clear steric block of one face of the olefin by the substituent at C(5), indicating the likeliness for a large degree of substrate control during any conjugate addition reaction (Figure 12).

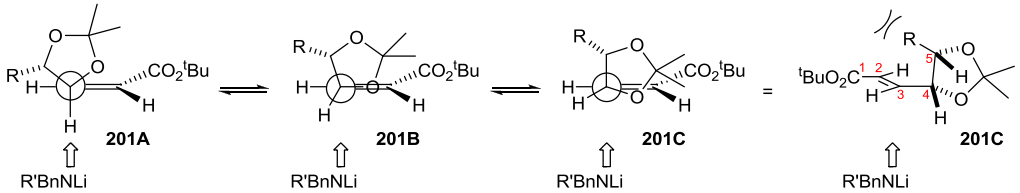


Figure 11. Possible reactive conformations of α,β-unsaturated esters **162** and **164**. [R = $CH_2OTBDMS$ or CH_2OBn; R' = α-methylbenzyl].

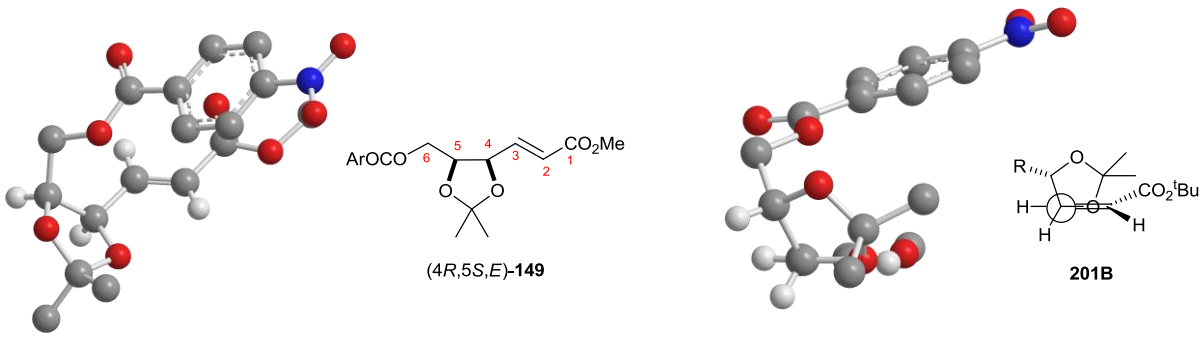


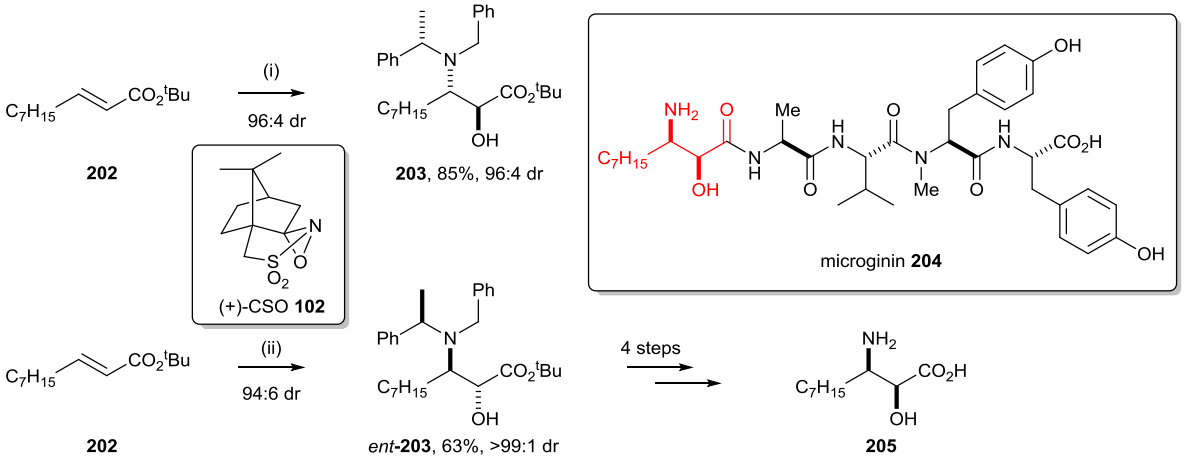
Figure 12. X-ray crystal structure of (4*R*,5*S*,*E*)-**149** (selected H atoms are omitted for clarity), viewed along the C(4)–C(5) bond [*right*], clearly showing the steric block of one face of the olefin by the C(5)-substituent. [Ar = *p*-$NO_2C_6H_4$, R = CH_2OCOAr].

2.10 Aminohydroxylation of α,β-unsaturated esters containing *cis*- and *trans*-dioxolane units

2.10.1 Introduction

With the "matched" doubly diastereoselective conjugate addition reactions to *cis*-dioxolane containing α,β-unsaturated esters **162** and **164** now identified, attention was next turned to the corresponding aminohydroxylation reactions. Davies *et al*. have established a highly diastereoselective method for the *anti*-aminohydroxylation of achiral α,β-unsaturated esters, involving the initial conjugate addition of enantiopure lithium *N*-benzyl-*N*-(α-methybenzyl)amide **106** to an α,β-unsaturated ester, followed by *in situ* oxidation of the resultant enolate with the requisite antipode of camphorsulfonyloxaziridine (CSO) **102**.[11,40] The stereochemical outcome of the oxidation step is predominantly determined by the stereochemistry of the intermediate lithium

(*Z*)-β-amino enolate and not by the CSO reagent; however, "matching" and "mismatching" effects have still been observed in some cases. Therefore, to achieve the aminohydroxylation of an α,β-unsaturated ester, the empirically "matched" reagent pairings have been established as lithium amide (*S*)-**106** with (+)-CSO **102**, and lithium amide (*R*)-**106** with (–)-CSO **102**.[11] This *anti*-aminohydroxylation procedure has successfully been applied by Davies *et al.* in the asymmetric synthesis of a range of natural products and derivatives.[41] For example, a key step in the synthesis of the *N*-terminal component of the linear pentapeptide microginin **204**[42] was the *anti*-aminohydroxylation of α,β-unsaturated ester **202**. Subjection of **202** to a conjugate addition reaction involving (*S*)-**106** followed by *in situ* enolate oxidation using (+)-CSO **102** (the empirically "matched" reagent pairing) gave α-hydroxy-β-amino ester **203** in 96:4 dr, with **203** being isolated in 85% yield and 96:4 dr. The corresponding conjugate addition reaction to **202** employing (*R*)-**106** and (+)-CSO **102** (the empirically "mismatched" reagent pairing) resulted in α-hydroxy-β-amino ester *ent*-**203** being produced in 94:6 dr, which was subsequently isolated in 63% yield as a single diastereoisomer. Subjection of *ent*-**203** to sequential hydrogenolysis, C(2)-epimerisation and deprotection steps allowed access to (2*S*,3*R*)-3-amino-2-hydroxydecanoic acid **205**, the *N*-terminal component of microginin **204** (Scheme 34).[43]



Scheme 34. *Reagents and conditions:* (i) (*S*)-**106**, THF, –78 °C, 2 h, then (+)-CSO **102**, –78 °C to rt, 12 h; (ii) (*R*)-**106**, THF, –78 °C, 2 h, then (+)-CSO **102**, –78 °C to rt, 12 h.

It was therefore envisaged that application of this *anti*-aminohydroxylation procedure to the *cis*-dioxolane containing α,β-unsaturated esters **134** already studied (as well as to the analogous *trans*-dioxolane containing α,β-unsaturated esters **136**) would allow access to biologically important amino and imino sugar targets **208** and **209**, respectively, as well as dihydroxyprolines **210** and trihydroxyhomoprolines **211** (Figure 13).

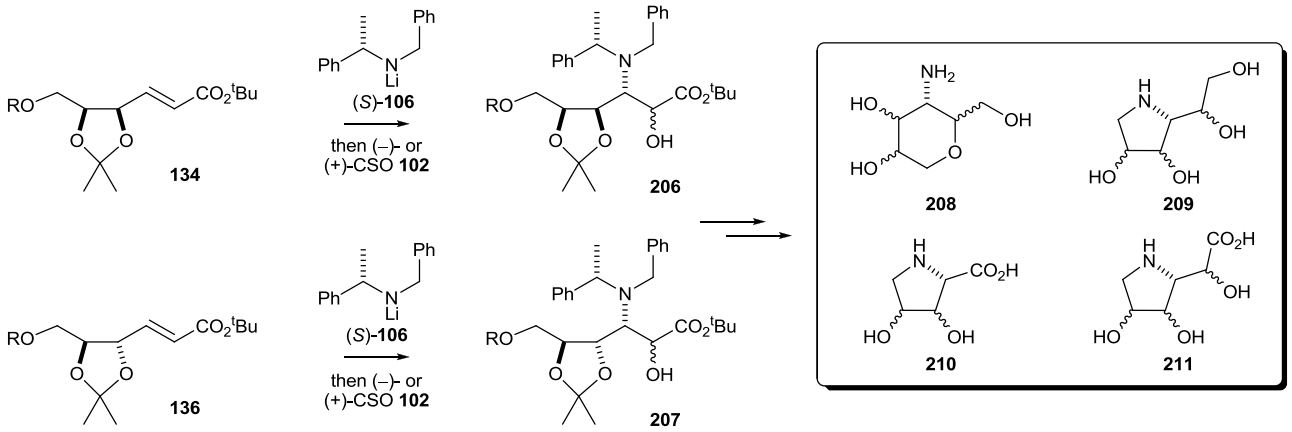
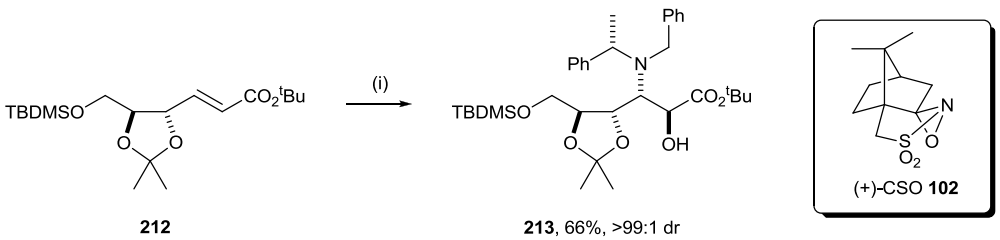


Figure 13. Proposed aminohydroxylation of *cis*- and *trans*-dioxolane containing α,β-unsaturated esters **134** and **136** as the key step in the synthesis of amino and imino sugars **208** and **209**, respectively, dihydroxyprolines **210** and trihydroxyhomoprolines **211**.

2.10.2 Aminohydroxylation of α,β-unsaturated esters 162 and 212

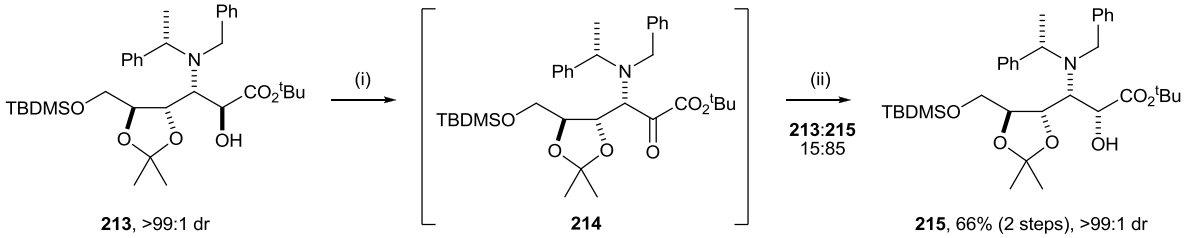
The doubly diastereoselective conjugate addition reactions of a range of *trans*-dioxolane containing α,β-unsaturated esters (including *O*-TBDMS protected **212**[44]) have already been studied by Davies *et al*., with the conjugate addition of (*S*)-**106** to **212** found to be the "matched" reaction (>99:1 dr).[29,44b] This knowledge was next applied to the analogous aminohydroxylation reaction of **212**: the "matched" conjugate addition of (*S*)-**106** to chiral α,β-unsaturated ester **212**[45] was coupled with an *in situ* enolate oxidation with (+)-CSO **102**[46] (in accordance with the established reagent pairing) to give **213** as the only diastereoisomeric product, which was isolated in 66% yield and >99:1 dr (Scheme 35). The 2,3-*anti* relationship within **213** was initially assigned by reference to the known stereochemical outcome of this highly diastereoselective aminohydroxylation procedure,[11,40] and later was confirmed unambiguously by single crystal X-ray diffraction analysis of a derivative (*vide infra*). Repetition of the reaction using (*S*)-**106** and the enantiomeric oxidant (–)-CSO **102** resulted in a mixture of products, including returned starting material **212**. Unfortunately, the presence of CSO **102** and CSI residues in the crude reaction mixture prevented a quantitative assessment of the product distribution or the diastereoselectivity of any enolate oxidation. This result is therefore consistent with the combination of (*S*)-**106** and (+)-CSO **102** being the most efficacious reagent pairing to effect aminohydroxylation in this case.



Scheme 35. *Reagents and conditions:* (i) (*S*)-**106**, THF, –78 °C, 2 h, then (+)-CSO **102**, –78 °C to rt, 12 h.

An authentic sample of the corresponding 2,3-*syn* diastereoisomer **215** was prepared via Swern oxidation[47] of 2,3-*anti*-**213** to ketone **214** and immediate reduction using $NaBH_4$ following a

procedure established by Davies *et al.*[48] The reduction of ketone **214** was found to proceed with incomplete diastereocontrol to give 2,3-*syn*-**215** (75:25 dr) and so a range of reducing agents, reaction times and reaction temperatures were investigated in the hope of improving diastereoselectivity. The optimal conditions were found to be treatment of **214** with $NaBH_4$ (1.0 equivalent) in MeOH at –20 ºC for 2 h, which gave a 15:85 mixture of **213** and **215**, respectively. Subsequent purification via column chromatography allowed isolation of 2,3-*syn*-**215** in 66% yield and >99:1 dr (Scheme 36).



reducing agent	solvent	conditions	product distribution 213:215
$NaBH_4$	MeOH	rt, 16 h	25:75
$NaBH_4$	MeOH	0 ºC to rt, 16 h	18:82
$NaBH_4$	**MeOH**	**–20 ºC, 2 h**	**15:85**
$NaBH_4$	MeOH	–78 ºC to rt, 16 h	24:76
$LiAl(O^tBu)_3H$	THF	–78 ºC, 2 h	58:42

Scheme 36. *Reagents and conditions:* (i) $(ClCO)_2$, DMSO, CH_2Cl_2, –78 °C, 15 min, then Et_3N, –78 °C, 10 min; (ii) $NaBH_4$, MeOH, –20 °C, 2 h.

The stereochemical outcome of this reduction is consistent with that predicted by the Felkin-Anh model,[49] where the amino group acts as the "large" group on both steric and stereoelectronic grounds. In this model, the favoured pathway for nucleophilic attack occurs in conformation **216B**, as this results in the least hindered trajectory for the nucleophile, to give 2,3-*syn*-**215** as the major product (Figure 14).

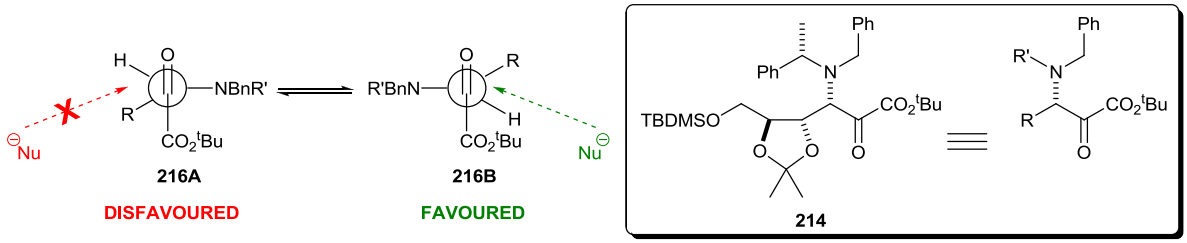
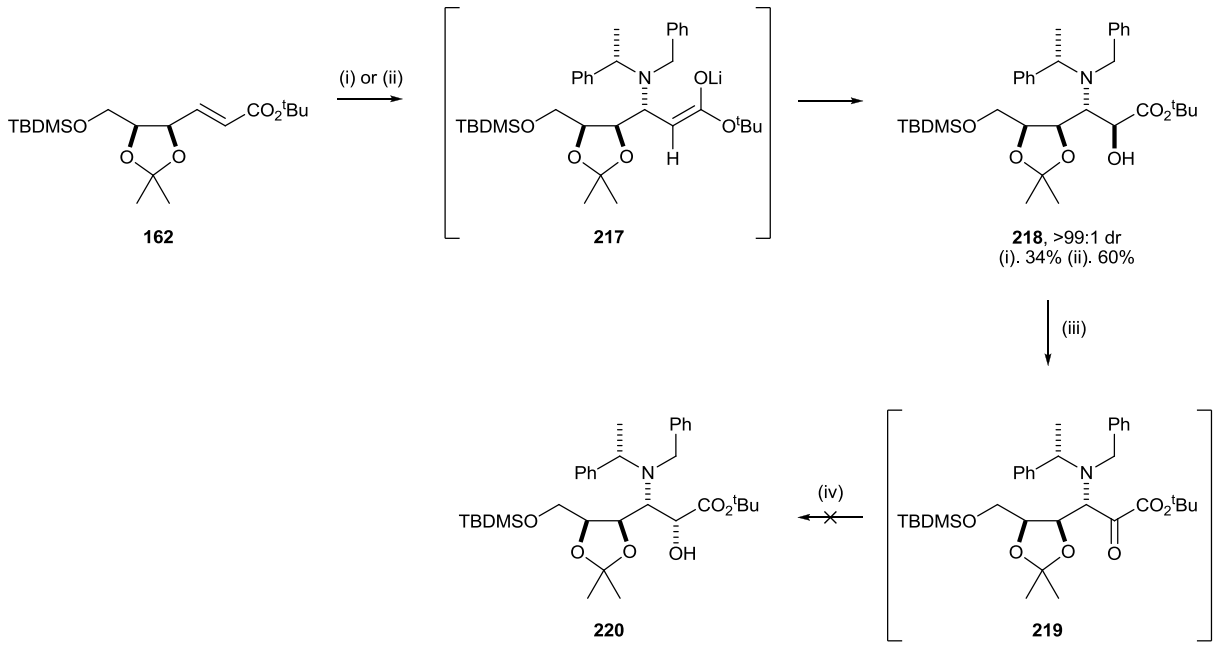


Figure 14. Felkin-Anh model to rationalise the diastereoselective reduction of ketone **214**.

Aminohydroxylation of *cis*-dioxolane containing α,β-unsaturated ester **162** was next investigated. Earlier studies had shown that the addition of (*S*)-**106** to **162** represented the "matched" conjugate addition reaction (*vide supra*) and so [based upon knowledge of the reported empirically "matched" reagent pairing of lithium amide (*S*)-**106** with (+)-CSO **102**], the aminohydroxylation of **162** was attempted with the initial conjugate addition of (*S*)-**106** followed by *in situ* enolate oxidation using (+)-CSO **102**. The reaction was found to be very unreliable: with several repeats, returned starting material **162** or the formation of β-amino ester **188** as the major product was primarily observed, with

the corresponding α-hydroxy-β-amino ester **218** being isolated in a maximum of 34% yield (and in >99:1 dr).[50] Interestingly, conjugate addition of (*S*)-**106** to **162** followed by *in situ* oxidation using (–)-CSO **102** gave **218** as the major product, which was isolated in 60% yield and >99:1 dr. The configuration within **218** was established unambiguously by single crystal X-ray diffraction analysis of a derivative (*vide infra*). It is therefore clear to see that the ultimate outcome of the doubly diastereoselective aminohydroxylation reaction is not only a result of control of the C(3)- and/or C(α)-stereogenic centres within the intermediate (*Z*)-β-amino enolate **217**, but also those at C(4) and/or C(5). In addition, the recognised "matched" reagent pairings of lithium amide **106** and CSO **102** do not always appear to result in the optimum reagent combination upon aminohydroxylation of chiral substrates such as **162**. The preparation of the corresponding 2,3-*syn* diastereoisomer was next investigated using the same oxidation/reduction method as earlier. Despite complete conversion of **218** to the corresponding ketone **219** under Swern oxidation conditions, subsequent reduction using $NaBH_4$ returned the starting alcohol **218** exclusively, which was isolated in 61% yield and >99:1 dr (Scheme 37).



Scheme 37. *Reagents and conditions:* (i) (*S*)-**106**, THF, –78 °C, 2 h, then (+)-CSO **102**, –78 °C to rt, 12 h; (ii) (*S*)-**106**, THF, –78 °C, 2 h, then (–)-CSO **102**, –78 °C to rt, 12 h; (iii) $(ClCO)_2$, DMSO, CH_2Cl_2, –78 °C, 15 min, then Et_3N, –78 °C, 10 min; (iv) $NaBH_4$, MeOH, –20 °C, 2 h.

2.11 Asymmetric synthesis of amino sugars, imino sugars, dihydroxyprolines and trihydroxyhomoprolines

Substantial quantities of α-hydroxy-β-amino esters **213**, **215** and **218** facilitated their elaboration towards some biologically significant amino and imino sugars **208** and **209**, respectively, in addition to some substituted proline derivatives **210** and homoproline derivatives **211**. The presence of several

heteroatoms within α-hydroxy-β-amino esters **221** renders them as ideal precursors to a range of heterocycles, namely pyrrolidine and tetrahydropyran derivatives, and it was envisaged that the course of the cyclisation could be directed by the choice of protecting group strategy and the relative configuration of the dioxolane unit. For example, it was anticipated that activation of the C(6)-hydroxyl group within **221** would provide access to intermediate **222**. In the case where **222** contains a *cis*-dioxolane, it was predicted that any cyclisation would preferentially occur through the nitrogen atom at C(3) to give a pyrrolidine product **223**, which could be elaborated towards imino sugars **209**, dihydroxyprolines **210** or trihydroxyhomoprolines **211**. On the other hand, when **222** contains a *trans*-dioxolane unit, it was expected that cyclisation would instead occur through the oxygen atom at C(2) to give the corresponding tetrahydropyran product **224**, as the alternative cyclisation pathway through the nitrogen atom at C(3) would involve the formation of a disfavoured *trans*-fused-[3.3.0]-bicycle. Sequential ester reduction, acetal hydrolysis and hydrogenolysis steps would then supply the desired 1,4,5-trideoxy-1,5-epoxy-4-aminohexoses **208** (Figure 15).

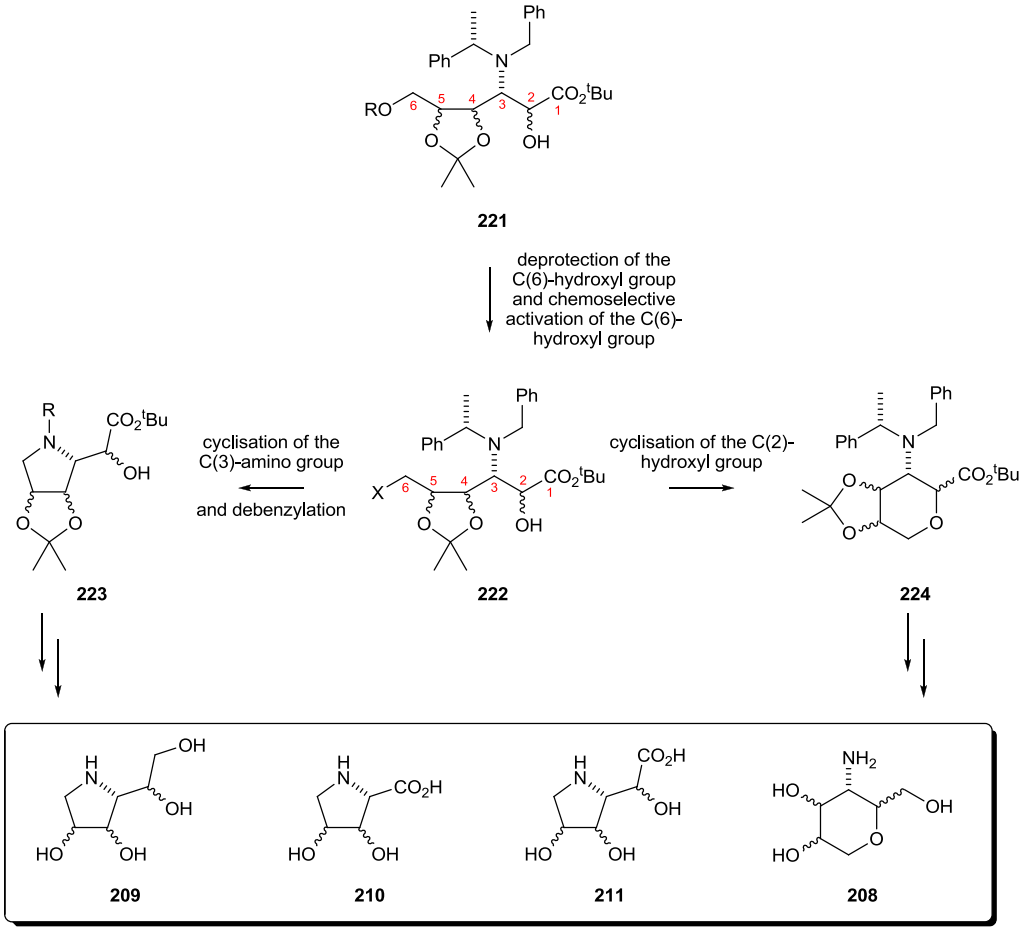
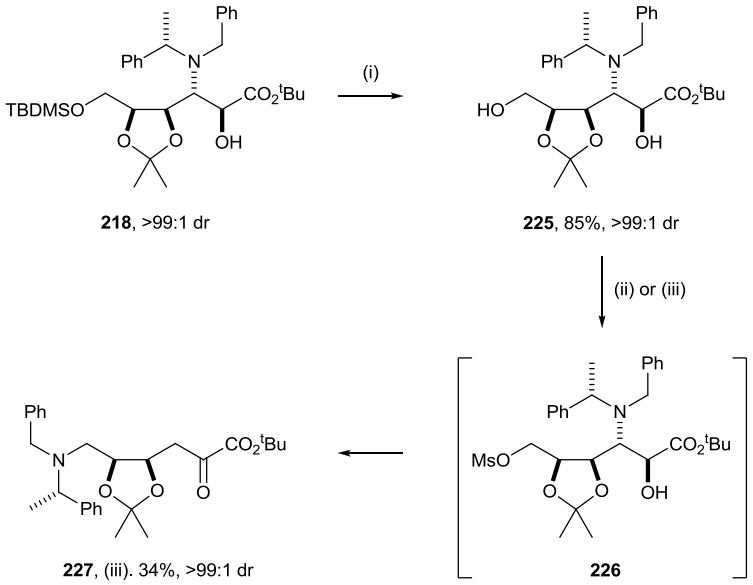


Figure 15. Proposed routes towards amino sugars **209**, imino sugars **210**, dihydroxyprolines **211** and trihydroxyhomoprolines **212**.

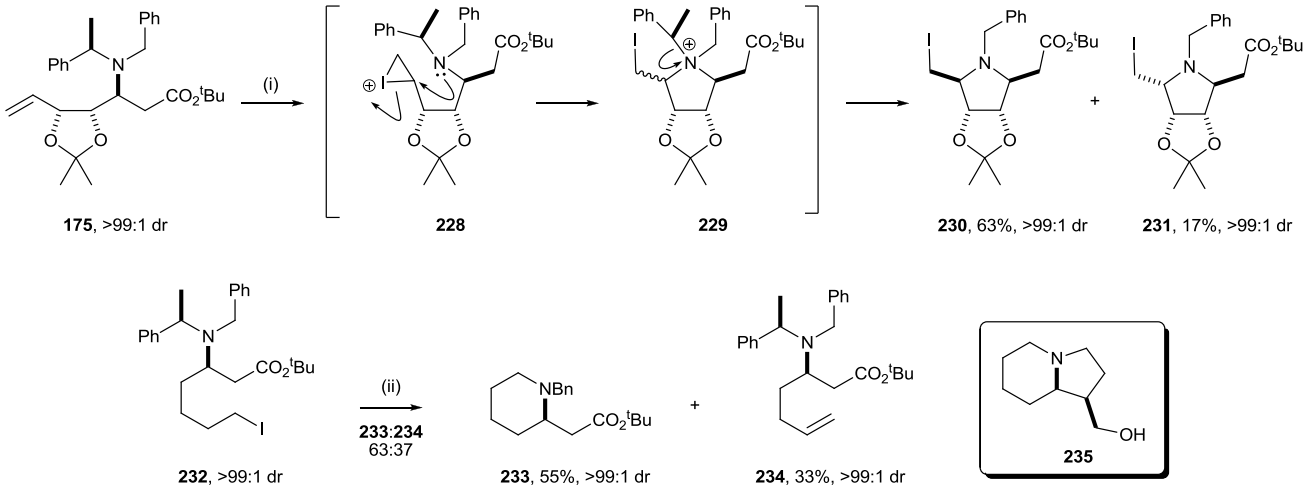
2.11.1 Investigation into 5-membered ring cyclisations involving *cis*-dioxolane containing substrates

Attention was first focussed on the deprotection of the C(6)-*O*-TBDMS functionality within α-hydroxy-β-amino ester **218** followed by chemoselective activation of the resultant diol. Desilylation of **218** using TBAF firstly gave diol **225** in 85% yield and >99:1 dr. An initial activation attempt involved subjection of diol **225** to mesylation conditions via treatment of **225** with MsCl in pyridine at rt; however, a complex mixture of products was returned. A low temperature mesylation was instead employed by treatment of **225** with MsCl and Et_3N at −10 ºC.[51] This reaction resulted in the formation of **227**, which presumably arises from nucleophilic attack of the nitrogen atom at C(3) on the newly formed leaving group at C(6), followed by a retro conjugate addition reaction. This observation is therefore in full agreement with the prediction that cyclisation through the C(3)-nitrogen atom would be favoured in this *cis*-dioxolane containing system (Scheme 38).



Scheme 38. *Reagents and conditions:* (i) TBAF, THF, rt, 16 h; (ii) MsCl (2.5 equiv), pyridine, rt, 18 h; (iii) MsCl, Et_3N, DMAP, CH_2Cl_2, −10 °C, 6 h.

Previous studies towards the synthesis of substituted pyrrolidines have shown that the treatment of **175** with I_2 in MeCN in the presence of $NaHCO_3$ gives ammonium **229**, which then undergoes loss of the *N*-α-methylbenzyl group with complete chemoselectivity (via an S_N1-type reaction pathway) to give **230** and **231** (Scheme 39).[52] This chemoselectivity has also been noted in 6-membered ring systems: treatment of primary iodide **232** with MeCN in the presence of $AgBF_4$ gave a 63:37 mixture of piperidine **233** and elimination product **234**. Piperidine **233** was isolated in 55% yield and >99:1 dr, and was subsequently elaborated to 1-(hydroxymethyl)octahydroindolizine **235** (Scheme 39).[53]



Scheme 39. *Reagents and conditions:* (i) I_2, $NaHCO_3$, MeCN, –20 °C to rt, 20 h then satd aq $Na_2S_2O_3$; (ii) $AgBF_4$, MeCN, 80 °C, 16 h.

Based upon this literature precedent, it was therefore anticipated that **225** could instead be converted into the corresponding primary iodide **236** via chemoselective C(6)-activation under Appel[54] reaction conditions. Ring closure of **236** to give ammonium **237**, followed by a similar *in situ* loss of the *N*-α-methylbenzyl group to give pyrrolidine **238** was therefore expected to occur (Figure 16).

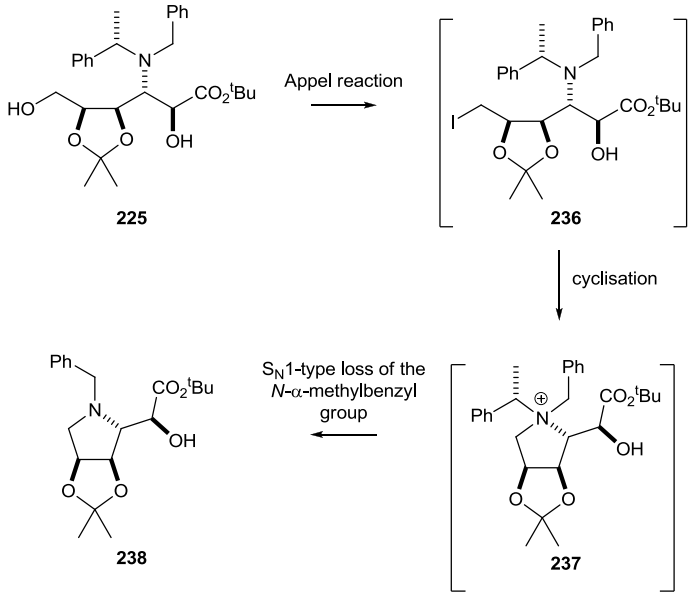
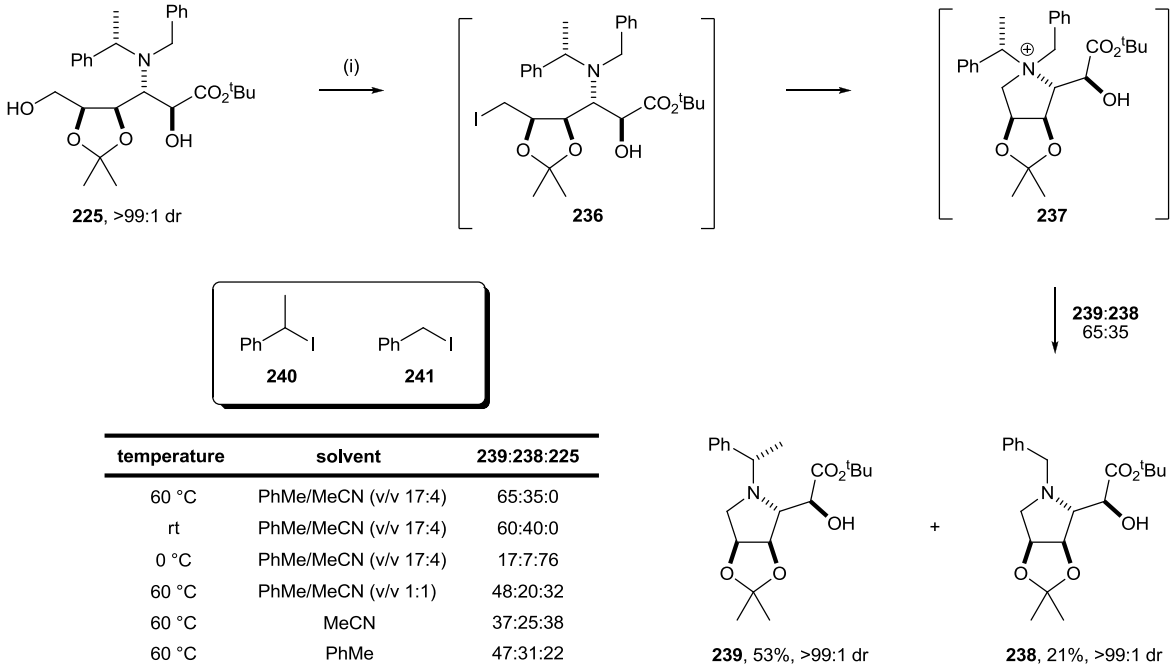


Figure 16. Proposed pathway towards pyrrolidine **238**.

Thus, diol **225** was subjected to standard Appel conditions (I_2 and PPh_3 in PhMe/MeCN), which interestingly gave a 65:35 mixture of *N*-α-methylbenzyl protected pyrrolidine **239** and *N*-benzyl protected pyrrolidine **238**. Purification of the crude reaction mixture via flash column chromatography resulted in **239** and **238** being isolated in 53 and 21% yield, respectively (Scheme 40). The mechanism to form **239** and **238** does therefore presumably involve chemoselective activation of the C(6)-hydroxyl group followed by *in situ* cyclisation of **236** to give an intermediate ammonium species **237**. Subsequent loss of either the *N*-benzyl or *N*-α-methylbenzyl groups within **237** then leads to **239** and **238**, respectively, with the former being the preferential reaction pathway. The preferential loss of the *N*-benzyl group from within **237** is an interesting observation as it is in complete contrast to the earlier results of Davies *et al*.[55] (*vide supra*). Side

products α-methylbenzyl iodide **240** and benzyl iodide **241** were observed in the ^{1}H NMR spectra of the crude reaction mixtures; however, the origin of the chemoselectivity of this reaction is not clear. The Appel reaction was repeated using different solvent combinations (ranging from 100% PhMe to 100% MeCN) and at a range of temperatures in an aim to further investigate the mechanism involved. Although no clear mechanistic conclusions could be drawn from the product ratios obtained, it is evident that both the reaction conversion and the product ratio of **239** and **238** are dependent on both variables (Scheme 40).



temperature	solvent	239:238:225
60 °C	PhMe/MeCN (v/v 17:4)	65:35:0
rt	PhMe/MeCN (v/v 17:4)	60:40:0
0 °C	PhMe/MeCN (v/v 17:4)	17:7:76
60 °C	PhMe/MeCN (v/v 1:1)	48:20:32
60 °C	MeCN	37:25:38
60 °C	PhMe	47:31:22

225, >99:1 dr

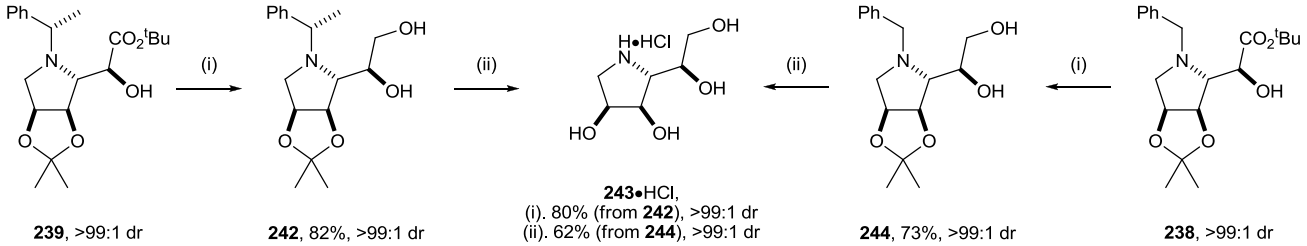
239, 53%, >99:1 dr + **238**, 21%, >99:1 dr

Scheme 40. *Reagents and conditions:* (i) I_2, PPh_3, PhMe/MeCN (v/v 17:4), 60 °C, 1 h.

2.11.1.1 Synthesis of 1,4-dideoxy-1,4-imino-D-allitol 243

With pyrrolidines **238** and **239** in hand, elaboration to the known imino sugar 1,4-dideoxy-1,4-imino-D-allitol **243**[56] was next undertaken. Reduction of the ester moiety within *N*-α-methylbenzyl substituted **239** with $LiAlH_4$ gave **242** in 82% yield and >99:1 dr. Hydrogenolysis of **242** in the presence of aqueous HCl effected *N*-debenzylation and acetal hydrolysis to give 1,4-dideoxy-1,4-imino-D-allitol **243** as the corresponding hydrochloride salt in 80% yield and >99:1 dr (Scheme 41). Similarly, reduction of the *N*-benzyl substituted analogue **238** gave **244** in 73% yield and >99:1 dr, and subsequent hydrogenolysis in the presence of aqueous HCl gave **243**·HCl in 62% yield and >99:1 dr (Scheme 41). In both instances, the samples of **243**·HCl displayed spectroscopic properties that were entirely consistent with those previously reported.[56] In addition, diol **242** proved to be crystalline and so the relative configuration within **242** was unambiguously confirmed by single crystal X-ray diffraction analysis,[16] with the absolute configuration being assigned relative to the known (*S*)-configuration of the α-methylbenzyl group and also to the known configuration of the

D-ribose derived dioxolane unit. This result also confirmed the absolute configurations within **218**, **225**, **238**, **239**, and **244** (Figure 17).



Scheme 41. *Reagents and conditions:* (i) $LiAlH_4$, THF, −78 °C to rt, 12 h; (ii) $Pd(OH)_2/C$, H_2 (1 atm), MeOH, HCl (3.0 M, aq), rt, 12 h.

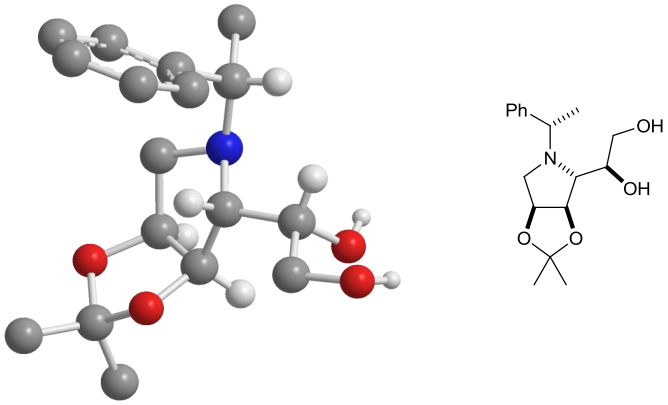


Figure 17. X-ray crystal structure of **242** (selected H atoms are omitted for clarity).

2.11.1.2 Synthesis of (2*S*,3*R*,4*S*)-3,4-dihydroxy-L-proline 246 and 1,4-dideoxy-1,4-imino-D-alluronic acid 251

In 1994, (2*S*,3*R*,4*S*)-3,4-dihydroxy-L-proline **246** was identified as the sixth residue in the repeating decapeptide sequence of Mefp1 **245**, a protein produced by the marine mussel *Mytilus edulis* (Figure 18).[57] This discovery represented the first instance that the position of a dihydroxyproline had been established in the primary sequence of a protein. The dihydroxyprolines have become highly desirable synthetic targets due to their ability to act as glycosidase inhibitors[58] and as such all eight of the possible stereoisomers have been synthesised in the laboratory.[59]

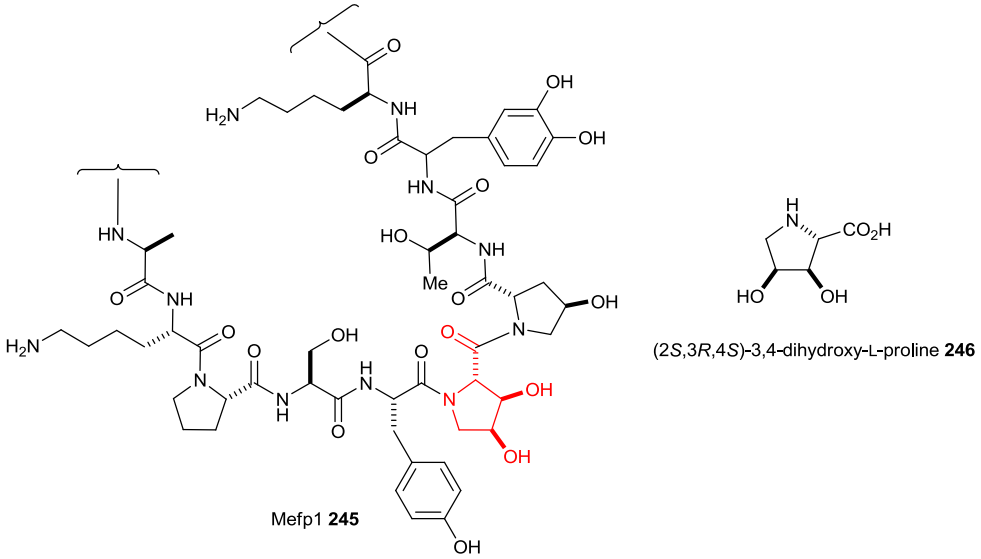
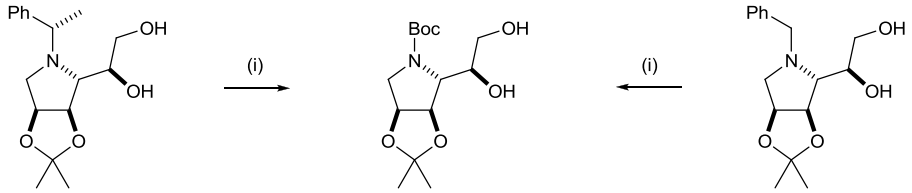


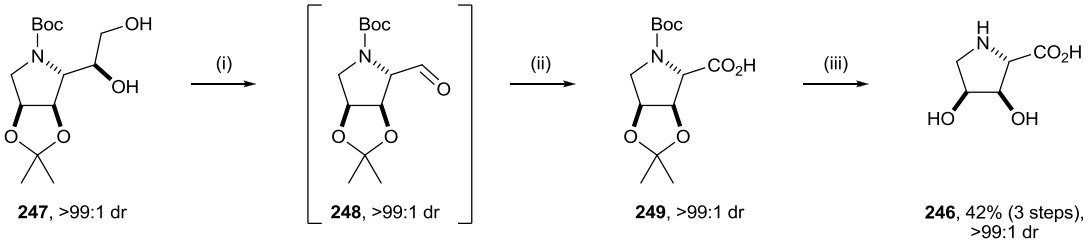
Figure 18. The Mefp1 decapeptide **245**, which contains a (2*S*,3*R*,4*S*)-3,4-dihydroxy-L-proline residue **246**.

It was anticipated that pyrrolidines **242** and **244** could also be elaborated to (2*S*,3*R*,4*S*)-3,4-dihydroxy-L-proline **246** in just a few chemical transformations. Hydrogenolysis of **242** in the presence of Boc_2O gave *N*-Boc protected pyrrolidine **247** in 98% yield and >99:1 dr, whilst subjection of pyrrolidine **244** to identical conditions gave **247** in 96% yield and >99:1 dr (Scheme 42).



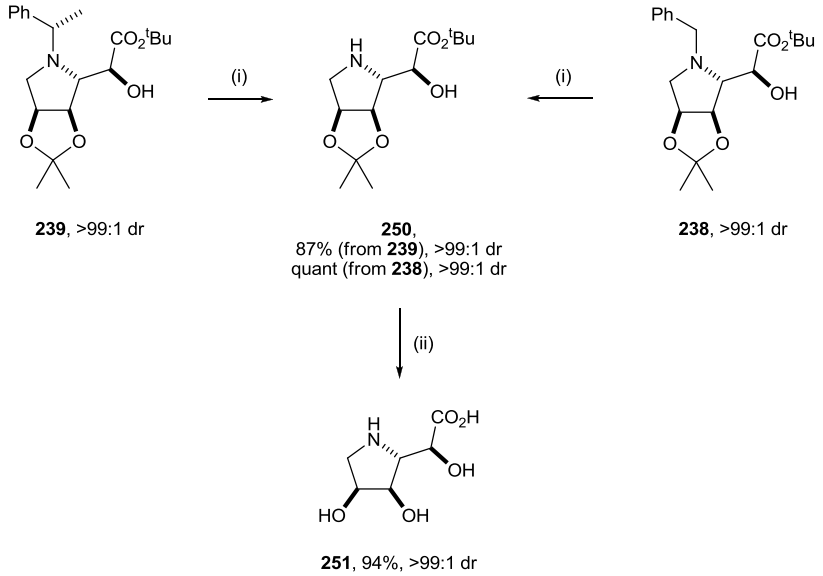
Scheme 42. *Reagents and conditions:* (i) Boc_2O, Pd/C, H_2 (1 atm), MeOH, rt, 18 h.

Following a literature procedure described by Fleet *et al.*,[56] **247** was then elaborated to the target compound (2*S*,3*R*,4*S*)-3,4-dihydroxy-L-proline **246** in three steps. Cleavage of the 1,2-diol functionality within **247** using $NaIO_4$ gave aldehyde **248**, which was immediately subjected to a Pinnick oxidation[60] with $NaClO_2$ to give carboxylic acid **249**. Global hydrolysis of **249** using 2.0 M aqueous HCl followed by purification via ion-exchange chromatography gave **246** in 42% yield and >99:1 dr over the three steps. The sample of **246** was found to have spectroscopic properties that were entirely consistent with those previously reported[56] (Scheme 43).



Scheme 43. *Reagents and conditions:* (i) $NaIO_4$, EtOH/H_2O (v/v 5:2), rt, 10 min; (ii) $NaClO_2$, KH_2PO_4, cyclohexene, ^{t}BuOH/H_2O (v/v 3:2), rt, 16 h; (iii) HCl (2.0 M, aq), reflux, 8 h then DOWEX 50WX8-200.

It was anticipated that pyrrolidines **238** and **239** could also be elaborated to 1,4-dideoxy-1,4-imino-D-alluronic acid **251**, a trihydroxyhomoproline. Hydrogenolysis of **239** and **238** gave **250** in 87% and quantitative yield, respectively, and in >99:1 dr in each case. Hydrolysis of **250** via treatment with 2.0 M aqueous HCl at 100 ºC effected complete deprotection and 1,4-dideoxy-1,4-imino-D-alluronic acid **251** was subsequently isolated in 94% yield and >99:1 dr after ion-exchange chromatography (Scheme 44).



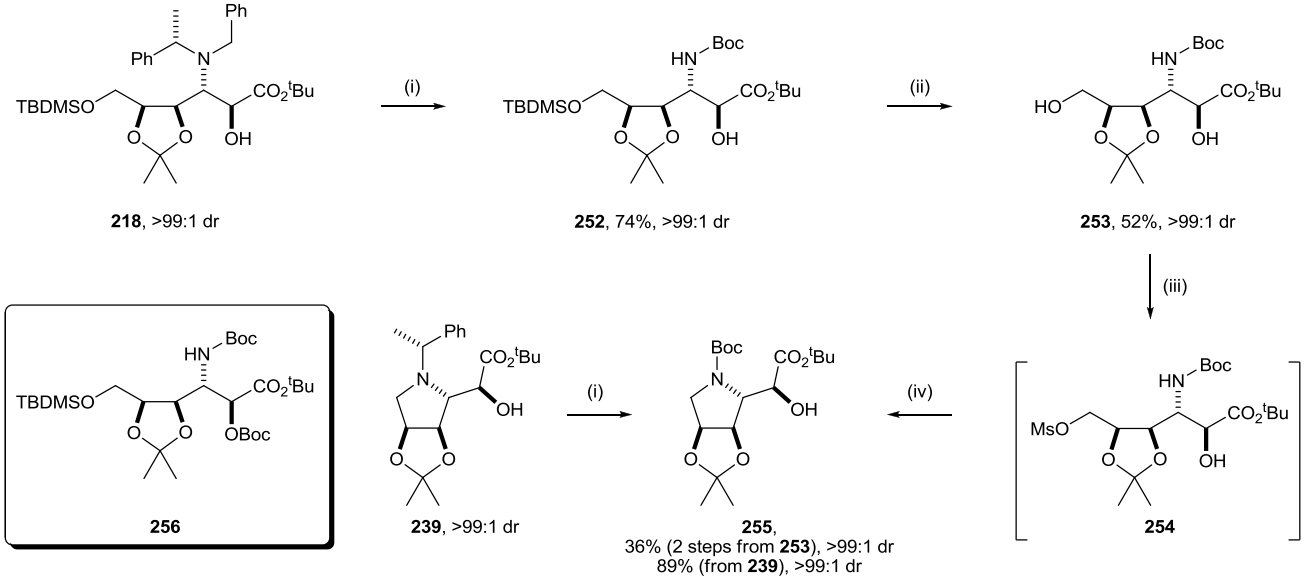
Scheme 44. *Reagents and conditions:* (i) $Pd(OH)_2/C$, H_2 (1 atm), MeOH, rt, 12 h; (ii) HCl (2.0 M, aq), reflux, 8 h then DOWEX 50WX8-200.

2.11.2 Investigation into 6-membered ring cyclisations involving *cis*-dioxolane containing substrates

2.11.2.1 *N*-Boc protection strategy

The successful elaboration of α-hydroxy-β-amino ester **218** to **243**, **246** and **251** had proven that cyclisation through the nitrogen atom at C(3) was the favoured ring-closing pathway for this *cis*-dioxolane containing substrate. It was hoped that an attempt to reduce the nucleophilicity of the C(3)-nitrogen atom might instead allow cyclisation though oxygen to occur, to give access to the tetrahydropyran scaffold required for the synthesis of 1,4,5-trideoxy-1,5-epoxy-4-aminohexoses **208**. It was decided that an *N*-Boc protecting group would be a good starting point, as this is a suitably electron-withdrawing functional group. Thus, treatment of **218** with H_2 and $Pd(OH)_2/C$ in the presence of Boc_2O gave a mixture of *N*-Boc protected **252** and *N*,*O*-di-Boc protected **256**, which were isolated in 74 and 9% yield, respectively. The sample of **252** proved to be crystalline and so the relative configuration within **252** was unambiguously established via single crystal X-ray diffraction analysis.[16] The absolute configuration within **252** was then assigned relative to the known configuration of the D-ribose derived dioxolane unit (Figure 19). Desilylation of **252** gave diol **253**,

which was selectively mesylated at the primary C(6)-hydroxyl group to give **254**. Unfortunately, treatment of **254** with NaH resulted in cyclisation through nitrogen to give the *N*-Boc pyrrolidine **255**[61] in >99:1 dr, which was isolated in 36% over the two steps.[62] An authentic sample of **255** was subsequently prepared by tandem hydrogenolysis and *N*-Boc protection of **239** which gave **255** in 89% yield and >99:1 dr (Scheme 45).



Scheme 45. *Reagents and conditions:* (i) Boc_2O, $Pd(OH)_2/C$, H_2 (1 atm), MeOH, rt, 18 h; (ii) TBAF, THF, rt, 16 h; (iii) MsCl, Et_3N, DMAP, CH_2Cl_2, –10 °C, 6 h; (iv) NaH, THF, rt, 16 h.

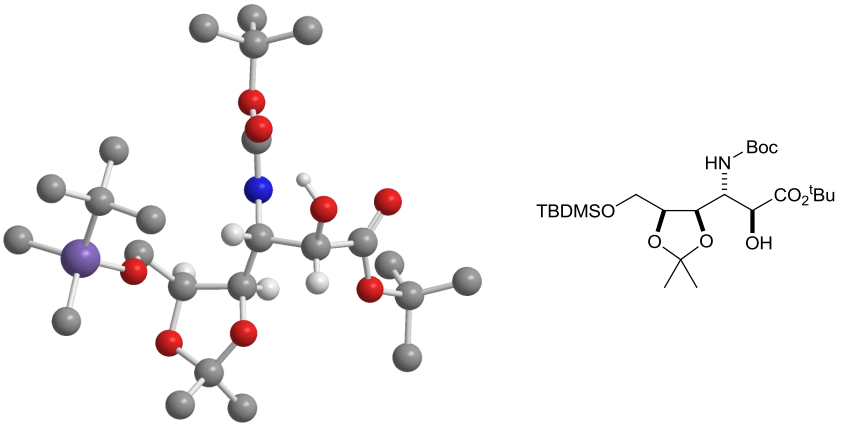
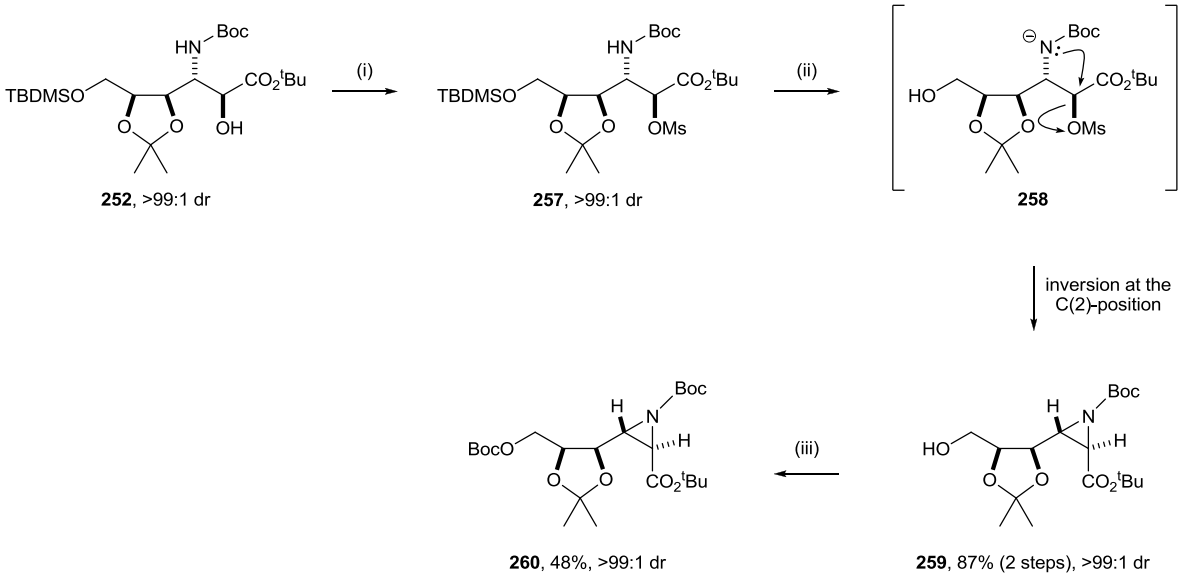


Figure 19. X-ray crystal structure of **252** (selected H atoms are omitted for clarity).

Due to problems encountered upon C(6)-hydroxyl group activation of **225** and **253**, it was decided to instead attempt activation of the C(2)-hydroxyl group within **252**, in the hope that this might prevent cyclisation through the C(3)-amino group. Therefore, **252** was initially treated with MsCl and Et_3N at –10 °C to give the C(2)-mesylate **257**. Treatment of **257** with TBAF successfully removed the *O*-TBDMS protecting group at C(6), but unfortunately the basic conditions of the reaction also promoted aziridine formation via attack of the nitrogen atom upon the mesylate group at C(2), giving aziridine **259** as the sole product which was isolated in 87% yield and >99:1 dr. Subjection of **259** to Boc_2O and Et_3N gave di-Boc protected aziridine **260** in 48% yield, which was isolated as a crystalline solid (Scheme 46). As such, the relative configuration within **260** was established

unambiguously by single crystal X-ray diffraction analysis.[16] The absolute configuration within **260** was then assigned relative to the known configuration of the D-ribose derived dioxolane unit. The X-ray crystal structure of **260** establishes the *trans*-configuration[63] of the aziridine component within **260** (and also that within **259**), an observation which is consistent with a mechanism involving inversion of configuration at the C(2)-position within **257** (Figure 20).



252, >99:1 dr **257**, >99:1 dr **258**

260, 48%, >99:1 dr **259**, 87% (2 steps), >99:1 dr

Scheme 46. *Reagents and conditions:* (i) MsCl, Et_3N, DMAP, CH_2Cl_2, −10 °C, 6 h; (ii) TBAF, THF, rt, 16 h; (iii) Boc_2O, Et_3N, THF, rt, 22 h.

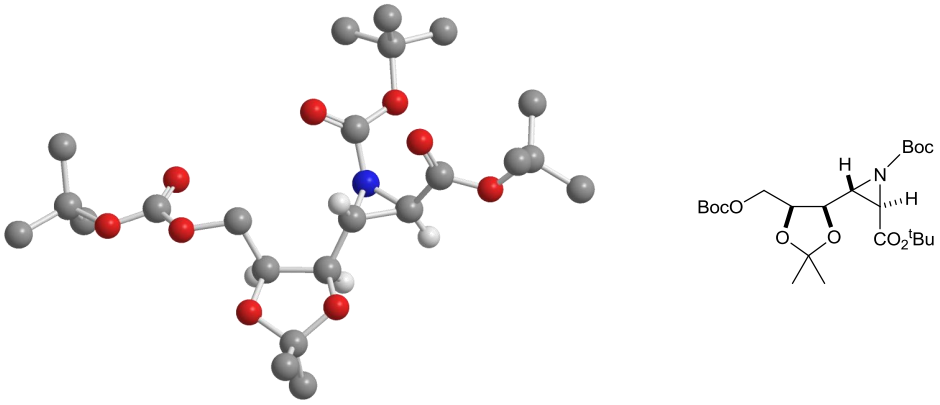
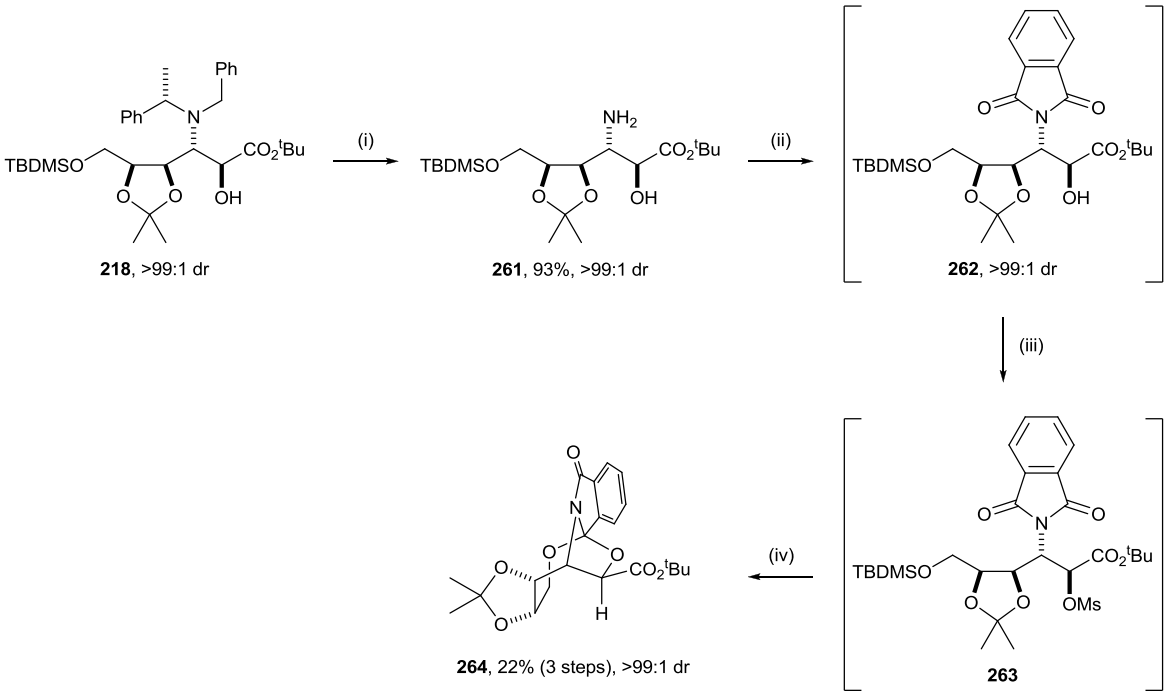


Figure 20. X-ray crystal structure of **260** (selected H atoms are omitted for clarity).

2.11.2.2 *N*-Phthaloyl protection strategy

As the *N*-Boc group did not prevent cyclisation through the nitrogen atom at C(3), the *N*-phthaloyl group was next investigated as this involves the incorporation of two carbonyl groups onto the nitrogen atom, as well as having the added advantage of the absence of any acidic protons. α-Hydroxy-β-amino ester **218** was firstly subjected to a hydrogenolysis reaction using H_2 and $Pd(OH)_2/C$ to give the corresponding primary amine **261** in 93% yield. Subsequent treatment of **261** with phthaloyl dichloride and Et_3N gave the desired *N*-phthaloyl protected product **262**. Mesylation of the C(2)-hydroxyl group within **262** proceeded cleanly to give mesylate **263**, and so the crude

reaction mixture was treated with TBAF with the aim of removing the *O*-TBDMS protecting group at C(6). Surprisingly, the desilylation reaction gave a complex mixture of products from which only **264** was isolated in a 22% three-step yield after column chromatography (Scheme 47). Substantial peak overlap in the ^{1}H NMR spectrum meant that it was difficult to determine the structure of this product from NMR spectroscopic data alone and so attention was turned to recrystallisation in the hope of obtaining some single crystals. Fortunately, this approach was successful and single crystal X-ray diffraction analysis[16] was able to identify the major product from this reaction as complex polycycle **264**, with the absolute configuration within **264** being assigned relative to the known configuration of the D-ribose derived dioxolane unit (Figure 21).



Scheme 47. *Reagents and conditions:* (i) $Pd(OH)_2/C$, H_2 (1 atm), MeOH, rt, 18 h; (ii) phthaloyl dichloride, Et_3N, CH_2Cl_2, rt, 16 h; (iii) MsCl, Et_3N, DMAP, CH_2Cl_2, –10 °C, 6 h; (iv) TBAF, THF, rt, 16 h.

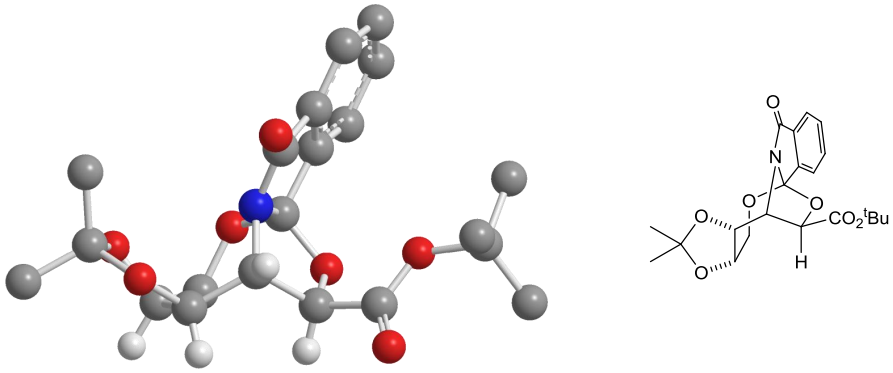


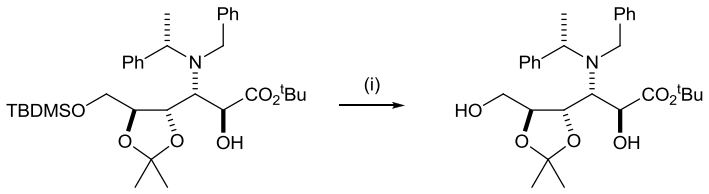
Figure 21. X-ray crystal structure of **264** (selected H atoms are omitted for clarity).

It is apparent that any mechanism involving cyclisation through oxygen is disfavoured in this system, even when the nitrogen atom is directly attached to a strong electron withdrawing group. In addition, it may be possible that there is significant steric clash in the transition state for the developing 6-membered ring (as a result of the presence of the *cis*-dioxolane unit) which disfavours its

formation, promoting instead the formation of a 3- or 5-membered ring. With these results in hand, attention was turned to the elaboration of α-hydroxy-β-amino esters **213** and **215** (which both contain a *trans*-dioxolane unit) towards the desired 1,4,5-trideoxy-1,5-epoxy-4-aminohexoses **208**. It was envisaged that the presence of the *trans*-dioxolane unit would prevent cyclisation through nitrogen to give the corresponding pyrrolidines, as this is a pathway that would involve the formation of a disfavoured *trans*-fused-[3.3.0]-bicycle. It was therefore expected that cyclisation would preferentially occur through oxygen to give a tetrahydropyran scaffold in these systems.

2.11.3 Investigation into 6-membered ring cyclisations involving *trans*-dioxolane containing substrates

Desilylation of **213** using TBAF gave diol **265** in 77% yield and >99:1 dr (Scheme 48). The relative configuration within **265** was unambiguously established via single crystal X-ray diffraction analysis[16] and the absolute configuration within **265** was assigned relative to the known (*S*)-configuration of the α-methylbenzyl group and also to the known configuration of the diethyl-L-tartrate derived dioxolane unit. This result also provided unequivocal evidence for the absolute configuration within **213**, thereby confirming the stereochemical outcome of the aminohydroxylation reaction of **212** upon treatment with (*S*)-**106** and (+)-CSO **102** (Figure 22).



213, >99:1 dr **265**, 77%, >99:1 dr

Scheme 48. *Reagents and conditions:* (i) TBAF, THF, rt, 16 h.

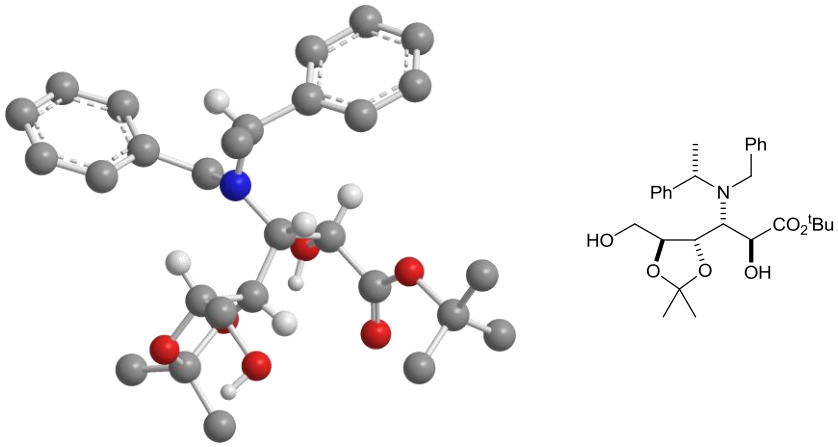
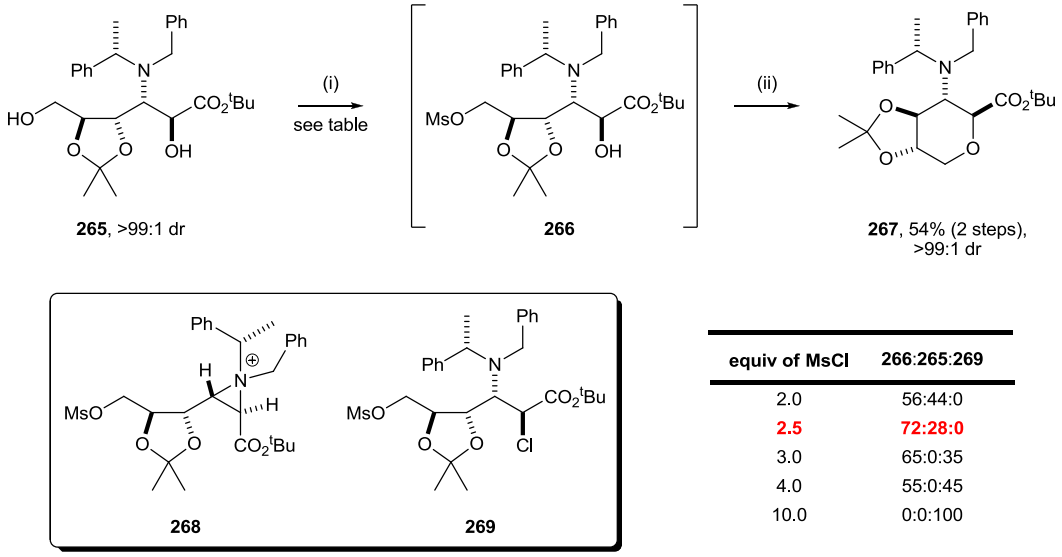


Figure 22. X-ray crystal structure of **265** (selected H atoms are omitted for clarity).

Chemoselective mesylation of the C(6)-hydroxyl group within **265** proved problematic. Initial investigations involved standard mesylation conditions (MsCl/pyridine); however, this reaction required much optimisation. It was found that reactions conducted using small equivalents of MsCl

resulted in poor conversion to the desired C(6)-mesylate **266**, but that as the number of MsCl equivalents was increased, evidence of a side product **269** was seen to a much greater extent. In an attempt to identify this side product, **265** was treated with 10 equivalents of MsCl to force the reaction to the sole production of **269**. The reaction proceeded to give **269** as a single diastereoisomer (which was subsequently isolated in 72% yield and >99:1 dr), and so could be identified as α-chloro-β-amino ester **269** after analysis of the NMR spectroscopic and mass spectrometric data. The regiochemistry within **269** was assigned following analysis of the HMBC spectrum. The formation of **269** therefore presumably results from mesylation of **266** followed by attack of the nitrogen atom at C(3) on the C(2)-mesylate group to give the corresponding aziridinium ion **268**. Subsequent attack of a residual chloride ion on the newly formed aziridinium intermediate **268** then gives **269**. The stereochemistry within **269** was therefore assigned on the basis of a mechanism involving two consecutive inversions of configuration at C(2).[64] It was found that the minimum number of equivalents of MsCl needed to give the best conversion to **266** (72% conversion) without the formation of any α-chloro-β-amino ester side product **269** was 2.5 equivalents. Reducing the reaction temperature was found to make no difference to the product distribution, and the use of DMAP as a nucleophilic catalyst only served to increase the formation of **269**. Repetition of the reaction using Ms_2O as an alternative mesylation reagent unfortunately resulted in a complex mixture of products. Therefore, subjection of the crude 72:28 mixture of **266** and **265** (obtained from the optimised mesylation reaction of **265** involving 2.5 equivalents of MsCl) to NaH in THF gave the desired cyclised product **267**, which was isolated in 54% yield and >99:1 dr over the two steps (Scheme 49).

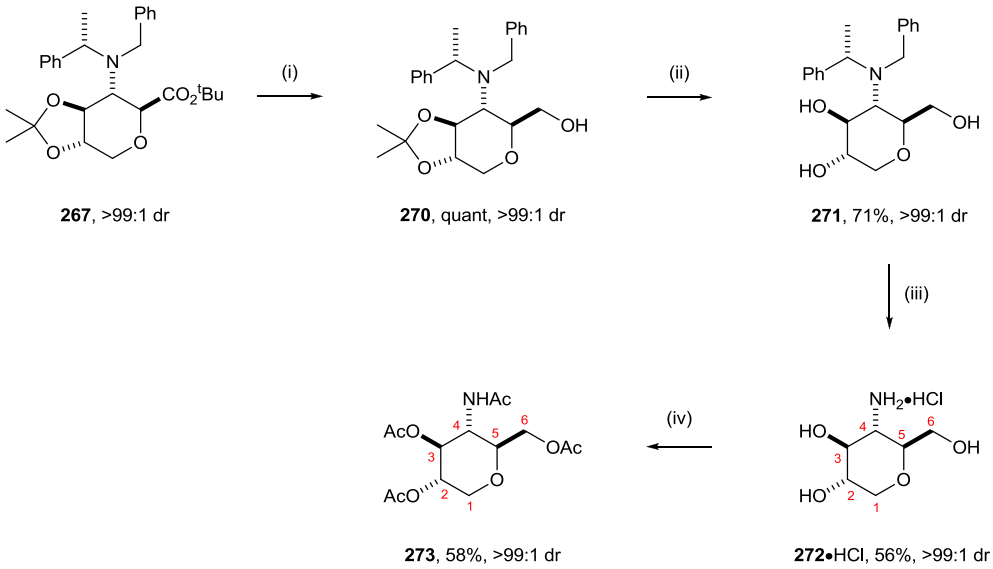


equiv of MsCl	266:265:269
2.0	56:44:0
2.5	**72:28:0**
3.0	65:0:35
4.0	55:0:45
10.0	0:0:100

Scheme 49. *Reagents and conditions:* (i) MsCl (2.5 equiv), pyridine, rt, 18 h; (ii) NaH, THF, rt, 16 h.

2.11.3.1 Synthesis of 1,4,5-trideoxy-1,5-epoxy-4-amino-D-glucose 272

Reduction of the ester moiety within **267** using $LiAlH_4$ gave **270** in quantitative yield and >99:1 dr. Subsequent acetal hydrolysis followed by hydrogenolysis gave 1,4,5-trideoxy-1,5-epoxy-4-amino-D-glucose **272**, which was isolated as the corresponding hydrochloride salt in 40% yield over the two steps. Further elaboration to the *N*,*O*,*O*,*O*-tetraacetate derivative **273** was achieved in 58% yield by treatment of **272**·HCl with Ac_2O in pyridine (Scheme 50). The relative configurations within both **272**·HCl and **273** were unambiguously established via single crystal X-ray diffraction analyses,[16] and the determination of a Flack *x* parameter[65] of –0.02(6) for the crystal structure of **272**·HCl allowed the absolute (*S*,*S*,*S*,*S*)-configuration within **272**·HCl (and therefore also the absolute configuration within **273**) to be unambiguously assigned (Figure 23).



Scheme 50. *Reagents and conditions:* (i) $LiAlH_4$, THF, –78 °C to rt, 16 h; (ii) HCl (3.0 M, aq), MeOH, 50 °C, 3 h; (iii) H_2 (1 atm), $Pd(OH)_2$/C, MeOH, rt, 18 h, then HCl, MeOH; (iv) Ac_2O, DMAP, pyridine, rt, 24 h.

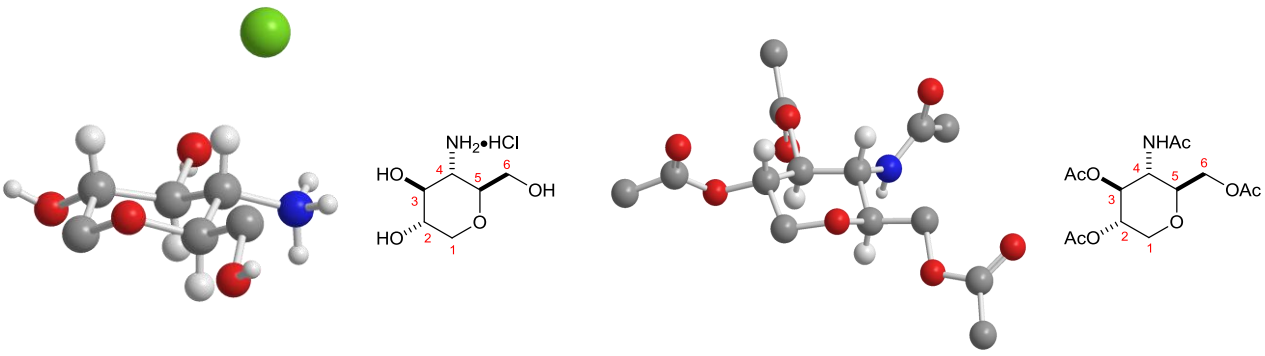
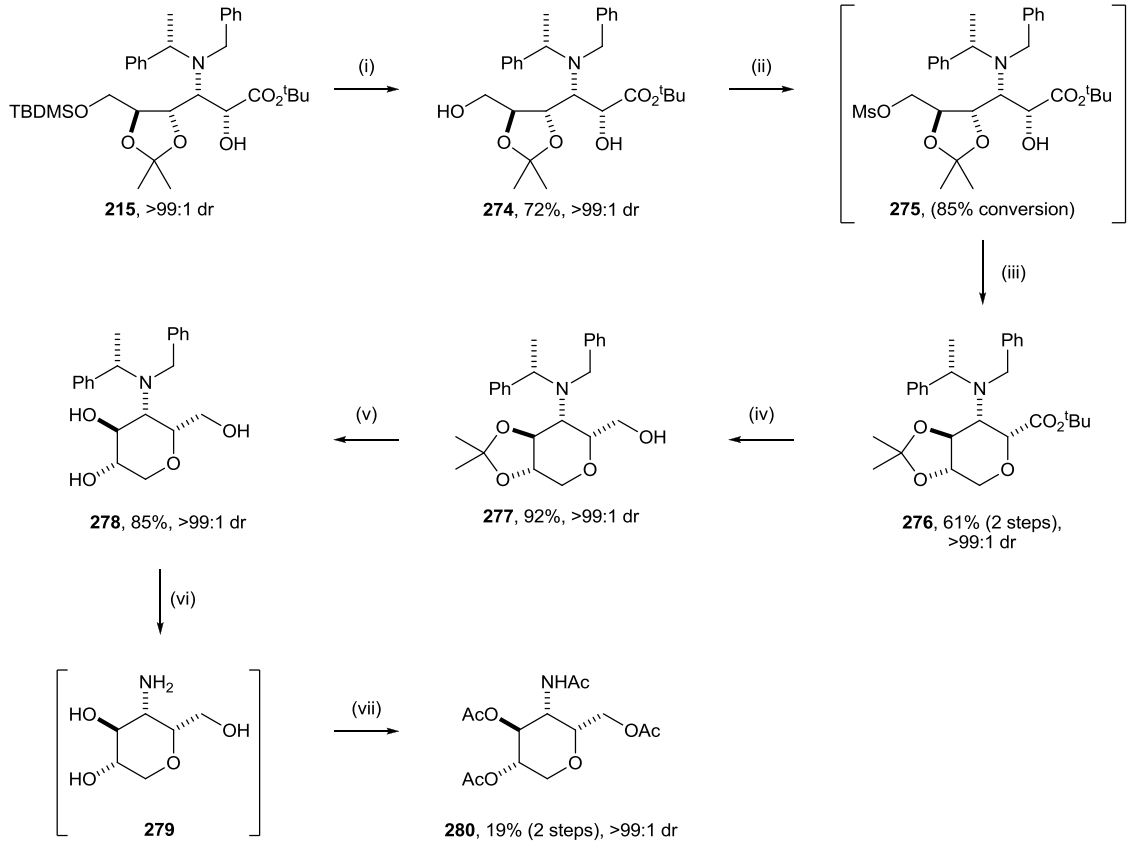


Figure 23. X-ray crystal structures of **272**·HCl [*left*] and **273** [*right*] (selected H atoms are omitted for clarity).

2.11.3.2 Synthesis of 1,4,5-trideoxy-1,5-epoxy-4-amino-L-idose 279

An identical sequence of reactions was next applied to α-hydroxy-β-amino ester **215** with the aim of ultimately synthesising another member of the 1,4,5-trideoxy-1,5-epoxy-4-aminohexose family. Desilylation of **215** gave diol **274** in 72% yield and in >99:1 dr. Treatment of **274** with MsCl under

the established optimal conditions gave **275** in 85% conversion, and subsequent treatment of the crude residue with NaH in THF effected cyclisation to **276**, which was isolated in 61% yield over the two steps. Tetrahydropyran **276** was then subjected to sequential ester reduction, acetal hydrolysis and hydrogenolysis steps to give 1,4,5-trideoxy-1,5-epoxy-4-amino-L-idose **279**, which was isolated as the *N*,*O*,*O*,*O*-tetraacetate derivative **280** in 15% yield over the four steps (Scheme 51).



Scheme 51. *Reagents and conditions:* (i) TBAF, THF, rt, 16 h; (ii) MsCl (2.5 equiv), pyridine, rt, 18 h; (iii) NaH, THF, rt, 16 h; (iv) $LiAlH_4$, THF, –78 °C to rt, 16 h; (v) HCl (3.0 M, aq), MeOH, 50 °C, 3 h; (vi) H_2 (1 atm), $Pd(OH)_2/C$, MeOH, rt, 18 h; (vii) Ac_2O, DMAP, pyridine, rt, 24 h.

2.12 Conclusions

In conclusion, the doubly diastereoselective conjugate addition reactions of (*R*)-**106** and (*S*)-**106** to chiral α,β-unsaturated esters **162** and **164** containing *cis*-dioxolane units have been shown to demonstrate "matching" and "mismatching" effects. The "matched" conjugate addition reaction of (*S*)-**106** to **162** [along with the already established "matched" conjugate addition reaction of (*S*)-**106** to **212**, the corresponding *trans*-dioxolane containing chiral α,β-unsaturated ester] was then successfully coupled with a highly diastereoselective *in situ* enolate oxidation using the requisite antipode of CSO **102**. This resulted in the production of the corresponding α-hydroxy-β-amino esters **218** and **213**, respectively, which were subsequently isolated in >99:1 dr. The diastereoselective aminohydroxylation reactions were found to proceed under the control of not only the C(3)- and/or C(α)-stereogenic centres of the intermediate (*Z*)-β-amino enolate, but also of those at C(4) and/or

C(5). A series of cyclisation strategies were then developed for these α-hydroxy-β-amino ester products, and it was found that the course of the cyclisation could be directed by the choice of protecting group strategy and the relative configuration of the dioxolane unit. Further elaboration then allowed access to imino sugar 1,4-dideoxy-1,4-imino-D-allitol **243**, the polyhydroxylated amino acids (2*S*,3*R*,4*S*)-3,4-dihydroxy-L-proline **246** and 1,4-dideoxy-1,4-imino-D-alluronic acid **251** (a trihydroxyhomoproline), and the amino sugars 1,4,5-trideoxy-1,5-epoxy-4-amino-D-glucose **272** and 1,4,5-trideoxy-1,5-epoxy-4-amino-L-idose **279**, which were isolated as the *N*,*O*,*O*,*O*-tetraacetate derivatives **273** and **280**, respectively (Figure 24).

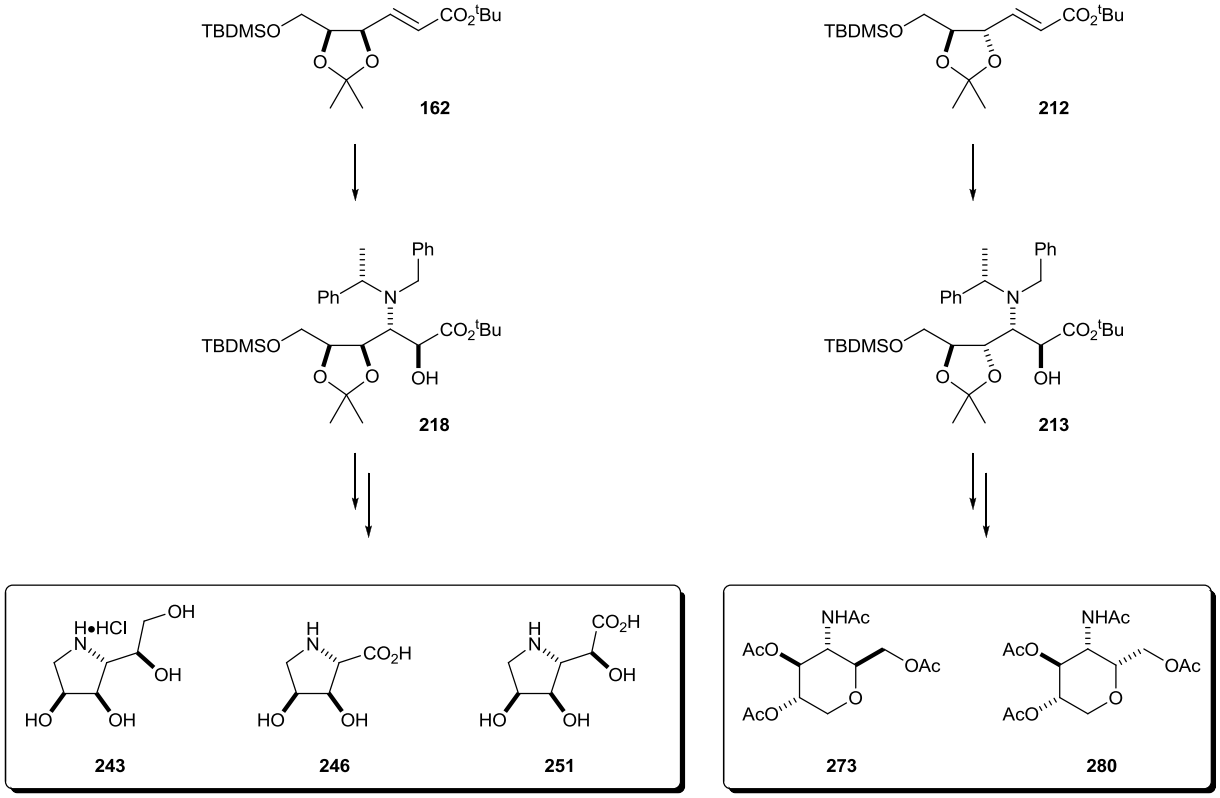


Figure 24. Successfully synthesised target amino polyols.

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[15] Methyl (triphenylphosphoranylidene)acetate **144** was prepared on a multigram scale from commercially available methyl bromoacetate.
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[60] Bal, B. S.; Childers, W. E., Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

[61] **255** was found to exist as a 61:39 mixture of rotamers in $CDCl_3$ at rt. High temperature ^{1}H NMR in PhMe-d_8 at 363 K was found to effect peak coalescence.

[62] Subjection of diol **253** to Appel conditions also resulted in the formation of **255**, however, the sample was contaminated with small amounts of some unidentifiable impurities.

[63] Davies *et al.* have noted that the ^{1}H NMR ^3J coupling constants for aziridines can be diagnostic. A $^3J_{2,3}$ value of ~2.5 Hz is usually observed for a *trans*-configured aziridine whilst a value of ~7 Hz is observed for a *cis*-configured aziridine; Davies, S. G.; Frost, A. B., unpublished results. The *trans*-configuration of the aziridine units within **259** and **260** was confirmed unambiguously by single crystal X-ray diffraction analysis, however, $^3J_{2,3}$ values of 2.5 Hz were also noted for both **259** and **260**.

[64] Upon standing for a significant amount of time (~3 months), the sample of **269** was found to undergo rearrangement (presumably also via aziridinium intermediate **268**) to give the corresponding α-amino-β-chloro ester**,** *tert*-butyl (2*S*,3*S*,4*R*,5*S*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-chloro-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(methylsulfonyloxy)hexanoate. The stereochemistry within the rearranged product was again assigned on the basis of a mechanism involving two consecutive inversions of configuration, one at C(2) and the other at C(3). The regiochemistry within the rearranged product was assigned following analysis of the HMBC spectrum.

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Chapter 3: Asymmetric Syntheses of Polyhydroxylated β-Amino Acids

3.1 The importance of β-amino acids

β-Amino acids are an important class of compounds which have been found to exhibit an array of interesting biological properties.[1] For example, the β-amino acids β-tyrosine and α-hydroxy-β-phenylalanine (shown in red) are subunits of the antibiotic edeine A **281** and the anticancer drug Taxol® **282**, respectively (Figure 25). β-Amino acids are also the building blocks of β-peptides[2,3] and of many peptidomimetics[4] and, more recently, have been found to play important roles as organocatalysts.[5]

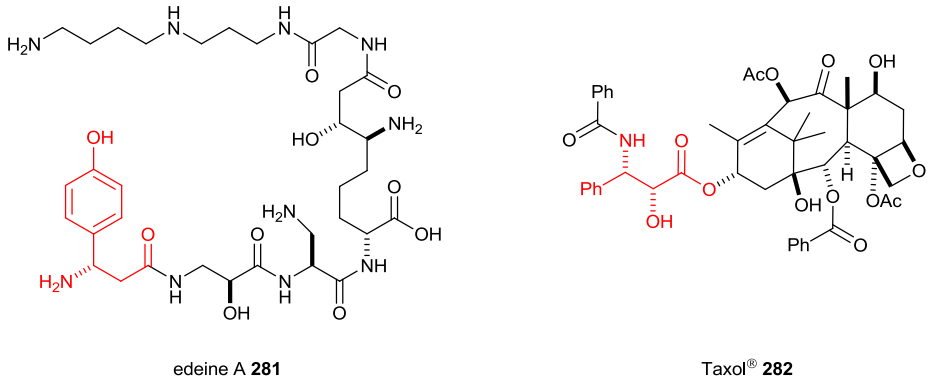
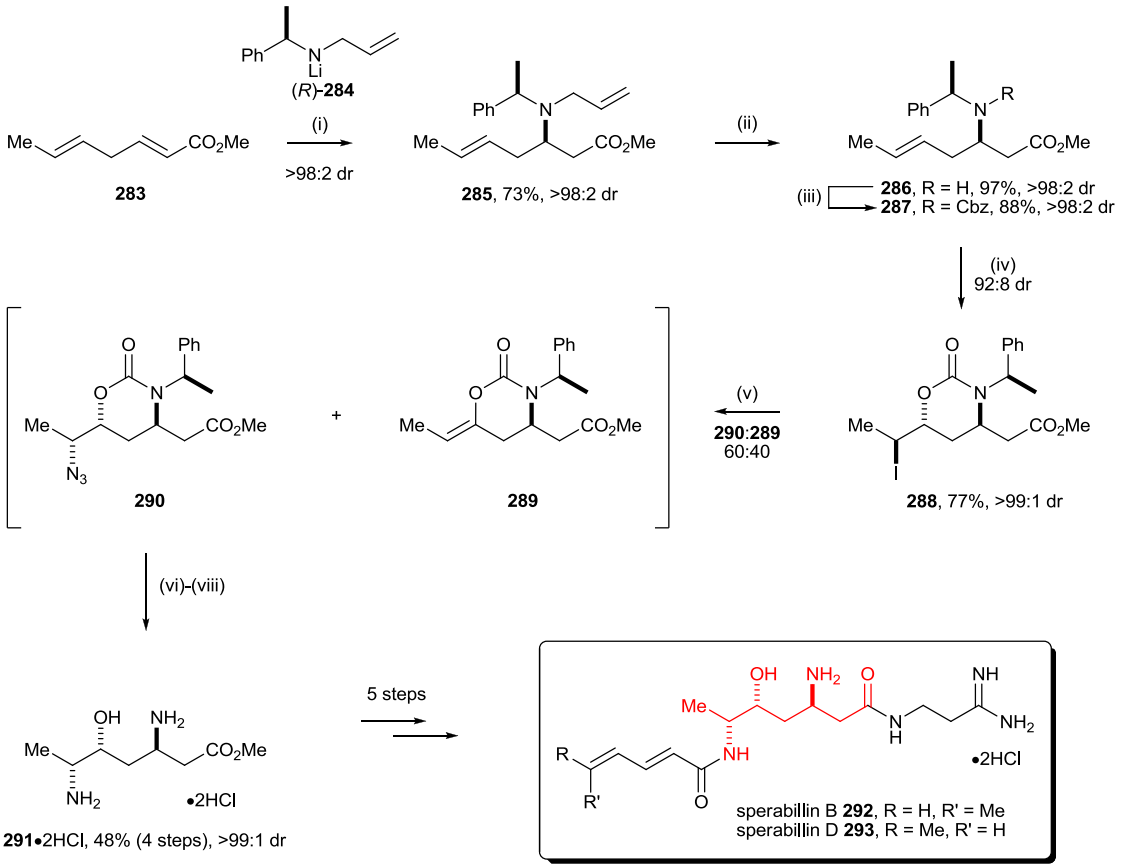


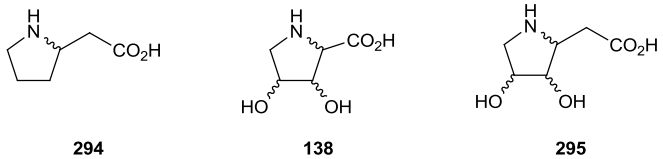
Figure 25. β-Amino acid containing drug molecules edeine A **281** and Taxol® **282**.

Many methods exist for the synthesis of β-amino acids and their derivatives, including Mannich reactions,[6] hydrogenation reactions,[7] and conjugate addition reactions.[8] For example, Davies *et al.* have reported the total asymmetric synthesis of the β-amino acid containing antibiotics sperabillin B **292** and sperabillin D **293**.[9] Conjugate addition of lithium (*R*)-*N*-allyl-*N*-(α-methylbenzyl)amide **284** to α,β,δ,ε-diunsaturated ester **283** gave β-amino ester **285** in 73% yield and >98:2 dr. Deallylation of **285** was achieved using Wilkinson's catalyst and the resultant deallylated product **286** was then treated with $(Cbz)_2O$ to give the corresponding *N*-Cbz protected β-amino ester **287** in 85% yield over the two steps. Iodocyclocarbamation of **287** using I_2 gave **288** in 92:8 dr, and **288** was subsequently isolated in 77% yield and >99:1 dr. Treatment of **288** with NaN_3 in DMF resulted in a 60:40 mixture of azide **290** and elimination product **289**. This mixture was subjected to sequential hydrogenolysis and acidic hydrolysis reactions, before treatment with $SOCl_2$ in MeOH to give methyl ester **291**, which was isolated as its dihydrochloride salt **291**·2HCl in 48% yield over the four steps. Dihydrochloride salt **291**·2HCl was then elaborated to sperabillin B **292** and sperabillin D **293** in a further five steps in each case (Scheme 52).



Scheme 52. *Reagents and conditions:* (i) (*R*)-**284**, THF, –78 °C, 2 h; (ii) Wilkinson's catalyst (5 mol%), MeCN/H_2O (v/v 4:1), reflux, 2 h; (iii) $(Cbz)_2O$, vacuum, 4 days; (iv) I_2, CH_2Cl_2, 0 °C, 5 h; (v) NaN_3, DMF/H_2O (v/v 25:1), 110 °C, 5 h; (vi) Pd/C, H_2 (1 atm), MeOH, rt, 18 h; (vii) HCl (5.0 M, aq), 100 °C, 24 h; (viii) MeOH, $SOCl_2$, reflux, 18 h.

Homoproline **294**, a pyrrolidine based β-amino acid, has been used both as an organocatalyst[5a,10] and in the construction of peptidomimetics,[11] and its conformational behaviour[12] and the secondary structure of its oligomers[13] has been studied. In addition to this, a range of derivatives of **294** have been synthesised which have been found to display significant biological activity.[14] It was highlighted in the preceding chapter that the diastereoisomers of dihydroxyproline **138** play important roles as glycosidase inhibitors,[15] and so it was therefore anticipated that the corresponding dihydroxyhomoprolines **295** might display similar useful properties. As such, an efficient route towards this type of compound would be highly desirable (Figure 26).



294 **138** **295**

Figure 26. Homoproline **294**, dihydroxyprolines **138** and dihydroxyhomoprolines **295**.

3.2 Chapter aims

The preceding chapter details how the doubly diastereoselective conjugate addition reactions of (*R*)-**106** and (*S*)-**106** to chiral α,β-unsaturated esters containing *cis*- and *trans*-dioxolane units were developed and applied to the synthesis of a range of biologically significant imino sugar and amino sugar targets. It was next anticipated that a range of deoxyamino sugars **298**-**301** could be synthesised

from α,β-unsaturated esters **296** containing *cis*- or *trans*-dioxolane units (themselves derived from naturally occurring D-pentose sugars) using doubly diastereoselective lithium amide conjugate addition methodology. Thus, conjugate addition of (*R*)-**106** or (*S*)-**106** followed by *in situ* oxidation of the intermediate enolates using the requisite antipode of CSO **102** was expected to give access to α-hydroxy-β-amino esters **297**, key intermediates required for the synthesis of **298**-**301**. Prior to this, however, the doubly diastereoselective nature of the lithium amide conjugate addition reactions to α,β-unsaturated esters **296** had to be investigated in order to first establish the "matching" and "mismatching" reagent/substrate pairings in the conjugate addition step (via protonation of the intermediate enolate with NH_4Cl). Furthermore, elaboration of β-amino esters **302** was expected to result in the synthesis of a range of dihydroxyhomoprolines **303**-**306** (Figure 27).

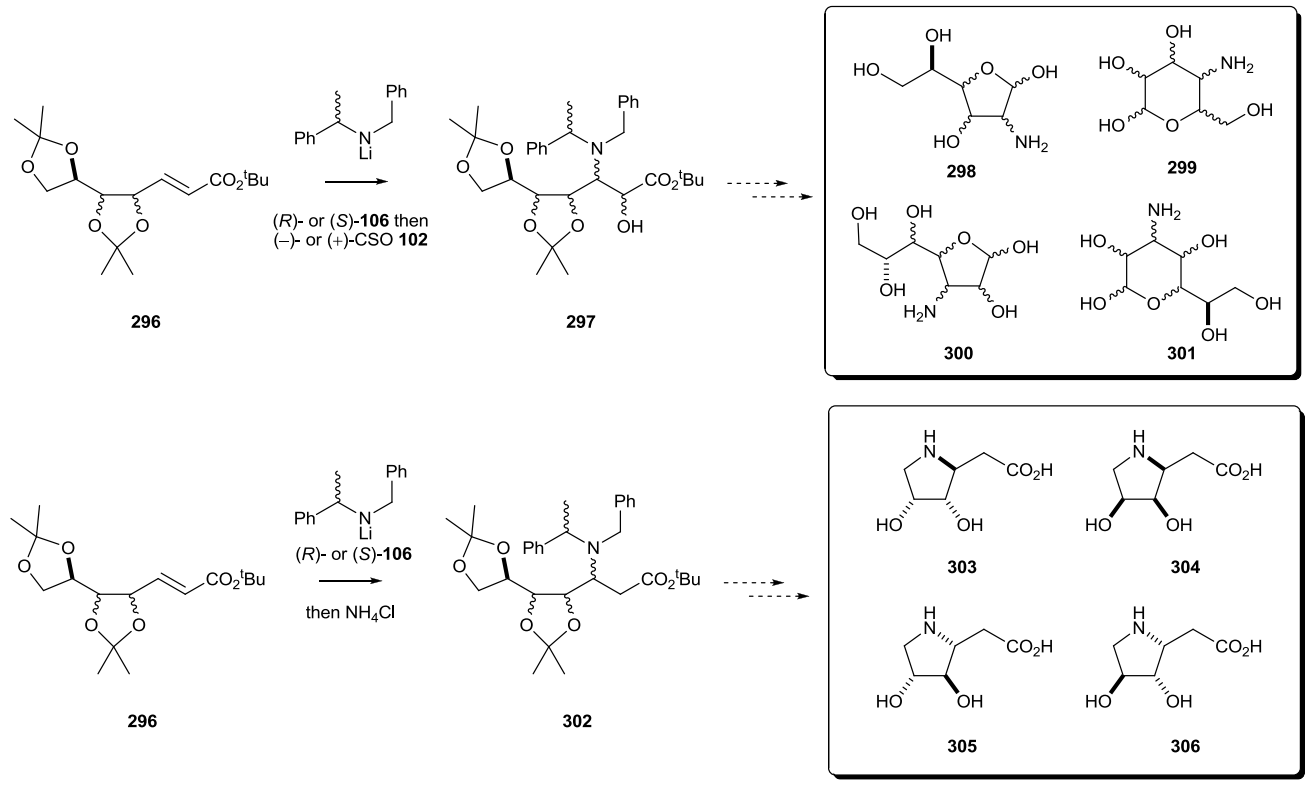
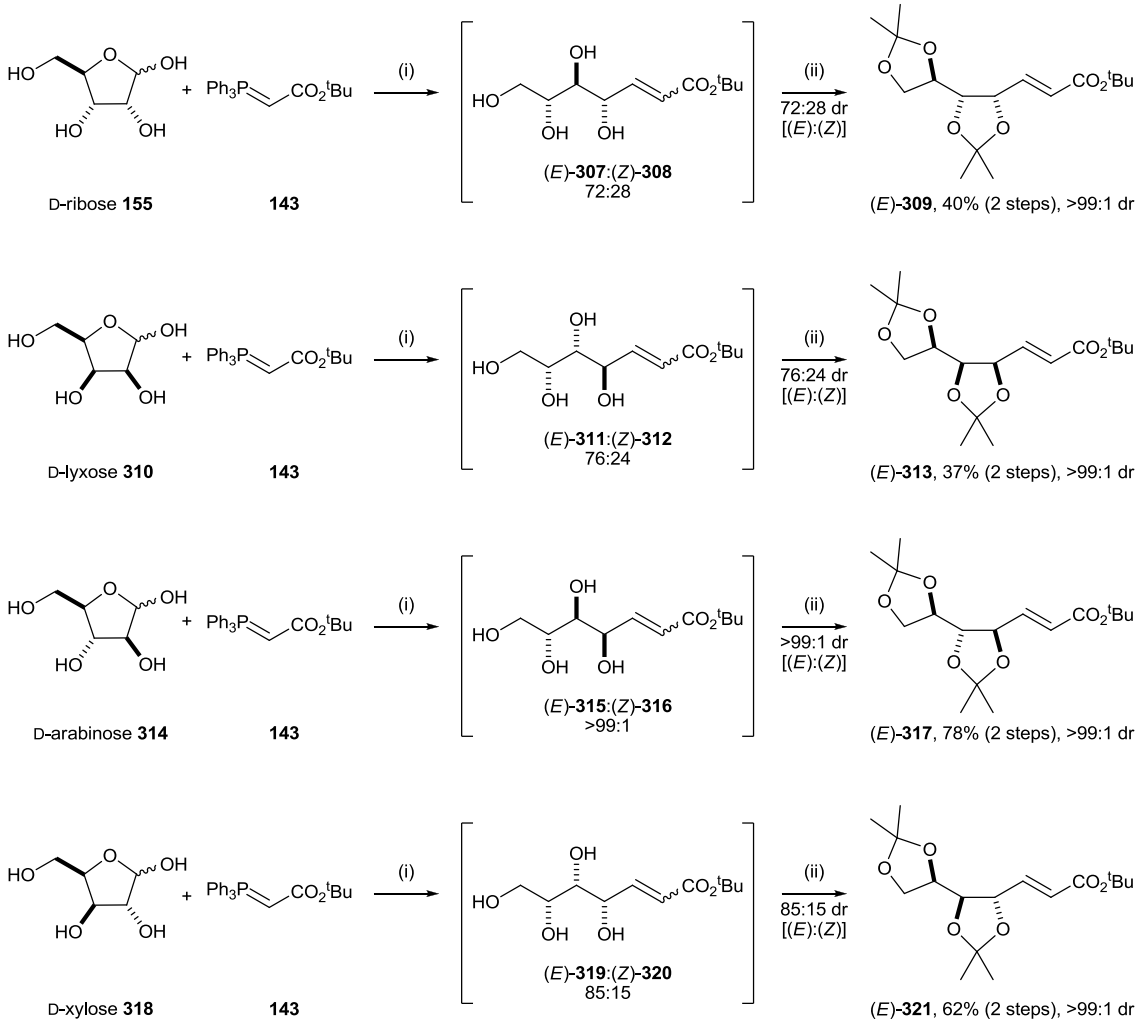


Figure 27. Doubly diastereoselective conjugate addition reactions of the antipodes of **106** to *cis*- and *trans*-dioxolane containing α,β-unsaturated esters **296**, and their application in target syntheses of deoxyamino sugars **298**-**301** and dihydroxyhomoprolines **303**-**306**.

3.3 Preparation of α,β-unsaturated esters containing *cis*- and *trans*-dioxolane units

It was envisaged that the α,β-unsaturated esters **309**, **313**, **317** and **321** required for the synthesis of deoxyamino sugars **298**-**301** and β-amino acids **303**-**306** could be synthesised from the naturally occurring pentose sugars D-ribose **155**, D-lyxose **310**, D-arabinose **314** and D-xylose **318**. Wittig reaction of a sugar using ylid **143** was expected to provide the corresponding tetraol, within which the free hydroxyl groups could easily be protected with isopropylidene groups. Thus, in the case of α,β-unsaturated ester **309**, subjection of D-ribose **155** to a Wittig reaction with **143** by heating in

dioxane[16] gave a 72:28 mixture of tetraols (*E*)-**307** and (*Z*)-**308**, respectively. The crude reaction mixture of (*E*)-**307** and (*Z*)-**308** was then treated with DMP and TsOH to give α,β-unsaturated ester (*E*)-**309** in 72:28 dr [(*E*):(*Z*)]. Purification via flash column chromatography then gave **309** in 40% yield and >99:1 dr [(*E*):(*Z*)] over the two steps. Repetition of this procedure using D-lyxose **310**, D-arabinose **314** and D-xylose **318** resulted in the production of the remaining α,β-unsaturated esters **313**, **317** and **321**, respectively, in 37-78% overall yield, and in >99:1 dr [(*E*):(*Z*)] in all cases (Scheme 53).



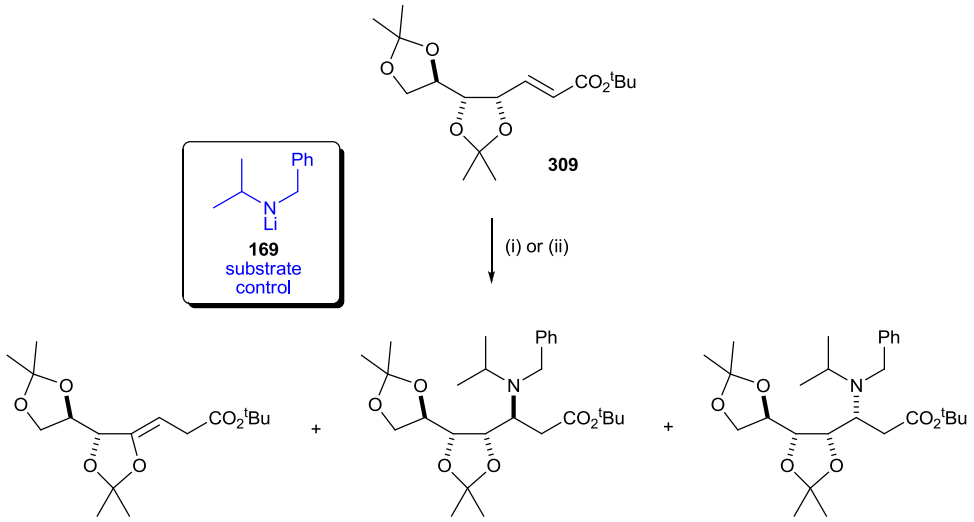
Scheme 53. *Reagents and conditions:* (i) dioxane, 90 °C, 6 h, then 50 °C, 12 h; (ii) DMP, TsOH, 18 h, rt.

A series of lithium amide conjugate addition reactions to α,β-unsaturated esters **309**, **313**, **317** and **321** could now be examined. In order to determine the inherent substrate control provided by the α,β-unsaturated ester substrates, the conjugate additions of achiral lithium *N*-isopropyl-*N*-benzylamide **169** and lithium dibenzylamide **168** were first performed. The stereochemical outcomes of the corresponding doubly diastereoselective conjugate additions of the antipodes of lithium *N*-benzyl-*N*-(α-methylbenzyl)amide **106** to **309**, **313**, **317** and **321** could then be predicted prior to their investigation.

3.4 Lithium amide conjugate additions to D-ribose derived α,β-unsaturated ester 309

3.4.1 Evaluation of substrate control

The substrate control provided by α,β-unsaturated ester **309** was first investigated via the conjugate additions of achiral lithium amides **168** and **169** to **309**. In THF at –78 °C, the conjugate addition of lithium *N*-isopropyl-*N*-benzylamide **169** to **309** resulted in a 93:7 mixture of β-amino ester **323** and (*Z*)-β,γ-unsaturated ester **322**,[17] respectively, which represented a diastereoselectivity of >99:1 dr for the conjugate addition reaction alone. Subsequent purification of the crude reaction mixture gave 3,4-*anti*-**323** in 73% yield and >99:1 dr. The relative configuration within **323** was unambiguously established via single crystal X-ray diffraction analysis,[18] with the absolute configuration within **323** being assigned relative to the known configurations of the D-ribose derived dioxolane units (Figure 28). Interestingly, in contrast to previous results, repetition of the reaction in Et_2O at –20 °C did not suppress the γ-deprotonation pathway, and instead served to enhance it: in this case an 80:20 mixture of **323** and **322** was recovered. The conjugate addition reaction to produce 3,4-*anti*-**323** did, however, still proceed in >99:1 dr under these conditions (Scheme 54).



conditions	product ratio A:B:C	dr B:C	yield B % (dr)
(i)	7:93:0	>99:1	73 (>99:1)
(ii)	20:80:0	>99:1	-

Scheme 54. *Reagents and conditions:* (i) **169**, THF, –78 °C, 2 h; (ii) **169**, Et_2O, –20 °C, 5 h.

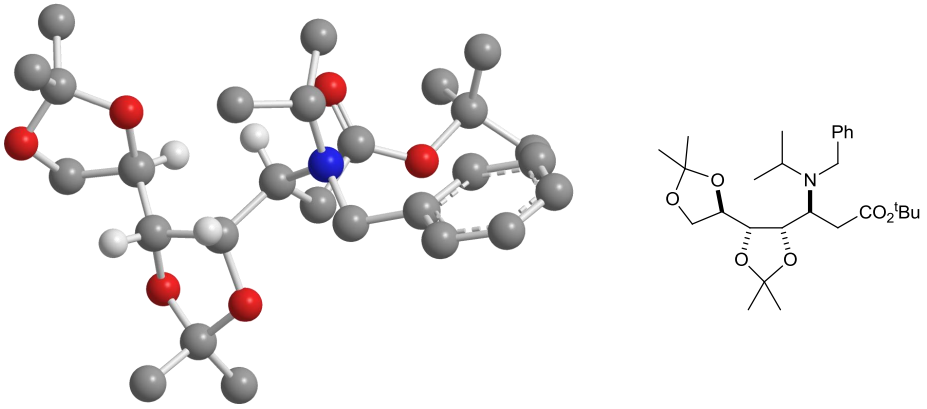
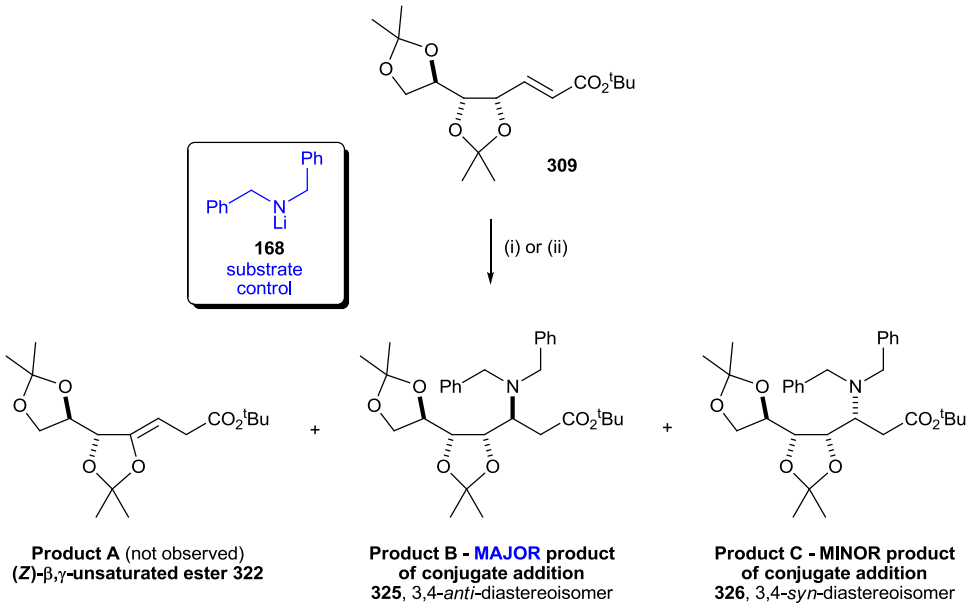


Figure 28. X-ray crystal structure of **323** (selected H atoms are omitted for clarity).

Conjugate addition of lithium dibenzylamide **168** to **309** was found to proceed with much lower levels of diastereofacial control than **169**, an observation which was also noted for the addition of **168** to **162** and **164** (*vide supra*). This observation has previously been attributed to the greater reactivity (and therefore faster conjugate addition reaction) of lithium amide **168**.[17a] In THF at –78 °C, β-amino esters 3,4-*anti*-**325** and 3,4-*syn*-**326** were produced in 90:10 dr, respectively. Subsequent purification via flash column chromatography gave major product 3,4-*anti*-**325** in 55% yield and >99:1 dr. Surprisingly, no evidence of γ-deprotonation product **322** was observed during this reaction. Repetition of the reaction in Et_2O at –20 °C resulted in a 62:38 mixture of **325** and **326**, respectively, and again side product **322** was absent from the ^1H NMR spectrum of the crude reaction mixture (Scheme 55). The absolute configurations within **325** and **326** were later unambiguously established via chemical correlation (*vide infra*).



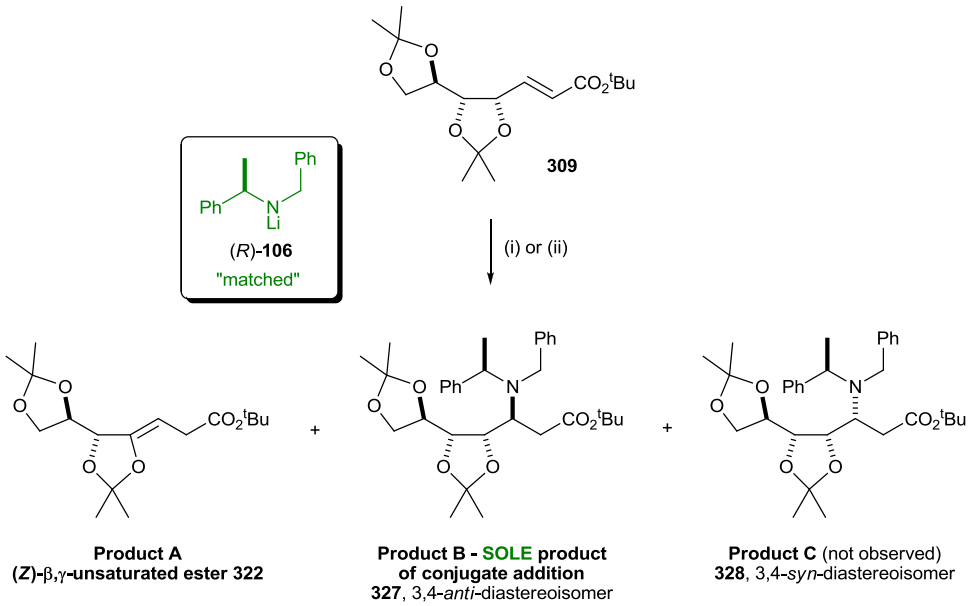
conditions	product ratio A:B:C	dr B:C	yield B % (dr)
(i)	0:90:10	90:10	55 (>99:1)
(ii)	0:62:38	62:38	-

Scheme 55. *Reagents and conditions:* (i) **168**, THF, –78 °C, 2 h; (ii) **168**, Et_2O, –20 °C, 5 h.

The exclusive (in the case of **169**) or preferential (in the case of **168**) production of the 3,4-*anti* β-amino esters **323** and **325** upon lithium amide conjugate addition to α,β-unsaturated ester **309** suggests that the substrate control is extremely high and serves to direct conjugate addition of the lithium amides to the *Si* face.

3.4.2 Evaluation of "matching" and "mismatching" effects

With the sense of substrate control now established, it was predicted that the conjugate addition of chiral lithium amide (*R*)-**106** to **309** would represent the doubly diastereoselective "matched" case due to the known diastereofacial selectivity of this lithium amide.[19] Thus, the conjugate addition of (*R*)-**106** to **309** was attempted in THF at −78 °C which led to 3,4-*anti*-**327** being produced in >99:1 dr. β-Amino ester **327** was subsequently isolated in 94% yield and >99:1 dr. The corresponding conjugate addition reaction in Et_2O at −20 °C gave a 97:3 mixture of β-amino ester **327** and (*Z*)-β,γ-unsaturated ester **322**, respectively. The absolute configuration within **327** was later unambiguously established via chemical correlation (*vide infra*). The formation of 3,4-*anti*-**327** as the sole product of conjugate addition served to support the prediction that the conjugate addition of (*R*)-**106** to **309** represents the "matched" combination of chiral reagent and chiral substrate (Scheme 56).

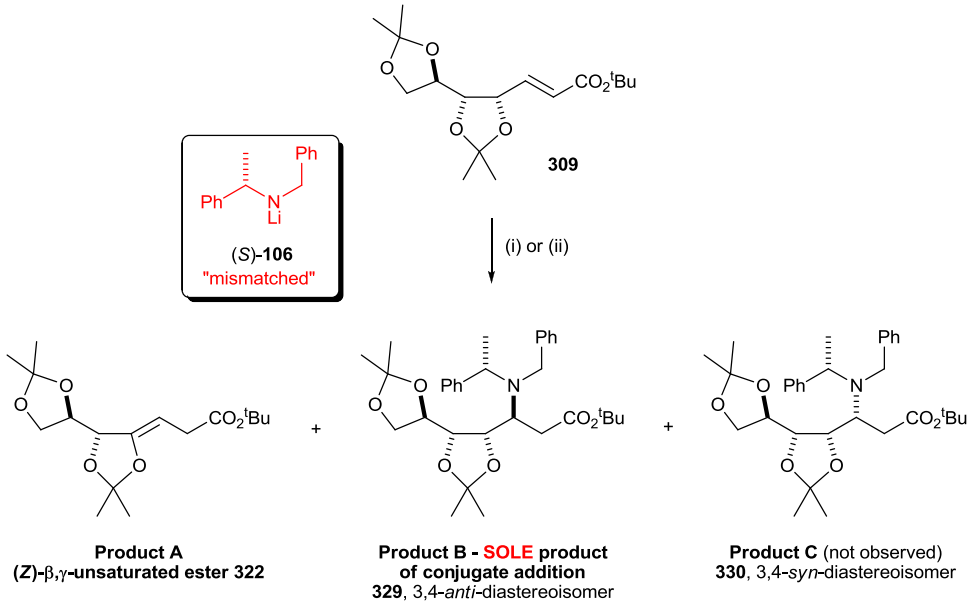


conditions	product ratio A:B:C	dr B:C	yield B % (dr)
(i)	0:100:0	>99:1	94 (>99:1)
(ii)	3:97:0	>99:1	-

Scheme 56. *Reagents and conditions:* (i) (*R*)-**106**, THF, −78 °C, 2 h; (ii) (*R*)-**106**, Et_2O, −20 °C, 5 h.

On the other hand, the conjugate addition of (*S*)-**106** to **309** was expected to represent the "mismatched" reagent/substrate pairing. The conjugate addition of (*S*)-**106** to **309** in THF at −78 °C gave a 24:76 mixture of β-amino ester **329** and (*Z*)-β,γ-unsaturated ester **322**, respectively.

Furthermore, upon consideration of the conjugate addition reaction alone, the observation that only 3,4-*anti*-**329** is produced suggests that the reaction is under the dominant control of the substrate **309**, rather than the lithium amide (*S*)-**106**. Subsequent purification via flash column chromatography gave 3,4-*anti*-**329** in 15% isolated yield and >99:1 dr, whilst (*Z*)-β,γ-unsaturated ester **322** was isolated in 75% yield and >99:1 dr. Repetition of the reaction in Et_2O at –20 °C gave a 70:30 mixture of **329** and **322**, respectively, indicating that these alternative conditions do not completely suppress the undesirable formation of **322** in this case. The absolute configuration within **329** was later unambiguously established via chemical correlation (*vide infra*) (Scheme 57).



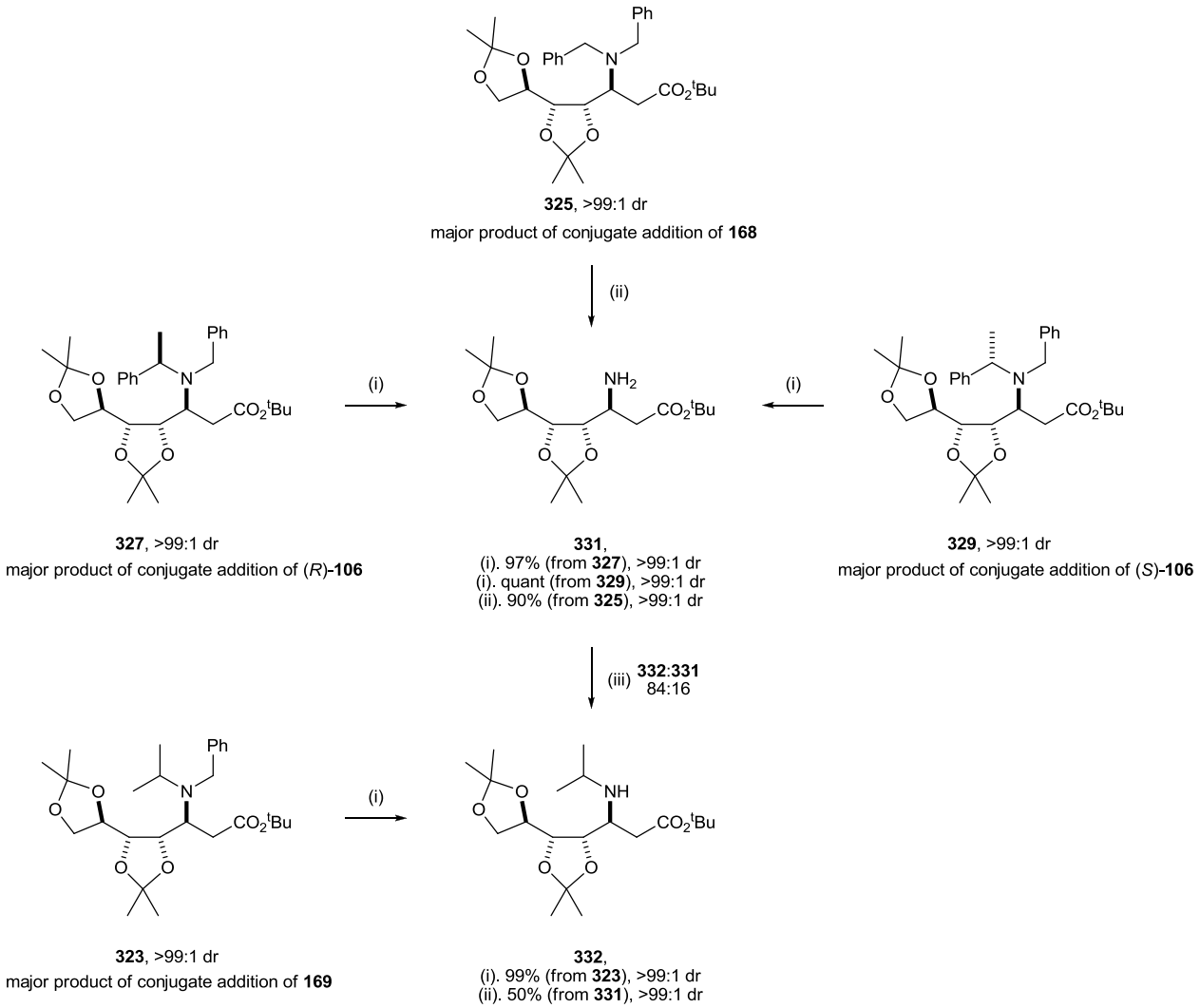
conditions	product ratio A:B:C	dr B:C	yield A % (dr)	yield B % (dr)
(i)	76:24:0	>99:1	75 (>99:1)	15 (>99:1)
(ii)	30:70:0	>99:1	-	-

Scheme 57. *Reagents and conditions:* (i) (*S*)-**106**, THF, –78 °C, 2 h; (ii) (*S*)-**106**, Et_2O, –20 °C, 5 h.

3.4.3 Correlation experiments

As 3,4-*anti*-**323** proved to be crystalline its absolute configuration had already been unambiguously established via X-ray single crystal diffraction analysis. A series of hydrogenolytic/reductive alkylation experiments were next conducted in order to correlate the configurations of the C(3)-stereogenic centres within all other β-amino ester products from this series of conjugate addition reactions. Hydrogenolysis of 3,4-*anti*-**327** (>99:1 dr) using $Pd(OH)_2/C$ gave primary β-amino ester 3,4-*anti*-**331** in 97% yield and >99:1 dr. Similar treatment of a sample of 3,4-*anti*-**329** [the sole product of conjugate addition in the "mismatched" reaction of (*S*)-**106** and **309**] gave **331** in quantitative yield and >99:1 dr. Subjection of 3,4-*anti*-**325** (>99:1 dr) to the same hydrogenolysis conditions gave **331** in 90% yield and >99:1 dr. The ^{1}H NMR spectra of the samples of **331** obtained from hydrogenolysis of **325**, **327** and **329** were found to be in complete agreement thereby serving to

confirm that these species are homochiral at C(3). Hydrogenolysis of 3,4-*anti*-**323**, obtained from the conjugate addition of **169** to **309**, gave an authentic sample of *N*-isopropyl substituted β-amino ester 3,4-*anti*-**332** in 99% yield and >99:1 dr. In order to correlate this result with results from the earlier hydrogenolysis reactions, primary β-amino ester **331** (>99:1 dr) was subjected to a reductive alkylation reaction using $NaBH_3CN$ and acetone to give **332** in 50% yield and >99:1 dr. The ^1H NMR spectra of the two samples of 3,4-*anti*-**332** were found to be in complete agreement, thus establishing the absolute configuration within **331** and therefore also those within **325**, **327** and **329** (Scheme 58).



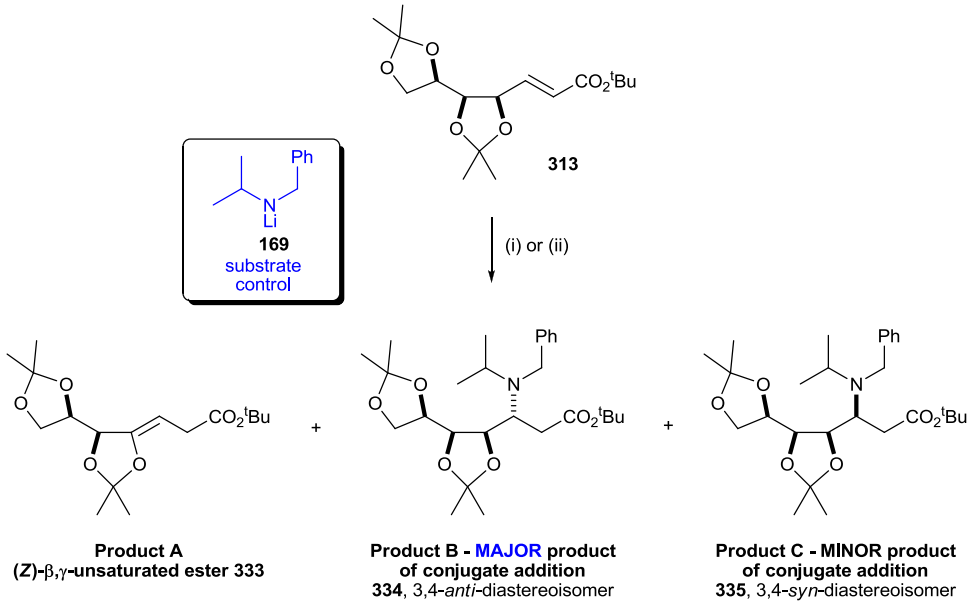
Scheme 58. *Reagents and conditions:* (i) $Pd(OH)_2/C$, H_2 (1 atm), EtOAc, rt, 18 h; (ii) $Pd(OH)_2/C$, H_2 (1 atm), MeOH, rt, 18 h; (iii) $NaBH_3CN$, acetone, MeOH, rt, 18 h.

With these results in hand, an investigation into the analogous lithium amide conjugate addition reactions to α,β-unsaturated esters **313**, **317** and **321** derived from D-lyxose **310**, D-arabinose **314** and D-xylose **318** was initiated.

3.5 Lithium amide conjugate additions to D-lyxose derived α,β-unsaturated ester 313

3.5.1 Evaluation of substrate control

The conjugate addition reactions of achiral lithium amides **168** and **169** to α,β-unsaturated ester **313** were first performed in order to determine the substrate control provided by **313**. Under standard conditions of THF at –78 °C, conjugate addition of lithium *N*-isopropyl-*N*-benzylamide **169** to **313** resulted in a 76:8:16 mixture of β-amino esters **334** and **335**, and (*Z*)-β,γ-unsaturated ester **333**, respectively. An 83:17 mixture of 3,4-*anti*-**334** (>99:1 dr) and (*Z*)-β,γ-unsaturated ester **333**[20] (>99:1 dr) was subsequently isolated. Upon changing the reaction conditions to Et_2O at –20 °C, the pathway resulting in the formation of **333** was found to be completely suppressed to give an 81:19 mixture of **334** and **335**, respectively. The absolute configurations within **334** and **335** were later unambiguously established via chemical correlation (*vide infra*) (Scheme 59).

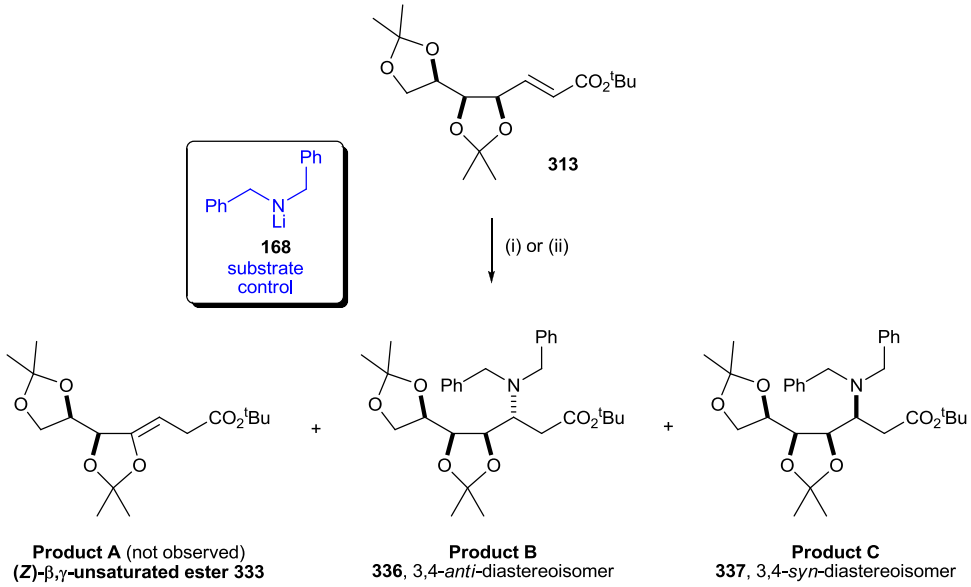


conditions	product ratio A:B:C	dr B:C	yield B % (dr)
(i)	16:76:8	90:10	-[a]
(ii)	0:81:19	81:19	-

Scheme 59. *Reagents and conditions:* (i) **169**, THF, –78 °C, 2 h; (ii) **169**, Et_2O, –20 °C, 5 h. [[a] In this case, **334** (>99:1 dr) and **333** (>99:1 dr) were isolated as an 83:17 mixture].

As was the case for α,β-unsaturated ester **309**, no evidence of (*Z*)-β,γ-unsaturated ester **333** was observed upon conjugate addition of lithium dibenzylamide **168** in THF at –78 °C, and a 50:50 mixture of β-amino esters 3,4-*anti*-**336** and 3,4-*syn*-**337** resulted. β-Amino esters **336** and **337** were subsequently isolated in 40 and 33% yield, respectively, and in >99:1 dr in each case. Repetition of the reaction in Et_2O at –20 °C also resulted in a 50:50 mixture of **336** and **337** (Scheme 60). The sample of 3,4-*syn*-**337** proved to be crystalline and so the relative configuration within **337** was unambiguously established via single crystal X-ray diffraction analysis,[18] with the absolute configuration within **337** being assigned relative to the known configurations of the D-lyxose derived

dioxolane units. The relative and absolute configurations within 3,4-*anti*-**336** could therefore also be unambiguously assigned (Figure 29).



conditions	product ratio A:B:C	dr B:C	yield B % (dr)	yield C % (dr)
(i)	0:50:50	50:50	40 (>99:1)	33 (>99:1)
(ii)	0:50:50	50:50	-	-

Scheme 60. *Reagents and conditions:* (i) **168**, THF, –78 °C, 2 h; (ii) **168**, Et_2O, –20 °C, 5 h.

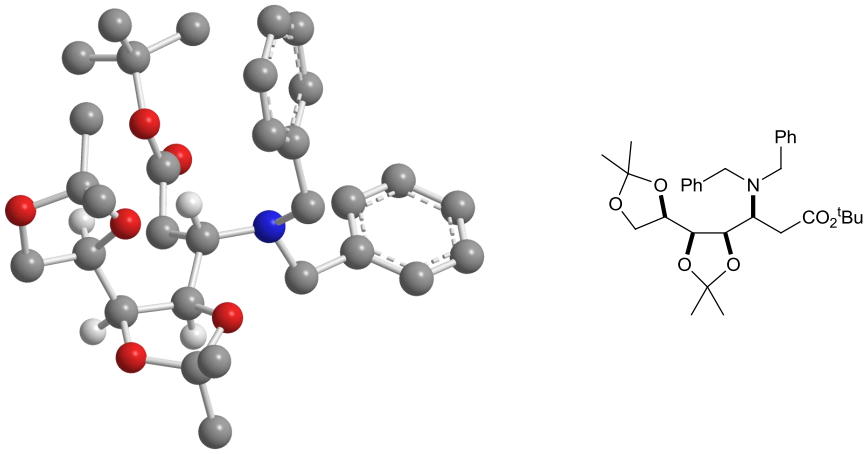
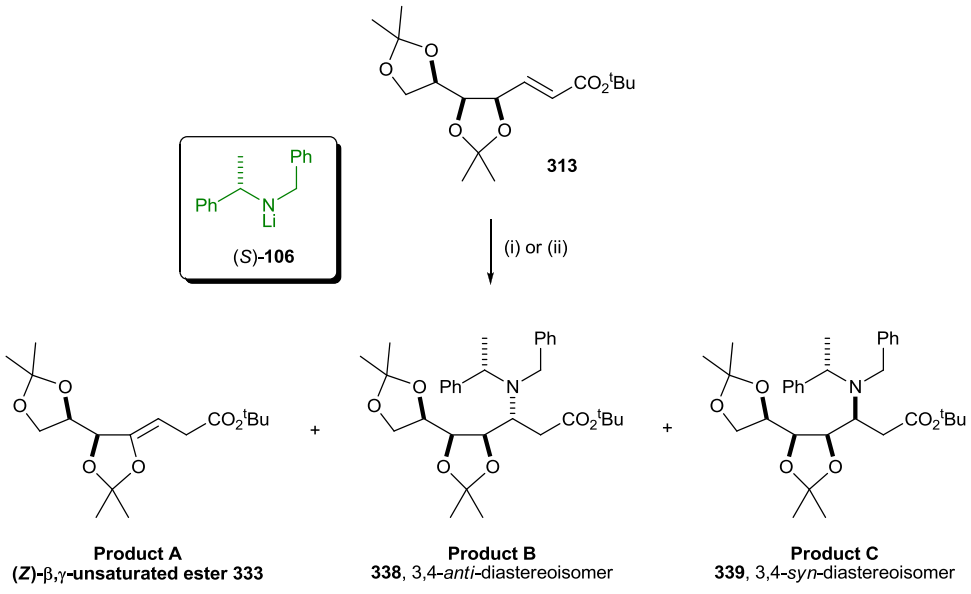


Figure 29. X-ray crystal structure of **337** (selected H atoms are omitted for clarity).

As the conjugate addition reaction of **168** to **313** resulted in a 50:50 mixture of the diastereoisomeric β-amino esters **336** and **337**, this indicates that essentially no substrate control is provided by α,β-unsaturated ester **313** upon conjugate addition of **168**. Fortunately, the conjugate addition of **169** to **313** had resulted in a strong preference for the formation of 3,4-*anti*-**334**, which therefore suggests that the α,β-unsaturated ester substrate **313** favours a conjugate addition pathway involving attack of the lithium amide reagent **169** on the *Re* face.

3.5.2 Evaluation of "matching" and "mismatching" effects

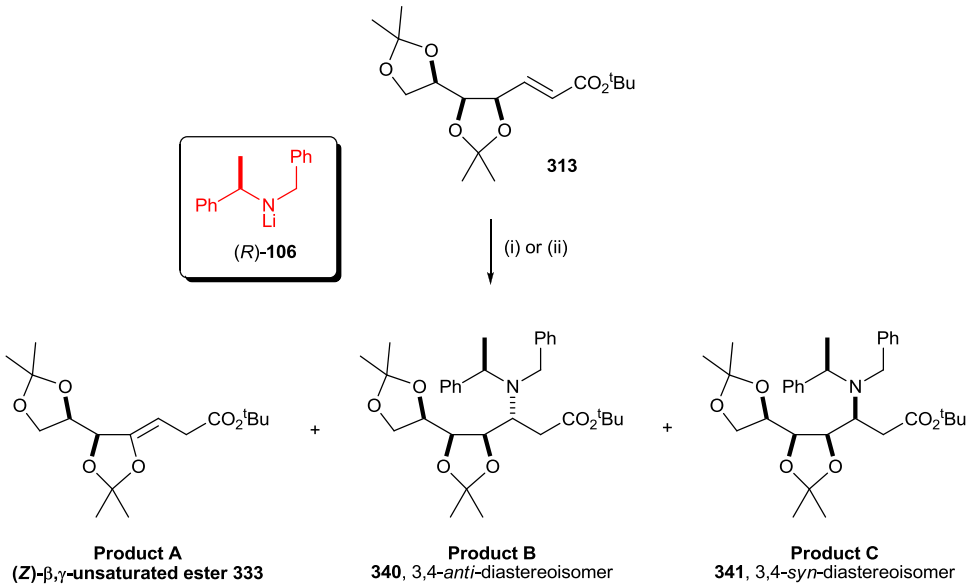
Based upon the substrate control provided by **313** (during conjugate addition of **169**) and the known diastereofacial selectivity of lithium amide (*S*)-**106**, it was expected that this reagent/substrate pairing would represent the doubly diastereoselective "matched" reaction. The conjugate addition of (*S*)-**106** to **313** was found to give a 71:21:8 mixture of β-amino esters **338** and **339**, and (*Z*)-β,γ-unsaturated ester **333**, respectively, which represented 77:23 dr (**338**:**339**) for the conjugate addition reaction. Subsequent purification via flash column chromatography resulted in 3,4-*syn*-**339** being isolated in 21% yield and >99:1 dr. An 86:14 mixture of 3,4-*anti*-**338** (>99:1 dr) and (*Z*)-β,γ-unsaturated ester **333** (>99:1 dr), respectively, was also isolated. The diastereoselectivity of this reaction (77:23 dr) is not only lower than would be expected from the known high diastereoselectivity of the conjugate addition of (*S*)-**106** to an achiral α,β-unsaturated ester,[21] but it is also inferior to that observed under substrate control alone (90:10 dr for the conjugate addition of **169** to **313**). This suggests that some other effect may be in operation to affect the normal mode of action of the lithium amide and therefore result in a lower than expected diastereoisomeric ratio for the reaction. When the same reaction was performed in Et_2O at –20 °C, a 42:52:6 mixture of **338**, **339** and **333** was isolated, which indicated that these conditions had resulted not only in a lower level of diastereoselectivity but also a reversal in the sense of diastereofacial control due to the slight preference for the formation of 3,4-*syn*-**339** (45:55 dr **338**:**339**). The absolute configurations within **338** and **339** were later unambiguously established via chemical correlation (*vide infra*) (Scheme 61).



conditions	product ratio A:B:C	dr B:C	yield B % (dr)	yield C % (dr)
(i)	8:71:21	77:23	-[a]	21 (>99:1)
(ii)	6:42:52	45:55	-	-

Scheme 61. *Reagents and conditions:* (i) (*S*)-**106**, THF, –78 °C, 2 h; (ii) (*S*)-**106**, Et_2O, –20 °C, 5 h. [[a] In this case, **338** (>99:1 dr) and **333** (>99:1 dr) were isolated as an 86:14 mixture].

The conjugate addition of lithium amide (*R*)-**106** to **313** was next investigated. When the reaction was conducted under the standard conditions of THF at −78 °C, a 15:23:62 mixture of β-amino esters **340** and **341**, and (*Z*)-β,γ-unsaturated ester **333**, respectively, resulted, from which a 12:88 mixture of **340** and **333** was isolated. Upon consideration of the products of conjugate addition alone, 3,4-*anti*-**340** and 3,4-*syn*-**341** were produced in 40:60 dr, respectively. The diastereoselectivity of this reaction is again inferior (and opposite) to that observed under substrate control alone (90:10 dr for the conjugate addition of **169** to **313**). When the reaction was instead conducted in Et_2O at −20 °C, the γ-deprotonation pathway was found to be completely suppressed and resulted in a 66:34 mixture of β-amino esters 3,4-*anti*-**340** and 3,4-*syn*-**341**, respectively, from which **340** was isolated in 42% yield and >99:1 dr, whilst **341** was isolated in 16% yield and 91:9 dr. The absolute configurations within **340** and **341** were later unambiguously established via chemical correlation (*vide infra*). This set of reactions therefore represents another example of a reversal in diastereofacial selectivity upon changing the reaction conditions from THF at −78 °C to Et_2O at −20 °C (Scheme 62).



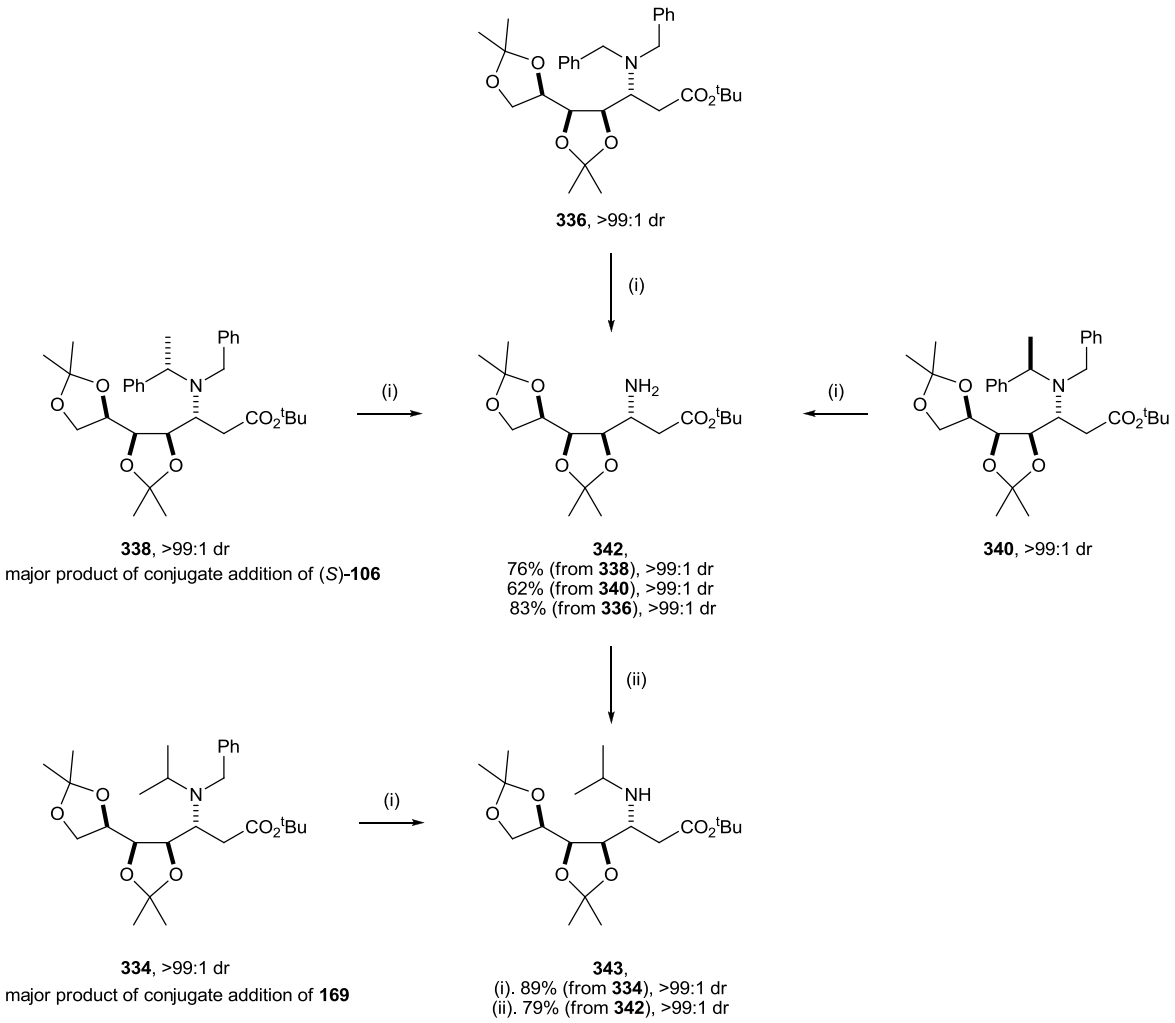
conditions	product ratio A:B:C	dr B:C	yield A % (dr)	yield B % (dr)	yield C % (dr)
(i)	62:15:23	40:60	-[a]	-	-
(ii)	0:66:34	66:34	-	42 (>99:1)	16 (91:9)

Scheme 62. *Reagents and conditions:* (i) (*R*)-**106**, THF, −78 °C, 2 h; (ii) (*R*)-**106**, Et_2O, −20 °C, 5 h. [[a] In this case, **333** (>99:1 dr) and **340** (>99:1 dr) were isolated as an 88:12 mixture].

This series of lithium amide conjugate addition reactions to **313** had shown that the sense of substrate control provided by **313** is not augmented upon conjugate addition of either antipode of chiral lithium amide **106**. Resultantly, the factors which influence the substrate and reagent control are not independent in this system and so the reactions cannot be classified according to the classical "matched" and "mismatched" definitions of Masamune *et al.*[17b,22]

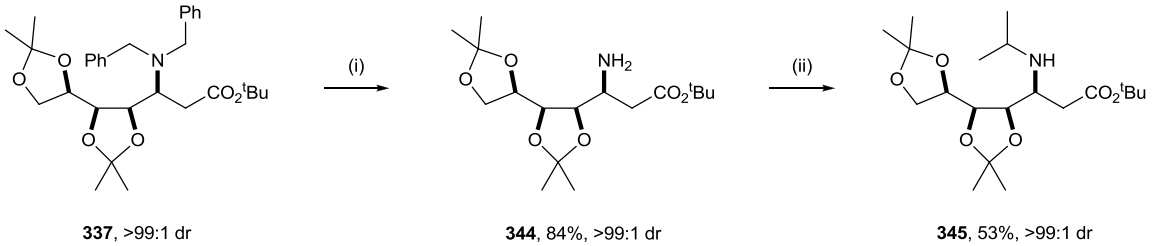
3.5.3 Correlation experiments

The absolute configurations within 3,4-*anti*-**336** and 3,4-*syn*-**337** had already been unambiguously established via single crystal X-ray diffraction analysis of **337** (*vide supra*) and so a series of hydrogenolytic/reductive alkylation correlation experiments were next performed to establish the configurations of the remaining β-amino esters generated during the conjugate addition reactions of (*S*)-**106**, (*R*)-**106** and **169** to **313**. In the first instance, hydrogenolysis of 3,4-*anti*-**336** (>99:1 dr) gave an authentic sample of primary β-amino ester **342** in 83% yield and >99:1 dr. Hydrogenolysis of a sample of **338** [the major product of conjugate addition from the reaction of (*S*)-**106** and **313**] then gave **342** in 76% yield and >99:1 dr whilst hydrogenolysis of a sample of **340** (>99:1 dr) also gave **342** in 62% yield and >99:1 dr. The ^{1}H NMR spectra of both samples of **342** were found to be in complete agreement with that of the authentic sample of **342**, thereby serving to establish the absolute configuration within **338** and **340**. Subjection of **342** (>99:1 dr) to a reductive alkylation reaction using $NaBH_3CN$ and acetone gave *N*-isopropyl substituted β-amino ester **343** in 79% yield and >99:1 dr. Hydrogenolysis of **334** (>99:1 dr) then gave **343** in 89% yield and >99:1 dr, with this sample found to display an identical ^{1}H NMR spectrum to that of the authentic sample of **343**. This therefore allowed the absolute configuration within **334** to also be established (Scheme 63).



Scheme 63. *Reagents and conditions:* (i) $Pd(OH)_2/C$, H_2 (1 atm), EtOAc, rt, 18 h; (ii) $NaBH_3CN$, acetone, MeOH, rt, 18 h.

Hydrogenolysis of 3,4-*syn*-**337** gave an authentic sample of primary β-amino ester **344** in 84% yield and >99:1 dr. Subjection of this sample to reductive alkylation conditions ($NaBH_3CN$/acetone) gave *N*-isopropyl β-amino ester **345** in 53% yield and >99:1 dr. The ^1H NMR spectra of **344** and **345** were found to be significantly different from those of **342** and **343**, respectively, thereby serving to further confirm the assigned configurations within this series of D-lyxose derived β-amino esters (Scheme 64).



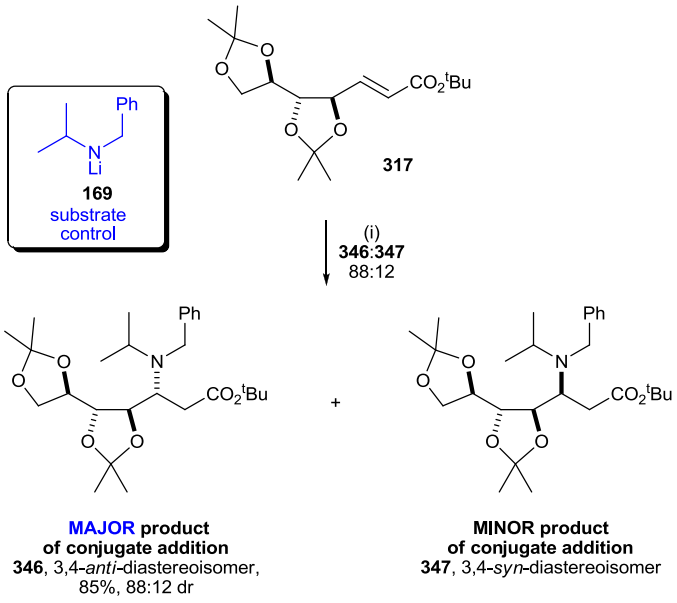
Scheme 64. *Reagents and conditions:* (i) $Pd(OH)_2/C$, H_2 (1 atm), EtOAc, rt, 18 h; (ii) $NaBH_3CN$, acetone, MeOH, rt, 18 h.

With the series of conjugate addition reactions to **313**, the α,β-unsaturated ester derived from D-lyxose **310** now completed, attention was turned to the analogous set of conjugate addition reactions involving **317**, the *trans*-dioxolane containing α,β-unsaturated ester derived from D-arabinose **314**.

3.6 Lithium amide conjugate additions to D-arabinose derived α,β-unsaturated ester 317

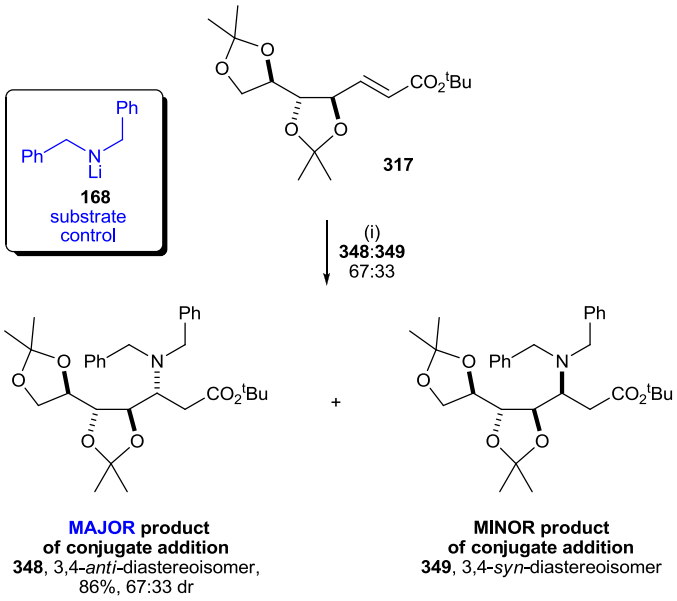
3.6.1 Evaluation of substrate control

The conjugate addition reaction of **169** to **317** was investigated first. Upon treatment of **317** with **169** in THF at –78 °C, an 88:12 mixture of β-amino esters 3,4-*anti*-**346** and 3,4-*syn*-**347**, respectively, was produced. Subsequent purification via flash column chromatography allowed the isolation of 3,4-*anti*-**346** in 85% yield and 88:12 dr. The absolute configurations within **346** and **347** were later unambiguously assigned via chemical correlation (*vide infra*). The absence of a product arising from a pathway involving the γ-deprotonation of α,β-unsaturated ester **317** under these reaction conditions is consistent with previous studies conducted by Davies *et al.* for the conjugate addition reactions of α,β-unsaturated esters containing a *trans*-dioxolane unit[17a,17b] (Scheme 65).



Scheme 65. *Reagents and conditions:* (i) **169**, THF, –78 °C, 2 h.

The conjugate addition of **168** to **317** in THF at –78 °C proceeded with a lower level of diastereocontrol to give a 67:33 mixture of 3,4-*anti*-**348** and 3,4-*syn*-**349**, respectively, which was isolated in an 86% combined yield. An aliquot of 3,4-*anti*-**348** was subsequently recrystallised to homogeneity (>99:1 dr) and the relative configuration within **348** was then unambiguously established via single crystal X-ray diffraction analysis,[18] with the absolute configuration within **348** being assigned relative to the known configurations of the D-arabinose derived dioxolane units. This result therefore enabled the sense of substrate control provided by **317** during the conjugate addition reaction of **168** to **317** to be confirmed (Figure 30). As was the case for the conjugate addition of **169** to **317**, the conjugate addition of **168** to **317** in THF at –78 °C proceeded without the formation of any product involving the γ-deprotonation of the α,β-unsaturated ester **317** (Scheme 66).



Scheme 66. *Reagents and conditions:* (i) **168**, THF, –78 °C, 2 h.

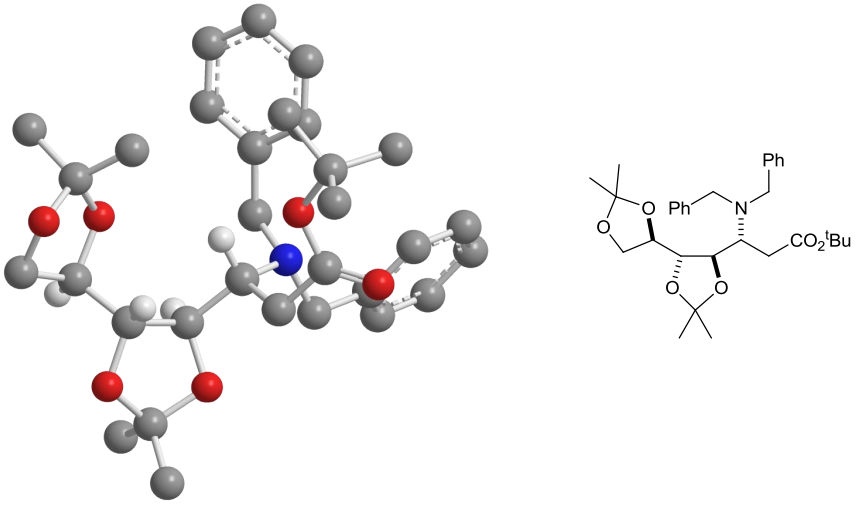
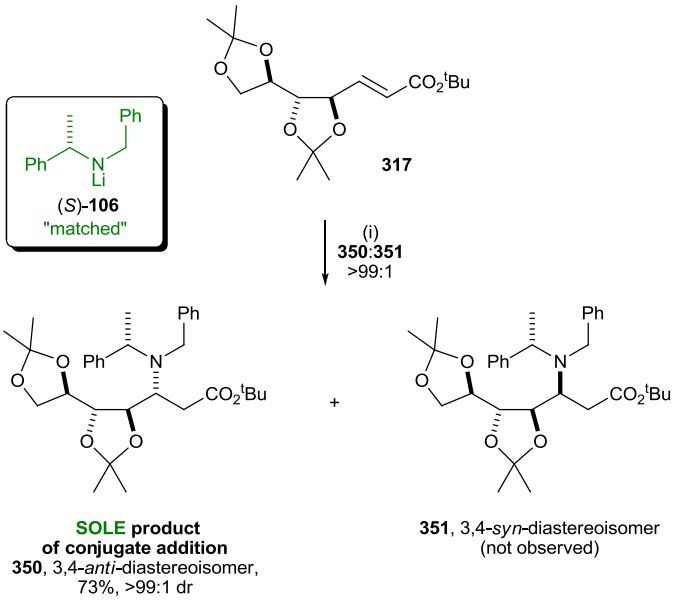


Figure 30. X-ray crystal structure of **348** (selected H atoms are omitted for clarity).

3.6.2 Evaluation of "matching" and "mismatching" effects

The conjugate addition reactions of both **168** and **169** to α,β-unsaturated ester **317** had shown that the substrate control provided by **317** was to direct the lithium amide to the *Re* face of the α,β-unsaturated ester. With this knowledge in hand, it was expected that the conjugate addition of (*S*)-**106** would represent the doubly diastereoselective "matched" reaction and, as expected, conjugate addition of (*S*)-**106** to **317** therefore proceeded to give 3,4-*anti*-**350** as the sole product (>99:1 dr), which was subsequently isolated in 73% yield and >99:1 dr. Any evidence of a γ-deprotonation pathway was again absent from the ^{1}H NMR spectrum of the crude reaction mixture (Scheme 67). As 3,4-*anti*-**350** proved to be crystalline, the relative configuration within **350** was unambiguously established via single crystal X-ray diffraction analysis,[18] with the absolute configuration within **350** being assigned relative to the known configurations of the D-arabinose derived dioxolane units and to the known configuration of the (*S*)-α-methylbenzyl group (Figure 31). This result therefore served to

confirm that the reagent/substrate pairing of lithium amide (*S*)-**106** with α,β-unsaturated ester **317** represents the doubly diastereoselective "matched" conjugate addition reaction.



Scheme 67. *Reagents and conditions:* (i) (*S*)-**106**, THF, –78 °C, 2 h.

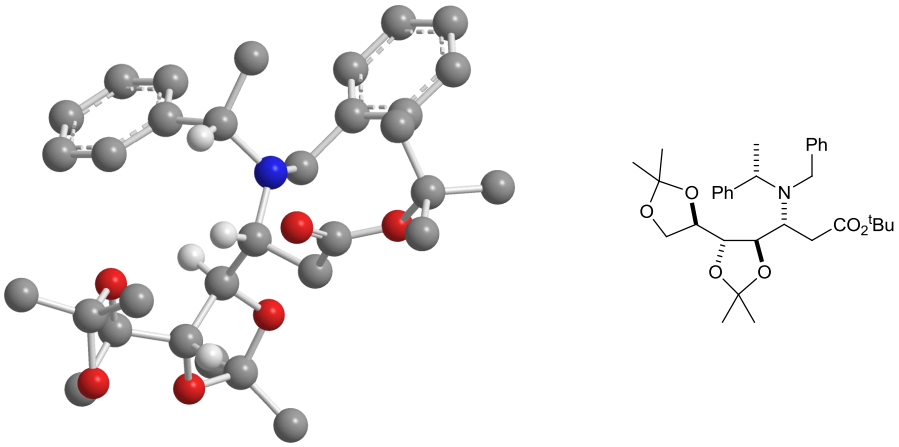
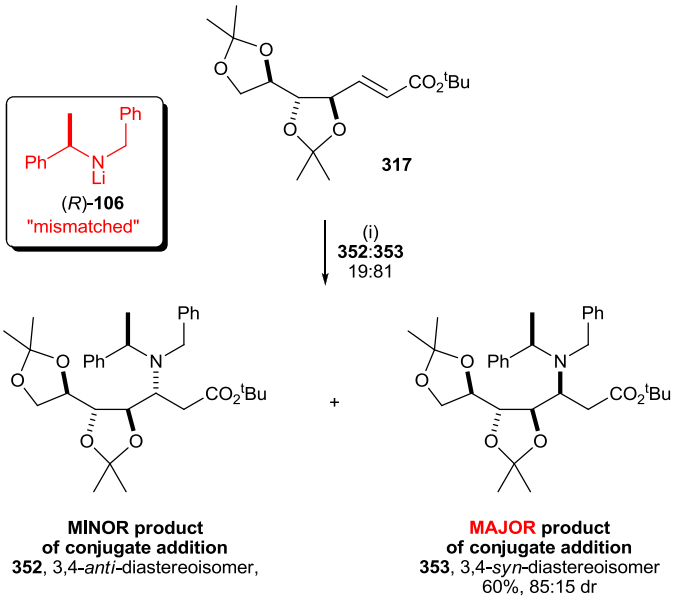


Figure 31. X-ray crystal structure of **350** (selected H atoms are omitted for clarity).

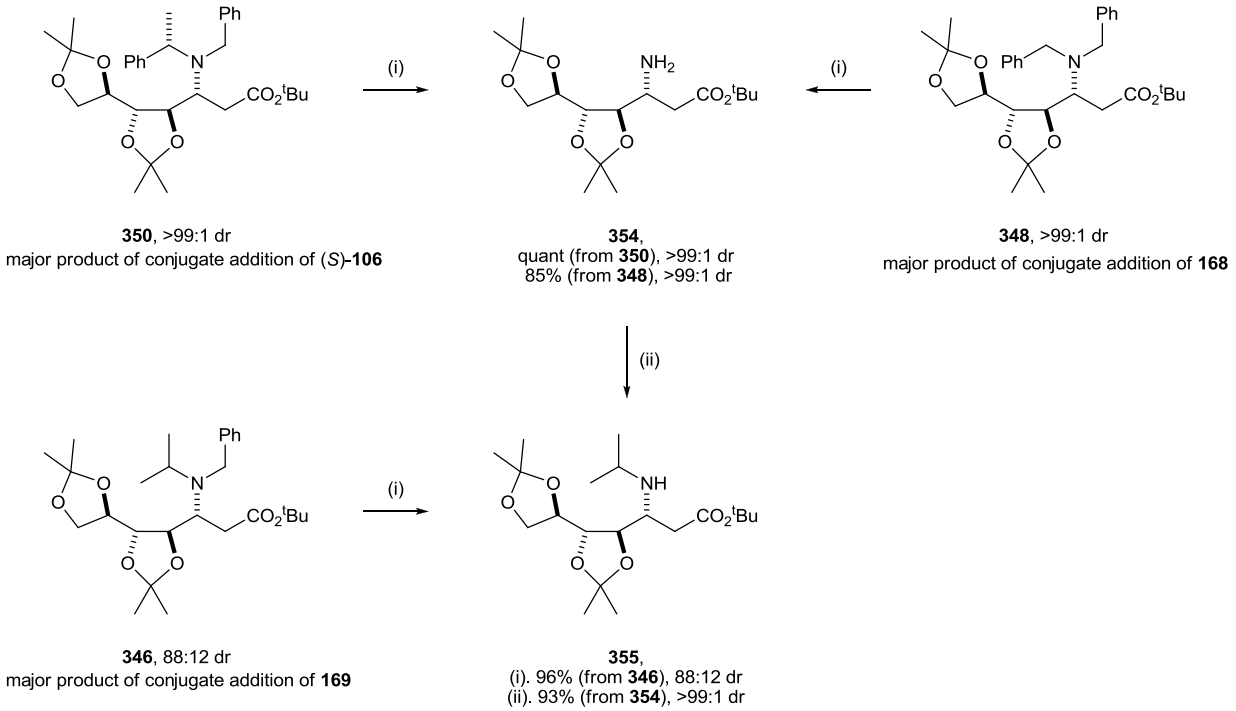
The conjugate addition of (*R*)-**106** to **317** (which was predicted to be the "mismatched" reagent/substrate pairing) was then investigated. Upon reaction in THF at –78 °C, conjugate addition of (*R*)-**106** to **317** gave a 19:81 mixture of 3,4-*anti*-**352** and 3,4-*syn*-**353**, respectively, from which major product 3,4-*syn*-**353** was subsequently isolated in 60% yield and 85:15 dr. The absolute configurations within **352** and **353** were later unambiguously established via chemical correlation (*vide infra*). As before, no evidence of a detritic γ-deprotonation pathway was observed. The incomplete stereocontrol observed upon conjugate addition of (*R*)-**106** to **317** [compared to >99:1 dr for the conjugate addition of (*S*)-**106** to **317**] supports the prediction that this reaction is the doubly diastereoselective "mismatched" pairing. In this case, the "mismatched" reaction must be proceeding under the dominant stereocontrol of the lithium amide reagent (*R*)-**106** due to the preferential formation of the 3,4-*syn*-diastereoisomer **353** (Scheme 68).



Scheme 68. *Reagents and conditions:* (i) (*R*)-**106**, THF, –78 °C, 2 h.

3.6.3 Correlation experiments

The absolute configurations within 3,4-*anti*-**348** and 3,4-*anti*-**350** had already been unambiguously established via single crystal X-ray diffraction analysis (*vide supra*). A series of hydrogenolytic/reductive alkylation experiments were next conducted to unambiguously establish the configurations of the C(3)-stereogenic centres within all the remaining β-amino ester products of conjugate addition to **317**. Firstly, an authentic sample of primary β-amino ester **354** was synthesised via hydrogenolysis of 3,4-*anti*-**350** (>99:1 dr) with $Pd(OH)_2/C$ to give **354** in quantitative yield and >99:1 dr. The ^{1}H NMR spectrum of this sample of **354** was entirely consistent with a sample obtained via hydrogenolysis of 3,4-*anti*-**348** (>99:1 dr), which resulted in **354** being produced in 85% yield and >99:1 dr. Subjection of **354** (>99:1 dr) to reductive alkylation conditions ($NaBH_3CN$/acetone) gave the 3,4-*anti* configured *N*-isopropyl substituted β-amino ester **355** in 93% yield and >99:1 dr. Subjection of **346** (88:12 dr) to hydrogenolysis conditions gave **355** in 96% yield and 88:12 dr, with the ^{1}H NMR spectrum for this sample of **355** found to be in complete accord with that of the authentic sample of **355** obtained from reductive alkylation of **354**, therefore allowing the absolute configuration within **346** to also be unambiguously assigned (Scheme 69).



350, >99:1 dr
major product of conjugate addition of (*S*)-**106**

354,
quant (from **350**), >99:1 dr
85% (from **348**), >99:1 dr

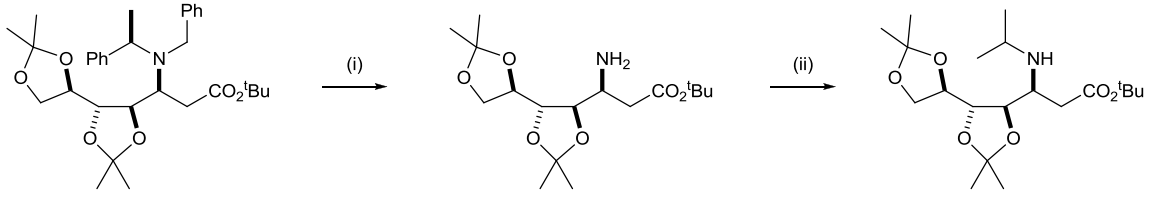
348, >99:1 dr
major product of conjugate addition of **168**

346, 88:12 dr
major product of conjugate addition of **169**

355,
(i). 96% (from **346**), 88:12 dr
(ii). 93% (from **354**), >99:1 dr

Scheme 69. *Reagents and conditions:* (i) $Pd(OH)_2/C$, H_2 (1 atm), EtOAc, rt, 18 h; (ii) $NaBH_3CN$, acetone, MeOH, rt, 18 h.

A sample of **353** [obtained as the major product of conjugate addition from the "mismatched" reaction of (*R*)-**106** to **317** and subsequently isolated in 85:15 dr] was subjected to hydrogenolysis in the presence of $Pd(OH)_2/C$ to give primary β-amino ester **356** in 87% yield and 85:15 dr. The ^1H NMR spectrum of **356** was found to be entirely different from that of **354**, serving to support the opposing configurations at C(3) within **354** and **356**. In addition, the ^1H NMR peaks for the minor component of the 85:15 dr sample of **356** were found to be consistent with those for the authentic sample of **354**. Primary β-amino ester **356** (85:15 dr) was then subjected to a reductive alkylation reaction to give *N*-isopropyl substituted β-amino ester **357** in 72% yield and 85:15 dr. As expected, the data for **357** were found to be distinct to those of **355**, again confirming the opposing C(3)-configurations within **355** and **357** (Scheme 70).



353, 85:15 dr
major product of conjugate addition of (*R*)-**106**

356, 87%, 85:15 dr

357, 72%, 85:15 dr

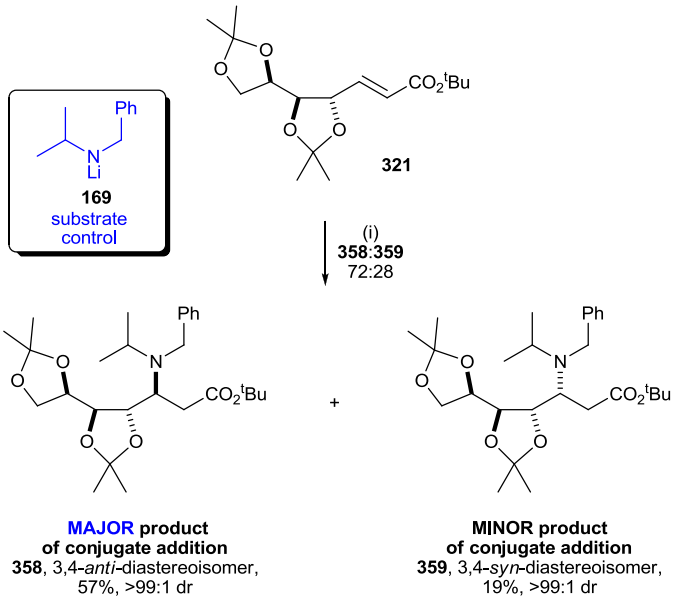
Scheme 70. *Reagents and conditions:* (i) $Pd(OH)_2/C$, H_2 (1 atm), EtOAc, rt, 18 h; (ii) $NaBH_3CN$, acetone, MeOH, rt, 18 h.

With the conjugate addition reactions to the D-arabinose derived α,β-unsaturated ester **317** now complete, the corresponding reactions to *trans*-dioxolane containing α,β-unsaturated ester **321** (derived from D-xylose **318**) were finally studied.

3.7 Lithium amide conjugate additions to D-xylose derived α,β-unsaturated ester 321

3.7.1 Evaluation of substrate control

The conjugate addition of lithium *N*-isopropyl-*N*-benzylamide **169** to **321** in THF at −78 °C gave a 72:28 mixture of 3,4-*anti*-**358** and 3,4-*syn*-**359**, respectively. β-Amino esters **358** and **359** were subsequently isolated in 57 and 19% yield, respectively, and in >99:1 dr in each case. As was the case for the D-arabinose derived α,β-unsaturated ester **317** (which also contains a *trans*-dioxolane unit), no evidence of a detritic γ-deprotonation pathway was observed during the conjugate addition reaction of **169** to **321** (Scheme 71). The relative configuration within 3,4-*anti*-**358** was unambiguously established via single crystal X-ray diffraction analysis,[18] with the absolute configuration within **358** being assigned relative to the known configurations of the D-xylose derived dioxolane units. This analysis therefore also allowed the unambiguous determination of the absolute configuration within 3,4-*syn*-**359** (Figure 32).



Scheme 71. *Reagents and conditions:* (i) **169**, THF, −78 °C, 2 h.

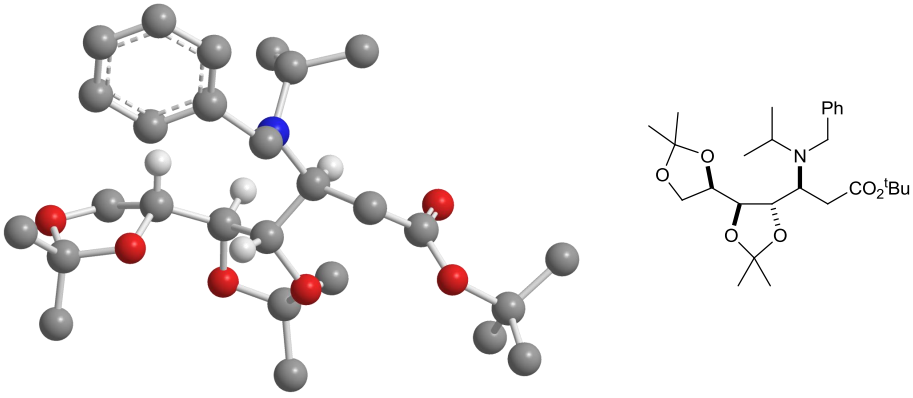
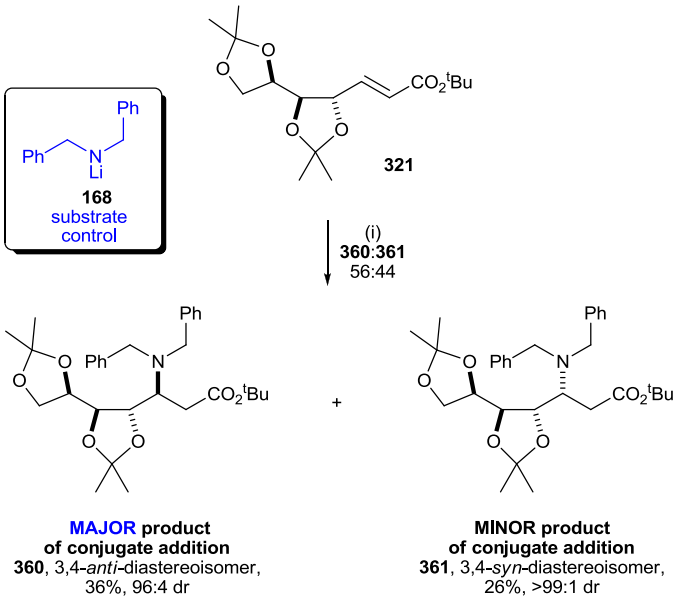


Figure 32. X-ray crystal structure of **358** (selected H atoms are omitted for clarity).

The conjugate addition of lithium dibenzylamide **168** to **321** in THF at −78 °C was found to proceed with a much lower level of diastereofacial control to give a 56:44 mixture of 3,4-*anti*-**360** and 3,4-*syn*-**361**, respectively. After purification, 3,4-*anti*-**360** was isolated in 36% yield and 96:4 dr

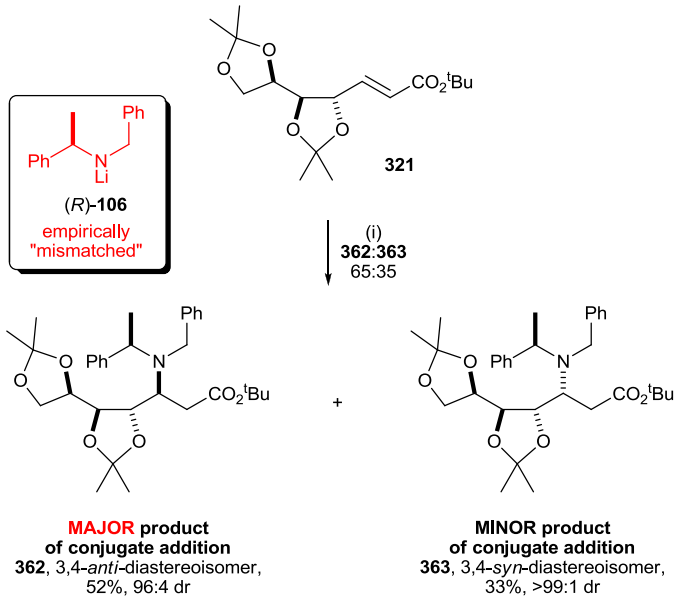
whilst 3,4-*syn*-**361** was isolated in 26% yield and >99:1 dr. The absolute configurations within **360** and **361** were later unambiguously established via chemical correlation (*vide infra*). No evidence of a γ-deprotonation pathway was observed during the conjugate addition reaction of **168** to **321** (Scheme 72).



Scheme 72. *Reagents and conditions:* (i) **168**, THF, –78 °C, 2 h.

3.7.2 Evaluation of "matching" and "mismatching" effects

The conjugate addition reaction of **169** to **321** had proceeded to give the 3,4-*anti* product **358** preferentially thereby indicating a preferred attack of the lithium amide **169** upon the *Si* face of the α,β-unsaturated ester **321**. Thus, it was expected that the conjugate addition of (*R*)-**106** would represent the doubly diastereoselective "matched" reaction, due to the known diastereofacial selectivity of this lithium amide.[19] Conjugate addition of (*R*)-**106** to **321** in THF at –78 °C did not, however, proceed with the expected high level of diastereocontrol usually associated with a doubly diastereoselective "matched" reaction; a 65:35 mixture of β-amino esters **362** and **363**, respectively, was observed. Upon purification, major product 3,4-*anti*-**362** was isolated in 52% yield and 96:4 dr and minor product 3,4-*syn*-**363** was isolated in 33% yield and >99:1 dr. Again, no evidence of any product associated with γ-deprotonation of α,β-unsaturated ester **321** was observed (Scheme 73). As 3,4-*syn*-**363** proved to be crystalline, the relative configuration within **363** was unambiguously established via single crystal X-ray diffraction analysis,[18] with the absolute configuration within **363** being assigned relative to the known configurations of the D-xylose derived dioxolane units and to the known configuration of the (*R*)-α-methylbenzyl group. This analysis therefore also allowed unambiguous assignment of the absolute configuration within 3,4-*anti*-**362** (Figure 33).



Scheme 73. *Reagents and conditions:* (i) (*R*)-**106**, THF, –78 °C, 2 h.

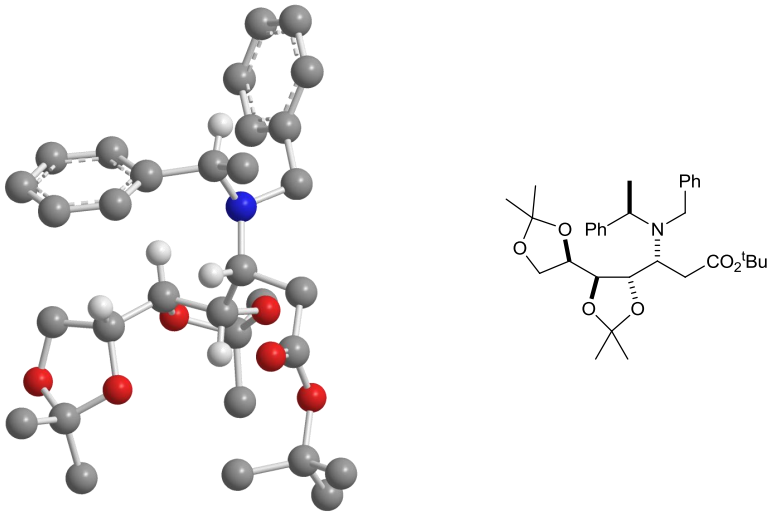
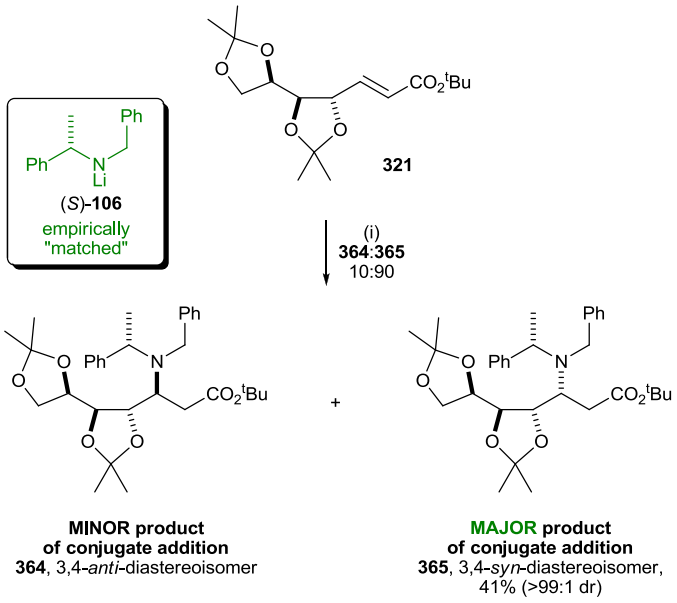


Figure 33. X-ray crystal structure of **363** (selected H atoms are omitted for clarity).

Conjugate addition of (*S*)-**106** to **321** resulted in a much higher level of diastereocontrol than expected, with a 90:10 mixture of 3,4-*syn*-**365** and 3,4-*anti*-**364** being produced upon reaction in THF at –78 °C. In addition, upon analysis of the ^{1}H NMR spectrum of the crude reaction mixture, there was no evidence of a γ-deprotonation pathway having been followed. β-Amino ester 3,4-*syn*-**365** was subsequently isolated in 41% yield and >99:1 dr (Scheme 74) and the absolute configuration within **365** was later unambiguously established via chemical correlation (*vide infra*). As the major product of this reaction was found to be the 3,4-*syn*-diastereoisomer **365**, this result is in complete contrast to the stereochemical outcome of the substrate control reaction of **169** to **321** (where the major product was found to be the 3,4-*anti*-diastereoisomer **358**). In addition, although the reaction had not proceeded to give a single diastereoisomeric product (as would be expected for a doubly diastereoselective "matched" reaction), the levels of diastereofacial control upon conjugate addition of (*S*)-**106** to **321** were found to be much higher (90:10 dr) than for the conjugate addition of (*R*)-**106** to **321** (65:35 dr). These observations therefore resulted in the reaction between (*S*)-**106** and **321**

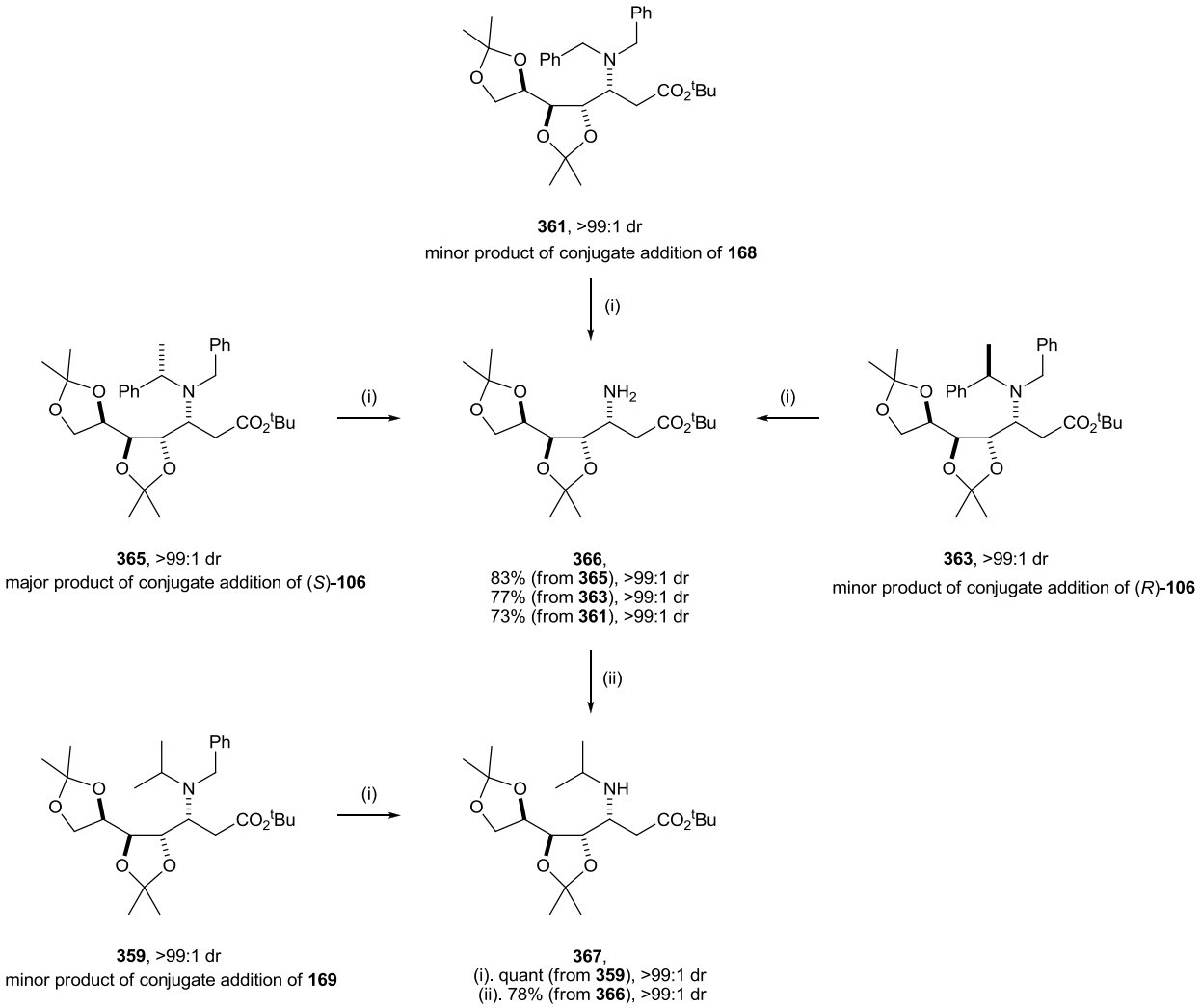
being assigned as the empirically "matched" reagent/substrate pairing and the reaction between (*R*)-**106** and **321** being assigned as the empirically "mismatched" reagent/substrate pairing.



Scheme 74. *Reagents and conditions:* (i) (*S*)-**106**, THF, –78 °C, 2 h.

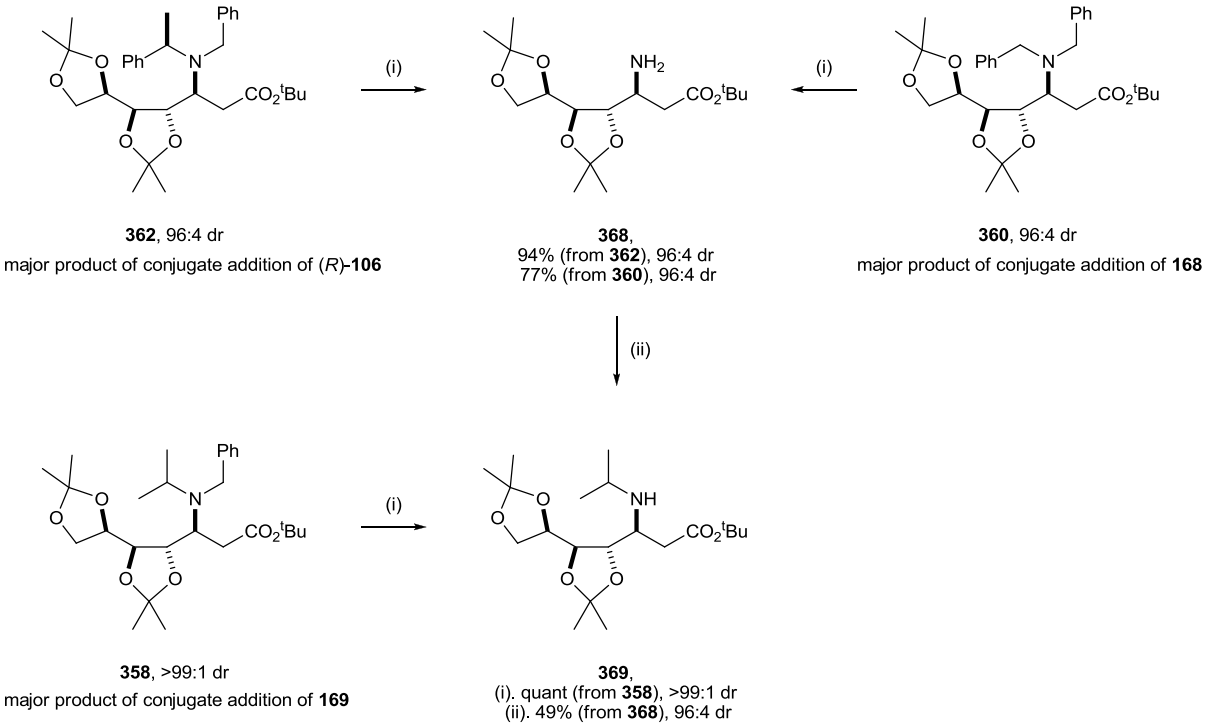
3.7.3 Correlation experiments

With all the conjugate addition reactions to **321** now complete, efforts were turned to the determination of the C(3)-configurations within all the isolated β-amino ester products via a series of hydrogenolytic/reductive alkylation experiments. The absolute configuration within 3,4-*syn*-**363** [obtained as the minor product in the conjugate addition of (*R*)-**106** to **321**] had already been unambiguously established via X-ray single crystal diffraction analysis (*vide supra*). Hydrogenolysis of **363** (>99:1 dr) using $Pd(OH)_2/C$ gave an authentic sample of primary β-amino ester **366** in 77% yield and >99:1 dr. Hydrogenolysis of **365** [obtained as the major product in the empirically "matched" conjugate addition of (*S*)-**106** to **321**] and of **361** [obtained as the minor product in the conjugate addition of **168** to **321**] gave **366** in 83 and 73% yield, respectively, and in >99:1 dr in both cases. Both samples of **366** were found to display ^{1}H NMR spectra that were entirely consistent with that of the authentic sample of **366**, thereby allowing the absolute configurations within **361** and **365** to be unambiguously established. Treatment of a sample of primary β-amino ester **366** (>99:1 dr) with $NaBH_3CN$ and acetone gave an authentic sample of *N*-isopropyl substituted β-amino ester **367** in 78% yield and >99:1 dr. Hydrogenolysis of **359** (obtained as the minor product in the conjugate addition of **169** to **321**) gave **367** in quantitative yield and >99:1 dr. The ^{1}H NMR spectra for both samples were found to be in complete agreement, allowing the absolute configuration within **359** to also be unambiguously established (Scheme 75).



Scheme 75. *Reagents and conditions:* (i) $Pd(OH)_2/C$, H_2 (1 atm), EtOAc, rt, 18 h; (ii) $NaBH_3CN$, acetone, MeOH, rt, 18 h.

The absolute configuration within 3,4-*anti*-**358** had already been unambiguously established via X-ray single crystal diffraction analysis (*vide supra*). Hydrogenolysis of 3,4-*anti*-**358** (>99:1 dr) gave an authentic sample of *N*-isopropyl substituted β-amino ester **369** in quantitative yield and >99:1 dr. A sample of **369** was also prepared from **360** and **362**: hydrogenolysis of **360** (96:4 dr) and **362** (96:4 dr) gave primary β-amino ester **368** in 77 and 94% yield, respectively, and in 96:4 dr in each case. Subsequent reductive alkylation of **368** (96:4 dr) using $NaBH_3CN$ and acetone gave **369** in 49% yield and 96:4 dr. The ^1H NMR spectrum of this sample of **369** was found to be entirely consistent with that of the authentic sample of **369**, thereby serving to further confirm the stereochemical assignments made. This series of correlation experiments had therefore allowed the absolute configurations within all the β-amino ester products from the conjugate addition reactions of (*R*)-**106**, (*S*)-**106**, **168** and **169** to α,β-unsaturated ester **321** to be unambiguously established (Scheme 76).



Scheme 76. *Reagents and conditions:* (i) $Pd(OH)_2/C$, H_2 (1 atm), EtOAc, rt, 18 h; (ii) $NaBH_3CN$, acetone, MeOH, rt, 18 h.

3.8 The origins of diastereoselectivity observed upon conjugate addition

The lithium amide conjugate addition reactions to α,β-unsaturated esters **309** and **317** had conformed to the predicted outcomes; the doubly diastereoselective "matched" reactions had proceeded with the same sense (and with an enhanced level) of diastereocontrol as those suggested by the substrate control experiments, resulting in the preferential formation of the corresponding 3,4-*anti*-β-amino ester products. These stereochemical outcomes were found to be consistent with previous results reported by Davies *et al.* for analogous α,β-unsaturated ester systems.[17a,17b] In contrast to this, in the case of **313**, an erosion in diastereoselectivity was observed for the conjugate addition reactions of both antipodes of **106** compared with the analogous reaction involving substrate control alone (conjugate addition of achiral **169** to **313**). Furthermore, in the case of **321**, the empirically "matched" conjugate addition reaction of (*S*)-**106** had proceeded to give the 3,4-*syn*-β-amino ester product preferentially, whilst the substrate control experiments had indicated preferential attack on the opposing face of the α,β-unsaturated ester **321**, giving 3,4-*anti*-β-amino esters as the major products. This therefore suggests an unusual reversal in the sense of substrate control in the two reactions [i.e., that conjugate addition of achiral **169** occurs on the *Si* face of **321** whilst addition of (*S*)-**106** occurs on the *Re* face of **321**]. Such behaviour has previously been noted by Davies *et al.* in related systems.[23] Of all the conjugate addition reactions investigated for **313** and **321**, in no case is the diastereoselectivity of the conjugate addition as high as would be expected from the reaction of the chiral lithium amide **106** with an achiral substrate (>95:5 dr in >200 examples).[21] According to

the classical definition by Masamune *et al.*,[22] the introduction of chirality into the substrate should presumably work to enhance the stereoselectivity of the conjugate addition reaction in the doubly diastereoselective "matched" case (compared to the analogous reactions proceeding under substrate control alone) although the results from these experiments have shown this not to be the case. This observation implies that the factors which influence the substrate and reagent control in these two instances are not independent and therefore that the usual mode of action of the antipodes of lithium amide **106** upon conjugate addition to these substrates must be disrupted in some way, possibly be due to the polyhydroxylated nature of the α,β-unsaturated ester substrates **313** and **321**: an abundance of oxygen atoms in the substrate could potentially allow chelation to occur between the substrate and the lithium amide, as this phenomenon has been noted in similar systems.[21,24] Such chelation could result in intramolecular delivery of the lithium amide *via* a substrate-lithium amide chelate or, alternatively, in intermolecular delivery from a substrate-lithium amide chelate to another substrate molecule. The ability of the substrate to chelate to the lithium amide would depend on the spatial arrangement of the oxygen atoms, and therefore on the relative configuration of the multiple stereogenic centres within the α,β-unsaturated ester. This may go some way to explain why the results from the conjugate addition reactions of the antipodes of **106** to **313** and **321** appear to be anomalous.

3.9 Synthesis of deoxyaminohexoses and deoxyaminoheptoses

Recently, Davies *et al.* have applied further the results of these studies to the development of protocols for the synthesis of a range of deoxyamino sugars.[25] In this work, the already identified "matched" conjugate addition reactions of the antipodes of lithium amide **106** to α,β-unsaturated esters **296** were coupled with *in situ* enolate oxidation using the requisite antipodes of CSO **102** to give α-hydroxy-β-amino esters **297**. α-Hydroxy-β-amino esters **297** were then elaborated to a series of 2-deoxy-2-aminohexoses **298**, 3-deoxy-3-aminoheptoses **300** and **301**, and 4-deoxy-4-aminohexoses **299** via manipulation and cyclisation of the intermediate aldehydes **370**, **371**, and **372**, respectively (Figure 34).

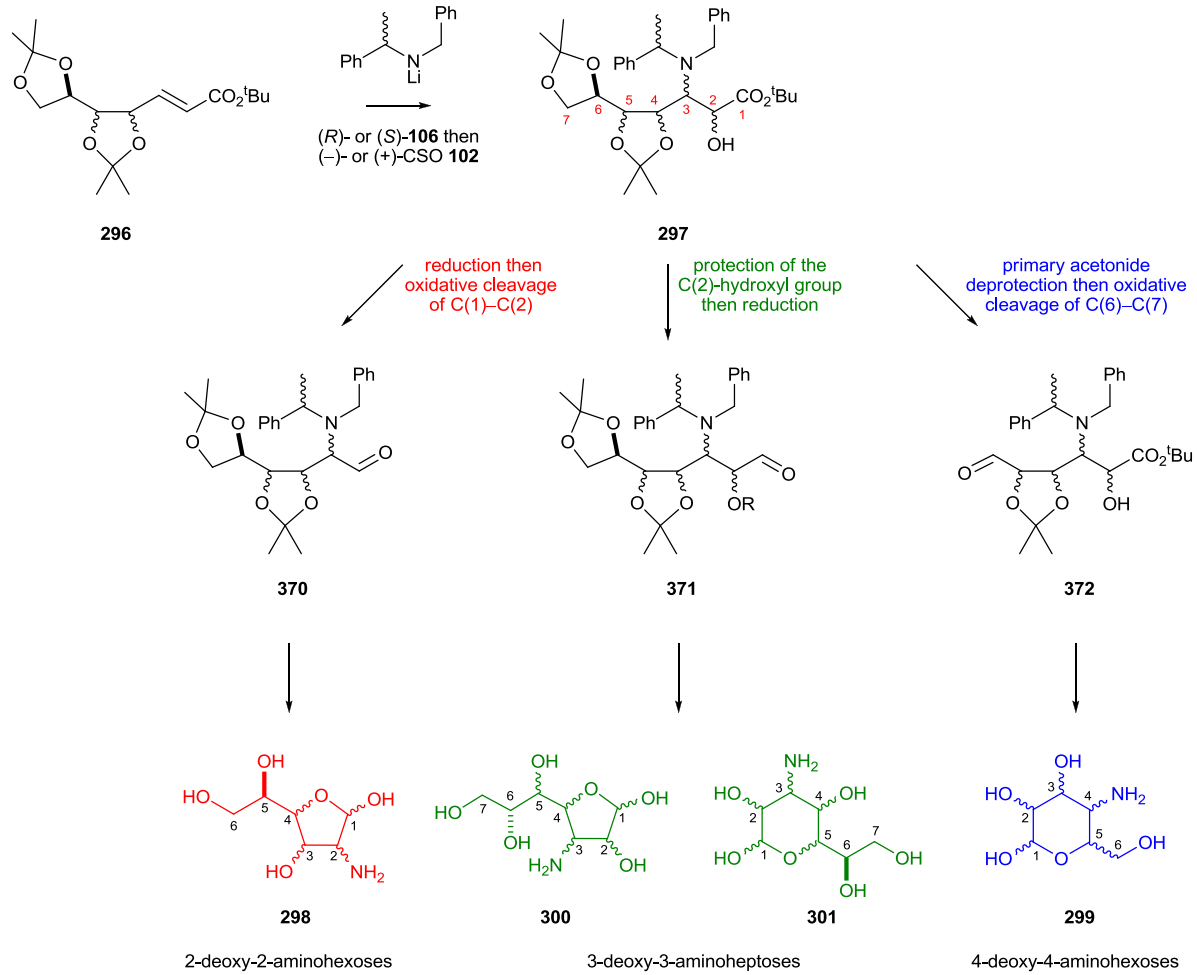


Figure 34. The synthesis of deoxyaminohexoses **298** and **299** and deoxyaminoheptoses **300** and **301**.

3.10 Synthesis of dihydroxyhomoprolines

Efforts were next turned to the elaboration of β-amino esters **302** (the products of conjugate addition of the antipodes of **106** to α,β-unsaturated esters **309**, **313**, **317** and **321**) to dihydroxyhomoprolines **295** (Figure 35).

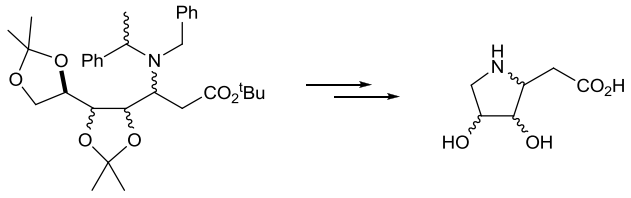
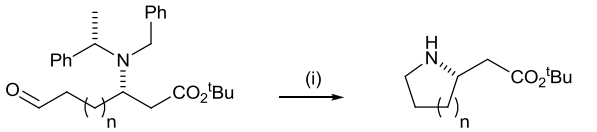


Figure 35. Elaboration of β-amino esters **302** to dihydroxyhomoprolines **295**.

Davies *et al.* have previously employed a cyclisation procedure involving a tandem hydrogenolysis/intramolecular reductive amination reaction. For example, aldehydes **373** and **374** were subjected to high pressure hydrogenolysis conditions using $Pd(OH)_2/C$ to give pyrrolidine **375** and piperidine **376** in 87 and 91% yield, respectively, and as single diastereoisomers (>99:1 dr) in each case. These conditions were therefore able to effect both the removal of the *N*-benzyl and *N*-α-methylbenzyl groups within **373** and **374**, as well as the reduction of the intermediate imines resulting from cyclisation of the C(3)-amino groups onto the aldehyde functionalities (Scheme 77).[26]

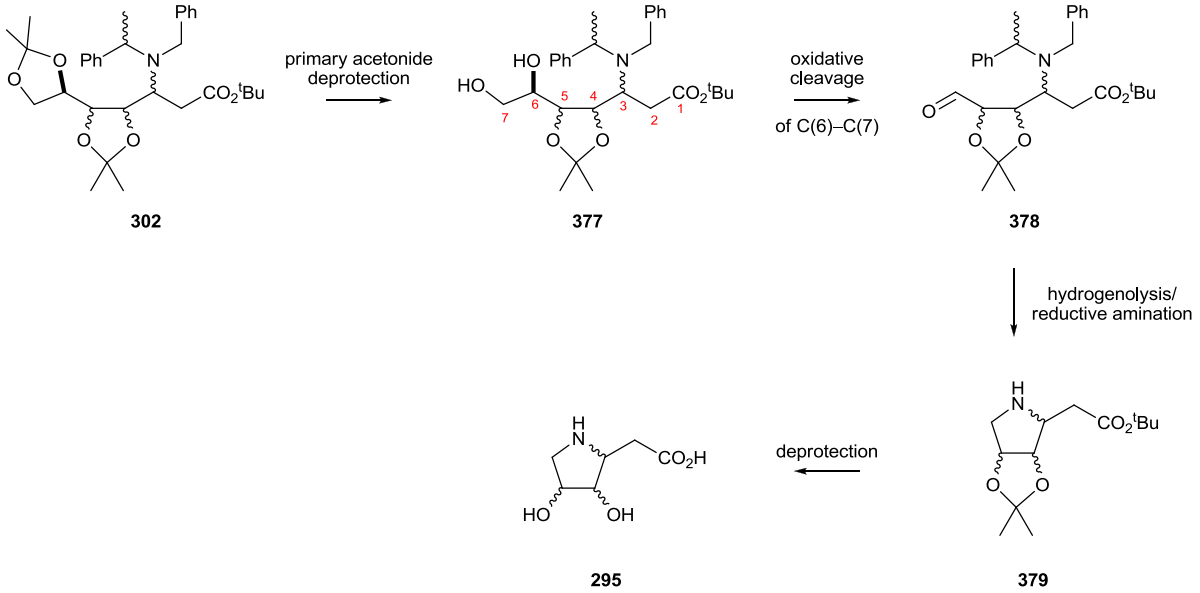


373, n = 1, >99:1 dr
374, n = 2, >99:1 dr

375, n = 1, 87%, >99:1 dr
376, n = 2, 91%, >99:1 dr

Scheme 77. *Reagents and conditions:* (i) $Pd(OH)_2/C$, H_2 (5 atm), MeOH, rt, 18 h.

It was therefore envisaged that the elaboration of β-amino esters **302** to β-amino acids **295** could also involve a similar tandem hydrogenolysis/reductive amination procedure as the key step. Thus, it was expected that chemoselective deprotection of the primary acetonide functionality within **302** would allow access to diols **377**. Oxidative cleavage of the C(6)–C(7) bond within **377** would then give the corresponding aldehydes **378**, which, upon subjection to the established high pressure hydrogenolysis conditions, was expected to give pyrrolidines **379**. Global deprotection of **379** upon treatment with acid would then finally reveal β-amino acids **295** as the target products (Figure 36).



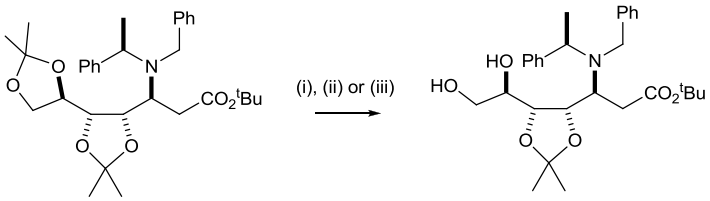
302 **377** **378** **295** **379**

Figure 36. General proposed synthetic route towards β-amino acids **295**.

3.10.1 Chemoselective primary acetonide deprotection

It was decided to employ β-amino ester 3,4-*anti*-**327** [the sole diastereoisomeric product in the doubly diastereoselective "matched" reaction of (*R*)-**106** and **309**] as a model system for the chemoselective primary acetonide deprotection step. The deprotection of primary acetonides in the presence of secondary acetonides can be a difficult transformation due to the tendency for over-deprotection to the corresponding tetraol, even under mild conditions.[27] As such, literature precedent exists in which many novel procedures have been developed for this purpose. Following one such literature procedure,[28] **327** was treated with 5 mol% $BiCl_3$ in $MeCN/H_2O$, however this unfortunately resulted in only returned starting material despite further attempts involving extended reaction times and increased catalyst loadings. A second procedure involved heating β-amino ester **327** in 80% aqueous AcOH at 50 °C;[25] however, the levels of conversion to diol **380** were variable

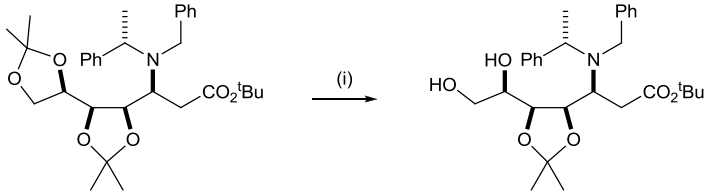
and **380** was only isolated in a maximum 21% yield. Finally, treatment of **327** with a catalytic amount of concentrated HCl in 70% aqueous EtOH at 60 °C[29] gave a mixture of diol **380** and starting material **327**, from which **380** was isolated in 32% yield. This procedure was found to be rather unreliable and upon several repeats of the reaction different conversions and isolated yields were obtained. Fortunately, the starting material **327** was easily recovered and recycled in all cases (Scheme 78).



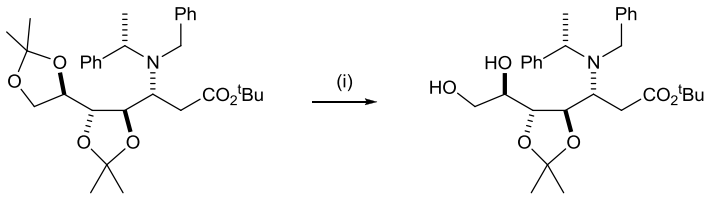
327 **380**,
(i). 0%
(ii). 21%, >99:1 dr
(iii). 32%, >99:1 dr

Scheme 78. *Reagents and conditions:* (i) $BiCl_3$ (5 mol%), MeCN/H_2O (v/v 100:1), rt, 16 h; (ii) AcOH/H_2O (v/v 4:1), 50 °C, 16 h; (iii) conc HCl, EtOH/H_2O (v/v 7:3), 60 °C, 6 h.

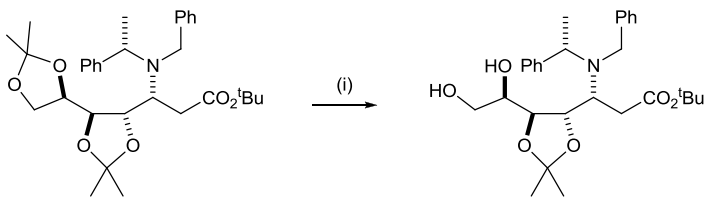
The chemoselective primary acetonide deprotections of 3,4-*syn*-**339**,[30] 3,4-*anti*-**350**[31] and 3,4-*syn*-**365**[31] under identical reaction conditions were found to proceed in a similar fashion: in all cases incomplete conversion was observed, however, the starting material was easily recovered and recycled in each case. Thus, under the optimised conditions, diols **381**-**383** were isolated in 31-70% yield and in >99:1 dr in each case (Scheme 79).



339, >99:1 dr **381**, 31%, >99:1 dr



350, >99:1 dr **382**, 39%, >99:1 dr

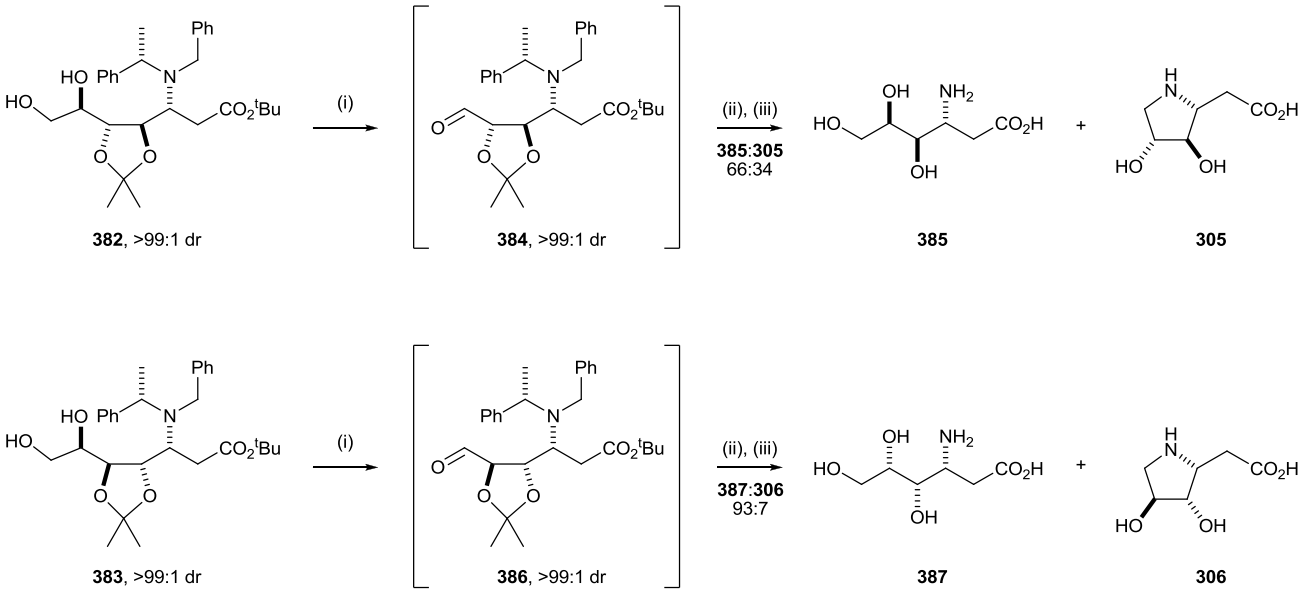


365, >99:1 dr **383**, 70%, >99:1 dr

Scheme 79. *Reagents and conditions:* (i) conc HCl, EtOH/H_2O (v/v 7:3), 60 °C, 6 h.

3.10.2 Synthesis of D-arabinose and D-xylose derived β-amino acids 305 and 306

The elaboration of diols **382** and **383** (each containing a *trans*-dioxolane unit) was first undertaken. Oxidative cleavage of the 1,2-diol unit within **382** using $NaIO_4$ gave aldehyde **384** as a single diastereoisomer. It was anticipated that the proposed tandem hydrogenolysis/intramolecular reductive amination of **384** would not proceed efficiently due to the presence of the *trans*-dioxolane unit, as the cyclisation would require the formation of a disfavoured *trans*-fused-[3.3.0]-bicycle. It was therefore decided to attempt the hydrogenolysis reaction in methanolic HCl with the aim being to deprotect the acetonide functionality within **384** *in situ*, thereby removing the cyclic constraints within **384** and allowing imine formation to occur. Thus, aldehyde **384** was subjected to a high pressure hydrogenolysis reaction using $Pd(OH)_2/C$ in the presence of 3.0 M aqueous HCl and the crude reaction mixture was then immediately treated with 2.0 M aqueous HCl and heated at reflux in order to ensure complete ester hydrolysis prior to purification. Purification of the crude reaction mixture via ion-exchange chromatography resulted in the isolation of a 66:34 mixture of β-amino acids **385** and **305**, respectively (Scheme 80).[32] The connectivities within **385** and **305** were initially assigned via analysis of the ^{1}H, ^{13}C, COSY, HSQC and HMBC NMR spectra of the mixture, however the identity of major product **385** was then confirmed via the synthesis of an authentic sample.[33] A similar outcome was observed in the case of diol **383**: treatment with $NaIO_4$ gave the corresponding aldehyde **386** as a single diastereoisomer. Aldehyde **386** was then also subjected to the tandem hydrogenolysis/intramolecular reductive amination procedure in the presence of 3.0 M aqueous HCl and subsequently treated with 2.0 M aqueous HCl. Ion-exchange chromatography then resulted in the isolation of a 93:7 mixture of β-amino acids **387** and **306**, respectively. The ^{1}H, ^{13}C, COSY, HSQC and HMBC NMR spectra of the mixture were also consistent with the assigned identities of **387** and **306** (Scheme 80). The formation of **385** and **387** under these reaction conditions is consistent with a mechanism involving reduction of the aldehyde functionality. This process may be proceeding at a competitive rate to the acetonide hydrolysis step as the intramolecular reductive amination pathway (to form the desired pyrrolidine scaffold) cannot occur until the conformational constraints of the acetonide protecting group have been removed.

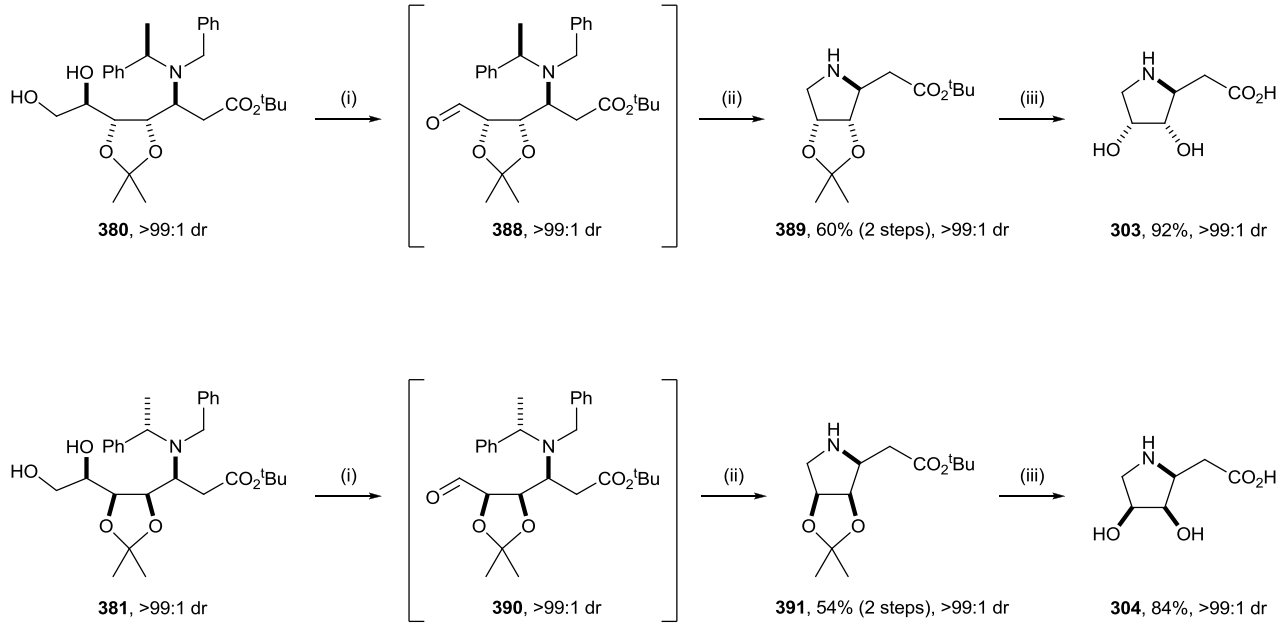


Scheme 80. *Reagents and conditions:* (i) $NaIO_4$, MeOH, rt, 16 h; (ii) $Pd(OH)_2/C$, H_2 (5 atm), HCl (3.0 M, aq), MeOH, rt, 18 h;[34] (iii) HCl (2.0 M, aq), reflux, 8 h then DOWEX 50WX8-200.

The fact that **385** and **387** were isolated as the major products from these hydrogenolysis reactions implies that the presence of the *trans*-dioxolane units within aldehydes **384** and **386** (and therefore the need to effect *in situ* acetonide deprotection prior to the desired cyclisation occurring) disfavours the formation of dihydroxyhomoprolines **305** and **306** (*vide infra*). Attention was therefore turned to the elaboration of diols **380** and **381**, which both contain a *cis*-dioxolane unit.

3.10.3 Synthesis of D-ribose and D-lyxose derived β-amino acids 303 and 304

It was anticipated that the tandem hydrogenolysis/intramolecular reductive amination and acetonide deprotection reactions of the corresponding *cis*-dioxolane containing aldehydes **388** and **390** could be performed in a stepwise manner. Thus, in the case of **380**, oxidative cleavage of the 1,2-diol unit within **380** upon treatment with $NaIO_4$ in MeOH gave aldehyde **388**. Aldehyde **388** was found to rapidly decompose on standing and so the crude sample of aldehyde **388** was immediately subjected to a high pressure hydrogenolysis reaction using $Pd(OH)_2/C$, which successfully resulted in tandem hydrogenolysis/intramolecular reductive amination to give pyrrolidine **389** in 60% yield and >99:1 dr over the two steps. Global deprotection of **389** by treatment with 2.0 M aqueous HCl and subsequent purification via ion-exchange chromatography gave the desired β-amino acid **303**[35] in 92% yield and >99:1 dr (Scheme 81). Similarly, treatment of diol **381** with $NaIO_4$ resulted in successful cleavage to the corresponding aldehyde **390**, which was again immediately subjected to the already established tandem hydrogenolysis/intramolecular reductive amination conditions to give pyrrolidine **391** in 54% yield and >99:1 dr over the two steps. Treatment of **391** with 2.0 M aqueous HCl under refluxing conditions resulted in global deprotection to give β-amino acid **304**[36] in 84% yield after purification via ion-exchange chromatography (Scheme 81).



Scheme 81. *Reagents and conditions:* (i) $NaIO_4$, MeOH, rt, 16 h; (ii) $Pd(OH)_2/C$, H_2 (5 atm), MeOH, rt, 18 h; (iii) HCl (2.0 M, aq), reflux, 8 h then DOWEX 50WX8-200.

This investigation had therefore shown that β-amino acids **303** and **304** could be produced in seven steps and in >99:1 dr from naturally occurring D-ribose **155** and D-lyxose **310**, respectively, by employing a lithium amide conjugate addition reaction and a tandem hydrogenolysis/intramolecular reductive amination as the key steps.

3.11 Conclusions

In conclusion, the doubly diastereoselective conjugate addition reactions of (*R*)-**106** and (*S*)-**106** to a range of chiral α,β-unsaturated esters **296** (derived from naturally occurring D-pentose sugars) have been fully investigated. Further elaboration of some of the β-amino ester products **302** from these conjugate addition reactions then allowed access to the novel β-amino acids (2'*S*,3'*S*,4'*R*)-dihydroxyhomoproline **303** and (2'*S*,3'*R*,4'*S*)-dihydroxyhomoproline **304** (Figure 37).

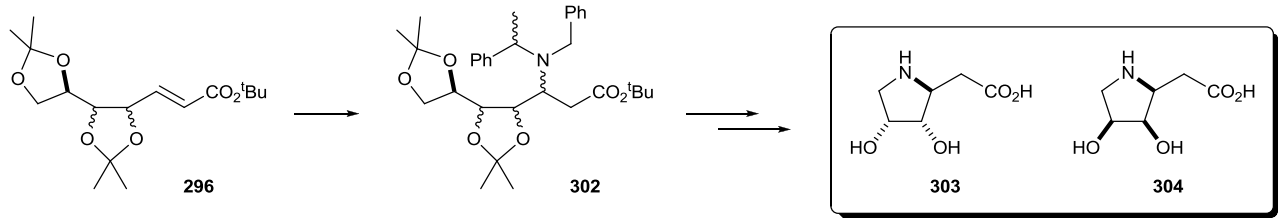


Figure 37. Successfully synthesised target β-amino acids **303** and **304**.

3.12 References and notes for chapter 3

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[23] For example, the empirically "matched" conjugate addition reaction of (*S*)-**106** to α,β-unsaturated ester **212** was found to give the 3,4-*syn*-β-amino ester product in >99:1 dr, whilst conjugate of addition of achiral **169** to **212** gave the corresponding 3,4-*anti*-β-amino ester product in 75:25 dr, see: (a) reference 17a. (b) Lorkin, T. J. A. *Part II Thesis*, University of Oxford, **2009**.

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[30] Elaboration of 3,4-*anti*-**338** [the major product of conjugate addition in the reaction of (*S*)-**106** to **313**] was expected to result in the enantiomer of **303**. As such, elaboration of the minor product of this reaction, 3,4-*syn*-**339** (>99:1 dr), was instead pursued to allow access to an alternative diastereoisomer in this series of dihydroxyhomoprolines.

[31] β-Amino esters 3,4-*anti*-**350** and 3,4-*syn*-**365** were chosen for elaboration as they represented the major products from the empirically "matched" conjugate addition reactions of (*S*)-**106** to **317** and **321**, respectively.

[32] An identical result was observed upon repetition of the reaction sequence.

[33] An authentic sample of *ent*-**385** was prepared via hydrogenolysis and global deprotection of a sample of (3*S*,4*S*,5*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-dihydroxy-4,5-*O*-isopropylidene-6-benzyloxyhexanoate, which was kindly donated by Mr T. J. A. Lorkin.

[34] In the case of **384**, incomplete debenzylation after 18 h resulted in the crude residue being resubjected to the hydrogenolysis conditions for a further 60 h.

[35] The connectivity within **303** was established via analysis of the ^{1}H, ^{13}C, COSY, HSQC and HMBC NMR spectra.

[36] The connectivity within **304** was established via analysis of the ^{1}H, ^{13}C, COSY, HSQC and HMBC NMR spectra.

Chapter 4: Asymmetric Syntheses of APTO and AETD – the β-Amino Acid Fragments within Microsclerodermins C, D and E

4.1 The microsclerodermin family

Microsclerodermins A–I **392-400** are a family of nine cyclic hexapeptide natural products which have been isolated from marine sponges of the *Microscleroderma* and *Theonella* genera, found in the waters around New Caledonia and the Philippines.[1] All nine natural products have been shown to possess antifungal activity against *Candida albicans* in a paper disk diffusion assay,[1] and microsclerodermins F–I **397-400** have been shown to display cytotoxicity towards the HCT-116 cell line,[1c] thereby also making them potential anti-tumour drug candidates (Figure 38). The basic structure of the microsclerodermin alkaloids involves a 23-membered ring comprised of six amino acid residues. Three of these amino acids are common to all members of the microsclerodermin family: namely glycine, *N*-methylglycine and (*R*)-4-amino-3-hydroxybutyric acid (Gamma-Amino-Beta-hydrOxyButyric acid, GABOB). The three remaining amino acids in each case comprise a substituted tryptophan residue, a 4-aminopyrrolidin-2-one-5-acetic acid residue, and a 2,4,5-trihydroxy substituted β-amino acid residue (shown in red). Microsclerodermins A **392** and B **393** were the first members of the family to be isolated in 1994, and the structural elucidation of these two complex natural products was performed by a combination of spectroscopic methods and chemical degradation experiments.[1a] The ^{1}H and ^{13}C NMR spectra of **392**, including HMBC and ROESY analyses, were used to initially identify the six constituent amino acids of microsclerodermin A **392**. The stereochemistry within **392** was then established by a series of degradation experiments, with derivatives of the four chiral amino acids being analysed by GCT-MS on a chiral capillary column. Hydrolysis of **392** using methanesulfonic acid gave (*R*)-3-hydroxy-4-aminobutyric acid, and thus identified the stereochemistry within the GABOB unit, whilst ozonolysis of **392** followed by an oxidative work-up and subsequent acidic hydrolysis gave (*R*)-aspartic acid, thus establishing the (*R*)-configuration at the α-carbon within the substituted tryptophan residue. Ozonolysis of the dehydrated form of **392** followed by acidic hydrolysis gave (2*S*,3*R*)-3-hydroxyaspartic acid, serving to confirm the stereochemistry in the pyrrolidone ring containing amino acid. The structural identity of the 2,4,5-trihydroxy substituted β-amino acid residue within microsclerodermin A **392** was determined via a combination of methods.[1a] These included: (i) ^{1}H NMR NOE spectroscopic analysis; (ii) derivatisation of the 4,5-dihydroxy unit to the corresponding *trans*-configured acetonide followed by ^{1}H NMR ^{3}J coupling constant analysis; and (iii) degradation of the residue to give (*S*,*S*)-3-hydroxyaspartic acid (via oxidative cleavage of the 4,5-dihydroxy unit followed by hydrolysis

of the resultant peptide). The structural and stereochemical identity of microsclerodermin B **393** was performed in an analogous manner.[1a] The same protocol was then applied to microsclerodermins C-I **394-400** upon their isolation a few years later.[1b,1c]

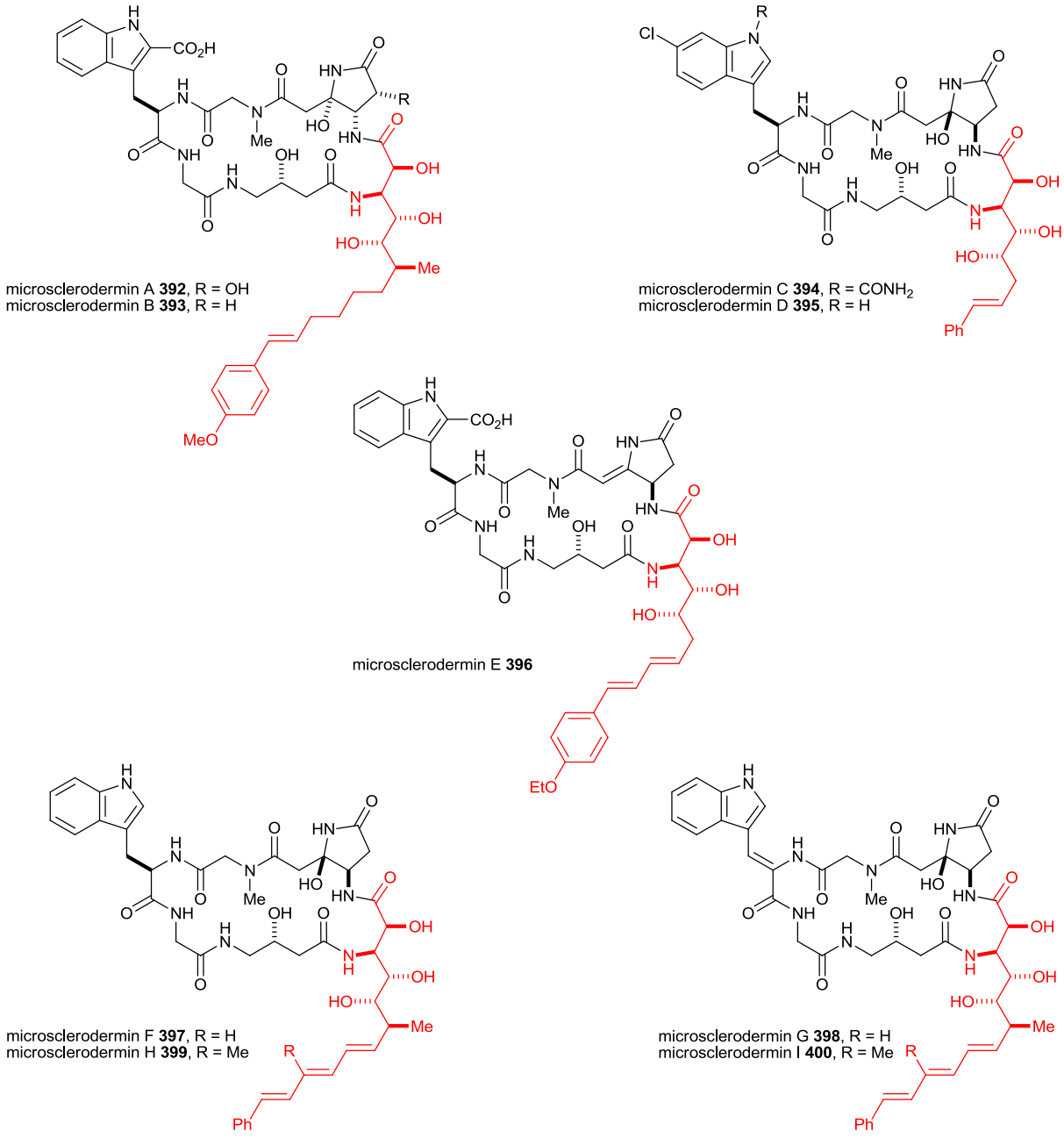
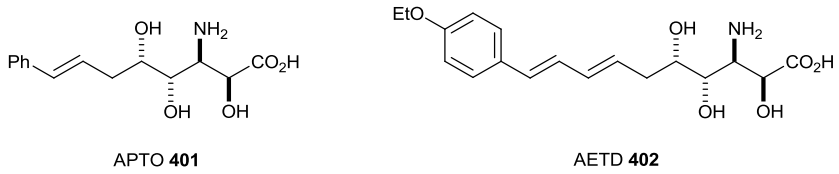


Figure 38. Microsclerodermins A-I **392-400**.

The microsclerodermins have only been isolated in minute quantities from nature and so efficient synthetic routes towards these complex natural products would be most useful, not only due to them being challenging synthetic targets, but also for the highly desirable biological properties that they possess. The structural complexity of this family of natural products is highlighted by the fact that to date there has only been one reported total synthesis of any member of the family, that of microsclerodermin E **396** in 2003 by Zhu and Ma.[2] Crucial building blocks required for construction of each of the microsclerodermins A–I **392-400** are the requisite 2,4,5-trihydroxy substituted β-amino acid residues. Microsclerodermin C **394** and microsclerodermin D **395**, for example, share the common β-amino acid residue (2*S*,3*R*,4*S*,5*S*,*E*)-3-Amino-8-Phenyl-2,4,5-TrihydroxyOct-7-enoic acid

(APTO) **401**, and microsclerodermin E **396** contains a (2*S*,3*R*,4*S*,5*S*,*E*,*E*)-3-Amino-10-(4'-Ethoxyphenyl)-2,4,5-Trihydroxydeca-7,9-Dienoic acid (AETD) **402** residue (Figure 39). As all the 2,4,5-trihydroxy substituted β-amino acid residues found within this family of natural products contain four or five contiguous stereogenic centres and at least one double bond, they are challenging targets in their own right and have been the subject of several syntheses.[2,3]



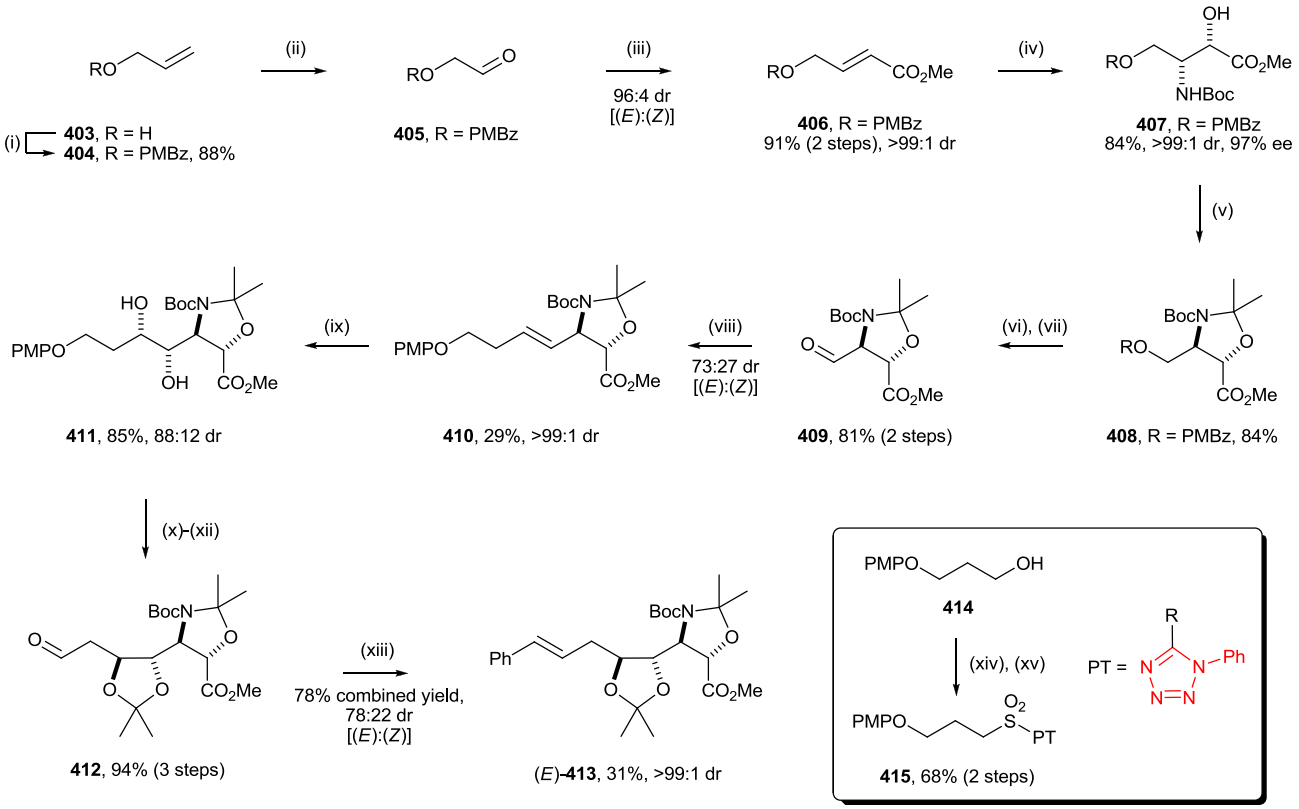
APTO **401** AETD **402**

Figure 39. 2,4,5-Trihydroxy substituted β-amino acid residues APTO **401** and AETD **402**.

4.2 Previous syntheses of APTO 401

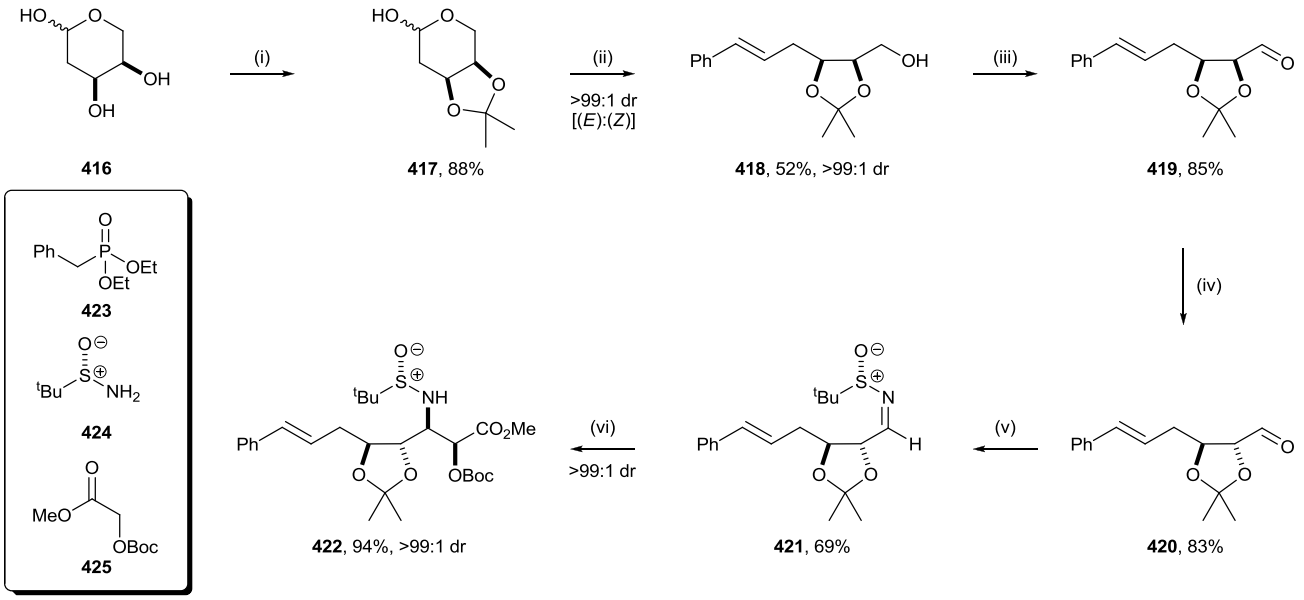
Of all the 2,4,5-trihydroxy substituted β-amino acid residues found within the microsclerodermins, it is APTO **401**, the β-amino acid residue found within microsclerodermins C **394** and D **395**, that has attracted the most interest. In 2007, McLeod *et al*. published a thirteen step synthetic route to **413**, a protected form of APTO **401**.[3c] The route employed successive Sharpless asymmetric aminohydroxylation and dihydroxylation reactions as its key steps, and **413** was isolated in 3% overall yield and >99:1 dr from allyl alcohol **403**. Initial esterification of **403** via treatment with *p*-methoxybenzoyl chloride gave allyl ester **404** in 88% yield. Oxidative cleavage of allyl ester **404** gave aldehyde **405**, which was subjected to a Wadsworth-Emmons reaction with methyl diethylphosphonoacetate to give **406** in 96:4 dr [(*E*):(*Z*)]. Purification via flash column chromatography gave (*E*)-**406** in 91% yield and >99:1 dr over the two steps. Sharpless asymmetric aminohydroxylation of **406** using $(DHQD)_2PHAL$ **51** gave β-amino alcohol **407** in 84% yield, >99:1 dr, and 97% ee. β-Amino alcohol **407** was then protected as the oxazolidine derivative **408** by treatment with DMP and PPTS to give **408** in 84% yield. Transesterification of **408** followed by oxidation of the resultant alcohol using Dess-Martin periodinane gave aldehyde **409** in 81% yield over the two steps. Julia-Kocieński olefination[4,5] of **409** using "PT-sulfone" **415** and KHMDS gave **410** in 73:27 dr [(*E*):(*Z*)], with (*E*)-**410** being subsequently isolated in 29% yield and >99:1 dr after flash column chromatography. Sharpless asymmetric dihydroxylation of **410** (>99:1 dr) using a DHQ-IND ligand gave diol **411** in 85% yield and 88:12 dr. Diol **411** (88:12 dr) was then protected as the corresponding acetonide compound by treatment with DMP and (+)-CSA, which proceeded in 99% yield. Oxidative deprotection of the PMP ether using CAN gave the corresponding primary alcohol, which was oxidised using Dess-Martin periodinane to give aldehyde **412** in 95% yield over the two steps. A Wittig olefination of **412** was then used to install the required styryl functionality:

reaction of **412** with the ylid derived from treatment of benzyltriphenylphosphonium chloride with KHMDS gave a 78:22 [(*E*):(*Z*)] mixture of diastereoisomeric olefins in 78% combined yield. Although the diastereoisomers were inseparable by flash column chromatography, preparative HPLC was then used to obtain a diastereoisomerically pure sample of (*E*)-**413** in 31% yield (Scheme 82).



Scheme 82. *Reagents and conditions:* (i) *p*-methoxybenzoyl chloride, Et_3N, DMAP, CH_2Cl_2, 3 h, rt; (ii) OsO_4 (1 mol%), $NaIO_4$, Et_2O/H_2O (v/v 6:4), rt, 39 h; (iii) $(EtO)_2POCH_2CO_2Me$, BuLi, THF, –78 °C to rt, 5 h; (iv) $^tBuOCONH_2$, $K_2OsO_2(OH)_4$ (5 mol%), $(DHQD)_2PHAL$ **51** (7 mol%), 1,3-dichloro-5,5-dimethylhydantoin, NaOH, PrOH, H_2O, rt, 48 h; (v) DMP, PPTS, PhMe, rt, 2 h then 110 °C, 3 h; (vi) Cs_2CO_3, MeOH, rt, 16 h; (vii) Dess-Martin periodinane, CH_2Cl_2, rt, 1 h; (viii) **415**, KHMDS, 1,2-DME, –60 °C, 45 min; (ix) $K_2OsO_2(OH)_4$ (1 mol%), DHQ-IND (6 mol%), $K_3Fe(CN)_6$ (3 equiv), K_2CO_3 (3.2 equiv), $NaHCO_3$ (3.2 equiv), $MeSO_2NH_2$ (3.2 equiv), $^tBuOH/H_2O$ (v/v 10:11), 17 °C, 10 h then 27 °C, 4 h; (x) DMP, CH_2Cl_2, (+)-CSA, 35 min; (xi) $(NH_4)_2Ce(NO_3)_6$, MeCN, H_2O, 0 °C, 18 min; (xii) Dess-Martin periodinane, CH_2Cl_2, rt, 45 min; (xiii) benzyltriphenylphosphonium chloride, KHMDS, C_6H_6, 0 °C to rt, 1 h; (xiv) PTSH, PPh_3, THF, DIAD, 0 °C to rt, 2.5 h; (xv) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2, EtOH, 0 °C to rt, 20 h.

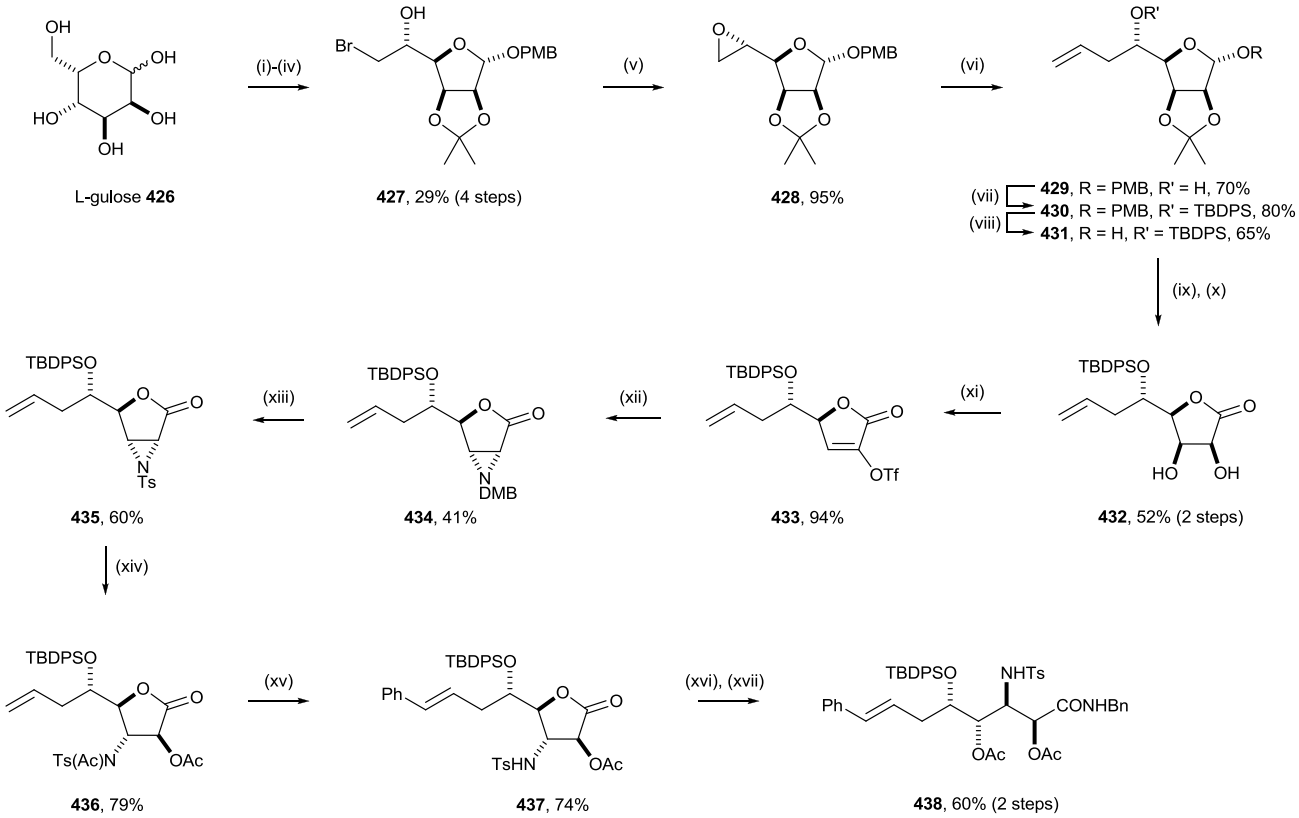
Aitken *et al.*[3a] next reported a short six step synthesis of **422**, a protected form of APTO **401**, from 2-deoxy-D-ribose **416** (21% overall yield from **416**). Acetonide protection of **416** gave 2-deoxy-D-ribose acetonide **417** in 88% average yield, which, upon treatment with phosphonate **423** and BuLi, resulted in opening of the lactone followed by Wadsworth-Emmons olefination of the intermediate aldehyde to give **418** in >99:1 dr [(*E*):(*Z*)]. Alcohol **418** was subsequently isolated in 52% yield and >99:1 dr. Swern oxidation[6] of **418** gave **419** in 85% yield and subsequent epimerisation of **419** using K_2CO_3 in MeOH gave **420** in 83% yield. Aldehyde **420** was then converted into chiral sulfinimine **421** by reaction of **420** with (*S*)-*tert*-butanesulfinimide **424** in the presence of $Ti(OEt)_4$. In the final step, diastereoselective addition of the enolate of **425** (derived from treatment of **425** with LiHMDS) to sulfinimine **421** gave **422**, a protected form of APTO **401**, as a single diastereoisomer which was isolated in 94% yield (Scheme 83).



Scheme 83. *Reagents and conditions:* (i) 2-methoxypropene, DMF, Drierite®, TsOH, 0 ºC, 3 h; (ii) **423**, BuLi, THF, 0 ºC, 20 min then 45 ºC, 19 h; (iii) $(ClCO)_2$, DMSO, CH_2Cl_2, −78 ºC, 1.5 h, then Et_3N, −78 ºC to −5 ºC, 2.5 h; (iv) K_2CO_3, MeOH, rt, 4 h; (v) **424**, $Ti(OEt)_4$, CH_2Cl_2, rt, 5 h; (vi) **425**, LiHMDS, THF, −78 ºC, 30 min.

More recently, Dauban *et al.* reported a synthesis of another protected form of APTO **401** from L-gulose **426** (fifteen steps, 0.7% overall yield from **426**).[3b] L-Gulose **426** was first transformed into primary bromide **427** in four steps and 29% overall yield. Treatment of **427** with CsF in acetone resulted in ring closure to give epoxide **428** in 95% yield. Epoxide **428** was then regioselectively opened by the organocuprate reagent derived from the reaction between vinylmagnesium bromide and catalytic CuI to give the homoallylic alcohol **429**, which was subsequently *O*-silyl protected to give **430** in 56% yield over two steps. Removal of the *O*-PMB protecting group within **430** was then achieved by treatment with DDQ to give lactol **431** in 65% yield. Oxidation of **431** followed by removal of the acetonide functionality gave **432** in 52% yield over the two steps. Treatment of diol **432** with Tf_2O and pyridine provided vinyl triflate **433** in 94% yield, which was then treated with $DMBNH_2$ to give aziridino-γ-lactone **434** in 41% isolated yield. Removal of the *N*-DMB group within **434** by DDQ followed by *N*-tosyl protection with TsCl gave *N*-tosylaziridino-γ-lactone **435** in 60% yield. Regioselective aziridine opening of **435** was then achieved by treatment of **435** with excess Ac_2O in the presence of PBu_3 under microwave irradiation to give **436** exclusively, in 79% isolated yield. In the final step, the required styryl functionality was installed by means of a Heck reaction. Thus, treatment of **436** with PhI, PPh_3, $Pd(OAc)_2$ and Et_3N gave lactone **437**, a protected form of APTO **401**, in 74% yield. In order to avoid product mixtures, it was found that excess Et_3N had to be used to ensure complete *N*-acetyl deprotection during the coupling reaction. As lactone **437** can directly be employed for the formation of a peptide bond, (as would be required for the total synthesis of microsclerodermin C **394** or D **395**) the authors decided to prove the potential of **437** to undergo peptide bond formation: treatment of **437** with $BnNH_2$, followed by treatment of the crude

reaction mixture with excess acetic anhydride in pyridine gave **438**, another protected form of APTO **401**, in 60% yield over the two steps (Scheme 84).



Scheme 84. *Reagents and conditions:* (i) DMP, TsOH, acetone, 36 h, rt; (ii) PMBCl, NaH, DMF, rt, 2.5 h; (iii) AcOH/H_2O (v/v 4:1), 18 h, 30 °C; (iv) CBr_4, PPh_3, THF, 0 °C to rt, 10 h; (v) CsF, acetone, reflux, 6 h; (vi) vinylmagnesium bromide, CuI, THF, –25 °C to rt, 2 h; (vii) TBDPSCl, imidazole, DMF, 0 °C to rt, 22 h; (viii) DDQ, CH_2Cl_2/H_2O (v/v 10:1), rt, 20 h; (ix) TPAP, NMO, MeCN, rt, 3 h; (x) AcOH/H_2O (v/v 4:1), Dean-Stark, 85 °C, 24 h; (xi) Tf_2O, pyridine, CH_2Cl_2, –78 °C to –25 °C, 3 h; (xii) $DMBNH_2$, DMF, –60 °C, 20 min; (xiii) DDQ, CH_2Cl_2/H_2O (v/v 10:1), 20 h, rt then TsCl, pyridine, rt, 2 h; (xiv) PBu_3, Ac_2O, microwave irradiation, PhMe, 90 °C, 2 h; (xv) $Pd(OAc)_2$, PPh_3, Et_3N, PhI, DMF, 110 °C, 24 h; (xvi) $BnNH_2$, THF, rt, 2 h; (xvii) Ac_2O, pyridine, 0 °C to rt, 18 h.

4.3 Chapter aims

It was proposed that new syntheses of APTO **401** (in the first instance) and AETD **402** could be achieved by employing three key steps: (i) a diastereoselective aminohydroxylation reaction involving conjugate addition of an enantiopure lithium amide to an α,β-unsaturated ester followed by *in situ* enolate oxidation using CSO **102**; (ii) a diastereoselective dihydroxylation using OsO_4; and (iii) an olefination reaction to install the terminal styryl unit (Figure 40). It was further anticipated that development of efficient synthetic routes towards APTO **401** and AETD **402** may also be applicable to the synthesis of the β-amino acid fragments of other members of the microsclerodermin family of natural products.

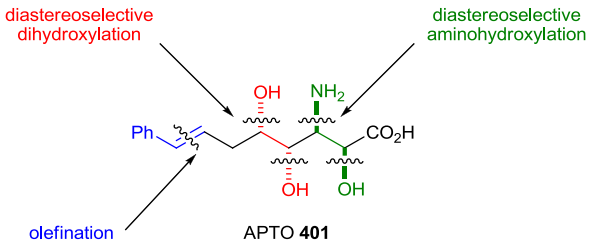
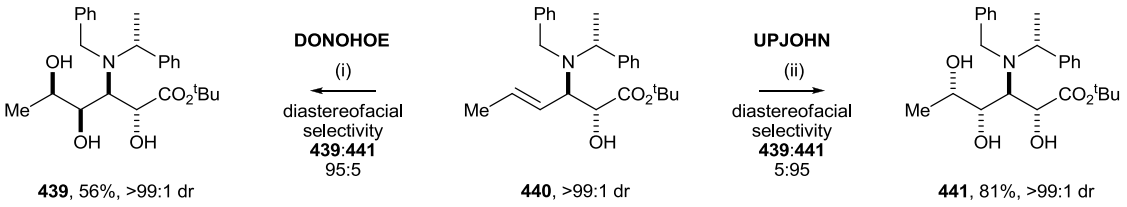


Figure 40. Proposed key steps in the synthesis of APTO **401**.

4.4 Previous work

4.4.1 Precedent for the installation of the required stereocentres within APTO 401

OsO_4 is an efficient reagent for the *syn*-dihydroxylation of olefins. For example, the well-established Upjohn oxidation[7] involves treatment of an olefin with a catalytic amount of OsO_4 in the presence of a tertiary amine *N*-oxide [typically *N*-methylmorpholine-*N*-oxide (NMO)], which acts as a reoxidant to continually oxidise all Os(VI) generated during the reaction back to the active Os(VIII) species. More recently, Donohoe *et al.* have developed alternative reaction conditions involving an OsO_4/TMEDA complex, which has been successful in effecting the highly diastereoselective dihydroxylation of a range of olefins.[8] Antipodal diastereoselectivity has previously been observed in dihydroxylation reactions under Upjohn[7] and Donohoe[8] conditions to substrates that are conformationally constrained and possess an allylic hydrogen-bond donor functionality.[8] In such systems, the opposing diastereofacial selectivities observed are usually explained in terms of the OsO_4/TMEDA complex (Donohoe conditions) being able to participate as a hydrogen-bond acceptor,[8] and therefore being directed to the face of the olefin proximal to the hydrogen bond donor, whilst reaction using OsO_4 alone (Upjohn conditions) is thought to typically proceed under steric or stereoelectronic control.[9] Previous work within the Davies group has focused on the application of the highly diastereoselective and diastereodivergent dihydroxylation reactions of α-hydroxy-β-amino ester **440** for the synthesis of 3,6-dideoxy-3-amino sugars.[10] Dihydroxylation of 2,3-*anti*-**440** under Donohoe conditions gave triol **439** in 95:5 dr and, after purification, **439** was isolated in 56% yield and >99:1 dr. Conversely, the dihydroxylation of 2,3-*anti*-**440** under Upjohn conditions proceeded with antipodal diastereofacial selectivity to give triol **441** in 95:5 dr, and in 81% yield and >99:1 dr after purification (Scheme 85).[10]



Scheme 85. *Reagents and conditions:* (i) OsO_4 (1.1 equiv), TMEDA, CH_2Cl_2, −78 °C, 1 h then $H_2N(CH_2)_2NH_2$, CH_2Cl_2, rt, 16 h; (ii) OsO_4 (10 mol%), NMO, THF/H_2O (v/v 4:1), 12 h, rt.

4.4.2 Previous synthetic efforts towards APTO 401

Previous work by Davies *et al.* towards the synthesis of APTO **401** has resulted in the formation of aldehyde **443** from **442** via a route that employed diastereoselective aminohydroxylation and dihydroxylation as its key steps.[11,12] It was anticipated that aldehyde **443** could be subjected to a Julia-Kocieński or Wittig olefination in order to install the required styryl unit, however, upon attempted Julia-Kocieński olefination and subjection of **443** to LDA and "BT-sulfone" **444**, the strongly basic conditions gave **445**, a result consistent with α-deprotonation of **443** and subsequent E1cB elimination of acetone (Figure 41).[11] A protecting group free strategy was next employed in an attempt to counteract the competing E1cB elimination step; however, when lactone **447** was instead obtained from **446** via the same key aminohydroxylation and dihydroxylation steps, all attempts at oxidation of **447** to aldehyde **448** returned either a complex mixture of products, or starting material **447**, meaning that an olefination reaction could not be attempted (Figure 41).[12]

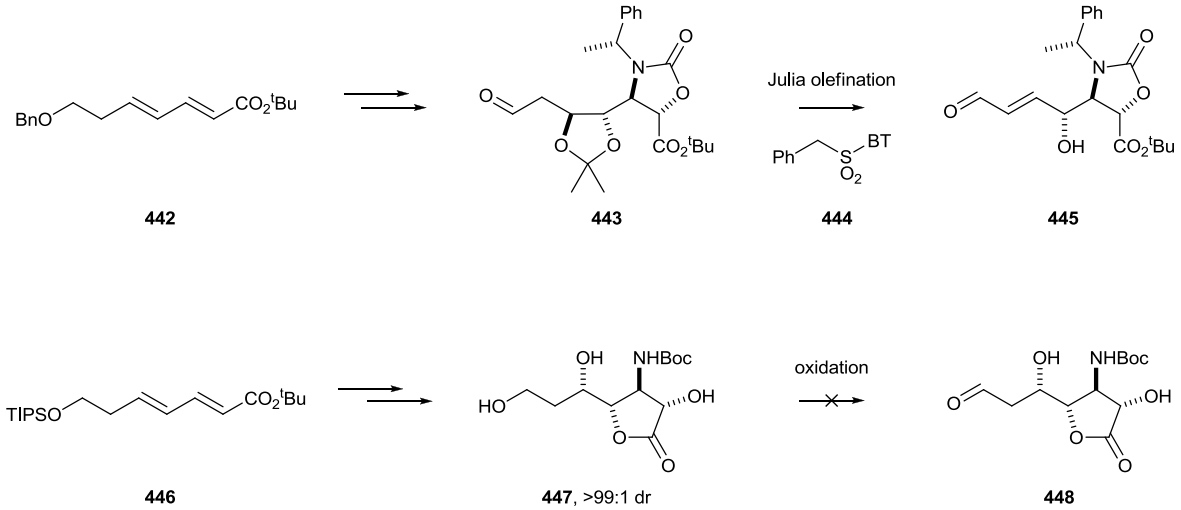


Figure 41. Unsuccessful synthetic routes towards APTO **401**.

In an attempt to counteract these problems, a chain extension protocol that reverses the polarity of the olefin forming step was adopted. It was envisaged that chloride **450** would act as a useful synthetic intermediate that could provide access to the corresponding phosphonium salt or sulfone, for use in a final stage Wittig or Julia-Kocieński olefination, respectively. Thus, chloride **450** was synthesised via *O*-silyl deprotection and subsequent Appel reaction of **449**, which in turn was synthesised from α,β,γ,δ-diunsaturated ester **446**. Unfortunately, all attempts at OsO_4-mediated dihydroxylation of **450** led to a complex mixture of unidentifiable products and so this synthetic route towards APTO **401** had to be abandoned (Figure 42).[12]

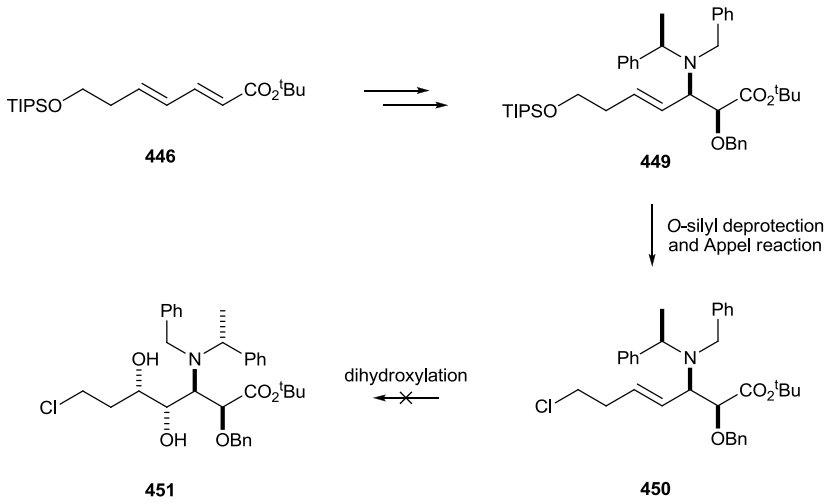


Figure 42. Unsuccessful synthetic route towards APTO **401** involving attempted dihydroxylation of chloride **450**.

4.5 Proposed synthesis of APTO 401

It was anticipated that a new synthesis of APTO **401** could originate from alkyne **452**. Hydrozirconation of **452** with subsequent *in situ* iodinolysis would allow the corresponding vinyl iodide **453** to be formed, which, after Heck coupling with an acrylate, would give α,β-unsaturated ester **454**. A diastereoselective aminohydroxylation reaction of **454** following the procedure established by Davies *et al.* [conjugate addition of lithium amide (*R*)-**106** followed by *in situ* enolate oxidation using (–)-CSO **102**][13] would then give 2,3-*anti*-**455**, which, after epimerisation at the C(2)-position via an oxidation/diastereoselective reduction protocol,[12] was expected to result in 2,3-*syn*-**456**. Diastereoselective dihydroxylation of **456** would then generate **457**, with a final stage olefination reaction involving the corresponding vinyl triflate being required to install the styryl functionality and give access to APTO **401** after global deprotection (Figure 43).

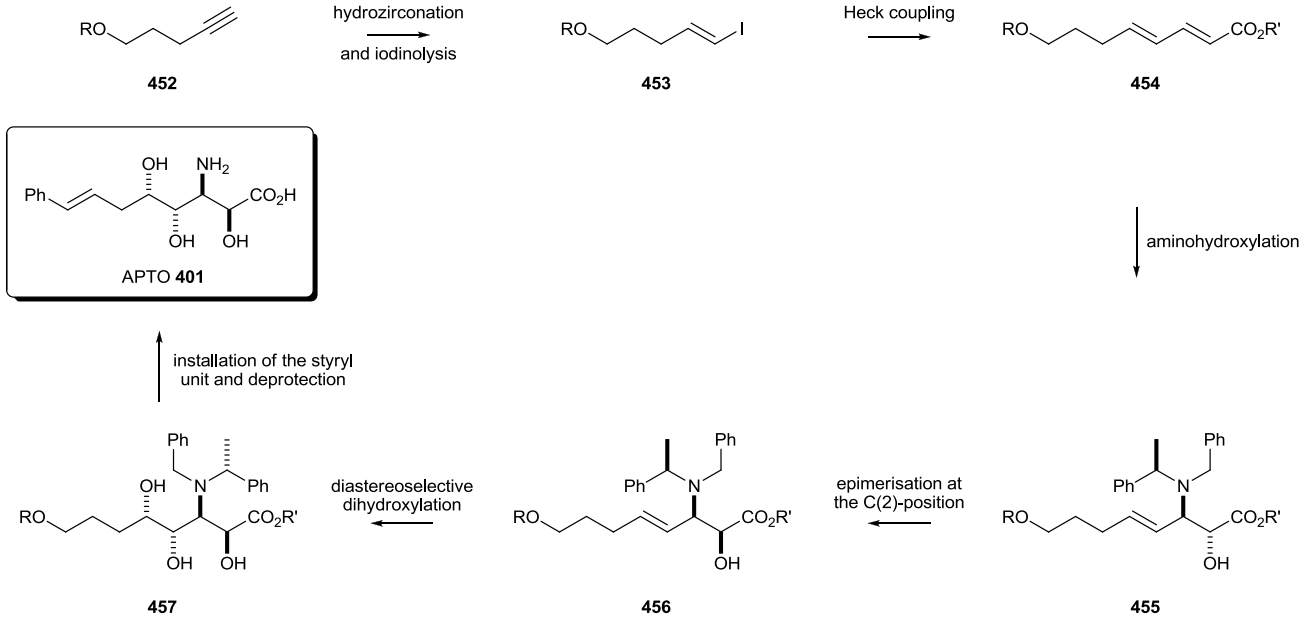
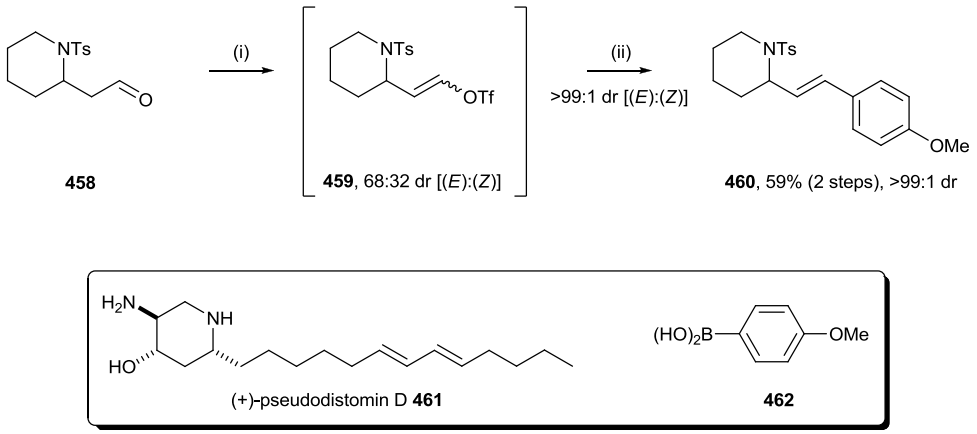


Figure 43. General proposed route for the formation of APTO **401**.

4.5.1 Precedent for the installation of the styryl unit required within APTO 401

Previous work within the Davies group towards the asymmetric synthesis of pseudodistomin D **461**[14] focussed on the development of a protocol for the formation of vinyl triflates and their subsequent reaction with arylboronic acids upon Suzuki coupling.[15] For example, treatment of aldehyde **458** with Tf_2O and $^iPr_2NEt$ in $ClCH_2CH_2Cl$ gave the corresponding vinyl triflate **459** as a 68:32 mixture of (*E*)- and (*Z*)-isomers, respectively. Subsequent Suzuki coupling of **459** with boronic acid **462** at low concentration (0.01 M) was found to give (*E*)-configured olefin **460** exclusively, which was isolated in 59% yield over the two steps (Scheme 86).[16]



Scheme 86. *Reagents and conditions:* (i) $^iPr_2NEt$, Tf_2O, $ClCH_2CH_2Cl$, 80 °C, 18 h; (ii) **462**, $Pd(OAc)_2$ (10 mol%), PPh_3 (22 mol%), 10% aq KOH, 50 °C, 3 h then rt, 16 h.

It was anticipated that this strategy could be applied to the asymmetric synthesis of APTO **401**. Protecting group manipulation of **457** followed by oxidation would allow transformation to aldehyde **463** which, due to the now extended carbon chain, was not expected to suffer the problems of E1cB elimination previously encountered during the final olefination step (*vide supra*). Subsequent subjection of aldehyde **463** to the optimised triflation conditions was therefore expected to give vinyl triflate **464**, which upon Suzuki coupling with phenylboronic acid **465** would allow installation of the required styryl functionality and give APTO **401** after global deprotection (Figure 44).

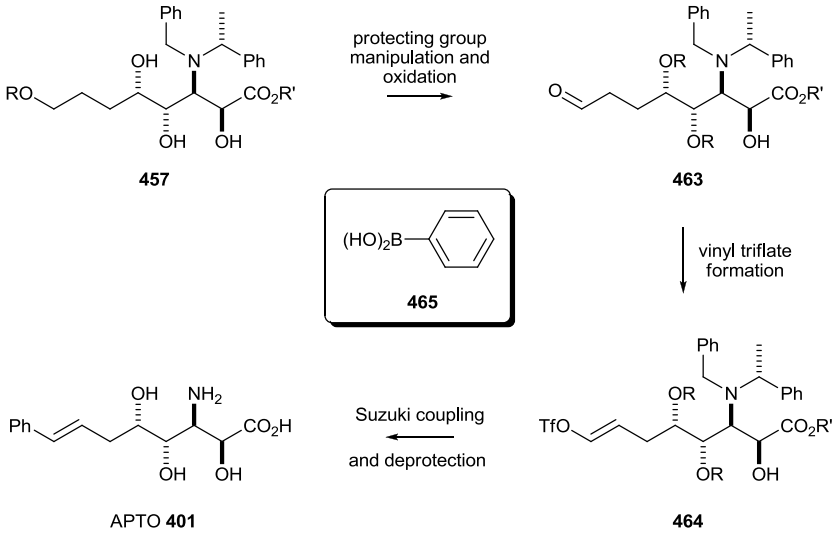
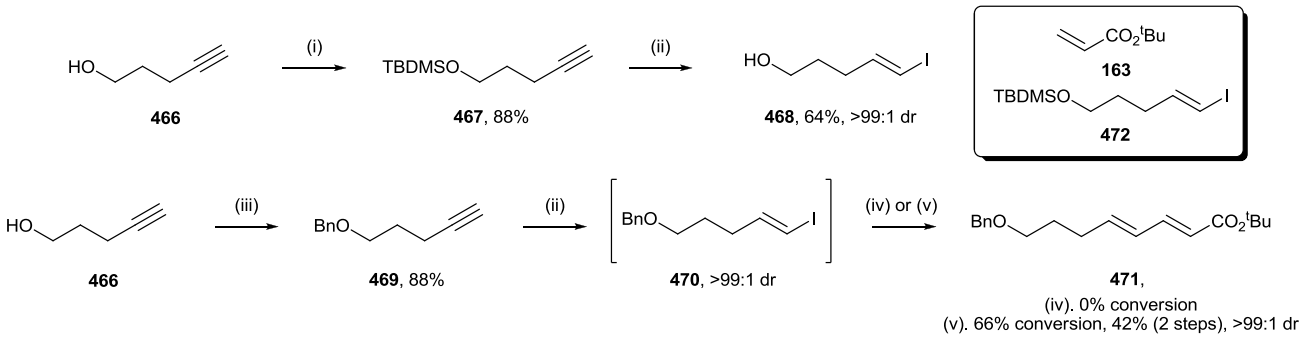


Figure 44. Proposed route for the formation of APTO **401**.

4.6 Synthetic approach to APTO 401 from 4-pentyn-1-ol 466

4.6.1 Substrate preparation

An initial route towards the desired α,β-unsaturated esters **454** involved *O*-TBDMS protection of commercially available 4-pentyn-1-ol **466**. Treatment of **466** with TBDMSCl in the presence of DMAP and imidazole gave **467** in 88% yield. Attempted reduction of **467** using the Schwartz reagent (generated *in situ* from DIBAL-H and Cp_2ZrCl_2),[17] followed by treatment with I_2 was intended to give vinyl iodide **472**. However, *in situ* desilylation also occurred to give alcohol **468**, which was isolated in 64% yield and >99:1 dr. In order to prevent such deprotection occurring, **466** was instead *O*-Bn protected via treatment with NaH and BnBr to give **469** in 88% yield. Reduction of **469** followed by treatment with I_2 gave vinyl iodide **470**, which was immediately subjected to a Heck coupling reaction with *tert*-butyl acrylate **163**. Starting material **470** was the only species recovered from a Heck coupling reaction using $Pd(OAc)_2$ in the presence of Ag_2CO_3 and Et_3N.[18] However, upon changing the conditions to $Pd(OAc)_2$ in the presence of Bu_4NCl and K_2CO_3,[19] the reaction resulted in the formation of α,β-unsaturated ester **471**. Although the reaction proceeded to 100% conversion on a small scale (~100 mg), it was found not to be amenable to scale up with much lower conversions being noted on reactions of ~3.0 g of starting material **470**. The reaction therefore had to be conducted in batches of 1.0 g of **470** and so, on this scale, 66% conversion to **471** was observed and **471** was isolated in 42% yield and >99:1 dr over the two steps. Fortunately, vinyl iodide **470** could easily be recovered and recycled (Scheme 87).

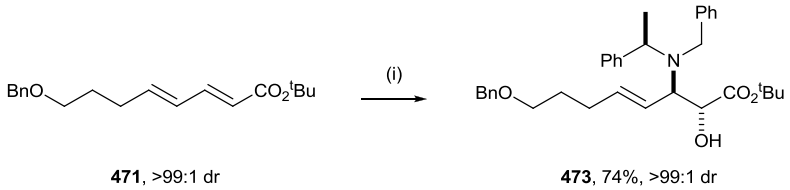


Scheme 87. *Reagents and conditions:* (i) TBDMSCl, DMAP, imidazole, CH_2Cl_2, rt, 16 h; (ii) DIBAL-H, Cp_2ZrCl_2, THF, 0 °C, 30 min then I_2, –78 °C, 1 h; (iii) NaH, THF, rt, 45 min then BnBr, rt, 16 h; (iv) *tert*-butyl acrylate **163**, $Pd(OAc)_2$, Ag_2CO_3, Et_3N, CH_2Cl_2, rt, 16 h; (v) *tert*-butyl acrylate **163**, $Pd(OAc)_2$, Bu_4NCl, K_2CO_3, DMF, rt, 48 h.

4.6.2 Aminohydroxylation and epimerisation at the C(2)-position

Conjugate addition of lithium amide (*R*)-**106** to α,β-unsaturated ester **471** followed by *in situ* enolate oxidation using (–)-CSO **102** gave α-hydroxy-β-amino ester **473** in 74% yield and >99:1 dr. The stereochemical outcome of this reaction was assigned by reference to the transition state mnemonic developed by Davies *et al*. for the conjugate addition of lithium amides to α,β-unsaturated esters[20]

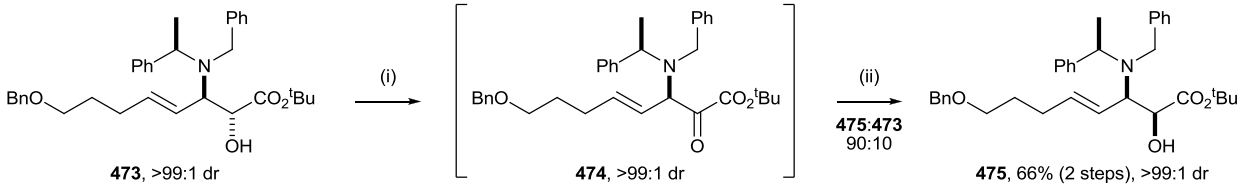
and by analogy to the many α-hydroxy-β-amino esters synthesised using this methodology (Scheme 88).



471, >99:1 dr **473**, 74%, >99:1 dr

Scheme 88. *Reagents and conditions:* (i) (*R*)-**106**, THF, –78 °C, 2 h then (–)-CSO **102**, –78 °C to rt, 12 h.

Epimerisation at the C(2)-position within **473** was achieved by an initial Swern oxidation to give ketone **474** in >99:1 dr, followed by immediate treatment of **474** with $NaBH_4$ in MeOH which gave a 90:10 mixture of **475** and **473**, respectively. The C(2)-epimers were found to be completely separable by flash column chromatography and so 2,3-*syn*-**475** was subsequently isolated as a single diastereoisomer (>99:1 dr) in 66% yield over the two steps. Fortunately, 2,3-*anti*-**473** could easily be recovered and recycled (Scheme 89).



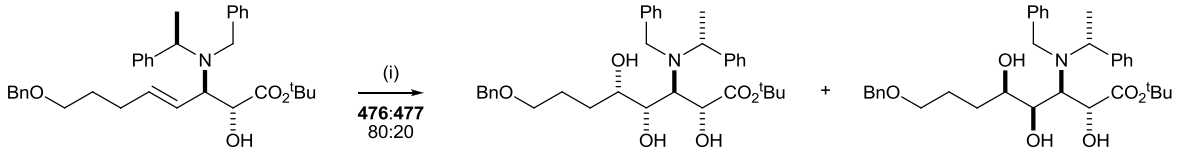
473, >99:1 dr **474**, >99:1 dr **475**, 66% (2 steps), >99:1 dr

Scheme 89. *Reagents and conditions:* (i) $(ClCO)_2$, DMSO, CH_2Cl_2, –78 °C, 15 min, then Et_3N, –78 °C, 10 min; (ii) $NaBH_4$, MeOH, –20 °C, 2 h.

With 2,3-*anti*-**473** and 2,3-*syn*-**475** in hand, it was necessary to embark upon a full investigation into the diastereoselectivity of their OsO_4-mediated dihydroxylation reactions.

4.6.3 OsO_4-mediated dihydroxylations of 473 and 475

Based upon previous results in analogous systems,[10] it was predicted that the Upjohn oxidation of 2,3-*anti*-**473** would result in attack of the OsO_4 reagent to give the (4*S*,5*S*)-diastereoisomer as the major product. The reaction proceeded to give an 80:20 mixture of **476** and **477**, with the stereochemical outcome initially being assigned based upon the result of Upjohn oxidation of **440**. Triols **476** and **477** proved to be completely separable upon flash column chromatography and were consequently isolated in 58 and 10% yield, respectively, and in >99:1 dr in each case (Scheme 90).

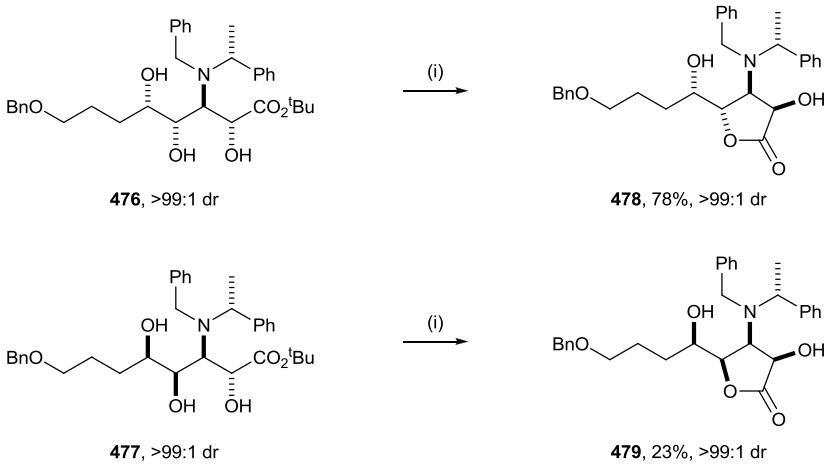


473, >99:1 dr **476**, 58%, >99:1 dr **477**, 10%, >99:1 dr

Scheme 90. *Reagents and conditions:* (i) OsO_4 (10 mol%), NMO, THF/H_2O (v/v 4:1), 12 h, rt.

In an attempt to confirm the stereochemical outcome of the Upjohn oxidation of **473**, **476** and **477** were treated with F_3CCO_2H to give the corresponding lactones **478** and **479**, with the aim that subsequent ^1H NMR NOE spectroscopic analyses might be able to indicate the relative configuration

within the 5-membered rings. Thus, treatment of **476** with F_3CCO_2H gave lactone **478** in 78% yield and >99:1 dr, whilst subjection of **477** to the same conditions gave lactone **479** in 23% yield and >99:1 dr. The low isolated yield for **479** was attributed to problems with purification, as a quantitative crude mass return was noted (Scheme 91).



Scheme 91. *Reagents and conditions:* (i) F_3CCO_2H, CH_2Cl_2, rt, 16 h.

The relative configurations within **478** and **479** were next established via ^{1}H NMR NOE spectroscopic analyses. The connectivity within **478** and **479** was first determined by ^{1}H-^{1}H COSY and ^{1}H-^{13}C HSQC and HMBC analyses. In the case of **479**, ^{1}H NMR NOE spectroscopic analysis displayed reciprocal enhancements between the C(2)*H* and C(3)*H* protons, suggesting a *cis*-relationship, consistent with the assigned stereochemical outcome of the earlier aminohydroxylation reaction. Reciprocal enhancements were also observed between the C(3)*H* and C(4)*H* protons, suggesting another *cis*-relationship across the ring. Finally, an enhancement was seen from the C(4)*H* proton to the C(2)*H* proton. This analysis highlighted that the C(2)*H*, C(3)*H* and C(4)*H* protons within **479** all lie on the same face of the 5-membered lactone ring. Given the well-established stereospecificity of the Upjohn dihydroxylation, the stereochemistry of the C(5)-stereocentre was confidently assigned. The absolute (2*R*,3*S*,4*R*,5*R*,α*R*)-configuration within **479** was therefore assigned by reference to the known (*S*)-configuration of the C(3)-stereocentre, which itself was assigned by reference to the transition state mnemonic for the conjugate addition of (*R*)-**106** to α,β-unsaturated esters.[20] A similar ^{1}H NMR NOE spectroscopic analysis was then carried out for **478**. Reciprocal enhancements were observed between the C(2)*H* and C(3)*H* protons, suggesting a *cis*-relationship across the 5-membered ring (in accord with the assigned stereochemical outcome of the earlier aminohydroxylation reaction). Enhancements from the C(3)*H* proton to the C(5)*H* proton, from the C(5)*H* proton to the C(2)*H* proton, and also from the C(4)*H* proton to the NC*H*$_2$Ph and the C(α)*Me* protons all also served to support the assigned configuration within **478** (Figure 45).

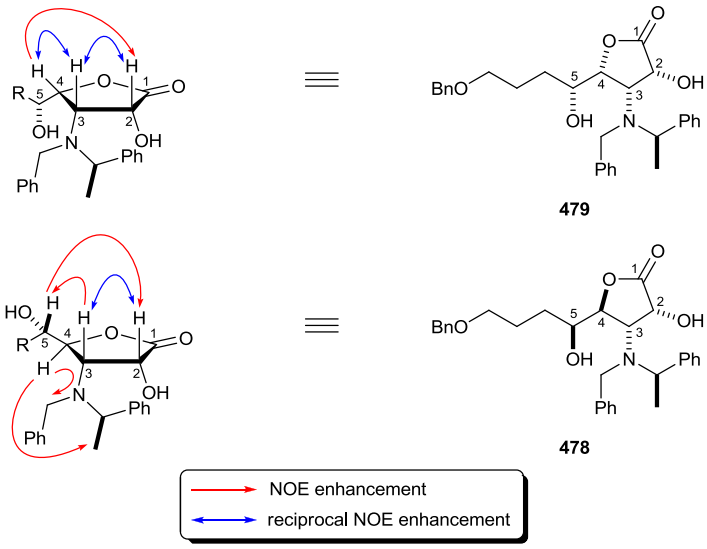
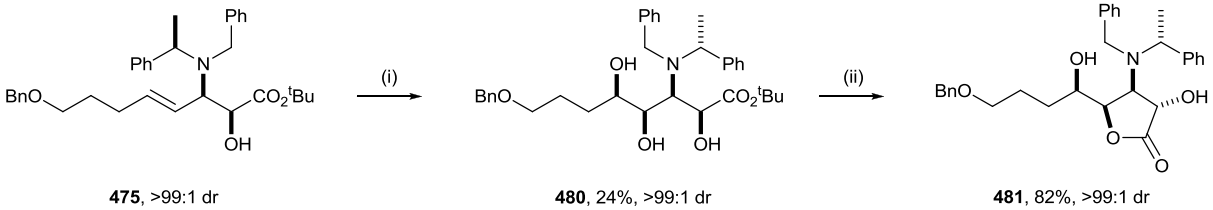


Figure 45. ^{1}H NMR NOE spectroscopic analyses of **478** and **479**. [R = C_3H_6OBn].

The Upjohn oxidation of 2,3-*syn*-**475** was next attempted and based on previous results[21] it was expected that the OsO_4 reagent would attack the olefin to give the (4*R*,5*R*)-diastereoisomer as the major product. Upon reaction of **475** with catalytic OsO_4 and NMO, triol **480** was generated as the sole product, which was subsequently treated with F_3CCO_2H to give lactone **481** in 82% yield and >99:1 dr (Scheme 92). ^{1}H NMR NOE spectroscopic analysis of lactone **481** again served to confirm the predicted stereochemical outcome of the dihydroxylation reaction (Figure 46).[22]



475, >99:1 dr **480**, 24%, >99:1 dr **481**, 82%, >99:1 dr

Scheme 92. *Reagents and conditions:* (i) OsO_4 (10 mol%), NMO, THF/H_2O (v/v 4:1), 12 h, rt; (ii) F_3CCO_2H, CH_2Cl_2, rt, 16 h.

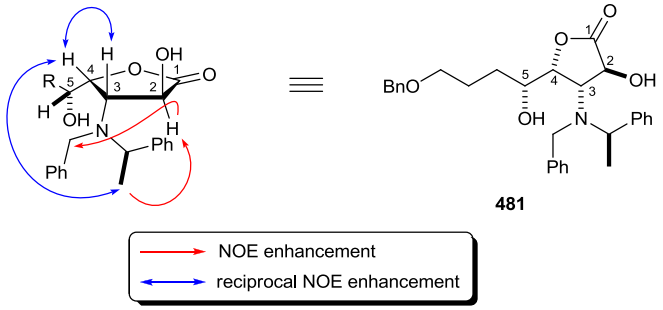
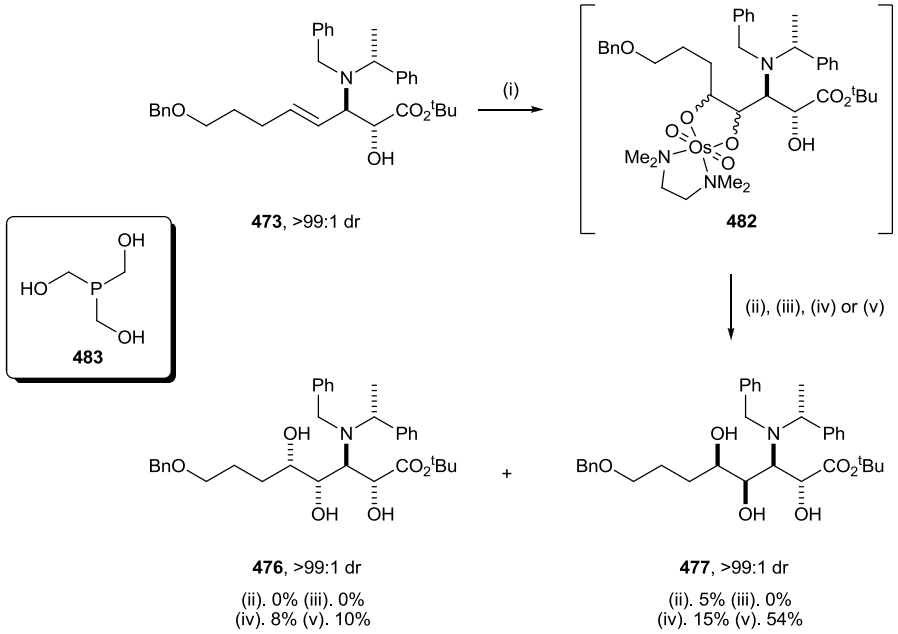


Figure 46. ^{1}H NMR NOE spectroscopic analysis of **481**. [R = C_3H_6OBn].

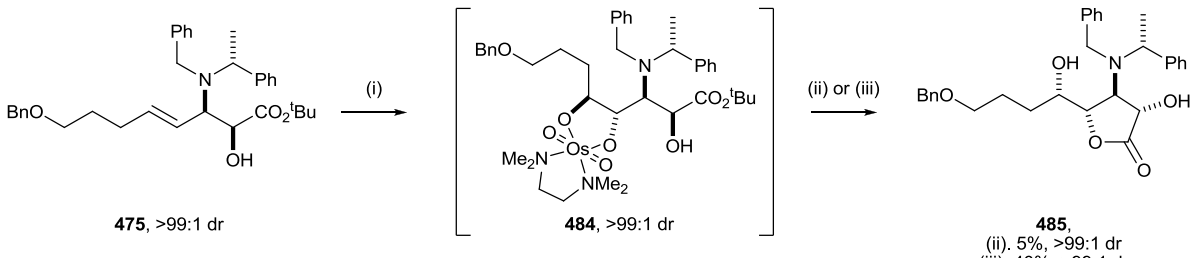
Oxidation of **473** and **475** was next attempted under Donohoe conditions, with the reactions predicted to proceed with antipodal diastereofacial selectivity to that noted during the analogous Upjohn oxidation reactions.[10] Treatment of 2,3-*anti*-**473** with stoicheiometric OsO_4 in the presence of TMEDA gave osmate ester **482**, however subsequent cleavage to the corresponding triol compounds proved problematic. The standard conditions for osmate ester cleavage used by Donohoe *et al.* involve treatment of the osmate ester with ethylenediamine in CH_2Cl_2, followed by filtration of the reaction mixture through SiO_2.[23] For these substrates, very poor mass return was always observed

using the ethylenediamine cleavage procedure, despite many attempts to recover all the mass by, for example, elution with polar solvents and stirring of the SiO_2 in EtOAc for an extended period of time. Alternative osmate ester cleavage procedures were also attempted: treatment of **482** with saturated aqueous Na_2SO_3 in THF at reflux[24] simply returned starting material **482**, whilst treatment of **482** with concentrated HCl in MeOH[8b] gave triols **476** and **477**, albeit in only 8 and 15% yield, respectively. Trishydroxymethylphosphine **483**[25] is a widely used scavenger for the removal of metal residues, particularly after metathesis reactions using the ruthenium-based Grubbs catalysts.[26] It was anticipated that **483** might also be able to act as a scavenger for osmium containing species and thereby allow the osmate ester **482** generated during the Donohoe oxidation of **473** to be cleaved to the corresponding triols. Thus, treatment of **482** with **483** in the presence of Et_3N and SiO_2 gave triols **476** and **477** in improved overall yields: **476** was isolated in 10% yield and >99:1 dr whilst **477** was isolated in 54% yield and >99:1 dr (Scheme 93).



Scheme 93. *Reagents and conditions:* (i) OsO_4 (1.1 equiv), TMEDA, CH_2Cl_2, −78 °C, 1 h; (ii) $H_2N(CH_2)_2NH_2$, CH_2Cl_2, rt, 48 h; (iii) satd aq Na_2SO_3, THF, reflux, 16 h; (iv) conc HCl, MeOH, rt, 16 h; (v) $P(CH_2OH)_3$ **483**, CH_2Cl_2, Et_3N, SiO_2, rt, 48 h.

The Donohoe dihydroxylation of 2,3-*syn*-**475** gave a single osmate ester **484**, within which the stereochemistry was initially assigned by analogy to previous results on similar systems[10] and also by analogy to the Upjohn dihydroxylation result in this system (*vide supra*). Various osmate ester cleavage reactions were again attempted and similar mass return problems were noted. For example, attempted cleavage using the standard conditions of ethylenediamine in CH_2Cl_2 (which also promoted *in situ* lactonisation in this case) gave lactone **485** in 5% isolated yield. The best yield was again observed upon treatment of **484** with **483**, which gave **485** in 40% yield and >99:1 dr (Scheme 94). ^{1}H NMR NOE spectroscopic analysis of lactone **485** served to confirm the predicted stereochemical outcome of the dihydroxylation reaction (Figure 47).[27]



Scheme 94. *Reagents and conditions:* (i) OsO_4 (1.1 equiv), TMEDA, CH_2Cl_2, −78 °C, 1 h; (ii) $H_2N(CH_2)_2NH_2$, CH_2Cl_2, rt, 48 h; (iii) $P(CH_2OH)_3$ **483**, CH_2Cl_2, Et_3N, SiO_2, rt, 48 h.

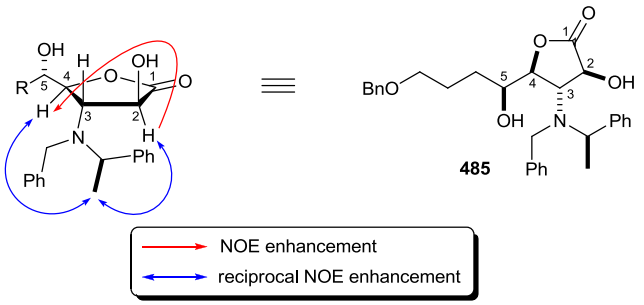


Figure 47. ^{1}H NMR NOE spectroscopic analysis of **485**. [R = C_3H_6OBn].

With a full investigation into the OsO_4-mediated dihydroxylation reactions of **473** and **475** completed, attention was now turned to the further elaboration of **485** towards APTO **401** (Figure 48).

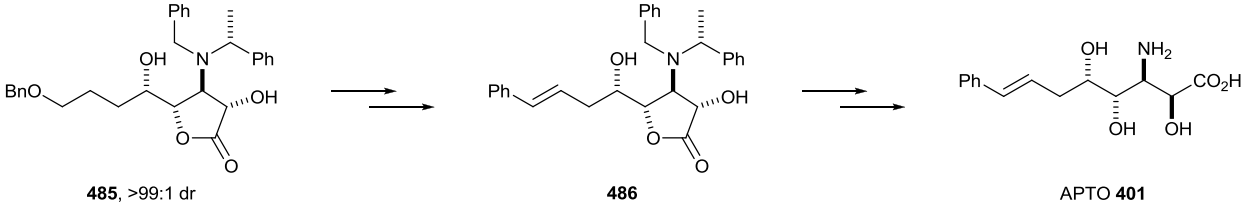
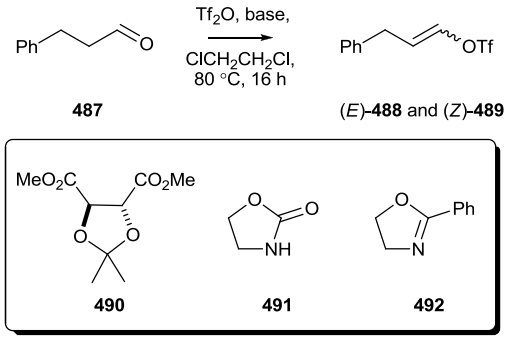


Figure 48. Elaboration of **485** to APTO **401**.

4.6.4 Vinyl triflate formation and Suzuki coupling in a model system

The proposed route towards APTO **401** intended for the use of a late stage Suzuki coupling of a vinyl triflate with phenylboronic acid **465** (*vide supra*). In the first instance, it was decided to test the vinyl triflate formation and subsequent coupling reactions on a model system and so hydrocinnamaldehyde **487** was chosen for this purpose. Subjection of **487** to the previously optimised conditions[16] for the formation of a vinyl triflate (i.e., heating at 80 °C in $ClCH_2CH_2Cl$ for 16 h in the presence of Tf_2O and $^iPr_2NEt$) gave a 12:88 mixture of (*E*)-**488** and (*Z*)-**489**, respectively. Employing 2,6-lutidine as an alternative base did little to improve the diastereoselectivity, as a 14:86 mixture of (*E*)-**488** and (*Z*)-**489** was instead recovered. It was clear to see that the formation of the (*Z*)-configured vinyl triflate **489** was favoured in this system and under these conditions (Scheme 95). It was decided to test the suitability of potential future protecting groups by repeating the reaction in the presence of a range of additives: a diester containing a *trans*-configured acetonide **490**, an oxazolidinone **491** and an oxazoline **492**. The (*E*):(*Z*) ratios were found to be variable; however, in all cases the (*Z*)-isomer **489** was still found to dominate. It was interesting to note that all of the added compounds **490**, **491**

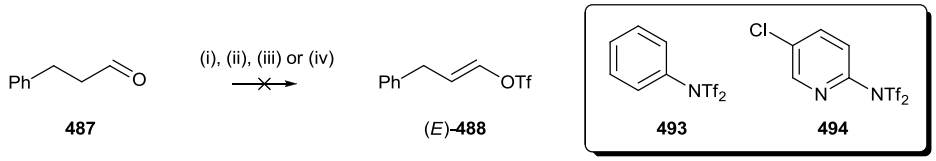
and **492** were found to be unstable to the reaction conditions, indicating that they would be incompatible with the proposed protecting group strategy for the synthesis of APTO **401** (Scheme 95).



base	additive	(*E*)-488:(*Z*)-489
$^{i}Pr_2NEt$	-	12:88
$^{i}Pr_2NEt$	**490**	2:98
$^{i}Pr_2NEt$	**491**	33:67
$^{i}Pr_2NEt$	**492**	7:93
2,6-lutidine	-	14:86

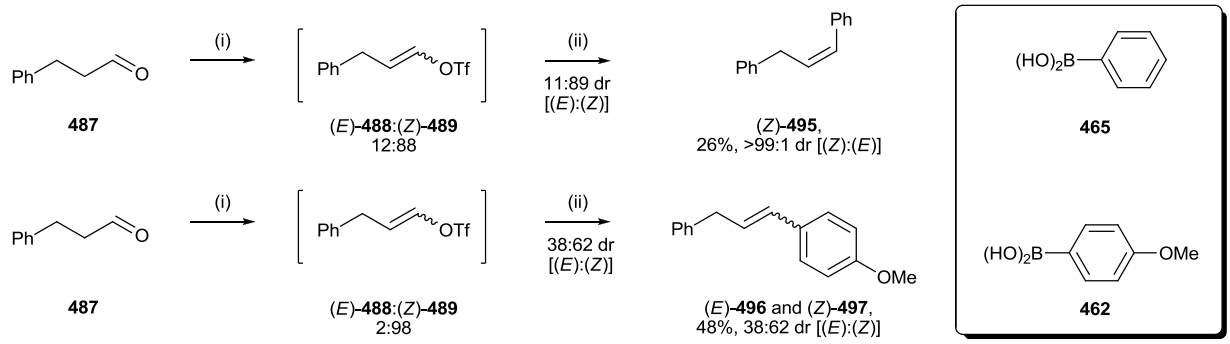
Scheme 95. *Reagents and conditions:* see table.

In the hope of finding an (*E*)-selective procedure for the formation of the required vinyl triflate **488**, a number of alternative procedures were attempted. A range of reaction conditions were attempted using alternative triflation reagents **493** and **494**[28] (Comin's triflimide); however, in all cases starting material **487** was returned (Scheme 96).



Scheme 96. *Reagents and conditions:* (i) **493**, $ClCH_2CH_2Cl$, $^{i}Pr_2NEt$, 80 °C, 16 h; (ii) **493**, NaHMDS, THF, –78 °C, 1.5 h; (iii) **493**, K_2CO_3, dioxane, H_2O, rt, 2 h; (iv) **494**, NaHMDS or KHMDS, THF, –78 °C, 1.5 h.

It was decided to attempt the Suzuki couplings on the obtained mixtures of vinyl triflates (*E*)-**488** and (*Z*)-**489**, as previous work had shown that conducting the coupling reactions at low concentrations could result in an enhancement of (*E*)-diastereoselectivity (*vide supra*).[16] A sample of a 12:88 mixture of (*E*)-**488** and (*Z*)-**489** was treated with phenylboronic acid **465**, $Pd(OAc)_2$, PPh_3 and 10% aqueous KOH to give (*Z*)-**495** in 89:11 dr [(*Z*):(*E*)], which was subsequently isolated in 26% yield and >99:1 dr. Similarly, a sample of a 2:98 mixture of (*E*)-**488** and (*Z*)-**489** was treated with *p*-methoxyphenylboronic acid **462** under the same conditions to give a 38:62 mixture of (*E*)-**496** and (*Z*)-**497**, respectively. It was therefore clear to see that the (Z)-configured coupling products were the major products of these Suzuki reactions, and that only a minor enhancement of the (*E*)-diastereoselectivity was apparent upon conducting the reactions under dilute conditions (Scheme 97).



Scheme 97. *Reagents and conditions:* (i) $^{i}Pr_2NEt$, Tf_2O, $ClCH_2CH_2Cl$, 80 °C, 18 h; (ii) **462** or **465**, $Pd(OAc)_2$ (10 mol%), PPh_3 (22 mol%), 10% aq KOH, 50 °C, 3 h then rt, 16 h.

A model system for the installation of a styryl unit via the Suzuki coupling of a vinyl triflate (derived from the corresponding aldehyde) with an arylboronic acid had therefore been investigated. Unfortunately, the coupling reactions gave mixtures of (*E*)- and (*Z*)-configured olefinic products, within which the (*Z*)-configured products were found to predominate. As the target β-amino acids APTO **401** and AETD **402** demand an (*E*)-configured double bond, it was apparent that this strategy was no longer a desirable route towards **401** and **402**. In addition, the proposed protecting group strategy would evidently not be compatible and so an alternative strategy was devised.

4.7 Synthetic approach to APTO 401 from 3-butyn-1-ol 502

Attention was again turned to a chain extension protocol in which the polarity of the olefin forming step is reversed, and two alternative strategies towards APTO **401** were proposed. The first approach (route A) would involve regioselective dihydroxylation of γ,δ,ζ,η-diunsaturated-α-hydroxy-β-amino ester **500** using Donohoe's conditions to give **498**, with **500** itself being derived from α-hydroxy-β-amino ester **501** via olefination involving the hydroxyl group at C(6) as a synthetic handle (by, for example, a Wittig or Julia-Kocieński reaction). This route also posed the benefit of being a model system for the olefination step. In the alternative approach (route B), it was anticipated that dihydroxylation of **501** under Donohoe's conditions could be attempted to give **499**, which, upon olefination involving elaboration of the hydroxyl group at C(6), could lead to **498**, a protected form of APTO **401**. Although both routes are reliant on the chemoselective functionalisation of a primary alcohol over a secondary alcohol, the wealth of literature precedent[29] suggested this to be a more viable option than the selective oxidation strategy previously employed (*vide supra*)[12] (Figure 49).

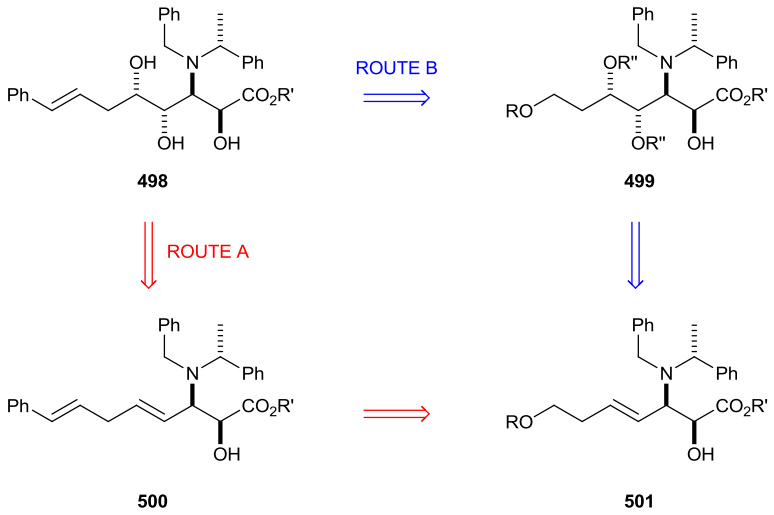
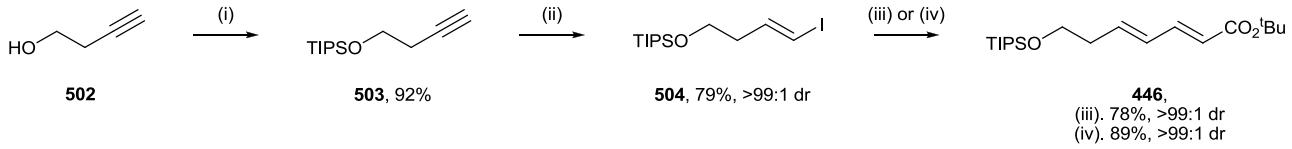


Figure 49. Revised strategies to access APTO **401**.

4.7.1 Substrate preparation and aminohydroxylation

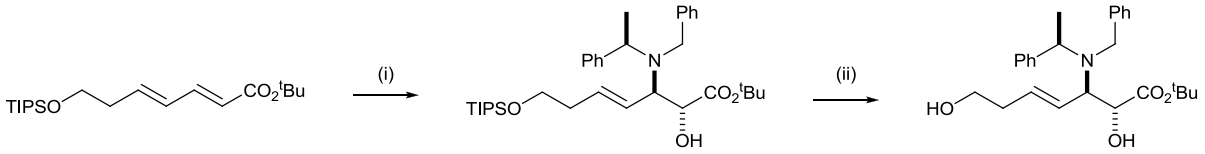
The required shortened chain α,β-unsaturated ester **446** was prepared from commercially available 3-butyn-1-ol **502** in three steps following a procedure already established by Davies *et al.*[12] Firstly, **502** was treated with TIPSCl in the presence of DMAP and imidazole to give **503** in 92% yield. Reduction of **503** using the *in situ* generated Schwartz reagent,[17] followed by treatment with I_2 gave vinyl iodide **504** in 79% yield in a completely (*E*)-selective process. Finally, Heck coupling of **504** with *tert*-butyl acrylate **163** [using $Pd(OAc)_2$ in the presence of Bu_4NCl and K_2CO_3][19] gave **446** in 78% yield and >99:1 dr. In contrast to earlier results for the synthesis of **471**, the alternative Heck coupling of **504** with *tert*-butyl acrylate **163** [using $Pd(OAc)_2$ in the presence of Ag_2CO_3 and Et_3N][18] gave α,β,γ,δ-diunsaturated ester **446**, which was isolated in an improved 89% yield and >99:1 dr (Scheme 98).



Scheme 98. *Reagents and conditions:* (i) TIPSCl, DMAP, imidazole, CH_2Cl_2, rt, 16 h; (ii) DIBAL-H, Cp_2ZrCl_2, THF, 0 °C, 30 min then I_2, –78 °C, 1 h; (iii) *tert*-butyl acrylate **163**, $Pd(OAc)_2$, Bu_4NCl, K_2CO_3, DMF, rt, 48 h; (iv) *tert*-butyl acrylate **163**, $Pd(OAc)_2$, Ag_2CO_3, Et_3N, CH_2Cl_2, rt, 16 h.

As before, conjugate addition of (*R*)-**106** to α,β-unsaturated ester **446** followed by *in situ* enolate oxidation using (–)-CSO **102** gave α-hydroxy-β-amino ester **505** as a single diastereoisomer (>99:1 dr), which was isolated in 72% yield and >99:1 dr. The stereochemical outcome of the conjugate addition reaction was again initially assigned by reference to the transition state mnemonic developed by Davies *et al.* for the conjugate addition of lithium amides to α,β-unsaturated esters.[20] Subsequent treatment of **505** with TBAF gave **506** in 90% yield and >99:1 dr (Scheme 99). As **506** proved to be crystalline, the relative configuration within **506** was unambiguously assigned via single crystal X-ray diffraction analysis,[30] with the absolute configuration being assigned from the known

(*R*)-configuration of the α-methylbenzyl stereocentre. The absolute configuration within **505** could therefore also be unambiguously assigned (Figure 50).



446, >99:1 dr **505**, 72%, >99:1 dr **506**, 90%, >99:1 dr

Scheme 99. *Reagents and conditions:* (i) (*R*)-**106**, THF, –78 °C, 2 h then (–)-CSO **102**, –78 °C to rt, 12 h; (ii) TBAF, THF, rt, 16 h.

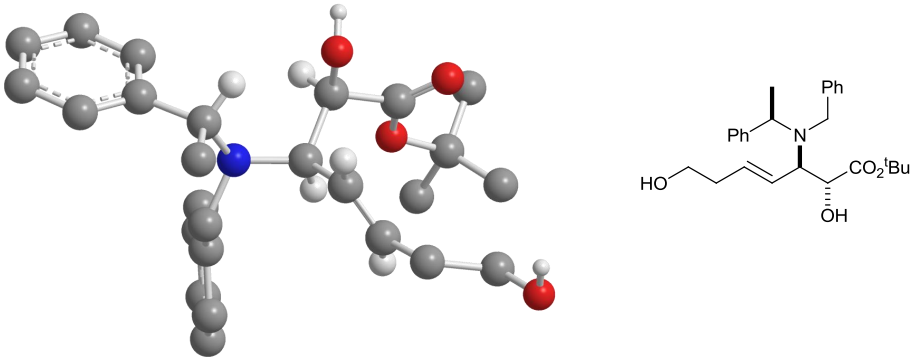
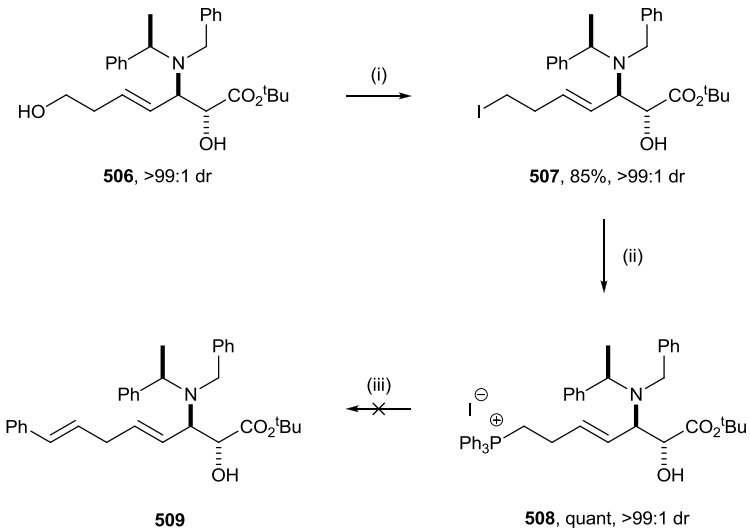


Figure 50. X-ray crystal structure of **506** (selected H atoms have been omitted for clarity).

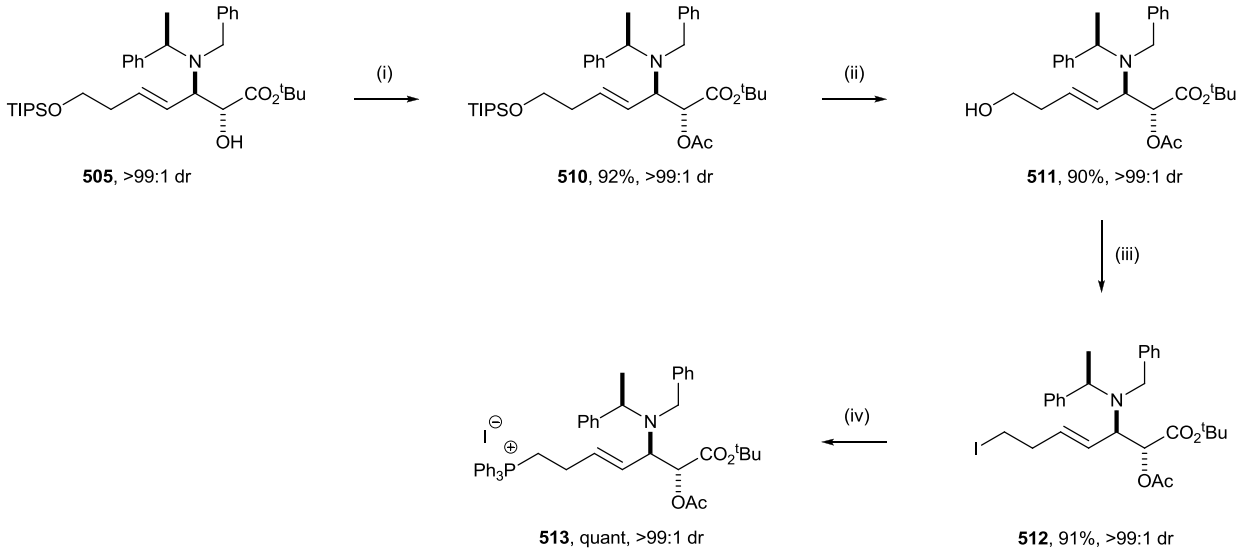
4.7.2 Olefination reactions for the installation of the styryl unit

With these results in hand, it was decided to follow route A (*vide supra*) and further elaborate 2,3-*anti*-**506** for use as a model system for the installation of the terminal styryl unit. Initial studies focussed on the use of a Wittig olefination, which therefore required the transformation of **506** into the corresponding phosphonium salt **508**. Thus, diol **506** was subjected to I_2 and PPh_3 in PhMe/MeCN to give iodide **507** in 85% yield and >99:1 dr, with no evidence of the corresponding diiodide being observed in the ^{1}H NMR spectrum of the crude reaction mixture. Subsequent treatment of **507** with PPh_3 in MeCN gave **508** in quantitative yield. A number of standard Wittig procedures were investigated: these involved treatment of **508** with a base (BuLi, NaHMDS or KHMDS) to form the corresponding ylid, followed by the addition of PhCHO. Unfortunately, all Wittig olefination attempts of **508** resulted in complex mixtures of products being formed (Scheme 100).



Scheme 100. *Reagents and conditions:* (i) I_2, PPh_3, imidazole, PhMe/MeCN (v/v 4:1), 60 °C, 1 h; (ii) PPh_3, MeCN, reflux, 48 h; (iii) BuLi, NaHMDS or KHMDS, then PhCHO.

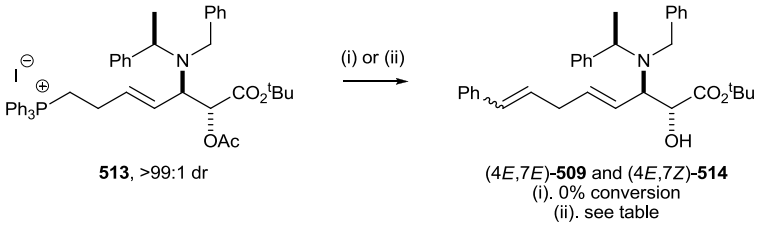
It was next decided to repeat the Wittig reactions using the corresponding C(2)-*O*-acetyl protected phosphonium iodide **513** in the hope of improving the olefination reaction outcome. Thus, the C(2)-hydroxyl functionality within **505** was firstly *O*-acetyl protected by treatment with Ac_2O and DMAP in pyridine to give **510** in 92% yield and >99:1 dr. Subsequent treatment of **510** with TBAF effected desilylation to give **511** in 90% yield and >99:1 dr. Appel reaction of **511** gave the corresponding iodide **512** in 91% yield, which was then dissolved in MeCN and heated at reflux in the presence of PPh_3 to effect a displacement reaction and give the desired phosphonium iodide **513** in quantitative yield (Scheme 101).



Scheme 101. *Reagents and conditions:* (i) Ac_2O, DMAP, pyridine, 24 h, rt; (ii) TBAF, THF, 16 h, rt; (iii) I_2, PPh_3, imidazole, PhMe/MeCN (v/v 4:1), 60 °C, 1 h; (iv) PPh_3, MeCN, reflux, 48 h.

An alternative Wittig literature procedure involving the use of K_2CO_3 as the base was first attempted.[31] Despite the procedure demanding harsh conditions with the reaction mixtures being held at reflux (in dioxane/H_2O) for 72 h, conversion to the olefinated products (4*E*,7*E*)-**509** and (4*E*,7*Z*)-**514** was indeed observed, along with hydrolysis of the C(2)-acetate group. Varying the dioxane/H_2O solvent ratios resulted in a change in the (*E*):(*Z*) diastereoselectivity for the olefination

reaction, with a 50:50 solvent mixture being found to most favour the formation of (4*E*,7*E*)-**509** [87:13 dr (4*E*,7*E*):(4*E*,7*Z*)]. Unfortunately, the olefination reactions always resulted in mixtures of (4*E*,7*E*)-**509** and (4*E*,7*Z*)-**514**, which proved to be inseparable via flash column chromatography (Scheme 102).



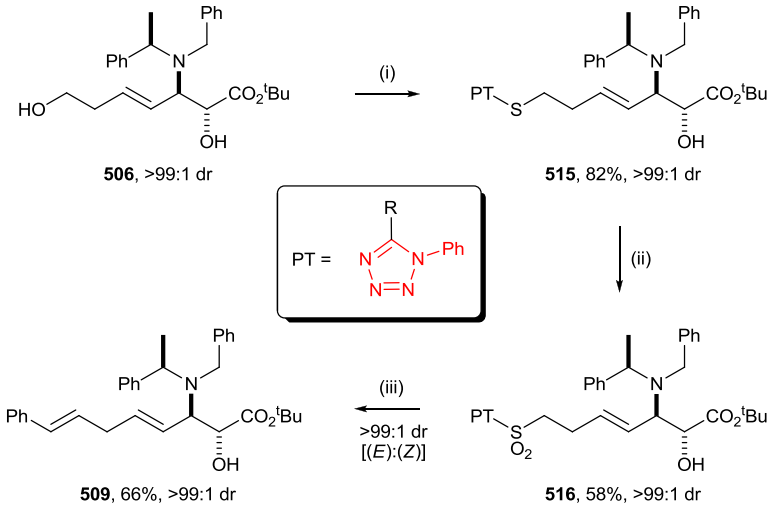
513, >99:1 dr

(4*E*,7*E*)-**509** and (4*E*,7*Z*)-**514**
(i). 0% conversion
(ii). see table

dioxane/H_2O (v/v)	509:514
33:67	65:35
50:50	87:13
67:33	70:30

Scheme 102. *Reagents and conditions:* (i) BuLi, NaHMDS or KHMDS, then PhCHO; (ii) K_2CO_3, PhCHO, dioxane/H_2O (v/v, see table), reflux, 72 h.

Due to the lack of success obtained from Wittig olefination reactions of **508** and **513**, it was decided to instead attempt to install the styryl unit via a Julia-Kocieński olefination of **516** with PhCHO. To this end, chemoselective Mitsunobu reaction[32] of the primary hydroxyl group within diol **506** with 1-phenyl-1*H*-tetrazole-5-thiol (PTSH) gave sulfide **515** in 82% yield and >99:1 dr. Oxidation of **515** to the corresponding sulfone **516** was achieved via treatment of **515** with H_2O_2 and ammonium molybdate tetrahydrate[33] to give **516** in 58% isolated yield and >99:1 dr. Subsequent Julia-Kocieński olefination of sulfone **516**, upon sequential treatment with KHMDS and PhCHO, gave **509** with complete (*E*)-diastereoselectivity; diene (4*E*,7*E*)-**509** was then isolated in 66% yield and >99:1 dr (Scheme 103).



506, >99:1 dr

515, 82%, >99:1 dr

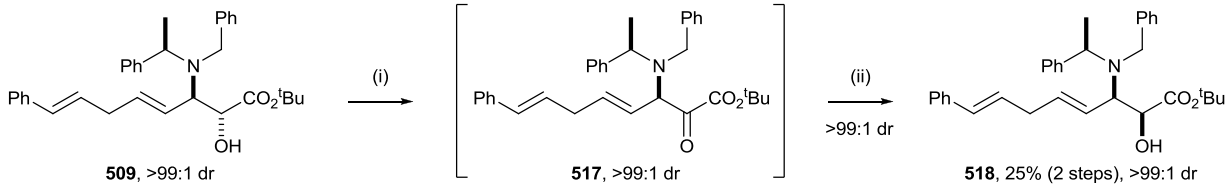
509, 66%, >99:1 dr

516, 58%, >99:1 dr

Scheme 103. *Reagents and conditions:* (i) PTSH, DEAD, PPh_3, THF, 0 °C to rt, 16 h; (ii) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2 (30% aq), EtOH, 0 °C to rt, 16 h; (iii) KHMDS, PhCHO, –78 °C, 30 min.

With an efficient protocol now in place for the installation of the terminal styryl group, attention was turned to the attempted regio- and diastereoselective dihydroxylation of **518**. As both APTO **401** and AETD **402** require a 2,3-*syn* configuration, it was therefore proposed that it would be possible to access the C(2)-epimer of **509** using the oxidation/diastereoselective reduction procedure already established.[12] Swern oxidation of 2,3-*anti*-**509** gave ketone **517** in 100% conversion and >99:1 dr, and then immediate treatment of **517** with $NaBH_4$ gave 2,3-*syn*-**518** as a single diastereoisomer

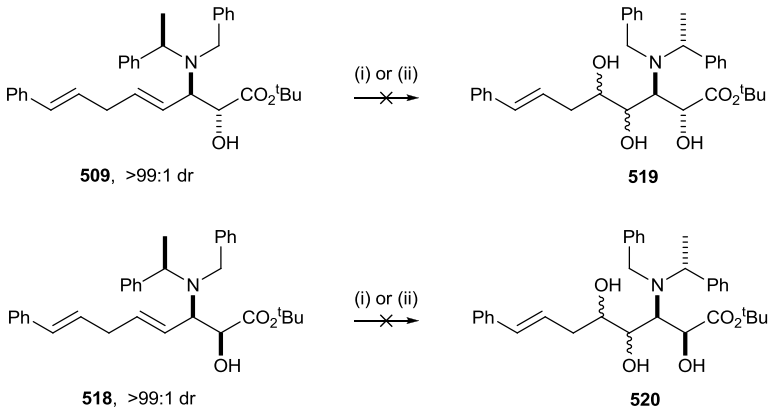
(>99:1 dr), which was isolated in 25% yield over the two steps and >99:1 dr. The low isolated yield was attributed to the small scale of the reaction (Scheme 104).



509, >99:1 dr **517**, >99:1 dr **518**, 25% (2 steps), >99:1 dr

Scheme 104. *Reagents and conditions:* (i) $(ClCO)_2$, DMSO, CH_2Cl_2, –78 °C, 15 min, then Et_3N, –78 °C, 10 min; (ii) $NaBH_4$, MeOH, –20 °C, 2 h.

Based on literature precedent,[8c,34] the regioselective dihydroxylations of the internal double bonds within **509** and **518** were next attempted. Upjohn oxidation [OsO_4 (10 mol%), and NMO] of **509** and **518** unfortunately resulted in over oxidation, as no olefinic protons could be observed in the ^{1}H NMR spectra of the crude reaction mixtures. Donohoe oxidation [OsO_4 (1.1 equivalents), and TMEDA] of **509** and **518** appeared to result in preferential oxidation of the styryl unit in both cases: despite the ^{1}H NMR spectra of the crude reaction mixtures being quite complex, simultaneous analysis of the ^{1}H-^{1}H COSY spectra confirmed the connectivities within the crude products to be consistent with the regioselective oxidation of the styryl unit (Scheme 105).



509, >99:1 dr **519**

518, >99:1 dr **520**

Scheme 105. *Reagents and conditions:* (i) OsO_4 (10 mol%), NMO, THF/H_2O (v/v 4:1), 12 h, rt; (ii) OsO_4 (1.1 equiv), TMEDA, CH_2Cl_2, –78 °C, 1 h.

These results had shown that it was not possible to selectively oxidise the C(4)=C(5) bond in the presence of the styryl unit, and as such an alternative synthetic route involving oxidation of this double bond prior to installation of the styryl unit had to be investigated (route B, *vide supra*). Although these dihydroxylation reactions had not been successful, the methodology developed to synthesise **509** and **518**, and in particular to install the terminal styryl unit via a Julia-Kocieński olefination, was now in place in this model system and would prove to be invaluable in the ultimate syntheses of APTO **401** and AETD **402**.

4.7.3 Epimerisation at the C(2)-position and OsO_4-mediated dihydroxylations

An alternative approach was therefore adopted starting from α-hydroxy-β-amino ester **521**. This route was proposed to involve epimerisation at the C(2)-stereocentre followed by OsO_4-mediated

oxidation of the double bond prior to the introduction of the styryl unit via a Julia-Kocieński olefination (Figure 51).

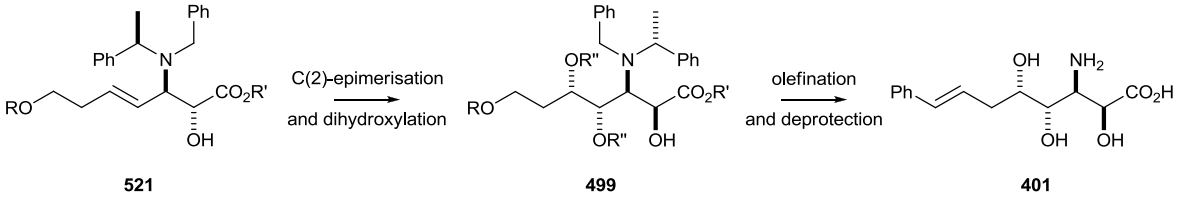
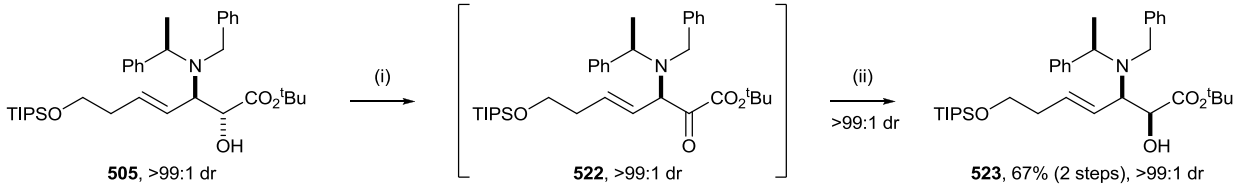


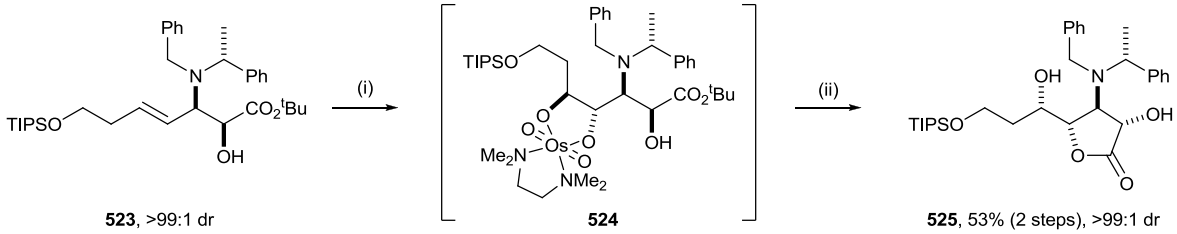
Figure 51. Revised route towards APTO **401**.

As the APTO **401** and AETD **402** fragments of microsclerodermins C, D and E **394**-**396** both demand a 2,3-*syn* configuration, the oxidation/diastereoselective reduction protocol was first applied to **505**. Thus, Swern oxidation of 2,3-*anti*-**505** gave ketone **522** in >99:1 dr, which was immediately reduced upon treatment with $NaBH_4$ in MeOH to give 2,3-*syn*-**523** in >99:1 dr, which was subsequently isolated in 67% yield and >99:1 dr over the two steps (Scheme 106).



Scheme 106. *Reagents and conditions:* (i) $(ClCO)_2$, DMSO, CH_2Cl_2, –78 °C, 15 min, then Et_3N, –78 °C, 10 min; (ii) $NaBH_4$, MeOH, –20 °C, 2 h.

By analogy to earlier work and studies on similar systems,[10] it was again anticipated that dihydroxylation of **523** using Donohoe oxidation conditions would result in the installation of a 4,5-diol unit with the correct configuration required to match the reported structures of APTO **401** and AETD **402**. Upjohn oxidation of **523** was therefore expected to give rise to dihydroxylation on the undesired opposing face of the olefin. Upon subjection of **523** to Donohoe oxidation conditions, osmate ester **524** was observed, and subsequent treatment of **524** with trishydroxymethylphosphine **483** in the presence of Et_3N and SiO_2 effected osmate ester cleavage and subsequent lactonisation to give **525** in 53% yield and >99:1 dr over the two steps (Scheme 107). The connectivity within **525** was determined first by ^1H-^1H COSY and ^1H-^{13}C HSQC and HMBC analyses, and the relative configuration within **525** was initially assigned via ^1H NMR NOE spectroscopic analysis (Figure 52).[12] This assignment was later confirmed by single crystal X-ray diffraction analysis of a derivative (*vide infra*).



Scheme 107. *Reagents and conditions:* (i) OsO_4 (1.1 equiv), TMEDA, CH_2Cl_2, –78 °C, 1 h; (ii) $P(CH_2OH)_3$ **483**, Et_3N, SiO_2, CH_2Cl_2, rt, 48 h.

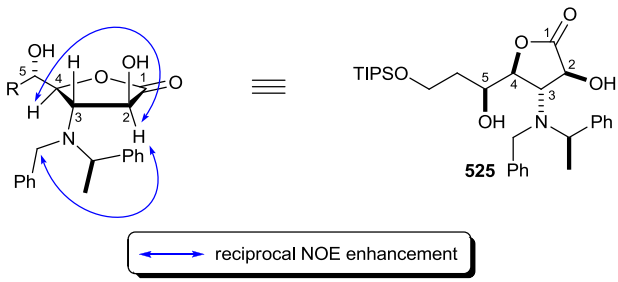
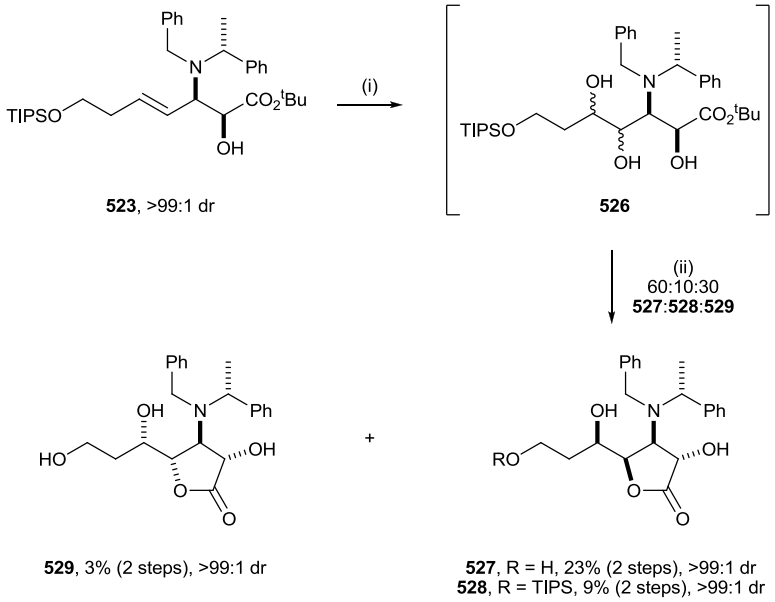


Figure 52. ^{1}H NMR NOE spectroscopic analysis of **525**. [R = C_2H_4OTIPS]

The corresponding Upjohn oxidation of **523** proceeded to give a mixture of amino triols **526** which was immediately subjected to the F_3CCO_2H-mediated lactonisation conditions. This resulted in a 60:10:30 mixture of lactones **527**, **528** and **529**, respectively, representing a 70:30 dr for the osmylation reaction [(4*R*,5*R*):(4*S*,5*S*)]. Lactone **528** and the corresponding desilylated lactone **527** were isolated in 9 and 23% yield, respectively, and in >99:1 dr in each case. The diastereoisomeric lactone **529** was also isolated in 3% yield and >99:1 dr (Scheme 108).



Scheme 108. *Reagents and conditions:* (i) OsO_4 (10 mol%), NMO, THF/H_2O (v/v 4:1), 12 h, rt; (ii) F_3CCO_2H, CH_2Cl_2, rt, 16 h.

As before, the relative configurations within **527-529** were initially assigned via ^{1}H NMR NOE spectroscopic analyses (Figure 53),[35] and were later confirmed by single crystal X-ray diffraction analysis of a derivative of **529** (*vide infra*).

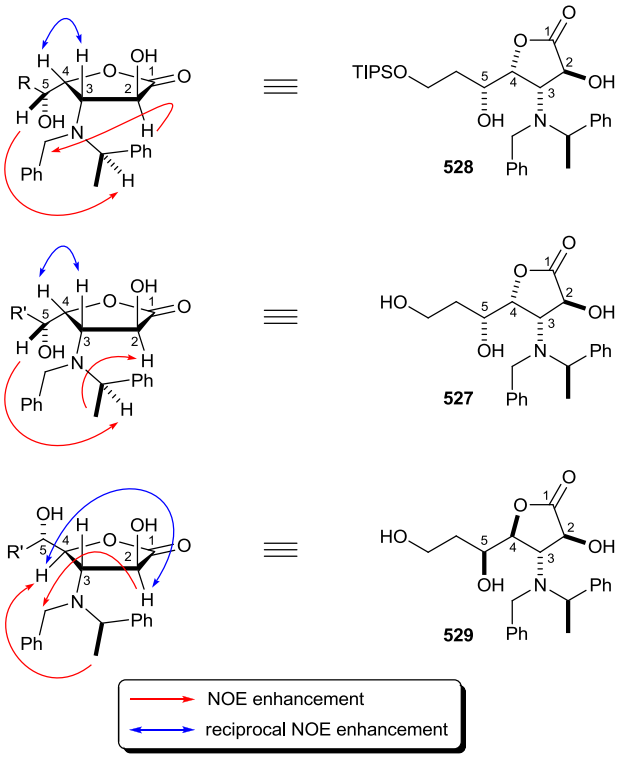


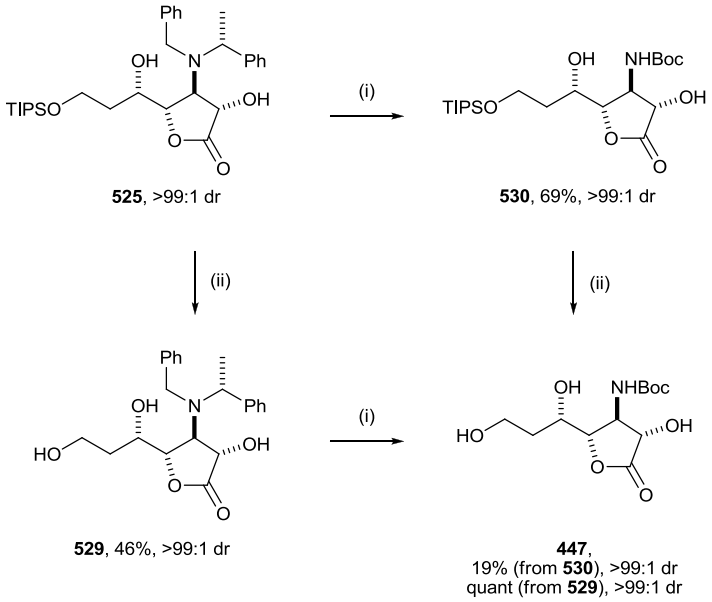
Figure 53. ^{1}H NMR NOE spectroscopic analyses of **527**, **528** and **529**. [R = C_2H_4OTIPS, R' = C_2H_4OH].

The synthesis of **525** represented a significant achievement in the endeavour towards APTO **401** and AETD **402**, as the lactone fragment possesses the correct configuration at the four contiguous stereocentres required for the synthesis of the natural product fragments. Attention was therefore turned to protecting group manipulations of **525** to prepare for the installation of the styryl unit via a Julia-Kocieński olefination procedure.

4.7.4 Elaboration of lactone 525 towards APTO 401

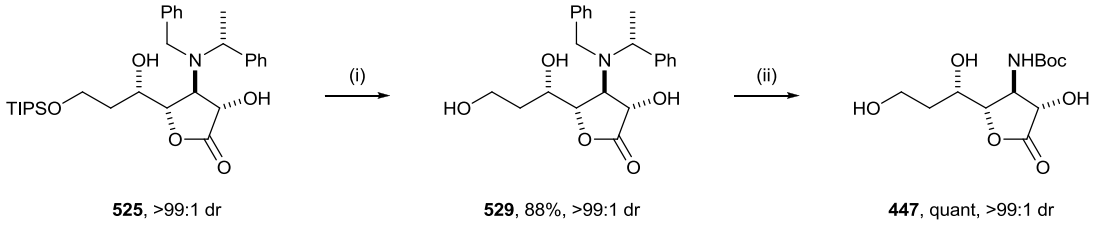
Protecting group manipulations of the C(3)-nitrogen atom and the C(7)-oxygen atom were the next points for consideration. Firstly, it was clear that the α-methylbenzyl and benzyl protecting groups on the C(3)-nitrogen atom had to be removed prior to the introduction of the styryl unit, as any hydrogenolysis reaction employed for their removal would also result in hydrogenation of the double bond. It was therefore proposed that the nitrogen atom could be *N*-Boc protected via a tandem hydrogenolysis/Boc_2O protection reaction, which Davies *et al.* have routinely used in natural product syntheses.[36] In addition, it was apparent that the terminal *O*-TIPS protected hydroxyl functionality also required deprotection to the corresponding alcohol in order that it could be further elaborated for the desired chain extension reactions. It was envisaged that these two procedures could be carried out in either order and so, firstly, treatment of **525** with H_2 and Pd/C in the presence of Boc_2O gave *N*-Boc protected **530** in 69% yield and >99:1 dr. Subsequent treatment of **530** with TBAF gave **447**, albeit in only 19% isolated yield, resulting in an overall yield of 13% over the two steps. Although a good crude mass return was noted for the desilylation reaction of **530**, the low isolated yield of

lactone **447** was attributed to the product being unstable on silica gel. Alternatively, desilylation of **525** with TBAF gave **529** in 46% yield and >99:1 dr. Subsequent hydrogenolysis/*N*-Boc protection of **529** gave **447** in quantitative yield, this time representing 46% overall yield for the two steps (Scheme 109).



Scheme 109. *Reagents and conditions:* (i) Boc_2O, Pd/C, H_2 (1 atm), MeOH, rt, 18 h; (ii) TBAF, THF, rt, 1 h.

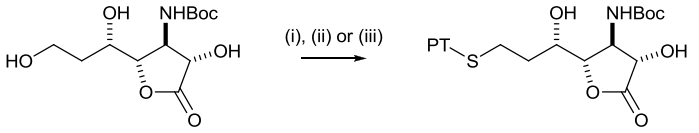
As desilylation prior to hydrogenolysis in the presence of Boc_2O had proven to be the more efficacious route (despite still proceeding in a modest overall yield), alternative methods for *O*-TIPS deprotection of **525** were investigated. HF·pyridine was found to be an excellent desilylating reagent for **525**: treatment of **525** with HF·pyridine in THF at 0 °C gave **529** in 88% isolated yield and >99:1 dr. Subsequent hydrogenolysis of **529** in the presence of Boc_2O gave **447** in quantitative yield and >99:1 dr, representing an 88% overall yield for the two-step procedure. Considerable mass loss was again observed during all attempts to purify **447** via silica gel column chromatography and so it was therefore used without purification in the subsequent steps[37] (Scheme 110).



Scheme 110. *Reagents and conditions:* (i) HF·pyridine, THF, 0 °C to rt, 16 h; (ii) Boc_2O, Pd/C, H_2 (1 atm), MeOH, rt, 18 h.

Mitsunobu reaction of **447** with PTSH was next attempted for the preparation of sulfide **531**. Standard Mitsunobu reaction conditions using DEAD and PPh_3 gave complete conversion of **447** to **531**; however, it was found that **531** was completely inseparable from the Ph_3PO side product residues, despite numerous attempts at purification through trituration and chromatography. As such, the reaction was repeated using the alternative phosphine PBu_3, and although the product **531** and the Bu_3PO residues were now found to be separable upon column chromatography, the isolated yield of

531 was very poor at just 10% (Scheme 111). The Mitsunobu reaction is renowned for generating side products that prove to be inseparable from the desired products, and as such a number of reagents have been developed to try and counteract this problem.[38] One example is of polymer-supported phosphines which comprise the desired phosphine bound to a polymer such as polystyrene. The Mitsunobu reaction then takes place on the surface of the polymer and upon completion the polymer-supported phosphine can simply be filtered off, thereby eliminating the need to separate the desired product from the side products. Due to the problems thus far encountered, the Mitsunobu reaction of **447** was next attempted using polymer-supported PPh_3. Unfortunately, the reaction proceeded much more slowly than expected and the starting material **447** was found to bind to the resin and was only recovered upon flushing the resin with MeOH (Scheme 111).

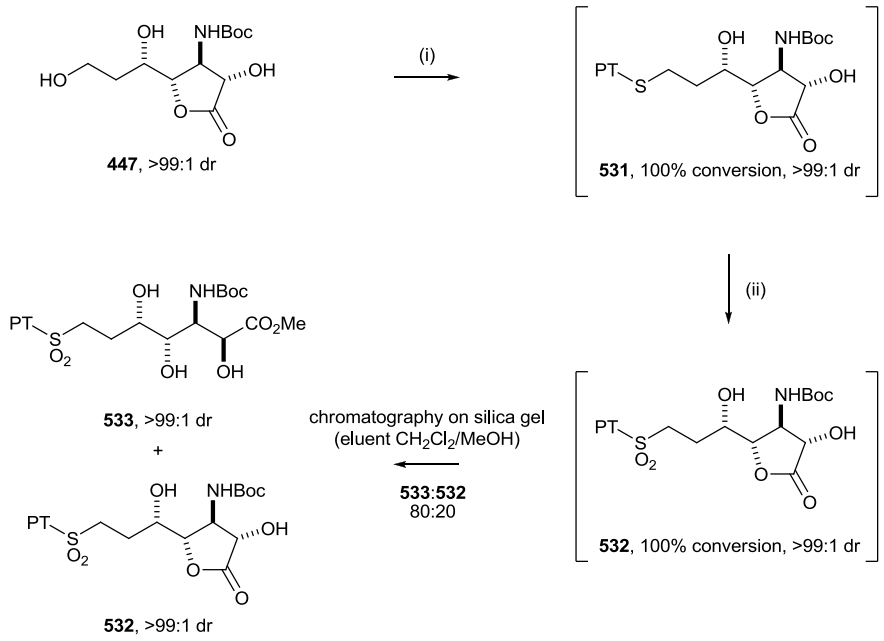


447, >99:1 dr

531,
(i). 100% conversion, >99:1 dr
(ii). 10% isolated yield, >99:1 dr
(iii). returned starting material

Scheme 111. *Reagents and conditions:* (i) PTSH, DEAD, PPh_3, THF, 0 °C to rt, 16 h; (ii) PTSH, DEAD, PBu_3, THF, 0 °C to rt, 16 h; (iii) PTSH, DEAD, polymer-supported PPh_3, THF, 0 °C to rt, 16 h.

As Mitsunobu reaction of **447** using PPh_3 and DEAD had proved most successful in that 100% conversion to **531** was observed, it was proposed that the crude product could be subjected to oxidation reaction conditions in the presence of the inseparable Ph_3PO residues. Therefore, Mitsunobu reaction of **447** gave **531** in 100% conversion and >99:1 dr and, after column chromatography to remove side products derived from the DEAD reagent, a pure mixture of **531** and Ph_3PO was isolated. Treatment of this mixture with H_2O_2 and ammonium molybdate tetrahydrate gave sulfone **532** in 100% conversion and >99:1 dr. Attempted separation of **532** from the residual Ph_3PO upon silica gel chromatography using petroleum ether/EtOAc as an eluent again proved unsuccessful and the mixture was returned. Upon changing the column eluent to CH_2Cl_2/MeOH, it was found that the Ph_3PO residues could now be separated from the desired product **532**. Interestingly, it was observed that an 80:20 mixture of methyl ester **533** and lactone **532** was isolated after this purification, indicating that partial lactone opening of **532** by MeOH had occurred upon chromatography (Scheme 112).



Scheme 112. *Reagents and conditions:* (i) PTSH, DEAD, PPh_3, THF, 0 °C to rt, 16 h; (ii) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2 (30% aq), EtOH, 0 °C to rt, 16 h.

The fact that lactone **532** could be opened relatively easily by MeOH was an important discovery in the synthesis of APTO **401** and AETD **402**, as it not only allowed access to an advanced intermediate **533** but also meant that correlation to a known literature compound would now be possible. McLeod *et al*. have previously reported the synthesis of **413**,[3c] a protected form of APTO **401** (*vide supra*), and so acetonide protection of **533** to give **534** followed by a Julia-Kocieński olefination was therefore expected to allow access to **413** in just two steps (Figure 54).

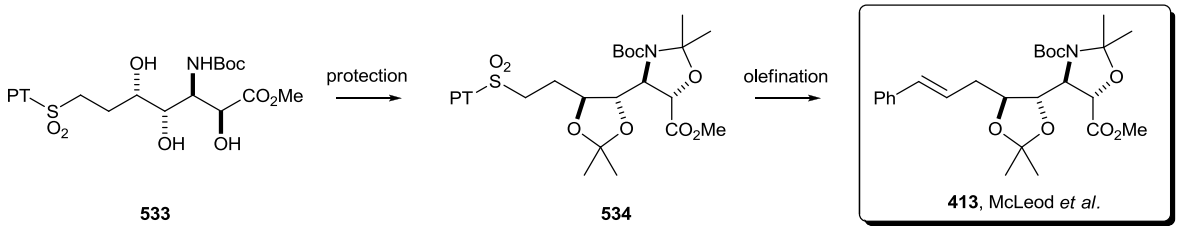
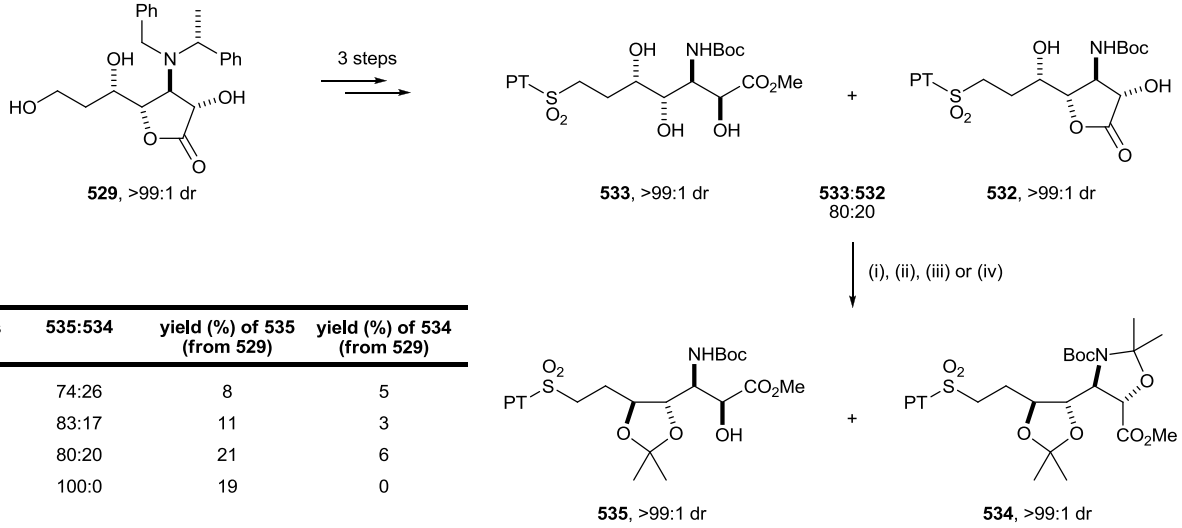


Figure 54. Elaboration of **533** to **413**, a protected form of APTO **401**.

Thus, with an 80:20 mixture of **533** and **532** in hand, attempts to force the lactone opening to conversion and simultaneously install isopropylidene groups across the 2,3- and 4,5-amino/hydroxyl functionalities were initiated. Treatment of the 80:20 mixture of **533** and **532** with DMP and $BF_3{\cdot}OEt_2$ in acetone gave a 74:26 mixture of **535** and **534**. Upon purification, **535** was isolated in 8% overall yield from **529**, with **535** being isolated in 5% overall yield from **529**, and in >99:1 dr in each case. Repetition of the reaction under refluxing conditions was found to give a complex mixture of products. Alternative procedures were attempted involving: (i) treatment of the **533** and **532** mixture with PPTS in acetone at reflux which gave an 83:17 mixture of **535** and **534**, and (ii) treatment of the **533** and **532** mixture with TsOH in acetone at 40 °C which resulted in an 80:20 mixture of **535** and **534**. It was becoming apparent that protection of the 4,5-diol functionality was facile; however, attempts to install an isopropylidene protecting group across the amino diol unit at C(2) and C(3) was

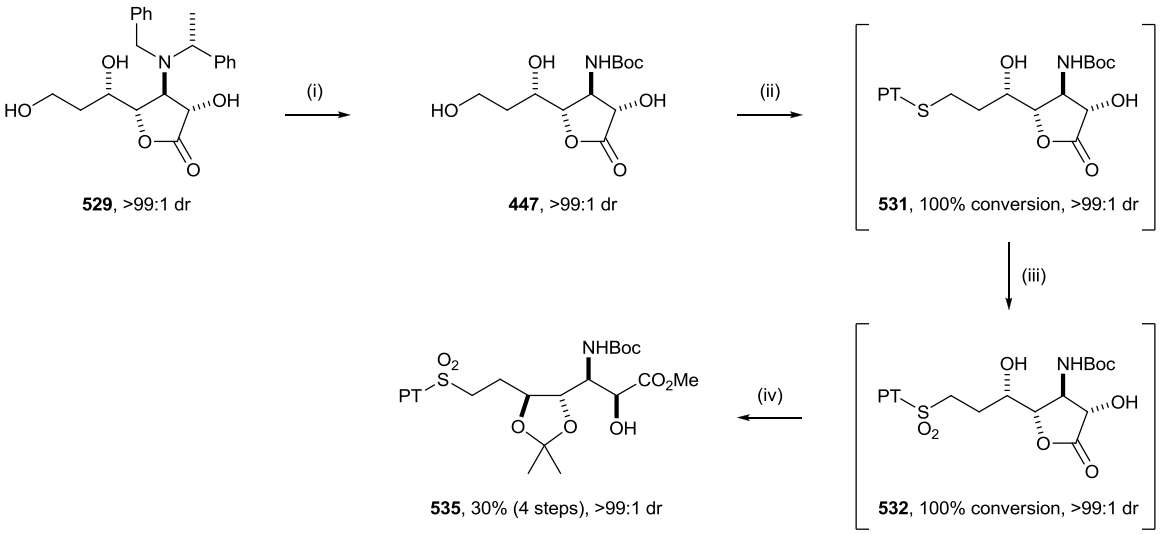
much more difficult, despite forcing conditions. It was therefore decided to optimise the synthesis of **535** and so treatment of the 80:20 mixture of **533** and **532** with the TsOH/acetone conditions at rt instead of at 40 °C then allowed 100% conversion to **535** to be achieved. Subsequent purification via flash column chromatography gave **535** as a single diastereoisomer in 19% overall yield from **529** (Scheme 113).



conditions	535:534	yield (%) of 535 (from 529)	yield (%) of 534 (from 529)
(i)	74:26	8	5
(ii)	83:17	11	3
(iii)	80:20	21	6
(iv)	100:0	19	0

Scheme 113. *Reagents and conditions:* (i) DMP, $BF_3{\cdot}OEt_2$, acetone, rt, 18 h; (ii) PPTS, acetone, reflux, 24 h; (iii) DMP, TsOH, acetone, 40 °C, 24 h; (iv) DMP, acetone, TsOH, rt, 24 h.

In order to streamline the synthesis and potentially improve the overall yield of **535**, it was proposed that sulfone **532** (still containing Ph_3PO residues from the earlier Mitsunobu reaction) could be treated with the optimised TsOH/acetone conditions directly; upon subjection of sulfone **532** to these conditions, full conversion to methyl ester **535** was observed. Upon chromatographic purification of the crude reaction mixture, **535** was isolated as a single diastereoisomer in 30% yield over the four steps. This yield therefore represented a significant improvement to the 19% four-step yield achieved earlier from the route involving purification of sulfone **532** (Scheme 114).



Scheme 114. *Reagents and conditions:* (i) Boc_2O, Pd/C, H_2 (1 atm), MeOH, rt, 1 h; (ii) PTSH, DEAD, PPh_3, THF, 0 °C to rt, 16 h; (iii) $(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$, H_2O_2 (30% aq), EtOH, 0 °C to rt, 16 h; (iv) DMP, acetone, TsOH, rt, 24 h.

The relative configuration within **535** was unambiguously assigned via single crystal X-ray diffraction analysis,[30] and the determination of a Flack *x* parameter[39] of +0.17(5) for the crystal structure of **535** allowed the absolute (*S*,*S*,*S*,*S*)-configuration within **535** (and therefore also the absolute configurations within all the precursors to **535**) to be unambiguously assigned. This result confirmed that the stereochemistry within **535** was in complete agreement with that found for the stereostructures of APTO **401** and AETD **402**, determined by Faulkner *et al.* during the original isolation studies from the microsclerodermin sponges[1b] (Figure 55).

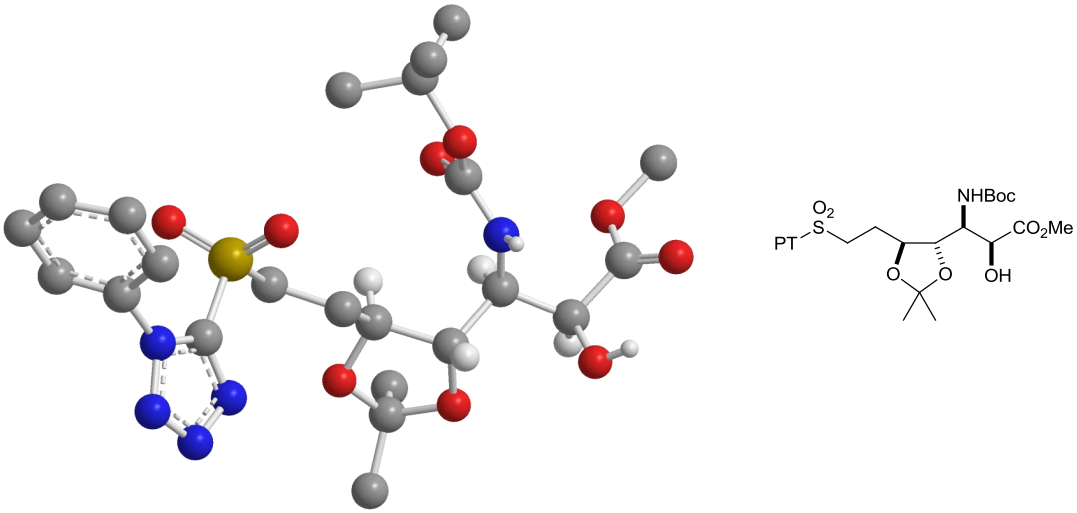
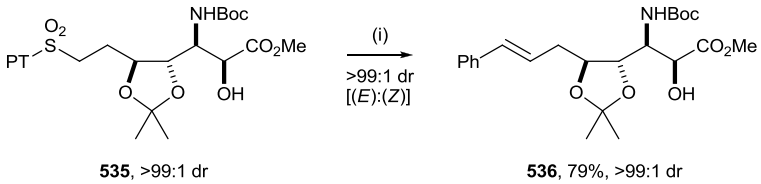


Figure 55. X-ray crystal structure of **535** (selected H atoms have been omitted for clarity).

With an optimised route to **535** in place, the final Julia-Kocieński olefination step could now be attempted. Treatment of sulfone **535** with KHMDS and PhCHO in THF at –78 °C gave **536** (a protected form of APTO **401**) in >99:1 dr [(*E*):(*Z*)], which was subsequently isolated in 79% yield and >99:1 dr (Scheme 115). The relative configuration within **536** was also unambiguously assigned via single crystal X-ray diffraction analysis,[30] and the determination of a Flack *x* parameter[39] of –0.08(9) for the crystal structure of **536** allowed the absolute (*S*,*S*,*S*,*S*,*E*)-configuration within **536** to be confirmed (Figure 56).



535, >99:1 dr **536**, 79%, >99:1 dr

Scheme 115. *Reagents and conditions:* (i) KHMDS, PhCHO, THF, –78 °C, 30 min.

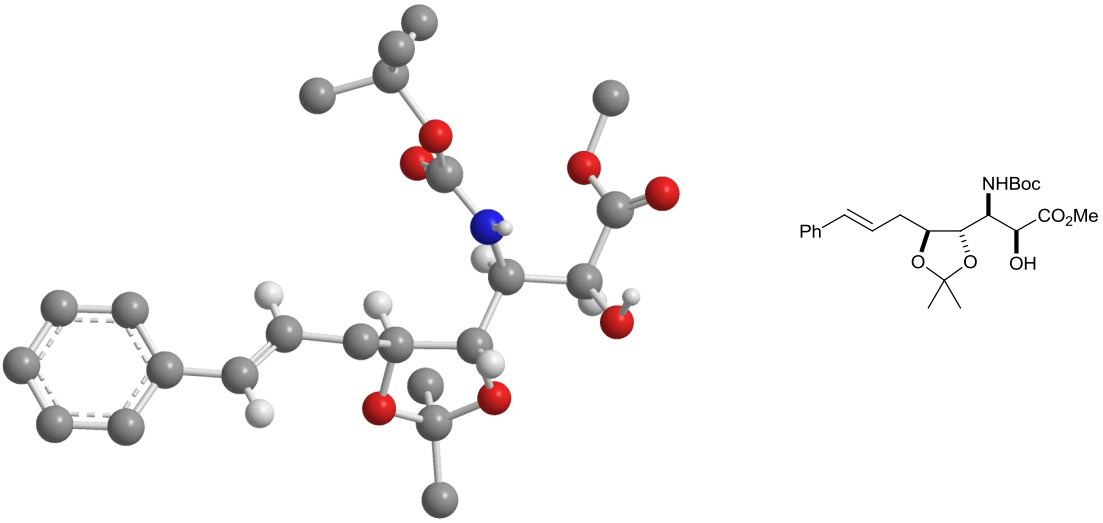


Figure 56. X-ray crystal structure of **536** (selected H atoms have been omitted for clarity).

The final stage Julia-Kocieński reaction to give **536** marked the completion of the synthesis of a protected form of APTO **401**, the 2,4,5-trihydroxy substituted β-amino acid residue found within microsclerodermins C **394** and D **395**. The synthetic route, which required the installation of four contiguous stereocentres and an (*E*)-configured double bond, resulted in **536** being synthesised as a single diastereoisomer in fourteen linear steps and in 3% overall yield from commercially available achiral 3-butyn-1-ol **502**. Previously, McLeod *et al.* have synthesised **413** from achiral allyl alcohol **403** in thirteen steps, 3% overall yield and >99:1 dr.[3c] The two remaining syntheses of protected forms of APTO **401** have started from sugar-derived compounds, meaning that these are only enantiospecific syntheses. Aitken *et al.* transformed 2-deoxy-D-ribose **416** into **422** in six steps and 21% overall yield,[3a] whilst Dauban *et al.* used L-gulose **426** to give **437** in just 0.7% yield over fifteen steps.[3b] In comparison with the three previous synthetic routes towards protected forms of APTO **401**, the synthesis of **536** from achiral starting material **502** therefore proceeds extremely efficiently and diastereoselectively to give a protected form of APTO **401** (Figure 57).

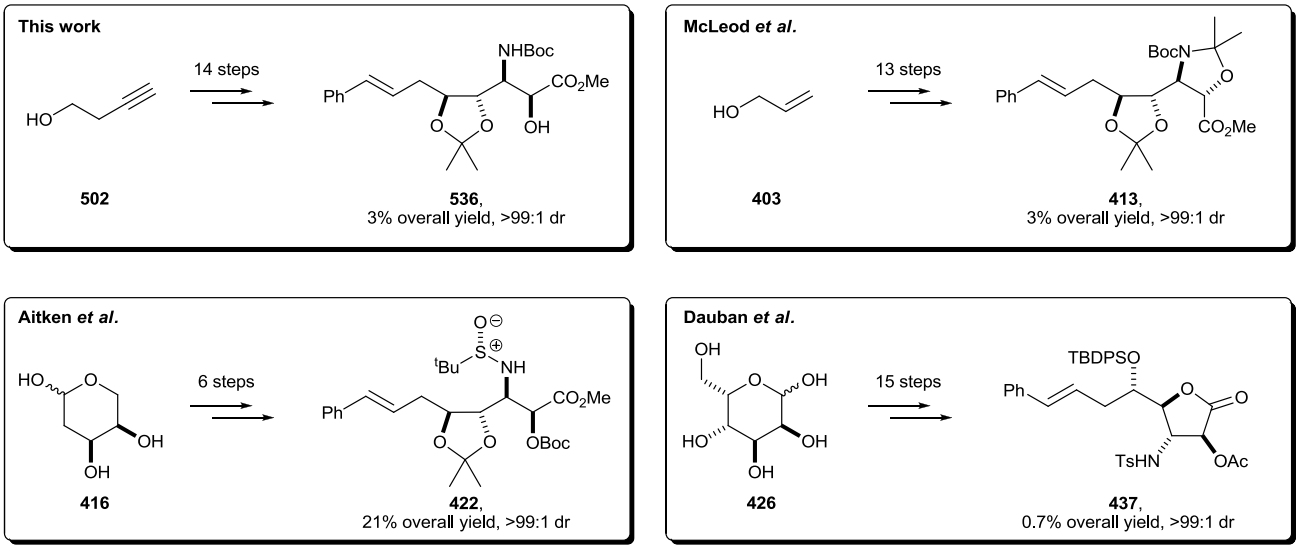
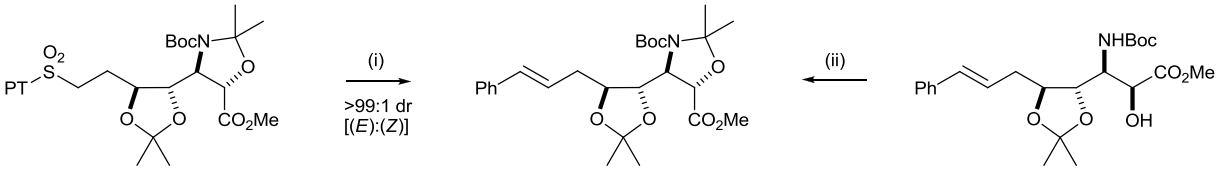


Figure 57. Syntheses of **413**, **422**, **437** and **536**, protected forms of APTO **401**.

The final task in the investigation towards APTO **401** was to complete the correlation to the known compound **413**, previously synthesised by McLeod *et al.*[3c] Attempted Julia-Kocieński olefination of a sample of **534** proceeded to only 28% conversion, from which **413** was isolated in 16% yield and >99:1 dr (with **534** being recovered in 31% yield and >99:1 dr). An alternative route involving treatment of **536** with DMP and $BF_3{\cdot}OEt_2$ in acetone gave **413** in 66% conversion and >99:1 dr, with **413** being subsequently isolated in 37% yield and >99:1 dr. The ^1H and ^{13}C NMR spectra of **413** were found to be in complete agreement with those reported by McLeod *et al.*[3c] (Scheme 116).



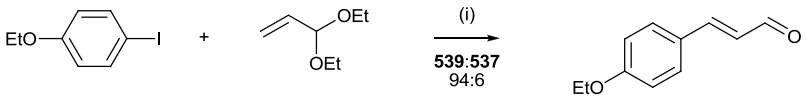
534, >99:1 dr **413**, **536**, >99:1 dr

(i). 28% conversion, 16% (from **534**), >99:1 dr
(ii). 66% conversion, 37% (from **536**), >99:1 dr

Scheme 116. *Reagents and conditions:* (i) KHMDS, PhCHO, THF, –78 °C, 30 min; (ii) DMP, $BF_3{\cdot}OEt_2$, acetone, rt, 18 h.

4.8 Synthetic approach to AETD 402

As the only difference between APTO **401** and AETD **402** is the nature of the terminal unsaturated unit, it was anticipated that **540**, the corresponding protected form of AETD **402**, could also be synthesised in an analogous fashion to **536** via the Julia-Kocieński olefination reaction of sulfone **535** and (*E*)-4-ethoxycinnamaldehyde **539**. Therefore, aldehyde **539** was synthesised via a literature procedure[40] involving a Heck coupling between 4-iodophenetole **537** and acrolein diethyl acetal **538** followed by an acidic hydrolysis of the crude reaction mixture to give **539** in 82% isolated yield and >99:1 dr (Scheme 117).

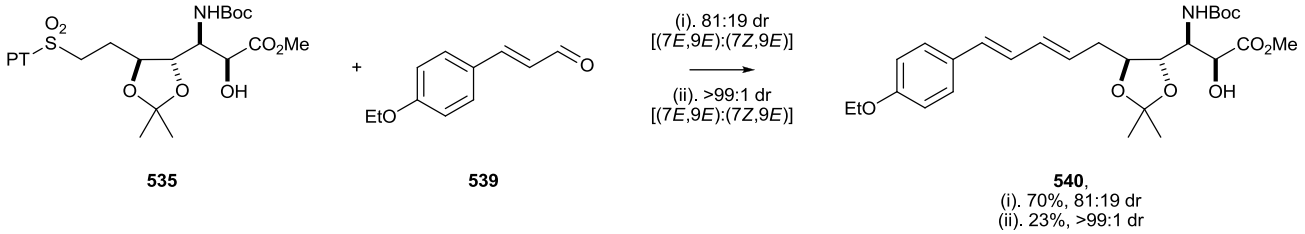


537 **538** **539**, 82%, >99:1 dr

Scheme 117. *Reagents and conditions:* (i) Bu_4NOAc, KCl, K_2CO_3, $Pd(OAc)_2$, DMF, 90 °C, 18 h then HCl (2.0 M, aq).

With aldehyde **539** in hand, Julia-Kocieński olefination of **535** could now be attempted. Thus, treatment of sulfone **535** with KHMDS and aldehyde **539** in THF (0.05 M with respect to **535**) at –78 °C gave **540** in 81:19 dr [(7*E*,9*E*):(7*Z*,9*E*)]. Subsequent purification via column chromatography gave **540** (a protected form of AETD **402**) in 70% yield and 81:19 dr. When the reaction was repeated at a significantly lower concentration (0.01 M with respect to **535**),[41] it was found that (7*E*,9*E*)-**540** was produced exclusively, and subsequently isolated in 23% yield and >99:1 dr (Scheme 118). The relative configuration within **540** was also unambiguously confirmed via single crystal X-ray diffraction analysis,[30] and the determination of a Flack *x* parameter[39] of 0.11(6) for the

crystal structure of **540** allowed the absolute (*S*,*S*,*S*,*S*,*E*,*E*)-configuration within **540** to be confirmed (Figure 58).



Scheme 118. *Reagents and conditions:* (i) KHMDS, THF (0.05 M), −78 °C, 30 min; (ii) KHMDS, THF (0.01 M), −78 °C, 30 min.

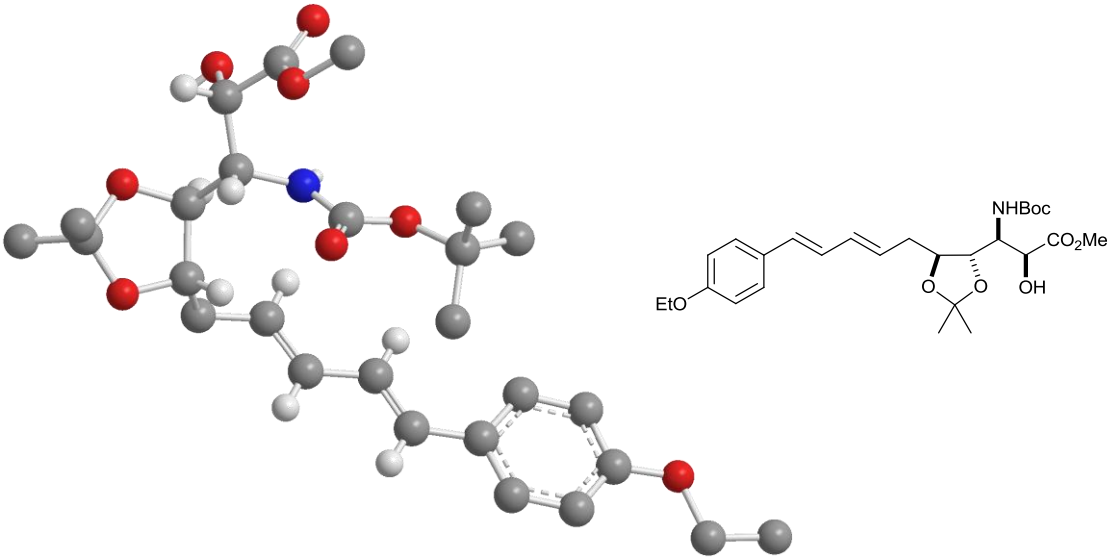


Figure 58. X-ray crystal structure of **540** (selected H atoms have been omitted for clarity).

In the literature, there have been three previous syntheses of protected forms of AETD **402**. The only asymmetric route was that reported by McLeod *et al.* in 2007 in which **541** was synthesised from achiral allyl alcohol **403** over thirteen steps in 2% overall yield and >99:1 dr.[3c] The two remaining routes towards protected forms of AETD **402** have been enantiospecific syntheses: Aitken *et al.* transformed 2-deoxy-D-ribose **416** into **542** in six steps with a 15% overall yield,[3a] whilst Ma *et al.* started with δ-gluconolactone **543** to synthesise **544** (a protected and reduced form of AETD **402**) in 10% overall yield over seventeen steps as part of their total synthesis of microsclerodermin E **396**.[2] The synthesis of **540** from achiral starting material **502** therefore proceeds well and completely diastereoselectively to give a protected form of AETD **402** in fourteen steps and in 1% overall yield as a single diastereoisomer (Figure 59).

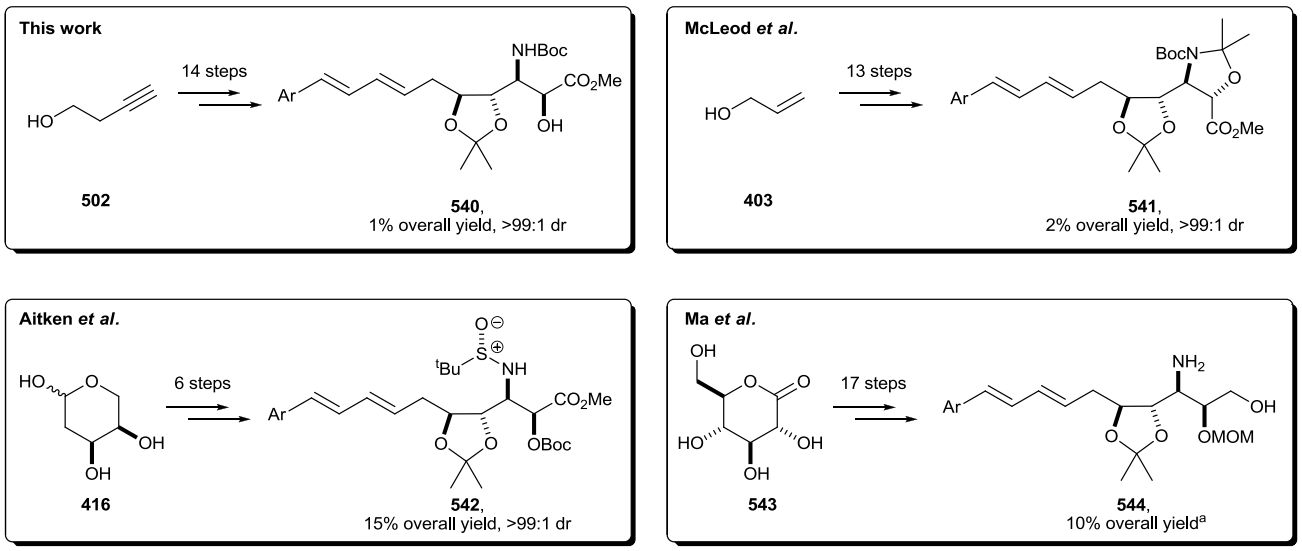


Figure 59. Syntheses of **540**-**542** and **544**, protected forms of AETD **402**. [Ar = *p*-$EtOC_6H_4$]. [[a] The dr of **544** was not reported].

4.9 Conclusions

Protected forms of APTO **401** and AETD **402**, the 2,4,5-trihydroxy substituted β-amino acid residues found within microsclerodermins C, D and E **394**-**396**, have each been successfully synthesised in fourteen linear steps from commercially available 3-butyn-1-ol **502**. The absolute configurations of the synthetic β-amino acid fragments **536** and **540** have been unambiguously determined via single crystal X-ray diffraction analyses and are in full agreement with the reported structures of APTO **401** and AETD **402**.[1b] Further to this, **536** has been correlated to the known compound **413** (previously synthesised by McLeod *et al.* in 2007)[3c] and the spectroscopic data were again found to be in complete accord.

The orthogonal protecting groups installed within **536** and **540** mean that these fragments have the potential to be easily coupled with other amino acid fragments to form new peptide bonds. Resultantly, the routes developed for the syntheses of **536** and **540** could be extremely valuable for future total syntheses of microsclerodermins C, D and E **394**-**396**. In addition, the routes established for the asymmetric synthesis of protected forms of APTO **401** and AETD **402** could now potentially be applied to the syntheses of **545**-**547**, the β-amino acid fragments found within the remaining members of the microsclerodermin family (Figure 60).

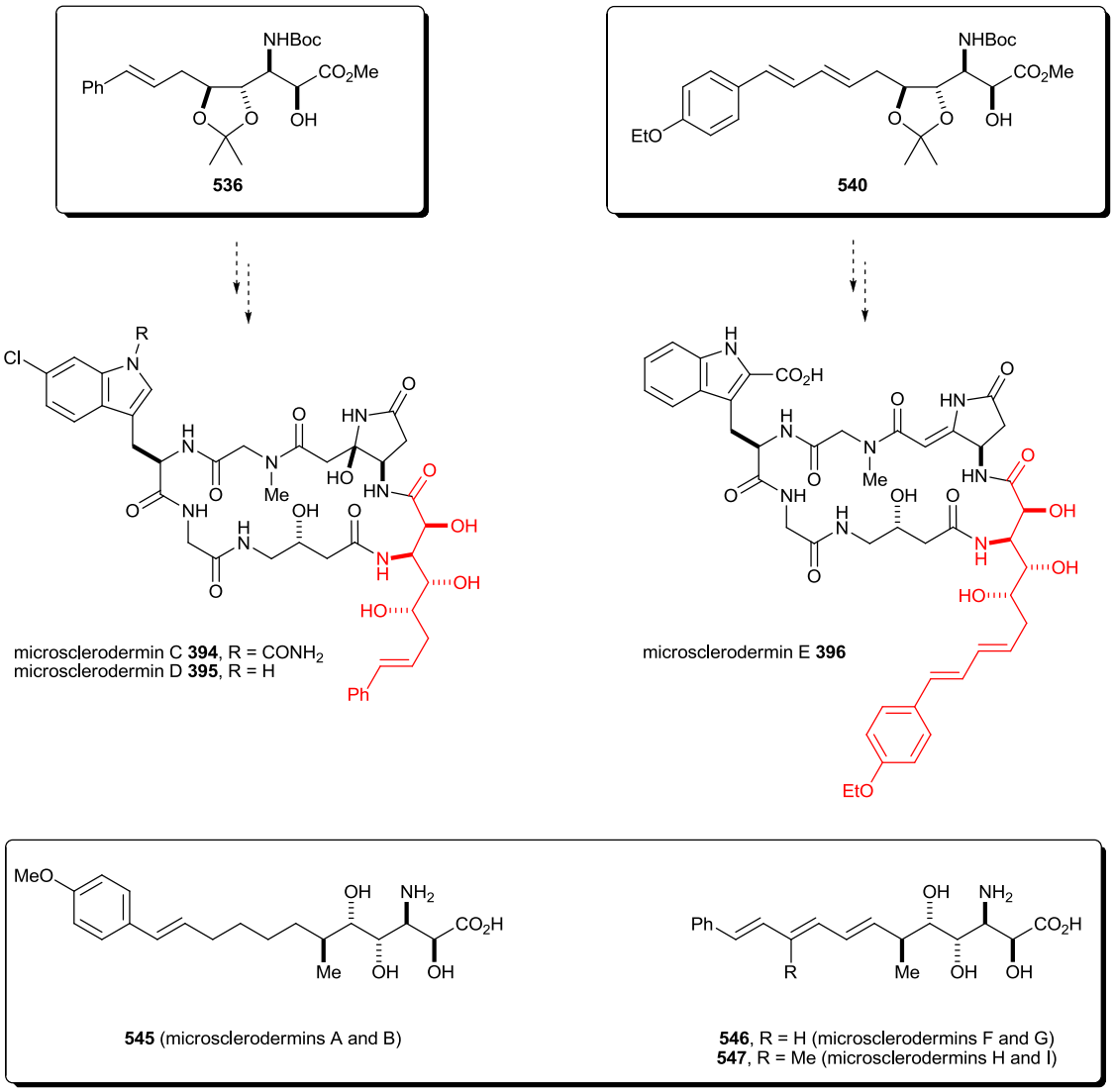


Figure 60. 536 and **540**, protected forms of APTO **401** and AETD **402**, microsclerodermins C, D and E **394-396**, and **545-547**, the β-amino acid fragments of microsclerodermins A **392**, B **393** and F-I **397-400**.

4.10 References and notes for chapter 4

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Chapter 5: Experimental

5.1 General experimental

All reactions involving organometallic or other moisture-sensitive reagents were carried out under a nitrogen or argon 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 $MgSO_4$. Thin layer chromatography was performed on aluminium plates coated with 60 F_{254} silica. Plates were visualised using UV light (254 nm), 1% aq $KMnO_4$, or Dragendorff's reagent. Flash column chromatography was performed on Kieselgel 60 silica. Elemental analyses were recorded by the microanalysis service of the London Metropolitan University, U.K. 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 mL. IR spectra were recorded on Bruker Tensor 27 FT-IR spectrometer as either a thin film on NaCl plates (film), a KBr disc (KBr) or on a diamond ATR module (ATR), as stated. 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. Chemical shifts (δ) are reported in ppm and coupling constants (*J*) in Hz. When the diastereotopic methyl groups of acetonide and isopropyl functionalities could not be unambiguously assigned, the descriptors *Me*CMe and *Me*CHMe were employed, respectively. In the ^{1}H and ^{13}C NMR spectra, these descriptors are intended to convey neither that the resonances are attributable to methyl groups that reside on the same, nor on different carbon atoms. 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 General procedures

General Procedure 1: Lithium amide conjugate addition to an α,β-unsaturated ester

BuLi was added dropwise to a stirred solution of the requisite amine in either THF or Et_2O (as stated) at −78 ºC or −20 ºC, respectively, and stirring was continued for 30 min. A solution of the requisite α,β-unsaturated ester in either THF or Et_2O (as stated) was then added via cannula and the reaction mixture was stirred for 2 h (for THF) or 5 h (for Et_2O). The reaction mixture was quenched with satd aq NH_4Cl and then diluted with Et_2O and H_2O. The layers were separated and the aqueous layer was extracted three times with Et_2O. The combined organic extracts were washed sequentially with 10% aq citric acid, satd aq $NaHCO_3$ and brine, then dried and concentrated *in vacuo*.

General Procedure 2: Hydrogenolysis with Pearlman's catalyst

$Pd(OH)_2/C$ was added to a stirred solution of the requisite amine in MeOH or EtOAc (as stated) at rt. The solution was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm) for 18 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH or EtOAc as stated) and the filtrate was concentrated *in vacuo*.

General Procedure 3: Reductive alkylation with $NaBH_3CN$

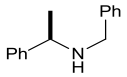
Acetone and $NaBH_3CN$ were added sequentially to a solution of the requisite primary amine in MeOH at rt. The resultant solution was stirred at rt for 18 h and then concentrated *in vacuo*. The residue was partitioned between CH_2Cl_2 and H_2O and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic extracts were then dried and concentrated *in vacuo*.

General Procedure 4: Lithium amide conjugate addition to an α,β-unsaturated ester and subsequent *in situ* enolate oxidation with CSO 102

BuLi was added dropwise to a stirred solution of the requisite amine in THF at −78 ºC and stirring was continued for 30 min. A solution of the requisite α,β-unsaturated ester in THF was then added via cannula and the reaction mixture was stirred for 2 h. Solid CSO **102** was then added and the reaction mixture was allowed to warm to rt over 12 h. The reaction mixture was quenched with satd aq NH_4Cl and then concentrated *in vacuo*. The residue was partitioned between Et_2O and H_2O and the aqueous layer was extracted three times with Et_2O. The combined organic extracts were washed sequentially with 10% aq citric acid, satd aq $NaHCO_3$ and brine, then dried and concentrated *in vacuo*.

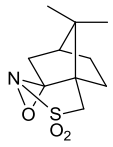
5.3 Experimental for chapter 2

(*R*)-*N*-Benzyl-*N*-(α-methylbenzyl)amine 123



Benzaldehyde (42.8 mL, 418 mmol) was added to a solution of (*R*)-α-methylbenzylamine (53.2 mL, 410 mmol) in EtOH (125 mL) at rt and the resultant mixture was then heated at reflux for 3 h. The reaction mixture was then allowed to cool to rt before being cooled to 0 ºC. $NaBH_4$ (15.6 g, 418 mmol) was added and the resultant suspension was stirred for 3 days at rt. The reaction mixture was then concentrated *in vacuo* and the residue was partitioned between H_2O (150 mL) and CH_2Cl_2 (200 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL) and the combined organic extracts were dried and concentrated *in vacuo*. The residue was slowly added to a stirred mixture of Et_2O (300 mL) and 10 M aq HCl (10 mL), to give a white precipitate which was isolated by filtration and recrystallised (CH_2Cl_2/pentane) to give **123**·HCl as a white solid (160 g, 78%, >99:1 ee[2]). The free amine was then regenerated quantitatively as required by treatment with 2.0 M aq NaOH followed by extraction with CH_2Cl_2. The combined organic extracts were dried and concentrated *in vacuo* to give (*R*)-**123** as a colourless oil;[3] $[\alpha]_D^{25}$+54.4 (*c* 1.0 in $CHCl_3$); {lit.[3] for enantiomer $[\alpha]_D^{25}$ −53.6 (*c* 3.8 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.7, C(α)*Me*), 1.66 (1H, br s, N*H*), 3.60 (1H, d, *J* 13.1, NC$H_A$$H_B$Ph), 3.68 (1H, d, *J* 13.1, NC$H_A$$H_B$Ph), 3.83 (1H, q, *J* 6.7, C(α)*H*), 7.22-7.41 (10H, m, *Ph*).

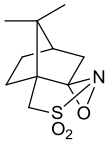
(−)-Camphorsulfonyloxaziridine [(−)-CSO] 102



$SOCl_2$ (252 mL, 3.47 mol) was added dropwise to a stirred solution of (−)-CSA (200 g, 864 mmol) in $CHCl_3$ (750 mL) and the resultant mixture was heated at reflux for 12 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (250 mL) and the resultant solution was added dropwise to a stirred solution of conc aq NH_4OH (2.0 L) at 0 °C. The resultant mixture was stirred for 4 h then the aqueous layer was extracted with CH_2Cl_2 (2 × 1.0 L) and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in PhMe (500 mL) and Amberlyst® 15 ion exchange resin (12 g) was added to the resultant solution. A Dean-Stark apparatus was fitted to the reaction flask and the reaction mixture was heated at reflux for 4 h before being allowed to cool to rt. The mixture was then filtered through Celite® (eluent CH_2Cl_2) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (1.5 L) and Aliquat 336 (17.0 g, 42.1

mmol) was added. 2.0 M aq K_2CO_3 (713 mL, 1.43 mol) was added dropwise at 0 °C, maintaining the reaction temperature below 5 °C. $MeCO_3H$ (36% in AcOH, 276 mL, 1.31 mol) was then added dropwise, maintaining the reaction temperature below 5 °C and the resultant mixture was allowed to warm to rt over 8 h. The reaction mixture was then quenched with satd aq Na_2SO_3 (80 mL) and 1.0 M aq NaOH (800 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 800 mL) and the combined organic layers were washed with H_2O (200 mL) and satd aq $NaHCO_3$ (400 mL), then dried and concentrated *in vacuo* to give **102** as a white solid (106 g, 53%);[4] mp 168-172 °C; {lit.[4] mp 165-167 °C}; $[\alpha]_D^{20}$ −45.0 (*c* 1.0 in $CHCl_3$); {lit.[4] $[\alpha]_D^{25}$ –43.6 (*c* 2.2 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.05 (3H, s, *Me*$_A$), 1.19 (3H, s, *Me*$_B$), 1.52-1.54 (1H, m, C*H*), 1.79 (1H, d, *J* 15.7, C*H*$_A$H$_B$), 1.89-2.15 (4H, m, 2 × C*H*$_2$), 2.63-2.65 (1H, m, CH$_A$*H*$_B$), 3.11 (1H, d, *J* 14.0, C*H*$_A$H$_B$SO$_2$), 3.28 (1H, d, *J* 14.0, CH$_A$*H*$_B$SO$_2$).

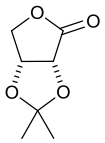
(+)-Camphorsulfonyloxaziridine [(+)-CSO] 102



$SOCl_2$ (252 mL, 3.44 mol) was added dropwise to a stirred solution of (+)-CSA (200 g, 864 mmol) in $CHCl_3$ (750 mL) and the resultant mixture was heated at reflux for 12 h, then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in $CHCl_3$ (250 mL) and the resultant solution was added dropwise to a stirred solution of conc aq NH_4OH (2.0 L) at 0 °C. The resultant mixture was stirred for 4 h then the aqueous layer was extracted with CH_2Cl_2 (2 × 1.0 L) and the combined organic extracts were dried and concentrated *in vacuo*. The residue was dissolved in PhMe (500 mL) and Amberlyst® 15 ion exchange resin (12 g) was added to the resultant solution. A Dean-Stark apparatus was fitted to the reaction flask and the reaction mixture was heated at reflux for 4 h before being allowed to cool to rt. The mixture was then filtered through Celite® (eluent CH_2Cl_2) and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (1.5 L) and Aliquat 336 (17.0 g, 42.1 mmol) was added. 2.0 M aq K_2CO_3 (713 mL, 1.43 mol) was added dropwise at 0 °C, maintaining the reaction temperature below 5 °C. $MeCO_3H$ (36% in AcOH, 276 mL, 1.31 mol) was then added dropwise, maintaining the reaction temperature below 5 °C and the resultant mixture was allowed to warm to rt over 8 h. The reaction mixture was then quenched with satd aq Na_2SO_3 (80 mL) and 1.0 M aq NaOH (800 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 800 mL) and the combined organic layers were washed with H_2O (200 mL) and satd aq $NaHCO_3$ (400 mL), then dried

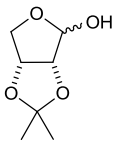
and concentrated *in vacuo* to give **102** as a white solid (163 g, 83%);[4] mp 164-175 °C; {lit.[4] mp 165-167 °C}; $[\alpha]_D^{20}$ +44.8 (*c* 1.0 in $CHCl_3$); {lit.[4] $[\alpha]_D^{25}$ +44.6 (*c* 2.2 in $CHCl_3$)}.

(*R*,*R*)-3,4-Dihydroxy-3,4-*O*-isopropylidenedihydrofuran-2(3*H*)-one 141



Na_2CO_3 (42.4 g, 400 mmol) was added portionwise to a solution of D-isoascorbic acid **139** (35.2 g, 200 mmol) in H_2O (500 mL) at 0 ºC. H_2O_2 (31.3% w/w in H_2O, 44.0 mL, 450 mmol) was then added dropwise over 30 min. The resultant solution was stirred at 0 ºC for 30 min then heated at 40 ºC for 1 h. Decolourising carbon (Norit A®, 8.00 g) was then added to decompose any excess peroxide and the reaction mixture was stirred until a negative starch-iodide test was observed (*ca*. 30 min). The reaction mixture was filtered through Celite® (eluent H_2O). The filtrate was acidified to pH 1 by the addition of 6.0 M aq HCl and then concentrated *in vacuo*. Acetone (175 mL) and $MgSO_4$ (50 g) were added to the residue and the resultant mixture was stirred as DMP (350 mL, 2.85 mol) and $TsOH \cdot H_2O$ (420 mg, 2.21 mmol) were added sequentially at rt. The reaction mixture was stirred at rt for 16 h then conc aq NH_4OH (20 mL) was added. The resultant mixture was stirred for a further 10 min then diluted with Et_2O (500 mL) and filtered. The filter cake was washed with Et_2O (300 mL) and the filtrate was concentrated *in vacuo*. The residue was dissolved in Et_2O (500 mL), then $MgSO_4$ (~10 g) was added. The mixture was filtered through Celite® (eluent Et_2O) and the filtrate was concentrated *in vacuo*. Purification via recrystallisation (Et_2O/30-40 ºC petrol) gave **141** as a pale yellow solid (13.5 g, 43%, >99:1 dr);[5] $[\alpha]_D^{25}$ −113 (*c* 1.0 in H_2O); {lit.[5] $[\alpha]_D^{25}$ −120 (*c* 1.0 in H_2O)}; mp 55-58 ºC; {lit.[5] 64-65 ºC}; δ_H (400 MHz, $CDCl_3$) 1.41 (3H, s, *Me*CMe), 1.49 (3H, s, *Me*CMe), 4.39-4.50 (2H, m, C(5)H_2), 4.76 (1H, d, *J* 5.7, C(3)*H*), 4.89 (1H, app dd, *J* 5.7, 3.8, C(4)*H*).

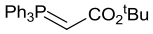
(*R*,*R*,*R*)- and (2*S*,3*R*,4*R*)-3,4-Dihydroxy-3,4-*O*-isopropylidenetetrahydrofuran-2-ol 142



DIBAL-H (1.0 M in CH_2Cl_2, 10.0 mL, 10.0 mmol) was added dropwise to a solution of **141** (1.00 g, 6.32 mmol, >99:1 dr) in CH_2Cl_2 (20 mL) at –78 ºC and stirring was continued at –78 ºC for 3 h. MeOH (3.2 mL) was then slowly added and the reaction mixture was allowed to warm to rt over 1 h. The resultant mixture was poured into a mixture of EtOAc and H_2O (v/v 1:1, 100 mL). The resultant mixture was then acidified to pH 3 with 1.0 M aq H_2SO_4 and the aqueous layer was extracted with

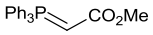
EtOAc (3 × 20 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **142** as a yellow oil (851 mg, 84%, 79:21 anomeric mixture).[6] Data for major lactol: δ_H (400 MHz, $CDCl_3$) 1.33 (3H, s, *Me*CMe), 1.48 (3H, s, *Me*CMe), 2.45 (1H, br s, O*H*), 4.04 (1H, app d, *J* 10.2, C(5)H_A), 4.09 (1H, dd, *J* 10.2, 3.4, C(5)H_B), 4.59 (1H, app d, *J* 5.8, C(3)*H*), 4.85 (1H, app dd, *J* 5.8, 3.4, C(4)*H*), 5.44 (1H, app br s, C(2)*H*).

tert-Butyl (triphenylphosphoranylidene)acetate 143



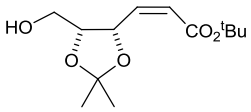
A solution of *tert*-butyl bromoacetate (50.0 g, 256 mmol) in EtOAc (125 mL) was added to a solution of PPh_3 (67.1 g, 256 mmol) in EtOAc (125 mL) at rt and stirring was continued at this temperature for 18 h during which time a precipitate formed. The reaction mixture was then filtered to give a white solid, which was dissolved in CH_2Cl_2 (300 mL). 2.0 M aq NaOH (300 mL) was added to the resultant solution and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **143** as a white solid (77.9 g, 81%);[7] mp 135-142 ºC; {lit.[7] 154-155 ºC}; δ_H (400 MHz, $CDCl_3$) 1.24 (9H, br s, CMe_3), 2.67 (1H, br s, PC*H*), 7.31-7.73 (15H, m, *Ph*).

Methyl (triphenylphosphoranylidene)acetate 144

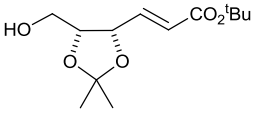


A solution of methyl bromoacetate (36.8 g, 241 mmol) in PhMe (100 mL) was added to a solution of PPh_3 (63.2 g, 241 mmol) in PhMe (100 mL) at rt and stirring was continued at this temperature for 18 h during which time a precipitate formed. The reaction mixture was then filtered to give a white solid, which was dissolved in CH_2Cl_2 (300 mL). 2.0 M aq NaOH (300 mL) was added to the resultant solution and the aqueous layer was extracted with CH_2Cl_2 (3 × 150 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **144** as a white solid (79.5 g, 99%);[8] mp 165-169 ºC; {lit.[8] 167-168 ºC}; δ_H (400 MHz, $CDCl_3$) 2.92 (1H, br s, PC*H*), 3.56 (3H, br s, O*Me*), 7.41-7.73 (15H, m, *Ph*).

***tert*-Butyl (4*S*,5*R*,*Z*)- and (4*S*,5*R*,*E*)-4,5,6-trihydroxy-4,5-*O*-isopropylidenehex-2-enoate 147 and 145**



147



145

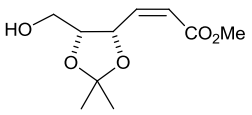
Method A: **143** (3.04 g, 8.08 mmol) was added to a solution of **142** (851 mg, 5.31 mmol, 79:21 anomeric mixture) in CH_2Cl_2 (17 mL) at rt. The resultant mixture was heated at reflux for 3 days then concentrated *in vacuo* to give a 75:25 mixture of (*Z*)-**147** and (*E*)-**145** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/EtOAc, 3:1) gave (*Z*)-**147** as a pale yellow oil (602 mg, 44%, >99:1 dr); $C_{13}H_{22}O_5$ requires C, 60.45; H, 8.6%; found C, 60.4; H, 8.4%; $[\alpha]_D^{25}$ +127.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3483 (O–H), 2982, 2936, 2877 (C–H), 1710 (C=O), 1643 (C=C); δ_H (400 MHz, $CDCl_3$) 1.41 (3H, s, *Me*CMe), 1.48 (9H, s, C*Me*$_3$), 1.53 (3H, s, *Me*CMe), 2.14 (1H, br s, O*H*), 3.44-3.53 (1H, m, C(6)H_A), 3.56-3.64 (1H, m, C(6)H_B), 4.54-4.59 (1H, m, C(5)*H*), 5.55-5.61 (1H, m, C(4)*H*), 5.85 (1H, dd, *J* 11.6, 1.7, C(2)*H*), 6.27 (1H, dd, *J* 11.6, 6.8, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 24.7, 27.4 (2 × *Me*CMe), 28.0 (C*Me*$_3$), 61.5 (*C*(6)), 74.6 (*C*(4)), 78.8 (*C*(5)), 81.0 (*C*Me$_3$), 108.7 (Me*C*Me), 122.9 (*C*(2)), 145.6 (*C*(3)), 165.3 (*C*(1)); *m/z* (ESI$^+$) 281 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{22}NaO_5^+$ ([M+Na]$^+$) requires 281.1359; found 281.1357. Further elution gave (*E*)-**145** as a pale yellow oil (343 mg, 25%, >99:1 dr); $[\alpha]_D^{25}$ +30.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3462 (O–H), 2983, 2936, 2888 (C–H), 1715 (C=O), 1658 (C=C); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, s, *Me*CMe), 1.47 (9H, s, C*Me*$_3$), 1.51 (3H, s, *Me*CMe), 2.25 (1H, br s, O*H*), 3.55 (2H, app d, *J* 6.1, C(6)H_2), 4.31-4.37 (1H, m, C(5)*H*), 4.74-4.79 (1H, m, C(4)*H*), 6.03 (1H, dd, *J* 15.6, 1.0, C(2)*H*), 6.76 (1H, dd, *J* 15.6, 5.8, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 25.2, 27.7 (2 × *Me*CMe), 28.1 (C*Me*$_3$), 61.9 (*C*(6)), 76.0 (*C*(4)), 78.3 (*C*(5)), 80.8 (*C*Me$_3$), 109.4 (Me*C*Me), 125.0 (*C*(2)), 140.7 (*C*(3)), 165.2 (*C*(1)); *m/z* (ESI$^+$) 281 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{22}NaO_5^+$ ([M+Na]$^+$) requires 281.1359; found 281.1359.

Method B: Dioxane (1.3 mL) was added to a mixture of **142** (84 mg, 0.52 mmol, 79:21 anomeric mixture) and **143** (237 mg, 0.630 mmol) and the resultant solution was stirred at 90 ºC for 6 h. The reaction mixture was allowed to cool to 50 ºC and stirring was continued at this temperature for a further 12 h. The reaction mixture was then concentrated *in vacuo* to give a 58:42 mixture of (*Z*)-**147** and (*E*)-**145** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/EtOAc, 3:2) gave (*Z*)-**147** as a pale yellow oil (80 mg, 58%, >99:1 dr). Further elution gave (*E*)-**145** as a pale yellow oil (56 mg, 42%, >99:1 dr).

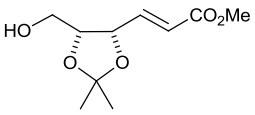
Method C: A solution of **153** (504 mg, 1.59 mmol) in PhMe (1.5 mL) was added to a solution of **142** (204 mg, 1.27 mmol, 79:21 anomeric mixture) and benzoic acid (31 mg, 0.25 mmol) in PhMe (6 mL). The reaction mixture was then heated at 90 ºC for 10 min, allowed to cool to rt and concentrated *in vacuo* to give a 35:15:50 mixture of (*E*)-**145**, (*Z*)-**147** and **142**, respectively.

Method D: BuLi (2.4 M, 0.30 mL, 0.70 mmol) was added dropwise to a stirred solution of *tert*-butyl diethylphosphonoacetate **154** (175 mg, 0.694 mmol) in THF (0.5 mL) at –78 ºC and stirring was continued at this temperature for 30 min. A solution of **141** (100 mg, 0.632 mmol, >99:1 dr) in THF (0.5 mL) at –78 ºC was then added via cannula. DIBAL-H (1.0 M in THF, 0.63 mL, 0.63 mmol) was then added dropwise and the reaction mixture was allowed to warm to rt over 16 h. Satd aq sodium potassium tartrate (1 mL) was then added and the reaction mixture was partitioned between EtOAc (10 mL) and 0.5 M aq HCl (10 mL). The organic layer was washed with 1.0 M aq K_2CO_3 (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give an 88:12 mixture of (*E*)-**145** and (*Z*)-**147** respectively; unreacted *tert*-butyl diethylphosphonoacetate **154** was also present in the crude reaction mixture. Purification via flash column chromatography (eluent 30-40 ºC petrol/EtOAc, 3:1) gave (*E*)-**145** as a pale yellow oil (44 mg, 27%, >99:1 dr).

Methyl (4*S*,5*R*,*Z*)- and (4*S*,5*R*,*E*)-4,5,6-trihydroxy-4,5-*O*-isopropylidenehex-2-enoate 148 and 146



148

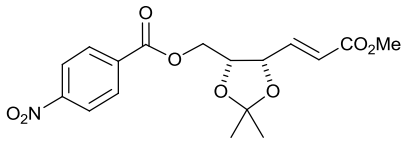


146

144 (933 mg, 2.79 mmol) was added to a solution of **142** (294 mg, 1.84 mmol, 79:21 anomeric mixture) in CH_2Cl_2 (6 mL) at rt. The resultant mixture was heated at reflux for 3 days then concentrated *in vacuo* to give a 72:28 mixture of (*Z*)-**148** and (*E*)-**146** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/EtOAc, 3:2) gave (*Z*)-**148** as a pale yellow oil (223 mg, 56%, >99:1 dr); $C_{10}H_{16}O_5$ requires C, 55.55; H, 7.5%; found C, 55.4; H, 7.4%; $[\alpha]_D^{25}$ +144.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3475 (O–H), 2988, 2978, 2953 (C–H), 1719 (C=O), 1647 (C=C); δ_H (400 MHz, $CDCl_3$) 1.40 (3H, s, *Me*CMe), 1.53 (3H, s, *Me*CMe), 2.10 (1H, br s, O*H*), 3.40-3.50 (1H, m, C(6)H_A), 3.55-3.64 (1H, m, C(6)H_B), 3.73 (3H, s, O*Me*), 4.54-4.60 (1H, m, C(5)*H*), 5.60 (1H, app td, *J* 7.0, 1.6, C(4)*H*), 5.93 (1H, dd, *J* 11.6, 1.6, C(2)*H*), 6.40 (1H, dd, *J* 11.6, 7.0, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 24.6, 27.4 (2 × *Me*CMe), 51.7 (O*Me*), 61.5 (*C*(6)), 74.8 (*C*(4)), 78.8 (*C*(5)), 108.9 (Me*C*Me), 120.5 (*C*(2)), 147.6 (*C*(3)), 166.4 (*C*(1)); *m/z* (ESI^+) 239 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{10}H_{16}NaO_5^+$ ($[M+Na]^+$) requires 239.0890; found 239.0891. Further elution

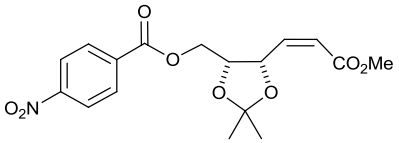
gave (*E*)-**146** as a pale yellow oil (92 mg, 23%, 94:6 dr); $C_{10}H_{16}O_5$ requires C, 55.55; H, 7.5%; found C, 55.7; H, 7.2%; ν_{max} (film) 3472 (O–H), 2989, 2952, 2938, 2890 (C–H), 1725 (C=O), 1662 (C=C); δ_H (400 MHz, $CDCl_3$) 1.37 (3H, s, *Me*CMe), 1.50 (3H, s, *Me*CMe), 2.37 (1H, br s, O*H*), 3.54 (2H, app d, *J* 5.6, C(6)H_2), 3.72 (3H, s, O*Me*), 4.31-4.38 (1H, m, C(5)*H*), 4.75-4.81 (1H, m, C(4)*H*), 6.11 (1H, dd, *J* 15.7, 1.5, C(2)*H*), 6.88 (1H, dd, *J* 15.7, 5.3, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 25.2, 27.6 (2 × *Me*CMe), 51.7 (O*Me*), 61.7 (*C*(6)), 75.9 (*C*(4)), 78.2 (*C*(5)), 109.5 (Me*C*Me), 122.5 (*C*(2)), 142.7 (*C*(3)), 166.3 (*C*(1)); *m/z* (ESI^+) 239 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{10}H_{16}NaO_5^+$ ($[M+Na]^+$) requires 239.0890; found 239.0890.

Methyl (4*S*,5*R*,*E*)-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(*p*-nitrobenzoyloxy)hex-2-enoate 149



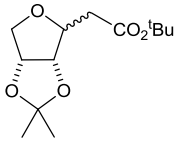
p-Nitrobenzoyl chloride (82 mg, 0.44 mmol) was added to a solution of **146** (87 mg, 0.40 mmol, 94:6 dr) in pyridine (5 mL) at rt and the resultant mixture was stirred at rt for 28 h. 1.0 M aq HCl (20 mL) was then added and the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (20 mL), H_2O (20 mL) and satd aq $NaHCO_3$ (20 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 ºC petrol/EtOAc, 4:1) gave **149** as a pale yellow solid (96 mg, 66%, >99:1 dr); $C_{17}H_{19}NO_8$ requires C, 55.9; H, 5.2; N, 3.8%; found C, 56.0; H, 5.1; N, 3.75%; mp 90-94 ºC; $[\alpha]_D^{25}$ +3.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2990, 2953 (C–H), 1728 (C=O), 1663 (C=C), 1530 (N=O); δ_H (400 MHz, $CDCl_3$) 1.42 (3H, s, *Me*CMe), 1.53 (3H, s, *Me*CMe), 3.70 (3H, s, O*Me*), 4.30 (1H, dd, *J* 11.7, 6.4, C(6)H_A), 4.35 (1H, dd, *J* 11.7, 5.7, C(6)H_B), 4.56-4.62 (1H, m, C(5)*H*), 4.88-4.95 (1H, m, C(4)*H*), 6.21 (1H, d, *J* 15.4, C(2)*H*), 6.94 (1H, dd, *J* 15.4, 5.3, C(3)*H*), 8.17-8.22 (2H, m, *Ar*), 8.26-8.31 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 25.3, 27.7 (2 × *Me*CMe), 51.8 (O*Me*), 63.9 (*C*(6)), 75.5 (*C*(5)), 75.9 (*C*(4)), 110.1 (Me*C*Me), 123.0 (*C*(2)), 123.6, 130.9, 135.0 (*Ar*), 141.3 (*C*(3)), 150.7 (*Ar*), 164.2 (O*C*OAr), 166.0 (*C*(1)); *m/z* (ESI^+) 388 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{17}H_{19}NNaO_8^+$ ($[M+Na]^+$) requires 388.1003; found 388.1002.

Methyl (4*S*,5*R*,*Z*)-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(*p*-nitrobenzoyloxy)hex-2-enoate 150



p-Nitrobenzoyl chloride (76 mg, 0.41 mmol) was added to a solution of **148** (80 mg, 0.37 mmol, >99:1 dr) in pyridine (4 mL) at rt and the resultant mixture was stirred at rt for 28 h. 1.0 M aq HCl (20 mL) was then added and the reaction mixture was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic extracts were washed sequentially with 1.0 M aq HCl (20 mL), H_2O (20 mL) and satd aq $NaHCO_3$ (20 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 ºC petrol/EtOAc, 7:1) gave **150** as a pale yellow oil (92 mg, 68%, >99:1 dr); $[\alpha]_D^{25}$ +176.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2990, 2954 (C–H), 1727 (C=O), 1650 (C=C), 1530 (N=O); δ_H (400 MHz, $CDCl_3$) 1.42 (3H, s, *Me*CMe), 1.52 (3H, s, *Me*CMe), 3.72 (3H, s, O*Me*), 4.18 (1H, dd, *J* 11.7, 5.4, C(6)H_A), 4.39 (1H, dd, *J* 11.7, 3.2, C(6)H_B), 4.83-4.89 (1H, m, C(5)*H*), 5.66-5.71 (1H, m, C(4)*H*), 5.95 (1H, dd, *J* 11.6, 1.3, C(2)*H*), 6.39 (1H, dd, *J* 11.6, 6.6, C(3)*H*), 8.18-8.23 (2H, m, *Ar*), 8.26-8.31 (2H, m, *Ar*); δ_C (100 MHz, $CDCl_3$) 24.8, 27.4 (2 × *Me*CMe), 51.7 (O*Me*), 64.6 (*C*(6)), 74.8 (*C*(4)), 75.8 (*C*(5)), 109.4 (Me*C*Me), 121.5 (*C*(2)), 123.6, 130.8, 135.3 (*Ar*), 146.2 (*C*(3)), 150.6 (*Ar*), 164.3 (O*C*OAr), 166.0 (*C*(1)); *m/z* (ESI^+) 388 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{17}H_{19}NNaO_8^+$ ($[M+Na]^+$) requires 388.1003; found 388.1003.

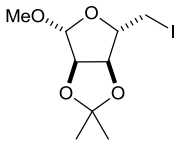
***tert*-Butyl (2'*RS**,3'*S*,4'*R*)- and (2'*RS**,3'*S*,4'*R*)-2-(3',4'-dihydroxy-3',4'-*O*-isopropylidenetetrahydrofuran-2'-yl)acetate 151 and 152**



A solution of **153** (705 mg, 2.23 mmol) in PhMe (3 mL) was added to a solution of **142** (119 mg, 0.743 mmol, 79:21 anomeric mixture) and benzoic acid (18 mg, 0.15 mmol) in PhMe (2 mL). The reaction mixture was then heated at 90 ºC for 10 min, allowed to cool to rt and concentrated *in vacuo* to give a 58:42 mixture of **151** and **152** respectively. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 5:1) gave a 58:42 mixture of **151** and **152** respectively as a yellow oil (189 mg, 98%). Data for mixture: ν_{max} (film) 2981, 2937 (C–H), 1730 (C=O); *m/z* (ESI^+) 281 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{13}H_{22}NaO_5^+$ ($[M+Na]^+$) requires 281.1359; found 281.1357. Data for **151**: δ_H (400 MHz, $CDCl_3$) 1.27 (3H, s, *Me*CMe), 1.40 (9H, s, C*Me*$_3$), 1.45 (3H, s, *Me*CMe), 2.28-2.39 (2H, m, C(2)H_2), 3.77-3.82 (1H, m, C(5')H_A), 3.87-3.96 (1H, m, C(5')H_B), 4.31-4.38 (1H, m, C(2')*H*), 4.48-4.53 (1H, m, C(3')*H*), 4.73-4.78 (1H, m, C(4')*H*); δ_C (100 MHz, $CDCl_3$)

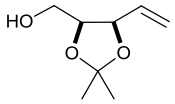
24.9, 26.5 (2 × *Me*CMe), 28.0 (C*Me*$_3$), 37.4 (*C*(2)), 72.1 (*C*(5')), 80.9 (*C*(4')), 80.9 (*C*Me$_3$), 81.2 (*C*(2')), 84.5 (*C*(3')), 112.7 (Me*C*Me), 169.6 (*C*(1)). Data for **152**: δ_H (400 MHz, $CDCl_3$) 1.27 (3H, s, *Me*CMe), 1.40 (3H, s, *Me*CMe), 1.41 (9H, s, C*Me*$_3$), 2.60 (1H, app ddd, *J* 16.8, 6.9, 2.5, C(2)*H*$_A$), 2.66 (1H, app ddd, *J* 16.8, 6.4, 2.5, C(2)*H*$_B$), 3.42 (1H, app ddd, *J* 10.6, 3.5, 2.5, C(5')*H*$_A$), 3.72-3.77 (1H, m, C(2')*H*), 3.87-3.96 (1H, m, C(5')*H*$_B$), 4.60-4.64 (1H, m, C(3')*H*), 4.68-4.73 (1H, m, C(4')*H*); δ_C (100 MHz, $CDCl_3$) 24.8, 26.0 (2 × *Me*CMe), 28.0 (C*Me*$_3$), 34.9 (*C*(2)), 72.6 (*C*(5')), 78.4 (*C*(2')), 80.6 (*C*Me$_3$), 80.8 (*C*(3')), 81.0 (*C*(4')), 112.0 (Me*C*Me), 170.4 (*C*(1)).

(2*R*,3*R*,4*S*,5*S*)-2-Methoxy-3,4-dihydroxy-3,4-*O*-isopropylidene-5-iodomethyltetrahydrofuran 156



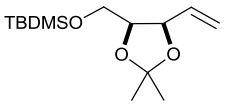
Conc aq HCl (2.0 mL) was added to a solution of D-ribose **155** (50.0 g, 333 mmol) in acetone (350 mL) and MeOH (350 mL) and the resultant solution was heated at 60 ºC for 1 h. The reaction mixture was allowed to cool to rt and was then neutralised by addition of solid Na_2CO_3 (~10 g). The resultant mixture was then filtered through Celite® (eluent EtOAc) and the filtrate was concentrated *in vacuo*. The residue was dissolved in EtOAc (300 mL) and was washed with H_2O (300 mL). The aqueous layer was extracted with EtOAc (2 × 300 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Imidazole (34.0 g, 500 mmol) and PPh_3 (105 g, 400 mmol) were added to the residue, and the mixture was dissolved in PhMe and MeCN (v/v 5:1, 1.05 L). I_2 (101 g, 400 mmol) was then added and the resultant mixture was heated at 60 ºC for 1 h. The reaction mixture was then allowed to cool to rt, diluted with Et_2O (500 mL) and the resultant mixture was washed sequentially with 10% aq $Na_2S_2O_3$ (1.0 L), H_2O (1.0 L) and brine (1.0 L), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 50:1) gave **156** as a pale yellow oil (67.2 g, 64%, >99:1 dr);[9] $[\alpha]_D^{25}$ –65.3 (*c* 1.0 in $CHCl_3$); {lit.[9] $[\alpha]_D^{25}$ –68.6 (*c* 2.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, s, *Me*CMe), 1.49 (3H, s, *Me*CMe), 3.17 (1H, app t, *J* 9.9, C*H*$_A$H$_B$I), 3.29 (1H, dd, *J* 9.9, 6.1, CH$_A$*H*$_B$I), 3.38 (3H, s, O*Me*), 4.45 (1H, app dd, *J* 9.9, 6.1, C(5)*H*), 4.63 (1H, app d, *J* 6.1, C(4)*H*), 4.77 (1H, app d, *J* 6.1, C(3)*H*), 5.06 (1H, app s, C(2)*H*).

(4*S*,5*R*)-2,2-Dimethyl-4-hydroxymethyl-5-vinyl-1,3-dioxolane 158



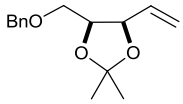
BuLi (2.5 M, 23.4 mL, 58.4 mmol) was added to a solution of **156** (18.4 g, 58.4 mmol) in THF (300 mL) at –78 ºC and the resultant solution was stirred at –78 ºC for 2 h. DIBAL-H (1.0 M in THF, 87.6 mL, 87.6 mmol) was then added and the reaction mixture was allowed to warm to rt over 16 h. Acetone (100 mL) and satd aq sodium potassium tartrate (150 mL) were then added sequentially and stirring was continued at rt for 30 min. The reaction mixture was partitioned between brine (300 mL) and EtOAc (300 mL) and the aqueous layer was extracted with EtOAc (3 × 200 mL). The combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 ºC petrol/EtOAc, 3:1) gave **158** as a yellow oil (7.74 g, 84%, >99:1 dr);[10] $[\alpha]_D^{25}$ –40.0 (*c* 1.0 in $CHCl_3$); {lit.[11] $[\alpha]_D^{25}$ –44.0 (*c* 4.9 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.40 (3H, s, *Me*CMe), 1.52 (3H, s, *Me*CMe), 1.86 (1H, br s, O*H*), 3.59 (2H, d, *J* 5.5, CH_2OH), 4.25-4.31 (1H, m, C(4)*H*), 4.66 (1H, app t, *J* 7.2, C(5)*H*), 5.29 (1H, dd, *J* 10.5, 2.6, CH=CH_AH_B), 5.41 (1H, dd, *J* 17.1, 2.6, CH=CH_AH_B), 5.88 (1H, ddd, *J* 17.1, 10.5, 7.2, C*H*=CH_2).

(4*S*,5*R*)-2,2-Dimethyl-4-(*tert*-butyldimethylsilyloxymethyl)-5-vinyl-1,3-dioxolane 159



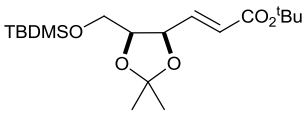
Imidazole (3.87 g, 56.9 mmol), DMAP (93 mg, 0.76 mmol) and TBDMSCl (3.43 g, 19.0 mmol) were sequentially added to a solution of **158** (3.00 g, 19.0 mmol) in CH_2Cl_2 (135 mL) at rt and the resultant solution was stirred at rt for 16 h. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in Et_2O (20 mL) and the resultant solution was washed with 1.0 M aq HCl (20 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 ºC petrol/EtOAc, 20:1) gave **159** as a pale yellow oil (5.06 g, 98%, >99:1 dr); $[\alpha]_D^{25}$ +1.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2988, 2956, 2931, 2858 (C–H), 1645 (C=C); δ_H (400 MHz, $CDCl_3$) 0.03 (3H, s, *Me*SiMe), 0.04 (3H, s, *Me*SiMe), 0.87 (9H, s, C*Me*$_3$), 1.35 (3H, s, *Me*CMe), 1.45 (3H, s, *Me*CMe), 3.59 (2H, app d, *J* 6.1, CH_2OSi), 4.18 (1H, app q, *J* 6.1, C(4)*H*), 4.60 (1H, app t, *J* 6.8, C(5)*H*), 5.19 (1H, app d, *J* 10.4, CH=CH_AH_B), 5.33 (1H, app d, *J* 17.2, CH=CH_AH_B), 5.87 (1H, ddd, *J* 17.2, 10.4, 6.8, C*H*=CH_2); δ_C (100 MHz, $CDCl_3$) –5.5, –5.4 (2 × *Me*SiMe), 18.2 (Si*C*Me$_3$), 25.3 (*Me*CMe), 25.9 (SiC*Me*$_3$), 27.8 (*Me*CMe), 62.3 (*C*H_2OSi), 78.5, 78.6 (*C*(4), *C*(5)), 108.5 (Me*C*Me), 117.6 (CH=*C*H_2), 133.7 (*C*H=CH_2); *m/z* (ESI^+) 295 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{14}H_{28}NaO_3Si^+$ ($[M+Na]^+$) requires 295.1700; found 295.1699.

(4*S*,5*R*)-2,2-Dimethyl-4-(benzyloxymethyl)-5-vinyl-1,3-dioxolane 160



NaH (60% dispersion in mineral oil, 1.89 g, 47.4 mmol) was stirred vigorously in 30-40 ºC petrol (20 mL) at rt for 10 min and then the solvent was decanted via cannula. THF (30 mL) was then added and the suspension was cooled to 0 ºC. A solution of **158** (3.00 g, 19.0 mmol) in THF (30 mL) was then added dropwise via cannula and the reaction mixture was stirred at rt for 45 min. BnBr (3.38 mL, 28.4 mmol) was then added at rt and stirring was continued at rt for 16 h. The solution was diluted with Et_2O (50 mL) and washed with satd aq $NaHCO_3$ (2 × 50 mL). The aqueous layer was extracted with Et_2O (2 × 50 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 ºC petrol/EtOAc, 20:1) gave **160** as a pale yellow oil (4.49 g, 95%, >99:1 dr); $[\alpha]_D^{25}$ +1.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3030, 2987, 2934, 2865 (C–H), 1644 (C=C); δ_H (400 MHz, $CDCl_3$) 1.40 (3H, s, *Me*CMe), 1.52 (3H, s, *Me*CMe), 3.46 (1H, dd, *J* 9.9, 5.4, C*H*$_A$H$_B$OCH$_2$Ph), 3.48 (1H, dd, *J* 9.9, 6.3, CH$_A$*H*$_B$OCH$_2$Ph), 4.37-4.43 (1H, m, C(4)*H*), 4.52 (1H, d, *J* 12.0, OC*H*$_A$H$_B$Ph), 4.60 (1H, d, *J* 12.0, OCH$_A$*H*$_B$Ph), 4.60-4.65 (1H, m, C(5)*H*), 5.23 (1H, app d, *J* 10.4, CH=C*H*$_A$H$_B$), 5.36 (1H, app d, *J* 17.4, CH=CH$_A$*H*$_B$), 5.82 (1H, ddd, *J* 17.4, 10.4, 7.3, C*H*=CH$_2$), 7.27-7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.4, 27.9 (2 × *Me*CMe), 69.5 (*C*H$_2$OCH$_2$Ph), 73.5 (OCH$_2$Ph), 76.9 (*C*(4)), 78.5 (*C*(5)), 108.9 (Me*C*Me), 118.2 (CH=*C*H$_2$), 127.7 (*p-Ph*), 127.8, 128.4 (*o*,*m-Ph*), 133.5 (*C*H=CH$_2$), 138.0 (*i-Ph*); *m/z* (ESI^+) 271 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{15}H_{20}NaO_3^+$ ($[M+Na]^+$) requires 271.1305; found 271.1305.

***tert*-Butyl (4*R*,5*S*,*E*)-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(*tert*-butyldimethylsilyloxy)hex-2-enoate 162**



Method A: Hoveyda-Grubbs II **165** (23 mg, 37 μmol) was added to a degassed solution of **159** (100 mg, 0.367 mmol, >99:1 dr) and *tert*-butyl acrylate **163** (0.16 mL, 1.1 mmol) in CH_2Cl_2 (2 mL) and the resultant mixture was heated at reflux for 22 h. The reaction mixture was then concentrated *in vacuo* to give **162** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 20:1) gave **162** as a colourless oil (93 mg, 68%, >99:1 dr); $[\alpha]_D^{25}$ +9.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2981, 2956, 2932, 2859 (C–H), 1717 (C=O), 1660 (C=C); δ_H (400 MHz, $CDCl_3$) 0.04 (6H, app s, 2 × *Me*SiMe), 0.87 (9H, s, SiC*Me*$_3$), 1.37 (3H, s, *Me*CMe), 1.48 (12H, app s, *Me*CMe, OC*Me*$_3$), 3.54 (1H, dd, *J* 10.1, 8.1, C(6)*H*$_A$), 3.62 (1H, dd, *J* 10.1, 4.6, C(6)*H*$_B$), 4.24-4.30 (1H, m,

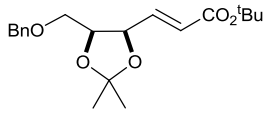
C(5)*H*), 4.78 (1H, app td, *J* 5.4, 1.3, C(4)*H*), 6.02 (1H, dd, *J* 15.5, 1.3, C(2)*H*), 6.85 (1H, dd, *J* 15.5, 5.4, C(3)*H*); δ_C (100 MHz, $CDCl_3$) –5.6, –5.5 (2 × *Me*SiMe), 18.2 (Si*C*Me$_3$), 25.2 (*Me*CMe), 25.9 (SiC*Me*$_3$), 27.7 (*Me*CMe), 28.1 (OC*Me*$_3$), 61.8 (*C*(6)), 76.7 (*C*(4)), 78.3 (*C*(5)), 80.4 (O*C*Me$_3$), 109.6 (Me*C*Me), 124.3 (*C*(2)), 141.6 (*C*(3)), 165.3 (*C*(1)); *m/z* (ESI^+) 395 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{19}H_{36}NaO_5Si^+$ ($[M+Na]^+$) requires 395.2224; found 395.2221.

Method B – Step 1: O_3 was bubbled through a solution of **159** (500 mg, 1.84 mmol, >99:1 dr) in CH_2Cl_2 (10 mL) at −78 °C until the solution turned blue, followed by O_2 until the solution turned colourless. Me_2S (0.5 mL) was then added dropwise and the resultant mixture was left to stir for 12 h. The reaction mixture was concentrated *in vacuo* and the residue was partitioned between Et_2O (50 mL) and H_2O (50 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **161** as a yellow oil (520 mg).

Method B – Step 2: $^iPr_2NEt$ (0.35 mL, 2.0 mmol), LiCl (521 mg, 12.2 mmol) and *tert*-butyl diethylphosphonoacetate **154** (555 mg, 2.20 mmol) were sequentially added to a solution of the residue (520 mg) in MeCN (5 mL) at rt and the resultant mixture was stirred at rt for 48 h. H_2O (2 mL) was then added and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **162** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 20:1) gave **162** as a colourless oil (222 mg, 32% over 2 steps, >99:1 dr).

Method C: O_3 was bubbled through a solution of **159** (11.0 g, 40.4 mmol, >99:1 dr) in CH_2Cl_2 (55 mL) at −78 °C until the solution turned blue, followed by O_2 until the solution turned colourless. PPh_3 (10.6 g, 42.2 mmol) was added portionwise and the reaction mixture was allowed to warm to rt over 1 h, then **143** (19.8 g, 52.5 mmol) was added. The resultant mixture was stirred at rt for 12 h and then concentrated *in vacuo* to give **162** in 56:44 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 20:1) gave **162** as a colourless oil (6.00 g, 40%, >99:1 dr).

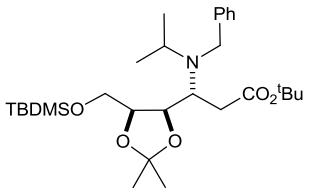
tert-Butyl (4*R*,5*S*,*E*)-4,5-dihydroxy-4,5-*O*-isopropylidene-6-benzyloxyhex-2-enoate 164



Hoveyda-Grubbs II **165** (25 mg, 40 μmol) was added to a degassed solution of **160** (100 mg, 0.400 mmol, >99:1 dr) and *tert*-butyl acrylate **163** (0.18 mL, 1.2 mmol) in CH_2Cl_2 (2 mL) and the resultant mixture was heated at reflux for 22 h. The reaction mixture was then concentrated *in vacuo* to give **164** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 ºC

petrol/EtOAc, 10:1) gave **164** as a colourless oil (109 mg, 78%, >99:1 dr); $[\alpha]_D^{25}$ +19.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2982, 2934, 2867 (C–H), 1714 (C=O), 1658 (C=C); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, s, *Me*CMe), 1.48 (9H, s, C*Me*$_3$), 1.51 (3H, s, *Me*CMe), 3.40 (1H, dd, *J* 9.6, 6.3, C(6)H_A), 3.49 (1H, dd, *J* 9.6, 6.8, C(6)H_B), 4.41-4.48 (1H, m, C(5)*H*), 4.48 (1H, d, *J* 12.0, OCH_AH$_B$Ph), 4.52 (1H, d, *J* 12.0, OCH$_A$$H_B$Ph), 4.77 (1H, app td, *J* 5.6, 1.3, C(4)*H*), 6.05 (1H, dd, *J* 15.5, 1.3, C(2)*H*), 6.82 (1H, dd, *J* 15.5, 5.6, C(3)*H*), 7.25-7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.3, 27.7 (2 × *Me*CMe), 28.1 (C*Me*$_3$), 69.1 (*C*(6)), 73.5 (O*C*H$_2$Ph), 76.3 (*C*(4)), 76.8 (*C*(5)), 80.6 (*C*Me$_3$), 109.4 (Me*C*Me), 124.6 (*C*(2)), 127.7 (*p-Ph*), 127.8, 128.4 (*o,m-Ph*), 137.7 (*i-Ph*), 141.3 (*C*(3)), 165.3 (*C*(1)); *m/z* (ESI^+) 371 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{20}H_{28}NaO_5^+$ ($[M+Na]^+$) requires 371.1829; found 371.1828.

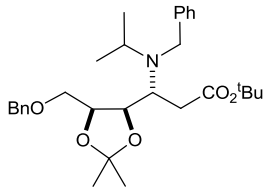
tert-Butyl (3*R*,4*R*,5*S*)-3-(*N*-benzyl-*N*-isopropylamino)-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(_tert_-butyldimethylsilyloxy)hexanoate 180



Method A: Following *General Procedure 1*, *N*-benzyl-*N*-isopropylamine (481 mg, 3.22 mmol) in Et_2O (24 mL), BuLi (2.5 M, 1.25 mL, 3.13 mmol) and **162** (600 mg, 1.61 mmol, >99:1 dr) in Et_2O (24 mL) at –20 ºC gave **180** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 30:1) gave **180** as a colourless oil (687 mg, 82%, >99:1 dr); $C_{29}H_{51}NO_5Si$ requires C, 66.75; H, 9.85; N, 2.7%; found C, 66.9; H, 9.8; N, 2.6%; $[\alpha]_D^{25}$ +36.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2960, 2932, 2884, 2858 (C–H), 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 0.13 (6H, app s, 2 × *Me*SiMe), 0.95 (9H, s, SiC*Me*$_3$), 1.03 (6H, d, *J* 6.7, 2 × *Me*CHMe), 1.34 (3H, s, *Me*CMe), 1.42 (3H, s, *Me*CMe), 1.52 (9H, s, OC*Me*$_3$), 2.22 (1H, dd, *J* 15.1, 3.5, C(2)H_A), 2.60 (1H, dd, *J* 15.1, 8.8, C(2)H_B), 2.94 (1H, septet, *J* 6.7, MeC*H*Me), 3.67 (1H, d, *J* 14.9, NCH_AH$_B$Ph), 3.74 (1H, app dt, *J* 8.8, 3.5, C(3)*H*), 3.78 (1H, dd, *J* 10.6, 6.3, C(6)H_A), 3.91 (1H, dd, *J* 10.6, 6.1, C(6)H_B), 3.99 (1H, d, *J* 14.9, NCH$_A$$H_B$Ph), 4.20-4.27 (1H, m, C(5)*H*), 4.35 (1H, dd, *J* 7.0, 3.5, C(4)*H*), 7.18-7.43 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) –5.2, –5.1 (2 × *Me*SiMe), 18.5 (Si*C*Me$_3$), 18.6, 21.7 (2 × *Me*CHMe), 24.9 (*Me*CMe), 26.1 (SiC*Me*$_3$), 26.9 (*Me*CMe), 28.2 (OC*Me*$_3$), 37.6 (*C*(2)), 49.8 (N*C*H$_2$Ph), 50.1 (Me*C*HMe), 53.2 (*C*(3)), 62.0 (*C*(6)), 78.2, 78.3 (*C*(4), *C*(5)), 79.8 (O*C*Me$_3$), 107.8 (Me*C*Me), 126.4 (*p-Ph*), 128.0, 128.3 (*o,m-Ph*), 142.0 (*i-Ph*), 172.0 (*C*(1)); *m/z* (ESI^+) 522 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{29}H_{52}NO_5Si^+$ ($[M+H]^+$) requires 522.3609; found 522.3602.

Method B: Following *General Procedure 1*, *N*-benzyl-*N*-isopropylamine (80 mg, 0.54 mmol) in THF (4 mL), BuLi (2.5 M, 0.21 mL, 0.52 mmol) and **162** (100 mg, 0.268 mmol, >99:1 dr) in THF (4 mL) at −78 ºC gave an 88:12 mixture of **180** and **178** respectively.

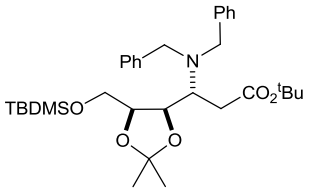
tert-Butyl (3*R*,4*R*,5*S*)-3-(*N*-benzyl-*N*-isopropylamino)-4,5-dihydroxy-4,5-*O*-isopropylidene-6-benzyloxyhexanoate 181



Method A: Following *General Procedure 1*, *N*-benzyl-*N*-isopropylamine (290 mg, 1.94 mmol) in Et_2O (15 mL), BuLi (2.5 M, 0.75 mL, 1.9 mmol) and **164** (338 mg, 0.970 mmol, >99:1 dr) in Et_2O (15 mL) at −20 ºC gave **181** in 95:5 dr. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 15:1) gave **181** as a colourless oil (309 mg, 64%, >99:1 dr); $[\alpha]_D^{25}$ +10.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3029, 2978, 2934, 2873 (C–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.01 (6H, d, *J* 6.6, 2 × *Me*CHMe), 1.33 (3H, s, *Me*CMe), 1.42 (3H, s, *Me*CMe), 1.52 (9H, s, C*Me*$_3$), 2.33 (1H, dd, *J* 15.1, 5.1, C(2)H_A), 2.64 (1H, dd, *J* 15.1, 7.3, C(2)H_B), 2.96 (1H, septet, *J* 6.6, MeC*H*Me), 3.53 (1H, dd, *J* 9.6, 7.1, C(6)H_A), 3.58-3.65 (2H, m, C(3)*H*, C(6)H_B), 3.67 (1H, d, *J* 14.9, NCH_AH$_B$Ph), 3.85 (1H, d, *J* 14.9, NCH$_A$$H_B$Ph), 4.29 (1H, dd, *J* 7.1, 5.1, C(4)*H*), 4.36 (1H, app td, *J* 7.1, 4.8, C(5)*H*), 4.57 (1H, d, *J* 12.4, OCH_AH$_B$Ph), 4.60 (1H, d, *J* 12.4, OCH$_A$$H_B$Ph), 7.21-7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.7, 21.3 (2 × *Me*CHMe), 25.1, 27.2 (*Me*CMe), 28.3 (C*Me*$_3$), 37.2 (*C*(2)), 49.6 (N*C*H$_2$Ph), 50.1 (Me*C*HMe), 53.9 (*C*(3)), 68.7 (*C*(6)), 73.5 (O*C*H$_2$Ph), 76.5 (*C*(5)), 78.2 (*C*(4)), 80.0 (*C*Me$_3$), 108.1 (Me*C*Me), 126.6, 127.6 (*p-Ph*), 127.9, 128.1, 128.3, 128.5 (*o*,*m-Ph*), 138.2, 141.6 (*i-Ph*), 172.1 (*C*(1)); *m/z* (ESI$^+$) 498 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{44}NO_5^+$ ([M+H]$^+$) requires 498.3214; found 498.3213.

Method B: Following *General Procedure 1*, *N*-benzyl-*N*-isopropylamine (86 mg, 0.57 mmol) in THF (4 mL), BuLi (2.5 M, 0.21 mL, 0.56 mmol) and **164** (100 mg, 0.287 mmol, >99:1 dr) in THF (4 mL) at −78 ºC gave an 85:15 mixture of **181** and **179** respectively.

tert-Butyl (3*R*,4*R*,5*S*)- and (3*S*,4*R*,5*S*)-3-(*N*,*N*-dibenzylamino)-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(_tert_-butyldimethylsilyloxy)hexanoate 184 and 186



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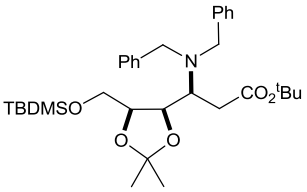
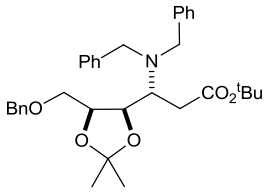


186

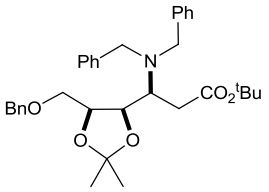
Method A: Following *General Procedure 1*, dibenzylamine (636 mg, 3.22 mmol) in Et_2O (24 mL), BuLi (2.5 M, 1.25 mL, 3.13 mmol) and **162** (600 mg, 1.61 mmol, >99:1 dr) in Et_2O (24 mL) at –20 ºC gave an 80:20 mixture of **184** and **186** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 10:1) gave an 83:17 mixture of **184** and **186**, respectively, as a colourless oil (375 mg, 41%). Data for mixture: $C_{33}H_{51}NO_5Si$ requires C, 69.55; H, 9.0; N, 2.5%; found C, 69.7; H, 8.9; N, 2.4%; ν_{max} (film) 2980, 2954, 2931, 2885, 2857 (C–H), 1730 (C=O); *m/z* (ESI^+) 570 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{33}H_{52}NO_5Si^+$ ($[M+H]^+$) requires 570.3609; found 570.3606. Data for **184**: δ_H (400 MHz, $CDCl_3$) 0.05 (6H, app s, 2 × *Me*SiMe), 0.91 (9H, s, SiC*Me*$_3$), 1.33 (3H, s, *Me*CMe), 1.42 (3H, s, *Me*CMe), 1.50 (9H, s, OC*Me*$_3$), 2.34 (1H, dd, *J* 15.2, 5.6, C(2)*H*$_A$), 2.68 (1H, dd, *J* 15.2, 7.1, C(2)*H*$_B$), 3.46-3.60 (3H, m, C(3)*H*, C(6)*H*$_2$), 3.64 (2H, d, *J* 13.9, N(C*H*$_A$H$_B$Ph)$_2$), 3.71 (2H, d, *J* 13.9, N(CH$_A$*H*$_B$Ph)$_2$), 4.17-4.24 (1H, m, C(5)*H*), 4.28-4.34 (1H, m, C(4)*H*), 7.19-7.42 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) –5.1, –5.0 (2 × *Me*SiMe), 18.5 (Si*C*Me$_3$), 25.3 (*Me*CMe), 26.1 (SiC*Me*$_3$), 27.4 (*Me*CMe), 28.2 (OC*Me*$_3$), 35.2 (*C*(2)), 54.6 (N(*C*H$_2$Ph)$_2$), 55.4 (*C*(3)), 62.3 (*C*(6)), 76.2 (*C*(4)), 78.7 (*C*(5)), 80.0 (O*C*Me$_3$), 107.9 (Me*C*Me), 127.1 (*p-Ph*), 128.2, 129.3 (*o,m-Ph*), 139.3 (*i-Ph*), 171.6 (*C*(1)). Data for **186**: δ_H (400 MHz, $CDCl_3$) –0.01 (3H, s, *Me*SiMe), 0.02 (3H, s, *Me*SiMe), 0.86 (9H, s, SiC*Me*$_3$), 1.46 (3H, s, *Me*CMe), 1.48 (9H, s, OC*Me*$_3$), 1.54 (3H, s, *Me*CMe), 2.36 (1H, dd, *J* 14.4, 9.4, C(2)*H*$_A$), 2.42 (1H, dd, *J* 14.4, 4.5, C(2)*H*$_B$), 3.46-3.60 (2H, m, C(3)*H*, C(6)*H*$_A$), 3.64-3.71 (1H, m, C(6)*H*$_B$), 3.85 (2H, d, *J* 13.3, N(C*H*$_A$H$_B$Ph)$_2$), 3.89 (2H, d, *J* 13.3, N(CH$_A$*H*$_B$Ph)$_2$), 3.98-4.04 (1H, m, C(5)*H*), 4.39 (1H, dd, *J* 10.0, 5.2, C(4)*H*), 7.19-7.42 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) –5.5, –5.4 (2 × *Me*SiMe), 18.4 (Si*C*Me$_3$), 25.6 (*Me*CMe), 25.9 (SiC*Me*$_3$), 27.4 (*Me*CMe), 28.4 (OC*Me*$_3$), 37.4 (*C*(2)), 53.7 (*C*(3)), 55.0 (N(*C*H$_2$Ph)$_2$), 62.6 (*C*(6)), 78.4 (*C*(5)), 79.3 (*C*(4)), 80.1 (O*C*Me$_3$), 107.9 (Me*C*Me), 126.7 (*p-Ph*), 127.9, 129.6 (*o,m-Ph*), 140.3 (*i-Ph*), 170.5 (*C*(1)).

Method B: Following *General Procedure 1*, dibenzylamine (106 mg, 0.537 mmol) in THF (4 mL), BuLi (2.5 M, 0.21 mL, 0.52 mmol) and **162** (100 mg, 0.268 mmol, >99:1 dr) in THF (4 mL) at –78 ºC gave a 61:39 mixture of **184** and **186** respectively.

tert-Butyl (3*R*,4*R*,5*S*)- and (3*S*,4*R*,5*S*)-3-(*N*,*N*-dibenzylamino)-4,5-dihydroxy-4,5-*O*-isopropylidene-6-benzyloxyhexanoate 185 and 187



185

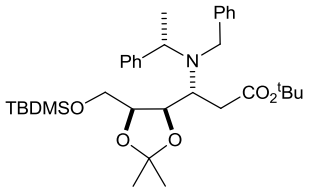


187

Method A: Following *General Procedure 1*, dibenzylamine (376 mg, 1.91 mmol) in Et_2O (15 mL), BuLi (2.1 M, 0.89 mL, 1.9 mmol) and **164** (317 mg, 0.910 mmol, >99:1 dr) in Et_2O (15 mL) at –20 ºC gave an 83:17 mixture of **185** and **187** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 4:1) gave an 83:17 mixture of **185** and **187**, respectively, as a yellow oil (225 mg, 45%). Data for mixture: ν_{max} (film) 3063, 3029, 2980, 2934, 2870, 2809 (C–H), 1729 (C=O); *m/z* (ESI^+) 546 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{34}H_{44}NO_5^+$ ($[M+H]^+$) requires 546.3214; found 546.3212. Data for **185**: δ_H (400 MHz, $CDCl_3$) 1.35 (3H, s, *Me*CMe), 1.40 (3H, s, *Me*CMe), 1.50 (9H, s, C*Me*$_3$), 2.36 (1H, dd, *J* 14.9, 6.6, C(2)H_A), 2.74 (1H, dd, *J* 14.9, 5.6, C(2)H_B), 3.17 (1H, dd, *J* 9.9, 4.3, C(6)H_A), 3.21 (1H, dd, *J* 9.9, 7.6, C(6)H_B), 3.47-3.53 (1H, m, C(3)*H*), 3.57 (2H, d, *J* 13.8, N(CH_AH$_B$Ph)$_2$), 3.68 (2H, d, *J* 13.8, N(CH$_A$$H_B$Ph)$_2$), 4.31-4.35 (1H, m, C(4)*H*) overlapping 4.32 (1H, d, *J* 12.4, OCH_AH$_B$Ph), 4.38 (1H, d, *J* 12.4, OCH$_A$$H_B$Ph), 4.38-4.42 (1H, m, C(5)*H*), 7.23-7.43 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.4, 27.6 (2 × *Me*CMe), 28.2 (C*Me*$_3$), 34.4 (*C*(2)), 54.6 (N(*C*H$_2$Ph)$_2$), 54.9 (*C*(3)), 68.5 (*C*(6)), 73.0 (O*C*H$_2$Ph), 76.5, 76.8 (*C*(4), *C*(5)), 80.2 (*C*Me$_3$), 108.3 (Me*C*Me), 127.2, 127.7 (*p-Ph*), 128.3, 128.3, 129.4, 129.4 (*o*,*m-Ph*), 138.4, 138.1 (*i-Ph*), 171.7 (*C*(1)). Data for **187**: δ_H (400 MHz, $CDCl_3$) 1.46 (3H, s, *Me*CMe), 1.47 (9H, s, C*Me*$_3$), 1.54 (3H, s, *Me*CMe), 2.30 (1H, dd, *J* 14.4, 3.8, C(2)H_A), 2.44 (1H, dd, *J* 14.4, 9.6, C(2)H_B), 3.37 (1H, dd, *J* 9.9, 6.3, C(6)H_A), 3.44-3.53 (2H, m, C(3)*H*, C(6)H_B), 3.84 (2H, d, *J* 13.4, N(CH_AH$_B$Ph)$_2$), 3.88 (2H, d, *J* 13.4, N(CH$_A$$H_B$Ph)$_2$), 4.18 (1H, app q, *J* 5.8, C(5)*H*), 4.26 (1H, d, *J* 12.1, OCH_AH$_B$Ph), 4.36-4.42 (1H, m, C(4)*H*), 4.46 (1H, d, *J* 12.1, OCH$_A$$H_B$Ph), 7.23-7.43 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.6 (*Me*CMe), 28.2 (C*Me*$_3$), 28.3 (*Me*CMe), 37.0 (*C*(2)), 53.5 (*C*(3)), 54.6 (N(*C*H$_2$Ph)$_2$), 69.4 (*C*(6)), 73.3 (O*C*H$_2$Ph), 76.6, 79.3 (*C*(4), *C*(5)), 80.2 (*C*Me$_3$), 108.3 (Me*C*Me), 126.8, 127.5 (*p-Ph*), 127.6, 127.8, 128.0, 129.7 (*o*,*m-Ph*), 138.1, 140.1 (*i-Ph*), 170.6 (*C*(1)).

Method B: Following *General Procedure 1*, dibenzylamine (113 mg, 0.574 mmol) in THF (4 mL), BuLi (2.5 M, 0.21 mL, 0.56 mmol) and **164** (100 mg, 0.287 mmol, >99:1 dr) in THF (4 mL) at –78 ºC gave a 75:25 mixture of **185** and **187** respectively.

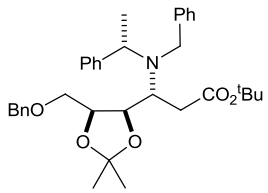
tert-Butyl (3*R*,4*R*,5*S*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(*tert*-butyldimethylsilyloxy)hexanoate 188



Method A: Following *General Procedure 1*, (*S*)-**123** (657 mg, 3.11 mmol) in Et_2O (23 mL), BuLi (2.5 M, 1.21 mL, 3.02 mmol) and **162** (579 mg, 1.56 mmol, >99:1 dr) in Et_2O (23 mL) at –20 ºC gave **188** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 30:1) gave **188** as a colourless oil (821 mg, 90%, >99:1 dr); $[\alpha]_D^{25}$ +13.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3063, 3028, 2932, 2857 (C–H), 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 0.14 (6H, app s, 2 × *Me*SiMe), 0.98 (9H, s, SiC*Me*$_3$), 1.30 (3H, s, *Me*CMe), 1.41 (3H, s, *Me*CMe), 1.43 (3H, d, *J* 6.8, C(α)*Me*), 1.48 (9H, s, OC*Me*$_3$), 2.25 (1H, dd, *J* 15.7, 5.1, C(2)H_A), 2.43 (1H, dd, *J* 15.7, 7.3, C(2)H_B), 3.69 (1H, dd, *J* 10.9, 6.6, C(6)H_A), 3.78 (1H, d, *J* 15.2, NCH_AH$_B$Ph), 3.80-3.84 (2H, m, C(3)*H*, C(6)H_B), 3.86 (1H, d, *J* 15.2, NCH$_A$$H_B$Ph), 4.07 (1H, q, *J* 6.8, C(α)*H*), 4.18-4.26 (2H, m, C(4)*H*, C(5)*H*), 7.20-7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) –5.1, –5.0 (2 × *Me*SiMe), 18.6 (Si*C*Me$_3$), 18.9 (C(α)*Me*), 25.0 (*Me*CMe), 26.1 (SiC*Me*$_3$), 27.3 (*Me*CMe), 28.2 (OC*Me*$_3$), 36.7 (*C*(2)), 50.1 (N*C*H$_2$Ph), 45.8 (*C*(3)), 60.0 (*C*(α)), 62.5 (*C*(6)), 77.5, 78.5 (*C*(4), *C*(5)), 79.8 (O*C*Me$_3$), 107.7 (Me*C*Me), 126.5, 127.0 (*p-Ph*), 128.0, 128.1, 128.2, 128.3 (*o,m-Ph*), 141.8, 143.5 (*i-Ph*), 171.5 (*C*(1)); *m/z* (ESI$^+$) 584 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{54}NO_5Si^+$ ([M+H]$^+$) requires 584.3766; found 584.3763.

Method B: Following *General Procedure 1*, (*S*)-**123** (114 mg, 0.540 mmol) in THF (4 mL), BuLi (2.5 M, 0.21 mL, 0.52 mmol) and **162** (100 mg, 0.268 mmol, >99:1 dr) in THF (4 mL) at –78 ºC gave a 75:25 mixture of **188** and **178** respectively.

tert-Butyl (3*R*,4*R*,5*S*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-dihydroxy-4,5-*O*-isopropylidene-6-benzyloxyhexanoate 189

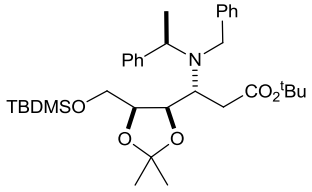


Method A: Following *General Procedure 1*, (*S*)-**123** (784 mg, 3.71 mmol) in Et_2O (28 mL), BuLi (2.5 M, 1.44 mL, 3.60 mmol) and **164** (646 mg, 1.86 mmol, >99:1 dr) in Et_2O (28 mL) at –20 ºC gave a 93:7 mixture of **189** and **191** respectively. Purification via flash column chromatography

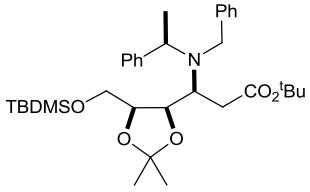
(eluent 30-40 ºC petrol/Et_2O, 10:1) gave **189** as a pale yellow oil (820 mg, 79%, 93:7 dr); $[\alpha]_D^{25}$ +3.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3062, 3029, 2979, 2933, 2877 (C–H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, s, *Me*CMe), 1.36 (3H, d, *J* 7.0, C(α)*Me*), 1.42 (3H, s, *Me*CMe), 1.47 (9H, s, C*Me*$_3$), 2.25 (1H, dd, *J* 15.5, 5.9, C(2)H_A), 2.42 (1H, dd, *J* 15.5, 5.9, C(2)H_B), 3.48 (1H, dd, *J* 9.9, 8.1, C(6)H_A), 3.56 (1H, dd, *J* 9.9, 4.3, C(6)H_B), 3.69 (1H, app q, *J* 5.9, C(3)*H*), 3.77 (1H, d, *J* 15.4, NCH_AH$_B$Ph), 3.82 (1H, d, *J* 15.4, NCH$_A$$H_B$Ph), 4.00 (1H, q, *J* 7.0, C(α)*H*), 4.27 (1H, dd, *J* 6.3, 5.9, C(4)*H*), 4.38-4.44 (1H, m, C(5)*H*), 4.56 (1H, d, *J* 12.6, OCH_AH$_B$Ph), 4.60 (1H, d, *J* 12.6, OCH$_A$$H_B$Ph), 7.22-7.44 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.8 (C(α)*Me*), 25.1, 27.4 (2 × *Me*CMe), 28.2 (C*Me*$_3$), 36.4 (*C*(2)), 50.4 (N*C*H$_2$Ph), 54.6 (*C*(3)), 59.4 (*C*(α)), 68.7 (*C*(6)), 73.3 (O*C*H$_2$Ph), 76.6 (*C*(5)), 77.7 (*C*(4)), 79.9 (*C*Me$_3$), 108.0 (Me*C*Me), 126.7, 127.1 (*p-Ph*), 127.8, 128.1, 128.2, 128.3, 128.3, 128.4 (*o,m-Ph*), 138.3, 141.5, 143.4 (*i-Ph*), 171.5 (*C*(1)); *m/z* (ESI$^+$) 560 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{46}NO_5^+$ ([M+H]$^+$) requires 560.3371; found 560.3370.

Method B: Following *General Procedure 1*, (*S*)-**123** (121 mg, 0.574 mmol) in THF (4 mL), BuLi (2.5 M, 0.21 mL, 0.56 mmol) and **164** (100 mg, 0.287 mmol, >99:1 dr) in THF (4 mL) at −78 ºC gave an 80:6:14 mixture of **189**, **191** and **179** respectively.

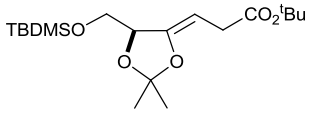
tert-Butyl (3*R*,4*R*,5*S*,α*R*)-and (3*S*,4*R*,5*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(*tert*-butyldimethylsilyloxy)hexanoate 192 and 194 and *tert*-butyl (*S*,*Z*)-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(*tert*-butyldimethylsilyloxy)hex-3-enoate 178



192



194



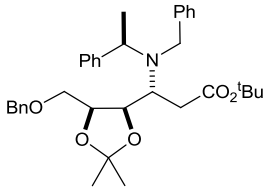
178

Method A: Following *General Procedure 1*, (*R*)-**123** (641 mg, 3.04 mmol) in Et_2O (23 mL), BuLi (2.5 M, 1.18 mL, 2.94 mmol) and **162** (565 mg, 1.52 mmol, >99:1 dr) in Et_2O (23 mL) at −20 ºC gave an 82:18 mixture of **192** and **194** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 30:1) gave **192** as a colourless oil (513 mg, 58%, >99:1 dr); $[\alpha]_D^{25}$ +34.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2978, 2955, 2932, 2884, 2857 (C–H), 1729 (C=O); δ_H (400 MHz, $CDCl_3$) 0.16 (6H, app s, 2 × *Me*SiMe), 0.98 (9H, s, SiC*Me*$_3$), 1.12 (3H, s, *Me*CMe), 1.34 (3H, s, *Me*CMe), 1.39 (3H, d, *J* 7.1, C(α)*Me*), 1.56 (9H, s, OC*Me*$_3$), 2.27 (1H, dd, *J* 15.4, 3.8, C(2)H_A), 2.55 (1H, dd, *J* 15.4, 9.1, C(2)H_B), 3.54 (1H, dd, *J* 6.7, 2.7, C(4)*H*), 3.56 (1H, d, *J* 15.2, NCH_AH$_B$Ph), 3.68 (1H, dd, *J* 10.7, 6.7, C(6)H_A), 3.74 (1H, dd, *J* 10.7, 5.3, C(6)H_B), 3.81-3.88 (1H, m, C(5)*H*)

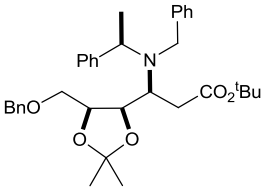
overlapping 3.82 (1H, q, *J* 7.1, C(α)*H*), 3.91-3.98 (1H, m, C(3)*H*), 4.05 (1H, d, *J* 15.2, NCH_AH_BPh), 7.23-7.50 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) –5.1, –5.1 (2 × *Me*SiMe), 18.7 ($SiCMe_3$), 19.4 (C(α)*Me*), 24.5 (*Me*CMe), 26.2 ($SiCMe_3$), 27.0 (*Me*CMe), 28.3 ($OCMe_3$), 37.2 (*C*(2)), 50.3 (NCH_2Ph), 52.5 (*C*(3)), 58.0 (*C*(α)), 62.5 (*C*(6)), 76.9 (*C*(4)), 78.2 (*C*(5)), 79.9 ($OCMe_3$), 107.5 (Me*C*Me), 126.6, 127.2 (*p-Ph*), 128.1, 128.1, 128.6, 128.6 (*o,m-Ph*), 141.5, 141.9 (*i-Ph*), 171.8 (*C*(1)); *m/z* (ESI^+) 584 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{34}H_{54}NO_5Si^+$ ($[M+H]^+$) requires 584.3766; found 584.3769. Further elution gave **194** as a colourless oil (109 mg, 12%, >99:1 dr); $[\alpha]_D^{25}$ –10.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2980, 2955, 2931, 2858 (C–H), 1732 (C=O); δ_H (400 MHz, $CDCl_3$) 0.04 (3H, s, *Me*SiMe), 0.05 (3H, s, *Me*SiMe), 0.87 (9H, s, $SiCMe_3$), 1.42 (3H, s, *Me*CMe), 1.48 (3H, s, *Me*CMe), 1.49 (9H, s, $OCMe_3$), 1.51 (3H, d, *J* 6.8, C(α)*Me*), 2.19 (1H, dd, *J* 15.4, 9.9, C(2)H_A), 2.28 (1H, dd, *J* 15.4, 3.5, C(2)H_B), 3.50 (1H, dd, *J* 10.6, 4.8, C(6)H_A), 3.75 (1H, dd, *J* 10.6, 7.3, C(6)H_B), 3.81 (1H, d, *J* 14.4, NCH_AH_BPh), 3.84-3.89 (1H, m, C(3)*H*), 3.88 (1H, d, *J* 14.4, NCH_AH_BPh), 3.95-4.01 (1H, m, C(5)*H*), 4.19 (1H, q, *J* 6.8, C(α)*H*), 4.37 (1H, dd, *J* 10.6, 5.1, C(4)*H*), 7.10-7.47 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) –5.5, –5.4 (2 × *Me*SiMe), 18.4 ($SiCMe_3$), 20.5 (C(α)*Me*), 25.5 (*Me*CMe), 26.1 ($SiCMe_3$), 28.2 ($OCMe_3$), 28.5 (*Me*CMe), 37.7 (*C*(2)), 51.4 (NCH_2Ph), 52.6 (*C*(3)), 60.9 (*C*(α)), 62.7 (*C*(6)), 78.5 (*C*(5)), 78.9 (*C*(4)), 79.9 ($OCMe_3$), 107.7 (Me*C*Me), 126.3, 126.3 (*p-Ph*), 127.7, 127.8, 128.0, 129.0 (*o,m-Ph*), 141.9, 146.7 (*i-Ph*), 170.7 (*C*(1)); *m/z* (ESI^+) 584 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{34}H_{54}NO_5Si^+$ ($[M+H]^+$) requires 584.3766; found 584.3766.

Method B: Following *General Procedure 1*, (*R*)-**123** (114 mg, 0.540 mmol) in THF (4 mL), BuLi (2.5 M, 0.21 mL, 0.52 mmol) and **162** (100 mg, 0.268 mmol, >99:1 dr) in THF (4 mL) at –78 ºC gave a complex mixture of which the main component was **178**. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 30:1) gave **178** as a colourless oil (72 mg, 72%, >99:1 dr); $[\alpha]_D^{25}$ –24.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2980, 2956, 2931, 2859 (C–H), 1735 (C=O); δ_H (400 MHz, $CDCl_3$) 0.08 (6H, app s, 2 × *Me*SiMe), 0.91 (9H, s, $SiCMe_3$), 1.40 (3H, s, *Me*CMe), 1.45 (9H, s, $OCMe_3$), 1.50 (3H, s, *Me*CMe), 2.99 (1H, ddd, *J* 17.7, 6.4, 1.4, C(2)H_A), 3.10 (1H, ddd, *J* 17.7, 7.3, 1.3, C(2)H_B), 3.70 (1H, dd, *J* 10.9, 5.6, C(6)H_A), 3.74 (1H, dd, *J* 10.9, 4.6, C(6)H_B), 4.40-4.45 (1H, m, C(3)*H*), 4.60-4.65 (1H, m, C(5)*H*); δ_C (100 MHz, $CDCl_3$) –5.3, –5.3 (2 × *Me*SiMe), 18.4 ($SiCMe_3$), 25.6 (*Me*CMe), 25.9 ($SiCMe_3$), 26.8 (*Me*CMe), 28.1 ($OCMe_3$), 32.1 (*C*(2)), 66.0 (*C*(6)), 78.1 (*C*(5)), 80.3 ($OCMe_3$), 87.8 (*C*(3)), 111.1 (Me*C*Me), 151.8 (*C*(4)), 171.7 (*C*(1)); *m/z* (ESI^+) 395 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{19}H_{36}NaO_5Si^+$ ($[M+Na]^+$) requires 395.2224; found 395.2222.

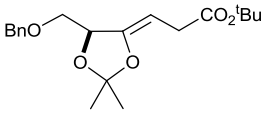
tert-Butyl (3*R*,4*R*,5*S*,α*R*)- and (3*S*,4*R*,5*S*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-dihydroxy-4,5-*O*-isopropylidene-6-benzyloxyhexanoate 193 and 195 and _tert_-butyl (*S*,*Z*)-4,5-dihydroxy-4,5-*O*-isopropylidene-6-benzyloxyhex-3-enoate 179



193



195



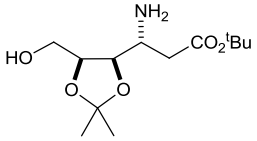
179

Method A: Following *General Procedure 1*, (*R*)-**123** (437 mg, 2.07 mmol) in Et_2O (15 mL), BuLi (2.5 M, 0.80 mL, 2.0 mmol) and **164** (360 mg, 1.03 mmol, >99:1 dr) in Et_2O (15 mL) at –20 ºC gave an 83:17 mixture of **193** and **195** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 15:1) gave **193** as a colourless oil (257 mg, 44%, >99:1 dr); $[\alpha]_D^{25}$ +25.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3062, 3028, 2978, 2933, 2872 (C–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.18 (3H, s, *Me*CMe), 1.34 (3H, d, *J* 7.1, C(α)*Me*), 1.38 (3H, s, *Me*CMe), 1.57 (9H, s, C*Me*$_3$), 2.29 (1H, dd, *J* 15.2, 4.6, C(2)H_A), 2.57 (1H, dd, *J* 15.2, 7.6, C(2)H_B), 3.44-3.54 (2H, m, C(6)H_2), 3.61 (1H, d, *J* 15.0, NCH_AH$_B$Ph), 3.62 (1H, dd, *J* 7.2, 4.0, C(4)*H*), 3.78-3.86 (1H, m, C(3)*H*) overlapping 3.81 (1H, q, *J* 7.1, C(α)*H*), 4.00 (1H, d, *J* 15.0, NCH$_A$$H_B$Ph), 4.06 (1H, app td, *J* 7.2, 5.1, C(5)*H*), 4.59 (1H, d, *J* 12.3, OCH_AH$_B$Ph), 4.63 (1H, d, *J* 12.3, OCH$_A$$H_B$Ph), 7.22-7.49 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.8 (C(α)*Me*), 24.7, 27.0 (2 × *Me*CMe), 28.3 (C*Me*$_3$), 37.3 (*C*(2)), 50.5 (N*C*H$_2$Ph), 53.2 (*C*(3)), 58.2 (*C*(α)), 68.7 (*C*(6)), 73.4 (O*C*H$_2$Ph), 76.4 (*C*(5)), 77.1 (*C*(4)), 80.1 (*C*Me$_3$), 107.9 (Me*C*Me), 126.8, 127.2, 127.7 (*p-Ph*), 128.0, 128.1, 128.2, 128.2, 128.4, 128.6 (*o,m-Ph*), 138.3, 141.4, 142.2 (*i-Ph*), 172.1 (*C*(1)); *m/z* (ESI$^+$) 560 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{46}NO_5^+$ ([M+H]$^+$) requires 560.3371; found 560.3367. Further elution gave **195** as a pale yellow solid (41 mg, 7%, >99:1 dr); mp 70-74 °C; $[\alpha]_D^{25}$ –26.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3062, 3028, 2980, 2933, 2864 (C–H), 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 1.43 (3H, s, *Me*CMe), 1.46 (9H, s, C*Me*$_3$), 1.49 (3H, s, *Me*CMe), 1.51 (3H, d, *J* 6.8, C(α)*Me*), 2.14 (1H, dd, *J* 15.3, 2.9, C(2)H_A), 2.26 (1H, dd, *J* 15.3, 10.1, C(2)H_B), 3.43 (1H, dd, *J* 9.9, 5.6, C(6)H_A), 3.52 (1H, dd, *J* 9.9, 6.1, C(6)H_B), 3.72-3.80 (1H, m, C(3)*H*), 3.78 (1H, d, *J* 14.2, NCH_AH$_B$Ph), 3.93 (1H, d, *J* 14.2, NCH$_A$$H_B$Ph), 4.12-4.17 (1H, m, C(5)*H*), 4.21 (1H, q, *J* 6.8, C(α)*H*), 4.35 (1H, dd, *J* 10.4, 5.1, C(4)*H*), 4.39 (1H, d, *J* 12.1, OCH_AH$_B$Ph), 4.53 (1H, d, *J* 12.1, OCH$_A$$H_B$Ph), 7.13-7.47 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.0 (C(α)*Me*), 25.6 (*Me*CMe), 28.1 (C*Me*$_3$), 28.4 (*Me*CMe), 37.6 (*C*(2)), 51.3 (N*C*H$_2$Ph), 52.9 (*C*(3)), 59.6 (*C*(α)), 69.4 (*C*(6)), 73.5 (O*C*H$_2$Ph), 76.7 (*C*(5)), 79.0 (*C*(4)), 80.2 (*C*Me$_3$), 108.2 (Me*C*Me), 126.3, 126.3, 127.6 (*p-Ph*), 127.7, 127.7, 127.8, 128.0, 128.3, 129.1 (*o,m-Ph*),

138.0, 141.6, 146.3 (*i-Ph*), 170.7 (*C*(1)); *m/z* (ESI$^+$) 560 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{46}NO_5^+$ ([M+H]$^+$) requires 560.3371; found 560.3373.

Method B: Following *General Procedure 1*, (*R*)-**123** (121 mg, 0.574 mmol) in THF (4 mL), BuLi (2.5 M, 0.21 mL, 0.56 mmol) and **164** (100 mg, 0.287 mmol, >99:1 dr) in THF (4 mL) at −78 ºC gave a 37:17:46 mixture of **193**, **195** and **179** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 10:1) gave **193** as a colourless oil (46 mg, 29%, >99:1 dr). Further elution gave a 70:30 mixture of **179** and **195** respectively as a pale yellow oil (38 mg). Data for **179**: δ_H (400 MHz, $CDCl_3$) 1.43 (3H, s, *Me*CMe), 1.45 (9H, s, C*Me*$_3$), 1.54 (3H, s, *Me*CMe), 3.01 (1H, ddd, *J* 17.8, 6.7, 1.3, C(2)H_A), 3.09 (1H, ddd, *J* 17.8, 7.2, 1.0, C(2)H_B), 3.56 (1H, dd, *J* 10.4, 7.3, C(6)H_A), 3.62 (1H, dd, *J* 10.4, 3.5, C(6)H_B), 4.35-4.40 (1H, m, C(3)*H*), 4.59 (1H, d, *J* 12.3, OCH_AH$_B$Ph), 4.67 (1H, d, *J* 12.3, OCH$_A$$H_B$Ph), 4.82 (1H, ddd, *J* 7.3, 3.5, 1.5, C(5)*H*), 7.12-7.46 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.4, 26.8 (2 × *Me*CMe), 28.1 (C*Me*$_3$), 32.0 (*C*(2)), 72.4 (*C*(6)), 73.5 (O*C*H$_2$Ph), 76.5 (*C*(5)), 80.3 (*C*Me$_3$), 87.8 (*C*(3)), 111.4 (Me*C*Me), 126.4 (*p-Ph*), 127.8, 128.4 (*o,m-Ph*), 137.9 (*i-Ph*), 151.2 (*C*(4)), 171.6 (*C*(1)); *m/z* (ESI$^+$) 371 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{28}NaO_5^+$ ([M+Na]$^+$) requires 371.1829; found 371.1826.

tert-Butyl (3*R*,4*R*,5*S*)-3-amino-4,5,6-trihydroxy-4,5-*O*-isopropylidenehexanoate 196



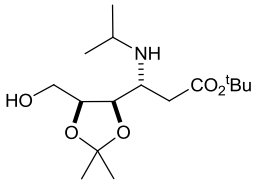
*Method A (From **189**):* Following *General Procedure 2*, **189** (310 mg, 0.554 mmol, 93:7 dr) in EtOAc (5 mL), Pd(OH)$_2$/C (50% w/w of substrate, 155 mg) and H_2 (1 atm) gave **196** as a pale yellow oil (124 mg, 81%, 93:7 dr); $[\alpha]_D^{25}$ +20.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3367, 3288 (N–H, O–H), 2983, 2935 (C–H), 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, s, *Me*CMe), 1.35 (3H, s, *Me*CMe), 1.43 (9H, s, C*Me*$_3$), 2.29 (1H, dd, *J* 16.8, 9.4, C(2)H_A), 2.75 (1H, dd, *J* 16.8, 2.8, C(2)H_B), 3.36 (1H, app td, *J* 9.4, 2.8, C(3)*H*), 3.53 (3H, br s, NH_2, O*H*), 3.63 (1H, dd, *J* 11.5, 3.9, C(6)H_A), 3.73 (1H, dd, *J* 11.5, 9.9, C(6)H_B), 3.97 (1H, dd, *J* 9.4, 5.8, C(4)*H*), 4.32-4.39 (1H, m, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 25.1, 27.7 (2 × *Me*CMe), 28.1 (C*Me*$_3$), 41.0 (*C*(2)), 48.1 (*C*(3)), 60.3 (*C*(6)), 77.6 (*C*(5)), 79.3 (*C*(4)), 81.2 (*C*Me$_3$), 108.2 (Me*C*Me), 171.5 (*C*(1)); *m/z* (ESI$^+$) 276 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{26}NO_5^+$ ([M+H]$^+$) requires 276.1805; found 276.1799.

*Method B (From **193**):* Following *General Procedure 2*, **193** (126 mg, 0.225 mmol, >99:1 dr) in EtOAc (5 mL), Pd(OH)$_2$/C (50% w/w of substrate, 63 mg) and H_2 (1 atm) gave a 79:21 mixture of

196 and **193** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/EtOAc, 1:2) gave **196** as a pale yellow oil (26 mg, 42%, >99:1 dr).

*Method C (From **185**)*: Following *General Procedure 2*, **185** (99 mg, 0.18 mmol, 83:17 dr) in EtOAc (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 50 mg) and H_2 (1 atm) gave **196** as a pale yellow oil (33 mg, 66%, 83:17 dr).

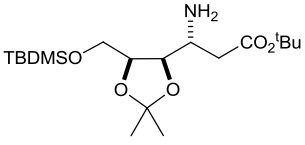
tert-Butyl (3*R*,4*R*,5*S*)-3-*N*-isopropylamino-4,5,6-trihydroxy-4,5-*O*-isopropylidenehexanoate 197



*Method A (From **181**):* Following *General Procedure 2*, **181** (185 mg, 0.372 mmol, >99:1 dr) in EtOAc (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 93 mg) and H_2 (1 atm) gave **197** as a pale yellow oil (118 mg, quant, >99:1 dr); $[\alpha]_D^{25}$ –4.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3261 (N–H, O–H), 2978, 2935, 2876 (C–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.10 (6H, d, *J* 6.1, 2 × *Me*CHMe), 1.30 (3H, s, *Me*CMe), 1.35 (3H, s, *Me*CMe), 1.43 (9H, s, C*Me*$_3$), 2.56 (1H, dd, *J* 16.5, 3.9, C(2)H_A), 2.69 (1H, dd, *J* 16.5, 4.6, C(2)H_B), 2.99-3.09 (1H, m, MeC*H*Me), 3.33 (1H, app dt, *J* 9.9, 4.4, C(3)*H*), 3.66 (1H, dd, *J* 11.6, 9.1, C(6)H_A), 3.69 (1H, dd, *J* 11.6, 5.1, C(6)H_B), 4.18 (1H, dd, *J* 9.9, 5.7, C(4)*H*), 4.40 (1H, app dt, *J* 9.1, 5.7, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 20.0, 23.9 (2 × *Me*CHMe), 25.1, 27.7 (2 × *Me*CMe), 28.1 (C*Me*$_3$), 34.1 (*C*(2)), 44.9 (Me*C*HMe), 50.9 (*C*(3)), 60.0 (*C*(6)), 77.4 (*C*(5)), 78.1 (*C*(4)), 81.0 (*C*Me$_3$), 108.1 (Me*C*Me), 171.1 (*C*(1)); *m/z* (ESI^+) 318 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{16}H_{32}NO_5^+$ ($[M+H]^+$) requires 318.2275; found 318.2270.

*Method B (From **196**):* Following *General Procedure 3*, **196** (95 mg, 0.35 mmol, >99:1 dr) in MeOH (3 mL), acetone (51 µL, 0.69 mmol) and $NaBH_3CN$ (87 mg, 1.4 mmol) at rt gave a 74:26 mixture of **197** and **196** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/EtOAc, 3:1) gave **197** as a pale yellow oil (67 mg, 61%, >99:1 dr).

tert-Butyl (3*R*,4*R*,5*S*)-3-amino-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(*tert*-butyldimethylsilyloxy)hexanoate 198



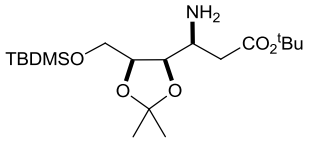
*Method A (From **188**):* Following *General Procedure 2*, **188** (140 mg, 0.240 mmol, >99:1 dr) in EtOAc (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 70 mg) and H_2 (1 atm) gave **198** as a pale yellow

oil (83 mg, 89%, >99:1 dr); $[\alpha]_D^{25}$ –6.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3320 (N–H), 2982, 2956, 2933, 2859 (C–H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 0.08 (6H, app s, 2 × *Me*SiMe), 0.89 (9H, s, SiC*Me*$_3$), 1.29 (3H, s, *Me*CMe), 1.34 (3H, s, *Me*CMe), 1.45 (9H, s, OC*Me*$_3$), 1.81 (2H, br s, N*H*$_2$), 2.27 (1H, dd, *J* 15.9, 9.1, C(2)*H*$_A$), 2.72 (1H, dd, *J* 15.9, 3.3, C(2)*H*$_B$), 3.40 (1H, app td, *J* 9.1, 3.3, C(3)*H*), 3.53 (1H, dd, *J* 10.2, 3.4, C(6)*H*$_A$), 3.75-3.82 (1H, m, C(6)*H*$_B$), 3.92 (1H, dd, *J* 9.1, 5.1, C(4)*H*), 4.14-4.20 (1H, m, C(5)*H*); δ_C (100 MHz, $CDCl_3$) –5.6, –5.6 (2 × *Me*SiMe), 18.2 (Si*C*Me$_3$), 25.5 (*Me*CMe), 25.9 (SiC*Me*$_3$), 28.1 (*Me*CMe), 28.2 (OC*Me*$_3$), 40.8 (*C*(2)), 47.4 (*C*(3)), 62.0 (*C*(6)), 77.6 (*C*(5)), 80.4 (O*C*Me$_3$), 81.3 (*C*(4)), 107.8 (Me*C*Me), 171.7 (*C*(1)); *m/z* (ESI^+) 390 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{40}NO_5Si^+$ ($[M+H]^+$) requires 390.2670; found 390.2665.

*Method B (From **192**):* Following *General Procedure 2*, **192** (89 mg, 0.15 mmol, >99:1 dr) in EtOAc (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 45 mg) and H_2 (1 atm) gave **198** as a pale yellow oil (38 mg, 64%, >99:1 dr).

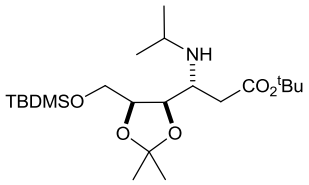
*Method C (From **184**):* Following *General Procedure 2*, **184** (219 mg, 0.384 mmol, 83:17 dr) in EtOAc (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 110 mg) and H_2 (1 atm) gave **198** as a pale yellow oil (102 mg, 68%, 83:17 dr).

tert-Butyl (3*S*,4*R*,5*S*)-3-amino-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(_tert_-butyldimethylsilyloxy)hexanoate 199



Following *General Procedure 2*, **194** (95 mg, 0.16 mmol, >99:1 dr) in EtOAc (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 48 mg) and H_2 (1 atm) gave **199** as a pale yellow oil (46 mg, 73%, >99:1 dr); $[\alpha]_D^{25}$ –7.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3320 (N–H), 2981, 2956, 2932, 2886, 2858 (C–H), 1729 (C=O); δ_H (400 MHz, $CDCl_3$) 0.06 (3H, s, *Me*SiMe), 0.07 (3H, s, *Me*SiMe), 0.88 (9H, s, SiC*Me*$_3$), 1.33 (3H, s, *Me*CMe), 1.40 (3H, s, *Me*CMe), 1.44 (9H, s, OC*Me*$_3$), 1.81 (2H, br s, N*H*$_2$), 2.26 (1H, dd, *J* 16.2, 9.6, C(2)*H*$_A$), 2.69 (1H, dd, *J* 16.2, 3.3, C(2)*H*$_B$) 3.41-3.48 (1H, m, C(3)*H*), 3.58 (1H, dd, *J* 10.4, 3.8, C(6)*H*$_A$), 3.81 (1H, dd, *J* 10.4, 8.6, C(6)*H*$_B$), 3.96 (1H, dd, *J* 7.6, 5.6, C(4)*H*), 4.08 (1H, ddd, *J* 8.6, 5.6, 3.8, C(5)*H*); δ_C (100 MHz, $CDCl_3$) –5.5, –5.5 (2 × *Me*SiMe), 18.3 (Si*C*Me$_3$), 25.4 (*Me*CMe), 25.9 (SiC*Me*$_3$), 27.9 (*Me*CMe), 28.2 (OC*Me*$_3$), 40.5 (*C*(2)), 47.0 (*C*(3)), 62.1 (*C*(6)), 77.4 (*C*(5)), 80.6 (O*C*Me$_3$), 80.6 (*C*(4)), 107.7 (Me*C*Me), 171.4 (*C*(1)); *m/z* (ESI^+) 390 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{19}H_{40}NO_5Si^+$ ($[M+H]^+$) requires 390.2670; found 390.2663.

tert-Butyl (3*R*,4*R*,5*S*)-3-*N*-isopropylamino-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(_tert_-butyldimethylsilyloxy)hexanoate 200

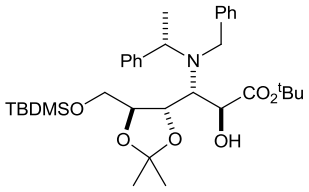


*Method A (From **180**):* Following *General Procedure 2*, **180** (133 mg, 0.255 mmol, >99:1 dr) in EtOAc (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 67 mg) and H_2 (1 atm) gave **200** as a pale yellow oil (72 mg, 65%, >99:1 dr); $[\alpha]_D^{25}$ –8.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3330 (N–H), 2960, 2932, 2858 (C–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 0.07 (6H, app s, 2 × *Me*SiMe), 0.89 (9H, s, SiC*Me*$_3$), 0.99 (3H, d, *J* 5.8, *Me*CHMe), 1.01 (3H, d, *J* 6.1, *Me*CHMe), 1.31 (3H, s, *Me*CMe), 1.41 (3H, s, *Me*CMe), 1.44 (9H, s, OC*Me*$_3$), 2.38 (1H, dd, *J* 15.4, 5.6, C(2)H_A), 2.53 (1H, dd, *J* 15.4, 4.0, C(2)H_B), 2.86-2.97 (1H, m, MeC*H*Me), 3.18-3.25 (1H, m, C(3)*H*), 3.72 (1H, dd, *J* 10.7, 6.4, C(6)H_A), 3.95 (1H, dd, *J* 10.7, 4.9, C(6)H_B), 4.05-4.11 (1H, m, C(4)*H*), 4.15-4.22 (1H, m, C(5)*H*); δ_C (100 MHz, $CDCl_3$) –5.3, –5.2 (2 × *Me*SiMe), 18.5 (Si*C*Me$_3$), 22.3, 24.2 (2 × *Me*CHMe), 25.3 (*Me*CMe), 26.0 (SiC*Me*$_3$), 27.5 (*Me*CMe), 28.1 (OC*Me*$_3$), 37.2 (*C*(2)), 44.9 (Me*C*HMe), 51.2 (*C*(3)), 62.3 (*C*(6)), 78.4, 78.5 (*C*(4), *C*(5)), 80.2 (O*C*Me$_3$), 107.8 (Me*C*Me), 171.7 (*C*(1)); *m/z* (ESI^+) 432 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{22}H_{46}NO_5Si^+$ ($[M+H]^+$) requires 432.3140; found 432.3134.

*Method B (From **198**):* Following *General Procedure 3*, **198** (65 mg, 0.17 mmol, >99:1 dr) in MeOH (3 mL), acetone (25 µL, 0.33 mmol) and $NaBH_3CN$ (42 mg, 0.67 mmol) at rt gave an 83:17 mixture of **200** and **198** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O) gave **200** as a pale yellow oil (45 mg, 62%, >99:1 dr).

*Method C (From **197**):* Imidazole (37 mg, 0.54 mmol), DMAP (1 mg, cat.) and TBDMSCl (27 mg, 0.18 mmol) were sequentially added to a solution of **197** (57 mg, 0.18 mmol, >99:1 dr) in CH_2Cl_2 (1.5 mL) at rt and the resultant solution was stirred at rt for 16 h. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL) and the resultant solution was washed with 1.0 M aq HCl (10 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 2:1) gave **200** as a pale yellow oil (45 mg, 58%, >99:1 dr).

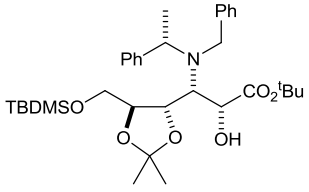
***tert*-Butyl (2*S*,3*R*,4*S*,5*S*,α*S*)-2,4,5-trihydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-*O*-isopropylidene-6-(*tert*-butyldimethylsilyloxy)hexanoate 213**



Method A: Following *General Procedure 4*, (*S*)-**123** (2.27 g, 10.7 mmol) in THF (130 mL), BuLi (2.5 M, 4.16 mL, 10.4 mmol) and **212** (2.50 g, 6.71 mmol, >99:1 dr) in THF (130 mL) were reacted at −78 °C, followed by the addition of (+)-CSO **102** (2.46 g, 10.7 mmol), to give **213** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 10:1) gave **213** as a colourless oil (2.63 g, 66%, >99:1 dr);[12] $[\alpha]_D^{25}$ +3.5 (*c* 1.0 in $CHCl_3$); {lit.[12] $[\alpha]_D^{25}$ +2.6 (*c* 2.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 0.06 (3H, s, *Me*SiMe), 0.09 (3H, s, *Me*SiMe), 0.90 (9H, s, Si*Me*$_3$), 1.29 (3H, s, *Me*CMe), 1.31 (3H, d, *J* 7.1, C(α)*Me*), 1.32 (3H, s, *Me*CMe), 1.50 (9H, s, OC*Me*$_3$), 3.33 (1H, d, *J* 9.2, O*H*), 3.42 (1H, dd, *J* 11.6, 3.4, C(6)H_A), 3.44-3.47 (1H, m, C(3)*H*), 3.74 (1H, dd, *J* 11.6, 3.8, C(6)H_B), 3.82-3.88 (1H, m, C(2)*H*) overlapping 3.85 (1H, d, *J* 15.2, NCH_AH_BPh), 3.99 (1H, q, *J* 7.1, C(α)*H*), 4.14 (1H, dd, *J* 8.2, 3.1, C(4)*H*), 4.44-4.49 (1H, m, C(5)*H*), 4.79 (1H, d, *J* 15.2, NCH$_A$$H_B$Ph), 7.22-7.39 (8H, m, *Ph*), 7.49-7.54 (2H, m, *Ph*).

Method B: Following *General Procedure 4*, (*S*)-**123** (91 mg, 0.43 mmol) in THF (4 mL), BuLi (2.5 M, 0.17 mL, 0.42 mmol) and **212** (100 mg, 0.268 mmol, >99:1 dr) in THF (4 mL) were reacted at −78 °C, followed by the addition of (−)-CSO **102** (98 mg, 0.43 mmol), to give a complex mixture of products including starting material **212**.[13]

***tert*-Butyl (2*R*,3*R*,4*S*,5*S*,α*S*)-2,4,5-trihydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-*O*-isopropylidene-6-(*tert*-butyldimethylsilyloxy)hexanoate 215**

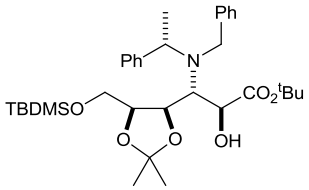


Step 1: DMSO (0.47 mL, 6.7 mmol) was added dropwise to a stirred solution of $(ClCO)_2$ (56 μL, 0.67 mmol) in CH_2Cl_2 (2.5 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 5 min. A solution of **213** (200 mg, 0.333 mmol, >99:1 dr) in CH_2Cl_2 (2.5 mL) was then added via cannula and the reaction mixture was stirred at −78 °C for 30 min. Et_3N (0.19 mL, 1.3 mmol) was then added and stirring was continued at −78 °C for 10 min. The reaction mixture was then allowed to warm to rt over 20 min. H_2O (20 mL) was added and the reaction mixture was extracted with CH_2Cl_2

(3 × 20 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **214** as a yellow oil (192 mg); δ_H (400 MHz, $CDCl_3$) 0.14 (6H, app s, 2 × *Me*SiMe), 0.97 (9H, s, SiC*Me*$_3$), 1.14 (3H, s, *Me*CMe), 1.36 (3H, s, *Me*CMe), 1.42 (3H, d, *J* 6.8, C(α)*Me*), 1.50 (9H, s, OC*Me*$_3$), 3.79 (1H, dd, *J* 11.4, 8.2, C(6)*H*$_A$), 3.94-4.04 (2H, m, C(5)*H*, C(6)*H*$_B$) overlapping 3.97 (1H, q, *J* 6.8, C(α)*H*), 4.19 (1H, d, *J* 16.5, NC*H*$_A$H$_B$Ph), 4.28 (1H, dd, *J* 9.0, 6.1, C(4)*H*), 4.46 (1H, d, *J* 16.5, NCH$_A$*H*$_B$Ph), 4.92 (1H, d, *J* 9.0, C(3)*H*), 7.24-7.34 (10H, m, *Ph*); *m/z* (ESI$^+$) 598 ([M+H]$^+$, 100%).

Step 2: The residue (192 mg) was dissolved in MeOH (4 mL) and the resultant solution was cooled to −20 °C. $NaBH_4$ (13 mg, 0.33 mmol) was added and stirring was continued at −20 °C for 2 h. The reaction mixture was then allowed to warm to rt and concentrated *in vacuo*. The residue was partitioned between H_2O (10 mL) and Et_2O (10 mL) and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give an 85:15 mixture of **215** and **213** respectively. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 20:1) gave **215** as a pale yellow oil (132 mg, 66% over 2 steps, >99:1 dr); $[\alpha]_D^{25}$ −11.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3496 (O–H), 3085, 3062, 3028, 2981, 2955, 2932, 2885, 2857 (C–H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 0.08 (3H, s, *Me*SiMe), 0.09 (3H, s, *Me*SiMe), 0.92 (9H, s, SiC*Me*$_3$), 1.36 (3H, s, *Me*CMe), 1.37 (3H, s, *Me*CMe), 1.42 (3H, d, *J* 7.0, C(α)*Me*), 1.47 (9H, s, OC*Me*$_3$), 2.72 (1H, d, *J* 6.8, O*H*), 3.36 (1H, app t, *J* 5.2, C(3)*H*), 3.52 (1H, dd, *J* 11.4, 3.5, C(6)*H*$_A$), 3.77 (1H, dd, *J* 11.4, 4.0, C(6)*H*$_B$), 4.05 (1H, d, *J* 15.0, NC*H*$_A$H$_B$Ph), 4.05-4.09 (1H, m, C(2)*H*), 4.21-4.27 (1H, m, C(5)*H*), 4.30 (1H, q, *J* 7.0, C(α)*H*), 4.32-4.38 (1H, m, C(4)*H*) overlapping 4.35 (1H, d, *J* 15.0, NCH$_A$*H*$_B$Ph), 7.18-7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) −5.5, −5.3 (2 × *Me*SiMe), 18.5 (Si*C*Me$_3$), 20.2 (C(α)*Me*), 26.1 (SiC*Me*$_3$), 26.4, 27.2 (2 × *Me*CMe), 28.0 (OC*Me*$_3$), 53.2 (N*C*H$_2$Ph), 59.9 (*C*(α)), 60.3 (*C*(3)), 63.3 (*C*(6)), 72.4 (*C*(2)), 77.3 (*C*(4)), 79.0 (*C*(5)), 82.5 (O*C*Me$_3$), 108.3 (Me*C*Me), 126.3, 126.9 (*p-Ph*), 128.1, 128.1, 128.1, 128.6 (*o,m-Ph*), 142.0, 144.0 (*i-Ph*), 173.2 (*C*(1)); *m/z* (ESI$^+$) 600 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{54}NO_6Si^+$ ([M+H]$^+$) requires 600.3715; found 600.3716.

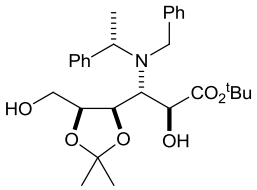
tert-Butyl (2*S*,3*R*,4*R*,5*S*,α*S*)-2,4,5-trihydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-*O*-isopropylidene-6-(*tert*-butyldimethylsilyloxy)hexanoate 218



Method A: Following *General Procedure 4*, (*S*)-**123** (3.18 g, 15.0 mmol) in THF (140 mL), BuLi (2.5 M, 5.82 mL, 14.6 mmol) and **162** (3.50 g, 9.39 mmol, >99:1 dr) in THF (140 mL) were reacted at −78 °C, followed by the addition of (−)-CSO **102** (4.31 g, 18.8 mmol), to give **218** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 10:1) gave **218** as a pale yellow oil (3.39 g, 60%, >99:1 dr); $[\alpha]_D^{25}$ –4.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3491 (O–H), 3085, 3063, 3029, 2928, 2855 (C–H), 1736 (C=O); δ_H (400 MHz, $CDCl_3$) 0.15 (3H, s, *Me*SiMe), 0.15 (3H, s, *Me*SiMe), 1.01 (9H, s, SiC*Me*$_3$), 1.26 (3H, s, *Me*CMe), 1.38 (3H, s, *Me*CMe), 1.44 (3H, d, *J* 6.9, C(α)*Me*), 1.54 (9H, s, OC*Me*$_3$), 3.13 (1H, d, *J* 7.1, O*H*), 3.52 (1H, dd, *J* 10.4, 8.9, C(6)H_A), 3.73-3.78 (2H, m, C(3)*H*, C(6)H_B), 3.79 (1H, d, *J* 16.2, NCH_AH$_B$Ph), 4.08 (1H, q, *J* 6.9, C(α)*H*), 4.13 (1H, d, *J* 7.1, C(2)*H*), 4.23 (1H, ddd, *J* 8.9, 5.7, 2.8, C(5)*H*), 4.42 (1H, dd, *J* 10.0, 5.7, C(4)*H*), 4.50 (1H, d, *J* 16.2, NCH$_A$$H_B$Ph), 7.23-7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) –4.8, –4.8 (2 × *Me*SiMe), 18.6 (Si*C*Me$_3$), 20.4 (C(α)*Me*), 25.7 (*Me*CMe), 26.2 (SiC*Me*$_3$), 28.2 (OC*Me*$_3$), 28.4 (*Me*CMe), 51.0 (N*C*H$_2$Ph), 58.0 (*C*(3)), 60.1 (*C*(α)), 63.0 (*C*(6)), 70.6 (*C*(2)), 74.1 (*C*(4)), 78.1 (*C*(5)), 81.9 (O*C*Me$_3$), 107.4 (Me*C*Me), 126.6, 127.6 (*p-Ph*), 127.7, 128.2, 128.4, 128.6 (*o,m-Ph*), 142.0, 142.2 (*i-Ph*), 172.9 (*C*(1)); *m/z* (ESI$^+$) 600 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{53}NNaO_6Si^+$ ([M+Na]$^+$) requires 622.3534; found 622.3535.

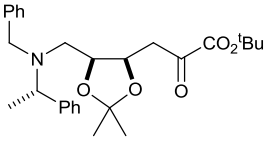
Method B: Following *General Procedure 4*, (*S*)-**123** (91 mg, 0.43 mmol) in THF (4 mL), BuLi (2.5 M, 0.17 mL, 0.42 mmol) and **162** (100 mg, 0.268 mmol, >99:1 dr) in THF (4 mL) were reacted at −78 °C, followed by the addition of (+)-CSO **102** (123 mg, 0.536 mmol), to give a mixture of products including **188**.[13] Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 10:1) gave **218** as a pale yellow oil (55 mg, 34%, >99:1 dr).

***tert*-Butyl (2*S*,3*R*,4*R*,5*S*,α*S*)-2,4,5,6-tetrahydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-*O*-isopropylidenehexanoate 225**



TBAF (1.0 M in THF, 9.75 mL, 9.75 mmol) was added dropwise to a stirred solution of **218** (1.17 g, 1.95 mmol, >99:1 dr) in THF (15 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (30 mL) and washed with H_2O (20 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 5:1) gave **225** as a white solid (807 mg, 85%, >99:1 dr); mp 83-89 °C; $[\alpha]_D^{25}$ +5.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3490 (O–H), 3085, 3062, 3029, 2980, 2935 (C–H), 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 1.25 (3H, s, *Me*CMe), 1.35 (3H, s, *Me*CMe), 1.42 (3H, d, *J* 6.8, C(α)*Me*), 1.51 (9H, s, C*Me*$_3$), 2.66 (1H, d, *J* 5.3, C(6)O*H*), 3.21 (1H, d, *J* 6.1, C(2)O*H*), 3.37-3.44 (1H, m, C(6)H_A), 3.46-3.54 (1H, m, C(6)H_B), 3.73-3.76 (1H, m, C(3)*H*), 3.78 (1H, d, *J* 13.1, NCH_AH$_B$Ph), 4.02 (1H, q, *J* 6.8, C(α)*H*), 4.12 (1H, d, *J* 6.1, C(2)*H*), 4.16-4.22 (1H, m, C(5)*H*), 4.46-4.52 (1H, m, C(4)*H*) overlapping 4.48 (1H, d, *J* 13.1, NCH$_A$$H_B$Ph), 7.22-7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.7 (C(α)*Me*), 25.5 (*Me*CMe), 28.2 (C*Me*$_3$), 28.3 (*Me*CMe), 51.5 (N*C*H$_2$Ph), 57.6 (*C*(3)), 60.3 (*C*(α)), 61.2 (*C*(6)), 70.0 (*C*(2)), 74.1 (*C*(4)), 77.5 (*C*(5)), 82.3 (*C*Me$_3$), 107.7 (Me*C*Me), 126.7, 127.7 (*p-Ph*), 127.8, 128.3, 128.5, 128.7 (*o*,*m-Ph*), 141.6, 142.0 (*i-Ph*), 173.0 (*C*(1)); *m/z* (ESI$^+$) 486 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{40}NO_6^+$ ([M+H]$^+$) requires 486.2850; found 486.2839.

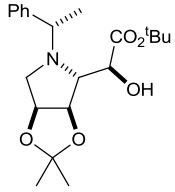
***tert*-Butyl (4*R*,5*S*,α*S*)-2-keto-4,5-dihydroxy-4,5-*O*-isopropylidene-6-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hexanoate 227**



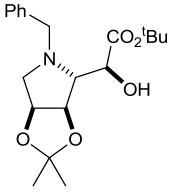
MsCl (40 μL, 0.52 mmol) was added dropwise to a stirred solution of **225** (50 mg, 0.10 mmol, >99:1 dr), Et_3N (0.14 mL, 1.0 mmol) and DMAP (5 mg, cat.) in CH_2Cl_2 (2 mL) at –10 ºC and the resultant mixture was stirred at –10 ºC for 6 h. H_2O (1 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed sequentially with 10% aq $CuSO_4$ (10 mL), H_2O (10 mL) and satd aq $NaHCO_3$ (10 mL). The organic layer was then

dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 10:1) gave **227** as a pale yellow oil (16 mg, 34%, >99:1 dr); $[\alpha]_D^{25}$ +13.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3085, 3062, 3029, 2982, 2934, 2837 (C–H), 1721 (C=O); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, s, *Me*CMe), 1.37 (3H, s, *Me*CMe), 1.41 (3H, d, *J* 6.9, C(α)*Me*), 1.55 (9H, s, C*Me*$_3$), 1.97 (1H, dd, *J* 16.1, 3.5, C(3)H_A), 2.55 (1H, dd, *J* 13.4, 6.9, C(6)H_A), 2.74 (1H, dd, *J* 16.1, 10.1, C(3)H_B), 2.75 (1H, dd, *J* 13.4, 5.5, C(6)H_B), 3.56 (1H, d, *J* 13.7, NCH_AH$_B$Ph), 3.74 (1H, d, *J* 13.7, NCH$_A$$H_B$Ph), 4.03 (1H, q, *J* 6.9, C(α)*H*), 4.27 (1H, app dt, *J* 6.9, 5.5, C(5)*H*), 4.49 (1H, ddd, *J* 10.1, 5.5, 3.5, C(4)*H*), 7.19-7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.4 (C(α)*Me*), 25.8, 28.2 (2 × *Me*CMe), 27.8 (C*Me*$_3$), 39.3 (*C*(3)), 48.5 (*C*(6)), 55.1 (N*C*H$_2$Ph), 57.8 (*C*(α)), 73.5 (*C*(4)), 75.8 (*C*(5)), 83.7 (*C*Me$_3$), 108.2 (Me*C*Me), 127.0, 127.1 (*p-Ph*), 128.1, 128.1, 128.3, 128.8 (*o,m-Ph*), 140.0, 143.2 (*i-Ph*), 160.2 (*C*(1)), 193.5 (*C*(2)); *m/z* (ESI$^+$) 468 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{38}NO_5^+$ ([M+H]$^+$) requires 468.2744; found 468.2728.

tert-Butyl (2*S*,2'*R*,3'*R*,4'*S*,α*S*)-2-hydroxy-2-[*N*(1')-α-methylbenzyl-3',4'-dihydroxy-3',4'-*O*-isopropylidenepyrrolidin-2'-yl]acetate 239 and _tert_-butyl (2*S*,2'*R*,3'*R*,4'*S*)-2-hydroxy-2-[*N*(1')-benzyl-3',4'-dihydroxy-3',4'-*O*-isopropylidenepyrrolidin-2'-yl]acetate 238



239

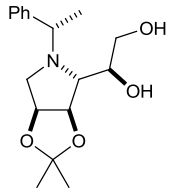


238

PPh_3 (65 mg, 0.25 mmol) and imidazole (21 mg, 0.31 mmol) were added to a solution of **225** (100 mg, 0.206 mmol, >99:1 dr) in PhMe and MeCN (v/v 17:4, 2.1 mL). I_2 (63 mg, 0.25 mmol) was then added and the resultant mixture was heated at 60 °C for 1 h. The reaction mixture was then allowed to cool to rt, diluted with H_2O (5 mL), and washed sequentially with satd aq $Na_2S_2O_3$ (10 mL), H_2O (10 mL) and brine (10 mL), then dried and concentrated *in vacuo* to give a 65:35 mixture of **239** and **238** respectively. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 2:1) gave **239** as a pale yellow oil (41 mg, 53%, >99:1 dr); $[\alpha]_D^{25}$ –8.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3437 (O–H), 2978, 2934, 2849 (C–H), 1717 (C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, s, *Me*CMe), 1.37 (9H, s, C*Me*$_3$), 1.42 (1H, d, *J* 6.6, C(α)*Me*), 1.50 (3H, s, *Me*CMe), 2.97 (1H, dd, *J* 10.1, 2.2, C(5')H_A), 2.99 (1H, br s, O*H*), 3.21 (1H, dd, *J* 10.1, 6.0, C(5')H_B), 3.28-3.30 (1H, m, C(2')*H*), 3.96 (1H, q, *J* 6.6, C(α)*H*), 4.31 (1H, app s, C(2)*H*), 4.43 (1H, dd, *J* 6.0, 1.3, C(3')*H*), 4.68 (1H, app td, *J* 6.0, 2.2, C(4')*H*), 7.20-7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 23.0 (C(α)*Me*), 25.4, 27.1 (2 × *Me*CMe), 27.9 (C*Me*$_3$), 55.9 (*C*(5')), 58.6 (*C*(α)), 67.6 (*C*(2')), 69.5 (*C*(2)),

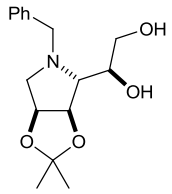
79.6 (*C*(4')), 81.0 (*C*(3')), 82.7 (*C*Me$_3$), 111.4 (Me*C*Me), 127.0 (*p-Ph*), 127.4, 128.3 (*o,m-Ph*), 143.4 (*i-Ph*), 173.1 (*C*(1)); *m/z* (ESI$^+$) 378 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{32}NO_5^+$ ([M+H]$^+$) requires 378.2275; found 378.2270. Further elution gave **238** as a pale yellow oil (16 mg, 21%, >99:1 dr); $[\alpha]_D^{25}$ –32.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3460 (O–H), 3063, 3028, 2980, 2934, 2850 (C–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, s, *Me*CMe), 1.50 (9H, s, C*Me*$_3$), 1.51 (3H, s, *Me*CMe), 2.63 (1H, dd, *J* 10.1, 3.0, C(5')H_A), 3.22 (1H, dd, *J* 10.1, 4.9, C(5')H_B), 3.26 (2H, app br s, C(2')*H*, O*H*), 3.67 (1H, d, *J* 13.2, NCH_AH$_B$Ph), 4.03 (1H, d, *J* 13.2, NCH$_A$$H_B$Ph), 4.35 (1H, d, *J* 2.5, C(2)*H*), 4.56-4.62 (2H, m, C(3')*H*, C(4')*H*), 7.24-7.34 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.2, 27.3 (2 × *Me*CMe), 28.0 (C*Me*$_3$), 57.1 (N*C*H$_2$Ph), 58.8 (*C*(5')), 69.3 (*C*(2)), 70.7 (*C*(2')), 78.5 (*C*(3')), 80.5 (*C*(4')), 83.0 (*C*Me$_3$), 112.4 (Me*C*Me), 127.2 (*p-Ph*), 128.4, 128.8 (*o,m-Ph*), 138.0 (*i-Ph*), 172.0 (*C*(1)); *m/z* (ESI$^+$) 364 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{30}NO_5^+$ ([M+H]$^+$) requires 364.2118; found 364.2111.

(α*S*)-*N*-(α-Methylbenzyl)-1,4-dideoxy-1,4-imino-2,3-*O*-isopropylidene-D-allitol 242



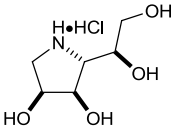
$LiAlH_4$ (1.0 M in THF, 0.69 mL, 0.69 mmol) was added dropwise to a stirred solution of **239** (127 mg, 0.336 mmol, >99:1 dr) in THF (10 mL) at –78 °C and the resultant mixture was allowed to warm to rt over 16 h. 1.0 M aq NaOH (1 mL) and EtOAc (2 mL) were then added and the resultant suspension was stirred at rt for 1 h. The mixture was then filtered through a short plug of Celite® (eluent EtOAc) and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent Et_2O) gave **242** as a white solid (85 mg, 82%, >99:1 dr); mp 103-107 °C; $[\alpha]_D^{25}$ –36.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3329 (O–H), 2922, 2888, 2851, 2836 (C–H); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, s, *Me*CMe), 1.45 (3H, s, *Me*CMe), 1.47 (3H, d, *J* 6.8, C(α)*Me*), 2.83 (1H, dd, *J* 12.0, 2.3, C(1)H_A), 3.08 (1H, dd, *J* 12.0, 5.3, C(1)H_B), 3.09-3.13 (1H, m, C(4)*H*), 3.38 (2H, br s, O*H*), 3.71 (1H, dd, *J* 10.9, 6.1, C(6)H_A), 3.76 (1H, dd, *J* 10.9, 5.8, C(6)H_B), 3.81 (1H, app q, *J* 5.8, C(5)*H*), 4.21 (1H, q, *J* 6.8, C(α)*H*), 4.59-4.64 (1H, m, C(2)*H*), 4.73 (1H, dd, *J* 6.3, 1.3, C(3)*H*), 7.21-7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.5 (C(α)*Me*), 24.5, 27.0 (2 × *Me*CMe), 54.0 (*C*(1)), 59.1 (*C*(α)), 65.6 (*C*(6)), 67.9 (*C*(5)), 68.7 (*C*(4)), 79.5 (*C*(2)), 81.8 (*C*(3)), 112.1 (Me*C*Me), 127.4 (*p-Ph*), 127.8, 128.5 (*o,m-Ph*), 141.9 (*i-Ph*); *m/z* (ESI$^+$) 308 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{26}NO_4^+$ ([M+H]$^+$) requires 308.1856; found 308.1856.

_N_-Benzyl-1,4-dideoxy-1,4-imino-2,3-_O_-isopropylidene-D-allitol 244



$LiAlH_4$ (1.0 M in THF, 0.36 mL, 0.36 mmol) was added dropwise to a stirred solution of **238** (66 mg, 0.18 mmol, >99:1 dr) in THF (10 mL) at −78 °C and the resultant mixture was allowed to warm to rt over 16 h. 1.0 M aq NaOH (1 mL) and EtOAc (2 mL) were then added and the resultant suspension was stirred at rt for 1 h. The mixture was then filtered through a short plug of Celite® (eluent EtOAc) and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent Et_2O) gave **244** as a pale yellow solid (39 mg, 73%, >99:1 dr);[14] mp 46-52 °C;[15] $[\alpha]_D^{25}$ −42.1 (*c* 1.0 in $CHCl_3$); {lit.[14] −48.2 (*c* 2.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.33 (3H, s, *Me*CMe), 1.53 (3H, s, *Me*CMe), 2.63 (1H, dd, *J* 10.9, 4.2, C(1)H_A), 2.83 (1H, app t, *J* 4.2, C(4)*H*), 3.24 (1H, dd, *J* 10.9, 6.3, C(1)H_B), 3.51 (1H, d, *J* 12.9, NCH_AH_BPh), 3.71 (1H, dd, *J* 11.4, 5.3, C(6)H_A), 3.82 (1H, dd, *J* 11.4, 6.1, C(6)H_B), 3.92 (1H, app td, *J* 5.6, 4.2, C(5)*H*), 4.07 (1H, d, *J* 12.9, NCH_AH_BPh), 4.59 (1H, app td, *J* 6.3, 4.3, C(2)*H*), 4.71 (1H, dd, *J* 6.3, 4.2, C(3)*H*), 7.26-7.37 (5H, m, *Ph*).

1,4-Dideoxy-1,4-imino-D-allitol hydrochloride 243·HCl

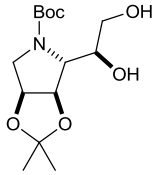


*Method A (from **242**):* $Pd(OH)_2$/C (47 mg, 50% w/w of substrate) was added to a solution of **242** (94 mg, 0.31 mmol, >99:1 dr) and 3.0 M aq HCl (1 mL) in MeOH (5 mL) at rt. The resultant solution was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm) at rt for 18 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 2:1) gave **243**·HCl as a white solid (49 mg, 80%, >99:1 dr);[14,16] $[\alpha]_D^{25}$ +24.4 (*c* 1.0 in H_2O); {lit.[14] +29.4 (*c* 0.53 in H_2O)}; δ_H (400 MHz, D_2O) 3.20 (1H, dd, *J* 12.6, 2.1, C(1)H_A), 3.31 (1H, dd, *J* 12.6, 3.8, C(1)H_B), 3.50 (1H, dd, *J* 8.0, 3.6, C(4)*H*), 3.60 (1H, dd, *J* 11.8, 6.5, C(6)H_A), 3.64 (1H, dd, *J* 11.8, 4.6, C(6)H_B), 3.96-4.00 (1H, m, C(5)*H*), 4.21-4.26 (1H, m, C(2)*H*), 4.28 (1H, dd, *J* 8.0, 4.3, C(3)*H*).

*Method B (from **244**):* $Pd(OH)_2$/C (18 mg, 50% w/w of substrate) was added to a solution of **244** (36 mg, 0.12 mmol, >99:1 dr) and 3.0 M aq HCl (1 mL) in MeOH (5 mL) at rt. The resultant solution was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm) at rt

for 18 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 2:1) gave **243**·HCl as a white solid (15 mg, 62%, >99:1 dr).

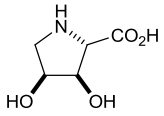
_N_-*tert*-Butoxycarbonyl-1,4-dideoxy-1,4-imino-2,3-_O_-isopropylidene-D-allitol 247



*Method A (From **242**):* Pd/C (50% w/w of substrate, 51 mg) was added to a stirred solution of **242** (102 mg, 0.332 mmol, >99:1 dr) and Boc_2O (80 mg, 0.37 mmol) in MeOH (3 mL) at rt. The resultant mixture was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm) for 18 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo* to give **247** as a white solid (99 mg, 98%, >99:1 dr);[14] mp 66-69 °C; {lit.[14] 73-74 °C}; $[\alpha]_D^{25}$ –24.2 (*c* 1.0 in $CHCl_3$); {lit.[14] $[\alpha]_D^{25}$ –33.5 (*c* 0.17 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) [major rotamer] 1.27 (3H, s, *Me*CMe), 1.39 (3H, s, *Me*CMe), 1.41 (9H, s, C*Me*$_3$), 3.28 (1H, dd, *J* 13.0, 4.7, C(1)H_A), 3.32-3.41 (1H, m, C(5)*H*), 3.52-3.62 (2H, m, C(6)H_2), 3.80 (1H, app d, *J* 13.0, C(1)H_B), 3.98 (1H, app d, *J* 8.6, C(4)*H*), 4.65-4.71 (1H, m, C(2)*H*), 4.77-4.83 (1H, m, C(3)*H*);[17] δ_C (100 MHz, $CDCl_3$) [major rotamer] 24.9, 26.9 (2 × *Me*CMe), 28.2 (C*Me*$_3$), 52.3 (*C*(1)), 62.9 (*C*(6)), 64.6 (*C*(4)), 70.7 (*C*(5)), 79.3 (*C*(2)), 80.8 (*C*Me$_3$), 82.0 (*C*(3)), 111.6 (Me*C*Me), 155.8 (N*C*O); δ_C (100 MHz, $CDCl_3$) [minor rotamer] 27.3, 28.3 (2 × *Me*CMe), 28.2 (C*Me*$_3$), 52.1 (*C*(1)), 63.9 (*C*(6)), 65.6 (*C*(4)), 71.8 (*C*(5)), 79.2 (*C*(2)), 80.4 (*C*Me$_3$), 81.6 (*C*(3)), 111.3 (Me*C*Me), 155.8 (N*C*O); *m/z* (ESI^+) 326 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{14}H_{25}NNaO_6^+$ ($[M+Na]^+$) requires 326.1574; found 326.1568.

*Method B (From **244**):* Pd/C (50% w/w of substrate, 48 mg) was added to a stirred solution of **244** (95 mg, 0.32 mmol, >99:1 dr) and Boc_2O (78 mg, 0.36 mmol) in MeOH (3 mL) at rt. The resultant mixture was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm) for 18 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo* to give **247** as a white solid (94 mg, 96%, >99:1 dr).

(2*S*,3*R*,4*S*)-3,4-Dihydroxy-L-proline 246

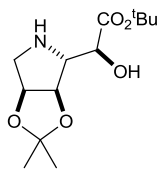


Step 1: $NaIO_4$ (356 mg, 1.66 mmol) was added to a solution of **247** (187 mg, 0.616 mmol, >99:1 dr) in EtOH and H_2O (v/v 5:2, 9.2 mL) at rt and the resultant suspension was stirred at rt for 15 min. The reaction mixture was then filtered through a short plug of Celite® (eluent EtOH) and the filtrate was concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL) and then filtered through a short plug of Celite® (eluent Et_2O) and the filtrate was concentrated *in vacuo* to give **248** in >99:1 dr (180 mg).

Step 2: Cyclohexene (0.60 mL) was added to a solution of the residue (180 mg) in ^tBuOH (9 mL) at rt. A solution of $NaClO_2$ (557 mg, 6.20 mmol) and KH_2PO_4 (839 mg, 6.20 mmol) in H_2O (6 mL) was then added dropwise at rt. The resultant mixture was stirred at rt for 18 h and then concentrated *in vacuo*. The residue was partitioned between EtOAc (50 mL) and H_2O (50 mL) and the aqueous layer was then extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried and concentrated *in vacuo* to give **249** in >99:1 dr (130 mg).

Step 3: A solution of the residue (130 mg) in 2.0 M aq HCl (4.5 mL) was heated at reflux for 8 h. The reaction mixture was allowed to cool to rt and was then concentrated *in vacuo*. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH) gave **246** as a white solid (38 mg, 42% over 3 steps, >99:1 dr);[14] mp 240-250 °C (dec); {lit.[14] mp 240-250 °C (dec)}; $[\alpha]_D^{25}$ +5.8 (*c* 1.0 in H_2O); {lit.[14] $[\alpha]_D^{25}$ +7.5 (*c* 0.16 in H_2O)}; δ_H (400 MHz, D_2O) 3.20 (1H, dd, *J* 12.3, 4.2, C(5)H_A), 3.44 (1H, dd, *J* 12.3, 4.8, C(5)H_B), 3.87 (1H, d, *J* 4.8, C(2)*H*), 4.21-4.28 (2H, m, C(3)*H*, C(4)*H*); δ_C (100 MHz, D_2O) 48.6 (*C*(5)), 64.6 (*C*(2)), 70.3, 74.5 (*C*(3), *C*(4)), 172.5 (*C*(1)); δ_C (125 MHz, D_2O, internal reference dioxane[18]) 48.4 (*C*(5)), 64.4 (*C*(2)), 70.0, 74.2 (*C*(3), *C*(4)), 172.2 (*C*(1)).

***tert*-Butyl (2*S*,2'*R*,3'*R*,4'*S*)-2-hydroxy-2-(3',4'-dihydroxy-3',4'-*O*-isopropylidenepyrrolidin-2'-yl)acetate 250**

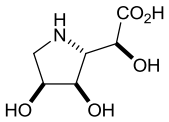


*Method A (From **239**):* Following *General Procedure 2*, **239** (54 mg, 0.14 mmol, >99:1 dr) in MeOH (1 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 27 mg) and H_2 (1 atm) gave **250** in >99:1 dr. Purification via flash column chromatography (eluent EtOAc) gave **250** as a white solid (34 mg, 87%, >99:1 dr);

mp 130-135 °C; $[\alpha]_D^{25}$ +21.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3293 (N–H), 3074, 2980, 2938 (C–H), 1736 (C=O); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, s, *Me*CMe), 1.44 (3H, s, *Me*CMe), 1.48 (9H, s, C*Me*$_3$), 2.97 (1H, app d, *J* 13.0, C(5')*H*$_A$), 3.12 (1H, dd, *J* 13.0, 4.4, C(5')*H*$_B$), 3.44 (1H, app d, *J* 2.8, C(2')*H*), 4.11 (1H, d, *J* 4.0, C(2)*H*), 4.60 (1H, app d, *J* 5.8, C(3')*H*), 4.66-4.69 (1H, m, C(4')*H*); δ_C (100 MHz, $CDCl_3$) 24.1, 26.5 (2 × *Me*CMe), 28.0 (C*Me*$_3$), 53.4 (*C*(5')), 67.8 (*C*(2')), 72.5 (*C*(2)), 82.1 (*C*(3')), 82.5 (*C*(4')), 83.0 (*C*Me$_3$), 111.3 (Me*C*Me), 172.5 (*C*(1)); *m/z* (ESI^+) 274 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{13}H_{24}NO_5^+$ ($[M+H]^+$) requires 274.1649; found 274.1653.

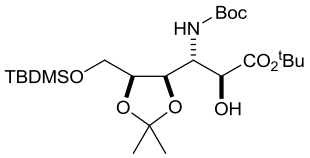
*Method B (From **238**):* Following *General Procedure 2*, **238** (49 mg, 0.13 mmol, >99:1 dr) in MeOH (1 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 25 mg) and H_2 (1 atm) gave **250** in >99:1 dr. Purification via flash column chromatography (eluent EtOAc) gave **250** as a white solid (36 mg, quant, >99:1 dr).

(2*S*,2'*S*,3'*R*,4'*S*)-2-Hydroxy-2-(3',4'-dihydroxypyrrolidin-2'-yl)acetic acid 251

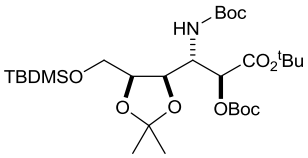


A solution of **250** (74 mg, 0.27 mmol, >99:1 dr) in 2.0 M aq HCl (2.8 mL) was heated at reflux for 8 h. The reaction mixture was allowed to cool to rt and was then concentrated *in vacuo*. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH) gave **251** as a white solid (45 mg, 94%, >99:1 dr); mp 238-243 °C (dec); $[\alpha]_D^{25}$ +42.7 (*c* 1.0 in 1.0 M aq HCl); ν_{max} (ATR) 3410 (O–H), 3100, 2997 (C–H), 2308 (NH_3^+), 1586, 1404 (CO_2^-); δ_H (500 MHz, D_2O) 3.26 (1H, dd, *J* 12.6, 2.5, C(5')*H*$_A$), 3.39 (1H, dd, *J* 12.6, 4.1, C(5')*H*$_B$), 3.76 (1H, dd, *J* 6.9, 3.8, C(2')*H*), 4.24-4.31 (3H, m, C(2)*H*, C(3')*H*, C(4')*H*); δ_C (125 MHz, D_2O) 49.5 (*C*(5')), 63.3 (*C*(2')), 68.8, 69.8, 70.3 (*C*(2), *C*(3'), *C*(4')), 175.9 (*C*(1)); *m/z* (ESI^+) 178 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_6H_{12}NO_5^+$ ($[M+H]^+$) requires 178.0710; found 178.0717.

tert-Butyl (2*S*,3*R*,4*R*,5*S*)-2,4,5-trihydroxy-3-(*N*-_tert_-butoxycarbonylamino)-4,5-*O*-isopropylidene-6-(_tert_-butyldimethylsilyloxy)hexanoate 252 and _tert_-Butyl (2*S*,3*S*,4*R*,5*S*)-2-(_tert_-butoxycarbonyloxy)-3-(*N*-_tert_-butoxycarbonylamino)-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(_tert_-butyldimethylsilyloxy)hexanoate 256



252

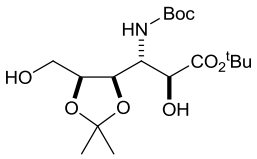


256

Pd/C (50% w/w of substrate, 256 mg) was added to a stirred solution of **218** (512 mg, 0.854 mmol, >99:1 dr) and Boc_2O (205 mg, 0.939 mmol) in MeOH (5 mL) at rt. The resultant solution was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm) at rt for 18 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petol/Et_2O, 2:1) gave **252** as a white solid (319 mg, 74%, >99:1 dr); mp 110-115 °C; $[\alpha]_D^{25}$ +2.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3250 (O–H), 3067, 3005, 2978, 2957, 2932, 2859 (C–H), 1748, 1672 (C=O); δ_H (400 MHz, $CDCl_3$) 0.09 (3H, s, *Me*SiMe), 0.09 (3H, s, *Me*SiMe), 0.91 (9H, s, SiC*Me*$_3$), 1.31 (3H, s, *Me*CMe), 1.41 (3H, s, *Me*CMe), 1.43 (9H, s, OC*Me*$_3$), 1.48 (9H, s, OC*Me*$_3$), 3.69 (1H, dd, *J* 10.9, 6.1, C(6)*H*$_A$), 3.77 (1H, dd, *J* 10.9, 5.8, C(6)*H*$_B$), 3.91 (1H, d, *J* 5.1, O*H*), 4.09-4.15 (2H, m, C(3)*H*, C(5)*H*), 4.28 (1H, dd, *J* 9.9, 5.6, C(4)*H*), 4.32 (1H, d, *J* 5.1, C(2)*H*), 5.32 (1H, d, *J* 6.6, N*H*); δ_C (100 MHz, $CDCl_3$) –5.3, –5.3 (2 × *Me*SiMe), 18.4 (Si*C*Me$_3$), 25.6 (*Me*CMe), 26.0 (SiC*Me*$_3$), 28.0 (OC*Me*$_3$), 28.1 (*Me*CMe), 28.3 (OC*Me*$_3$), 53.2 (*C*(3)), 62.0 (*C*(6)), 72.6 (*C*(2)), 74.3 (*C*(4)), 77.6 (*C*(5)), 80.1, 82.4 (2 × O*C*Me$_3$), 108.7 (Me*C*Me), 155.7 (N*C*O), 171.2 (*C*(1)); *m/z* (ESI$^+$) 528 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{47}NNaO_8Si^+$ ([M+Na]$^+$) requires 528.2963; found 528.2956. Further elution gave **256** as a pale yellow oil (44 mg, 9%, >99:1 dr); $[\alpha]_D^{25}$ –14.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3370 (N–H), 2981, 2956, 2933, 2858 (C–H), 1746, 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 0.09 (3H, s, *Me*SiMe), 0.09 (3H, s, *Me*SiMe), 0.90 (9H, s, SiC*Me*$_3$), 1.31 (3H, s, *Me*CMe), 1.42 (12H, s, *Me*CMe, OC*Me*$_3$), 1.46 (9H, s, OC*Me*$_3$), 1.48 (9H, s, OC*Me*$_3$), 3.71 (1H, dd, *J* 11.0, 5.9, C(6)*H*$_A$), 3.81 (1H, dd, *J* 11.0, 4.7, C(6)*H*$_B$), 4.11 (1H, app q, *J* 5.5, C(5)*H*), 4.22 (1H, dd, *J* 8.5, 5.9, C(4)*H*), 4.38 (1H, app br s, C(3)*H*), 5.06 (1H, d, *J* 3.5, C(2)*H*), 5.31 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) –5.4, –5.3 (2 × *Me*SiMe), 18.5 (Si*C*Me$_3$), 25.5 (*Me*CMe), 26.0 (SiC*Me*$_3$), 27.7 (OC*Me*$_3$), 27.8 (*Me*CMe), 27.9, 28.3 (2 × OC*Me*$_3$), 50.5 (*C*(3)), 61.9 (*C*(6)), 74.7 (*C*(4)), 75.1 (*C*(2)), 77.9 (*C*(5)), 79.7, 82.4, 82.8 (3 × O*C*Me$_3$), 108.6 (Me*C*Me), 152.5, 154.9

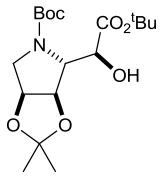
(N*C*O, *C*=O), 166.7 (*C*(1)); *m/z* (ESI$^+$) 628 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{55}NNaO_{10}Si^+$ ([M+Na]$^+$) requires 628.3487; found 628.3478.

tert-Butyl (2*S*,3*R*,4*R*,5*S*)-2,4,5,6-tetrahydroxy-3-(_tert_-butoxycarbonylamino)-4,5-*O*-isopropylidenehexanoate 253



TBAF (1.0 M in THF, 2.52 mL, 2.52 mmol) was added dropwise to a stirred solution of **252** (254 mg, 0.502 mmol, >99:1 dr) in THF (5 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was diluted with Et_2O (20 mL) and the resultant solution was washed with H_2O (20 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 1:2) gave **253** as a white solid (103 mg, 52%, >99:1 dr); mp 47-55 °C; $[\alpha]_D^{25}$ –6.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3344 (O–H), 2981, 2936 (C–H), 1713 (C=O); δ_H (400 MHz, $CDCl_3$) 1.29 (3H, s, *Me*CMe), 1.39 (3H, s, *Me*CMe), 1.42 (9H, s, C*Me*$_3$), 1.48 (9H, s, C*Me*$_3$), 2.60 (1H, br s, C(6)O*H*), 3.38 (1H, br s, C(2)O*H*), 3.53-3.61 (1H, m, C(6)H_A), 3.68-3.77 (1H, m, C(6)H_B), 4.12-4.18 (2H, m, C(2)*H*, C(5)*H*), 4.22-4.30 (2H, m, C(3)*H*, C(4)*H*), 5.21 (1H, br s, N*H*); δ_C (100 MHz, $CDCl_3$) 25.3 (*Me*CMe), 28.0 (C*Me*$_3$), 28.2 (*Me*CMe), 28.3 (C*Me*$_3$), 50.9 (*C*(3)), 61.6 (*C*(6)), 72.8 (*C*(2)), 74.1 (*C*(4)), 77.7 (*C*(5)), 80.5, 83.0 (2 × *C*Me$_3$), 108.8 (Me*C*Me), 155.3 (N*C*O), 170.1 (*C*(1)); *m/z* (ESI$^+$) 414 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{33}NNaO_8^+$ ([M+Na]$^+$) requires 414.2098; found 414.2091.

tert-Butyl (2*S*,2'*R*,3'*R*,4'*S*)-2-hydroxy-2-[*N*(1')-_tert_-butoxycarbonyl-3',4'-dihydroxy-3',4'-*O*-isopropylidenepyrrolidin-2'-yl]acetate 255



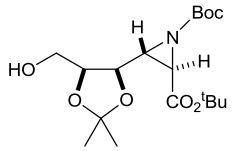
*Method A (from **239**):* Pd/C (50% w/w of substrate, 68 mg) was added to a stirred solution of **239** (136 mg, 0.360 mmol, >99:1 dr) and Boc_2O (87 mg, 0.40 mmol) in MeOH (3 mL) at rt. The resultant solution was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm) at rt for 18 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography

(eluent 30-40 °C petol/Et_2O, 2:1) gave **255** as a colourless oil (120 mg, 89%, >99:1 dr); $[\alpha]_D^{25}$ –23.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3436 (O–H), 2979, 2936 (C–H), 1731, 1697 (C=O); δ_H (400 MHz, $CDCl_3$) [major rotamer] 1.27 (3H, s, *Me*CMe), 1.43 (3H, s, *Me*CMe), 1.45 (9H, s, C*Me*$_3$), 1.49 (9H, s, C*Me*$_3$), 3.39 (1H, d, *J* 4.6, O*H*), 3.57 (1H, dd, *J* 12.2, 5.2, C(5')H_A), 3.66 (1H, app d, *J* 12.2, C(5')H_B), 4.34 (1H, app s, C(2')*H*), 4.47 (1H, app d, *J* 6.1, C(3')*H*), 4.49-4.52 (1H, m, C(2)*H*), 4.66-4.73 (1H, m, C(4')*H*); δ_C (100 MHz, $CDCl_3$) [major rotamer] 24.9, 27.0 (2 × *Me*CMe), 28.0, 28.4 (2 × C*Me*$_3$), 53.7 (*C*(5')), 66.3 (*C*(2')), 71.4 (*C*(2)), 79.6 (*C*(4')), 80.1 (*C*Me$_3$), 80.7 (*C*(3')), 83.5 (*C*Me$_3$), 111.5 (Me*C*Me), 154.6 (N*C*O), 172.3 (*C*(1)); δ_H (400 MHz, $CDCl_3$) [minor rotamer] 1.27 (3H, s, *Me*CMe), 1.43 (3H, s, *Me*CMe), 1.46 (9H, s, C*Me*$_3$), 1.50 (9H, s, C*Me*$_3$), 2.99 (1H, d, *J* 3.8, O*H*), 3.58 (1H, dd, *J* 12.2, 5.4, C(5')H_A), 3.74 (1H, app d, *J* 12.2, C(5')H_B), 4.23 (1H, app s, C(2')*H*), 4.32-4.36 (1H, m, C(2)*H*), 4.44 (1H, app d, *J* 5.8, C(3')*H*), 4.66-4.73 (1H, m, C(4')*H*); δ_C (100 MHz, $CDCl_3$) [minor rotamer] 24.9, 26.9 (2 × *Me*CMe), 28.0, 28.4 (2 × C*Me*$_3$), 53.1 (*C*(5')), 66.3 (*C*(2')), 72.1 (*C*(2)), 79.2 (*C*(4')), 79.9 (*C*Me$_3$), 80.8 (*C*(3')), 83.5 (*C*Me$_3$), 111.4 (Me*C*Me), 153.7 (N*C*O), 172.0 (*C*(1)); *m/z* (ESI^+) 396 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{18}H_{31}NNaO_7^+$ ($[M+Na]^+$) requires 396.1993; found 396.1986.

*Method B (from **253**) – Step 1:* MsCl (20 μL, 0.26 mmol) was added dropwise to a stirred solution of **253** (50 mg, 0.13 mmol, >99:1 dr), Et_3N (71 μL, 0.51 mmol) and DMAP (5 mg, cat.) in CH_2Cl_2 (2 mL) at –10 °C and the resultant mixture was stirred at –10 °C for 6 h. H_2O (1 mL) was then added and the reaction mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed sequentially with 10% aq $CuSO_4$ (10 mL), H_2O (10 mL) and satd aq $NaHCO_3$ (10 mL). The organic layer was then dried and concentrated *in vacuo* to give **254** as a yellow oil (52 mg); δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.31 (3H, s, *Me*CMe), 1.44 (3H, s, *Me*CMe), 1.46 (9H, s, C*Me*$_3$), 1.51 (9H, s, C*Me*$_3$), 3.10 (3H, s, SO_2*Me*), 3.28 (1H, d, *J* 4.1, O*H*), 5.02 (1H, d, *J* 10.1, N*H*).

*Method B (from **253**) – Step 2:* NaH (60% dispersion in mineral oil, 4 mg, 90 μmol) was added to a stirred solution of the residue (52 mg) in THF (5 mL) at rt and the resultant suspension was stirred at rt for 16 h. The reaction mixture was then diluted with H_2O (10 mL) and the aqueous layer was extracted with Et_2O (3 × 10 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 4:1) gave **255** as a colourless oil (17 mg, 36% over 2 steps, >99:1 dr).

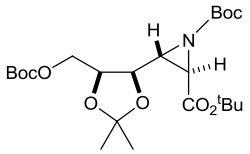
Di-*tert*-butyl (2*R*,3*R*,1'*R*,2'*S*)-3-(1',2',3'-trihydroxy-1',2'-*O*-isopropylidineprop-1'-yl)aziridine-1,2-dicarboxylate 259



Step 1: MsCl (38 μL, 0.49 mmol) was added dropwise to a stirred solution of **252** (50 mg, 0.10 mmol, >99:1 dr), Et_3N (0.14 mL, 1.0 mmol) and DMAP (5 mg, cat.) in CH_2Cl_2 (2 mL) at –10 °C and the resultant mixture was stirred at –10 °C for 6 h. H_2O (1 mL) was then added and the reaction mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed sequentially with 10% aq $CuSO_4$ (10 mL), H_2O (10 mL) and satd aq $NaHCO_3$ (10 mL). The organic layer was then dried and concentrated *in vacuo* to give **257** in >99:1 dr (70 mg); δ_H (400 MHz, $CDCl_3$) [selected peaks] 0.11 (6H, app s, 2 × *Me*SiMe), 0.92 (9H, s, SiC*Me*$_3$), 1.33 (3H, s, *Me*CMe), 1.44 (12H, s, *Me*CMe, C*Me*$_3$), 1.51 (9H, s, C*Me*$_3$), 3.16 (3H, s, SO_2*Me*), 3.73 (1H, dd, *J* 11.0, 5.6, C(6)*H*$_A$), 3.82 (1H, dd, *J* 11.0, 4.8, C(6)*H*$_B$).

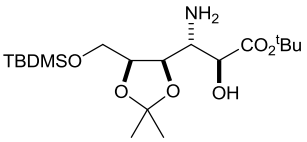
Step 2: TBAF (1.0 M in THF, 0.61 mL, 0.61 mmol) was added dropwise to a stirred solution of the residue (70 mg) in THF (2 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was diluted with Et_2O (10 mL) and washed with H_2O (10 mL). The aqueous layer was then extracted with Et_2O (3 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 4:1) gave **259** as a pale yellow oil (32 mg, 87% over 2 steps, >99:1 dr); $[\alpha]_D^{25}$ +16.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3449 (O–H), 2981, 2935 (C–H), 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 1.35 (3H, s, *Me*CMe), 1.46 (9H, s, C*Me*$_3$), 1.47 (3H, s, *Me*CMe), 1.51 (9H, s, C*Me*$_3$), 2.93 (1H, d, *J* 2.5, C(2)*H*), 3.01 (1H, dd, *J* 8.5, 2.5, C(3)*H*), 3.55 (1H, br s, O*H*), 3.72 (1H, dd, *J* 8.5, 6.6, C(1')*H*), 3.92 (1H, dd, *J* 12.3, 3.5, C(3')*H*$_A$), 4.05 (1H, dd, *J* 12.3, 6.3, C(3')*H*$_B$), 4.32-4.38 (1H, m, C(2')*H*); δ_C (100 MHz, $CDCl_3$) 24.9, 27.5 (2 × *Me*CMe), 27.9, 28.0 (C*Me*$_3$), 40.4 (*C*(2)), 41.3 (*C*(3)), 60.2 (*C*(3')), 77.8, 77.9 (*C*(1'), *C*(2')), 83.0, 83.0 (2 × *C*Me$_3$), 109.0 (Me*C*Me), 159.7 (N*C*O), 166.5 (*C*O^{t}Bu); *m/z* (ESI$^+$) 396 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{18}H_{31}NNaO_7^+$ ([M+Na]$^+$) requires 396.1993; found 396.1985.

Di-*tert*-butyl (2*R*,3*R*,1'*R*,2'*S*)-3-[1',2'-dihydroxy-1',2'-*O*-isopropylidine-3'-(*tert*-butoxycarbonyloxy)prop-1'-yl]aziridine-1,2-dicarboxylate 260



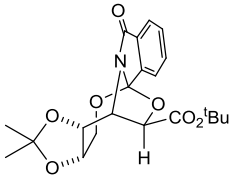
Boc_2O (87 mg, 0.40 mmol), Et_3N (6 μL, 42 μmol), and DMAP (5 mg, cat.) were added to a solution of **259** (14 mg, 37 μmol, >99:1 dr) in THF (1 mL) at rt. The resultant mixture was stirred at rt for 22 h then concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 4:1) gave **260** as a pale yellow solid (9 mg, 48%, >99:1 dr); mp 137-143 °C; $[\alpha]_D^{25}$ –4.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2981, 2936, 2850 (C–H), 1743, 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, s, *Me*CMe), 1.46 (9H, s, C*Me*$_3$), 1.48 (9H, s, C*Me*$_3$), 1.49 (9H, s, C*Me*$_3$), 1.49 (3H, s, *Me*CMe), 2.88 (1H, dd, *J* 7.1, 2.5, C(3)*H*), 2.93 (1H, d, *J* 2.5, C(2)*H*), 3.87 (1H, dd, *J* 7.1, 6.6, C(1')*H*), 4.36 (1H, dd, *J* 11.4, 7.6, C(3')H_A), 4.45 (1H, ddd, *J* 7.6, 6.6, 3.6, C(2')*H*), 4.53 (1H, dd, *J* 11.4, 3.6, C(3')H_B); δ_C (100 MHz, $CDCl_3$) 25.2, 27.5 (2 × *Me*CMe), 27.7, 27.9, 28.0 (3 × C*Me*$_3$), 39.7 (*C*(3)), 41.1 (*C*(2)), 65.2 (*C*(3')), 75.5 (*C*(2')), 76.4 (*C*(1')), 82.2, 82.3, 82.9 (3 × *C*Me$_3$), 109.8 (Me*C*Me), 153.1, 158.1 (N*C*O, C(3')O*C*O), 166.5 (*C*O_2^{t}Bu); *m/z* (ESI$^+$) 496 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{39}NNaO_9^+$ ([M+Na]$^+$) requires 496.2517; found 496.2513.

***tert*-Butyl (2*S*,3*R*,4*R*,5*S*)-2,4,5-trihydroxy-3-amino-4,5-*O*-isopropylidene-6-(*tert*-butyldimethylsilyloxy)hexanoate 261**



Following *General Procedure 2*, **218** (200 mg, 0.333 mmol, >99:1 dr) in MeOH (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 100 mg) and H_2 (1 atm) gave **261** as a pale yellow oil (126 mg, 93%, >99:1 dr); $[\alpha]_D^{25}$ +5.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3501, 3387 (N–H, O–H), 2983, 2954, 2932, 2886, 2858 (C–H), 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 0.10 (3H, s, *Me*SiMe), 0.10 (3H, s, *Me*SiMe), 0.91 (9H, s, SiC*Me*$_3$), 1.31 (3H, s, *Me*CMe), 1.34 (3H, s, *Me*CMe), 1.51 (9H, s, OC*Me*$_3$), 3.33 (1H, d, *J* 5.4, O*H*), 3.39 (1H, dd, *J* 9.8, 2.5, C(3)*H*), 3.50 (1H, br s, N*H*), 3.52 (1H, dd, *J* 10.3, 3.4, C(6)H_A), 3.76 (1H, dd, *J* 10.3, 9.4, C(6)H_B), 4.14-4.20 (1H, m, C(5)*H*), 4.22 (1H, dd, *J* 9.8, 5.4, C(2)*H*), 4.27 (1H, dd, *J* 5.5, 2.5, C(4)*H*); δ_C (100 MHz, $CDCl_3$) –5.6, –5.6 (2 × *Me*SiMe), 18.3 (Si*C*Me$_3$), 25.4, 28.2 (2 × *Me*CMe), 25.9 (SiC*Me*$_3$), 28.1 (OC*Me*$_3$), 52.7 (*C*(3)), 62.1 (*C*(6)), 73.2 (*C*(4)), 77.4, 78.1 (*C*(2), *C*(5)), 82.3 (O*C*Me$_3$), 108.1 (Me*C*Me), 172.1 (*C*(1)); *m/z* (ESI$^+$) 406 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{19}H_{40}NO_6Si^+$ ([M+H]$^+$) requires 406.2619; found 406.2612.

(3*S*,4*R*,13*R*)-3,4-Dihydroxy-3,4-*O*-isopropylidene-4,5-dihydro-2*H*-11b,5-(epoxymethano)-13-(*tert*-butoxycarbonyl)-[1,3]oxazepino[2,3-a]isoindol-7(3*H*)-one 264



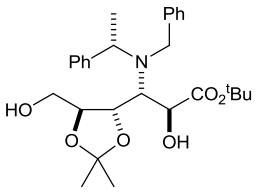
Step 1: Phthaloyl dichloride (36 μL, 0.25 mmol) and Et_3N (0.14 mL, 0.99 mmol) were added to a solution of **261** (100 mg, 0.247 mmol, >99:1 dr), in CH_2Cl_2 (5 mL) was stirred at rt for 16 h. H_2O (5 mL) was then added and the reaction mixture was partitioned between CH_2Cl_2 (10 mL) and 1.0 M aq HCl (10 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **262** in >99:1 dr (70 mg); δ_H (400 MHz, $CDCl_3$) –0.11 (3H, s, *Me*SiMe), –0.08 (3H, s, *Me*SiMe), 0.76 (9H, s, SiC*Me*$_3$), 1.39 (3H, s, *Me*CMe), 1.47 (3H, s, *Me*CMe), 1.57 (9H, s, C*Me*$_3$), 3.25 (1H, d, *J* 5.5, O*H*), 3.57 (1H, dd, *J* 11.0, 5.9, C(6)H_A), 3.70 (1H, dd, *J* 11.0, 4.7, C(6)H_B), 4.17 (1H, app td, *J* 5.9, 4.7, C(5)*H*), 4.51 (1H, dd, *J* 5.5, 2.1, C(2)*H*), 4.67 (1H, dd, *J* 10.2, 2.1, C(3)*H*), 4.78 (1H, dd, *J* 10.2, 5.9, C(4)*H*), 7.71-7.82 (2H, m, *Ar*), 7.88-7.96 (2H, m, *Ar*); *m/z* (ESI^+) 558 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{27}H_{41}NNaO_8Si^+$ ($[M+Na]^+$) requires 558.2494; found 558.2478.

Step 2: MsCl (51 μL, 0.65 mmol) was added dropwise to a stirred solution of the residue (70 mg), Et_3N (0.18 mL, 1.3 mmol) and DMAP (5 mg, cat.) in CH_2Cl_2 (2 mL) at –10 ºC and the resultant mixture was stirred at –10 ºC for 6 h. H_2O (1 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (2 × 10 mL). The combined organic extracts were washed sequentially with 10% aq $CuSO_4$ (10 mL), H_2O (10 mL) and satd aq $NaHCO_3$ (10 mL). The organic layer was then dried and concentrated *in vacuo* to give **263** in >99:1 dr (80 mg).

Step 3: TBAF (1.0 M in THF, 0.65 mL, 0.65 mmol) was added dropwise to a stirred solution of the residue (80 mg) in THF (2 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (10 mL) and washed with H_2O (10 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 2:1→3:2 30-40 °C petrol/Et_2O) gave **264** as a white solid (22 mg, 22% over 3 steps, >99:1 dr); mp 164-167 °C; $[\alpha]_D^{25}$ +22.2 (*c* 0.5 in $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 1.23 (9H, s, C*Me*$_3$), 1.39 (3H, s, *Me*CMe), 1.51 (3H, s, *Me*CMe), 4.26-4.34 (2H, m, C(2)H_2), 4.42-4.48 (2H, m, C(3)*H*, C(4)*H*), 4.63-4.65 (1H, m, C(5)*H*), 4.65-4.66 (1H, m, C(13)*H*), 7.55 (1H, t, *J* 7.6, C(9)*H*), 7.64 (1H, t, *J* 7.6, C(10)*H*), 7.68 (1H, d, *J* 7.6, C(11)*H*), 7.75 (1H, d, *J* 7.6, C(8)*H*); δ_C (125 MHz, $CDCl_3$)

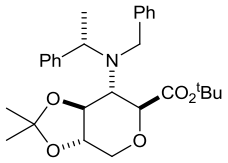
25.2, 27.0 (2 × *Me*CMe), 27.3 (C*Me*$_3$), 60.8 (*C*(2)), 61.0 (*C*(5)), 76.8, 78.7 (*C*(3), *C*(4)), 83.0 (*C*(13)), 83.3 (*C*Me$_3$), 109.2 (Me*C*Me), 117.6 (*C*(11b)), 122.6 (*C*(11)), 123.9 (*C*(8)), 130.8 (*C*(9)), 131.3 (*C*(7a)), 133.6 (*C*(10)), 142.1 (*C*(11a)), 168.5, 169.8 (*C*(7), *C*O$_2$^{t}Bu); *m/z* (ESI$^+$) 426 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{25}NNaO_7^+$ ([M+Na]$^+$) requires 426.1523; found 426.1513.

tert-Butyl (2*S*,3*R*,4*S*,5*S*,α*S*)-2,4,5,6-tetrahydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-*O*-isopropylidenehexanoate 265



TBAF (1.0 M in THF, 16.4 mL, 16.4 mmol) was added dropwise to a stirred solution of **213** (1.97 g, 3.28 mmol, >99:1 dr) in THF (20 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (30 mL) and the resultant solution was washed with H_2O (20 mL). The aqueous layer was extracted with Et_2O (3 × 20 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 1:1) gave **265** as a white solid (1.22 g, 77%, >99:1 dr);[12] mp 93-94 °C; {lit.[12] 89-90 °C}; $[\alpha]_D^{25}$ +10.2 (*c* 1.0 in $CHCl_3$); {lit.[12] $[\alpha]_D^{25}$ +10.1 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.30 (3H, s, *Me*CMe), 1.30 (3H, d, *J* 7.2, C(α)*Me*), 1.34 (3H, s, *Me*CMe), 1.49 (9H, s, C*Me*$_3$), 1.67 (1H, dd, *J* 7.9, 5.1, C(6)O*H*), 3.20 (1H, d, *J* 8.2, C(2)O*H*), 3.32 (1H, ddd, *J* 12.0, 7.9, 4.1, C(6)H_A), 3.40-3.43 (1H, m, C(3)*H*), 3.64 (1H, ddd, *J* 12.0, 5.1, 3.8, C(6)H_B), 3.83 (1H, d, *J* 15.5, NCH_AH$_B$Ph), 3.97-4.06 (3H, m, C(2)*H*, C(4)*H*, C(α)*H*), 4.34-4.40 (1H, m, C(5)*H*), 4.78 (1H, d, *J* 15.5, NCH$_A$$H_B$Ph), 7.20-7.40 (8H, m, *Ph*), 7.48-7.54 (2H, m, *Ph*).

(*S*,*S*,*S*,*S*,*S*)-3,4-Dihydroxy-3,4-*O*-isopropylidene-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6-(*tert*-butoxycarbonyl)tetrahydro-2*H*-pyran 267

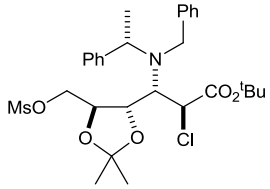


Step 1: MsCl (0.12 mL, 1.5 mmol) was added dropwise to a stirred solution of **265** (300 mg, 0.618 mmol) in pyridine (15 mL) and the resultant mixture was stirred at rt for 18 h. The reaction mixture was then diluted with Et_2O (50 mL) and washed sequentially with H_2O (2 × 50 mL), 1.0 M aq HCl (50 mL) and satd aq $NaHCO_3$ (50 mL). The organic layer was then dried and concentrated *in vacuo* to give a 72:28 mixture of **266** and **265** respectively as a yellow oil (208 mg). Data for **266**:

δ_H (400 MHz, $CDCl_3$) 1.31 (3H, s, *Me*CMe), 1.34 (3H, d, *J* 7.2, C(α)*Me*), 1.36 (3H, s, *Me*CMe), 1.50 (9H, s, C*Me*$_3$), 3.01 (3H, s, SO_2*Me*), 3.12 (1H, d, *J* 6.8, O*H*), 3.51 (1H, dd, *J* 3.8, 1.7, C(3)*H*), 3.85 (1H, d, *J* 15.7, NC*H*$_A$H$_B$Ph), 3.92-3.97 (2H, m, C(2)*H*, C(6)*H*$_A$), 4.01 (1H, dd, *J* 8.1, 3.8, C(4)*H*), 4.04 (1H, q, *J* 7.2, C(α)*H*), 4.27 (1H, dd, *J* 11.4, 2.8, C(6)*H*$_B$), 4.55 (1H, ddd, *J* 8.1, 5.1, 2.8, C(5)*H*), 4.71 (1H, d, *J* 15.7, NCH$_A$*H*$_B$Ph), 7.23-7.40 (8H, m, *Ph*), 7.47-7.52 (2H, m, *Ph*).

Step 2: NaH (60% dispersion in mineral oil, 15 mg, 0.36 mmol) was added to a stirred solution of the residue (208 mg) in THF (30 mL) at rt and the resultant suspension was stirred at rt for 16 h. The reaction mixture was diluted with H_2O (30 mL) and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 3:1) gave **267** as a pale yellow oil (155 mg, 54% over 2 steps, >99:1 dr);[12] $[\alpha]_D^{25}$ +24.3 (*c* 1.0 in $CHCl_3$); {lit.[12] $[\alpha]_D^{25}$ +25.3 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, C_6D_6) 1.29 (3H, s, *Me*CMe), 1.35 (3H, s, *Me*CMe), 1.44 (9H, s, C*Me*$_3$), 1.53 (3H, d, *J* 6.8, C(α)*Me*), 3.02 (1H, app t, *J* 9.9, C(2)*H*$_A$), 3.29-3.35 (1H, m, C(3)*H*), 3.47 (1H, dd, *J* 10.8, 8.5, C(4)*H*), 3.61 (1H, d, *J* 9.2, C(6)*H*), 3.74 (1H, dd, *J* 10.8, 9.2, C(5)*H*), 3.80 (1H, d, *J* 14.2, NC*H*$_A$H$_B$Ph), 3.95 (1H, dd, *J* 9.9, 4.4, C(2)*H*$_B$), 3.98 (1H, d, *J* 14.2, NCH$_A$*H*$_B$Ph), 4.20 (1H, q, *J* 6.8, C(α)*H*), 7.08-7.27 (6H, m, *Ph*), 7.37-7.41 (2H, m, *Ph*), 7.46-7.51 (2H, m, *Ph*).

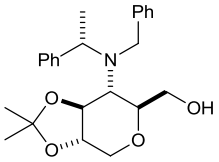
tert-Butyl (*S*,*S*,*S*,*S*,*S*)-2-chloro-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(methylsulfonyloxy)hexanoate 269



MsCl (0.42 mL, 5.4 mmol) was added dropwise to a stirred solution of **265** (260 mg, 0.535 mmol, >99:1 dr) and DMAP (10 mg, cat.) in pyridine (12.5 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (20 mL) and was washed sequentially with H_2O (2 × 50 mL), 1.0 M aq HCl (50 mL) and satd aq $NaHCO_3$ (50 mL). The organic layer was then dried and concentrated *in vacuo* to give **269** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 1:1) gave **269** as a pale yellow oil (209 mg, 72%, >99:1 dr); $[\alpha]_D^{25}$ –12.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3062, 3028, 2982, 2936 (C–H), 1732 (C=O); δ_H (400 MHz, $CDCl_3$) 1.35 (3H, s, *Me*CMe), 1.39 (3H, s, *Me*CMe), 1.38 (3H, d, *J* 6.6, C(α)*Me*), 1.45 (9H, s, C*Me*$_3$), 3.01 (3H, s, SO_2*Me*), 3.55-3.61 (1H, m, C(6)*H*$_A$) overlapping 3.58 (1H, dd, *J* 6.6, 2.5, C(3)*H*), 3.89 (1H, d, *J* 14.7, NC*H*$_A$H$_B$Ph), 3.96 (1H, app d, *J* 10.9, C(6)*H*$_B$), 4.25-4.35 (4H, m,

C(2)*H*, C(4)*H*, C(5)*H*, C(α)*H*), 4.53 (1H, d, *J* 14.7, NCH$_A$*H*$_B$Ph), 7.25-7.52 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.4 (C(α)*Me*), 26.0, 27.0 (2 × *Me*CMe), 27.7 (C*Me*$_3$), 37.4 (SO_2*Me*), 51.8 (N*C*H$_2$Ph), 56.7 (*C*(2)), 57.2 (*C*(3)), 59.1 (*C*(α)), 68.4 (*C*(6)), 75.0, 76.7 (*C*(4), *C*(5)), 82.9 (*C*Me$_3$), 109.3 (Me*C*Me), 126.9, 127.5 (*p-Ph*), 127.9, 128.4, 128.6, 128.8 (*o*,*m-Ph*), 141.3, 143.4 (*i-Ph*), 168.4 (*C*(1)); *m/z* (ESI$^+$) 546 ([M–Cl]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{40}NO_7S^+$ ([M–Cl]$^+$) requires 546.2520; found 546.2514. Upon standing for extended periods of time (~3 months), the sample of **269** was found to undergo rearrangement to *tert*-butyl (2*S*,3*S*,4*R*,5*S*,α*S*)-2-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-3-chloro-4,5-dihydroxy-4,5-*O*-isopropylidene-6-(methylsulfonyloxy)hexanoate; $[\alpha]_D^{25}$ +3.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3029, 2980, 2936 (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.03 (3H, s, *Me*CMe), 1.23 (3H, s, *Me*CMe), 1.33 (3H, d, *J* 7.1, C(α)*Me*), 1.48 (9H, s, C*Me*$_3$), 2.93 (3H, s, SO_2*Me*), 3.77 (1H, d, *J* 4.2, C(2)*H*), 3.90-4.06 (6H, m, C(3)*H*, C(4)*H*, C(5)*H*, C(6)*H*$_A$, C(α)*H*, NC*H*$_A$H$_B$Ph), 4.10 (1H, app d, *J* 10.8, C(6)*H*$_B$), 4.31 (1H, d, *J* 14.9, NCH$_A$*H*$_B$Ph), 7.11-7.46 (10H, m, Ph); δ_C (100 MHz, $CDCl_3$) 12.9 (C(α)*Me*), 26.7, 26.9 (2 × *Me*CMe), 28.2 (C*Me*$_3$), 37.8 (SO_2*Me*), 53.0 (N*C*H$_2$Ph), 56.7 (*C*(α)), 61.1 (*C*(6)), 64.5 (*C*(2)), 70.0 (*C*(3)), 76.8, 78.3 (*C*(4), *C*(5)), 82.3 (*C*Me$_3$), 110.4 (Me*C*Me), 127.2, 127.2 (*p-Ph*), 128.2, 128.3, 128.4, 128.9 (*o*,*m-Ph*), 140.5, 142.7 (*i-Ph*), 169.8 (*C*(1)); *m/z* (ESI$^+$) 604 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{40}ClNNaO_7S^+$ ([M+Na]$^+$) requires 604.2106; found 604.2108.

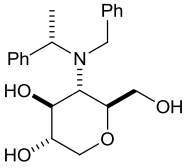
(α*S*)-1,4,5-Trideoxy-1,5-epoxy-2,3-*O*-isopropylidene-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-D-glucose 270



$LiAlH_4$ (1.0 M in THF, 0.66 mL, 0.66 mmol) was added dropwise to a stirred solution of **267** (155 mg, 0.331 mmol, >99:1 dr) in THF (10 mL) at −78 °C and the resultant mixture was allowed to warm to rt over 16 h. 1.0 M aq NaOH (1 mL) and EtOAc (2 mL) were then added and the resultant suspension was stirred at rt for 1 h. The mixture was filtered through a short plug of Celite® (eluent EtOAc) and the filtrate was concentrated *in vacuo* to give **270** as a pale yellow oil (132 mg, quant, >99:1 dr); $[\alpha]_D^{25}$ +57.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3454 (O–H), 3061, 3028, 2983, 2918, 2877, 2850 (C–H); δ_H (400 MHz, $CDCl_3$) 1.53 (3H, s, *Me*CMe), 1.53 (3H, d, *J* 6.8, C(α)*Me*), 1.54 (3H, s, *Me*CMe), 1.95 (1H, br s, O*H*), 2.93 (1H, dd, *J* 10.6, 9.1, C(4)*H*), 3.20-3.27 (1H, m, C(5)*H*), 3.28 (1H, dd, *J* 11.3, 5.8, C(6)*H*$_A$), 3.33-3.45 (2H, m, C(1)*H*$_A$, C(2)*H*), 3.56 (1H, dd, *J* 11.3, 3.2, C(6)*H*$_B$), 3.67 (1H, dd, *J* 10.6, 8.2, C(3)*H*), 3.87 (1H, d, *J* 13.1, NC*H*$_A$H$_B$Ph), 3.94 (1H, d, *J* 13.1,

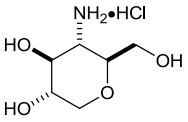
NCH_AH_BPh), 4.07 (1H, q, *J* 6.8, C(α)*H*), 4.12 (1H, dd, *J* 8.8, 3.3, C(1)H_B), 7.23-7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.8 (C(α)*Me*), 26.7, 26.9 (2 × *Me*CMe), 51.7 (NCH_2Ph), 56.3 (*C*(α)), 58.2 (*C*(4)), 63.4 (*C*(6)), 68.0 (*C*(1)), 75.4 (*C*(2)), 78.5 (*C*(5)), 79.8 (*C*(3)), 110.1 (Me*C*Me), 127.1, 127.3 (*p-Ph*), 128.1, 128.3, 128.5, 129.3 (*o,m-Ph*), 139.9, 143.7 (*i-Ph*); *m/z* (ESI^+) 398 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{24}H_{32}NO_4^+$ ($[M+H]^+$) requires 398.2326; found 398.2308

(α*S*)-1,4,5-Trideoxy-1,5-epoxy-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-D-glucose 271



3.0 M aq HCl (1 mL) was added dropwise to a stirred solution of **270** (100 mg, 0.252 mmol, >99:1 dr) in MeOH (5 mL) at rt and the resultant solution was then heated at 50 °C for 3 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL) and the resultant solution was washed with 2.0 M aq NaOH (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give **271** as a pale yellow oil (64 mg, 71%, >99:1 dr); $[\alpha]_D^{25}$ –4.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3417 (O–H), 3085, 3062, 3028, 2968, 2922, 2852 (C–H); δ_H (400 MHz, $CDCl_3$) 1.52 (3H, app br s, C(α)*Me*), 2.75 (1H, app t, *J* 9.2, C(4)*H*), 2.91 (1H, br s, O*H*), 3.07 (1H, app t, *J* 10.5, C(1)H_A), 3.16-3.27 (1H, m, C(5)*H*), 3.28-3.39 (1H, m, C(6)H_A), 3.48 (1H, ddd, *J* 10.5, 8.8, 5.3, C(2)*H*), 3.53-3.60 (1H, m, C(6)H_B), 3.61-3.71 (1H, m, C(3)*H*), 3.80 (1H, d, *J* 14.4, NCH_AH_BPh), 3.87 (1H, dd, *J* 11.1, 5.3, C(1)H_B), 4.09-4.19 (2H, m, NCH_AH_BPh, C(α)*H*), 7.22-7.41 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.8 (C(α)*Me*), 50.0 (NCH_2Ph), 59.9 (*C*(4)), 63.2 (*C*(6)), 69.1 (*C*(1)), 71.8 (*C*(2)), 74.6 (*C*(3)), 79.1 (*C*(5)), 127.3, 127.5 (*p-Ph*), 127.7, 128.6, 128.6, 128.7 (*o,m-Ph*), 144.3, 144.3 (*i-Ph*);[19] *m/z* (ESI^+) 358 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{21}H_{28}NO_4^+$ ($[M+H]^+$) requires 358.2013; found 358.2008.

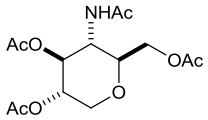
1,4,5-Trideoxy-1,5-epoxy-4-amino-D-glucose hydrochloride 272·HCl



Following *General Procedure 2*, **271** (85 mg, 0.24 mmol, >99:1 dr) in MeOH (3 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 43 mg) and H_2 (1 atm) gave **272** in >99:1 dr. The residue was dissolved in HCl (2.0 M in Et_2O, 2 mL) and the solvent was removed *in vacuo*. Purification via recrystallisation (CH_2Cl_2/MeOH, 3:1) gave **272**·HCl as a pale yellow solid (27 mg, 56%, >99:1 dr); $[\alpha]_D^{25}$ –3.2

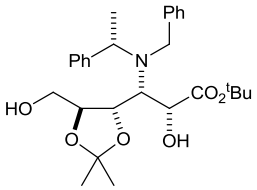
(*c* 1.0 in MeOH); ν_{max} (film) 3359, 3275 (N–H, O–H), 3134, 3086, 2936, 2870 (C–H); δ_H (400 MHz, MeOH-d_4) 3.06 (1H, app t, *J* 9.9, C(4)*H*), 3.22 (1H, dd, *J* 11.1, 10.1, C(1)H_A), 3.45-3.56 (3H, m, C(2)*H*, C(3)*H*, C(5)*H*), 3.74 (1H, dd, *J* 11.7, 4.8, C(6)H_A), 3.78 (1H, dd, *J* 11.7, 4.6, C(6)H_B), 3.96 (1H, dd, *J* 11.1, 5.1, C(1)H_B); δ_C (100 MHz, MeOH-d_4) 54.4 (*C*(4)), 62.1 (*C*(6)), 70.0 (*C*(1)), 70.5 (*C*(2)), 74.6, 76.9 (*C*(3), *C*(5)); *m/z* (ESI^+) 186 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_6H_{13}NNaO_4^+$ ($[M+Na]^+$) requires 186.0737; found 186.0746.

(*N*,*O*,*O*,*O*-Tetraacetyl)-1,4,5-trideoxy-1,5-epoxy-4-amino-D-glucose 273



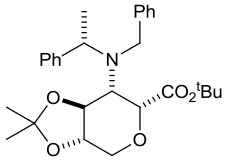
Ac_2O (60 μL, 0.64 mmol) and DMAP (5 mg, cat.) were added to a solution of **272**·HCl (26 mg, 0.13 mmol, >99:1 dr) in pyridine (1 mL) at rt and the resultant solution was stirred at rt for 24 h. The reaction mixture was then diluted with CH_2Cl_2 (3 mL), EtOAc (3 mL) and satd aq $CuSO_4$ (3 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were washed with satd aq $NaHCO_3$ (2 × 3 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 20:1) gave **273** as a white solid (25 mg, 58%, >99:1 dr); mp 182-188 °C; $[\alpha]_D^{25}$ +46.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3306 (N–H), 2949, 2864 (C–H), 1731, 1659 (C=O); δ_H (500 MHz, $CDCl_3$) 1.95 (3H, s, CO*Me*), 2.04 (3H, s, CO*Me*), 2.07 (3H, s, CO*Me*), 2.10 (3H, s, CO*Me*), 3.25 (1H, dd, *J* 11.1, 9.7, C(1)H_A), 3.49 (1H, ddd, *J* 10.4, 6.2, 2.1, C(5)*H*), 4.06-4.13 (1H, m, C(4)*H*), 4.13 (1H, dd, *J* 12.5, 6.2, C(6)H_A), 4.18 (1H, dd, *J* 11.1, 5.3, C(1)H_B), 4.24 (1H, dd, *J* 12.5, 2.1, C(6)H_B), 5.00 (1H, app td, *J* 9.7, 5.3, C(2)*H*), 5.05 (1H, app t, *J* 9.7, C(3)*H*), 5.63 (1H, d, *J* 9.1, N*H*); δ_C (125 MHz, $CDCl_3$) 20.7, 20.7, 20.9, 23.1 (4 × CO*Me*), 50.6 (*C*(4)), 63.4 (*C*(6)), 66.8 (*C*(1)), 68.9 (*C*(2)), 73.6 (*C*(3)), 78.1 (*C*(5)), 169.6, 170.2, 171.0, 171.6 (4 × *C*OMe); *m/z* (ESI^+) 354 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{14}H_{21}NNaO_8^+$ ($[M+Na]^+$) requires 354.1159; found 354.1156.

tert-Butyl (2*R*,3*R*,4*S*,5*S*,α*S*)-2,4,5,6-tetrahydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5-*O*-isopropylidenehexanoate 274



TBAF (1.0 M in THF, 3.63 mL, 3.63 mmol) was added dropwise to a stirred solution of **215** (435 mg, 0.725 mmol, >99:1 dr) in THF (6 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (20 mL) and washed with H_2O (10 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 1:1) gave **274** as a pale yellow oil (253 mg, 72%, >99:1 dr); $[\alpha]_D^{25}$ −11.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3453 (O–H), 3085, 3062, 3038, 2982, 2934 (C–H), 1723 (C=O); δ_H (400 MHz, $CDCl_3$) 1.36 (3H, s, *Me*CMe), 1.39 (3H, s, *Me*CMe), 1.42 (3H, d, *J* 7.0, C(α)*Me*), 1.48 (9H, s, C*Me*$_3$), 2.42 (1H, br s, C(6)O*H*), 3.02 (1H, br s, C(2)O*H*), 3.34 (1H, app t, *J* 5.6, C(3)*H*), 3.44 (1H, dd, *J* 12.1, 4.3, C(6)H_A), 3.68 (1H, dd, *J* 12.1, 3.5, C(6)H_B), 4.06 (1H, d, *J* 14.9, NCH_AH_BPh), 4.15 (1H, d, *J* 5.6, C(2)*H*), 4.19-4.24 (1H, m, C(5)*H*), 4.31 (1H, dd, *J* 8.3, 5.6, C(4)*H*), 4.36 (1H, d, *J* 14.9, NCH$_A$$H_B$Ph), 4.42 (1H, q, *J* 7.0, C(α)*H*), 7.18-7.40 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.5 (C(α)*Me*), 26.5, 27.1 (2 × *Me*CMe), 28.0 (C*Me*$_3$), 52.9 (NCH_2Ph), 60.3 (*C*(3)), 60.7 (*C*(α)), 62.4 (*C*(6)), 72.8 (*C*(2)), 77.1 (*C*(4)), 79.0 (*C*(5)), 83.0 (*C*Me$_3$), 108.5 (Me*C*Me), 126.4, 127.0 (*p-Ph*), 128.1, 128.1, 128.1, 128.6 (*o,m-Ph*), 142.1, 144.5 (*i-Ph*), 172.9 (*C*(1)); *m/z* (ESI$^+$) 486 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{40}NO_6^+$ ([M+H]$^+$) requires 486.2850; found 486.2849.

(2*S*,3*S*,4*S*,5*R*,α*S*)-3,4-Dihydroxy-3,4-*O*-isopropylidene-5-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-6-(*tert*-butoxycarbonyl)tetrahydro-2*H*-pyran 276

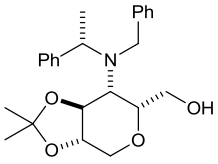


Step 1: MsCl (99 μL, 1.3 mmol) was added dropwise to a stirred solution of **274** (247 mg, 0.509 mmol, >99:1 dr) in pyridine (12.5 mL) and the resultant mixture was stirred at rt for 18 h. The reaction mixture was then diluted with Et_2O (30 mL) and washed sequentially with H_2O (2 × 30 mL), 1.0 M aq HCl (30 mL) and satd aq $NaHCO_3$ (30 mL). The organic layer was then dried and concentrated *in vacuo* to give an 85:15 mixture of **275** and **274** respectively as a yellow oil (260 mg). Data for **275**: δ_H (400 MHz, $CDCl_3$) 1.31 (3H, s, *Me*CMe), 1.36 (3H, s, *Me*CMe), 1.46 (3H, d, *J* 6.3,

C(α)*Me*), 1.47 (9H, s, C*Me*$_3$), 2.68 (1H, d, *J* 6.4, O*H*), 3.00 (3H, s, SO_2*Me*), 3.27 (1H, app t, *J* 5.3, C(3)*H*), 3.86 (1H, dd, *J* 11.4, 5.3, C(6)H_A), 4.02 (1H, d, *J* 14.9, NCH_AH$_B$Ph), 4.10 (1H, dd, *J* 6.4, 5.3, C(2)*H*), 4.21 (1H, dd, *J* 8.4, 5.3, C(4)*H*), 4.28 (1H, dd, *J* 11.4, 2.6, C(6)H_B), 4.36 (1H, d, *J* 14.9, NCH$_A$$H_B$Ph), 4.36-4.42 (2H, m, C(5)*H*, C(α)*H*), 7.19-7.39 (10H, m, *Ph*).

Step 2: NaH (60% dispersion in mineral oil, 18 mg, 0.44 mmol) was added to a stirred solution of the residue (260 mg) in THF (35 mL) at rt and the resultant suspension was stirred at rt for 16 h. The reaction mixture was then diluted with H_2O (30 mL) and the aqueous layer was extracted with Et_2O (3 × 30 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 10:1) gave **276** as a colourless oil (144 mg, 61% over 2 steps, >99:1 dr); $[\alpha]_D^{25}$ –52.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3087, 3062, 3029, 2981, 2934, 2900 (C–H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.40 (3H, d, *J* 6.6, C(α)*Me*), 1.50 (3H, s, *Me*CMe), 1.52 (3H, s, *Me*CMe), 1.53 (9H, s, C*Me*$_3$), 3.13 (1H, dd, *J* 11.4, 6.7, C(5)*H*), 3.32 (1H, ddd, *J* 13.4, 8.6, 4.8, C(3)*H*), 3.67 (1H, d, *J* 6.7, C(6)*H*), 3.94-4.09 (2H, m, C(2)H_A, C(α)*H*) overlapping 3.98 (1H, d, *J* 13.6, NCH_AH$_B$Ph), 4.06 (1H, app t, *J* 10.2, C(2)H_B), 4.23 (1H, d, *J* 13.6, NCH$_A$$H_B$Ph), 4.33 (1H, dd, *J* 11.4, 8.6, C(4)*H*), 7.22-7.57 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 11.2 (C(α)*Me*), 26.7, 27.0 (2 × *Me*CMe), 28.2 (C*Me*$_3$), 51.5 (N*C*H$_2$Ph), 54.6 (*C*(α)), 58.6 (*C*(5)), 65.4 (*C*(2)), 74.9 (*C*(4)), 75.7 (*C*(3)), 77.6 (*C*(6)), 81.9 (*C*Me$_3$), 109.5 (Me*C*Me), 126.9, 127.0 (*p-Ph*), 128.0, 128.2, 128.2, 128.9 (*o,m-Ph*), 140.2, 143.4 (*i-Ph*), 169.9 (*C*O$_2$^{t}Bu); *m/z* (ESI$^+$) 468 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{37}NNaO_5^+$ ([M+Na]$^+$) requires 490.2564; found 490.2555.

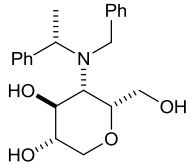
(α*S*)-1,4,5-Trideoxy-1,5-epoxy-2,3-*O*-isopropylidene-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-L-idose 277



$LiAlH_4$ (1.0 M in THF, 0.62 mL, 0.62 mmol) was added dropwise to a stirred solution of **276** (144 mg, 0.308 mmol, >99:1 dr) in THF (10 mL) at –78 °C and the resultant mixture was allowed to warm to rt over 16 h. 1.0 M aq NaOH (1 mL) and EtOAc (2 mL) were then added and the resultant suspension was stirred at rt for 1 h. The mixture was then filtered through a short plug of Celite® (eluent EtOAc) and the filtrate was concentrated *in vacuo* to give **277** as a pale yellow oil (113 mg, 92%, >99:1 dr); $[\alpha]_D^{25}$ +17.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3443 (O–H), 3086, 3062, 3029, 2983, 2934, 2890 (C–H); δ_H (400 MHz, $CDCl_3$) 1.43 (3H, d, *J* 6.8, C(α)*Me*), 1.46 (3H, s, *Me*CMe), 1.50 (3H, s, *Me*CMe), 2.37 (1H, br s, O*H*), 3.22 (1H, dd, *J* 11.0, 6.4, C(4)*H*), 3.44-3.52 (2H, m, C(2)*H*, C(5)*H*),

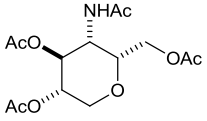
3.60 (1H, app t, *J* 10.2, C(6)H_A), 3.76 (1H, dd, *J* 11.0, 8.7, C(3)*H*), 3.82-3.89 (1H, m, C(1)H_A), 3.92-4.02 (2H, m, C(6)H_B, C(α)*H*) overlapping 3.95 (1H, dd, *J* 9.9, 4.8, C(1)H_B) and 3.97 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 4.01 (1H, d, *J* 14.4, NCH$_A$$H_B$Ph), 7.22-7.42 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.3 (C(α)*Me*), 26.7, 27.0 (2 × *Me*CMe), 52.2 (N*C*H$_2$Ph), 55.5 (*C*(α)), 58.7 (*C*(4)), 59.1 (*C*(1)), 63.8 (*C*(6)), 75.5, 78.2 (*C*(2), *C*(5)), 76.1 (*C*(3)), 110.1 (Me*C*Me), 127.0, 127.2 (*p-Ph*), 128.1, 128.3, 128.6, 128.7 (*o,m-Ph*), 139.9, 143.1 (*i-Ph*); *m/z* (ESI$^+$) 398 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{24}H_{32}NO_4^+$ ([M+H]$^+$) requires 398.2326; found 398.2334.

(α*S*)-1,4,5-Trideoxy-1,5-epoxy-4-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-L-idose 278



3.0 M aq HCl (1 mL) was added dropwise to a stirred solution of **277** (113 mg, 0.284 mmol, >99:1 dr) in MeOH (5 mL) at rt and the resultant solution was then heated at 50 °C for 3 h. The reaction mixture was allowed to cool to rt and concentrated *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 mL) and the resultant solution was washed with 2.0 M aq NaOH (50 mL). The aqueous layer was extracted with CH_2Cl_2 (3 × 20 mL) and the combined organic extracts were then dried and concentrated *in vacuo* to give **278** as a white solid (86 mg, 85%, >99:1 dr); mp 62-64 °C; $[\alpha]_D^{25}$ –31.4 (*c* 1.0 in MeOH); ν_{max} (film) 3381 (O–H), 2927 (C–H); δ_H (400 MHz, MeOH-d_4) 1.38 (3H, d, *J* 6.8, C(α)*Me*), 2.90 (1H, dd, *J* 10.1, 6.1, C(4)*H*), 3.11 (1H, ddd, *J* 10.1, 6.1, 2.8, C(5)*H*), 3.40-3.49 (2H, m, C(1)H_A, C(2)*H*), 3.52-3.61 (1H, m, C(1)H_B), 3.73-3.81 (2H, m, C(3)*H*, C(6)H_A), 3.90 (1H, q, *J* 6.8, C(α)*H*), 3.98 (1H, dd, *J* 11.9, 10.1, C(6)H_B), 4.03 (1H, d, *J* 14.1, NC$H_A$$H_B$Ph), 4.17 (1H, d, *J* 14.1, NCH$_A$$H_B$Ph), 7.15-7.59 (10H, m, *Ph*); δ_C (100 MHz, MeOH-d_4) 12.1 (C(α)*Me*), 52.1 (N*C*H$_2$Ph), 55.5 (*C*(α)), 57.5 (*C*(6)), 58.5 (*C*(4)), 63.9 (*C*(1)), 71.4 (*C*(3)), 72.6 (*C*(2)), 79.5 (*C*(5)), 126.8, 127.1 (*p-Ph*), 128.1, 128.3, 128.5, 128.8 (*o,m-Ph*), 141.3, 144.3 (*i-Ph*); *m/z* (ESI$^+$) 358 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{21}H_{28}NO_4^+$ ([M+H]$^+$) requires 358.2013; found 358.2006.

(*N*,*O*,*O*,*O*-Tetraacetyl)-1,4,5-trideoxy-1,5-epoxy-4-amino-L-idose 280

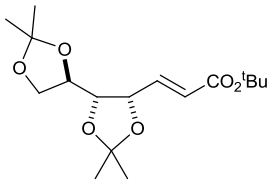


Step 1: Following *General Procedure 2*, **278** (86 mg, 0.24 mmol, >99:1 dr) in MeOH (3 mL), $Pd(OH)_2$/C (50% w/w of substrate, 43 mg) and H_2 (1 atm) gave **279** in >99:1 dr (15 mg).

Step 2: Ac_2O (82 μL, 1.4 mmol) and DMAP (5 mg, cat.) were added to a solution of the residue (15 mg) in pyridine (0.5 mL) at rt and the resultant mixture was stirred at rt for 24 h. The reaction mixture was then diluted with CH_2Cl_2 (3 mL), EtOAc (3 mL) and satd aq $CuSO_4$ (3 mL). The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were washed with satd aq $NaHCO_3$ (2 × 5 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 20:1) gave **280** as a white solid (15 mg, 19% over 2 steps, >99:1 dr); mp 129-132 °C; $[\alpha]_D^{25}$ +22.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3271 (N–H), 3046, 2962, 2925 (C–H), 1734, 1633 (C=O); δ_H (500 MHz, $CDCl_3$) 2.03 (3H, s, CO*Me*), 2.09 (3H, s, CO*Me*), 2.14 (3H, s, CO*Me*), 2.16 (3H, s, CO*Me*), 3.87 (1H, dd, *J* 13.6, 1.6, C(1)H_A), 4.00-4.05 (2H, m, C(1)H_B, C(5)*H*), 4.11 (1H, dd, *J* 12.0, 4.4, C(6)H_A), 4.14 (1H, dd, *J* 12.0, 7.7, C(6)H_B), 4.23-4.27 (1H, m, C(4)*H*), 4.76-4.79 (1H, m, C(2)*H*), 4.89-4.91 (1H, m, C(3)*H*), 6.20 (1H, d, *J* 10.1, N*H*); δ_C (125 MHz, $CDCl_3$) 20.8, 20.8, 21.1, 23.3 (4 × CO*Me*), 46.0 (*C*(4)), 63.5 (*C*(6)), 66.8 (*C*(1)), 67.1 (*C*(2)), 67.3 (*C*(3)), 73.2 (*C*(5)), 168.6, 168.7, 169.3, 170.7 (4 × *C*OMe); *m/z* (ESI^+) 354 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{14}H_{21}NNaO_8^+$ ($[M+Na]^+$) requires 354.1159; found 354.1153.

5.4 Experimental for chapter 3

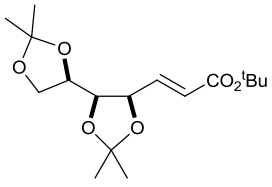
tert-Butyl (4*S*,5*S*,6*R*,*E*)-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylidenehept-2-enoate 309



Step 1: Dioxane (20 mL) was added to a mixture of D-ribose **155** (2.00 g, 13.3 mmol) and **143** (6.02 g, 16.0 mmol) and the resultant solution was stirred at 90 ºC for 6 h. The reaction mixture was allowed to cool to 50 ºC and stirring was continued at this temperature for a further 12 h. The reaction mixture was then concentrated *in vacuo* to give a 72:28 mixture of (*E*)-**307** and (*Z*)-**308** respectively. Data for (*E*)-**307**: δ_H (400 MHz, MeOH-d_4) [selected peaks] 6.05 (1H, dd, *J* 15.7, 1.7, C(2)*H*), 6.99 (1H, dd, *J* 15.7, 5.1, C(3)*H*). Data for (*Z*)-**308**: δ_H (400 MHz, MeOH-d_4) [selected peaks] 5.88 (1H, dd, *J* 12.0, 1.4, C(2)*H*), 6.29 (1H, dd, *J* 12.0, 8.5, C(3)*H*).

Step 2: The residue was dissolved in DMP (50 mL), the resultant solution was stirred and TsOH·H_2O (780 mg, 4.10 mmol) was added. Stirring was continued at rt for 18 h then satd aq $NaHCO_3$ (20 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried and concentrated *in vacuo* to give (*E*)-**309** in 72:28 dr. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 20:1) gave (*E*)-**309** as a colourless oil (1.76 g, 40% over 2 steps, >99:1 dr);[20] $C_{17}H_{28}O_6$ requires C, 62.2; H, 8.6%; found C, 62.2; H, 8.7%; $[\alpha]_D^{25}$ −17.2 (*c* 1.0 in $CHCl_3$); {lit.[20] $[\alpha]_D^{25}$ −26.6 (*c* 0.6 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.32 (3H, s, *Me*CMe), 1.38 (3H, s, *Me*CMe), 1.41 (3H, s, *Me*CMe), 1.49 (12H, app s, C*Me*$_3$, *Me*CMe), 3.88 (1H, dd, *J* 8.2, 5.7, C(7)H_A), 3.97 (1H, app dt, *J* 8.5, 5.7, C(6)*H*), 4.07 (1H, dd, *J* 8.2, 5.7, C(7)H_B), 4.16 (1H, dd, *J* 8.5, 6.7, C(5)*H*), 4.83 (1H, ddd, *J* 6.7, 4.8, 1.7, C(4)*H*), 6.07 (1H, dd, *J* 15.4, 1.7, C(2)*H*), 6.94 (1H, dd, *J* 15.4, 4.8, C(3)*H*).

tert-Butyl (*R*,*R*,*R*,*E*)-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylidenehept-2-enoate 313

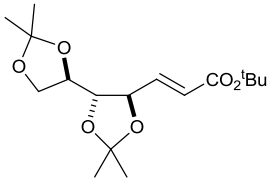


Step 1: Dioxane (167 mL) was added to a mixture of D-lyxose **310** (10.0 g, 66.6 mmol) and **143** (30.1 g, 79.9 mmol) and the resultant solution was stirred at 90 ºC for 6 h. The reaction mixture was allowed to cool to 50 ºC and stirring was continued at this temperature for a further 12 h. The reaction mixture was then concentrated *in vacuo* to give a 76:24 mixture of (*E*)-**311** and (*Z*)-**312** respectively. Data for (*E*)-**311**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 6.03 (1H, dd, *J* 15.7, 1.7,

C(2)*H*), 7.12 (1H, dd, *J* 15.7, 4.8, C(3)*H*). Data for (*Z*)-**312**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 5.87 (1H, dd, *J* 12.0, 1.4, C(2)*H*), 6.27 (1H, dd, *J* 12.0, 8.5, C(3)*H*).

Step 2: The residue was dissolved in DMP (300 mL), the resultant solution was stirred and $TsOH \cdot H_2O$ (4.75 g, 25.0 mmol) was added. Stirring was continued at rt for 18 h then satd aq $NaHCO_3$ (100 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried and concentrated *in vacuo* to give (*E*)-**313** in 76:24 dr. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 6:1) gave (*E*)-**313** as a pale yellow solid (8.12 g, 37% over 2 steps, >99:1 dr); $C_{17}H_{28}O_6$ requires C, 62.2; H, 8.6%; found C, 62.3; H, 8.6%; mp 64-67 ºC; $[\alpha]_D^{25}$ +4.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2985, 2937, 2888 (C–H), 1716 (C=O), 1658 (C=C); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, s, *Me*CMe), 1.39 (3H, s, *Me*CMe), 1.44 (3H, s, *Me*CMe), 1.47 (9H, s, C*Me*$_3$), 1.55 (3H, s, *Me*CMe), 3.54-3.60 (1H, m, C(7)H_A), 3.94-3.99 (1H, m, C(7)H_B), 4.03-4.11 (1H, m, C(6)*H*), 4.18-4.24 (1H, m, C(5)*H*), 4.64-4.69 (1H, m, C(4)*H*), 5.98 (1H, d, *J* 15.7, C(2)*H*), 6.67 (1H, dd, *J* 15.7, 7.1, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 25.2, 25.3, 26.6, 27.6 (4 × *Me*CMe), 28.1 (C*Me*$_3$), 65.8 (*C*(7)), 75.0 (*C*(6)), 76.0 (*C*(4)), 80.0 (*C*(5)), 81.0 (*C*Me$_3$), 109.9, 110.3 (2 × Me*C*Me), 126.1 (*C*(2)), 140.8 (*C*(3)), 164.8 (*C*(1)); *m/z* (ESI^+) 351 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{17}H_{28}NaO_6^+$ ($[M+Na]^+$) requires 351.1778; found 351.1780.

tert-Butyl (4*R*,5*S*,6*R*,*E*)-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylidenehept-2-enoate 317

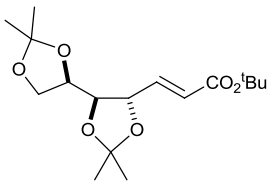


Step 1: Dioxane (167 mL) was added to a mixture of D-arabinose **314** (10.0 g, 66.6 mmol) and **143** (30.1 g, 79.9 mmol) and the resultant solution was stirred at 90 ºC for 6 h. The reaction mixture was allowed to cool to 50 ºC and stirring was continued at this temperature for a further 12 h. The reaction mixture was then concentrated *in vacuo* to give (*E*)-**315** in >99:1 dr; δ_H (400 MHz, MeOH-d_4) [selected peaks] 6.07 (1H, d, *J* 15.7, C(2)*H*), 7.00 (1H, dd, *J* 15.7, 4.4, C(3)*H*).

Step 2: The residue was dissolved in DMP (300 mL), the resultant solution was stirred and $TsOH \cdot H_2O$ (4.75 g, 25.0 mmol) was added. Stirring was continued at rt for 18 h then satd aq $NaHCO_3$ (100 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 100 mL). The combined organic extracts were dried and concentrated *in vacuo* to give (*E*)-**317** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O,

10:1) gave (*E*)-**317** as a pale yellow oil (17.1 g, 78% over 2 steps, >99:1 dr); $C_{17}H_{28}O_6$ requires C, 62.2; H, 8.6%; found C, 62.2; H, 8.5%; $[\alpha]_D^{25}$ –1.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2986, 2936 (C–H), 1716 (C=O), 1661 (C=C); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, s, *Me*CMe), 1.41 (6H, app s, 2 × *Me*CMe), 1.42 (3H, s, *Me*CMe), 1.48 (9H, s, C*Me*$_3$), 3.66-3.72 (1H, m, C(5)*H*), 3.92-3.98 (1H, m, C(7)H_A), 4.09-4.15 (2H, m, C(6)*H*, C(7)H_B), 4.51 (1H, ddd, *J* 7.9, 4.7, 1.7, C(4)*H*), 6.07 (1H, dd, *J* 15.7, 1.7, C(2)*H*), 6.89 (1H, dd, *J* 15.7, 4.7, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 25.2, 26.7, 26.7, 27.0 (4 × *Me*CMe), 28.1 (C*Me*$_3$), 67.5 (*C*(7)), 77.0 (*C*(6)), 78.9 (*C*(4)), 80.5 (*C*Me$_3$), 81.1 (*C*(5)), 109.8, 110.2 (2 × Me*C*Me), 123.4 (*C*(2)), 143.7 (*C*(3)), 165.5 (*C*(1)); *m/z* (ESI^+) 351 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{17}H_{28}NaO_6^+$ ($[M+Na]^+$) requires 351.1778; found 351.1779.

tert-Butyl (4*S*,5*R*,6*R*,*E*)-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylidenehept-2-enoate 321

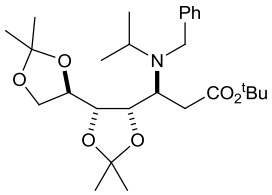


Step 1: Dioxane (20 mL) was added to a mixture of D-xylose **318** (1.00 g, 6.66 mmol) and **143** (3.00 g, 7.99 mmol) and the resultant solution was stirred at 90 ºC for 6 h. The reaction mixture was allowed to cool to 50 ºC and stirring was continued at this temperature for a further 12 h. The reaction mixture was then concentrated *in vacuo* to give an 85:15 mixture of (*E*)-**319** and (*Z*)-**320** respectively. Data for (*E*)-**319**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 6.09 (1H, d, *J* 15.7, C(2)*H*), 6.85 (1H, dd, *J* 15.7, 4.8, C(3)*H*). Data for (*Z*)-**320**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 5.92 (1H, dd, *J* 12.0, 1.4, C(2)*H*), 6.26 (1H, dd, *J* 12.0, 7.5, C(3)*H*).

Step 2: The residue was dissolved in DMP (30 mL), the resultant solution was stirred and $TsOH \cdot H_2O$ (500 mg, 2.63 mmol) was added. Stirring was continued at rt for 18 h then satd aq $NaHCO_3$ (10 mL) was added. The layers were separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic extracts were dried and concentrated *in vacuo* to give (*E*)-**321** in 85:15 dr. Purification via flash column chromatography (eluent 30-40 ºC petrol/EtOAc, 15:1) gave (*E*)-**321** as a white solid (1.36 g, 62% over 2 steps, >99:1 dr); $C_{17}H_{28}O_6$ requires C, 62.2; H, 8.6%; found C, 62.2; H, 8.5%; mp 74-78 ºC; $[\alpha]_D^{25}$ –20.4 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 2985, 2936 (C–H), 1716 (C=O), 1661 (C=C); δ_H (400 MHz, $CDCl_3$) 1.34 (3H, s, *Me*CMe), 1.39 (6H, app s, 2 × *Me*CMe), 1.41 (3H, s, *Me*CMe), 1.44 (9H, s, C*Me*$_3$), 3.75-3.81 (2H, m, C(5)*H*, C(7)H_A), 3.96-4.02 (1H, m, C(7)H_B), 4.12-4.18 (1H, m, C(6)*H*), 4.40-4.45 (1H, m, C(4)*H*), 6.01 (1H, d, *J* 15.7, C(2)*H*), 6.71 (1H, dd, *J* 15.7, 6.0, C(3)*H*); δ_C (100 MHz, $CDCl_3$) 25.4, 26.1, 26.7, 26.7 (4 × *Me*CMe),

28.1 (C*Me*$_3$), 65.5 (*C*(7)), 74.5 (*C*(6)), 76.5 (*C*(4)), 80.4 (*C*(5)), 80.8 (*C*Me$_3$), 109.8, 110.3 (2 × Me*C*Me), 125.1 (*C*(2)), 142.4 (*C*(3)), 165.0 (*C*(1)); *m/z* (ESI$^+$) 679 ([2M+Na]$^+$, 100%), 351 ([M+Na]$^+$, 40%); HRMS (ESI$^+$) $C_{17}H_{28}NaO_6^+$ ([M+Na]$^+$) requires 351.1778; found 351.1783.

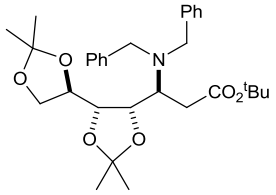
tert-Butyl (3*S*,4*S*,5*S*,6*R*)-3-(*N*-benzyl-*N*-isopropylamino)-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 323



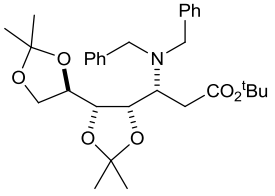
Method A: Following *General Procedure 1*, *N*-benzyl-*N*-isopropylamine (1.36 g, 9.14 mmol) in THF (60 mL), BuLi (2.5 M, 3.54 mL, 8.86 mmol) and **309** (1.50 g, 4.57 mmol, >99:1 dr) in THF (60 mL) at −78 ºC gave a 93:7 mixture of **323** and **322** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 10:1) gave **323** as a white solid (1.59 g, 73%, >99:1 dr);[20] $C_{27}H_{43}NO_6$ requires C, 67.9; H, 9.1; N, 2.9%; found C, 67.8; H, 9.15; N, 2.9%; mp 50-57 ºC; $[\alpha]_D^{25}$ −43.2 (*c* 1.0 in $CHCl_3$);[21] δ_H (400 MHz, $CDCl_3$) 1.02 (6H, d, *J* 6.8, 2 × *Me*CHMe), 1.31 (3H, s, *Me*CMe), 1.38 (3H, s, *Me*CMe), 1.39 (3H, s, *Me*CMe), 1.44 (3H, s, *Me*CMe), 1.50 (9H, s, C*Me*$_3$), 2.21 (1H, dd, *J* 14.7, 3.4, C(2)H_A), 2.59 (1H, dd, *J* 14.7, 9.6, C(2)H_B), 2.89 (1H, sept, *J* 6.8, MeC*H*Me), 3.63 (1H, d, *J* 14.9, NCH_AH_BPh), 3.88 (1H, dd, *J* 8.5, 5.5, C(7)H_A), 3.96-4.00 (1H, m, C(3)*H*), 4.00 (1H, d, *J* 14.9, NCH$_A$$H_B$Ph), 4.06 (1H, dd, *J* 8.5, 6.1, C(7)H_B), 4.13 (1H, dd, *J* 8.7, 7.0, C(5)*H*), 4.28 (1H, app dt, *J* 8.7, 5.8, C(6)*H*), 4.41 (1H, dd, *J* 7.0, 2.2, C(4)*H*), 7.19-7.32 (3H, m, *Ph*), 7.39-7.43 (2H, m, *Ph*). Further elution gave an impure sample of **322** as a pale yellow oil (267 mg, >99:1 dr).

Method B: Following *General Procedure 1*, *N*-benzyl-*N*-isopropylamine (91 mg, 0.61 mmol) in Et_2O (4 mL), BuLi (2.5 M, 0.24 mL, 0.59 mmol) and **309** (100 mg, 0.31 mmol, >99:1 dr) in Et_2O (4 mL) at −20 ºC gave an 80:20 mixture of **323** and **322** respectively (160 mg).

tert-Butyl (3*S*,4*S*,5*S*,6*R*)- and (3*R*,4*S*,5*S*,6*R*)-3-(*N*,*N*-dibenzylamino)-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 325 and 326



325

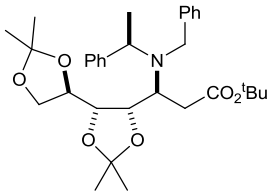


326

Method A: Following *General Procedure 1*, dibenzylamine (1.80 g, 9.14 mmol) in THF (60 mL), BuLi (2.2 M, 4.03 mL, 8.86 mmol) and **309** (1.50 g, 4.57 mmol, >99:1 dr) in THF (60 mL) at −78 ºC gave a 90:10 mixture of **325** and **326** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 10:1) gave **325** as a pale yellow oil (1.33 g, 55%, >99:1 dr);[20] $C_{31}H_{43}NO_6$ requires C, 70.8; H, 8.2; N, 2.7%; found C, 70.8; H, 8.3; N, 2.6%; $[\alpha]_D^{25}$ −5.8 (*c* 1.7 in $CHCl_3$); {lit.[20] $[\alpha]_D^{25}$ −7.2 (*c* 1.7 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.21 (3H, s, *Me*CMe), 1.30 (3H, s, *Me*CMe), 1.39 (3H, s, *Me*CMe), 1.41 (3H, s, *Me*CMe), 1.45 (9H, s, C*Me*$_3$), 2.26 (1H, dd, *J* 14.7, 5.5, C(2)*H*$_A$), 2.67 (1H, dd, *J* 14.7, 7.2, C(2)*H*$_B$), 3.61 (2H, d, *J* 13.8, N(C*H*$_A$H$_B$Ph)$_2$), 3.68-3.74 (2H, m, C(3)*H*, C(7)*H*$_A$), 3.69 (2H, d, *J* 13.8, N(CH$_A$*H*$_B$Ph)$_2$), 3.79 (1H, dd, *J* 8.2, 5.8, C(7)*H*$_B$), 4.04 (1H, app q, *J* 6.4, C(6)*H*), 4.18 (1H, app t, *J* 7.0, C(5)*H*), 4.41 (1H, dd, *J* 6.5, 5.3, C(4)*H*), 7.22-7.36 (10H, m, *Ph*). Further elution gave a 69:31 mixture of **325** and **326**, respectively, as a pale yellow oil (777 mg, 32%). Data for mixture: ν_{max} (film) 3028, 2984, 2935, 2881 (C–H), 1729 (C=O); *m/z* (ESI$^+$) 526 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{44}NO_6^+$ ([M+H]$^+$) requires 526.3163; found 526.3165. Data for **326**: δ_H (400 MHz, $CDCl_3$) 1.18 (3H, s, *Me*CMe), 1.34 (3H, s, *Me*CMe), 1.45 (3H, s, *Me*CMe), 1.47 (9H, s, C*Me*$_3$), 1.53 (3H, s, *Me*CMe), 2.33 (1H, dd, *J* 14.4, 10.1, C(2)*H*$_A$), 2.46 (1H, dd, *J* 14.4, 3.5, C(2)*H*$_B$), 3.72-3.80 (1H, m, C(3)*H*), 3.80-3.85 (1H, m, C(6)*H*), 3.86 (2H, d, *J* 13.1, N(C*H*$_A$H$_B$Ph)$_2$), 3.89-3.95 (1H, m, C(5)*H*) overlapping 3.92 (2H, d, *J* 13.1, N(CH$_A$*H*$_B$Ph)$_2$), 4.02-4.14 (2H, m, C(7)*H*$_2$), 4.37 (1H, dd, *J* 10.2, 5.2, C(4)*H*), 7.19-7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.3, 25.5, 26.6, 26.7 (4 × *Me*CMe), 28.2 (C*Me*$_3$), 37.4 (*C*(2)), 55.6 (*C*(3)), 54.9 (N(*C*H$_2$Ph)$_2$), 68.0 (*C*(7)), 73.1 (*C*(6)), 78.5 (*C*(5)), 79.6 (*C*(4)), 79.8 (*C*Me$_3$), 108.2, 109.2 (2 × Me*C*Me), 126.7 (*p-Ph*), 127.9, 129.6 (*o*,*m-Ph*), 140.3 (*i-Ph*), 170.5 (*C*(1)).

Method B: Following *General Procedure 1*, dibenzylamine (120 mg, 0.608 mmol) in Et_2O (4 mL), BuLi (2.5 M, 0.24 mL, 0.59 mmol) and **309** (100 mg, 0.305 mmol, >99:1 dr) in Et_2O (4 mL) at −20 ºC gave a 62:38 mixture of **325** and **326** respectively.

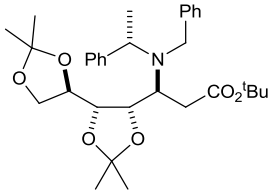
***tert*-Butyl (3*S*,4*S*,5*S*,6*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 327**



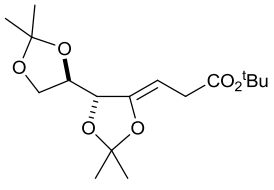
Method A: Following *General Procedure 1*, (*R*)-**123** (129 mg, 0.611 mmol) in THF (5 mL), BuLi (2.4 M, 0.25 mL, 0.59 mmol) and **309** (100 mg, 0.305 mmol, >99:1 dr) in THF (5 mL) at −78 ºC gave **327** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 10:1) gave **327** as a white solid (155 mg, 94%, >99:1 dr);[20] mp 65-75 ºC;[22] $[\alpha]_D^{25}$ −18.8 (*c* 1.0 in $CHCl_3$); {lit.[20] $[\alpha]_D^{25}$ −17.2 (*c* 1.0 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.25 (3H, s, *Me*CMe), 1.35 (3H, s, *Me*CMe), 1.36 (3H, s, *Me*CMe), 1.41 (3H, d, *J* 6.8, C(α)*Me*) overlapping 1.41 (9H, s, C*Me*$_3$), 1.48 (3H, s, *Me*CMe), 2.19 (1H, dd, *J* 15.4, 4.4, C(2)H_A), 2.47 (1H, dd, *J* 15.4, 8.2, C(2)H_B), 3.69 (1H, d, *J* 15.0, NCH_AH$_B$Ph), 3.85 (1H, dd, *J* 8.5, 6.1, C(7)H_A), 3.88 (1H, d, *J* 15.0, NCH$_A$$H_B$Ph), 3.99-4.05 (2H, m, C(5)*H*, C(7)H_B), 4.06-4.10 (1H, m, C(α)*H*), 4.11 (1H, app dd, *J* 8.5, 6.8, C(3)*H*), 4.22 (1H, app dt, *J* 8.4, 6.1, C(6)*H*), 4.31 (1H, dd, *J* 6.5, 3.1, C(4)*H*), 7.19-7.37 (10H, m, *Ph*).

Method B: Following *General Procedure 1*, (*R*)-**123** (129 mg, 0.611 mmol) in Et_2O (4 mL), BuLi (2.5 M, 0.24 mL, 0.59 mmol) and **309** (100 mg, 0.305 mmol, >99:1 dr) in Et_2O (4 mL) at −20 ºC gave a 97:3 mixture of **327** and **322** respectively (170 mg).

***tert*-Butyl (3*S*,4*S*,5*S*,6*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 329 and *tert*-butyl (*R*,*R*,*Z*)-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylidenehept-3-enoate 322**



329



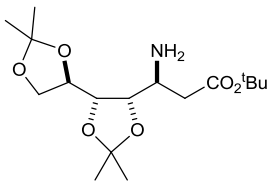
322

Method A: Following *General Procedure 1*, (*S*)-**123** (1.93 g, 9.14 mmol) in THF (60 mL), BuLi (2.0 M, 4.41 mL, 8.86 mmol) and **309** (1.50 g, 4.57 mmol, >99:1 dr) in THF (60 mL) at −78 ºC gave a 24:76 mixture of **329** and **322** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 10:1) gave **329** as a pale yellow solid (361 mg, 15%, >99:1 dr);[20] mp 110-118 ºC; $[\alpha]_D^{25}$ −27.1 (*c* 1.0 in $CHCl_3$); {lit.[20] $[\alpha]_D^{25}$ −24.6 (*c* 0.3 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.08 (3H, s, *Me*CMe), 1.31 (3H, s, *Me*CMe), 1.41 (3H, d, *J* 7.2, C(α)*Me*), 1.46 (3H, s, *Me*CMe), 1.56 (9H, s, C*Me*$_3$), 1.59 (3H, s, *Me*CMe), 2.23 (1H, dd, *J* 15.0, 3.5, C(2)H_A), 2.55 (1H, dd,

J 15.0, 9.4, C(2)H_B), 3.50 (1H, d, *J* 15.3, NCH_AH$_B$Ph), 3.63 (1H, dd, *J* 6.8, 2.3, C(4)*H*), 3.77-3.83 (2H, m, C(5)*H*, C(α)*H*), 3.85 (1H, dd, *J* 8.5, 6.4, C(7)H_A) 4.08 (1H, d, *J* 15.3, NCH$_A$$H_B$Ph), 4.12 (1H, dd, *J* 8.5, 6.1, C(7)H_B), 4.19-4.26 (1H, m, C(6)*H*), 4.31-4.37 (1H, m, C(3)*H*), 7.23-7.39 (8H, m, *Ph*), 7.47-7.52 (2H, m, *Ph*). Further elution gave **322** as a pale yellow oil (1.13 g, 75%, >99:1 dr);[20] $C_{17}H_{28}O_6$ requires C, 62.2; H, 8.6%; found C, 62.3; H, 8.5%; $[\alpha]_D^{25}$ +35.5 (*c* 1.0 in $CHCl_3$); {lit.[20] $[\alpha]_D^{25}$ +11.9 (*c* 0.2 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.37 (3H, s, *Me*CMe), 1.40 (3H, s, *Me*CMe), 1.45 (9H, s, C*Me*$_3$), 1.46 (3H, s, *Me*CMe), 1.50 (3H, s, *Me*CMe), 2.96-3.04 (1H, m, C(2)H_A), 3.06-3.13 (1H, m, C(2)H_B), 3.93 (1H, dd, *J* 8.5, 5.8, C(7)H_A), 4.06 (1H, dd, *J* 8.5, 6.5, C(7)H_B), 4.13 (1H, app q, *J* 6.1, C(6)*H*), 4.58-4.65 (2H, m, C(3)*H*, C(5)*H*).

Method B: Following *General Procedure 1*, (*S*)-**123** (129 mg, 0.611 mmol) in Et_2O (4 mL), BuLi (2.5 M, 0.24 mL, 0.59 mmol) and **309** (100 mg, 0.305 mmol, >99:1 dr) in Et_2O (4 mL) at –20 ºC gave a 70:30 mixture of **329** and **322** respectively (150 mg).

tert-Butyl (3*S*,4*S*,5*S*,6*R*)-3-amino-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 331

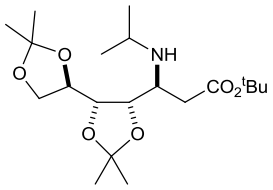


*Method A (From **327**):* Following *General Procedure 2*, **327** (270 mg, 0.500 mmol, >99:1 dr) in EtOAc (5 mL), $Pd(OH)_2$/C (50% w/w of substrate, 135 mg) and H_2 (1 atm) gave **331** as a pale yellow oil (167 mg, 97%, >99:1 dr);[20] $C_{17}H_{31}NO_6$ requires C, 59.1; H, 9.05; N, 4.05%; found C, 59.2; H, 9.0; N, 4.1%; $[\alpha]_D^{25}$ +25.0 (*c* 1.0 in $CHCl_3$); {lit.[20] $[\alpha]_D^{25}$ +25.9 (*c* 0.5 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.24 (3H, s, *Me*CMe), 1.29 (3H, s, *Me*CMe), 1.30 (3H, s, *Me*CMe), 1.35 (3H, s, *Me*CMe), 1.41 (9H, s, C*Me*$_3$), 1.94 (2H, br s, NH_2), 2.27 (1H, dd, *J* 16.2, 8.9, C(2)H_A), 2.67 (1H, dd, *J* 16.2, 3.4, C(2)H_B), 3.42 (1H, app td, *J* 9.2, 3.4, C(3)*H*), 3.84-3.92 (2H, m, C(4)*H*, C(7)H_A), 3.96 (1H, dd, *J* 9.2, 4.8, C(5)*H*), 4.03-4.14 (2H, m, C(6)*H*, C(7)H_B).

*Method B (From **329**):* Following *General Procedure 2*, **329** (196 mg, 0.363 mmol, >99:1 dr) in EtOAc (5 mL), $Pd(OH)_2$/C (50% w/w of substrate, 98 mg) and H_2 (1 atm) gave **331** as a pale yellow oil (125 mg, quant, >99:1 dr).

*Method C (From **325**):* Following *General Procedure 2*, **325** (214 mg, 0.407 mmol, >99:1 dr) in MeOH (5 mL), $Pd(OH)_2$/C (50% w/w of substrate, 107 mg) and H_2 (1 atm) gave **331** as a pale yellow oil (127 mg, 90%, >99:1 dr).

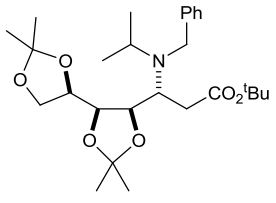
tert-Butyl (3*S*,4*S*,5*S*,6*R*)-3-*N*-isopropylamino-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 332



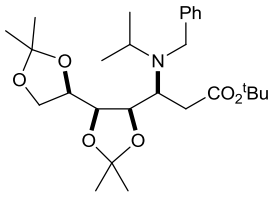
*Method A (From **323**):* Following *General Procedure 2*, **323** (200 mg, 0.418 mmol, >99:1 dr) in EtOAc (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 100 mg) and H_2 (1 atm) gave **332** as a colourless oil (161 mg, 99%, >99:1 dr);[20] $C_{20}H_{37}NO_6$ requires C, 62.0; H, 9.6; N, 3.6%; found C, 62.1; H, 9.7; N, 3.7%; $[\alpha]_D^{25}$ +22.7 (*c* 1.0 in $CHCl_3$); {lit.[20] $[\alpha]_D^{25}$ +12.3 (*c* 1.1 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.05 (3H, d, *J* 2.7, *Me*CHMe), 1.06 (3H, d, *J* 2.7, *Me*CHMe), 1.32 (3H, s, *Me*CMe), 1.36 (3H, s, *Me*CMe), 1.38 (3H, s, *Me*CMe), 1.42 (3H, s, *Me*CMe), 1.46 (9H, s, C*Me*$_3$), 1.61 (1H, br s, N*H*), 2.45 (1H, dd, *J* 15.2, 5.1, C(2)H_A), 2.54 (1H, dd, *J* 15.2, 4.8, C(2)H_B), 2.96 (1H, app septet, *J* 6.1, MeC*H*Me), 3.42-3.49 (1H, m, C(3)*H*), 3.90 (1H, dd, *J* 8.5, 6.5, C(7)H_A), 4.05-4.12 (2H, m, C(5)*H*, C(7)H_B), 4.16-4.21 (1H, m, C(4)*H*), 4.22-4.29 (1H, m, C(6)*H*).

*Method B (From **331**):* Following *General Procedure 3*, **331** (116 mg, 0.336 mmol, >99:1 dr) in MeOH (3 mL), acetone (49 μL, 0.67 mmol) and $NaBH_3CN$ (84 mg, 1.3 mmol) at rt gave an 84:16 mixture of **332**:**331** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/EtOAc, 4:1) gave **332** as a colourless oil (65 mg, 50%, >99:1 dr).

tert-Butyl (*R*,*R*,*R*,*R*)- and (3*S*,4*R*,5*R*,6*R*)-3-(*N*-benzyl-*N*-isopropylamino)-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 334 and 335



334



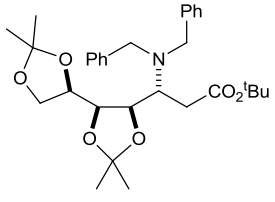
335

Method A: Following *General Procedure 1*, *N*-benzyl-*N*-isopropylamine (1.36 g, 9.14 mmol) in THF (60 mL), BuLi (2.5 M, 3.54 mL, 8.86 mmol) and **313** (1.50 g, 4.57 mmol, >99:1 dr) in THF (60 mL) at −78 ºC gave a 76:8:16 mixture of **334**, **335** and **333** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 4:1) gave an 83:17 mixture of **334** and **333**, respectively, as a pale yellow oil (1.50 g). Data for mixture: ν_{max} (film) 2981, 2936, 2886 (C–H), 1730 (C=O). Data for **334**: δ_H (400 MHz, $CDCl_3$) 1.05 (6H, d, *J* 6.6, 2 × *Me*CHMe), 1.32 (3H, s, *Me*CMe), 1.33 (3H, s, *Me*CMe), 1.43 (3H, s, *Me*CMe), 1.47 (3H, s, *Me*CMe), 1.49 (9H, s, C*Me*$_3$), 2.40 (1H, dd, *J* 15.4, 3.3, C(2)H_A), 2.59 (1H, dd, *J* 15.4, 8.6, C(2)H_B), 3.03-3.11 (1H, m, MeC*H*Me),

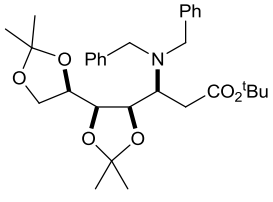
3.33-3.40 (1H, m, C(3)*H*), 3.51-3.57 (1H, m, C(7)H_A), 3.65 (1H, d, *J* 15.1, NC$H_A$$H_B$Ph), 3.89 (1H, d, *J* 15.1, NCH$_A$$H_B$Ph), 3.93-3.99 (1H, m, C(7)H_B), 4.02-4.07 (1H, m, C(5)*H*), 4.28 (1H, dd, *J* 7.3, 2.5, C(4)*H*), 4.29-4.36 (1H, m, C(6)*H*), 7.18-7.36 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.8, 21.6 (2 × *Me*CHMe), 24.8, 25.3, 26.3, 26.6 (4 × *Me*CMe), 28.2 (C*Me*$_3$), 36.9 (*C*(2)), 49.2 (Me*C*HMe), 49.6 (N*C*H$_2$Ph), 54.7 (*C*(3)), 66.2 (*C*(7)), 73.9 (*C*(6)), 78.6, 78.7 (*C*(4), *C*(5)), 80.1 (*C*Me$_3$), 108.8, 109.6 (2 × Me*C*Me), 126.7 (*p-Ph*), 128.1, 128.3 (*o*, *m-Ph*), 141.6 (*i-Ph*), 172.1 (*C*(1)); *m/z* (ESI$^+$) 478 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{44}NO_6^+$ ([M+H]$^+$) requires 478.3163; found 478.3164. Further elution gave a complex mixture containing **335** as the major product in >99:1 dr (164 mg). Data for mixture: ν_{max} (film) 2982, 2935, 2890 (C–H), 1731 (C=O). Data for **335**: δ_H (400 MHz, $CDCl_3$) 1.04 (3H, d, *J* 6.6, *Me*CHMe), 1.11 (3H, d, *J* 6.6, *Me*CHMe), 1.32 (3H, s, *Me*CMe), 1.39 (3H, s, *Me*CMe), 1.45 (9H, s, C*Me*$_3$), 1.53 (3H, s, *Me*CMe), 1.57 (3H, s, *Me*CMe), 1.89 (1H, dd, *J* 14.2, 2.5, C(2)H_A), 2.38 (1H, dd, *J* 14.2, 10.4, C(2)H_B), 3.10-3.21 (1H, m, Me*C*HMe), 3.67-3.79 (2H, m, C(3)*H*, C(7)H_A), 3.84 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 3.85-3.96 (2H, m, C(5)*H*, C(7)H_B) overlapping 3.92 (1H, d, *J* 14.8, NCH$_A$$H_B$Ph), 4.11-4.20 (2H, m, C(4)*H*, C(6)*H*), 7.17-7.44 (5H, m, *Ph*); δ_C (400 MHz, $CDCl_3$) 20.2, 22.6 (2 × *Me*CHMe), 25.3, 25.7, 26.6, 26.8 (4 × *Me*CMe), 28.2 (C*Me*$_3$), 39.0 (*C*(2)), 49.0 (Me*C*HMe), 49.5 (N*C*H$_2$Ph), 53.9 (*C*(3)), 66.2 (*C*(7)), 73.9 (*C*(4)), 75.8 (*C*(6)), 78.2 (*C*(5)), 80.4 (*C*Me$_3$), 108.8, 109.2 (2 × Me*C*Me), 126.3 (*p-Ph*), 127.8, 129.0 (*o*,*m-Ph*), 142.2 (*i-Ph*), 170.6 (*C*(1)); *m/z* (ESI$^+$) 478 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{44}NO_6^+$ ([M+H]$^+$) requires 478.3163; found 478.3163.

Method B: Following *General Procedure 1*, *N*-benzyl-*N*-isopropylamine (91 mg, 0.61 mmol) in Et_2O (4 mL), BuLi (2.5 M, 0.24 mL, 0.59 mmol) and **313** (100 mg, 0.305 mmol, >99:1 dr) in Et_2O (4 mL) at –20 ºC gave an 81:19 mixture of **334** and **335** respectively.

tert-Butyl (*R*,*R*,*R*,*R*)- and (3*S*,4*R*,5*R*,6*R*)-3-(*N*,*N*-dibenzylamino)-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 336 and 337



336



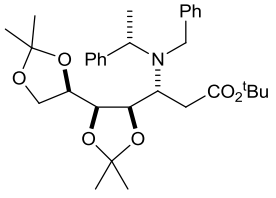
337

Method A: Following *General Procedure 1*, dibenzylamine (1.80 g, 9.14 mmol) in THF (60 mL), BuLi (2.5 M, 3.54 mL, 8.86 mmol) and **313** (1.50 g, 4.57 mmol, >99:1 dr) in THF (60 mL) at –78 ºC gave a 50:50 mixture of **336** and **337** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 4:1) gave **336** as a white solid (964 mg, 40%, >99:1 dr); mp 55-62 ºC;

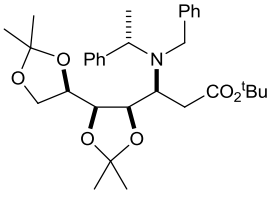
$[\alpha]_D^{25}$ +26.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3028, 2982, 2935, 2887 (C–H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.26 (3H, s, *Me*CMe), 1.37 (3H, s, *Me*CMe), 1.43 (3H, s, *Me*CMe), 1.51 (3H, s, *Me*CMe), 1.53 (9H, s, C*Me*$_3$), 2.43 (1H, dd, *J* 15.4, 3.5, C(2)H_A), 2.70 (1H, dd, *J* 15.4, 8.3, C(2)H_B), 3.26-3.32 (1H, m, C(3)*H*), 3.32-3.37 (1H, m, C(7)H_A), 3.54 (1H, dd, *J* 8.1, 6.3, C(7)H_B), 3.62 (2H, d, *J* 14.2, N(CH_AH$_B$Ph)$_2$), 3.79 (2H, d, *J* 14.2, N(CH$_A$$H_B$Ph)$_2$), 4.09-4.20 (2H, m, C(5)*H*, C(6)*H*), 4.45 (1H, dd, *J* 6.8, 2.8, C(4)*H*), 7.22-7.38 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 24.8, 25.2, 26.3, 26.7 (4 × *Me*CMe), 28.2 (C*Me*$_3$), 35.0 (*C*(2)), 54.6 (N(*C*H$_2$Ph)$_2$), 55.7 (*C*(3)), 65.9 (*C*(7)), 73.8 (*C*(6)), 76.1 (*C*(4)), 79.1 (*C*(5)), 80.3 (*C*Me$_3$), 109.1, 109.6 (2 × Me*C*Me), 127.2 (*p-Ph*), 128.3, 129.0 (*o,m-Ph*), 139.6 (*i-Ph*), 171.8 (*C*(1)); *m/z* (ESI$^+$) 526 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{44}NO_6^+$ ([M+H]$^+$) requires 526.3163; found 526.3163. Further elution gave **337** as a white solid (799 mg, 33%, >99:1 dr); $C_{31}H_{43}NO_6$ requires C, 70.8; H, 8.2; N, 2.7%; found C, 70.9; H, 8.4; N, 2.45%; mp 122-124 ºC; $[\alpha]_D^{25}$ –29.9 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3062, 3027, 2982, 2934, 2891 (C–H), 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, s, *Me*CMe), 1.43 (9H, s, C*Me*$_3$), 1.44 (3H, s, *Me*CMe), 1.46 (3H, s, *Me*CMe), 1.61 (3H, s, *Me*CMe), 2.06 (1H, dd, *J* 14.4, 4.3, C(2)H_A), 2.53 (1H, dd, *J* 14.4, 9.1, C(2)H_B), 3.51-3.56 (1H, m, C(7)H_A), 3.56-3.63 (2H, m, C(3)*H*, C(7)H_B), 3.72 (2H, d, *J* 13.3, N(CH_AH$_B$Ph)$_2$), 3.95 (2H, d, *J* 13.3, N(CH$_A$$H_B$Ph)$_2$), 4.00 (1H, dd, *J* 6.3, 4.6, C(5)*H*), 4.20-4.27 (1H, m, C(6)*H*), 4.32 (1H, dd, *J* 8.6, 6.3, C(4)*H*), 7.19-7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.2, 25.5, 26.7, 26.8 (4 × *Me*CMe), 28.1 (C*Me*$_3$), 36.6 (*C*(2)), 53.7 (*C*(3)), 54.7 (N(*C*H$_2$Ph)$_2$), 65.9 (*C*(7)), 73.8 (*C*(6)), 76.7 (*C*(5)), 79.0 (*C*(4)), 80.5 (*C*Me$_3$), 109.0, 109.3 (2 × Me*C*Me), 126.8 (*p-Ph*), 128.0, 129.7 (*o,m-Ph*), 140.0 (*i-Ph*), 170.5 (*C*(1)); *m/z* (ESI$^+$) 526 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{44}NO_6^+$ ([M+H]$^+$) requires 526.3163; found 526.3161.

Method B: Following *General Procedure 1*, dibenzylamine (120 g, 0.608 mmol) in Et_2O (4 mL), BuLi (2.5 M, 0.24 mL, 0.59 mmol) and **313** (100 mg, 0.305 mmol, >99:1 dr) in Et_2O (4 mL) at –20 ºC gave a complex mixture containing a 50:50 mixture of **336** and **337** respectively.

tert-Butyl (3*R*,4*R*,5*R*,6*R*,α*S*)- and (3*S*,4*R*,5*R*,6*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 338 and 339



338



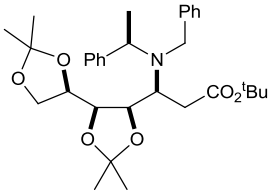
339

Method A: Following *General Procedure 1,* (*S*)-**123** (1.93 g, 9.14 mmol) in THF (60 mL), BuLi (2.5 M, 3.54 mL, 8.86 mmol) and **313** (1.50 g, 4.57 mmol, >99:1 dr) in THF (60 mL) at –78 ºC gave

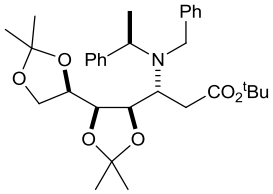
a 71:21:8 mixture of **338**, **339** and **333** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 4:1) gave an 86:14 mixture of **338** and **333**, respectively, as a pale yellow oil (1.42 g). Data for mixture: ν_{max} (film) 3062, 3027, 2982, 2936, 2886 (C–H), 1728 (C=O). Data for **338**: δ_H (400 MHz, $CDCl_3$) 1.30 (3H, s, *Me*CMe), 1.33 (3H, s, *Me*CMe), 1.40 (3H, d, *J* 6.6, C(α)*Me*), 1.43 (3H, s, *Me*CMe), 1.46 (3H, s, *Me*CMe), 1.48 (9H, s, C*Me*$_3$), 2.41 (1H, dd, *J* 15.8, 2.8, C(2)H_A), 2.58 (1H, dd, *J* 15.8, 8.3, C(2)H_B), 3.33-3.43 (2H, m, C(3)*H*, C(7)H_A), 3.63-3.69 (1H, m, C(7)H_B), 3.80 (1H, d, *J* 15.8, NCH_AH$_B$Ph), 3.85 (1H, d, *J* 15.8, NCH$_A$$H_B$Ph), 4.04-4.11 (1H, m, C(5)*H*), 4.16 (1H, q, *J* 6.6, C(α)*H*), 4.20-4.26 (1H, m, C(6)*H*), 4.38-4.44 (1H, m, C(4)*H*), 7.17-7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.3 (C(α)*Me*), 24.6, 25.3, 26.3, 26.7 (4 × *Me*CMe), 28.2 (C*Me*$_3$), 36.1 (*C*(2)), 50.3 (N*C*H$_2$Ph), 55.7 (*C*(3)), 58.0 (*C*(α)), 65.9 (*C*(7)), 73.8 (*C*(6)), 77.7 (*C*(4)), 78.9 (*C*(5)), 80.0 (*C*Me$_3$), 108.8, 109.5 (2 × Me*C*Me), 126.8, 126.9 (*p-Ph*), 128.0, 128.1, 128.2, 128.3 (*o,m-Ph*), 141.4, 144.7 (*i-Ph*), 171.7 (*C*(1)); *m/z* (ESI$^+$) 540 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{46}NO_6^+$ ([M+H]$^+$) requires 540.3320; found 540.3320. Further elution gave **339** as a pale yellow oil (527 mg, 21%, >99:1 dr); $[\alpha]_D^{25}$ –27.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2982, 2933, 2889 (C–H), 1729 (C=O); δ_H (400 MHz, $CDCl_3$) 1.20 (3H, s, *Me*CMe), 1.21 (3H, d, *J* 6.8, C(α)*Me*), 1.37 (3H, s, *Me*CMe), 1.41 (3H, s, *Me*CMe), 1.51 (9H, s, C*Me*$_3$), 1.57 (3H, s, *Me*CMe), 1.86 (1H, dd, *J* 14.9, 2.3, C(2)H_A), 2.38 (1H, dd, *J* 14.9, 9.9, C(2)H_B), 3.51-3.57 (1H, m, C(7)H_A), 3.61-3.67 (1H, m, C(7)H_B), 3.70 (1H, app dd, *J* 10.0, 2.3, C(3)*H*), 3.85-3.91 (1H, m, C(5)*H*) overlapping 3.88 (1H, d, *J* 15.5, NCH_AH$_B$Ph), 3.96-4.02 (1H, m, C(6)*H*), 4.08 (1H, d, *J* 15.5, NCH$_A$$H_B$Ph), 4.19 (1H, dd, *J* 10.0, 5.8, C(4)*H*), 4.40 (1H, q, *J* 6.8, C(α)*H*), 7.19-7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 21.9 (C(α)*Me*), 25.3, 25.5, 26.6, 27.2 (4 × *Me*CMe), 28.2 (C*Me*$_3$), 38.8 (*C*(2)), 50.0 (N*C*H$_2$Ph), 54.5 (*C*(3)), 62.6 (*C*(α)), 66.1 (*C*(7)), 73.9 (*C*(6)), 76.8 (*C*(5)), 78.5 (*C*(4)), 80.6 (*C*Me$_3$), 108.8, 109.0 (2 × Me*C*Me), 126.3, 126.6 (*p-Ph*), 127.9, 128.0, 128.1, 128.6 (*o,m-Ph*), 143.2, 145.4 (*i-Ph*), 170.4 (*C*(1)); *m/z* (ESI$^+$) 540 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{46}NO_6^+$ ([M+H]$^+$) requires 540.3320; found 540.3313.

Method B: Following *General Procedure 1*, (*S*)-**123** (129 mg, 0.611 mmol) in Et_2O (4 mL), BuLi (2.5 M, 0.24 mL, 0.59 mmol) and **313** (100 mg, 0.305 mmol, >99:1 dr) in Et_2O (4 mL) at –20 ºC gave a 42:52:6 mixture of **338**, **339** and **333** respectively.

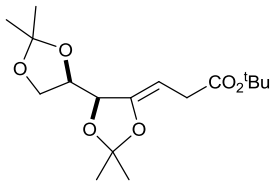
tert-Butyl (3*S*,4*R*,5*R*,6*R*,α*R*)- and (*R*,*R*,*R*,*R*,*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 341 and 340 and (5*S*,6*R*,*Z*)-_tert_-butyl 4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylidenehept-3-enoate 333



341



340



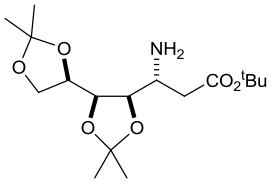
333

Method A: Following *General Procedure 1*, (*R*)-**123** (1.93 g, 9.14 mmol) in Et_2O (60 mL), BuLi (2.5 M, 3.54 mL, 8.86 mmol) and **313** (1.50 g, 4.57 mmol, >99:1 dr) in Et_2O (60 mL) at –20 ºC gave a 66:34 mixture of **340** and **341** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 4:1) gave **340** as a white solid (1.04 g, 42%, >99:1 dr); $C_{32}H_{45}NO_6$ requires C, 71.2; H, 8.4; N, 2.6%; found C, 71.2; H, 8.4; N, 2.6%; $[\alpha]_D^{25}$ +44.2 (*c* 1.0 in $CHCl_3$); mp 86-91 ºC; ν_{max} (film) 2981, 2934, 2888 (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.22 (3H, s, *Me*CMe), 1.34 (3H, s, *Me*CMe) overlapping 1.34 (3H, d, *J* 6.8, C(α)*Me*), 1.42 (3H, s, *Me*CMe), 1.44 (3H, s, *Me*CMe), 1.56 (9H, s, C*Me*$_3$), 2.45-2.60 (2H, m, C(2)*H*$_2$), 3.33 (1H, app t, *J* 7.8, C(7)*H*$_A$), 3.51-3.58 (1H, m, C(3)*H*), 3.69 (1H, d, *J* 15.2, NC*H*$_A$H$_B$Ph), 3.71-3.80 (2H, m, C(5)*H*, C(7)*H*$_B$), 3.89 (1H, dd, *J* 7.3, 2.3, C(4)*H*), 3.97 (1H, q, *J* 6.8, C(α)*H*), 4.08 (1H, d, *J* 15.2, NCH$_A$*H*$_B$Ph), 4.16-4.23 (1H, m, C(6)*H*), 7.21-7.45 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.6 (C(α)*Me*), 24.7, 25.5, 26.4, 26.6 (4 × *Me*CMe), 28.2 (C*Me*$_3$), 36.4 (*C*(2)), 50.9 (N*C*H$_2$Ph), 54.4 (*C*(3)), 58.9 (*C*(α)), 66.0 (*C*(7)), 73.8 (*C*(6)), 77.9, 78.2 (*C*(4), *C*(5)), 80.2 (*C*Me$_3$), 108.6, 109.5 (2 × Me*C*Me), 126.7, 127.3 (*p-Ph*), 127.9, 128.2, 128.3, 128.4 (*o,m-Ph*), 141.9, 143.3 (*i-Ph*), 172.1 (*C*(1)); *m/z* (ESI$^+$) 540 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{45}NNaO_6^+$ ([M+Na]$^+$) requires 562.3139; found 562.3137. Further elution gave **341** as a white solid (384 mg, 16%, 91:9 dr); mp 105-115 ºC; ν_{max} (film) 2982, 2935, 2891 (C–H), 1731 (C=O); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, s, *Me*CMe), 1.46 (3H, s, *Me*CMe), 1.48 (3H, s, *Me*CMe), 1.49 (9H, s, C*Me*$_3$), 1.55 (3H, d, *J* 6.7, C(α)*Me*), 1.64 (3H, s, *Me*CMe), 1.85 (1H, dd, *J* 14.9, 2.0, C(2)*H*$_A$), 2.34 (1H, dd, *J* 14.9, 10.1, C(2)*H*$_B$), 3.73-3.80 (1H, m, C(7)*H*$_A$), 3.81 (1H, d, *J* 14.2, NC*H*$_A$H$_B$Ph), 3.89-3.93 (1H, m, C(7)*H*$_B$), 3.95 (1H, d, *J* 14.2, NCH$_A$*H*$_B$Ph), 3.96-4.00 (1H, m, C(5)*H*), 4.07 (1H, app td, *J* 10.1, 2.0, C(3)*H*), 4.12-4.18 (1H, m, C(6)*H*), 4.25 (1H, q, *J* 6.7, C(α)*H*), 4.40 (1H, dd, *J* 10.1, 5.8, C(4)*H*), 7.11-7.49 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.7 (C(α)*Me*), 25.5, 25.8, 26.7, 26.9 (4 × *Me*CMe), 28.2 (C*Me*$_3$), 38.3 (*C*(2)), 51.4 (N*C*H$_2$Ph), 53.4 (*C*(3)), 65.9 (*C*(α)), 66.2 (*C*(7)), 73.8 (*C*(6)), 75.7 (*C*(5)), 78.5 (*C*(4)), 80.4 (*C*Me$_3$), 108.9, 109.4 (2 × Me*C*Me), 126.3, 126.3 (*p-Ph*), 127.7, 127.7, 128.1, 129.2 (*o,m-Ph*), 141.6, 146.5 (*i-Ph*),

170.5 (*C*(1)); *m/z* (ESI$^+$) 540 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{45}NNaO_6^+$ ([M+Na]$^+$) requires 562.3139; found 562.3140.

Method B: Following *General Procedure 1*, (*R*)-**123** (1.93 g, 9.14 mmol) in THF (60 mL), BuLi (2.5 M, 3.54 mL, 8.86 mmol) and **313** (1.50 g, 4.57 mmol, >99:1 dr) in THF (60 mL) at −78 ºC gave a 62:15:23 mixture of **333**, **340** and **341** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 6:1) gave an 88:12 mixture of **333** and **340**, respectively, as a pale yellow oil (746 mg). Data for mixture: ν_{max} (film) 2983, 2936, 2888 (C–H), 1732 (C=O), 1642 (C=C); *m/z* (ESI$^+$) 351 ([M(**333**)+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{28}NaO_6^+$ ([M(**333**)+Na]$^+$) requires 351.1778; found 351.1777. Data for **333**: δ_H (400 MHz, $CDCl_3$) 1.38 (3H, s, *Me*CMe), 1.40 (3H, s, *Me*CMe), 1.44 (12H, app s, C*Me*$_3$, *Me*CMe), 1.54 (3H, s, *Me*CMe), 3.02 (1H, dd, *J* 17.8, 6.6, C(2)H_A), 3.10 (1H, dd, *J* 17.8, 7.3, C(2)H_B), 3.80-3.85 (1H, m, C(7)H_A), 4.07-4.13 (1H, m, C(7)H_B), 4.16-4.22 (1H, m, C(6)*H*), 4.40-4.46 (1H, m, C(3)*H*), 4.60-4.64 (1H, m, C(5)*H*); δ_C (100 MHz, $CDCl_3$) 25.5, 25.6, 26.4, 26.6 (4 × *Me*CMe), 28.1 (C*Me*$_3$), 32.2 (*C*(2)), 65.8 (*C*(7)), 77.0 (*C*(6)), 77.6 (*C*(5)), 80.4 (*C*Me$_3$), 89.3 (*C*(3)), 109.8, 111.5 (2 × Me*C*Me), 150.4 (*C*(4)), 171.4 (*C*(1)).

tert-Butyl (*R*,*R*,*R*,*R*)-3-amino-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 342

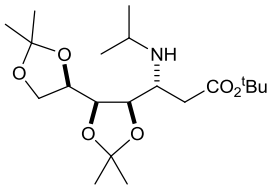


*Method A (From **336**):* Following *General Procedure 2*, **336** (199 mg, 0.379 mmol, >99:1 dr) in EtOAc (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 100 mg) and H_2 (1 atm) gave **342** as a pale yellow oil (109 mg, 83%, >99:1 dr); $[\alpha]_D^{25}$ +1.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3388, 3319 (N–H), 2983, 2936 (C–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, s, *Me*CMe), 1.30 (3H, s, *Me*CMe), 1.39 (12H, app s, *Me*CMe, C*Me*$_3$), 1.41 (3H, s, *Me*CMe), 2.13 (1H, dd, *J* 16.2, 9.1, C(2)H_A), 2.72 (1H, dd, *J* 16.2, 2.8, C(2)H_B), 3.17-3.27 (1H, m, C(3)*H*), 3.72-3.80 (2H, m, C(4)*H*, C(7)H_A), 4.05-4.11 (2H, m, C(5)*H*, C(7)H_B), 4.32-4.39 (1H, m, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 25.2, 25.5, 26.6, 27.3 (4 × *Me*CMe), 28.1 (C*Me*$_3$), 42.0 (*C*(2)), 48.1 (*C*(3)), 67.0 (*C*(7)), 74.2 (*C*(6)), 78.0 (*C*(5)), 79.8 (*C*(4)), 80.6 (*C*Me$_3$), 108.6, 109.4 (2 × Me*C*Me), 171.7 (*C*(1)); *m/z* (ESI$^+$) 346 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{32}NO_6^+$ ([M+H]$^+$) requires 346.2224; found 346.2231.

*Method B (From **338**):* Following *General Procedure 2*, **338** (188 mg, 0.348 mmol, >99:1 dr) in EtOAc (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 94 mg) and H_2 (1 atm) gave **342** as a pale yellow oil (92 mg, 76%, >99:1 dr).

*Method C (From **340**):* Following *General Procedure 2*, **340** (212 mg, 0.393 mmol, >99:1 dr) in EtOAc (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 106 mg) and H_2 (1 atm) gave **342** as a pale yellow oil (84 mg, 62%, >99:1 dr).

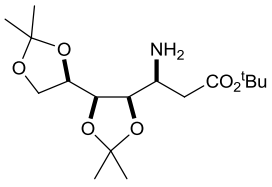
tert-Butyl (*R*,*R*,*R*,*R*)-3-*N*-isopropylamino-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 343



*Method A (From **342**):* Following *General Procedure 3*, **342** (102 mg, 0.295 mmol, >99:1 dr) in MeOH (3 mL), acetone (43 µL, 0.59 mmol) and $NaBH_3CN$ (74 mg, 1.2 mmol) at rt gave **343** as a pale yellow oil (90 mg, 79%, >99:1 dr); $[\alpha]_D^{25}$ –8.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2981, 2935, 2888 (C–H), 1720 (C=O); δ_H (400 MHz, $CDCl_3$) 0.99 (3H, d, *J* 6.1, *Me*CHMe), 1.01 (3H, d, *J* 6.5, *Me*CHMe), 1.33 (6H, app s, 2 × *Me*CMe), 1.42 (9H, s, C*Me*$_3$), 1.43 (3H, s, *Me*CMe), 1.44 (3H, s, *Me*CMe), 2.47 (1H, dd, *J* 16.0, 4.1, C(2)H_A), 2.64 (1H, dd, *J* 16.0, 4.1, C(2)H_B), 2.89-3.01 (1H, m, MeC*H*Me), 3.15-3.24 (1H, m, C(3)*H*), 3.70-3.76 (1H, m, C(7)H_A), 3.99 (1H, dd, *J* 8.9, 5.8, C(4)*H*), 4.06-4.11 (1H, m, C(5)*H*), 4.14 (1H, dd, *J* 8.2, 6.8, C(7)H_B), 4.42 (1H, app q, *J* 6.5, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 21.4, 24.2 (2 × *Me*CHMe), 25.2, 25.5, 26.7, 27.2 (4 × *Me*CMe), 28.1 (C*Me*$_3$), 34.9 (*C*(2)), 44.9 (Me*C*HMe), 51.3 (*C*(3)), 67.1 (*C*(7)), 74.0 (*C*(6)), 77.7 (*C*(4)), 78.2 (*C*(5)), 80.6 (*C*Me$_3$), 108.5, 109.4 (2 × Me*C*Me), 171.1 (*C*(1)); *m/z* (ESI^+) 388 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{38}NO_6^+$ ($[M+H]^+$) requires 388.2694; found 388.2695.

*Method B (From **334**):* Following *General Procedure 2*, **334** (205 mg, 0.429 mmol, >99:1 dr) in EtOAc (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 103 mg) and H_2 (1 atm) gave **343** as a pale yellow oil (148 mg, 89%, >99:1 dr).

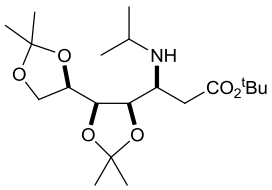
tert-Butyl (3*S*,4*R*,5*R*,6*R*)-3-amino-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 344



Following *General Procedure 2*, **337** (203 mg, 0.386 mmol, >99:1 dr) in EtOAc (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 102 mg) and H_2 (1 atm) gave **344** as a pale yellow oil (112 mg, 84%, >99:1 dr); $C_{17}H_{31}NO_6$ requires C, 59.1; H, 9.05; N, 4.05%; found C, 59.3; H, 8.9; N, 4.0%;

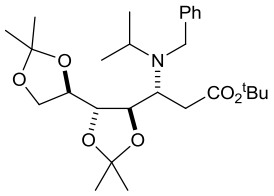
$[\alpha]_D^{25}$ +1.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3389, 3322 (N–H), 2983, 2936, 2891 (C–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.30 (6H, app s, 2 × *Me*CMe), 1.38 (12H, app s, *Me*CMe, C*Me*$_3$), 1.46 (3H, s, *Me*CMe), 2.26 (1H, dd, *J* 15.9, 8.1, C(2)H_A), 2.34 (1H, dd, *J* 15.9, 5.1, C(2)H_B), 3.10-3.17 (1H, m, C(3)*H*), 3.64-3.70 (1H, m, C(7)H_A), 3.95 (1H, dd, *J* 6.8, 3.8, C(4)*H*), 4.03-4.08 (2H, m, C(5)*H*, C(7)H_B), 4.40-4.47 (1H, app q, *J* 6.6, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 24.9, 25.3, 26.5, 26.6 (4 × *Me*CMe), 28.1 (C*Me*$_3$), 42.2 (*C*(2)), 48.2 (*C*(3)), 66.3 (*C*(7)), 74.3 (*C*(6)), 78.0 (*C*(5)), 78.9 (*C*(4)), 80.7 (*C*Me$_3$), 108.7, 109.5 (2 × Me*C*Me), 171.1 (*C*(1)); *m/z* (ESI^+) 346 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{17}H_{32}NO_6^+$ ($[M+H]^+$) requires 346.2224; found 346.2223.

tert-Butyl (3*S*,4*R*,5*R*,6*R*)-3-*N*-isopropylamino-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 345

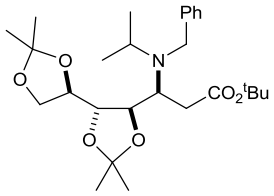


Following *General Procedure 3*, **344** (106 mg, 0.307 mmol, >99:1 dr) in MeOH (3 mL), acetone (45 µL, 0.61 mmol) and $NaBH_3CN$ (77 mg, 1.2 mmol) were reacted at rt. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 2:1) gave **345** as a pale yellow oil (64 mg, 53%, >99:1 dr); $[\alpha]_D^{25}$ +35.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3347 (N–H), 2981, 2936, 2888 (C–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 0.97 (3H, d, *J* 6.1, *Me*CHMe), 1.02 (3H, d, *J* 6.1, *Me*CHMe), 1.33 (6H, app s, 2 × *Me*CMe), 1.41 (9H, s, C*Me*$_3$), 1.44 (3H, s, *Me*CMe), 1.47 (3H, s, *Me*CMe), 2.30 (1H, dd, *J* 15.4, 8.1, C(2)H_A), 2.48 (1H, dd, *J* 15.4, 4.0, C(2)H_B), 2.85 (1H, app septet, *J* 6.1, MeC*H*Me), 2.96-3.03 (1H, m, C(3)*H*), 3.64-3.70 (1H, m C(7)H_A), 4.08-4.15 (3H, m, C(4)*H*, C(5)*H*, C(7)H_B), 4.75-4.84 (1H, m, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 21.6, 24.4 (2 × *Me*CHMe), 24.5, 25.0, 26.6, 26.8 (4 × *Me*CMe), 28.1 (C*Me*$_3$), 37.8 (*C*(2)), 44.4 (Me*C*HMe), 51.1 (*C*(3)), 66.1 (*C*(7)), 74.5 (*C*(6)), 78.3, 79.4 (*C*(4), *C*(5)), 80.5 (*C*Me$_3$), 108.6, 109.2 (2 × Me*C*Me), 171.6 (*C*(1)); *m/z* (ESI^+) 388 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{38}NO_6^+$ ($[M+H]^+$) requires 388.2694; found 388.2698.

***tert*-Butyl (3*R*,4*R*,5*S*,6*R*)- and (3*S*,4*R*,5*S*,6*R*)-3-(*N*-benzyl-*N*-isopropylamino)-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 346 and 347**



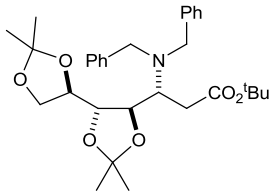
346



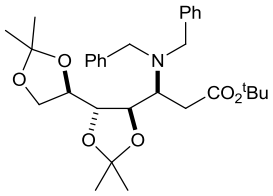
347

Following *General Procedure 1*, *N*-benzyl-*N*-isopropylamine (1.36 g, 9.14 mmol) in THF (60 mL), BuLi (2.1 M, 4.22 mL, 8.86 mmol) and **317** (1.50 g, 4.57 mmol, >99:1 dr) in THF (60 mL) at −78 ºC gave an 88:12 mixture of **346** and **347** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 6:1) gave an 88:12 mixture of **346** and **347**, respectively, as a colourless oil (1.86 g, 85%). Data for mixture: $C_{27}H_{43}NO_6$ requires C, 67.9; H, 9.1; N, 2.9%; found C, 67.8; H, 9.2; N, 2.9%; ν_{max} (film) 3027, 2982, 2934 (C–H), 1730 (C=O); *m/z* (ESI^+) 478 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{27}H_{44}NO_6^+$ ($[M+H]^+$) requires 478.3163; found 478.3166. Data for **346**: δ_H (400 MHz, $CDCl_3$) 1.04 (3H, d, *J* 6.8, *Me*CHMe), 1.05 (3H, d, *J* 6.8, *Me*CHMe), 1.35 (9H, app s, 3 × *Me*CMe), 1.41 (3H, s, *Me*CMe), 1.48 (9H, s, C*Me*$_3$), 2.32 (1H, dd, *J* 14.9, 3.8, C(2)H_A), 2.60 (1H, dd, *J* 14.9, 9.5, C(2)H_B), 2.98 (1H, app sept, *J* 6.8, MeC*H*Me), 3.57-3.62 (1H, m, C(5)*H*), 3.65 (1H, d, *J* 14.7, NCH_AH_BPh), 3.70 (1H, ddd, *J* 9.5, 3.8, 2.1, C(3)*H*), 3.91-3.95 (1H, m, C(7)H_A), 3.95 (1H, d, *J* 14.7, NCH$_A$$H_B$Ph), 4.05-4.14 (2H, m, C(6)*H*, C(7)H_B), 4.20 (1H, dd, *J* 7.9, 2.1, C(4)*H*), 7.18-7.41 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 18.5, 21.1 (2 × *Me*CHMe), 25.4, 26.8, 27.1, 27.2 (4 × *Me*CMe), 28.2 (C*Me*$_3$), 34.8 (*C*(2)), 48.3 (Me*C*HMe), 50.0 (N*C*H$_2$Ph), 54.7 (*C*(3)), 67.7 (*C*(7)), 77.6 (*C*(6)), 79.4 (*C*(5)), 79.8 (*C*Me$_3$), 81.9 (*C*(4)), 109.5, 109.6 (2 × Me*C*Me), 126.4 (*p-Ph*), 127.9, 128.6 (*o,m-Ph*), 141.6 (*i-Ph*), 172.2 (*C*(1)). Data for **347**: δ_H (400 MHz, $CDCl_3$) 1.01 (3H, d, *J* 6.6, *Me*CHMe), 1.09 (3H, d, *J* 6.6, *Me*CHMe), 1.27 (3H, s, *Me*CMe), 1.31 (3H, s, *Me*CMe), 1.38 (3H, s, *Me*CMe), 1.45 (3H, s, *Me*CMe), 1.49 (9H, s, C*Me*$_3$), 2.67 (1H, dd, *J* 14.3, 3.8, C(2)H_A), 2.76 (1H, dd, *J* 14.3, 9.6, C(2)H_B), 2.94-3.09 (1H, m, MeC*H*Me), 3.35-3.40 (1H, m, C(3)*H*), 3.57 (1H, d, *J* 14.9, NCH_AH_BPh), 3.78 (1H, app t, *J* 7.9, C(7)H_A), 3.90-3.96 (1H, m, C(6)*H*), 4.04 (1H, dd, *J* 7.9, 2.7, C(7)H_B), 4.08-4.12 (1H, m, C(4)*H*), 4.19 (1H, d, *J* 14.9, NCH$_A$$H_B$Ph), 4.30-4.35 (1H, m, C(5)*H*), 7.18-7.42 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.6, 22.6 (2 × *Me*CHMe), 25.5, 26.3, 26.3, 26.9 (4 × *Me*CMe), 28.1 (C*Me*$_3$), 36.5 (*C*(2)), 49.6 (Me*C*HMe), 52.0 (*C*(3)), 52.1 (N*C*H$_2$Ph), 67.7 (*C*(7)), 77.4, 77.5 (*C*(5), *C*(6)), 80.2 (*C*Me$_3$), 82.9 (*C*(4)), 108.7, 109.3 (2 × Me*C*Me), 126.5 (*p-Ph*), 128.1, 128.2 (*o,m-Ph*), 141.6 (*i-Ph*), 171.9 (*C*(1)).

***tert*-Butyl (3*R*,4*R*,5*S*,6*R*)- and (3*S*,4*R*,5*S*,6*R*)-3-(*N*,*N*-dibenzylamino)-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 348 and 349**



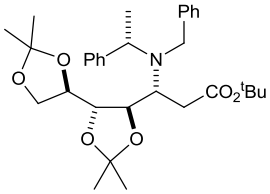
348



349

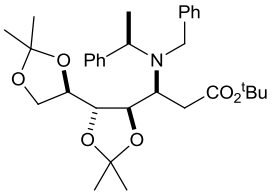
Following *General Procedure 1*, dibenzylamine (1.62 g, 8.22 mmol) in THF (60 mL), BuLi (2.1 M, 3.80 mL, 7.98 mmol) and **317** (1.35 g, 4.11 mmol, >99:1 dr) in THF (60 mL) at −78 ºC gave a 67:33 mixture of **348** and **349** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 6:1) gave a 67:33 mixture of **348** and **349**, respectively, as a colourless oil (2.07 g, 86%). Recrystallisation of an aliquot from 30-40 ºC petrol gave **348** as a white solid (>99:1 dr); $C_{31}H_{43}NO_6$ requires C, 70.8; H, 8.2; N, 2.7%; found C, 70.9; H, 8.3; N, 2.7%; mp 82-86 ºC; $[\alpha]_D^{25}$ +18.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2984, 2934, 2881 (C–H), 1729 (C=O); δ_H (400 MHz, $CDCl_3$) 1.15 (3H, s, *Me*CMe), 1.31 (3H, s, *Me*CMe), 1.35 (3H, s, *Me*CMe), 1.38 (3H, s, *Me*CMe), 1.45 (9H, s, C*Me*$_3$), 2.39 (1H, dd, *J* 14.8, 4.3, C(2)H_A), 2.69 (1H, dd, *J* 14.8, 8.8, C(2)H_B), 3.52-3.59 (2H, m, C(3)*H*, C(5)*H*), 3.62 (2H, d, *J* 14.2, N(CH_AH_BPh)$_2$), 3.77 (2H, d, *J* 14.2, N(CH_AH_BPh)$_2$), 3.86-3.93 (1H, m, C(7)H_A), 4.04-4.11 (2H, m, C(6)*H*, C(7)H_B), 4.37 (1H, dd, *J* 7.3, 2.0, C(4)*H*), 7.18-7.42 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.4, 26.5, 27.2, 27.3 (4 × *Me*CMe), 28.1 (C*Me*$_3$), 33.0 (*C*(2)), 54.5 (N(*C*H$_2$Ph)$_2$), 56.8 (*C*(3)), 67.5 (*C*(7)), 77.6 (*C*(6)), 79.0 (*C*(5)), 79.3 (*C*(4)), 80.2 (*C*Me$_3$), 109.7, 109.8 (2 × Me*C*Me), 126.8 (*p-Ph*), 128.0, 129.2 (*o,m-Ph*), 139.9 (*i-Ph*), 172.1 (*C*(1)); *m/z* (ESI$^+$) 526 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{44}NO_6^+$ ([M+H]$^+$) requires 526.3163; found 526.3172. Data for **349**: δ_H (400 MHz, $CDCl_3$) 1.27 (3H, s, *Me*CMe), 1.28 (3H, s, *Me*CMe), 1.36 (3H, s, *Me*CMe), 1.37 (3H, s, *Me*CMe), 1.50 (9H, s, C*Me*$_3$), 2.67 (1H, dd, *J* 14.3, 9.2, C(2)H_A), 2.75 (1H, dd, *J* 14.3, 4.4, C(2)H_B), 3.19-3.26 (1H, m, C(3)*H*), 3.38-3.44 (1H, m, C(7)H_A) overlapping 3.39 (2H, d, *J* 13.9, N(CH_AH_BPh)$_2$), 3.68-3.77 (2H, m, C(6)*H*, C(7)H_B), 4.00 (1H, dd, *J* 7.6, 3.0, C(4)*H*), 4.10 (2H, d, *J* 13.9, N(CH_AH_BPh)$_2$), 4.35-4.40 (1H, m, C(5)*H*), 7.18-7.42 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.4, 26.3, 26.4, 27.2 (4 × *Me*CMe), 28.1 (C*Me*$_3$), 32.8 (*C*(2)), 54.8 (*C*(3)), 55.8 (N(*C*H$_2$Ph)$_2$), 65.9 (*C*(7)), 76.2 (*C*(6)), 76.8 (*C*(5)), 80.6 (*C*Me$_3$), 80.8 (*C*(4)), 109.1, 109.8 (2 × Me*C*Me), 127.1 (*p-Ph*), 128.3, 129.3 (*o,m-Ph*), 139.8 (*i-Ph*), 171.9 (*C*(1)).

***tert*-Butyl (3*R*,4*R*,5*S*,6*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 350**

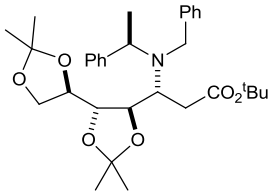


Following *General Procedure 1*, (*S*)-**123** (1.93 g, 9.14 mmol) in THF (60 mL), BuLi (2.1 M, 4.22 mL, 8.86 mmol) and **317** (1.50 g, 4.57 mmol, >99:1 dr) in THF (60 mL) at −78 ºC gave **350** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 10:1) gave **350** as a white solid (1.79 g, 73%, >99:1 dr); $C_{32}H_{45}NO_6$ requires C, 71.2; H, 8.4; N, 2.6%; found C, 71.1; H, 8.3; N, 2.7%; mp 53-58 ºC; $[\alpha]_D^{25}$ +23.5 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3028, 2983, 2934 (C–H), 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 1.36 (3H, s, *Me*CMe), 1.40 (3H, s, *Me*CMe), 1.42 (6H, app s, 2 × *Me*CMe), 1.46 (9H, s, C*Me*$_3$), 1.51 (3H, d, *J* 6.8, C(α)*Me*), 2.36 (1H, dd, *J* 15.4, 5.3, C(2)H_A), 2.43 (1H, dd, *J* 15.4, 7.1, C(2)H_B), 3.71-3.76 (1H, m, C(5)*H*), 3.79-3.83 (1H, m, C(3)*H*), 3.82 (1H, d, *J* 13.9, NCH_AH$_B$Ph), 3.86 (1H, d, *J* 13.9, NCH$_A$$H_B$Ph), 3.96 (1H, dd, *J* 7.8, 5.6, C(7)H_A), 4.08-4.21 (3H, m, C(6)*H*, C(7)H_B, C(α)*H*), 4.32 (1H, dd, *J* 7.3, 1.3, C(4)*H*), 7.21-7.47 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.6 (C(α)*Me*), 25.6, 26.6, 27.1, 27.2 (4 × *Me*CMe), 28.1 (C*Me*$_3$), 34.2 (*C*(2)), 50.8 (N*C*H$_2$Ph), 55.7 (*C*(3)), 57.2 (*C*(α)), 67.4 (*C*(7)), 77.6 (*C*(6)), 79.4 (*C*Me$_3$), 79.9 (*C*(5)), 81.6 (*C*(4)), 109.6, 109.8 (2 × Me*C*Me), 126.6, 126.7 (*p-Ph*), 127.9, 128.0, 128.3, 128.7 (*o,m-Ph*), 141.3, 143.9 (*i-Ph*), 171.8 (*C*(1)); *m/z* (ESI$^+$) 540 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{46}NO_6^+$ ([M+H]$^+$) requires 540.3320; found 540.3320.

***tert*-Butyl (3*S*,4*R*,5*S*,6*R*,α*R*)- and (3*R*,4*R*,5*S*,6*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 353 and 352**



353

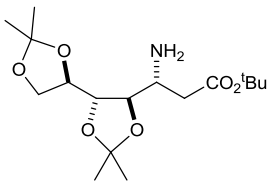


352

Following *General Procedure 1*, (*R*)-**123** (1.93 g, 9.14 mmol) in THF (60 mL), BuLi (2.1 M, 4.22 mL, 8.86 mmol) and **317** (1.50 g, 4.57 mmol, >99:1 dr) in THF (60 mL) at −78 ºC gave an 81:19 mixture of **353** and **352** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 10:1) gave an 85:15 mixture of **353** and **352**, respectively, as a colourless oil (1.49 g, 60%). Data for mixture: ν_{max} (film) 3027, 2983, 2935 (C–H), 1727 (C=O); *m/z* (ESI$^+$) 540 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{46}NO_6^+$ ([M+H]$^+$) requires 540.3320; found 540.3306. Data for

353: δ_H (400 MHz, $CDCl_3$) 1.30 (3H, s, *Me*CMe), 1.33 (3H, s, *Me*CMe), 1.42 (3H, d, *J* 7.1, C(α)*Me*), 1.44 (3H, s, *Me*CMe), 1.49 (9H, s, C*Me*$_3$), 1.51 (3H, s, *Me*CMe), 1.64 (1H, dd, *J* 14.8, 1.5, C(2)H_A), 2.46 (1H, dd, *J* 14.8, 11.4, C(2)H_B), 3.56 (1H, d, *J* 14.5, NCH_AH$_B$Ph), 3.69-3.76 (1H, m, C(3)*H*), 3.80 (1H, q, *J* 7.1, C(α)*H*), 3.91-3.96 (1H, m, C(7)H_A), 4.10 (1H, dd, *J* 7.3, 2.0, C(4)*H*), 4.11-4.16 (1H, m, C(5)*H*), 4.18-4.23 (1H, m, C(7)H_B), 4.38 (1H, d, *J* 14.5, NCH$_A$$H_B$Ph), 4.52-4.58 (1H, m, C(6)*H*), 7.22-7.58 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.0 (C(α)*Me*), 25.6, 26.3, 26.5, 27.0 (4 × *Me*CMe), 28.1 (C*Me*$_3$), 34.8 (*C*(2)), 50.9 (*C*(3)), 53.1 (NCH_2Ph), 57.3 (*C*(α)), 68.0 (*C*(7)), 77.5, 77.7 (*C*(5), *C*(6)), 80.1 (*C*Me$_3$), 83.0 (*C*(4)), 108.9, 109.6 (2 × Me*C*Me), 126.6, 127.2 (*p-Ph*), 128.1, 128.2, 128.2, 128.4 (*o,m-Ph*), 140.7, 141.4 (*i-Ph*), 171.5 (*C*(1)). Data for **352**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 1.22 (3H, s, *Me*CMe), 1.31 (3H, s, *Me*CMe), 1.39 (3H, s, *Me*CMe), 1.41 (3H, d, *J* 7.8, C(α)*Me*), 1.52 (3H, s, *Me*CMe), 1.56 (9H, s, C*Me*$_3$), 2.41-2.50 (1H, m, C(2)H_A), 2.67 (1H, dd, *J* 15.4, 8.3, C(2)H_B), 7.22-7.58 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 17.5 (C(α)*Me*), 25.5, 26.7, 27.0. 27.1 (4 × *Me*CMe), 28.2 (C*Me*$_3$), 34.8 (*C*(2)), 50.9 (NCH_2Ph), 54.2 (*C*(3)), 57.1 (*C*(α)), 67.2 (*C*(7)), 77.5 (*C*(6)), 79.0 (*C*(4)), 80.2 (*C*Me$_3$), 81.7 (*C*(5)), 109.2, 109.6 (2 × Me*C*Me), 126.6, 126.9 (*p-Ph*), 127.9, 128.4, 128.7 (*o,m-Ph*), 141.5, 143.2 (*i-Ph*), 172.2 (*C*(1)).

tert-Butyl (3*R*,4*R*,5*S*,6*R*)-3-amino-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate **354**

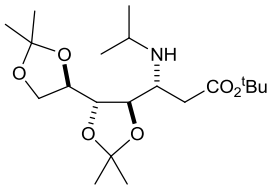


*Method A (From **350**):* Following *General Procedure 2*, **350** (200 mg, 0.371 mmol, >99:1 dr) in EtOAc (5 mL), $Pd(OH)_2$/C (50% w/w of substrate, 100 mg) and H_2 (1 atm) gave **354** as a pale yellow oil (130 mg, quant, >99:1 dr); $[\alpha]_D^{25}$ +18.3 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3326 (N–H), 2985, 2935, 2884 (C–H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (6H, app s, 2 × *Me*CMe), 1.31 (3H, s, *Me*CMe), 1.36 (3H, s, *Me*CMe), 1.40 (9H, s, C*Me*$_3$), 1.70 (2H, br s, NH_2), 2.21 (1H, dd, *J* 16.2, 9.5, C(2)H_A), 2.57 (1H, dd, *J* 16.2, 3.3, C(2)H_B), 3.26 (1H, ddd, *J* 9.5, 6.3, 3.3, C(3)*H*), 3.69-3.74 (1H, m, C(5)*H*), 3.75-3.80 (1H, m, C(4)*H*), 3.90 (1H, dd, *J* 8.2, 5.6, C(7)H_A), 3.98-4.02 (1H, m, C(6)*H*), 4.09 (1H, dd, *J* 8.2, 6.1, C(7)H_B); δ_C (100 MHz, $CDCl_3$) 25.2, 26.5, 27.0, 27.1 (4 × *Me*CMe), 28.1 (C*Me*$_3$), 39.7 (*C*(2)), 50.6 (*C*(3)), 67.8 (*C*(7)), 77.0 (*C*(6)), 80.1 (*C*(5)), 80.4 (*C*Me$_3$), 83.8 (*C*(4)),

109.1, 109.7 (2 × Me*C*Me), 171.8 (*C*(1)); *m/z* (ESI^+) 346 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{17}H_{32}NO_6^+$ ($[M+H]^+$) requires 346.2224; found 346.2225.

*Method B (From **348**):* Following *General Procedure 2*, **348** (194 mg, 0.369 mmol, >99:1 dr) in EtOAc (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 97 mg) and H_2 (1 atm) gave **354** as a pale yellow oil (108 mg, 85%, >99:1 dr).

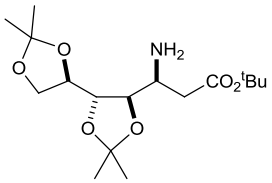
tert-Butyl (3*R*,4*R*,5*S*,6*R*)-3-*N*-isopropylamino-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 355



*Method A (From **354**):* Following *General Procedure 3*, **354** (82 mg, 0.24 mmol, >99:1 dr) in MeOH (3 mL), acetone (35 µL, 0.47 mmol) and $NaBH_3CN$ (60 mg, 0.95 mmol) at rt gave **355** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 5:1) gave **355** as a colourless oil (85 mg, 93%, >99:1 dr); $C_{20}H_{37}NO_6$ requires C, 62.0; H, 9.6; N, 3.6%; found C, 62.1; H, 9.5; N, 3.45%; $[\alpha]_D^{25}$ +7.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3326 (N–H), 2983, 2935, 2879 (C–H), 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 1.02 (6H, d, *J* 6.3, 2 × *Me*CHMe), 1.32 (3H, s, *Me*CMe), 1.33 (3H, s, *Me*CMe), 1.36 (3H, s, *Me*CMe), 1.42 (3H, s, *Me*CMe), 1.43 (9H, s, C*Me*$_3$), 2.31 (1H, dd, *J* 15.2, 7.3, C(2)H_A), 2.48 (1H, dd, *J* 15.2, 4.3, C(2)H_B), 2.87-2.98 (1H, m, MeC*H*Me), 3.21-3.26 (1H, m, C(3)*H*), 3.70-3.76 (1H, m, C(5)*H*), 3.91-4.00 (2H, m, C(4)*H*, C(7)H_A), 4.06-4.12 (2H, m, C(6)*H*, C(7)H_B); δ_C (100 MHz, $CDCl_3$) 23.1, 23.4 (2 × *Me*CHMe), 25.2, 26.7, 27.1, 27.2 (4 × *Me*CMe), 28.1 (C*Me*$_3$), 37.5 (*C*(2)), 45.7 (Me*C*HMe), 54.0 (*C*(3)), 67.4 (*C*(7)), 77.4 (*C*(6)), 79.4 (*C*(5)), 80.2 (*C*Me$_3$), 81.7 (*C*(4)), 109.5, 109.6 (2 × Me*C*Me), 171.9 (*C*(1)); *m/z* (ESI^+) 388 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{38}NO_6^+$ ($[M+H]^+$) requires 388.2694; found 388.2694.

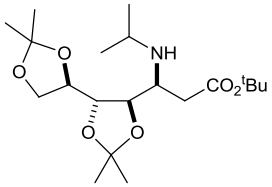
*Method B (From **346**):* Following *General Procedure 2*, **346** (218 mg, 0.456 mmol, 88:12 dr) in EtOAc (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 109 mg) and H_2 (1 atm) gave **355** as a colourless oil (169 mg, 96%, 88:12 dr).

tert-Butyl (3*S*,4*R*,5*S*,6*R*)-3-amino-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 356



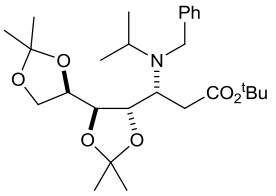
Following *General Procedure 2*, **353** (252 mg, 0.467 mmol, 85:15 dr) in EtOAc (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 126 mg) and H_2 (1 atm) gave **356** as a pale yellow oil (140 mg, 87%, 85:15 dr); ν_{max} (film) 3329 (N–H), 2985, 2935, 2881 (C–H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, s, *Me*CMe), 1.29 (3H, s, *Me*CMe), 1.34 (3H, s, *Me*CMe), 1.35 (3H, s, *Me*CMe), 1.40 (9H, s, C*Me*$_3$), 1.49 (2H, br s, N*H*$_2$), 2.29 (1H, dd, *J* 15.9, 9.6, C(2)*H*$_A$), 2.47 (1H, dd, *J* 15.9, 3.8, C(2)*H*$_B$), 3.23 (1H, app dt, *J* 9.6, 3.8, C(3)*H*), 3.80 (1H, dd, *J* 7.1, 3.8, C(4)*H*), 3.84-3.92 (2H, m, C(5)*H*, C(7)*H*$_A$), 3.96-4.01 (1H, m, C(6)*H*), 4.07 (1H, dd, *J* 8.3, 6.1, C(7)*H*$_B$); δ_C (100 MHz, $CDCl_3$) 25.3, 26.6, 27.1, 27.2 (4 × *Me*CMe), 28.1 (C*Me*$_3$), 41.9 (*C*(2)), 49.2 (*C*(3)), 67.8 (*C*(7)), 77.3 (*C*(6)), 78.0 (*C*(5)), 80.5 (*C*Me$_3$), 83.2 (*C*(4)), 109.2, 109.6 (2 × Me*C*Me), 171.5 (*C*(1)); *m/z* (ESI^+) 346 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{17}H_{32}NO_6^+$ ($[M+H]^+$) requires 346.2224; found 346.2224.

tert-Butyl (3*S*,4*R*,5*S*,6*R*)-3-*N*-isopropylamino-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 357



Following *General Procedure 3*, **356** (94 mg, 0.27 mmol, 85:15 dr) in MeOH (3 mL), acetone (40 µL, 0.54 mmol) and $NaBH_3CN$ (68 mg, 1.1 mmol) at rt gave **357** as a colourless oil (76 mg, 72%, 85:15 dr); ν_{max} (film) 3341 (N–H), 2983, 2935, 2878 (C–H), 1729 (C=O); δ_H (400 MHz, $CDCl_3$) 0.96 (3H, d, *J* 5.8, *Me*CHMe), 1.02 (3H, d, *J* 6.1, *Me*CHMe), 1.31 (3H, s, *Me*CMe), 1.32 (3H, s, *Me*CMe), 1.37 (3H, s, *Me*CMe), 1.38 (3H, s, *Me*CMe), 1.43 (9H, s, C*Me*$_3$), 2.39 (1H, dd, *J* 14.5, 6.3, C(2)*H*$_A$), 2.44 (1H, dd, *J* 14.5, 6.0, C(2)*H*$_B$), 2.86-2.97 (1H, m, MeC*H*Me), 3.23-3.28 (1H, m, C(3)*H*), 3.88-3.93 (1H, m, C(7)*H*$_A$), 3.96-4.01 (3H, m, C(4)*H*, C(5)*H*, C(6)*H*), 4.09-4.15 (1H, m, C(7)*H*$_B$); δ_C (100 MHz, $CDCl_3$) 22.4, 24.0 (2 × *Me*CHMe), 25.3, 26.6, 27.0, 27.1 (4 × *Me*CMe), 28.6 (C*Me*$_3$), 40.0 (*C*(2)), 45.1 (Me*C*HMe), 51.6 (*C*(3)), 67.9 (*C*(7)), 77.4, 77.7, 82.5 (*C*(4), *C*(5), *C*(6)), 80.3 (*C*Me$_3$), 109.0, 109.6 (2 × Me*C*Me), 171.6 (*C*(1)); *m/z* (ESI^+) 388 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{38}NO_6^+$ ($[M+H]^+$) requires 388.2694; found 388.2694.

***tert*-Butyl (3*R*,4*S*,5*R*,6*R*)- and (3*S*,4*S*,5*R*,6*R*)-3-(*N*-benzyl-*N*-isopropylamino)-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 359 and 358**



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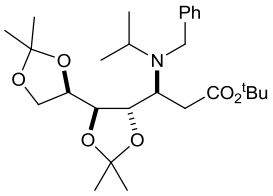
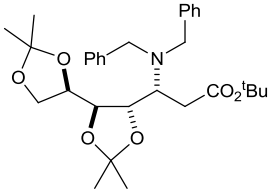


358

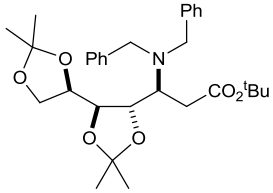
Following *General Procedure 1*, *N*-benzyl-*N*-isopropylamine (1.36 g, 9.14 mmol) in THF (60 mL), BuLi (2.5 M, 3.54 mL, 8.86 mmol) and **321** (1.50 g, 4.57 mmol, >99:1 dr) in THF (60 mL) at −78 ºC gave a 28:72 mixture of **359** and **358** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 10:1) gave **359** as a white solid (412 mg, 19%, >99:1 dr); $C_{27}H_{43}NO_6$ requires C, 67.9; H, 9.1; N, 2.9%; found C, 68.0; H, 9.1; N, 3.0%; mp 70-76 ºC; $[\alpha]_D^{25}$ −10.4 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 2982, 2936 (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.02 (3H, d, *J* 6.8, *Me*CHMe), 1.11 (3H, d, *J* 6.5, *Me*CHMe), 1.27 (3H, s, *Me*CMe), 1.30 (3H, s, *Me*CMe), 1.33 (3H, s, *Me*CMe), 1.34 (3H, s, *Me*CMe), 1.47 (9H, s, C*Me*$_3$), 2.68 (1H, dd, *J* 14.7, 9.2, C(2)H_A), 2.76 (1H, dd, *J* 14.7, 4.8, C(2)H_B), 3.08-3.15 (1H, m, C(3)*H*), 3.27-3.39 (2H, m, C(6)*H*, MeC*H*Me), 3.46 (1H, d, *J* 13.7, NCH_AH_BPh), 3.51-3.58 (1H, m, C(7)H_A), 3.71-3.77 (1H, m, C(7)H_B), 3.92-4.00 (2H, m, C(4)*H*, NCH$_A$$H_B$Ph), 4.03 (1H, dd, *J* 8.2, 3.1, C(5)*H*), 7.19-7.38 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 17.6, 23.2 (2 × *Me*CHMe), 25.9, 26.1, 26.2, 27.2 (4 × *Me*CMe), 28.0 (C*Me*$_3$), 35.9 (*C*(2)), 48.7 (Me*C*HMe), 50.9 (N*C*H$_2$Ph), 51.6 (*C*(3)), 65.8 (*C*(7)), 74.6 (*C*(6)), 76.1 (*C*(4)), 80.1 (*C*(5)), 80.7 (*C*Me$_3$), 108.5, 109.1 (2 × Me*C*Me), 126.7 (*p-Ph*), 128.1, 129.2 (*o,m-Ph*), 141.1 (*i-Ph*), 172.0 (*C*(1)); *m/z* (ESI$^+$) 478 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{44}NO_6^+$ ([M+H]$^+$) requires 478.3163; found 478.3158. Further elution gave **358** as a white solid (1.24 g, 57%, >99:1 dr); $C_{27}H_{43}NO_6$ requires C, 67.9; H, 9.1; N, 2.9%; found C, 68.0; H, 9.2; N, 2.9%; mp 94-100 ºC; $[\alpha]_D^{25}$ −28.5 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 2982, 2935 (C–H), 1729 (C=O); δ_H (400 MHz, $CDCl_3$) 1.05 (3H, d, *J* 6.1, *Me*CHMe), 1.07 (3H, d, *J* 6.1, *Me*CHMe), 1.34 (3H, s, *Me*CMe), 1.38 (3H, s, *Me*CMe), 1.41 (6H, app s, 2 × *Me*CMe), 1.48 (9H, s, C*Me*$_3$), 2.44 (1H, dd, *J* 15.4, 5.8, C(2)H_A), 2.61 (1H, dd, *J* 15.4, 6.1, C(2)H_B), 3.05 (1H, app septet, *J* 6.7, MeC*H*Me), 3.40 (1H, app q, *J* 5.6, C(3)*H*), 3.44 (1H, dd, *J* 8.1, 2.5, C(5)*H*), 3.67 (1H, d, *J* 14.2, NCH_AH_BPh), 3.71 (1H, d, *J* 14.2, NCH$_A$$H_B$Ph), 3.78-3.83 (1H, m, C(7)H_A), 3.88-3.93 (1H, m, C(7)H_B), 4.15-4.23 (2H, m, C(4)*H*, C(6)*H*), 7.20-7.37 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.3, 21.1 (2 × *Me*CHMe), 26.0, 26.1, 26.8, 27.3 (4 × *Me*CMe), 28.2 (C*Me*$_3$), 35.2 (*C*(2)), 47.9 (Me*C*HMe), 50.1 (N*C*H$_2$Ph), 55.2 (*C*(3)), 65.9 (*C*(7)), 75.4 (*C*(6)), 78.4 (*C*(4)), 79.3 (*C*(5)), 80.2 (*C*Me$_3$), 109.1, 109.3 (2 × Me*C*Me),

126.8 (*p-Ph*), 128.0, 129.0 (*o,m-Ph*), 140.8 (*i-Ph*), 172.4 (*C*(1)); *m/z* (ESI$^+$) 478 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{44}NO_6^+$ ([M+H]$^+$) requires 478.3163; found 478.3158.

tert-Butyl (3*R*,4*S*,5*R*,6*R*)- and (3*S*,4*S*,5*R*,6*R*)-3-(*N*,*N*-dibenzylamino)-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 361 and 360



361

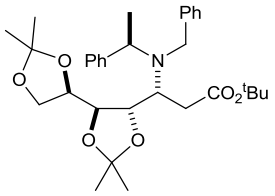


360

Following *General Procedure 1*, dibenzylamine (1.62 g, 8.22 mmol) in THF (60 mL), BuLi (2.1 M, 3.80 mL, 7.98 mmol) and **321** (1.35 g, 4.11 mmol, >99:1 dr) in THF (60 mL) at −78 ºC gave a 56:44 mixture of **360** and **361** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 6:1) gave **361** as a colourless oil (616 mg, 26%, >99:1 dr); $C_{31}H_{43}NO_6$ requires C, 70.8; H, 8.2; N, 2.7%; found C, 70.8; H, 8.3; N, 2.7%; $[\alpha]_D^{25}$ +21.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3064, 3029, 2984, 2935 (C–H), 1721 (C=O); δ_H (400 MHz, $CDCl_3$) 1.25 (3H, s, *Me*CMe), 1.30 (3H, s, *Me*CMe), 1.32 (3H, s, *Me*CMe), 1.36 (3H, s, *Me*CMe). 1.49 (9H, s, C*Me*$_3$), 2.66 (1H, dd, *J* 14.2, 9.9, C(2)H_A), 2.87 (1H, dd, *J* 14.2, 4.1, C(2)H_B), 2.98-3.04 (1H, m, C(6)*H*) overlapping 3.04 (1H, ddd, *J* 9.9, 4.1, 2.1, C(3)*H*), 3.13-3.19 (1H, m, C(7)H_A), 3.28 (2H, d, *J* 13.0, N(CH_AH$_B$Ph)$_2$), 3.54 (1H, dd, *J* 7.9, 6.5, C(7)H_B), 3.92 (1H, dd, *J* 8.2, 2.1, C(4)*H*), 4.08 (2H, app br s, N(CH$_A$$H_B$Ph)$_2$), 4.09 (1H, dd, *J* 8.2, 4.1, C(5)*H*), 7.23-7.39 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.0, 26.1, 26.3, 27.2 (4 × *Me*CMe), 28.1 (C*Me*$_3$), 32.5 (*C*(2)), 52.3 (*C*(3)), 55.9 (N(*C*H$_2$Ph)$_2$), 65.5 (*C*(7)), 75.0 (*C*(6)), 76.2 (*C*(5)), 79.8 (*C*(4)), 80.7 (*C*Me$_3$), 108.9, 109.0 (2 × Me*C*Me), 127.1 (*p-Ph*), 128.3, 129.5 (*o,m-Ph*), 139.9 (*i-Ph*), 171.9 (*C*(1)); *m/z* (ESI$^+$) 526 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{44}NO_6^+$ ([M+H]$^+$) requires 526.3163; found 526.3161. Further elution gave a 43:57 mixture of **361** and **360**, respectively, as a pale yellow oil (286 mg, 12%). Further elution gave **360** as a colourless oil (866 mg, 36%, 96:4 dr); $C_{31}H_{43}NO_6$ requires C, 70.8; H, 8.2; N, 2.7; found C, 70.9; H, 8.15; N, 2.8%; $[\alpha]_D^{25}$ −31.8 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3029, 2984, 2934, 2892 (C–H), 1728 (C=O); δ_H (400 MHz, $CDCl_3$) 1.32 (3H, s, *Me*CMe), 1.40 (6H, app s, 2 × *Me*CMe), 1.44 (3H, s, *Me*CMe), 1.48 (9H, s, C*Me*$_3$), 2.48 (1H, dd, *J* 15.4, 6.1, C(2)H_A), 2.69 (1H, dd, *J* 15.4, 6.1, C(2)H_B), 3.27 (1H, app td, *J* 6.1, 4.4, C(3)*H*) overlapping 3.30 (1H, dd, *J* 8.4, 3.3, C(5)*H*), 3.55 (2H, d, *J* 13.5, N(CH_AH$_B$Ph)$_2$), 3.61-3.74 (2H, m, C(7)H_2) overlapping 3.69 (2H, d, *J* 13.5, N(CH$_A$$H_B$Ph)$_2$), 4.06 (1H, ddd, *J* 9.9, 6.8, 3.3, C(6)*H*), 4.31 (1H, dd, *J* 8.4, 4.4, C(4)*H*), 7.22-7.36 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 26.2, 26.2, 26.9, 27.2 (4 × *Me*CMe), 28.2 (C*Me*$_3$), 32.5 (*C*(2)), 54.6 (N(*C*H$_2$Ph)$_2$), 56.2 (*C*(3)),

65.7 (*C*(7)), 75.2 (*C*(6)), 76.9 (*C*(4)), 79.0 (*C*(5)), 80.3 (*C*Me$_3$), 109.3, 109.4 (2 × Me*C*Me), 127.2 (*p-Ph*), 128.2, 128.3, 129.3, 129.5 (*o,m-Ph*), 139.5 (*i-Ph*), 172.2 (*C*(1)); *m/z* (ESI$^+$) 526 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{31}H_{44}NO_6^+$ ([M+H]$^+$) requires 526.3163; found 526.3165.

tert-Butyl (3*R*,4*S*,5*R*,6*R*,α*R*)- and (3*S*,4*S*,5*R*,6*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino)]-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 363 and 362



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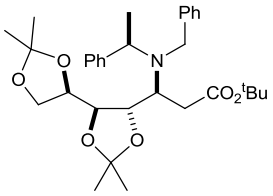
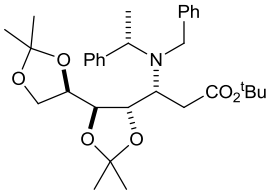


362

Following *General Procedure 1*, (*R*)-**123** (1.93 g, 9.14 mmol) in THF (60 mL), BuLi (2.5 M, 3.54 mL, 8.86 mmol) and **321** (1.50 g, 4.57 mmol, >99:1 dr) in THF (60 mL) at −78 ºC gave a 35:65 mixture of **363** and **362** respectively. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et$_2$O, 10:1) gave **363** as a white solid (815 mg, 33%, >99:1 dr); $C_{32}H_{45}NO_6$ requires C, 71.2; H, 8.4; N, 2.6%; found C, 71.2; H, 8.45; N, 2.6%; mp 94-98 ºC; $[\alpha]_D^{25}$ +41.3 (*c* 1.0 in $CHCl_3$); ν_{max} (KBr) 2983, 2935 (C–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.20 (3H, s, *Me*CMe), 1.28 (6H, app s, 2 × *Me*CMe), 1.37 (3H, s, *Me*CMe), 1.40 (3H, d, *J* 7.1, C(α)*Me*), 1.49 (9H, s, C*Me*$_3$), 2.58-2.65 (1H, m, C(6)*H*), 2.76-2.90 (2H, m, C(2)*H*$_2$), 3.15-3.20 (1H, m, C(3)*H*), 3.23-3.28 (1H, m, C(7)*H*$_A$), 3.40-3.45 (1H, m, C(7)*H*$_B$), 3.65 (1H, d, *J* 13.3, NC*H*$_A$H$_B$Ph) overlapping 3.67 (1H, dd, *J* 8.6, 2.4, C(5)*H*), 3.90 (1H, dd, *J* 8.6, 2.0, C(4)*H*), 3.91-3.97 (1H, m, C(α)*H*), 4.39 (1H, d, *J* 13.3, NCH$_A$*H*$_B$Ph), 7.20-7.42 (8H, m, *Ph*), 7.47-7.52 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 25.8, 25.9, 26.4, 27.2 (4 × *Me*CMe), 28.0 (C*Me*$_3$), 31.0 (C(α)*Me*), 37.0 (*C*(2)), 49.5 (*C*(3)), 53.0 (N*C*H$_2$Ph), 56.0 (*C*(α)), 65.8 (*C*(7)), 73.5 (*C*(6)), 75.5 (*C*(5)), 80.0 (*C*(4)), 80.8 (*C*Me$_3$), 108.8, 108.8 (2 × Me*C*Me), 127.0, 127.1 (*p-Ph*), 128.0, 128.3, 128.7, 129.2 (*o,m-Ph*), 141.0, 141.1 (*i-Ph*), 171.8 (*C*(1)); *m/z* (ESI$^+$) 540 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{46}NO_6^+$ ([M+H]$^+$) requires 540.3320; found 540.3315. Further elution gave **362** as a pale yellow oil (1.29 g, 52%, 96:4 dr); $C_{32}H_{45}NO_6$ requires C, 71.2; H, 8.4; N, 2.6%; found C, 71.2; H, 8.3; N, 2.55%; $[\alpha]_D^{25}$ −26.2 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2983, 2934 (C–H), 1729 (C=O); δ_H (400 MHz, $CDCl_3$) 1.37 (3H, s, *Me*CMe) overlapping 1.37 (3H, d, *J* 6.8, C(α)*Me*), 1.39 (3H, s, *Me*CMe), 1.42 (12H, app s, *Me*CMe, C*Me*$_3$), 1.45 (3H, s, *Me*CMe), 2.14 (1H, dd, *J* 15.9, 4.3, C(2)*H*$_A$), 2.35 (1H, dd, *J* 15.9, 7.1, C(2)*H*$_B$), 3.54-3.62 (2H, m, C(3)*H*, C(5)*H*) overlapping 3.58 (1H, d, *J* 14.3, NC*H*$_A$H$_B$Ph), 3.77-3.83 (1H, m, C(7)*H*$_A$), 3.84-3.90 (1H, m, C(7)*H*$_B$) overlapping 3.88 (1H, d, *J* 14.3, NCH$_A$*H*$_B$Ph), 3.95 (1H, q, *J* 6.8, C(α)*H*), 4.17-4.23 (1H, m, C(6)*H*), 4.30 (1H, dd, *J* 8.4, 4.6, C(4)*H*), 7.22-7.42 (10H, m, *Ph*);

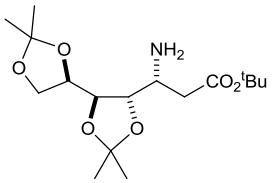
δ_C (100 MHz, $CDCl_3$) 19.4 (C(α)*Me*), 26.1, 26.2, 26.7, 27.2 (4 × *Me*CMe), 28.1 (C*Me*$_3$), 33.6 (*C*(2)), 51.3 (NCH_2Ph), 54.8 (*C*(3)), 57.3 (*C*(α)), 65.8 (*C*(7)), 75.3 (*C*(6)), 78.7 (*C*(4)), 79.2 (*C*(5)), 80.1 (*C*Me$_3$), 109.2, 109.4 (2 × Me*C*Me), 126.8, 127.0 (*p-Ph*), 128.0, 128.1, 128.2, 128.7 (*o,m-Ph*), 140.8, 143.1 (*i-Ph*), 171.9 (*C*(1)); *m/z* (ESI$^+$) 540 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{46}NO_6^+$ ([M+H]$^+$) requires 540.3320; found 540.3309.

tert-Butyl (3*R*,4*S*,5*R*,6*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 365



Following *General Procedure 1*, (*S*)-**123** (1.93 g, 9.14 mmol) in THF (60 mL), BuLi (2.1 M, 4.18 mL, 8.86 mmol) and **321** (1.50 g, 4.57 mmol, >99:1 dr) in THF (60 mL) at –78 ºC gave **365** in 90:10 dr. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 10:1) gave **365** as a pale yellow oil (1.01 g, 41%, >99:1 dr); $C_{32}H_{45}NO_6$ requires C, 71.2; H, 8.4; N, 2.6%; found C, 71.05; H, 8.4; N, 2.5%; $[\alpha]_D^{25}$ +4.7 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 2983, 2935 (C–H), 1725 (C=O); δ_H (400 MHz, $CDCl_3$) 1.27 (3H, s, *Me*CMe), 1.29 (3H, d, *J* 7.1, C(α)*Me*), 1.33 (3H, s, *Me*CMe), 1.37 (3H, s, *Me*CMe), 1.43 (3H, s, *Me*CMe), 1.44 (9H, s, C*Me*$_3$), 1.92 (1H, dd, *J* 15.2, 2.3, C(2)H_A), 2.49 (1H, dd, *J* 15.2, 10.6, C(2)H_B), 3.34-3.39 (1H, m, C(3)*H*), 3.52 (1H, d, *J* 14.7, NCH_AH_BPh), 3.72-3.88 (3H, m, C(α)*H*, C(6)*H*, C(7)H_A), 3.96-4.01 (1H, m, C(7)H_B), 4.03 (1H, dd, *J* 8.1, 1.8, C(4)*H*), 4.39-4.44 (1H, m, C(5)*H*) overlapping 4.40 (1H, d, *J* 14.7, NCH_AH_BPh), 7.25-7.40 (8H, m, *Ph*), 7.48-7.54 (2H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.7 (C(α)*Me*), 26.0, 26.1, 26.3, 27.0 (4 × *Me*CMe), 28.0 (C*Me*$_3$), 34.2 (*C*(2)), 51.3 (*C*(3)), 53.2 (NCH_2Ph), 58.7 (*C*(6)), 65.8 (*C*(7)), 75.6 (*C*(α)), 76.4 (*C*(5)), 79.9 (*C*(4)), 80.5 (*C*Me$_3$), 108.9, 109.3 (2 × Me*C*Me), 126.5, 127.3 (*p-Ph*), 128.1, 128.2, 128.3, 128.4 (*o,m-Ph*), 141.8 141.9 (*i-Ph*), 171.6 (*C*(1)); *m/z* (ESI$^+$) 540 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{32}H_{46}NO_6^+$ ([M+H]$^+$) requires 540.3320; found 540.3309.

***tert*-Butyl (3*R*,4*S*,5*R*,6*R*)-3-amino-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 366**

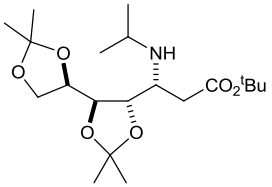


*Method A (From **365**):* Following *General Procedure 2*, **365** (205 mg, 0.380 mmol, >99:1 dr) in EtOAc (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 103 mg) and H_2 (1 atm) gave **366** as a yellow oil (109 mg, 83%, >99:1 dr); $[\alpha]_D^{25}$ –10.0 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3328 (N–H), 2985, 2935 (C–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.35 (3H, s, *Me*CMe), 1.38 (3H, s, *Me*CMe), 1.40 (6H, app s, 2 × *Me*CMe), 1.43 (9H, s, C*Me*$_3$), 1.72 (2H, br s, N*H*$_2$), 2.36 (1H, dd, *J* 15.9, 9.4, C(2)*H*$_A$), 2.47 (1H, dd, *J* 15.9, 4.3, C(2)*H*$_B$), 3.11-3.18 (1H, m, C(3)*H*), 3.82-3.87 (1H, m, C(7)*H*$_A$), 3.88 (1H, dd, *J* 7.7, 2.8, C(4)*H*), 4.00-4.05 (1H, m, C(7)*H*$_B$), 4.08 (1H, dd, *J* 7.7, 3.8, C(5)*H*), 4.10-4.16 (1H, m, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 25.6, 26.2, 27.1, 27.2 (4 × *Me*CMe), 28.1 (C*Me*$_3$), 42.2 (*C*(2)), 48.6 (*C*(3)), 65.8 (*C*(7)), 75.1 (*C*(6)), 76.8 (*C*(5)), 79.8 (*C*(4)), 80.8 (*C*Me$_3$), 109.4, 109.6 (2 × Me*C*Me), 171.4 (*C*(1)); *m/z* (ESI^+) 346 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{17}H_{32}NO_6^+$ ($[M+H]^+$) requires 346.2224; found 346.2215.

*Method B (From **363**):* Following *General Procedure 2*, **363** (208 mg, 0.385 mmol, >99:1 dr) in EtOAc (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 104 mg) and H_2 (1 atm) gave **366** as a yellow oil (102 mg, 77%, >99:1 dr).

*Method C (From **361**):* Following *General Procedure 2*, **361** (150 mg, 0.285 mmol, >99:1 dr) in EtOAc (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 75 mg) and H_2 (1 atm) gave **366** as a yellow oil (72 mg, 73%, >99:1 dr).

***tert*-Butyl (3*R*,4*S*,5*R*,6*R*)-3-*N*-isopropylamino-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 367**

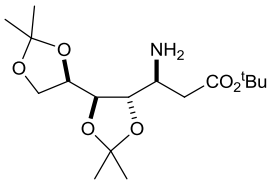


*Method A (From **359**):* Following *General Procedure 2*, **359** (188 mg, 0.394 mmol, >99:1 dr) in EtOAc (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 94 mg) and H_2 (1 atm) gave **367** as a pale yellow oil (156 mg, quant, >99:1 dr); $[\alpha]_D^{25}$ –32.6 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3344 (N–H), 2983, 2935 (C–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 0.94 (3H, d, *J* 6.1, *Me*CHMe), 1.01 (3H, d, *J* 6.3, *Me*CHMe), 1.34 (3H, s, *Me*CMe), 1.37 (3H, s, *Me*CMe), 1.39 (6H, app s, 2 × *Me*CMe), 1.42 (9H, s,

C*Me*$_3$), 2.36-2.46 (2H, m, C(2)*H*$_2$), 2.87 (1H, app septet, *J* 6.1, MeC*H*Me), 3.05 (1H, app td, *J* 6.3, 2.3, C(3)*H*), 3.78-3.84 (1H, m, C(7)*H*$_A$), 3.98 (1H, dd, *J* 7.6, 2.3, C(4)*H*), 4.00-4.05 (1H, m, C(7)*H*$_B$), 4.07-4.14 (2H, m, C(5)*H*, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 22.5, 23.9 (2 × *Me*CHMe), 25.7, 26.2, 27.0, 27.2 (4 × *Me*CMe), 28.0 (C*Me*$_3$), 38.4 (*C*(2)), 45.2 (Me*C*HMe), 51.2 (*C*(3)), 65.8 (*C*(7)), 76.0, 76.8 (*C*(5), *C*(6)), 79.1 (*C*(4)), 80.5 (*C*Me$_3$), 109.2, 109.4 (2 × Me*C*Me), 171.6 (*C*(1)); *m/z* (ESI$^+$) 388 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{20}H_{38}NO_6^+$ ([M+H]$^+$) requires 388.2694; found 388.2691.

*Method B (From **366**):* Following *General Procedure 3*, **366** (82 mg, 0.24 mmol, >99:1 dr) in MeOH (3 mL), acetone (35 µL, 0.47 mmol) and $NaBH_3CN$ (60 mg, 0.95 mmol) at rt gave **367** as a pale yellow oil (71 mg, 78%, >99:1 dr).

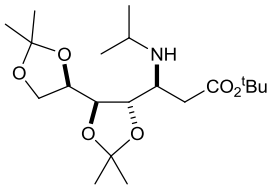
tert-Butyl (3*S*,4*S*,5*R*,6*R*)-3-amino-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 368



*Method A (From **362**):* Following *General Procedure 2*, **362** (206 mg, 0.382 mmol, 96:4 dr) in EtOAc (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 103 mg) and H_2 (1 atm) gave **368** as a yellow oil (124 mg, 94%, 96:4 dr); $[\alpha]_D^{25}$ −18.4 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3322 (N–H), 2984, 2935 (C–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.35 (3H, s, *Me*CMe), 1.37 (3H, s, *Me*CMe), 1.38 (3H, s, *Me*CMe), 1.40 (3H, s, *Me*CMe), 1.43 (9H, s, C*Me*$_3$), 1.60 (2H, br s, N*H*$_2$), 2.20 (1H, dd, *J* 16.2, 9.6, C(2)*H*$_A$), 2.62 (1H, dd, *J* 16.2, 3.0, C(2)*H*$_B$), 3.18-3.26 (1H, m, C(3)*H*), 3.81-3.93 (2H, m, C(4)*H*, C(7)*H*$_A$), 3.95 (1H, dd, *J* 7.1, 3.8, C(5)*H*), 3.99-4.04 (1H, m, C(7)*H*$_B$), 4.21 (1H, app td, *J* 7.1, 3.8, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 25.6, 26.2, 27.1, 27.4 (4 × *Me*CMe), 28.1 (C*Me*$_3$), 40.5 (*C*(2)), 51.0 (*C*(3)), 66.0 (*C*(7)), 75.9 (*C*(6)), 78.7 (*C*(5)), 80.2 (*C*(4)), 80.8 (*C*Me$_3$), 109.4, 109.5 (2 × Me*C*Me), 171.6 (*C*(1)); *m/z* (ESI$^+$) 346 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{17}H_{32}NO_6^+$ ([M+H]$^+$) requires 346.2224; found 346.2219.

*Method B (From **360**):* Following *General Procedure 2*, **360** (200 mg, 0.380 mmol, 96:4 dr) in EtOAc (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 100 mg) and H_2 (1 atm) gave **368** as a yellow oil (101 mg, 77%, 96:4 dr).

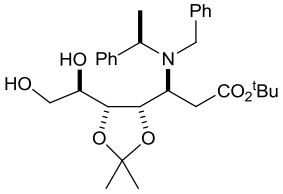
***tert*-Butyl (3*S*,4*S*,5*R*,6*R*)-3-*N*-isopropylamino-4,5,6,7-tetrahydroxy-4,5,6,7-di-*O*-isopropylideneheptanoate 369**



*Method A (From **358**):* Following *General Procedure 2*, **358** (188 mg, 0.394 mmol, >99:1 dr) in EtOAc (5 mL), $Pd(OH)_2/C$ (50% w/w of substrate, 94 mg) and H_2 (1 atm) gave **369** as a pale yellow oil (157 mg, quant, >99:1 dr); $[\alpha]_D^{25}$ –3.1 (*c* 1.0 in $CHCl_3$); ν_{max} (film) 3328 (N–H), 2985, 2935 (C–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 0.91 (3H, d, *J* 6.1, *Me*CHMe), 0.95 (3H, d, *J* 6.3, *Me*CHMe), 1.29 (3H, s, *Me*CMe), 1.31 (3H, s, *Me*CMe), 1.33 (3H, s, *Me*CMe), 1.34 (3H, s, *Me*CMe), 1.37 (9H, s, C*Me*$_3$), 2.31 (1H, dd, *J* 15.4, 5.6, C(2)H_A), 2.47 (1H, dd, *J* 15.4, 4.8, C(2)H_B), 2.83 (1H, app septet, *J* 6.2, MeC*H*Me), 2.96 (1H, app q, *J* 5.6, C(3)*H*), 3.76-3.83 (2H, m, C(4)*H*, C(5)*H*), 3.84-3.94 (2H, m, C(7)H_2), 4.13-4.19 (1H, m, C(6)*H*); δ_C (100 MHz, $CDCl_3$) 22.6, 23.9 (2 × *Me*CHMe), 25.7, 26.2, 27.1, 27.3 (4 × *Me*CMe), 28.0 (C*Me*$_3$), 37.2 (*C*(2)), 45.4 (Me*C*HMe), 54.7 (*C*(3)), 66.0 (*C*(7)), 76.5 (*C*(6)), 79.2, 80.0 (*C*(4), *C*(5)), 80.4 (*C*Me$_3$), 109.3, 109.4 (2 × Me*C*Me), 171.6 (*C*(1)); *m/z* (ESI^+) 388 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{20}H_{38}NO_6^+$ ($[M+H]^+$) requires 388.2694; found 388.2688.

*Method B (From **368**):* Following *General Procedure 3*, **368** (97 mg, 0.28 mmol, 96:4 dr) in MeOH (3 mL), acetone (41 µL, 0.56 mmol) and $NaBH_3CN$ (71 mg, 1.1 mmol) at rt gave **369** as a pale yellow oil (53 mg, 49%, 96:4 dr).

***tert*-Butyl (3*S*,4*S*,5*R*,6*R*,α*R*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5,6,7-tetrahydroxy-4,5-*O*-isopropylideneheptanoate 380**



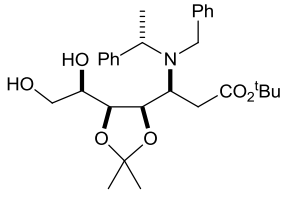
Method A: Conc HCl (1 drop) was added to a solution of **327** (50 mg, 93 µmol, >99:1 dr) in 70% aq EtOH (1.1 mL) at 60 °C and the resultant mixture was heated at 60 °C for 6 h. The reaction mixture was cooled to rt, filtered through a short plug of basic alumina (eluent EtOH) and then the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 2:1→1:2 30-40 °C petrol/Et_2O) gave **380** as a colourless oil (15 mg, 32%, >99:1 dr); $[\alpha]_D^{25}$ –7.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3436 (O–H), 3086, 3062, 3028, 2980, 2935 (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$)

1.27 (3H, s, *Me*CMe), 1.33 (3H, s, *Me*CMe), 1.41 (9H, s, C*Me*$_3$), 1.57 (3H, d, *J* 6.8, C(α)*Me*), 2.21-2.28 (3H, m, C(2)*H*$_2$, C(7)O*H*), 3.56-3.66 (2H, m, C(6)*H*, C(7)*H*$_A$) overlapping 3.62 (1H, d, *J* 14.2, NC*H*$_A$H$_B$Ph), 3.71-3.79 (1H, m, C(7)*H*$_B$), 3.86 (1H, d, *J* 14.2, NCH$_A$*H*$_B$Ph), 3.96-4.04 (2H, m, C(3)*H*, C(α)*H*), 4.08 (1H, dd, *J* 8.9, 6.7, C(5)*H*), 4.41 (1H, dd, *J* 7.5, 6.7, C(4)*H*), 6.09 (1H, br s, C(6)O*H*), 7.27-7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.1 (C(α)*Me*), 24.6, 26.8 (2 × *Me*CMe), 28.1 (C*Me*$_3$), 35.1 (*C*(2)), 51.7 (N*C*H$_2$Ph), 54.1, 59.3 (*C*(3), *C*(α)), 64.8 (*C*(7)), 68.3 (*C*(6)), 78.0 (*C*(5)), 78.6 (*C*(4)), 80.3 (*C*Me$_3$), 108.1 (Me*C*Me), 127.5, 127.7 (*p-Ph*), 128.4, 128.5, 128.7, 129.4 (*o,m-Ph*), 138.4, 141.4 (*i-Ph*), 171.5 (*C*(1)); *m/z* (ESI$^+$) 522 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{41}NNaO_6^+$ ([M+Na]$^+$) requires 522.2826; found 522.2809.

Method B: A solution of **327** (50 mg, 93 μmol, >99:1 dr) in 80% aq AcOH (1.0 mL) was heated at 50 °C for 16 h. The reaction mixture was then cooled to 0 °C and 5.0 M aq NaOH was added dropwise until pH 14 was achieved. The resultant mixture was extracted with CH_2Cl_2 (3 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 2:1→1:2 30-40 °C petrol/Et$_2$O) gave **380** as a colourless oil (10 mg, 21%, >99:1 dr).

Method C: $BiCl_3$ (2 mg, 4.6 μmol) and H_2O (2 drops) were added sequentially to a solution of **327** (50 mg, 93 μmol, >99:1 dr) in MeCN (0.9 mL) at rt and the resultant mixture was stirred at rt for 16 h. $NaHCO_3$ (~50 mg) was then added and the reaction mixture was concentrated *in vacuo*. The residue was partitioned between EtOAc (10 mL) and H_2O (10 mL) and the aqueous layer was then extracted with EtOAc (3 × 10 mL). The combined organic extracts were washed with brine (20 mL) then dried and concentrated *in vacuo* to give returned starting material **327** (50 mg).

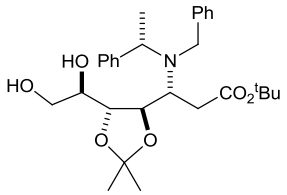
tert-Butyl (3*S*,4*R*,5*S*,6*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5,6,7-tetrahydroxy-4,5-*O*-isopropylideneheptanoate 381



Conc HCl (1 drop) was added to a solution of **339** (50 mg, 93 μmol, >99:1 dr) in 70% aq EtOH (1.1 mL) at 60 °C and the resultant mixture was heated at 60 °C for 6 h. The reaction mixture was cooled to rt, filtered through a short plug of basic alumina (eluent EtOH) and then the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 2:1→1:2 30-40 °C petrol/Et$_2$O) gave **381** as a colourless oil (14 mg, 31%, >99:1 dr); $[\alpha]_D^{25}$ –29.3 (*c* 1.0 in

$CHCl_3$); ν_{max} (ATR) 3062, 3028, 2979, 2934, 2880 (C–H), 1724 (C=O); δ_H (400 MHz, $CDCl_3$) 1.33 (3H, s, *Me*CMe), 1.35 (3H, d, *J* 7.1, C(α)*Me*), 1.51 (9H, s, C*Me*$_3$), 1.60 (3H, s, *Me*CMe), 2.07 (1H, br s, C(7)O*H*), 2.50 (1H, dd, *J* 15.7, 8.1, C(2)H_A), 2.57-2.64 (2H, m, C(2)H_B, C(6)*H*), 3.36-3.44 (1H, m, C(7)H_A), 3.50-3.56 (1H, m, C(7)H_B), 3.72 (1H, d, *J* 13.8, NCH_AH$_B$Ph), 3.80-3.89 (2H, m, C(3)*H*, C(5)*H*), 4.12 (1H, dd, *J* 6.6, 3.8, C(4)*H*), 4.15 (1H, q, *J* 7.1, C(α)*H*), 4.31 (1H, d, *J* 13.8, NCH$_A$$H_B$Ph), 5.00 (1H, br s, C(6)O*H*), 7.24-7.52 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 16.6 (C(α)*Me*), 25.0, 26.4 (2 × *Me*CMe), 28.2 (C*Me*$_3$), 37.5 (*C*(2)), 52.0 (NCH_2Ph), 52.1 (*C*(3)), 60.5 (*C*(α)), 64.3 (*C*(7)), 68.8 (*C*(6)), 78.8 (*C*(5)), 80.3 (*C*(4)), 81.2 (*C*Me$_3$), 108.4 (Me*C*Me), 127.1, 127.6 (*p-Ph*), 128.1, 128.5, 129.1, 129.1 (*o,m-Ph*), 140.0, 141.8 (*i-Ph*), 171.3 (*C*(1)); *m/z* (ESI$^+$) 500 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{42}NO_6^+$ ([M+H]$^+$) requires 500.3007; found 500.3011.

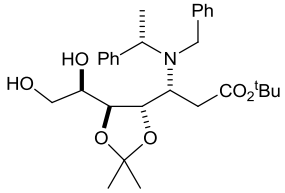
tert-Butyl (3*R*,4*R*,5*R*,6*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5,6,7-tetrahydroxy-4,5-*O*-isopropylideneheptanoate 382



Conc HCl (4 drops) was added to a solution of **350** (200 mg, 0.371 mmol, >99:1 dr) in 70% aq EtOH (4.4 mL) at 60 °C and the resultant mixture was heated at 60 °C for 6 h. The reaction mixture was cooled to rt, filtered through a short plug of basic alumina (eluent EtOH) and then the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 1:1→1:2 30-40 °C petrol/Et_2O) gave **382** as a pale yellow oil (73 mg, 39%, >99:1 dr); $[\alpha]_D^{25}$ +12.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3402 (O–H), 3086, 3062, 3029, 2980, 2933, 2880 (C–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.32 (6H, app s, 2 × *Me*CMe), 1.44 (9H, s, C*Me*$_3$), 1.52 (3H, d, *J* 6.8, C(α)*Me*), 2.20 (1H, dd, *J* 16.2, 2.3, C(2)H_A), 2.31 (1H, dd, *J* 16.2, 8.3, C(2)H_B), 2.52 (1H, br s, O*H*), 3.54 (1H, d, *J* 13.9, NCH_AH$_B$Ph), 3.62-3.71 (3H, m, C(5)*H*, C(6)*H*, C(7)H_A), 3.75-3.81 (1H, m, C(7)H_B) overlapping 3.81 (1H, d, *J* 13.9, NCH$_A$$H_B$Ph), 3.90-3.96 (1H, m, C(3)*H*) overlapping 3.96 (1H, q, *J* 6.8, C(α)*H*), 3.99-4.04 (1H, m, C(4)*H*), 5.35 (1H, br s, O*H*), 7.23-7.47 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.4 (C(α)*Me*), 26.7, 26.8 (2 × *Me*CMe), 28.1 (C*Me*$_3$), 33.9 (*C*(2)), 52.4 (NCH_2Ph), 55.3 (*C*(3)), 58.0 (*C*(α)), 64.3 (*C*(7)), 72.6 (*C*(6)), 80.3 (*C*Me$_3$), 80.4 (*C*(5)), 82.0 (*C*(4)), 109.0 (Me*C*Me), 127.4, 127.5 (*p-Ph*), 128.3, 128.5, 128.5, 129.5 (*o,m-Ph*), 138.5, 140.9

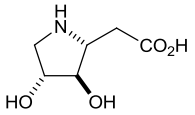
(*i-Ph*), 171.7 (*C*(1)); *m/z* (ESI$^+$) 500 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{42}NO_6^+$ ([M+H]$^+$) requires 500.3007; found 500.2994.

tert-Butyl (3*R*,4*S*,5*S*,6*R*,α*S*)-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4,5,6,7-tetrahydroxy-4,5-*O*-isopropylideneheptanoate 383

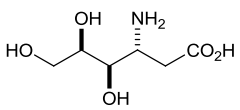


Conc HCl (1 drop) was added to a solution of **365** (50 mg, 93 μmol, >99:1 dr) in 70% aq EtOH (1.1 mL) at 60 °C and the resultant mixture was heated at 60 °C for 6 h. The reaction mixture was cooled to rt, filtered through a short plug of basic alumina (eluent EtOH) and then the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 1:1→1:2 30-40 °C petrol/Et_2O) gave **383** as a pale yellow oil (32 mg, 70%, >99:1 dr); $[\alpha]_D^{25}$ –8.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3435 (O–H), 3084, 3062, 3026, 2978, 2934 (C–H), 1720 (C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, s, *Me*CMe), 1.33 (3H, d, *J* 6.9, C(α)*Me*), 1.35 (3H, s, *Me*CMe), 1.43 (9H, s, C*Me*$_3$), 1.82 (1H, dd, *J* 15.8, 2.3, C(2)H_A), 2.47 (1H, dd, *J* 15.8, 10.7, C(2)H_B), 2.89 (2H, br s, 2 × O*H*), 3.45-3.53 (2H, m, C(3)*H*, C(6)*H*), 3.55 (1H, d, *J* 14.7, NCH_AH$_B$Ph), 3.70-3.79 (2H, m, C(7)H_2), 3.83 (1H, q, *J* 6.9, C(α)*H*), 4.12 (1H, dd, *J* 8.4, 2.3, C(5)*H*), 4.36 (1H, d, *J* 14.7, NCH$_A$$H_B$Ph), 4.45 (1H, dd, *J* 8.4, 2.4, C(4)*H*), 7.22-7.53 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 20.3 (C(α)*Me*), 26.2, 27.1 (2 × *Me*CMe), 28.0 (C*Me*$_3$), 34.0 (*C*(2)), 50.4 (*C*(3)), 53.1 (N*C*H$_2$Ph), 58.1 (*C*(α)), 65.3 (*C*(7)), 69.7 (*C*(6)), 78.3 (*C*(4)), 79.7 (*C*(5)), 80.6 (*C*Me$_3$), 108.8 (Me*C*Me), 126.6, 127.3 (*p-Ph*), 128.0, 128.1, 128.3, 128.3 (*o*,*m-Ph*), 141.4, 141.5 (*i-Ph*), 171.6 (*C*(1)); *m/z* (ESI$^+$) 500 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{42}NO_6^+$ ([M+H]$^+$) requires 500.3007; found 500.3000.

(*R*,*R*,*R*)-2-[*N*(1')-3',4'-Dihydroxypyrrolidin-2'-yl]acetic acid 305 and (*R*,*R*,*R*)-3-amino-4,5,6-trihydroxyhexanoic acid 385



305



385

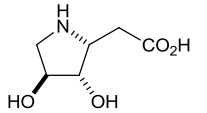
Step 1: $NaIO_4$ (477 mg, 2.23 mmol) was added to a solution of **382** (223 mg, 0.446 mmol, >99:1 dr) in MeOH (9 mL) at rt and the resultant suspension was stirred at rt for 16 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and the filtrate was concentrated *in*

vacuo. The residue was dissolved in Et_2O (10 mL) and then filtered through a short plug of Celite® (eluent Et_2O) and the filtrate was concentrated *in vacuo* to give **384** in >99:1 dr (202 mg).

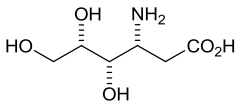
Step 2: $Pd(OH)_2/C$ (50% w/w of substrate, 101 mg) was added to a stirred solution of the residue (202 mg) in MeOH (3.5 mL) and 3.0 M aq HCl (0.70 mL) at rt. The resultant mixture was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (5 atm) for 18 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. Due to incomplete conversion, the residue (180 mg) was resubjected to the reaction conditions for a further 60 h. The reaction mixture was filtered through a short plug of Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo* to give a yellow oil (150 mg).

Step 3: A solution of the residue (150 mg) in 2.0 M aq HCl (5 mL) was heated at reflux for 8 h. The reaction mixture was allowed to cool to rt and was then concentrated *in vacuo*. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH) gave a 34:66 mixture of **305** and **385** respectively (42 mg). Data for mixture: ν_{max} (ATR) 3194 (O–H), 2931 (C–H), 2361 (NH_3^+), 1563, 1392 (CO_2^-); *m/z* (ESI^+) 180 ([M(**385**)+H]$^+$, 100%), 162 ([M(**305**)+H]$^+$, 64%); HRMS (ESI^+) $C_6H_{12}NO_4^+$ ([M(**305**)+H]$^+$) requires 162.0761; found 162.0763.[23] Data for **385**: δ_H (500 MHz, D_2O) 2.46 (1H, dd, *J* 16.9, 9.5, C(2)H_A), 2.53 (1H, dd, *J* 16.9, 4.6, C(2)H_B), 3.53 (1H, dd, *J* 11.7, 6.3, C(6)H_A), 3.58 (1H, dd, *J* 11.7, 5.0, C(6)H_B), 3.59-3.64 (1H, m, C(3)*H*), 3.71-3.75 (1H, m, C(5)*H*), 3.76-3.79 (1H, m, C(4)*H*); δ_C (125 MHz, D_2O) 34.6 (*C*(2)), 52.1 (*C*(3)), 62.4 (*C*(6)), 68.9 (*C*(4)), 70.9 (*C*(5)), 177.6 (*C*(1)). Data for **305**: δ_H (500 MHz, D_2O) [selected peaks] 2.61 (1H, dd, *J* 17.0, 9.1, C(2)H_A), 2.69 (1H, dd, *J* 17.0, 5.7, C(2)H_B), 3.22 (1H, dd, *J* 12.6, 2.8, C(5')H_A), 3.45 (1H, dd, *J* 12.6, 5.0, C(5')H_B), 3.94-3.97 (1H, m, C(3')*H*), 4.20-4.23 (1H, m, C(4')*H*); δ_C (125 MHz, D_2O) 37.4 (*C*(2)), 49.6 (*C*(5')), 62.6 (*C*(2')), 74.3 (*C*(4')), 78.3 (*C*(3')), 177.3 (*C*(1)).

(2'*R*,3'*S*,4'*S*)-2-[*N*(1')-3',4'-Dihydroxypyrrolidin-2'-yl]acetic acid 306 and (3*R*,4*S*,5*S*)-3-amino-4,5,6-trihydroxyhexanoic acid 387



306



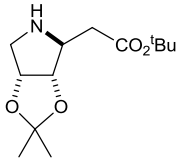
387

Step 1: $NaIO_4$ (366 mg, 1.71 mmol) was added to a solution of **383** (171 mg, 0.342 mmol, >99:1 dr) in MeOH (7 mL) at rt and the resultant suspension was stirred at rt for 16 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. The residue was dissolved in Et_2O (10 mL) and then filtered through a short plug of Celite® (eluent Et_2O) and the filtrate was concentrated *in vacuo* to give **386** in >99:1 dr (133 mg).

Step 2: $Pd(OH)_2/C$ (50% w/w of substrate, 67 mg) was added to a stirred solution of the residue (133 mg) in MeOH (2.3 mL) and 3.0 M aq HCl (0.5 mL) at rt. The resultant mixture was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (5 atm) for 18 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo* to give a pale yellow oil (38 mg).

Step 3: A solution of the residue (38 mg) in 2.0 M aq HCl (2.5 mL) was heated at reflux for 8 h. The reaction mixture was allowed to cool to rt and was then concentrated *in vacuo*. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH) gave a 7:93 mixture of **306** and **387** respectively (25 mg). Data for mixture: ν_{max} (ATR) 3163 (O–H), 2945, 2883 (C–H), 2327 (NH_3^+), 1563, 1391 (CO_2^-); *m/z* (ESI^+) 341 ([M(**387**)+M(**306**)+H]$^+$, 100%), 180 ([M(**387**)+H]$^+$, 87%), 162 ([M(**306**)+H]$^+$, 41%); HRMS (ESI^+) $C_6H_{12}NO_4^+$ ([M(**306**)+H]$^+$) requires 162.0761; found 162.0766.[24] Data for **387**: δ_H (500 MHz, D_2O) 2.43 (1H, dd, *J* 17.0, 8.2, C(2)H_A), 2.53 (1H, dd, *J* 17.0, 5.0, C(2)H_B), 3.51-3.59 (3H, m, C(3)*H*, C(6)H_2), 3.69 (1H, dd, *J* 6.0, 1.9, C(4)*H*), 3.73 (1H, app td, *J* 5.4, 1.9, C(5)*H*); δ_C (125 MHz, D_2O) 36.2 (*C*(2)), 51.8 (*C*(3)), 62.5 (*C*(6)), 69.1 (*C*(4)), 71.7 (*C*(5)), 177.5 (*C*(1)). Data for **306**: δ_H (500 MHz, D_2O) [selected peaks] 3.15 (1H, app d, *J* 13.2, C(5')H_A), 3.51 (1H, dd, *J* 13.2, 4.7, C(5')H_B), 3.93 (1H, ddd, *J* 8.5, 6.2, 3.3, C(2')*H*), 4.13-4.15 (1H, m, C(3')*H*), 4.26-4.29 (1H, m, C(4')*H*); δ_C (125 MHz, D_2O) [selected peaks] 50.3 (*C*(5')), 59.4 (*C*(2')), 74.1 (*C*(4')), 75.2 (*C*(3')), 177.7 (*C*(1)).

tert-Butyl (2'*S*,3'*S*,4'*R*)-2-[*N*(1')-3',4'-dihydroxy-3',4'-*O*-isopropylidenepyrrolidin-2'-yl]acetate 389

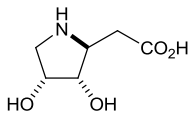


Step 1: $NaIO_4$ (139 mg, 0.650 mmol) was added to a solution of **380** (65 mg, 0.13 mmol, >99:1 dr) in MeOH (2.5 mL) at rt and the resultant suspension was stirred at rt for 16 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. The residue was dissolved in Et_2O (5 mL) and then filtered through a short plug of Celite® (eluent Et_2O) and the filtrate was concentrated *in vacuo* to give **388** in >99:1 dr (57 mg). An aliquot of **388** was purified via flash column chromatography (gradient elution, 10:1→5:1 30-40 °C petrol/Et_2O) to give **388** as a white solid;[25] mp 38-42 °C; $[\alpha]_D^{25}$ +3.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2979, 2934 (C–H), 1730 (C=O); δ_H (500 MHz, $CDCl_3$) 1.27 (3H, s, *Me*CMe), 1.40 (3H, d, *J* 6.9, C(α)*Me*), 1.43 (9H, s, C*Me*$_3$), 1.46 (3H, s, *Me*CMe), 2.13 (1H, dd, *J* 15.7, 7.9, C(2)H_A), 2.19 (1H, dd,

J 15.7, 3.8, C(2)H_B), 3.66 (1H, d, *J* 15.0, NCH_AH$_B$Ph), 3.79 (1H, d, *J* 15.0, NCH$_A$$H_B$Ph), 3.91 (1H, ddd, *J* 14.2, 7.9, 3.8, C(3)*H*) overlapping 3.91 (1H, q, *J* 6.9, C(α)*H*), 4.29 (1H, dd, *J* 14.2, 6.6, C(4)*H*), 4.31 (1H, dd, *J* 6.6, 3.5, C(5)*H*), 7.23-7.36 (10H, m, *Ph*), 9.53 (1H, d, *J* 3.5, C(6)*H*); δ_C (125 MHz, $CDCl_3$) 18.9 (C(α)*Me*), 25.0, 27.3 (2 × *Me*CMe), 28.0 (C*Me*$_3$), 35.9 (*C*(2)), 50.3 (N*C*H$_2$Ph), 53.8, 59.7 (*C*(3), *C*(α)), 80.2 (*C*(4)), 80.6 (*C*(5)), 81.1 (*C*Me$_3$), 110.3 (Me*C*Me), 127.0, 127.4 (*p-Ph*), 128.3, 128.3, 128.4, 128.4 (*o,m-Ph*), 140.3, 141.9 (*i-Ph*), 170.8 (*C*(1)), 198.7 (*C*(6)); *m/z* (ESI$^+$) 500 ([M+MeOH+H]$^+$, 100%); HRMS (ESI$^+$) $C_{29}H_{42}NO_6^+$ ([M+MeOH+H]$^+$) requires 500.3007; found 500.3003.

Step 2: Pd(OH)$_2$/C (50% w/w of substrate, 29 mg) was added to a stirred solution of the residue (57 mg) in MeOH (1 mL) at rt. The resultant mixture was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (5 atm) for 18 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 4:1→1:1 30-40 °C petrol/EtOAc) gave **389** as a pale yellow oil (20 mg, 60% over 2 steps, >99:1 dr); $[\alpha]_D^{25}$ –24.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3417 (N–H), 2979, 2934 (C–H), 1726 (C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, s, *Me*CMe), 1.44 (9H, s, C*Me*$_3$), 1.45 (3H, s, *Me*CMe), 2.24 (2H, d, *J* 7.8, C(2)H_2), 2.53 (1H, br s, N*H*), 2.85 (1H, dd, *J* 13.5, 4.2, C(5')H_A), 3.02 (1H, app d, *J* 13.5, C(5')H_B), 3.50-3.56 (1H, m, C(2')*H*), 4.41 (1H, app d, *J* 5.6, C(3')*H*), 4.65-4.70 (1H, m, C(4')*H*); δ_C (100 MHz, $CDCl_3$) 24.0, 26.3 (2 × *Me*CMe), 28.1 (C*Me*$_3$), 37.3 (*C*(2)), 51.9 (*C*(5')), 61.9 (*C*(2')), 80.7 (*C*Me$_3$), 81.7 (*C*(4')), 85.4 (*C*(3')), 111.1 (Me*C*Me), 170.7 (*C*(1)); *m/z* (ESI$^+$) 258 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{24}NO_4^+$ ([M+H]$^+$) requires 258.1700; found 258.1699.

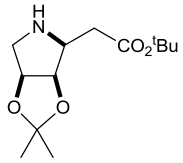
(2'*S*,3'*S*,4'*R*)-2-[*N*(1')-3',4'-Dihydroxypyrrolidin-2'-yl]acetic acid 303



A solution of **389** (80 mg, 0.31 mmol, >99:1 dr) in 2.0 M aq HCl (3 mL) was heated at reflux for 8 h. The reaction mixture was allowed to cool to rt and was then concentrated *in vacuo*. Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH) gave **303** as an orange solid (46 mg, 92%, >99:1 dr); mp 219-223 °C (dec); $[\alpha]_D^{25}$ –43.5 (*c* 1.0 in H_2O); ν_{max} (ATR) 3338 (O–H), 3064, 2922, 2867 (C–H), 2246, 2139 (NH_3^+), 1537, 1397 (CO_2^-); δ_H (500 MHz, D_2O) 2.50 (1H, dd, *J* 17.2, 8.5, C(2)H_A), 2.71 (1H, dd, *J* 17.2, 4.4, C(2)H_B), 3.24 (1H, dd, *J* 13.1, 2.1, C(5')H_A), 3.45 (1H, dd, *J* 13.1, 4.4, C(5')H_B), 3.64 (1H, app td, *J* 8.5, 4.4, C(2')*H*), 4.00 (1H, dd, *J* 8.5, 4.4, C(3')*H*), 4.29 (1H, app td, *J* 4.4, 2.1, C(4')*H*); δ_C (125 MHz, D_2O) 36.6 (*C*(2)), 49.0 (*C*(5')),

57.8 (*C*(2')), 69.1 (*C*(3')), 74.0 (*C*(4')), 177.4 (*C*(1)); *m/z* (ESI$^+$) 162 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_6H_{12}NO_4^+$ ([M+H]$^+$) requires 162.0761; found 162.0767.

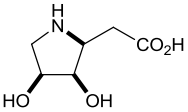
tert-Butyl (2'*S*,3'*R*,4'*S*)-2-[*N*(1')-3',4'-dihydroxy-3',4'-*O*-isopropylidenepyrrolidin-2'-yl]acetate 391



Step 1: $NaIO_4$ (321 mg, 1.50 mmol) was added to a solution of **381** (150 mg, 0.300 mmol, >99:1 dr) in MeOH (6 mL) at rt and the resultant suspension was stirred at rt for 16 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. The residue was dissolved in Et_2O (6 mL) and then filtered through a short plug of Celite® (eluent Et_2O) and the filtrate was concentrated *in vacuo* to give **390** in >99:1 dr (134 mg).

Step 2: $Pd(OH)_2$/C (50% w/w of substrate, 67 mg) was added to a stirred solution of the residue (134 mg) in MeOH (3 mL) at rt. The resultant mixture was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (5 atm) for 18 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (eluent EtOAc) gave **391** as a pale yellow oil (42 mg, 54% over 2 steps, >99:1 dr); $[\alpha]_D^{25}$ +46.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3292 (N–H), 2979, 2934 (C–H), 1727 (C=O); δ_H (400 MHz, $CDCl_3$) 1.28 (3H, s, *Me*CMe), 1.41 (3H, s, *Me*CMe), 1.43 (9H, s, C*Me*$_3$), 2.28 (1H, br s, N*H*), 2.50 (1H, dd, *J* 16.5, 6.7, C(2)H_A), 2.59 (1H, dd, *J* 16.5, 7.1, C(2)H_B), 2.61 (1H, dd, *J* 13.1, 3.9, C(5')H_A), 2.98 (1H, app td, *J* 6.8, 4.2, C(2')*H*), 3.04 (1H, app d, *J* 13.1, C(5')H_B), 4.56 (1H, dd, *J* 5.5, 4.2, C(3')*H*), 4.65 (1H, app dd, *J* 5.5, 3.9, C(4')*H*); δ_C (100 MHz, $CDCl_3$) 23.9, 25.7 (2 × *Me*CMe), 28.1 (C*Me*$_3$), 34.6 (*C*(2)), 52.8 (*C*(5')), 59.7 (*C*(2')), 80.6 (*C*Me$_3$), 81.3 (*C*(3')), 81.6 (*C*(4')), 110.5 (Me*C*Me), 171.1 (*C*(1)); *m/z* (ESI$^+$) 258 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{13}H_{24}NO_4^+$ ([M+H]$^+$) requires 258.1700; found 258.1696.

(2'*S*,3'*R*,4'*S*)-2-[*N*(1')-3',4'-Dihydroxypyrrolidin-2'-yl]acetic acid 304

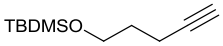


A solution of **391** (42 mg, 0.16 mmol, >99:1 dr) in 2.0 M aq HCl (2 mL) was heated at reflux for 8 h. The reaction mixture was allowed to cool to rt and was then concentrated *in vacuo.* Purification via ion exchange chromatography (DOWEX 50WX8-200, eluent 1.0 M aq NH_4OH) gave **304** as a pale

orange solid (22 mg, 84%, >99:1 dr); mp 160-170 °C (dec); $[\alpha]_D^{25}$ –9.9 (*c* 1.0 in H_2O); ν_{max} (ATR) 3368 (O–H), 3085, 2932 (C–H), 2323, 2139 (NH_3^+) 1526, 1396 (CO_2^-); δ_H (500 MHz, D_2O) 2.58 (1H, dd, *J* 16.9, 8.5, C(2)H_A), 2.63 (1H, dd, *J* 16.9, 6.0, C(2)H_B), 3.05 (1H, dd, *J* 12.0, 7.9, C(5')H_A), 3.42 (1H, dd, *J* 12.0, 7.9, C(5')H_B), 3.75 (1H, ddd, *J* 8.5, 6.0, 4.0, C(2')*H*), 4.15 (1H, app t, *J* 4.0, C(3')*H*), 4.42 (1H, app td, *J* 7.9, 4.0, C(4')*H*); δ_C (125 MHz, D_2O) 34.0 (*C*(2)), 46.8 (*C*(5')), 59.2 (*C*(2')), 70.0 (*C*(4')), 70.7 (*C*(3')), 177.6 (*C*(1)); *m/z* (ESI^+) 162 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_6H_{12}NO_4^+$ ($[M+H]^+$) requires 162.0761; found 162.0765.

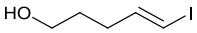
5.5 Experimental for chapter 4

5-(*tert*-Butyldimethylsilyloxy)pent-1-yne 467



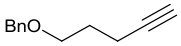
Imidazole (12.1 g, 178 mmol), DMAP (290 mg, 2.38 mmol) and TBDMSCl (10.7 g, 59.4 mmol) were sequentially added to a solution of **466** (1.00 g, 59.4 mmol) in CH_2Cl_2 (425 mL) at rt and the resultant solution was stirred at rt for 16 h. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in Et_2O (200 mL) and the resultant solution was washed with 1.0 M aq HCl (10 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 ºC petrol/Et_2O, 50:1) gave **467** as a colourless oil (10.4 g, 88%);[26] δ_H (400 MHz, $CDCl_3$) 0.06 (6H, app s, 2 × *Me*SiMe), 0.90 (9H, s, SiC*Me*$_3$), 1.70-1.77 (2H, m, C(4)*H*$_2$), 1.94 (1H, t, *J* 2.6, C(1)*H*), 2.28 (1H, td, *J* 7.1, 2.6, C(3)*H*$_2$), 3.70 (2H, t, *J* 6.1, C(5)*H*$_2$).

(*E*)-1-Iodo-5-hydroxypent-1-ene 468



DIBAL-H (1.0 M in THF, 2.77 mL, 2.77 mmol) was added to a solution of Cp_2ZrCl_2 (810 mg, 2.77 mmol) in THF (14.5 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 30 min and then a solution of **467** (500 mg, 2.52 mmol) in THF (3.5 mL) was added via cannula. The reaction mixture was then allowed to warm to rt and stirring was continued at rt until a homogenous solution resulted (*ca.* 30 min). The reaction mixture was then cooled to −78 °C and a solution of I_2 (832 mg, 3.28 mmol) in THF (11 mL) was added via cannula. The reaction mixture was stirred at −78 °C for 1 h then 1.0 M aq HCl (50 mL) was then added and the resultant mixture was extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed sequentially with satd aq $Na_2S_2O_3$ (100 mL) and satd aq $NaHCO_3$ (100 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 3:1) gave **468** as a pale yellow oil (343 mg, 64%, >99:1 dr);[27] δ_H (400 MHz, $CDCl_3$) 1.62-1.72 (2H, m, C(4)*H*$_2$), 2.17 (2H, app q, *J* 7.3, C(3)*H*$_2$), 3.64-3.70 (2H, m, C(5)*H*$_2$), 6.05 (1H, d, *J* 14.3, C(1)*H*), 6.54 (1H, dt, *J* 14.3, 7.3, C(2)*H*).

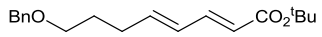
5-Benzyloxypent-1-yne 469



NaH (60% dispersion in mineral oil, 5.94 g, 149 mmol) was stirred vigorously in 30-40 °C petrol (50 mL) at rt for 10 min and then the solvent was decanted off via cannula. THF (100 mL) was then added to the residue and the resultant suspension was cooled to 0 °C. A solution of **466** (5.00 g, 59.4 mmol) in THF (100 mL) was then added dropwise via cannula and the reaction mixture was

stirred at rt for 45 min. BnBr (10.6 mL, 89.2 mmol) was then added and stirring was continued at rt for 16 h. The reaction mixture was then diluted with Et_2O (150 mL) and the resultant solution was washed with satd aq $NaHCO_3$ (2 × 100 mL). The aqueous layer was extracted with Et_2O (2 × 100 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 4:1) gave **469** as a pale yellow oil (9.10 g, 88%);[28] δ_H (400 MHz, $CDCl_3$) 1.80-1.88 (2H, m, C(4)H_2), 1.95 (1H, t, *J* 2.7, C(1)*H*), 2.33 (2H, td, *J* 7.2, 2.7, C(3)H_2), 3.59 (2H, t, *J* 6.1, C(5)H_2), 4.53 (2H, s, OCH_2Ph), 7.25-7.39 (5H, m, *Ph*).

tert-Butyl (*E*,*E*)-8-(benzyloxy)octa-2,4-dienoate 471

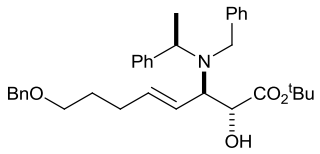


Step 1: DIBAL-H (1.0 M in THF, 5.27 mL, 5.27 mmol) was added to a stirred solution of Cp_2ZrCl_2 (1.53 g, 5.27 mmol) in THF (15 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 30 min and then a solution of **469** (833 mg, 4.77 mmol) in THF (3 mL) was added via cannula. The reaction mixture was then allowed to warm to rt and stirring was continued at rt until a homogenous solution resulted (*ca.* 30 min). The reaction mixture was then cooled to −78 °C and a solution of I_2 (1.58 g, 6.23 mmol) in THF (8 mL) was added via cannula. The reaction mixture was stirred at −78 °C for 1 h then 1.0 M aq HCl (50 mL) was added and the resultant mixture was extracted with Et_2O (2 × 50 mL). The combined organic extracts were washed sequentially with satd aq $Na_2S_2O_3$ (100 mL) and satd aq $NaHCO_3$ (100 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 50:1) gave an 82:18 mixture of **470** and **469** respectively (1.27 g). Data for **470**:[28] δ_H (400 MHz, $CDCl_3$) 1.67-1.76 (2H, m, C(4)H_2), 2.17 (2H, app dq, *J* 7.3, 1.4, C(3)H_2), 3.47 (2H, t, *J* 6.2, C(5)H_2), 4.50 (2H, s, OCH_2Ph), 6.00 (1H, dt, *J* 14.3, 1.4, C(1)*H*), 6.51 (1H, dt, *J* 14.3, 7.3, C(2)*H*), 7.25-7.41 (5H, m, *Ph*).

Step 2: tert-Butyl acrylate **163** (1.23 mL, 8.43 mmol) then $Pd(OAc)_2$ (95 mg, 0.42 mmol) were added to a desgassed solution of the residue (1.27 g), Bu_4NCl (1.17 g, 4.20 mmol) and $NaHCO_3$ (883 mg, 10.5 mmol) in DMF (27 mL) at rt and the resultant mixture was stirred in the dark for 48 h. The reaction mixture was then partitioned between H_2O (50 mL) and Et_2O (50 mL) and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic extracts were washed with H_2O (100 mL) and brine (100 mL), then dried and concentrated *in vacuo* to give a 66:34 mixture of **471** and **470** respectively. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 15:1) gave **471** as a colourless oil (607 mg, 42% over 2 steps, >99:1 dr); ν_{max} (ATR) 3029, 2977, 2933, 2856 (C–H), 1703 (C=O), 1643, 1616 (C=C); δ_H (400 MHz, $CDCl_3$) 1.50 (9H, s, CMe_3),

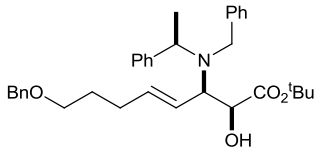
1.71-1.79 (2H, m, C(7)H_2), 2.28 (2H, app q, *J* 7.1, C(6)H_2), 3.49 (2H, t, *J* 6.3, C(8)H_2), 4.50 (2H, s, OCH_2Ph), 5.73 (1H, d, *J* 15.4, C(2)*H*), 6.03-6.20 (2H, m, C(4)*H*, C(5)*H*), 7.16 (1H, dd, *J* 15.4, 10.4, C(3)*H*), 7.25-7.39 (5H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 28.2 (CMe_3), 28.9 (*C*(7)), 29.6 (*C*(6)), 69.4 (*C*(8)), 72.9 (O*C*H_2Ph), 80.0 (*C*Me$_3$), 121.4 (*C*(2)), 127.6 (*p-Ph*), 127.6, 128.4 (*o,m-Ph*), 128.8 (*C*(4)), 138.5 (*i-Ph*), 142.9 (*C*(5)), 143.8 (*C*(3)), 166.6 (*C*(1)); *m/z* (ESI^+) 325 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{19}H_{26}NaO_3^+$ ($[M+Na]^+$) requires 325.1774; found 325.1769.

tert-Butyl (*R,R,R,E*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-8-(benzyloxy)oct-4-enoate 473



Following *General Procedure 4*, (*R*)-**123** (4.96 g, 11.7 mmol) in THF (95 mL), BuLi (2.4 M, 9.49 mL, 22.8 mmol) and **471** (3.55 g, 11.7 mmol, >99:1 dr) were reacted in THF (95 mL) at –78 °C, followed by the addition of (–)-CSO **102** (5.39 g, 23.5 mmol), to give **473** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 10:1) gave **473** as a colourless oil (4.59 g, 74%, >99:1 dr); $[\alpha]_D^{25}$ –56.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3501 (O–H), 3085, 3062, 3028, 2976, 2934, 2854 (C–H), 1723 (C=O), 1602 (C=C); δ_H (400 MHz, $CDCl_3$) 1.35 (9H, s, CMe_3), 1.38 (3H, d, *J* 6.8, C(α)*Me*), 1.68-1.77 (2H, m, C(7)H_2), 2.10-2.24 (2H, m, C(6)H_2), 2.94 (1H, br s, O*H*), 3.50 (2H, t, *J* 6.4, C(8)H_2), 3.57 (1H, dd, *J* 9.2, 2.1, C(3)*H*), 3.79 (1H, d, *J* 14.4, NCH_AH_BPh), 4.01 (1H, d, *J* 14.4, NCH_AH_BPh), 4.14 (1H, d, *J* 2.1, C(2)*H*), 4.26 (1H, q, *J* 6.8, C(α)*H*), 4.53 (2H, s, OCH_2Ph), 5.54 (1H, dt, *J* 15.3, 6.7, C(5)*H*), 5.74 (1H, dd, *J* 15.3, 9.2, C(4)*H*), 7.20-7.46 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.0 (C(α)*Me*), 28.0 (CMe_3), 29.3, 29.3 (*C*(6), *C*(7)), 51.4 (NCH_2Ph), 56.8 (*C*(α)), 62.9 (*C*(3)), 69.7 (*C*(8)), 73.0 (O*C*H_2Ph), 74.7 (*C*(2)), 81.9 (*C*Me$_3$), 125.9 (*C*(4)), 126.6, 126.7, 127.5 (*p-Ph*), 127.7, 128.0, 128.0, 128.2, 128.4, 128.5 (*o,m-Ph*), 134.4 (*C*(5)), 138.6, 141.6, 144.3 (*i-Ph*), 172.8 (*C*(1)); *m/z* (ESI^+) 530 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{34}H_{44}NO_4^+$ ($[M+H]^+$) requires 530.3265; found 530.3263.

***tert*-Butyl (2*S*,3*R*,α*R*,*E*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-8-(benzyloxy)oct-4-enoate 475**

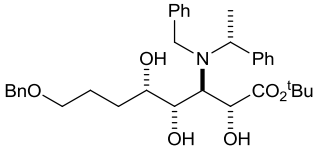


Step 1: DMSO (1.34 mL, 18.9 mmol) was added dropwise to a stirred solution of $(ClCO)_2$ (0.16 mL, 1.9 mmol) in CH_2Cl_2 (10 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 5 min. A solution of **473** (500 mg, 0.944 mmol, >99:1 dr) in CH_2Cl_2 (10 mL) was then added via cannula and the reaction mixture was stirred at −78 °C for 30 min. Et_3N (0.53 mL, 3.8 mmol) was then added and stirring was continued at −78 °C for a further 10 min. The reaction mixture was allowed to warm to rt over 20 min. H_2O (20 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **474** as a yellow oil (566 mg); δ_H (400 MHz, $CDCl_3$) 1.37 (3H, d, *J* 6.8, C(α)*Me*), 1.46 (9H, s, C*Me*$_3$), 1.64-1.73 (2H, m, C(7)*H*$_2$), 2.12-2.20 (2H, m, C(6)*H*$_2$), 3.45 (2H, t, *J* 6.5, C(8)*H*$_2$), 3.80 (1H, d, *J* 14.7, NC*H*$_A$H$_B$Ph), 3.87 (1H, d, *J* 14.7, NCH$_A$*H*$_B$Ph), 4.01 (1H, q, *J* 6.8, C(α)*H*), 4.48 (2H, s, OC*H*$_2$Ph), 4.59 (1H, d, *J* 8.4, C(3)*H*), 5.58 (1H, dt, *J* 15.6, 6.5, C(5)*H*), 5.69 (1H, dd, *J* 15.6, 8.4, C(4)*H*), 7.20-7.38 (15H, m, *Ph*); *m/z* (ESI$^+$) 528 ([M+H]$^+$, 100%).

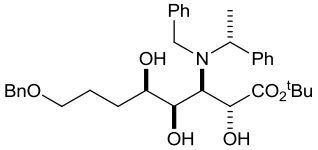
Step 2: The residue (566 mg) was dissolved in MeOH (4 mL) and the resultant solution was cooled to –20 °C. $NaBH_4$ (36 mg, 0.94 mmol) was added portionwise and the reaction mixture was then stirred at –20 °C for 2 h. The reaction mixture was then allowed to warm to rt and concentrated *in vacuo*. The residue was partitioned between H_2O (30 mL) and Et_2O (30 mL) and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give a 90:10 mixture of **475** and **473** respectively. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 10:1) gave **475** as a pale yellow oil (330 mg, 66% over 2 steps, >99:1 dr); $[\alpha]_D^{25}$ −66.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3411 (O–H), 3087, 3062, 3029, 2976, 2933, 2854 (C–H), 1731 (C=O), 1602 (C=C); δ_H (400 MHz, $CDCl_3$) 1.36 (9H, s, C*Me*$_3$), 1.44 (3H, d, *J* 6.8, C(α)*Me*), 1.70-1.81 (2H, m, C(7)*H*$_2$), 2.17-2.24 (2H, m, C(6)*H*$_2$), 3.36 (1H, ddd, *J* 8.9, 5.9, 2.4, C(3)*H*), 3.53 (2H, t, *J* 6.6, C(8)*H*$_2$), 3.63 (1H, d, *J* 13.5, NC*H*$_A$H$_B$Ph), 3.84 (1H, d, *J* 13.5, NCH$_A$*H*$_B$Ph), 3.86 (1H, d, *J* 8.9, C(2)*H*), 4.10 (1H, q, *J* 6.8, C(α)*H*), 4.55 (2H, s, OC*H*$_2$Ph), 5.56-5.68 (2H, m, C(4)*H*, C(5)*H*), 7.21-7.39 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.7 (C(α)*Me*), 27.9 (C*Me*$_3$), 29.2, 29.4 (*C*(6), *C*(7)), 50.2 (NCH_2Ph), 56.5 (*C*(α)), 62.5 (*C*(3)), 69.7 (*C*(8)), 71.9 (*C*(2)), 73.0 (OCH_2Ph), 81.1 (*C*Me$_3$), 125.9 (*C*(4)), 127.2, 127.2, 127.6 (*p-Ph*), 127.6, 127.8, 128.4, 128.4, 128.5, 129.0 (*o,m-Ph*), 135.9 (*C*(5)), 138.6, 139.5, 143.2 (*i-Ph*), 171.5 (*C*(1));

m/z (ESI$^+$) 530 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{44}NO_4^+$ ([M+H]$^+$) requires 530.3265; found 530.3270.

tert-Butyl (2*R*,3*R*,4*S*,5*S*,α*R*)- and (*R*,*R*,*R*,*R*,*R*)-2,4,5-trihydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-8-(benzyloxy)octanoate 476 and 477



476



477

Method A: OsO_4 (10 mg, 38 μmol) was added to a stirred solution of **473** (200 mg, 0.378 mmol, >99:1 dr) in THF (1.3 mL) and H_2O (0.31 mL) at rt. A solution of NMO (181 mg, 1.55 mmol) in H_2O (0.25 mL) was then added and the resultant mixture was stirred at rt for 12 h. Satd aq Na_2SO_3 (1 mL) was then added and the resultant mixture was left to stir at rt for 1 h. The reaction mixture was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give an 80:20 mixture of **476** and **477** respectively. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 2:1) gave **477** as a pale yellow oil (21 mg, 10%, >99:1 dr); $[\alpha]_D^{25}$ –28.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3483 (O–H), 3086, 3062, 3029, 2973, 2933, 2856 (C–H), 1716 (C=O); δ_H (500 MHz, $CDCl_3$) 1.43 (3H, d, *J* 7.3, C(α)*Me*), 1.56 (9H, s, C*Me*$_3$), 1.61-1.82 (4H, m, C(6)*H*$_2$, C(7)*H*$_2$), 2.37 (1H, br s, O*H*), 3.03 (1H, d, *J* 3.0, O*H*), 3.20 (1H, app dd, *J* 7.0, 4.1, C(5)*H*), 3.49 (2H, t, *J* 6.2, C(8)*H*$_2$), 3.61 (1H, d, *J* 14.8, NC*H*$_A$H$_B$Ph), 3.62 (1H, app s, C(2)*H*), 3.82 (1H, app d, *J* 8.8, C(4)*H*), 3.93 (1H, app d, *J* 8.8, C(3)*H*), 4.03 (1H, q, *J* 7.3, C(α)*H*), 4.29 (1H, d, *J* 14.8, NCH$_A$*H*$_B$Ph), 4.49 (1H, d, *J* 12.0, OC*H*$_A$H$_B$Ph), 4.52 (1H, d, *J* 12.0, OCH$_A$*H*$_B$Ph), 7.25-7.44 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 20.0 (C(α)*Me*), 26.6 (*C*(7)), 27.7 (C*Me*$_3$), 32.5 (*C*(6)), 51.4 (N*C*H$_2$Ph), 57.1 (*C*(α)), 58.5 (*C*(3)), 67.4 (*C*(4)), 69.3, 69.5 (*C*(2), *C*(5)), 70.4 (*C*(8)), 72.9 (O*C*H$_2$Ph), 83.9 (*C*Me$_3$), 127.1, 127.5, 127.6 (*p-Ph*), 127.7, 128.1, 128.3, 128.6, 128.6, 128.7 (*o,m-Ph*), 138.5, 139.7, 140.0 (*i-Ph*), 174.0 (*C*(1)); *m/z* (ESI$^+$) 564 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{46}NO_6^+$ ([M+H]$^+$) requires 564.3320; found 564.3316. Further elution gave **476** as a pale yellow oil (124 mg, 58%, >99:1 dr); $[\alpha]_D^{25}$ –20.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3483 (O–H), 3085, 3062, 3028, 2973, 2932, 2856 (C–H), 1718 (C=O); δ_H (400 MHz, $CDCl_3$) 1.41 (3H, d, *J* 7.1, C(α)*Me*), 1.52 (9H, s, C*Me*$_3$), 1.57-1.87 (4H, m, C(6)*H*$_2$, C(7)*H*$_2$), 2.40 (2H, br s, O*H*), 3.23 (1H, br s, O*H*), 3.50-3.60 (2H, m, C(8)*H*$_2$), 3.63 (1H, app s, C(2)*H*), 3.67-3.73 (1H, m, C(4)*H*) overlapping 3.69 (1H, d, *J* 15.5, NC*H*$_A$H$_B$Ph), 3.87 (1H, app d, *J* 9.9, C(3)*H*), 3.92 (1H, q, *J* 7.1, C(α)*H*), 4.23 (1H, app dd, *J* 8.5, 4.7, C(5)*H*), 4.33 (1H, d, *J* 15.5, NCH$_A$*H*$_B$Ph), 4.53 (1H, d, *J* 12.1,

OC*H*$_A$H$_B$Ph), 4.57 (1H, d, *J* 12.1, OCH$_A$*H*$_B$Ph), 7.21-7.44 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 19.8 (C(α)*Me*), 26.5, 31.5 (*C*(6), *C*(7)), 28.0 (C*Me*$_3$), 51.7 (N*C*H$_2$Ph), 58.3 (*C*(α)), 59.1 (*C*(3)), 69.4 (*C*(5)), 70.3 (*C*(2)), 70.6 (*C*(8)), 71.2 (*C*(4)), 73.0 (O*C*H$_2$Ph), 82.2 (*C*Me$_3$), 126.6, 127.3, 127.6 (*p-Ph*), 127.7, 127.7, 128.0, 128.1, 128.4, 128.4 (*o,m-Ph*), 138.3, 141.6, 141.6 (*i-Ph*), 174.3 (*C*(1)); *m/z* (ESI$^+$) 564 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{46}NO_6^+$ ([M+H]$^+$) requires 564.3320; found 564.3319.

Method B – Step 1: OsO_4 (106 mg, 0.417 mmol) was added to a stirred solution of **473** (200 mg, 0.378 mmol, >99:1 dr) and TMEDA (79 μL, 0.53 mmol) in CH_2Cl_2 (11.5 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 1 h. The reaction mixture was allowed to warm to rt over 15 min and was then concentrated *in vacuo*. The residue was then passed through a short plug of silica gel (eluent $CHCl_3$/MeOH, 20:1) and was concentrated *in vacuo* to give **482** as a brown oil (200 mg).

Method B – Step 2: The residue (200 mg) was dissolved in CH_2Cl_2 (4 mL) and $H_2N(CH_2)_2NH_2$ (0.18 mL, 2.6 mmol) was added at rt and the resultant mixture was stirred at rt for 48 h. The residue was then passed through a short plug of silica gel (eluent EtOAc) and was concentrated *in vacuo* to give **477** as a pale yellow oil (11 mg, 5% over 2 steps, >99:1 dr).

Method C – Step 1: OsO_4 (104 mg, 0.409 mmol) was added to a stirred solution of **473** (197 mg, 0.372 mmol, >99:1 dr) and TMEDA (78 μL, 0.52 mmol) in CH_2Cl_2 (11.5 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 1 h. The reaction mixture was allowed to warm to rt over 15 min and was then concentrated *in vacuo*. The residue was then passed through a short plug of silica gel (eluent $CHCl_3$/MeOH, 20:1) and was concentrated *in vacuo* to give **482** as a brown oil (318 mg).

Method C – Step 2: The residue (318 mg) was dissolved in THF (10 mL) and satd aq Na_2SO_3 (10 mL) was added. The resultant mixture was heated at reflux for 16 h, then allowed to cool to rt and EtOH (10 mL) was added. The resultant mixture was stirred for 1 h at rt, then filtered through Celite© (eluent EtOH) and the filtrate was concentrated *in vacuo* to give **482** as a brown oil (300 mg).

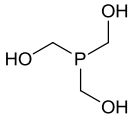
Method D – Step 1: OsO_4 (104 mg, 0.409 mmol) was added to a stirred solution of **473** (197 mg, 0.372 mmol, >99:1 dr) and TMEDA (78 μL, 0.52 mmol) in CH_2Cl_2 (11.5 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 1 h. The reaction mixture was allowed to warm to rt over 15 min and was then concentrated *in vacuo*. The residue was then passed through a short plug of silica gel (eluent $CHCl_3$/MeOH, 20:1) and was concentrated *in vacuo* gave **482** as a brown oil (318 mg).

Method D – Step 2: The residue (318 mg) was dissolved in MeOH (4 mL) and conc HCl (5 drops) was added at rt. The resultant mixture was stirred at rt for 16 h then concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 2:1) gave **477** as a pale yellow oil (32 mg, 15%, >99:1 dr). Further elution gave **476** as a pale yellow oil (17 mg, 8% over 2 steps, >99:1 dr).

Method E – Step 1: OsO_4 (106 mg, 0.417 mmol) was added to a stirred solution of **473** (200 mg, 0.378 mmol, >99:1 dr) and TMEDA (79 μL, 0.53 mmol) in CH_2Cl_2 (11.5 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 1 h. The reaction mixture was allowed to warm to rt over 15 min and was then concentrated *in vacuo*. The residue was then passed through a short plug of silica gel (eluent $CHCl_3$/MeOH, 20:1) and was concentrated *in vacuo* to give **482** as a brown oil (318 mg).

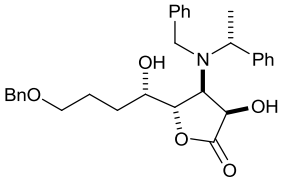
Method E – Step 2: The residue (318 mg) was dissolved in CH_2Cl_2 (20 mL) and then $P(CH_2OH)_3$ **483** (2.34 g, 18.9 mmol) and Et_3N (1.05 mL, 7.55 mmol) were added sequentially. The reaction mixture was stirred at rt for 5 min then SiO_2 (~1.0 g) was added. The resultant mixture was stirred at rt for 48 h then concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 2:1) gave **477** as a pale yellow oil (115 mg, 54% over 2 steps, >99:1 dr). Further elution gave **476** as a pale yellow oil (21 mg, 10% over 2 steps, >99:1 dr).

Tris(hydroxymethyl)phosphine 483



Dry tetrakis(hydroxymethyl)phosphonium chloride[29] (321 g, 1.68 mmol) was dissolved in Et_3N (3.0 L) and the resultant mixture was heated at 60 °C for 1 h. The reaction mixture was then allowed to cool to rt and filtered (eluent Et_3N), then the filtrate was concentrated *in vacuo* to give **483** as a colourless oil (136 g, 65%);[30] δ_H (400 MHz, MeOH-d_4) 4.13 (6H, d, *J* 6.1, $P(CH_2OH)_3$).

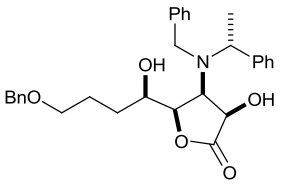
(2*R*,3*S*,4*S*,5*S*,α*R*)-2,5-Dihydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-8-benzyloxy-4-octylolactone 478



F_3CCO_2H (1 mL) was added to a solution of **476** (106 mg, 0.188 mmol, >99:1 dr) in CH_2Cl_2 (5 mL) at rt and the resultant solution was stirred at rt for 16 h. The reaction mixture was then cooled to 0 °C

and neutralised by the dropwise addition of satd aq $NaHCO_3$ (~10 mL). The resultant mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 2:1) gave **478** as a colourless oil (72 mg, 78%, >99:1 dr); $[\alpha]_D^{25}$ +31.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3425 (O–H), 3062, 3030, 2934, 2859 (C–H), 1775 (C=O); δ_H (400 MHz, $CDCl_3$) 1.39 (3H, d, *J* 6.7, C(α)*Me*), 1.70-1.90 (4H, m, C(6)H_2, C(7)H_2), 3.44-3.51 (1H, m, C(8)H_A), 3.56-3.63 (1H, m, C(8)H_B), 3.68 (1H, d, *J* 13.1, NC$H_A$$H_B$Ph), 3.73 (1H, app d, *J* 8.7, C(3)*H*), 3.77-3.81 (1H, m, C(5)*H*) overlapping 3.81 (1H, d, *J* 13.1, NC$H_A$$H_B$Ph), 4.07 (1H, q, *J* 6.7, C(α)*H*), 4.28 (1H, d, *J* 8.7, C(2)*H*), 4.50 (1H, d, *J* 11.9, OC$H_A$$H_B$Ph), 4.54 (1H, d, *J* 11.9, OC$H_A$$H_B$Ph), 4.57 (1H, app br s, C(4)*H*), 7.16-7.45 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.9 (C(α)*Me*), 26.6 (*C*(7)), 31.9 (*C*(6)), 50.6 (N*C*H_2Ph), 55.1 (*C*(α)), 57.2 (*C*(3)), 64.8 (*C*(2)), 70.4 (*C*(8)), 72.0 (*C*(5)), 73.4 (O*C*H_2Ph), 81.8 (*C*(4)), 127.4, 127.9, 128.0 (*p-Ph*), 127.5, 127.9, 128.6, 128.6, 128.9, 129.1 (*o,m-Ph*), 137.3, 137.7, 141.9 (*i-Ph*), 177.4 (*C*(1)); *m/z* (ESI^+) 512 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{30}H_{35}NNaO_5^+$ ($[M+Na]^+$) requires 512.2407; found 512.2408.

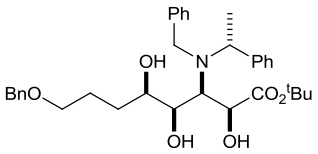
(2*R*,3*S*,4*R*,5*R*,α*R*)-2,5-Dihydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-8-benzyloxy-4-octylolactone 479



F_3CCO_2H (0.5 mL) was added to a solution of **477** (50 mg, 89 μmol, >99:1 dr) in CH_2Cl_2 (3 mL) at rt and the resultant solution was stirred at rt for 16 h. The reaction mixture was then cooled to 0 °C and was neutralised by the dropwise addition of satd aq $NaHCO_3$ (~5 mL). The resultant mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 2:1) gave **479** as a colourless oil (10 mg, 23%, >99:1 dr); $[\alpha]_D^{25}$ +47.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3358 (O–H), 3061, 3029, 2923, 2853 (C–H), 1774 (C=O); δ_H (400 MHz, $CDCl_3$) 1.38 (3H, d, *J* 7.1, C(α)*Me*), 1.63-1.73 (3H, m, C(6)H_2, C(7)H_A), 1.75-1.84 (1H, m, C(7)H_B), 3.43-3.49 (1H, m, C(8)H_A), 3.53-3.59 (1H, m, C(8)H_B), 3.61 (1H, app t, *J* 6.9, C(3)*H*), 3.82 (1H, d, *J* 15.6, NC$H_A$$H_B$Ph), 3.85-3.89 (1H, m, C(5)*H*), 4.10 (1H, br s, C(2)*H*), 4.17 (1H, d, *J* 15.6, NC$H_A$$H_B$Ph), 4.24 (1H, dd, *J* 6.9, 2.8, C(4)*H*), 4.33 (1H, q, *J* 7.1, C(α)*H*), 4.47 (1H, br s, O*H*), 4.50 (1H, d, *J* 12.3, OC$H_A$$H_B$Ph), 4.53 (1H, d, *J* 12.3, OC$H_A$$H_B$Ph), 4.79 (1H, br s, O*H*), 7.21-7.44 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$)

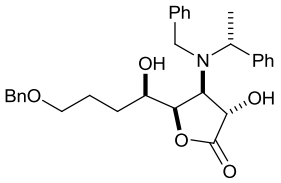
19.7 (C(α)*Me*), 26.4 (*C*(7)), 31.5 (*C*(6)), 52.9 (N*C*H$_2$Ph), 58.4 (*C*(α)), 61.1 (*C*(3)), 68.0 (*C*(5)), 68.5 (*C*(2)), 70.4 (*C*(8)), 73.4 (O*C*H$_2$Ph), 84.4 (*C*(4)), 127.0, 127.6, 128.0 (*p-Ph*), 127.9, 127.9, 128.0, 128.5, 128.5, 128.6 (*o*,*m-Ph*), 137.1, 140.9, 141.4 (*i-Ph*), 175.5 (*C*(1)); *m/z* (ESI$^+$) 512 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{35}NNaO_5^+$ ([M+Na]$^+$) requires 512.2407; found 512.2418.

tert-Butyl (2*S*,3*R*,4*R*,5*R*,α*R*)-2,4,5-trihydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-8-(benzyloxy)octanoate 480



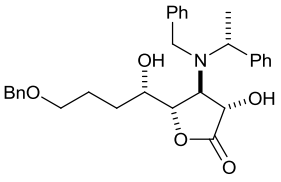
OsO_4 (7 mg, 30 μmol) was added to a stirred solution of **475** (154 mg, 0.291 mmol, >99:1 dr) in THF (1.0 mL) and H_2O (0.25 mL) at rt. A solution of NMO (140 mg, 1.19 mmol) in H_2O (0.25 mL) was then added and the resultant mixture was stirred at rt for 12 h. Satd aq Na_2SO_3 (1 mL) was then added and the resultant mixture was left to stir at rt for 1 h. The reaction mixture was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 4:1) gave **480** as a pale yellow oil (40 mg, 24%, >99:1 dr); $[\alpha]_D^{25}$ +50.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3439 (O–H), 3086, 3062, 3029, 2974, 2931, 2856 (C–H), 1721 (C=O); δ_H (500 MHz, $CDCl_3$) 1.41 (3H, d, *J* 6.9, C(α)*Me*), 1.48 (9H, s, C*Me*$_3$), 1.57-1.83 (4H, m, C(6)*H*$_2$, C(7)*H*$_2$), 2.73 (1H, br s, O*H*), 2.88 (1H, d, *J* 4.7, O*H*), 3.50 (2H, t, *J* 6.2, C(8)*H*$_2$), 3.54-3.63 (3H, m, C(3)*H*, C(4)*H*, C(5)*H*), 3.89 (1H, d, *J* 14.6, NC*H*$_A$H$_B$Ph), 3.90 (1H, app s, C(2)*H*), 4.15 (1H, q, *J* 6.9, C(α)*H*), 4.27 (1H, d, *J* 14.6, NCH$_A$*H*$_B$Ph), 4.49 (1H, d, *J* 12.0, OC*H*$_A$H$_B$Ph), 4.52 (1H, d, *J* 12.0, OCH$_A$*H*$_B$Ph), 7.24-7.41 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 20.5 (C(α)*Me*), 26.4, 31.7 (*C*(6), *C*(7)), 28.0 (C*Me*$_3$), 51.9 (N*C*H$_2$Ph), 59.6 (*C*(α)), 62.1 (*C*(3)), 70.3 (*C*(8)), 70.5, 70.5, 71.2 (*C*(2), *C*(4), *C*(5)), 72.9 (O*C*H$_2$Ph), 83.4 (*C*Me$_3$), 127.0, 127.5, 127.6 (*p-Ph*), 127.6, 128.0, 128.3, 128.5, 128.5, 128.6 (*o*,*m-Ph*), 138.4, 140.6, 142.4 (*i-Ph*), 173.0 (*C*(1)); *m/z* (ESI$^+$) 564 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{34}H_{46}NO_6^+$ ([M+H]$^+$) requires 564.3320; found 564.3311.

(2*S*,3*S*,4*R*,5*R*,α*R*)-2,5-Dihydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-8-benzyloxy-4-octylolactone 481



F_3CCO_2H (1 mL) was added to a solution of **480** (147 mg, 0.261 mmol, >99:1 dr) in CH_2Cl_2 (5 mL) at rt and the resultant solution was stirred at rt for 16 h. The reaction mixture was then cooled to 0 °C and was neutralised by the dropwise addition of satd aq $NaHCO_3$ (~10 mL). The resultant mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 3:1) gave **481** as a colourless oil (105 mg, 82%, >99:1 dr); $[\alpha]_D^{25}$ −14.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3422 (O–H), 3061, 3029, 2923, 2853 (C–H), 1768 (C=O); δ_H (400 MHz, $CDCl_3$) 1.48 (3H, d, *J* 6.8, C(α)*Me*), 1.67-1.84 (4H, m, C(6)H_2, C(7)H_2), 3.48-3.59 (2H, m, C(8)H_2), 3.87 (1H, dd, *J* 10.2, 7.7, C(3)*H*), 3.88 (1H, d, *J* 15.0, NC$H_A$$H_B$Ph), 3.96 (1H, d, *J* 15.0, NCH$_A$$H_B$Ph), 4.11 (1H, q, *J* 6.8, C(α)*H*), 4.25-4.32 (1H, m, C(5)*H*), 4.36 (1H, app d, *J* 7.7, C(4)*H*), 4.46 (1H, app dd, *J* 10.2, 3.6, C(2)*H*), 4.47 (1H, d, *J* 11.9, OC$H_A$$H_B$Ph), 4.51 (1H, d, *J* 11.9, OCH$_A$$H_B$Ph), 7.18-7.50 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 13.4 (C(α)*Me*), 26.4 (*C*(7)), 30.7 (*C*(6)), 50.6 (N*C*H$_2$Ph), 58.4 (*C*(α)), 65.5 (*C*(3)), 68.2 (*C*(2)), 69.1 (*C*(5)), 70.3 (*C*(8)), 73.2 (O*C*H$_2$Ph), 81.4 (*C*(4)), 127.1, 127.6, 127.8 (*p-Ph*), 127.7, 127.7, 127.9, 128.4, 128.6, 128.6 (*o*,*m-Ph*), 137.9, 141.1, 142.3 (*i-Ph*), 176.3 (*C*(1)); *m/z* (ESI$^+$) 512 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{30}H_{35}NNaO_5^+$ ([M+Na]$^+$) requires 512.2407; found 512.2412.

(2*S*,3*S*,4*S*,5*S*,α*R*)-2,5-Dihydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-8-benzyloxy-4-octylolactone 485



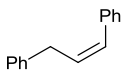
Method A – Step 1: OsO_4 (106 mg, 0.417 mmol) was added to a stirred solution of **475** (200 mg, 0.378 mmol, >99:1 dr) and TMEDA (79 μL, 0.53 mmol) in CH_2Cl_2 (11.5 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 1 h. The reaction mixture was allowed to warm to rt over 15 min, then concentrated *in vacuo*. The residue was then passed through a short plug of silica gel (eluent $CHCl_3$/MeOH, 20:1) and was concentrated *in vacuo* to give **484** as a brown oil (150 mg).

Method A – Step 2: The residue (150 mg) was dissolved in CH_2Cl_2 (4 mL) and $H_2N(CH_2)_2NH_2$ (0.18 mL, 2.6 mmol) was added. The resultant mixture was stirred at rt for 48 h then passed through a short plug of silica gel (eluent EtOAc) and was concentrated *in vacuo* to give **485** as a yellow oil (9 mg, 5% over 2 steps, >99:1 dr); $[\alpha]_D^{25}$ +29.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3408 (O–H), 3062, 3029, 2936, 2859 (C–H), 1774 (C=O); δ_H (500 MHz, $CDCl_3$) 1.45 (3H, d, *J* 6.9, C(α)*Me*), 1.62-1.76 (4H, m, C(6)H_2, C(7)H_2), 2.99 (1H, br s, C(2)O*H*), 3.08 (1H, br s, C(5)O*H*), 3.46-3.52 (1H, m, C(8)H_A), 3.53-3.58 (1H, m, C(8)H_B), 3.80-3.83 (1H, m, C(5)*H*) overlapping 3.80 (1H, d, *J* 15.5, NCH_AH_BPh), 3.84 (1H, d, *J* 15.5, NCH_AH_BPh), 3.88 (1H, app t, *J* 7.4, C(3)*H*), 3.93 (1H, dd, *J* 7.4, 1.0, C(4)*H*), 4.09 (1H, q, *J* 6.9, C(α)*H*), 4.36 (1H, d, *J* 7.4, C(2)*H*), 4.52 (1H, d, *J* 11.8, OCH_AH_BPh), 4.55 (1H, d, *J* 11.8, OCH_AH_BPh), 7.21-7.44 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 16.3 (C(α)*Me*), 26.5 (*C*(7)), 31.6 (*C*(6)), 50.0 (N*C*H_2Ph), 60.4 (*C*(α)), 64.5 (*C*(3)), 68.8 (*C*(2)), 69.2 (*C*(5)), 70.2 (*C*(8)), 73.3 (O*C*H_2Ph), 81.9 (*C*(4)), 127.2, 127.5, 127.9 (*p-Ph*), 127.8, 127.9, 127.9, 128.5, 128.5, 128.6 (*o,m-Ph*), 137.6, 140.3, 143.0 (*i-Ph*), 175.8 (*C*(1)); *m/z* (ESI^+) 490 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{30}H_{35}NNaO_5^+$ ($[M+Na]^+$) requires 512.2407; found 512.2403.

Method B – Step 1: OsO_4 (106 mg, 0.417 mmol) was added to a stirred solution of **475** (200 mg, 0.378 mmol, >99:1 dr) and TMEDA (79 μL, 0.53 mmol) in CH_2Cl_2 (11.5 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 1 h. The reaction mixture was allowed to warm to rt over 15 min, then concentrated *in vacuo*. The residue was then passed through a short plug of silica gel (eluent $CHCl_3$/MeOH, 20:1) and was concentrated *in vacuo* to give **484** as a brown oil (152 mg).

Method B – Step 2: The residue (152 mg) was dissolved in CH_2Cl_2 (20 mL) and then $P(CH_2OH)_3$ **483** (2.34 g, 18.9 mmol) and Et_3N (1.05 mL, 7.55 mmol) were added sequentially. The reaction mixture was stirred at rt for 5 min then SiO_2 (~1.0 g) was added. The resultant mixture was stirred at rt for 48 h then concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 2:1) gave **485** as a yellow oil (74 mg, 40% over 2 steps, >99:1 dr).

(*Z*)-1,3-Diphenylprop-1-ene 495

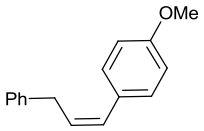


Step 1: Tf_2O (0.28 mL, 1.6 mmol) was added to a solution of **487** (100 mg, 0.745 mmol) and $^iPr_2NEt$ (0.29 mL, 1.6 mmol) in $ClCH_2CH_2Cl$ (5 mL) at 0 °C and the resultant solution was then heated at 80 °C for 18 h. The reaction mixture was then allowed to cool to rt, diluted with Et_2O (10 mL), and filtered. The filtrate was then washed sequentially with satd aq $NaHCO_3$ (50 mL) and brine (50 mL),

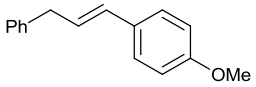
then dried and concentrated *in vacuo* to give an 88:12 mixture of (*Z*)-**489** and (*E*)-**488** respectively (215 mg).

Step 2: The residue (215 mg) was immediately dissolved in THF (7.5 mL), then phenylboronic acid **465** (101 mg, 0.828 mmol), PPh_3 (43 mg, 0.16 mmol) and $Pd(OAc)_2$ (17 mg, 76 μmol) were added sequentially. The resultant mixture was then degassed and 10% aq KOH (1.5 mL) was added. The reaction mixture was heated at 50 °C for 3 h, then allowed to cool to rt and stirred at rt for 16 h. The reaction mixture was then partitioned between EtOAc (50 mL) and H_2O (50 mL), and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give (*Z*)-**495** in 89:11 dr. Purification via flash column chromatography (eluent 30-40 °C petrol) gave (*Z*)-**495** as a colourless oil (37 mg, 26% over 2 steps, >99:1 dr);[31] δ_H (400 MHz, $CDCl_3$) 3.69 (2H, d, *J* 7.5, C(3)H_2), 5.88 (1H, dt, *J* 11.4, 7.5, C(2)*H*), 6.61 (1H, d, *J* 11.4, C(1)*H*), 7.18-7.40 (10H, m, *Ph*).

(*Z*)- and (*E*)-1-(*p*-Methoxyphenyl)-3-phenylprop-1-ene 497 and 496



497



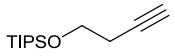
496

Step 1: Tf_2O (0.28 mL, 1.6 mmol) was added to a solution of **487** (100 mg, 0.745 mmol), **490** (163 mg, 0.745 mmol) and $^iPr_2NEt$ (0.29 mL, 1.6 mmol) in $ClCH_2CH_2Cl$ (5 mL) at 0 °C and the resultant solution was then heated at 80 °C for 18 h. The reaction mixture was then allowed to cool to rt, diluted with Et_2O (10 mL), and filtered. The filtrate was then washed sequentially with satd aq $NaHCO_3$ (50 mL) and brine (50 mL), then dried and concentrated *in vacuo* to give a 98:2 mixture of (*Z*)-**489** and (*E*)-**488** respectively (210 mg).

Step 2: The residue (210 mg) was immediately dissolved in THF (7.5 mL), then *p*-methoxyphenylboronic acid **462** (125 mg, 0.823 mmol), PPh_3 (43 mg, 0.16 mmol) and $Pd(OAc)_2$ (17 mg, 76 μmol) were added sequentially. The resultant mixture was then degassed and 10% aq KOH (1.5 mL) was added. The reaction mixture was heated at 50 °C for 3 h, then allowed to cool to rt and then stirred at rt for a further 16 h. The reaction mixture was then partitioned between EtOAc (50 mL) and H_2O (50 mL) and the aqueous layer was extracted with EtOAc (3 × 50 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give a 62:38 mixture of (*Z*)-**497** and (*E*)-**496** respectively. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 100:1) gave a 62:38 mixture of (*Z*)-**497** and (*E*)-**496** respectively as a colourless oil (70 mg, 48% over 2 steps).[32] Data for (*Z*)-**497**: [selected peaks] 3.69 (2H, d, *J* 7.5, C(3)H_2), 3.83 (3H,

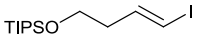
s, O*Me*), 5.78 (1H, dt, *J* 11.5, 7.5, C(2)*H*), 6.54 (1H, d, *J* 11.5, C(1)*H*). Data for (*E*)-**496**: [selected peaks] 3.54 (2H, d, *J* 6.9, C(3)H_2), 3.81 (3H, s, O*Me*), 6.22 (1H, dt, *J* 15.8, 6.9, C(2)*H*), 6.54 (1H, d, *J* 15.8, C(1)*H*).

4-(Triisopropylsilyloxy)but-1-yne 503



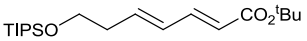
Imidazole (14.6 g, 214 mmol), DMAP (350 mg, 2.85 mmol) then TIPSCl (15.3 mL, 71.3 mmol) were sequentially added to a solution of **502** (5.00 g, 71.3 mmol) in CH_2Cl_2 (500 mL) at rt and the resultant solution was stirred at rt for 16 h. The reaction mixture was then concentrated *in vacuo*. The residue was dissolved in Et_2O (500 mL) and the resultant solution was washed with 1.0 M aq HCl (250 mL), then dried and concentrated *in vacuo*. Purification *via* flash column chromatography (eluent 30-40 °C petroleum ether) gave **503** as a colourless oil (14.8 g, 92%);[33] δ_H (400 MHz, $CDCl_3$) 1.01-1.14 (21H, m, Si(C*HMe*$_2$)$_3$), 1.97 (1H, t, *J* 2.6, C(1)*H*), 2.45 (2H, td, *J* 7.3, 2.6, C(3)H_2), 3.83 (2H, t, *J* 7.3, C(4)H_2).

(*E*)-1-Iodo-4-(triisopropylsilyloxy)but-1-ene 504



DIBAL-H (1.0 M in THF, 9.72 mL, 9.72 mmol) was added to a solution of Cp_2ZrCl_2 (2.84 g, 9.72 mmol) in THF (50 mL) at 0 °C. The resultant mixture was stirred at 0 °C for 30 min and then a solution of **503** (2.00 g, 8.83 mmol) in THF (12 mL) was added via cannula. The reaction mixture was allowed to warm to rt and stirring was continued at rt until a homogenous solution resulted (*ca*. 30 min). The reaction mixture was then cooled to −78 °C and a solution of I_2 (2.91 g, 11.4 mmol) in THF (38 mL) was added via cannula. The reaction mixture was stirred at −78 °C for 1 h then 1.0 M aq HCl (40 mL) was added and the resultant mixture was extracted with Et_2O (2 × 40 mL). The combined organic extracts were washed sequentially with satd aq $Na_2S_2O_3$ (40 mL) and satd aq $NaHCO_3$ (40 mL), then dried and concentrated *in vacuo*. The residue was passed through a short plug of silica gel (eluent 40-60 °C petrol/Et_2O, 200:1) to give **504** as a pale yellow oil (2.46 g, 79%, >99:1 dr);[34] δ_H (400 MHz, $CDCl_3$) 1.02-1.14 (21H, m, Si(C*HMe*$_2$)$_3$), 2.30 (2H, m, C(3)H_2), 3.73 (2H, t, *J* 6.5, C(4)H_2), 6.09 (1H, d, *J* 14.4, C(1)*H*), 6.58 (1H, dt, *J* 14.4, 7.2, C(2)*H*).

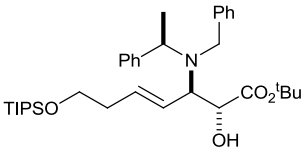
tert-Butyl (2*E*,4*E*)-7-(triisopropylsilyloxy)hepta-2,4-dienoate 446



Method A: $Pd(OAc)_2$ (68 mg, 0.30 mmol) was added to a solution of **504** (2.13 g, 6.01 mmol, >99:1 dr), *tert*-butyl acrylate **163** (1.74 mL, 11.9 mmol), Ag_2CO_3 (1.82 g, 6.61 mmol) and Et_3N (1.72 mL, 12.3 mmol) in CH_2Cl_2 (30 mL) at rt and the resultant mixture was stirred at rt for 16 h. Satd aq $NaHCO_3$ (15 mL) was then added and the resultant mixture was extracted with Et_2O (3 × 20 mL). The combined organic extracts were then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 40:1) gave **446** as a pale yellow oil (1.90 g, 89%, >99:1 dr);[35] δ_H (400 MHz, $CDCl_3$) 1.02-1.09 (21H, m, Si(C*H*Me$_2$)$_3$), 1.49 (9H, s, C*Me*$_3$), 2.40 (2H, app q, *J* 6.5, C(6)*H*$_2$), 3.76 (2H, t, *J* 6.5, C(7)*H*$_2$), 5.73 (1H, d, *J* 15.4, C(2)*H*), 6.13 (1H, dt, *J* 15.4, 6.5, C(5)*H*), 6.22 (1H, dd, *J* 15.4, 10.3, C(4)*H*), 7.16 (1H, dd, *J* 15.4, 10.3, C(3)*H*).

Method B: tert-Butyl acrylate **163** (9.92 mL, 67.7 mmol) then $Pd(OAc)_2$ (1.52 g, 6.77 mmol) were added to a degassed solution of **504** (12.0 g, 33.9 mmol, >99:1 dr), Bu_4NCl (9.41 g, 33.9 mmol) and $NaHCO_3$ (7.11 g, 84.7 mmol) in DMF (240 mL) at rt and the resultant mixture was stirred in the dark for 48 h. The reaction mixture was then partitioned between H_2O (250 mL) and Et_2O (250 mL) and the aqueous layer was then extracted with Et_2O (3 × 150 mL). The combined organic extracts were washed with H_2O (200 mL) and brine (200 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 100:1→40:1 30-40 °C petrol/Et_2O) gave **446** as a pale yellow oil (9.40 g, 78%, >99:1 dr).

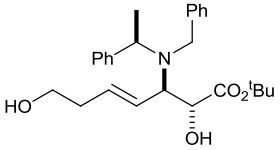
tert-Butyl (*R*,*R*,*R*,*E*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-7-(triisopropylsilyloxy)hept-4-enoate 505



Following *General Procedure 4*, (*R*)-**123** (8.70 g, 41.2 mmol) in THF (180 mL), BuLi (2.5 M, 16.3 mL, 39.9 mmol) and **446** (7.30 g, 20.6 mmol, >99:1 dr) in THF (180 mL) were reacted at −78 °C, followed by the addition of (−)-CSO **102** (9.44 g, 41.2 mmol), to give **505** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 10:1) gave **505** as a pale yellow oil (10.3 g, 72%, >99:1 dr);[35] $[\alpha]_D^{25}$ −41.2 (*c* 1.0 in $CHCl_3$); {lit.[35] $[\alpha]_D^{25}$ −19.8 (*c* 0.15 in $CHCl_3$)}; δ_H (400 MHz, $CDCl_3$) 1.05-1.10 (21H, m, Si(C*H*Me$_2$)$_3$), 1.33 (9H, s, C*Me*$_3$), 1.37 (3H, d, *J* 6.8, C(α)*Me*), 2.29 (2H, app q, *J* 6.7, C(6)*H*$_2$), 2.93 (1H, d, *J* 5.6, O*H*), 3.55 (1H, dd, *J* 9.1, 2.7,

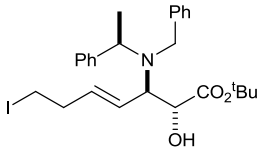
C(3)*H*), 3.71 (2H, t, *J* 6.7, C(7)H_2), 3.77 (1H, d, *J* 14.3, NC$H_A$$H_B$Ph), 3.97 (1H, d, *J* 14.3, NCH$_A$$H_B$Ph), 4.08 (1H, app dd, *J* 5.6, 2.7, C(2)*H*), 4.23 (1H, q, *J* 6.8, C(α)*H*), 5.60 (1H, dt, *J* 15.6, 6.7, C(5)*H*), 5.75 (1H, dd, *J* 15.6, 9.1, C(4)*H*), 7.18-7.43 (10H, m, *Ph*).

tert-Butyl (*R*,*R*,*R*,*E*)-2,7-dihydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]hept-4-enoate 506



TBAF (1.0 M in THF, 15.0 mL, 15.0 mmol) was added dropwise to a stirred solution of **505** (1.74 g, 2.99 mmol, >99:1 dr) in THF (50 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was diluted with Et_2O (50 mL) and washed with H_2O (50 mL). The aqueous layer was extracted with Et_2O (3 × 50 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 1:1) gave **506** as a white solid (1.15 g, 90%, >99:1 dr); mp 61-65 °C; $[\alpha]_D^{25}$ –53.8 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3474, 3318 (O–H), 3064, 3027, 2983, 2968, 2931, 2882 (C–H), 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 1.35 (9H, s, C*Me*$_3$), 1.39 (3H, d, *J* 6.8, C(α)*Me*), 2.05 (1H, br s, C(7)O*H*), 2.24-2.39 (2H, m, C(6)H_2), 3.01 (1H, br s, C(2)O*H*), 3.52-3.60 (2H, m, C(3)*H*, C(7)H_A), 3.61-3.69 (1H, m, C(7)H_B), 3.85 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 4.04 (1H, d, *J* 14.4, NCH$_A$$H_B$Ph), 4.17 (1H, app s, C(2)*H*), 4.24 (1H, q, *J* 6.8, C(α)*H*), 5.47 (1H, dt, *J* 15.4, 7.4, C(5)*H*), 5.85 (1H, dd, *J* 15.4, 9.4, C(4)*H*), 7.20-7.46 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.9 (C(α)*Me*), 27.9 (C*Me*$_3$), 36.1 (*C*(6)), 51.4 (N*C*H$_2$Ph), 56.9 (*C*(α)), 61.4 (*C*(7)), 63.0 (*C*(3)), 74.8 (*C*(2)), 82.2 (*C*Me$_3$), 126.7, 126.8 (*p-Ph*), 127.0, 128.1, 128.2, 128.4 (*o,m-Ph*), 129.2 (*C*(4)), 130.6 (*C*(5)), 141.4, 144.0 (*i-Ph*), 173.3 (*C*(1)); *m/z* (ESI$^+$) 426 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{36}NO_4^+$ ([M+H]$^+$) requires 426.2639; found 426.2640.

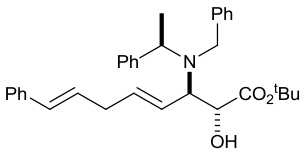
tert-Butyl (*R*,*R*,*R*,*E*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-7-iodohept-4-enoate 507



PPh_3 (89 mg, 0.34 mmol) and imidazole (29 mg, 0.42 mmol) were added to a solution of **506** (120 mg, 0.282 mmol, >99:1 dr) in PhMe and MeCN (v/v 17:4, 3.42 mL). I_2 (86 mg, 0.34 mmol) was then added and the resultant mixture was heated to 60 °C for 1 h. The reaction mixture was allowed to cool to rt and diluted with Et_2O (5 mL) then the resultant solution was washed sequentially with satd aq $Na_2S_2O_3$ (10 mL), H_2O (10 mL) and brine (10 mL). The organic layer was then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O,

10:1) gave **507** as a colourless oil (129 mg, 85%, >99:1 dr); $[\alpha]_D^{25}$ –55.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3499 (O–H), 3061, 3027, 2976, 2933 (C–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.36 (9H, s, C*Me*$_3$), 1.42 (3H, d, *J* 6.8, C(α)*Me*), 2.56-2.71 (2H, m, C(6)*H*$_2$), 2.94 (1H, br s, O*H*), 3.16 (1H, dt, *J* 14.8, 7.2, C(7)*H*$_A$) overlapping 3.18 (1H, dt, *J* 14.8, 7.2, C(7)*H*$_B$), 3.61 (1H, dd, *J* 9.1, 2.3, C(3)*H*), 3.85 (1H, d, *J* 14.5, NC*H*$_A$H$_B$Ph), 4.02 (1H, d, *J* 14.5, NCH$_A$*H*$_B$Ph), 4.14 (1H, d, *J* 2.3, C(2)*H*), 4.28 (1H, q, *J* 6.8, C(α)*H*), 5.49 (1H, dt, *J* 15.4, 6.8, C(5)*H*), 5.83 (1H, dd, *J* 15.4, 9.1, C(4)*H*), 7.20-7.47 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 5.0 (*C*(7)), 15.3 (C(α)*Me*), 28.0 (C*Me*$_3$), 36.5 (*C*(6)), 51.4 (N*C*H$_2$Ph), 56.9 (*C*(α)), 62.7 (*C*(3)), 74.4 (*C*(2)), 82.1 (*C*Me$_3$), 126.7, 126.7 (*p-Ph*), 128.0, 128.1, 128.2, 128.4 (*o,m-Ph*), 128.5 (*C*(4)), 132.7 (*C*(5)), 141.4, 144.2 (*i-Ph*), 172.7 (*C*(1)); *m/z* (ESI^+) 536 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{26}H_{35}INO_3^+$ ($[M+H]^+$) requires 536.1656; found 536.1667.

tert-Butyl (*R,R,R,E,E*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-8-phenylocta-4,7-dienoate 509



*Method A (From **516**):* KHMDS (0.5 M in PhMe, 0.47 mL, 0.24 mmol) was added dropwise to a solution of **516** (66 mg, 0.11 mmol, >99:1 dr) and PhCHO (13 μL, 0.13 mmol) in THF (2.5 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. H_2O (2 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were washed sequentially with satd aq NH_4Cl (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give **509** in >99:1 dr. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 10:1) gave **509** as a pale yellow oil (35 mg, 66%, >99:1 dr); $[\alpha]_D^{25}$ –49.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3499 (O–H), 3083, 3066, 3026, 2977, 2933, 2824 (C–H), 1722 (C=O), 1600 (C=C); δ_H (500 MHz, $CDCl_3$) 1.33 (9H, s, C*Me*$_3$), 1.40 (3H, d, *J* 6.8, C(α)*Me*), 2.96 (2H, app t, *J* 6.6, C(6)*H*$_2$), 3.61 (1H, dd, *J* 9.1, 2.5, C(3)*H*), 3.83 (1H, d, *J* 14.5, NC*H*$_A$H$_B$Ph), 3.99 (1H, d, *J* 14.5, NCH$_A$*H*$_B$Ph), 4.14 (1H, d, *J* 2.5, C(2)*H*), 4.26 (1H, q, *J* 6.8, C(α)*H*), 5.58 (1H, dt, *J* 15.5, 6.6, C(5)*H*), 5.79 (1H, dd, *J* 15.5, 9.1, C(4)*H*), 6.17 (1H, dt, *J* 15.9, 6.6, C(7)*H*), 6.41 (1H, d, *J* 15.9, C(8)*H*), 7.18-7.45 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 15.1 (C(α)*Me*), 27.9 (C*Me*$_3$), 36.0 (*C*(6)), 51.4 (N*C*H$_2$Ph), 56.9 (*C*(α)), 62.9 (*C*(3)), 74.4 (*C*(2)), 82.0 (*C*Me$_3$), 126.6, 126.7, 127.0 (*p-Ph*), 127.0 (*C*(4)), 126.0, 127.9, 128.0, 128.2, 128.4, 128.5 (*o,m-Ph*), 128.1 (*C*(7)), 130.8 (*C*(8)), 132.3 (*C*(5)), 137.5, 141.5, 144.1 (*i-Ph*), 172.7 (*C*(1));

m/z (ESI$^+$) 498 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{40}NO_3^+$ ([M+H]$^+$) requires 498.3003; found 498.3011.

*Method B (From **507**) – Step 1:* PPh_3 (43 mg, 0.16 mmol) was added to a solution of **507** (88 mg, 0.16 mmol, >99:1 dr) in MeCN (4 mL) at rt and the resultant mixture was heated at reflux for 48 h. The reaction mixture was then concentrated *in vacuo* to give **508** as a pale yellow solid (131 mg, quant, >99:1 dr); mp 73-77 °C; $[\alpha]_D^{25}$ –47.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3324 (O–H), 3057, 3027, 2976, 2932, 2872 (C–H), 1730 (C=O); δ_H (400 MHz, $CDCl_3$) 1.31 (9H, s, C*Me*$_3$), 1.33 (3H, d, *J* 6.8, C(α)*Me*), 2.32-2.44 (2H, m, C(6)*H*$_2$), 2.96 (1H, br s, O*H*), 3.50-3.68 (3H, m, C(3)*H*, C(7)*H*$_2$), 3.82 (1H, d, *J* 14.9, NC*H*$_A$H$_B$Ph), 3.88 (1H, d, *J* 14.9, NCH$_A$*H*$_B$Ph), 4.05 (1H, app s, C(2)*H*), 4.10 (1H, q, *J* 6.8, C(α)*H*), 5.69 (1H, dd, *J* 15.4, 8.8, C(4)*H*), 5.86 (1H, dt, *J* 15.4, 6.6, C(5)*H*), 7.09-7.82 (25H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) [selected peaks] 16.2 (C(α)*Me*), 22.6 (*C*(7)), 25.7 (*C*(6)), 28.0 (C*Me*$_3$), 51.4 (N*C*H$_2$Ph), 57.5 (*C*(α)), 62.3 (*C*(3)), 73.4 (*C*(2)), 82.3 (*C*Me$_3$), 172.6 (*C*(1)); *m/z* (ESI$^+$) 670 ([M]$^+$, 100%); HRMS (ESI$^+$) $C_{44}H_{49}NO_3P^+$ ([M]$^+$) requires 670.3445; found 670.3453.

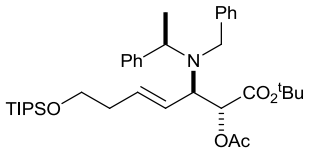
*Method B (From **507**) – Step 2:* KHMDS (0.5 M in PhMe, 0.93 mL, 0.47 mmol) was added dropwise to a solution of **508** (169 mg, 0.212 mmol, >99:1 dr) and PhCHO (26 µL, 0.25 mmol) in THF (4.5 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. H_2O (2 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were washed sequentially with satd aq NH_4Cl (20 mL) and brine (20 mL), then dried and concentrated *in vacuo* to give a complex mixture of products.

*Method C (From **512**) – Step 1:* PPh_3 (977 mg, 3.72 mmol) was added to a solution of **512** (2.15 g, 3.72 mmol, >99:1 dr) in MeCN (35 mL) at rt and the resultant mixture was heated at reflux for 48 h. The reaction mixture was then concentrated *in vacuo* to give **513** as a pale yellow solid (3.13 g, quant, >99:1 dr); mp 80-84 °C; $[\alpha]_D^{25}$ –30.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3056, 3026, 2977, 2931, 2870 (C–H), 1736 (C=O); δ_H (400 MHz, $CDCl_3$) 1.27 (9H, s, C*Me*$_3$), 1.33 (3H, d, *J* 6.7, C(α)*Me*), 2.01 (3H, s, CO*Me*), 2.28-2.51 (2H, m, C(6)*H*$_2$), 3.56-3.69 (2H, m, C(7)*H*$_2$), 3.76 (1H, dd, *J* 8.8, 2.9, C(3)*H*), 3.82 (1H, d, *J* 15.0, NC*H*$_A$H$_B$Ph), 3.87 (1H, d, *J* 15.0, NCH$_A$*H*$_B$Ph), 4.01 (1H, q, *J* 6.7, C(α)*H*), 4.94 (1H, d, *J* 2.9, C(2)*H*), 5.73 (1H, dd, *J* 15.4, 8.8, C(4)*H*), 5.95 (1H, dt, *J* 15.4, 6.7, C(5)*H*), 7.09-7.85 (25H, m, *Ph*); δ_C [selected peaks] (100 MHz, $CDCl_3$) 16.1 (C(α)*Me*), 20.9 (CO*Me*), 23.1 (*C*(7)), 25.7 (*C*(6)), 28.0 (C*Me*$_3$), 51.5 (N*C*H$_2$Ph), 57.9 (*C*(α)), 59.8 (*C*(3)),

76.1 (*C*(2)), 82.2 (*C*Me$_3$), 128.7 (*C*(4)), 131.6 (*C*(5)), 167.6, 170.1 (*C*(1), *C*OMe); *m/z* (ESI$^+$) 712 ([M]$^+$, 100%); HRMS (ESI$^+$) $C_{46}H_{51}NO_4P^+$ ([M]$^+$) requires 712.3550; found 712.3553.

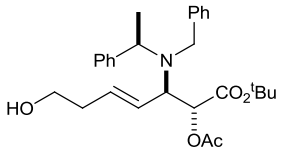
*Method C (From **512**) – Step 2:* PhCHO (91 μL, 0.89 mmol) and K_2CO_3 (49 mg, 0.36 mmol) were added to a solution of **513** (150 mg, 0.179 mmol, >99:1 dr) in dioxane and H_2O (v/v 2:1, 3 mL) and the resultant mixture was heated at 100 °C for 72 h. The reaction mixture was then allowed to cool to rt and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 20:1→10:1 30-40 °C petrol/Et$_2$O) gave a 70:30 mixture of **509** and **514** respectively (50 mg, 56%). Data for **514**: δ_H (400 MHz, $CDCl_3$) [selected peaks] 5.67 (1H, dt, *J* 11.7, 7.6, C(7)*H*), 6.52 (1H, d, *J* 11.7, C(8)*H*).

tert-Butyl (*R*,*R*,*R*,*E*)-2-acetoxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-7-(triisopropylsilyloxy)hept-4-enoate 510



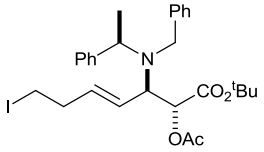
Ac_2O (2.51 mL, 26.5 mmol) and DMAP (5 mg, cat.) were added to a solution of **505** (3.86 g, 6.63 mmol, >99:1 dr) in pyridine (150 mL) at rt and the resultant mixture was stirred at rt for 24 h. The reaction mixture was then diluted with CH_2Cl_2 (50 mL), EtOAc (50 mL) and satd aq $CuSO_4$ (100 mL). The aqueous layer was extracted with EtOAc (3 × 50 mL) and the combined organic extracts were washed with satd aq $NaHCO_3$ (2 × 100 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et$_2$O, 4:1) gave **510** as a yellow oil (3.81 g, 92%, >99:1 dr); $[\alpha]_D^{25}$ −14.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3086, 3062, 3028, 2942, 2892, 2866 (C–H), 1746 (C=O); δ_H (400 MHz, $CDCl_3$) 1.07-1.12 (21H, m, Si(C*HMe*$_2$)$_3$), 1.31 (9H, s, C*Me*$_3$), 1.37 (3H, d, *J* 6.8, C(α)*Me*), 2.04 (3H, s, CO*Me*), 2.31 (2H, app q, *J* 6.7, C(6)*H*$_2$), 3.72 (2H, t, *J* 6.7, C(7)*H*$_2$), 3.76 (1H, dd, *J* 8.8, 3.0, C(3)*H*), 3.82 (1H, d, *J* 14.7, NC*H*$_A$H$_B$Ph), 3.92 (1H, d, *J* 14.7, NCH$_A$*H*$_B$Ph), 4.11 (1H, q, *J* 6.8, C(α)*H*), 5.02 (1H, d, *J* 3.0, C(2)*H*), 5.67 (1H, dt, *J* 15.5, 6.7, C(5)*H*), 5.78 (1H, dd, *J* 15.5, 8.8, C(4)*H*), 7.19-7.43 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 15.1 (C(α)*Me*), 18.0 (Si(CH*Me*$_2$)$_3$), 20.8 (CO*Me*), 27.9 (C*Me*$_3$), 36.4 (*C*(6)), 51.6 (N*C*H$_2$Ph), 57.4 (*C*(α)), 60.5 (*C*(3)), 63.1 (*C*(7)), 76.7 (*C*(2)), 81.6 (*C*Me$_3$), 126.6, 126.7, 126.7 (*C*(4), *p-Ph*), 127.8, 128.1, 128.2, 128.2 (*o*,*m-Ph*), 132.5 (*C*(5)), 141.5, 143.9 (*i-Ph*), 167.4, 170.3 (*C*(1), *C*OMe); *m/z* (ESI$^+$) 646 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{37}H_{57}NNaO_5Si^+$ ([M+Na]$^+$) requires 646.3898; found 646.3889.

***tert*-Butyl (*R*,*R*,*R*,*E*)-2-acetoxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-7-hydroxyhept-4-enoate 511**



TBAF (1.0 M in THF, 0.89 mL, 0.89 mmol) was added dropwise to a stirred solution of **510** (111 mg, 0.178 mmol, >99:1 dr) in THF (3 mL) at rt and the resultant mixture was stirred at rt for 16 h. The reaction mixture was then diluted with Et_2O (10 mL) and washed with H_2O (10 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 4:1→1:1 30-40 °C petrol/Et_2O) gave **511** as a colourless oil (75 mg, 90%, >99:1 dr); $[\alpha]_D^{25}$ –33.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3500 (O–H), 3061, 3028, 2976, 2934 (C–H), 1741 (C=O); δ_H (400 MHz, $CDCl_3$) 1.32 (9H, s, C*Me*$_3$), 1.37 (3H, d, *J* 6.8, C(α)*Me*), 2.04 (3H, s, CO*Me*), 2.25-2.36 (2H, m, C(6)H_2), 3.52-3.58 (1H, m, C(7)H_A), 3.60-3.69 (1H, m, C(7)H_B), 3.71 (1H, dd, *J* 9.3, 2.5, C(3)*H*), 3.84 (1H, d, *J* 14.7, NCH_AH$_B$Ph), 3.96 (1H, d, *J* 14.7, NCH$_A$$H_B$Ph), 4.11 (1H, q, *J* 6.8, C(α)*H*), 4.98 (1H, d, *J* 2.5, C(2)*H*), 5.42-5.52 (1H, m, C(5)*H*), 5.86 (1H, dd, *J* 15.4, 9.3, C(4)*H*), 7.20-7.44 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 14.8 (C(α)*Me*), 20.7 (CO*Me*), 27.9 (C*Me*$_3$), 36.0 (*C*(6)), 51.5 (N*C*H$_2$Ph), 57.5 (*C*(α)), 60.9 (*C*(3)), 61.2 (*C*(7)), 77.2 (*C*(2)), 82.0 (*C*Me$_3$), 126.7, 126.8 (*p-Ph*), 127.8, 128.1, 128.1, 128.2 (*o,m-Ph*), 129.1 (*C*(4)), 131.0 (*C*(5)), 141.3, 143.7 (*i-Ph*), 168.2, 170.3 (*C*(1), *C*OMe); *m/z* (ESI$^+$) 490 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{37}NNaO_5^+$ ([M+Na]$^+$) requires 490.2564; found 490.2566.

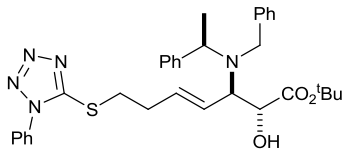
***tert*-Butyl (*R*,*R*,*R*,*E*)-2-acetoxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-7-iodohept-4-enoate 512**



PPh_3 (1.58 g, 6.01 mmol) and imidazole (511 mg, 7.51 mmol) were added to a solution of **511** (2.34 g, 5.00 mmol, >99:1 dr) in PhMe and MeCN (v/v 17:4, 62.5 mL). I_2 (1.52 g, 6.01 mmol) was then added and the resultant mixture was heated to 60 °C for 1 h. The reaction mixture was allowed to cool to rt, diluted with Et_2O (50 mL) and then the resultant solution was washed sequentially with satd aq $Na_2S_2O_3$ (50 mL), H_2O (50 mL) and brine (50 mL). The organic layer was then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 10:1) gave **512** as a pale yellow oil (2.64 g, 91%, >99:1 dr); $[\alpha]_D^{25}$ –29.4 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3085, 3061, 3027, 2976, 2933, 2848 (C–H), 1743 (C=O); δ_H (400 MHz, $CDCl_3$) 1.32 (9H, s, C*Me*$_3$),

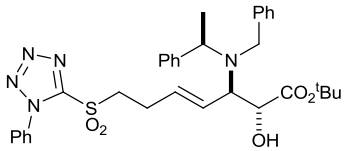
1.39 (3H, d, *J* 6.8, C(α)*Me*), 2.05 (3H, s, CO*Me*), 2.56-2.70 (2H, m, C(6)H_2), 3.10-3.22 (2H, m, C(7)H_2), 3.78 (1H, dd, *J* 8.8, 3.0, C(3)*H*), 3.86 (1H, d, *J* 14.7, NC$H_A$$H_B$Ph), 3.94 (1H, d, *J* 14.7, NCH$_A$$H_B$Ph), 4.12 (1H, q, *J* 6.8, C(α)*H*), 5.03 (1H, d, *J* 3.0, C(2)*H*), 5.55 (1H, dt, *J* 15.4, 6.8, C(5)*H*), 5.82 (1H, dd, *J* 15.4, 8.8, C(4)*H*), 7.19-7.46 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 4.8 (*C*(7)), 15.5 (C(α)*Me*), 20.8 (CO*Me*), 27.9 (C*Me*$_3$), 36.5 (*C*(6)), 51.6 (N*C*H$_2$Ph), 57.5 (*C*(α)), 60.2 (*C*(3)), 76.4 (*C*(2)), 81.8 (*C*Me$_3$), 126.7, 126.8 (*p-Ph*), 127.8 (*C*(4)), 127.8, 128.2, 128.2, 128.2 (*o,m-Ph*), 133.6 (*C*(5)), 141.3, 143.7 (*i-Ph*), 167.4, 170.2 (*C*(1), *C*OMe); *m/z* (ESI$^+$) 600 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{28}H_{36}INNaO_4^+$ ([M+Na]$^+$) requires 600.1581; found 600.1579.

tert-Butyl (*R,R,R,E*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-7-(1'-phenyl-1*H*-tetrazol-5'-ylthio)hept-4-enoate 515



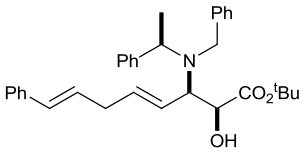
DEAD (48 μL, 0.31 mmol) was added dropwise to a solution of **506** (100 mg, 0.235 mmol, >99:1 dr), PTSH (50 mg, 0.28 mmol) and PPh_3 (74 mg, 0.28 mmol) in THF (2 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 16 h. EtOAc (10 mL) was then added and the reaction mixture was washed sequentially with brine (10 mL) and H_2O (10 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/Et_2O, 2:1) gave **515** as a colourless oil (113 mg, 82%, >99:1 dr); $[\alpha]_D^{25}$ –53.2 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3493 (O–H), 3061, 3027, 2976, 2933 (C–H), 1722 (C=O); δ_H (400 MHz, $CDCl_3$) 1.32 (9H, s, C*Me*$_3$), 1.33 (3H, d, *J* 6.8, C(α)*Me*), 2.60 (2H, app q, *J* 7.0, C(6)H_2), 2.90 (1H, br s, O*H*), 3.45 (2H, t, *J* 7.0, C(7)H_2), 3.58 (1H, dd, *J* 9.1, 2.4, C(3)*H*), 3.77 (1H, d, *J* 14.4, NC$H_A$$H_B$Ph), 3.97 (1H, d, *J* 14.4, NCH$_A$$H_B$Ph), 4.12 (1H, app s, C(2)*H*), 4.22 (1H, q, *J* 6.8, C(α)*H*), 5.55 (1H, dt, *J* 15.4, 7.0, C(5)*H*), 5.83 (1H, dd, *J* 15.4, 9.1, C(4)*H*), 7.17-7.60 (15H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 15.1 (C(α)*Me*), 27.9 (C*Me*$_3$), 32.1 (*C*(6)), 32.8 (*C*(7)), 51.3 (N*C*H$_2$Ph), 56.9 (*C*(α)), 62.6 (*C*(3)), 74.4 (*C*(2)), 82.1 (*C*Me$_3$), 123.8, 127.9, 128.1, 128.2, 128.3, 129.8 (*o,m-Ph*), 126.7, 126.8, 130.1 (*p-Ph*), 129.1 (*C*(4)), 130.9 (*C*(5)), 133.7, 141.4, 144.0 (*i-Ph*), 154.2 (*C*(5')), 172.6 (*C*(1)); *m/z* (ESI$^+$) 608 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{33}H_{39}N_5NaO_3S^+$ ([M+Na]$^+$) requires 608.2666; found 608.2664.

tert-Butyl (*R*,*R*,*R*,*E*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-7-(1'-phenyl-1*H*-tetrazol-5'-ylsulfonyl)hept-4-enoate 516



$(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (48 mg, 39 μmol) was dissolved in 30% aq H_2O_2 (0.33 mL, 2.9 mmol) at 0 °C and the resultant solution was added dropwise to a solution of **515** (113 mg, 0.193 mmol, >99:1 dr) in EtOH (3 mL) at 0 °C. The resultant suspension was stirred at rt for 16 h and was then added to brine (10 mL). The resultant mixture was then 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 petrol/Et_2O, 2:1) gave **516** as a pale yellow oil (69 mg, 58%, >99:1 dr); $[\alpha]_D^{25}$ –46.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3507 (O–H), 3062, 3028, 2977, 2934 (C–H), 1722 (C=O), 1345, 1150 (S=O); δ_H (400 MHz, $CDCl_3$) 1.35 (9H, s, C*Me*$_3$), 1.37 (3H, d, *J* 6.8, C(α)*Me*), 2.65-2.80 (2H, m, C(6)*H*$_2$), 2.93 (1H, br s, O*H*), 3.61 (1H, dd, *J* 9.1, 2.3, C(3)*H*), 3.72-3.78 (2H, m, C(7)*H*$_2$), 3.86 (1H, d, *J* 14.7, NC*H*$_A$H$_B$Ph), 3.98 (1H, d, *J* 14.7, NCH$_A$*H*$_B$Ph), 4.15 (1H, app s, C(2)*H*), 4.23 (1H, q, *J* 6.8, C(α)*H*), 5.56 (1H, dt, *J* 15.4, 6.8, C(5)*H*), 5.89 (1H, dd, *J* 15.4, 9.1, C(4)*H*), 7.20-7.73 (15H, m, Ph); δ_C (100 MHz, $CDCl_3$) 15.7 (C(α)*Me*), 25.3 (*C*(6)), 28.0 (C*Me*$_3$), 51.3 (N*C*H$_2$Ph), 55.4 (*C*(7)), 57.0 (*C*(α)), 62.3 (*C*(3)), 74.2 (*C*(2)), 82.3 (*C*Me$_3$), 125.0, 127.9, 128.1, 128.3, 128.3, 129.8 (*o,m-Ph*), 126.7, 126.8, 131.5 (*p-Ph*), 127.9 (*C*(5)), 130.1 (*C*(4)), 133.0, 143.8, 141.4 (*i-Ph*), 153.4 (*C*(5')), 172.6 (*C*(1)); *m/z* (ESI^+) 640 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{33}H_{39}N_5NaO_5S^+$ ($[M+Na]^+$) requires 640.2564; found 640.2546.

tert-Butyl (2*S*,3*R*,α*R*,*E*,*E*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-8-phenylocta-4,7-dienoate 518

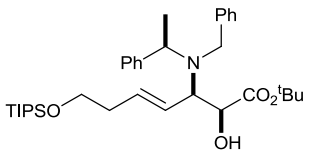


Step 1: DMSO (0.43 mL, 6.8 mmol) was added dropwise to a stirred solution of $(ClCO)_2$ (51 μL, 0.60 mmol) in CH_2Cl_2 (2 mL) at −78 °C and the resultant mixture was stirred at −78 °C for 5 min. A solution of **509** (150 mg, 0.301 mmol, >99:1 dr) in CH_2Cl_2 (2 mL) was then added via cannula and the reaction mixture was stirred at −78 °C for 30 min. Et_3N (0.17 mL, 1.2 mmol) was then added and stirring was continued at −78 °C for a further 10 min. The reaction mixture was allowed to warm to rt over 20 min. H_2O (20 mL) was added and the reaction mixture was extracted with CH_2Cl_2

(3 × 50 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **517** as a yellow oil (175 mg); *m/z* (ESI^+) 496 ($[M+H]^+$, 100%).

Step 2: The residue (175 mg) was dissolved in MeOH (6 mL) and the resultant solution was cooled to –20 °C. $NaBH_4$ (11 mg, 0.30 mmol) was then added and the reaction mixture was stirred at –20 °C for 2 h. The reaction mixture was then allowed to warm to rt and concentrated *in vacuo*. The residue was partitioned between H_2O (30 mL) and Et_2O (30 mL) and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **518** in >99:1 dr. Purification via flash column chromatography (gradient elution, 20:1→10:1 30-40 °C petrol/Et_2O) gave **518** as a pale yellow oil (37 mg, 25% over 2 steps, >99:1 dr); $[\alpha]_D^{25}$ –37.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3387 (O–H), 3027, 2977, 2932 (C–H), 1736 (C=O), 1585 (C=C); δ_H (500 MHz, $CDCl_3$) 1.36 (9H, s, C*Me*$_3$), 1.48 (3H, d, *J* 6.9, C(α)*Me*), 2.98-3.03 (2H, m, C(6)*H*$_2$), 3.37-3.44 (1H, m, C(3)*H*), 3.68 (1H, d, *J* 13.6, NC*H*$_A$H$_B$Ph), 3.88 (1H, d, *J* 13.6, NCH$_A$*H*$_B$Ph), 3.90 (1H, d, *J* 9.1, C(2)*H*), 4.12 (1H, q, *J* 6.9, C(α)*H*), 5.65-5.75 (2H, m, C(4)*H*, C(5)*H*), 6.22 (1H, dt, *J* 15.8, 6.8, C(7)*H*), 6.46 (1H, d, *J* 15.8, C(8)*H*), 7.21-7.39 (15H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 14.8 (C(α)*Me*), 27.9 (C*Me*$_3$), 36.0 (*C*(6)), 50.2 (N*C*H$_2$Ph), 56.5 (*C*(α)), 62.6 (*C*(3)), 71.8 (*C*(2)), 81.3 (*C*Me$_3$), 126.8 (*C*(4)), 127.2, 127.2, 127.3 (*p-Ph*), 127.5 (*C*(7)), 126.0, 127.8, 128.4, 128.5, 128.5, 129.0 (*o,m-Ph*), 131.2 (*C*(8)), 133.9 (*C*(5)), 137.4, 139.4, 143.2 (*i-Ph*), 171.4 (*C*(1)); *m/z* (ESI^+) 498 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{33}H_{40}NO_3^+$ ($[M+H]^+$) requires 498.3003; found 498.3007.

tert-Butyl (2*S*,3*R*,α*R*,*E*)-2-hydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-7-(triisopropylsilyloxy)hept-4-enoate 523

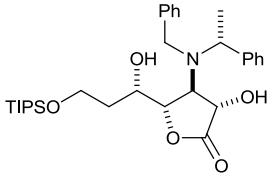


Step 1: DMSO (1.22 mL, 17.2 mmol) was added dropwise to a stirred solution of $(ClCO)_2$ (0.15 mL, 1.7 mmol) in CH_2Cl_2 (6 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 5 min. A solution of **505** (500 mg, 0.859 mmol, >99:1 dr) in CH_2Cl_2 (6 mL) was then added via cannula and the reaction mixture was stirred at –78 °C for 30 min. Et_3N (0.45 mL, 3.4 mmol) was then added and stirring was continued at –78 °C for a further 10 min. The reaction mixture was allowed to warm to rt over 20 min. H_2O (20 mL) was added and the reaction mixture was extracted with CH_2Cl_2 (3 × 50 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **522** as a yellow oil (570 mg); δ_H (400 MHz, $CDCl_3$) 1.04-1.09 (21H, m, Si(C*HMe*$_2$)$_3$), 1.39 (3H, d, *J* 6.8,

C(α)*Me*), 1.46 (9H, s, C*Me*$_3$), 2.32 (2H, app q, *J* 6.6, C(6)*H*$_2$), 3.70 (2H, t, *J* 6.6, C(7)*H*$_2$), 3.81 (1H, d, *J* 14.6, NC*H*$_A$H$_B$Ph), 3.88 (1H, d, *J* 14.6, NCH$_A$*H*$_B$Ph), 4.02 (1H, q, *J* 6.8, C(α)*H*), 4.60 (1H, d, *J* 8.1, C(3)*H*), 5.66 (1H, dt, *J* 15.9, 6.6, C(5)*H*), 5.75 (1H, dd, *J* 15.9, 8.1, C(4)*H*), 7.20-7.37 (10H, m, *Ph*); *m/z* (ESI$^+$) 580 ([M+H]$^+$, 100%).

Step 2: The residue (570 mg) was dissolved in MeOH (6 mL) and the resultant solution was cooled to –20 °C. $NaBH_4$ (33 mg, 0.86 mmol) was added portionwise and the reaction mixture was stirred at –20 °C for 2 h. The reaction mixture was then allowed to warm to rt and concentrated *in vacuo*. The residue was partitioned between H_2O (30 mL) and Et_2O (30 mL) and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic extracts were then dried and concentrated *in vacuo* to give **523** in >99:1 dr. Purification via flash column chromatography (gradient elution, 20:1→10:1 30-40 °C petrol/Et_2O) gave **523** as a pale yellow oil (333 mg, 67% over 2 steps, >99:1 dr); $[\alpha]_D^{25}$ –49.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3439 (O–H), 3087, 3062, 3028, 2942, 2892, 2866 (C–H), 1733 (C=O), 1630 (C=C); δ_H (400 MHz, $CDCl_3$) 1.08-1.15 (21H, m, Si(C*HMe*$_2$)$_3$), 1.36 (9H, s, C*Me*$_3$), 1.47 (3H, d, *J* 6.8, C(α)*Me*), 2.30-2.40 (2H, m, C(6)*H*$_2$), 3.33-3.40 (1H, m, C(3)*H*), 3.66 (1H, d, *J* 13.3, NC*H*$_A$H$_B$Ph), 3.75-3.81 (3H, m, C(7)*H*$_2$, O*H*), 3.86 (1H, d, *J* 13.3, NCH$_A$*H*$_B$Ph), 3.88 (1H, d, *J* 6.6, C(2)*H*), 4.11 (1H, q, *J* 6.8, C(α)*H*), 5.63-5.75 (2H, m, C(4)*H*, C(5)*H*), 7.20-7.36 (10H, m, *Ph*); δ_C (100 MHz, $CDCl_3$) 12.0 (Si(*C*HMe$_2$)$_3$), 14.7 (C(α)*Me*), 18.0 (Si(CH*Me*$_2$)$_3$), 27.9 (C*Me*$_3$), 36.6 (*C*(6)), 50.1 (N*C*H$_2$Ph), 56.5 (*C*(α)), 62.6 (*C*(3)), 62.9 (*C*(7)), 71.8 (*C*(2)), 81.1 (*C*Me$_3$), 127.2 (*C*(4)), 127.2, 127.2 (*p-Ph*), 127.8, 128.4, 128.5, 129.1 (*o,m-Ph*), 133.3 (*C*(5)), 139.5, 143.3 (*i-Ph*), 171.5 (*C*(1)); *m/z* (ESI$^+$) 582 ([M+H]$^+$, 100%); HRMS (ESI$^+$) $C_{35}H_{56}NO_4Si^+$ ([M+H]$^+$) requires 582.3973; found 582.3969.

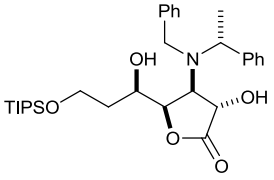
(2*S*,3*S*,4*S*,5*S*,α*R*)-2,5-Dihydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-7-(triisopropylsilyloxy)-4-heptylolactone 525



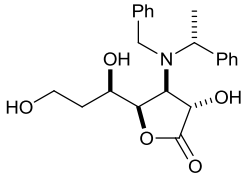
Step 1: OsO_4 (265 mg, 1.04 mmol) was added to a stirred solution of **523** (552 mg, 0.949 mmol, >99:1 dr) and TMEDA (0.21 mL, 1.3 mmol) in CH_2Cl_2 (40 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 1 h. The reaction mixture was allowed to warm to rt over 15 min and was then concentrated *in vacuo*. The residue was then passed through a short plug of silica gel (eluent CH_2Cl_2/MeOH, 20:1) and was concentrated *in vacuo* to give **524** as a brown oil (900 mg).

Step 2: The residue (900 mg) was dissolved in CH_2Cl_2 (150 mL) and then $P(CH_2OH)_3$ **483** (5.89 g, 47.5 mmol) and Et_3N (2.64 mL, 19.0 mmol) were added sequentially. The reaction mixture was stirred at rt for 5 min then SiO_2 (~2.0 g) was added. The resultant mixture was stirred at rt for 48 h then concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 3:1) gave **525** as a colourless oil (272 mg, 53% over 2 steps, >99:1 dr); $[\alpha]_D^{25}$ +36.6 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3454 (O–H), 3086, 3062, 3030, 2942, 2891, 2866 (C–H), 1770 (C=O); δ_H (500 MHz, $CDCl_3$) 1.07-1.14 (21H, m, (Si(C*H*Me_2)$_3$), 1.47 (3H, d, *J* 6.9, C(α)*Me*), 1.56-1.63 (1H, m, C(6)H_A), 1.91-2.00 (1H, m, C(6)H_B), 2.92 (1H, d, *J* 6.3, C(2)O*H*), 3.45 (1H, d, *J* 3.8, C(5)O*H*), 3.79 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 3.83 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 3.89-3.95 (3H, m, C(3)*H*, C(4)*H*, C(7)H_A), 3.99-4.04 (1H, m, C(7)H_B), 4.09 (1H, q, *J* 6.9, C(α)*H*), 4.13-4.18 (1H, m, C(5)*H*), 4.28-4.33 (1H, m, C(2)*H*), 7.21-7.46 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 11.7 (Si(*C*HMe_2)$_3$), 17.9 (Si(CH*Me*$_2$)$_3$), 18.1 (C(α)*Me*), 35.2 (*C*(6)), 50.0 (N*C*H_2Ph), 60.1 (*C*(α)), 62.3 (*C*(7)), 64.1 (*C*(3)), 68.8 (*C*(2)), 69.1 (*C*(5)), 82.7 (*C*(4)), 127.2, 127.5 (*p-Ph*), 127.9, 128.0, 128.4, 128.6 (*o,m-Ph*), 140.2, 142.8 (*i-Ph*), 175.7 (*C*(1)); *m/z* (ESI^+) 564 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{31}H_{47}NNaO_5Si^+$ ($[M+Na]^+$) requires 564.3116; found 564.3115.

(2*S*,3*S*,4*R*,5*R*,α*R*)-2,5-Dihydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-7-(triisopropylsilyloxy)-4-heptylolactone 528 and (2*S*,3*S*,4*R*,5*R*,α*R*)-2,5,7-trihydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-heptylolactone 527



528



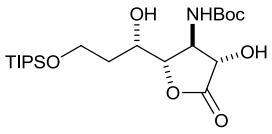
527

Step 1: OsO_4 (5 mg, 17 μmol) was added to a stirred solution of **523** (100 mg, 0.167 mmol, >99:1 dr) in THF (1 mL) and H_2O (0.25 mL) at rt. A solution of NMO (83 mg, 0.70 mmol) in H_2O (0.25 mL) was then added and the resultant mixture was stirred at rt for 12 h. Satd aq Na_2SO_3 (1 mL) was then added and the resultant mixture was left to stir at rt for 1 h. The reaction mixture was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give a complex mixture of products as a yellow oil (109 mg).

Step 2: F_3CCO_2H (0.4 mL) was added to a solution of the residue (109 mg) in CH_2Cl_2 (2 mL) at rt and the resultant solution was stirred at rt for 16 h. The reaction mixture was then cooled to 0 °C and neutralised by the dropwise addition of satd aq $NaHCO_3$ (~10 mL). The resultant mixture was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried and concentrated *in*

vacuo to give a 60:10:30 mixture of **527**, **528** and **529** respectively. Purification via flash column chromatography (gradient elution, 1:3→1:100 30-40 °C petrol/Et_2O) gave **528** as a pale yellow oil (8 mg, 9% over 2 steps, >99:1 dr); $[\alpha]_D^{25}$ –3.0 (*c* 0.2 in $CHCl_3$); ν_{max} (ATR) 3464 (O–H), 2942, 2866 (C–H), 1773 (C=O); δ_H (500 MHz, $CDCl_3$) 1.04-1.10 (21H, m, Si(C*H*Me_2)$_3$), 1.50 (3H, d, *J* 6.9, C(α)*Me*), 1.59-1.65 (1H, m, C(6)H_A), 1.95-2.04 (1H, m, C(6)H_B), 2.21 (1H, br s, O*H*), 3.64 (1H, br s, O*H*), 3.87 (1H, dd, *J* 10.4, 7.6, C(3)*H*), 3.88-3.92 (1H, m, C(7)H_A), 3.94 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 3.97-4.02 (1H, m, C(7)H_B), 4.06 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 4.17 (1H, q, *J* 6.9, C(α)*H*), 4.27 (1H, app d, *J* 7.6, C(4)*H*), 4.54 (1H, app dd, *J* 9.5, 2.5, C(5)*H*), 4.60 (1H, app dd, *J* 10.4, 1.9, C(2)*H*), 7.15-7.52 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 11.7 (Si(*C*HMe_2)$_3$), 14.4 (C(α)*Me*), 17.9 (Si(CH*Me*$_2$)$_3$), 34.7 (*C*(6)), 50.7 (N*C*H_2Ph), 58.2 (*C*(α)), 62.2 (*C*(7)), 65.5 (*C*(3)), 68.1 (*C*(2)), 68.8 (*C*(5)), 81.8 (*C*(4)), 127.0, 127.5 (*p-Ph*), 127.7, 127.9, 128.5, 128.5 (*o,m-Ph*), 141.3, 142.5 (*i-Ph*), 176.2 (*C*(1)); *m/z* (ESI^+) 542 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{31}H_{47}NNaO_5Si^+$ ($[M+Na]^+$) requires 564.3116; found 564.3096. Further elution gave **527** as a colourless oil (15 mg, 23% over 2 steps, >99:1 dr); $[\alpha]_D^{25}$ –14.5 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3401 (O–H), 2969, 2889 (C–H), 1769 (C=O); δ_H (500 MHz, $CDCl_3$) 1.52 (3H, d, *J* 6.6, C(α)*Me*), 1.66-1.74 (1H, m, C(6)H_A), 1.89-1.98 (1H, m, C(6)H_B), 2.70 (1H, br s, C(2)O*H*), 3.42 (1H, br s, C(5)O*H*), 3.80-3.91 (3H, m, C(3)*H*, C(7)H_2) overlapping 3.90 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 3.96 (1H, d, *J* 14.8, NC$H_A$$H_B$Ph), 4.16 (1H, q, *J* 6.6, C(α)*H*), 4.37 (1H, app d, *J* 7.6, C(4)*H*), 4.44 (1H, app dd, *J* 9.8, 2.8, C(2)*H*), 4.55 (1H, app d, *J* 8.8, C(5)*H*), 7.17-7.52 (10H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 13.1 (C(α)*Me*), 34.4 (*C*(6)), 50.5 (N*C*H_2Ph), 58.5 (*C*(α)), 60.8 (*C*(7)), 65.6 (*C*(3)), 68.1 (*C*(2)), 68.6 (*C*(5)), 81.5 (*C*(4)), 127.2, 127.7 (*p-Ph*), 127.6, 128.0, 128.6, 128.7 (*o,m-Ph*), 141.1, 142.1 (*i-Ph*), 176.3 (*C*(1)); *m/z* (ESI^+) 386 ($[M+H]^+$, 100%); HRMS (ESI^+) $C_{22}H_{27}NNaO_5^+$ ($[M+Na]^+$) requires 408.1781; found 408.1778. Further elution gave **529** as a pale yellow oil (2 mg, 3% over 2 steps, >99:1 dr).

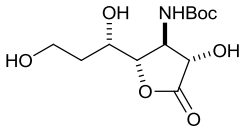
(*S*,*S*,*S*,*S*)-2,5-Dihydroxy-3-(*N*-*tert*-butoxycarbonylamino)-7-(triisopropylsilyloxy)-4-heptylolactone 530



Pd/C (50% w/w of substrate, 204 mg) was added to a stirred solution of **525** (408 mg, 0.753 mmol, >99:1 dr) and Boc_2O (181 mg, 0.829 mmol) in MeOH (10 mL) at rt. The resultant mixture was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm) for 18 h.

The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 3:1→2:1 30-40 °C petrol/EtOAc) gave **530** as a colourless oil (232 mg, 69%, >99:1 dr); $[\alpha]_D^{25}$ +10.9 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3366 (O–H), 2943, 2867 (C–H), 1782, 1689 (C=O); δ_H (500 MHz, $CDCl_3$) 1.01-1.15 (21H, m, (Si(C*H*Me_2)$_3$), 1.45 (9H, s, CMe_3), 1.70-1.80 (1H, m, C(6)H_A), 1.90-2.01 (1H, m, C(6)H_B), 3.91-4.04 (2H, m, C(7)H_2), 4.05-4.18 (2H, m, C(3)*H*, C(5)*H*), 4.23-4.29 (1H, m, C(4)*H*), 4.51 (1H, d, *J* 7.6, C(2)*H*), 4.69 (1H, br s, O*H*), 5.47 (1H, br s, N*H*); δ_C (125 MHz, $CDCl_3$) 11.7 (Si(*C*HMe_2)$_3$), 17.9 (Si(CH*Me*$_2$)$_3$), 28.2 (C*Me*$_3$), 33.5 (*C*(6)), 56.4 (*C*(3)), 61.8 (*C*(7)), 69.6 (*C*(5)), 72.7 (*C*(2)), 81.1 (*C*Me_3), 81.3 (*C*(4)), 156.4 (N*C*O), 173.6 (*C*(1)); *m/z* (ESI^+) 470 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{21}H_{41}NNaO_7Si^+$ ($[M+Na]^+$) requires 470.2545; found 470.2531.

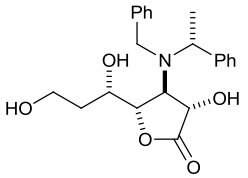
(*S*,*S*,*S*,*S*)-2,5,7-Trihydroxy-3-(*N*-*tert*-butoxycarbonylamino)-4-heptylolactone 447



*Method A (From **530**):* TBAF (1.0 M in THF, 0.32 mL, 0.32 mmol) was added dropwise to a stirred solution of **530** (121 mg, 0.270 mmol, >99:1 dr) in THF (4 mL) at rt and the resultant mixture was stirred at rt for 1 h. The reaction mixture was then diluted with Et_2O (10 mL) and washed with H_2O (10 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent EtOAc) gave **447** as a colourless oil (15 mg, 19%, >99:1 dr); $[\alpha]_D^{25}$ +21.8 (*c* 1.0 in MeOH); ν_{max} (ATR) 3347 (O–H), 2977, 2934 (C–H), 1778, 1689 (C=O); δ_H (500 MHz, MeOH-d_4) 1.48 (9H, s, CMe_3), 1.72-1.92 (2H, m, C(6)H_2), 3.70-3.77 (2H, m, C(7)H_2), 3.86-3.92 (1H, m, C(5)*H*), 4.10 (1H, dd, *J* 9.6, 2.2, C(4)*H*), 4.27 (1H, app t, *J* 9.6, C(3)*H*), 4.49 (1H, d, *J* 9.6, C(2)*H*); δ_C (125 MHz, MeOH-d_4) 28.7 (CMe_3), 37.0 (*C*(6)), 56.6 (*C*(3)), 59.6 (*C*(7)), 66.8 (*C*(5)), 72.9 (*C*(2)), 80.9 (*C*Me_3), 82.9 (*C*(4)), 158.0 (N*C*O), 176.1 (*C*(1)); *m/z* (ESI^+) 314 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{12}H_{21}NNaO_7^+$ ($[M+Na]^+$) requires 314.1210; found 314.1213.

*Method B (From **529**):* Pd/C (50% w/w of substrate, 258 mg) was added to a stirred solution of **529** (516 mg, 1.34 mmol, >99:1 dr) and Boc_2O (321 mg, 1.47 mmol) in MeOH (10 mL) at rt. The resultant mixture was degassed and saturated with H_2 before being left to stir under an atmosphere of H_2 (1 atm) for 18 h. The reaction mixture was then filtered through a short plug of Celite® (eluent MeOH) and the filtrate was concentrated *in vacuo* to give **447** as a milky yellow oil (390 mg, quant, >99:1 dr).[36]

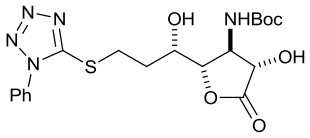
(2*S*,3*S*,4*S*,5*S*,α*R*)-2,5,7-Trihydroxy-3-[*N*-benzyl-*N*-(α-methylbenzyl)amino]-4-heptylolactone 529



Method A: TBAF (1.0 M in THF, 0.20 mL, 0.20 mmol) was added dropwise to a stirred solution of **525** (92 mg, 0.17 mmol, >99:1 dr) in THF (4 mL) at rt and the resultant mixture was stirred at rt for 1 h. The reaction mixture was then diluted with Et_2O (10 mL) and washed with H_2O (10 mL). The aqueous layer was extracted with Et_2O (3 × 10 mL) and the combined organic extracts were dried and concentrated *in vacuo*. Purification via flash column chromatography (eluent 30-40 °C petrol/EtOAc, 1:2) gave **529** as a pale yellow oil (30 mg, 46%, >99:1 dr); $[\alpha]_D^{25}$ +22.7 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3362 (O–H), 2933 (C–H), 1769 (C=O); δ_H (500 MHz, C_6D_6) 1.29-1.34 (1H, m, C(6)H_A), 1.35 (3H, d, *J* 6.9, C(α)*Me*), 1.63-1.71 (2H, m, C(6)H_B, C(7)O*H*), 2.55 (1H, d, *J* 6.3, C(5)O*H*), 2.78 (1H, d, *J* 4.9, C(2)O*H*), 3.32-3.39 (1H, m, C(7)H_A), 3.41-3.48 (1H, m, C(7)H_B), 3.57 (1H, d, *J* 15.1, NCH_AH_BPh), 3.61 (1H, d, *J* 15.1, NCH_AH_BPh), 3.70 (1H, dd, *J* 8.1, 1.4, C(4)*H*), 3.98-4.03 (1H, m, C(5)*H*), 4.04 (1H, app t, *J* 8.1, C(3)*H*), 4.09 (1H, q, *J* 6.9, C(α)*H*), 4.32 (1H, dd, *J* 8.1, 4.9, C(2)*H*), 7.10-7.49 (10H, m, *Ph*); δ_C (125 MHz, C_6D_6) [selected peaks] 19.0 (C(α)*Me*), 35.5 (*C*(6)), 50.1 (NCH_2Ph), 60.7 (*C*(7)), 61.4 (*C*(α)), 64.9 (*C*(3)), 68.5 (*C*(5)), 68.8 (*C*(2)), 81.3 (*C*(4)), 141.4, 143.8 (*i-Ph*), 175.2 (*C*(1)); *m/z* (ESI^+) 408 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{22}H_{27}NNaO_5^+$ ($[M+Na]^+$) requires 408.1781; found 408.1769.

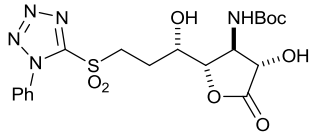
Method B: HF-pyridine solution (70%, 1.27 mL, 49.3 mmol) was added dropwise to a stirred solution of **525** (922 mg, 1.70 mmol, >99:1 dr) in THF (6 mL) at 0 °C. The resultant solution was stirred at rt for 16 h and was then neutralised by the dropwise addition of satd aq $NaHCO_3$ (~50 mL). The reaction mixture was extracted with EtOAc (3 × 100 mL) and the combined organic extracts were then dried and concentrated *in vacuo*. The residue was passed through a short plug of silica gel (eluent 30-40 °C petrol/EtOAc, 1:2) to give **529** as a pale yellow oil (579 mg, 88%, >99:1 dr).

(*S*,*S*,*S*,*S*)-2,5-Dihydroxy-3-(*N*-*tert*-butoxycarbonylamino)-7-(1'-phenyl-1*H*-tetrazol-5'-ylthio)-4-heptylolactone 531

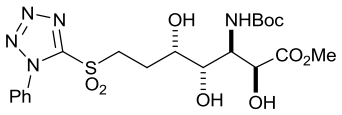


DEAD (98 μL, 0.62 mmol) was added dropwise to a solution of **447** (140 mg, 0.481 mmol, >99:1 dr), PTSH (103 mg, 0.578 mmol) and PPh_3 (151 mg, 0.576 mmol) in THF (6 mL) at 0 °C and the resultant mixture was allowed to warm to rt over 16 h. EtOAc (10 mL) was then added and the reaction mixture was washed sequentially with brine (10 mL) and H_2O (10 mL), then dried and concentrated *in vacuo*. Purification via flash column chromatography (gradient elution, 10:1→2:1 30-40 °C petrol/acetone) gave a sample of **531** contaminated with Ph_3PO (258 mg); δ_H (400 MHz, MeOH-d_4) [selected peaks] 1.41 (9H, s, CMe_3), 2.03-2.18 (2H, m, C(6)H_2), 3.40-3.51 (1H, m, C(7)H_A), 3.55-3.65 (1H, m, C(7)H_B), 3.86-3.94 (1H, m, C(5)*H*), 4.10-4.16 (1H, m, C(4)*H*), 4.33 (1H, app t, *J* 9.8, C(3)*H*), 4.55 (1H, d, *J* 9.8, C(2)*H*); δ_C (100 MHz, MeOH-d_4) [selected peaks] 27.8 (CMe_3), 30.0 (*C*(6)), 33.0 (*C*(7)), 55.7 (*C*(3)), 67.5 (*C*(5)), 71.9 (*C*(2)), 79.9 (*C*Me_3), 81.7 (*C*(4)), 155.0 (*C*(5')), 156.9 (N*C*O), 174.9 (*C*(1)); *m/z* (ESI^+) 474 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{19}H_{25}N_5NaO_6S^+$ ($[M+Na]^+$) requires 474.1418; found 474.1405.

(*S*,*S*,*S*,*S*)-2,5-Dihydroxy-3-(*N*-*tert*-butoxycarbonylamino)-7-[*N*(1')-phenyl-1*H*-tetrazol-5'-ylsulfonyl]-4-heptylolactone 532 and methyl (2*S*,3*R*,4*S*,5*S*)-2,4,5-trihydroxy-3-(*N*-*tert*-butoxycarbonylamino)-7-[*N*(1')-phenyl-1*H*-tetrazol-5'-ylsulfonyl]heptanoate 533



532

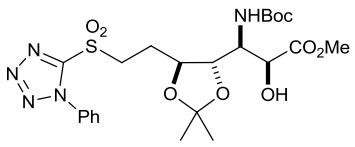


533

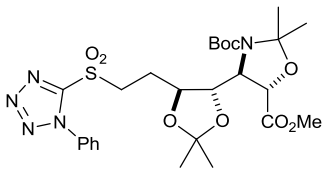
$(NH_4)_6Mo_7O_{24}{\cdot}4H_2O$ (60 mg, 49 μmol) was dissolved in 30% aq H_2O_2 (0.42 mL, 3.7 mmol) at 0 °C and the resultant mixture was added dropwise to a solution of **531** (258 mg, contaminated with Ph_3PO) in EtOH (4.5 mL) at 0 °C. The resultant suspension was stirred at rt for 16 h and was then added to brine (10 mL). The resultant mixture was then extracted with EtOAc (3 × 20 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **532** (contaminated with Ph_3PO). Purification via flash column chromatography (eluent CH_2Cl_2/MeOH, 50:1) gave an 80:20 mixture of **533** and **532** respectively as a white solid (67 mg). Data for mixture: mp 177-181 °C; ν_{max} (ATR) 3514, 3415, 3385 (N–H, O–H), 2985, 2953, 2913 (C–H), 1740, 1668 (C=O), 1332, 1151 (S=O); *m/z* (ESI^+) 538 ($[M(\mathbf{533})+Na]^+$, 100%), 506 ($[M(\mathbf{532})+Na]^+$, 100%); HRMS (ESI^+) $C_{20}H_{28}N_5Na_2O_9S^+$ ($[M(\mathbf{533})–H+2Na]^+$) requires 560.1398; found 560.1383; HRMS (ESI^+)

$C_{19}H_{25}N_5NaO_8S^+$ ([M(**532**)+Na]$^+$) requires 506.1316; found 506.1308. Data for **533**: δ_H (500 MHz, DMSO-d_6) 1.35 (9H, s, CMe_3), 1.76-1.84 (1H, m, C(6)H_A), 1.93-2.03 (1H, m, C(6)H_B), 3.26-3.32 (1H, m, C(2)*H*), 3.50-3.56 (1H, m, C(5)*H*), 3.58 (3H, s, O*Me*), 3.75-3.82 (2H, m, C(7)H_2), 3.91 (1H, app td, *J* 10.0, 1.6, C(3)*H*), 4.40 (1H, d, *J* 7.3, C(5)O*H*), 4.43 (1H, dd, *J* 7.6, 1.6, C(4)*H*), 4.91 (1H, d, *J* 8.2, C(2)O*H*), 5.11 (1H, d, *J* 7.6, C(4)O*H*), 6.29 (1H, d, *J* 10.0, N*H*), 7.63-7.79 (5H, m, *Ph*); δ_C (125 MHz, DMSO-d_6) 26.3 (*C*(6)), 28.1 (CMe_3), 51.4 (O*Me*), 53.5 (*C*(7)), 54.3 (*C*(3)), 67.2 (*C*(5)), 68.9 (*C*(4)), 70.1 (*C*(2)), 78.1 (*C*Me$_3$), 126.4, 129.4 (*o*,*m*-*Ph*), 131.5 (*p*-*Ph*), 133.0 (*C*(5')), 153.3 (*i*-*Ph*), 155.3 (N*C*O), 174.0 (*C*(1)). Data for **532**: δ_H (500 MHz, DMSO-d_6) [selected peaks] 1.39 (9H, s, CMe_3), 1.89-2.04 (2H, m, C(6)H_2), 3.18 (1H, d, *J* 5.0, C(2)O*H*), 3.60-3.67 (1H, m, C(5)*H*), 3.75-3.82 (1H, m, C(7)H_A), 3.84-3.92 (1H, m, C(7)H_B), 3.99 (1H, dd, *J* 8.8, 2.2, C(4)*H*), 4.10-4.18 (1H, m, C(2)*H*), 4.33-4.38 (1H, m, C(3)*H*), 5.39 (1H, d, *J* 7.3, C(5)O*H*), 6.18 (1H, d, *J* 7.2, N*H*); δ_C (125 MHz, DMSO-d_6) [selected peaks] 25.8 (*C*(6)), 28.2 (CMe_3), 53.0 (*C*(7)), 54.6 (*C*(2)), 65.9 (*C*(5)), 71.0 (*C*(3)), 78.4 (*C*Me$_3$), 80.8 (*C*(4)), 153.3 (*C*(5')), 155.1 (N*C*O), 174.2 (*C*(1)).

Methyl (*S*,*S*,*S*,*S*)-2,4,5-trihydroxy-3-(*N*-*tert*-butoxycarbonylamino)-4,5-*O*-isopropylidine-7-[*N*(1')-phenyl-1*H*-tetrazol-5'-ylsulfonyl]heptanoate 535 and (5*S*,4*R*,1'*S*,2'*S*)-2,2-dimethyl-*N*(3)-(*tert*-butoxycarbonyl)-4-(1',2'-dihydroxy-1',2'-*O*-isopropylidene-4'-{[*N*(1'')-phenyl-1*H*-tetrazol-5''-yl]sulfonyl}but-1'-yl)-5-methoxycarbonyloxazolidine 534



535



534

Method A: PPTS (5 mg, cat.) was added to a solution of an 80:20 mixture of **533** and **532** (50 mg) in acetone (2.5 mL) at rt. The resultant mixture was then heated at reflux for 24 h. The reaction mixture was allowed to cool to rt, $NaHCO_3$ was then added until pH 7 was achieved and the reaction mixture was filtered and concentrated *in vacuo* to give a 83:17 mixture of **535** and **534** respectively. Purification via flash column chromatography (gradient elution, 5:1→2:1 30-40 °C petrol/EtOAc) gave **534** as a colourless oil (7 mg, 3% from **529**, >99:1 dr); $[\alpha]_D^{25}$ –5.7 (*c* 0.6 in $CHCl_3$); ν_{max} (ATR) 2984, 2938 (C–H), 1740, 1691 (C=O), 1369, 1153 (S=O); δ_H (500 MHz, $CDCl_3$) 1.40 (6H, app s, 2 × *Me*CMe), 1.47 (9H, s, CMe_3), 1.56 (3H, s, *Me*CMe), 1.60 (3H, s, *Me*CMe), 2.11-2.21 (1H, m, C(3')H_A), 2.23-2.34 (1H, m, C(3')H_B), 3.78-3.92 (2H, m, C(1')*H*, C(4')H_A) overlapping 3.80 (3H, s, O*Me*), 3.96-4.06 (1H, m, C(4')H_B), 4.27 (1H, app br s, C(2')*H*), 4.49 (1H, app br s, C(4)*H*),

4.72 (1H, app br s, C(5)*H*), 7.57-7.75 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 26.0 (*C*(3')), 26.9, 27.2, 27.2, 27.3 (4 × *Me*CMe), 28.3 (C*Me*$_3$), 52.6 (O*Me*), 53.3 (*C*(4')), 61.4 (*C*(4)), 75.0 (*C*(5)), 76.4 (*C*(2')), 80.3 (*C*(1')), 81.4 (*C*Me$_3$), 96.5 (*C*(2)), 109.4 (Me*C*Me), 125.1, 129.7 (*o,m-Ph*), 131.5 (*p-Ph*), 133.0 (*i-Ph*), 152.3 (N*C*O), 154.4 (*C*(5")), 171.8 (*C*O_2Me); *m/z* (ESI^+) 618 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{26}H_{37}N_5NaO_9S^+$ ($[M+Na]^+$) requires 618.2204; found 618.2181. Further elution gave **535** as a white solid (20 mg, 11% from **529**, >99:1 dr); mp 143-146 °C; $[\alpha]_D^{25}$ −3.0 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3388 (O–H, N–H), 2984, 2936 (C–H), 1741, 1712 (C=O), 1341, 1156 (S=O); δ_H (500 MHz, $CDCl_3$) 1.40 (9H, s, C*Me*$_3$), 1.42 (6H, app s, 2 × *Me*CMe), 2.11-2.21 (1H, m, C(6)H_A), 2.27-2.36 (1H, m, C(6)H_B), 3.11 (1H, br s, O*H*), 3.77 (1H, dd, *J* 9.5, 7.3, C(4)*H*), 3.78-3.84 (1H, m, C(7)H_A) overlapping 3.81 (3H, s, O*Me*), 3.98 (1H, app ddd, *J* 15.3, 11.5, 4.4, C(7)H_B), 4.16-4.22 (2H, m, C(3)*H*, C(5)*H*), 4.57 (1H, app br s, C(2)*H*), 4.91 (1H, d, *J* 10.1, N*H*), 7.58-7.72 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 26.9 (*C*(6)), 27.0, 27.3 (2 × *Me*CMe), 28.1 (C*Me*$_3$), 53.0 (*C*(7)), 53.0 (O*Me*), 55.2 (*C*(5)), 69.8 (*C*(2)), 77.4 (*C*(3)), 78.7 (*C*(4)), 80.5 (*C*Me$_3$), 109.8 (Me*C*Me), 125.0, 129.7 (*o,m-Ph*), 131.5 (*p-Ph*), 133.0 (*i-Ph*), 153.3 (*C*(5')), 155.2 (N*C*O), 173.8 (*C*(1)); *m/z* (ESI^+) 578 ($[M+Na]^+$, 100%); HRMS (ESI^+) $C_{23}H_{33}N_5NaO_9S^+$ ($[M+Na]^+$) requires 578.1891; found 578.1894.

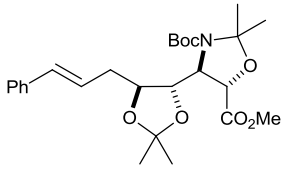
Method B: BF_3 (1.0 M in Et_2O, ~2 drops) was added dropwise to a solution of an 80:20 mixture of **533** and **532** (30 mg) and DMP (0.4 mL) in acetone (2.0 mL) at rt until a permanent colour change from colourless to dark orange was observed. The resultant mixture was stirred at rt for 18 h. Et_3N (~0.1 mL) was added until pH 7 was achieved and the reaction mixture was then concentrated *in vacuo* gave a 74:26 mixture of **535** and **534** respectively. Purification via flash column chromatography (gradient elution, 5:1→2:1 30-40 °C petrol/EtOAc) gave **534** as a colourless oil (6 mg, 5% from **529**, >99:1 dr). Further elution gave **535** as a white solid (9 mg, 8% from **529**, >99:1 dr).

Method C: $TsOH{\cdot}H_2O$ (6 mg, cat.) was added to a solution of an 80:20 mixture of **533** and **532** (32 mg) in acetone (2.8 mL) and DMP (0.2 mL) at rt and the resultant solution was then heated at 40 °C for 24 h. The reaction mixture was allowed to cool to rt and solid Na_2CO_3 was then added until pH 7 was achieved. The resultant mixture was then filtered and concentrated *in vacuo* to give an 80:20 mixture of **535** and **534** respectively. Purification via flash column chromatography (gradient elution, 5:1→2:1 30-40 °C petrol/EtOAc) gave **534** as a colourless oil (7 mg, 6% from **529**, >99:1 dr). Further elution gave **535** as a white solid (24 mg, 21% from **529**, >99:1 dr).

Method D: TsOH·H_2O (7 mg, cat.) was added to a solution of an 80:20 mixture of **533** and **532** (36 mg) in acetone (2.8 mL) and DMP (0.2 mL) at rt. The resultant solution was then stirred at rt for 24 h, then solid Na_2CO_3 was added until pH 7 was achieved. The resultant mixture was then filtered and concentrated *in vacuo* to give **535** in >99:1 dr. Purification via flash column chromatography (gradient elution, 5:1→2:1 30-40 °C petrol/EtOAc) gave **535** as a white solid (24 mg, 19% from **529**, >99:1 dr).

Method E: TsOH·H_2O (7 mg, cat.) was added to a solution of **532** (34 mg, contaminated with Ph_3PO) in acetone (2.8 mL) and DMP (0.2 mL) at rt. The resultant solution was then stirred at rt for 24 h, then solid Na_2CO_3 was added until pH 7 was achieved. The resultant mixture was then filtered and concentrated *in vacuo* to give **535** in >99:1 dr. Purification via flash column chromatography (gradient elution, 5:1→2:1 30-40 °C petrol/EtOAc) gave **535** as a white solid (20 mg, 30% from **529**, >99:1 dr).

(5*S*,4*R*,1'*S*,2'*S*,*E*)-2,2-Dimethyl-*N*(3)-(*tert*-butoxycarbonyl)-4-(1',2'-dihydroxy-1',2'-*O*-isopropylidene-5'-phenylpent-4'-en-1'-yl)-5-methoxycarbonyloxazolidine 413

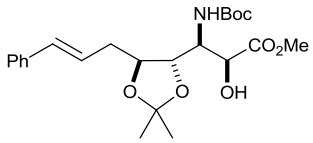


*Method A (From **536**):* A solution of **536** (37 mg, 85 μmol, >99:1 dr) in acetone (2.9 mL) and DMP (0.58 mL) was stirred at rt and BF_3 (1.0 M in Et_2O, ~3 drops) was added dropwise until a permanent colour change from colourless to dark orange was observed. The resultant mixture was then stirred at rt for 18 h. Et_3N (~5 drops) was then added until pH 7 was achieved and the reaction mixture was concentrated *in vacuo* to give a 66:34 mixture of **413** and **536** respectively. Purification via flash column chromatography (gradient elution, 20:1→10:1 30-40 °C petrol/EtOAc) gave **413** as a pale yellow oil (15 mg, 37%, >99:1 dr);[37] $[\alpha]_D^{25}$ –0.4 (*c* 1.0 in CH_2Cl_2); {lit.[37] $[\alpha]_D^{21}$ –3.1 (*c* 3.8 in CH_2Cl_2)}; $[\alpha]_D^{25}$ –2.3 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 2983, 2936 (C–H), 1740, 1697 (C=O); δ_H (250 MHz, $CDCl_3$, 327 K) 1.43 (6H, app s, 2 × *Me*CMe), 1.52 (9H, s, C*Me*$_3$), 1.58 (3H, s, *Me*CMe), 1.63 (3H, s, *Me*CMe), 2.40-2.66 (2H, m, C(3')*H*$_2$), 3.76 (3H, s, O*Me*), 4.02 (1H, dd, *J* 7.9, 5.5, C(1')*H*), 4.12-4.23 (1H, m, C(2')*H*), 4.45-4.53 (1H, m, C(4)*H*), 4.73 (1H, d, *J* 2.1, C(5)*H*), 6.29 (1H, dt, *J* 15.8, 7.0, C(4')*H*), 6.51 (1H, d, *J* 15.8, C(5')*H*), 7.16-7.39 (5H, m, *Ph*); δ_C (62.5 MHz, $CDCl_3$, 327 K) 27.2, 27.2, 27.4, 27.7 (4 × *Me*CMe), 28.5 (C*Me*$_3$), 36.5 (*C*(3')), 52.3 (O*Me*), 61.3 (*C*(4)), 75.2, 78.3, 80.0 (*C*(5), *C*(1'), *C*(2')), 80.9 (*C*Me$_3$), 96.7 (*C*(2)), 109.0 (Me*C*Me), 125.5 (*C*(4')), 126.2, 128.5 (*o,m-Ph*), 127.2 (*p-Ph*), 132.9 (*C*(5')), 137.6 (*i-Ph*), 151.8 (N*C*O),

172.1 (*C*O_2Me); *m/z* (ESI$^+$) 498 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{26}H_{37}NNaO_7^+$ ([M+Na]$^+$) requires 498.2462; found 498.2464.

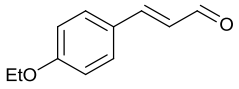
*Method B (From **534**):* KHMDS (0.5 M in PhMe, 64 µL, 32 µmol) was added dropwise to a solution of **534** (16 mg, 27 µmol, >99:1 dr) and PhCHO (4 µL, 30 µmol) in THF (0.6 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. H_2O (1 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give a 28:72 mixture of **413** and **534** respectively. Purification via flash column chromatography (gradient elution, 20:1→5:1 30-40 °C petrol/EtOAc) gave **413** as a yellow oil (2 mg, 16%, >99:1 dr). Further elution gave **534** as a colourless oil (5 mg, 31%, >99:1 dr).

Methyl (*S*,*S*,*S*,*S*,*E*)-2,4,5-trihydroxy-3-(*N*-*tert*-butoxycarbonylamino)-4,5-*O*-isopropylidine-8-phenylocta-7-enoate 536



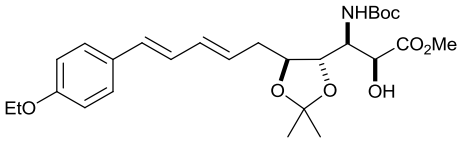
KHMDS (0.5 M in PhMe, 0.70 mL, 0.35 mmol) was added dropwise to a solution of **535** (61 mg, 0.11 mmol, >99:1 dr) and PhCHO (36 µL, 0.13 mmol) in THF (2.2 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. H_2O (1 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **536** in >99:1 dr. Purification via flash column chromatography (gradient elution, 10:1→3:1 30-40 °C petrol/EtOAc) gave **536** as a white solid (38 mg, 79%, >99:1 dr); mp 131-135 °C; $[\alpha]_D^{25}$ –7.9 (*c* 0.4 in $CHCl_3$); ν_{max} (ATR) 3437, 3360 (N–H, O–H), 3027, 2983, 2935 (C–H), 1741, 1716 (C=O); δ_H (500 MHz, $CDCl_3$) 1.42 (9H, s, C*Me*$_3$), 1.45 (6H, app s, 2 × *Me*CMe), 2.45-2.52 (1H, m, C(6)H_A), 2.53-2.60 (1H, m, C(6)H_B), 3.08 (1H, br s, O*H*), 3.78-3.83 (1H, m, C(4)*H*) overlapping 3.80 (3H, s, O*Me*), 4.17-4.23 (2H, m, C(3)*H*, C(5)*H*), 4.59 (1H, app s, C(2)*H*), 4.84 (1H, d, *J* 10.1, N*H*), 6.24 (1H, dt, *J* 15.8, 7.3, C(7)*H*), 6.46 (1H, d, *J* 15.8, C(8)*H*), 7.19-7.38 (5H, m, *Ph*); δ_C (125 MHz, $CDCl_3$) 27.1, 27.5 (2 × *Me*CMe), 28.2 (C*Me*$_3$), 37.7 (*C*(6)), 52.9 (O*Me*), 55.3 (*C*(5)), 69.9 (*C*(2)), 78.4 (*C*(4)), 79.5 (*C*(3)), 80.1 (*C*Me$_3$), 109.4 (Me*C*Me), 125.5 (*C*(7)), 126.1, 128.5 (*o,m-Ph*), 127.2 (*p-Ph*), 132.6 (*C*(8)), 137.3 (*i-Ph*), 155.0 (N*C*O), 174.0 (*C*(1)); *m/z* (ESI$^+$) 458 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{23}H_{33}NNaO_7^+$ ([M+Na]$^+$) requires 458.2149; found 458.2135.

(*E*)-4-Ethoxycinnamaldehyde 539



4-Iodophenetole **537** (120 mg, 0.484 mmol) was dissolved in DMF (2 mL) at rt and then acrolein diethyl acetal **538** (0.22 mL, 1.5 mmol), Bu_4NOAc (292 mg, 0.968 mmol), K_2CO_3 (100 mg, 0.724 mmol), KCl (36 mg, 0.48 mmol) and $Pd(OAc)_2$ (3 mg, 13 μmol) were sequentially added. The reaction vessel was evacuated and placed under an atmosphere of N_2 and then heated at 90 °C for 18 h. The reaction mixture was allowed to cool to rt and then 2.0 M aq HCl (7 mL) was added dropwise and the resultant mixture was stirred at rt for 10 min. The reaction mixture was diluted with Et_2O (50 mL) and washed with H_2O (3 × 50 mL) and then the organic layer was dried and concentrated *in vacuo* to give a 94:6 mixture of **539** and **537** respectively. Purification via flash column chromatography (gradient elution, 40:1→10:1 30-40 °C petrol/EtOAc) gave **539** as a yellow solid (70 mg, 82%, >99:1 dr); mp 50-52 °C; ν_{max} (ATR) 2983, 2931 (C–H), 1673 (C=O), 1600 (C=C); δ_H (400 MHz, $CDCl_3$) 1.45 (3H, t, *J* 7.0, CH_2CH_3), 4.10 (2H, q, *J* 7.0, CH_2CH_3), 6.62 (1H, dd, *J* 15.9, 7.9, CH=C*H*CHO), 6.94 (2H, d, *J* 8.7, C(3)*H*, C(5)*H*), 7.43 (1H, d, *J* 15.9, C*H*=CHCHO), 7.52 (2H, d, *J* 8.7, C(2)*H*, C(6)*H*), 9.66 (1H, d, *J* 7.9, C*H*O); δ_C (100 MHz, $CDCl_3$) 14.7 (CH_2CH_3), 63.7 (CH_2CH_3), 115.0 (*C*(3), *C*(5)), 126.4 (CH=*C*HCHO), 126.6 (*C*(1)), 130.4 (*C*(2), *C*(6)), 152.9 (*C*H=CHCHO), 161.6 (*C*(4)), 193.8 (*C*HO); *m/z* (FI^+) 176 ($[M]^+$, 100%); HRMS (FI^+) $C_{11}H_{12}O_2^+$ ($[M]^+$) requires 176.0832; found 176.0841.

Methyl (*S*,*S*,*S*,*S*,*E*,*E*)-2,4,5-trihydroxy-3-(*N*-*tert*-butoxycarbonylamino)-4,5-*O*-isopropylidine-10-(4'-ethoxyphenyl)deca-7,9-dienoate 540



Method A: KHMDS (0.5 M in PhMe, 1.89 mL, 0.945 mmol) was added dropwise to a solution of **535** (164 mg, 0.295 mmol, >99:1 dr) and **539** (166 mg, 0.945 mmol, >99:1 dr) in THF (30 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. H_2O (5 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with EtOAc (3 × 20 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **540** in >99:1 dr. Purification via flash column chromatography (gradient elution, 7:1→5:1 30-40 °C petrol/EtOAc) gave **540** as a yellow solid (35 mg, 23%, >99:1 dr); mp 116-120 °C; $[\alpha]_D^{25}$ –11.1 (*c* 1.0 in $CHCl_3$); ν_{max} (ATR) 3364 (N–H, O–H), 2982, 2934 (C–H), 1741, 1716 (C=O), 1604, 1510 (C=C); δ_H (500 MHz, $CDCl_3$) 1.42-1.45 (18H, m, CMe_3, 2 × *Me*CMe, CH_2CH_3), 2.37-2.44 (1H, m,

C(6)H_A), 2.46-2.52 (1H, m, C(6)H_B), 3.09 (1H, d, *J* 3.8, O*H*), 3.76 (1H, dd, *J* 9.5, 6.5, C(4)*H*), 3.80 (3H, s, O*Me*), 4.04 (2H, q, *J* 7.1, CH_2CH$_3$), 4.13-4.22 (2H, m, C(3)*H*, C(5)*H*), 4.58 (1H, app s, C(2)*H*), 4.82 (1H, d, *J* 10.1, N*H*), 5.76 (1H, dt, *J* 15.1, 7.4, C(7)*H*), 6.25 (1H, dd, *J* 15.1, 10.5, C(8)*H*), 6.41 (1H, d, *J* 15.5, C(10)*H*), 6.63 (1H, dd, *J* 15.5, 10.5, C(9)*H*), 6.84 (2H, d, *J* 8.7, C(3')*H*, C(5')*H*), 7.30 (2H, d, *J* 8.7, C(2')*H*, C(6')*H*); δ_C (125 MHz, $CDCl_3$) 14.8 (CH$_2$*C*H$_3$), 27.1, 27.5 (2 × *Me*CMe), 28.2 (C*Me*$_3$), 37.5 (*C*(6)), 52.9 (O*Me*), 55.3 (*C*(3)), 63.4 (*C*H$_2$CH$_3$), 69.9 (*C*(2)), 78.4 (*C*(4)), 79.5 (*C*(5)), 80.1 (*C*Me$_3$), 109.3 (Me*C*Me), 114.6 (*C*(3'), *C*(5')), 126.8 (*C*(9)), 127.4 (*C*(2'), *C*(6')), 128.6 (*C*(7)), 130.0 (*C*(1')), 130.8 (*C*(10)), 133.4 (*C*(8)), 155.0 (N*C*O), 158.4 (*C*(4')), 174.0 (*C*(1)); *m/z* (ESI$^+$) 528 ([M+Na]$^+$, 100%); HRMS (ESI$^+$) $C_{27}H_{39}NNaO_8^+$ ([M+Na]$^+$) requires 528.2568; found 528.2564.

Method B: KHMDS (0.5 M in PhMe, 0.28 mL, 0.14 mmol) was added dropwise to a solution of **535** (24 mg, 43 μmol, >99:1 dr) and **539** (24 mg, 0.14 mmol, >99:1 dr) in THF (0.9 mL) at –78 °C and the resultant mixture was stirred at –78 °C for 30 min. H_2O (1 mL) was then added and the reaction mixture was allowed to warm to rt. The aqueous layer was extracted with EtOAc (3 × 5 mL) and the combined organic extracts were dried and concentrated *in vacuo* to give **540** in 81:19 dr. Purification via flash column chromatography (gradient elution, 7:1→5:1 30-40 °C petrol/EtOAc) gave **540** as a yellow oil (15 mg, 70%, 81:19 dr). Data for minor [(7*Z*,9*E*)]: δ_H (500 MHz, $CDCl_3$) [selected peaks] 5.51 (1H, dt, *J* 10.7, 7.4, C(7)*H*), 6.51 (1H, d, *J* 15.5, C(10)*H*).

5.6 References and notes for chapter 5

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[15] **244** has previously been isolated as a pale yellow oil, see: reference 14.
[16] **243**·HCl was found to be a very hygroscopic solid.
[17] Unfortunately, the ^{1}H NMR resonances for the minor rotamer of **247** were indistinguishable due to significant peak overlap.
[18] For the NMR spectrum of **246** in D_2O, dioxane (δ_C 67.6 ppm) was used as an internal reference.
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[21] In the literature, **323** was isolated as a mixture with starting material and so no mp or specific rotation data was reported, see: reference 20.
[22] In the literature, **327** was isolated as a colourless oil and so no mp data was reported, see: reference 20.
[23] An *m/z* peak corresponding to **385** could not be found in the HRMS spectrum of the mixture of **305** and **385**, despite attempts involving different forms of ionisation.
[24] An *m/z* peak corresponding to **387** could not be found in the HRMS spectrum of the mixture of **306** and **387**, despite attempts involving different forms of ionisation.
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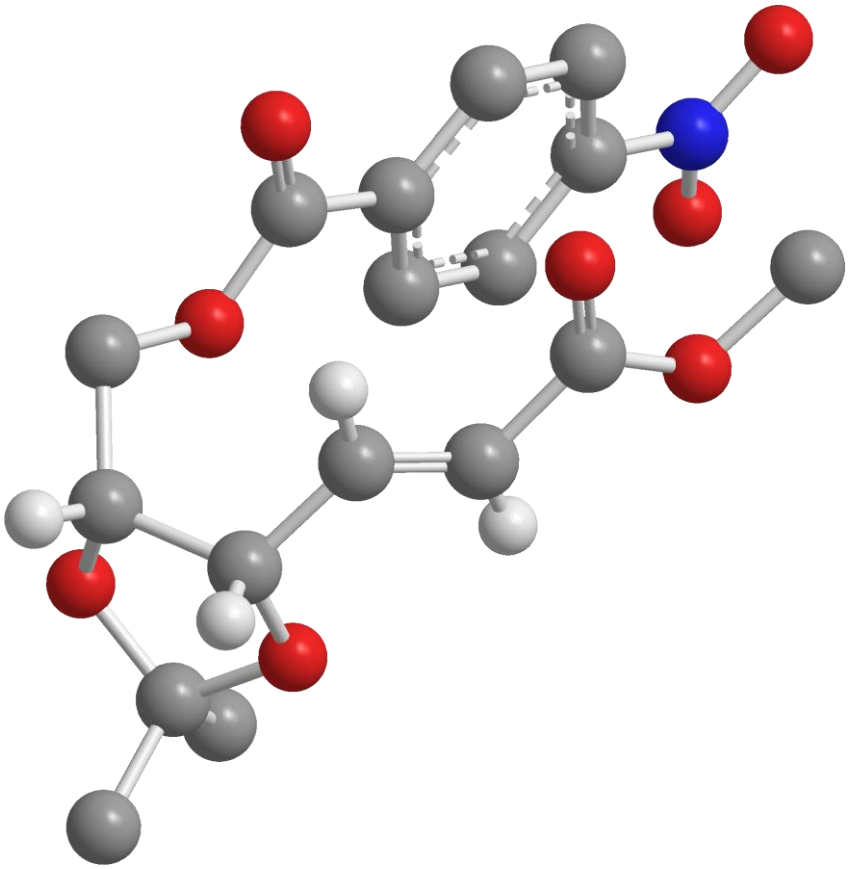
X-Ray crystal structure data for (4*S*,5*R*,*E*)-149

(selected H atoms omitted for clarity)



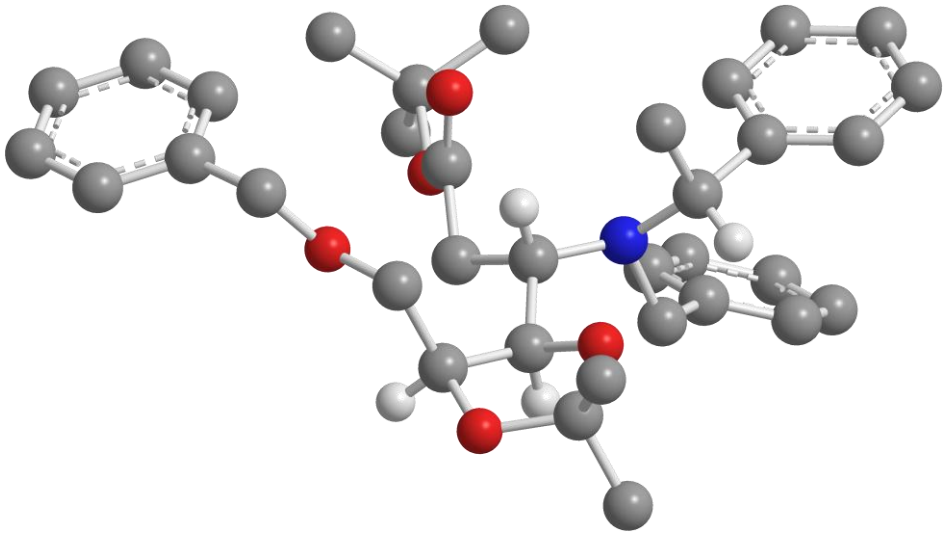
X-Ray crystal structure determination for 149

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-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 **149** [$C_{17}H_{19}NO_8$]: M = 365.34, triclinic, space group $P\ 1$, a = 6.4158(2) Å, b = 8.0401(2) Å, c = 9.2337(4) Å, α = 73.5130(12)º, β = 79.6666(12)º, γ = 71.2553(16)º, V = 430.46(3) Å^3, Z = 1, μ = 0.11 mm^{-1}, colourless block, crystal dimensions = 0.10 × 0.13 × 0.19 mm^3. A total of 1949 unique reflections were measured for 5 < θ < 27 and 1949 reflections were used in the refinement. The final parameters were wR_2 = 0.093 and R_1 = 0.039 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (3*S*,4*R*,5*S*,α*R*)-195

(selected H atoms are omitted for clarity)



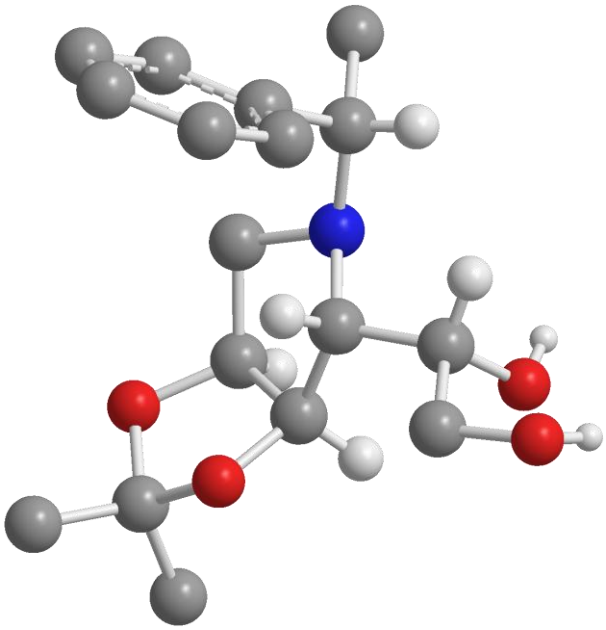
X-ray crystal structure determination for 195

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-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 **195** [$C_{35}H_{45}NO_5$]: M = 559.75, monoclinic, space group $P\ 2_1$, a = 11.9837(5) Å, b = 7.5408(3) Å, c = 17.6653(8) Å, β = 91.750(2)°, V = 1595.61(12) Å^3, Z = 2, μ = 0.077 mm^{-1}, colourless prism, crystal dimensions = 0.09 × 0.13 × 0.28 mm^3. A total of 3826 unique reflections were measured for 5 < θ < 27 and 3061 reflections were used in the refinement. The final parameters were wR_2 = 0.094 and R_1 = 0.47 [I>−3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (2*S*,3*R*,4*R*,5*S*,α*S*)-242

(selected H atoms are omitted for clarity)



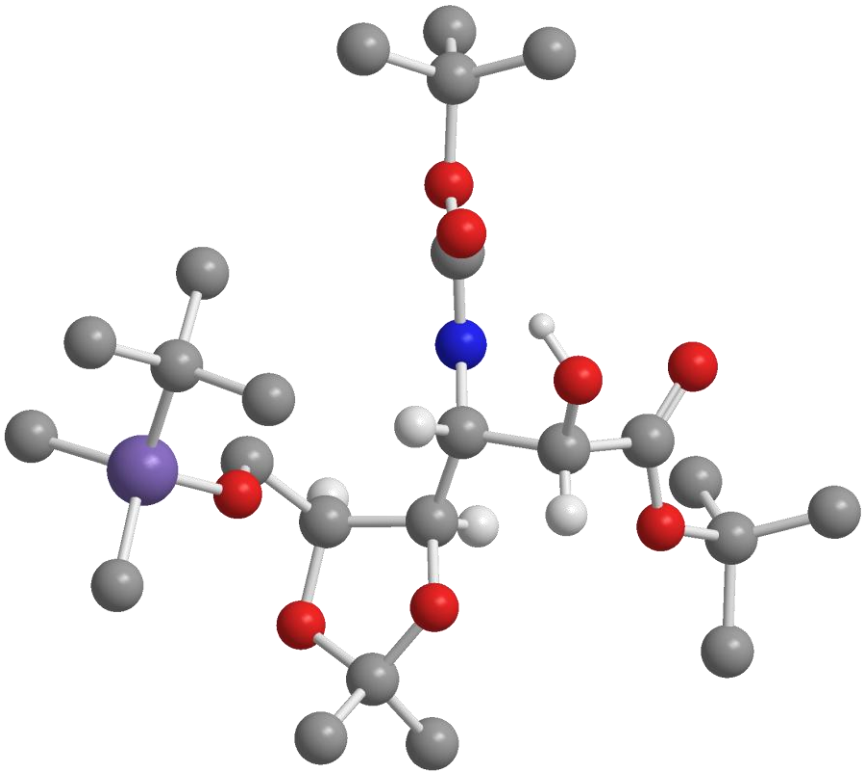
X-ray crystal structure determination for 242

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-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 **242** [$C_{17}H_{25}NO_5$]: M = 307.39, monoclinic, space group $P\ 2_1$, a = 8.3116(2) Å, b = 7.9434(2) Å, c = 12.1109(3) Å, β = 91.6599(13)°, V = 799.25(3) Å^3, Z = 2, μ = 0.090 mm^{-1}, colourless block, crystal dimensions = 0.15 × 0.23 × 0.29 mm^3. A total of 1944 unique reflections were measured for 5 < θ < 27 and 1944 reflections were used in the refinement. The final parameters were wR_2 = 0.081 and R_1 = 0.038 [I>−3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (2*S*,3*R*,4*R*,5*S*)-252

(selected H atoms are omitted for clarity)



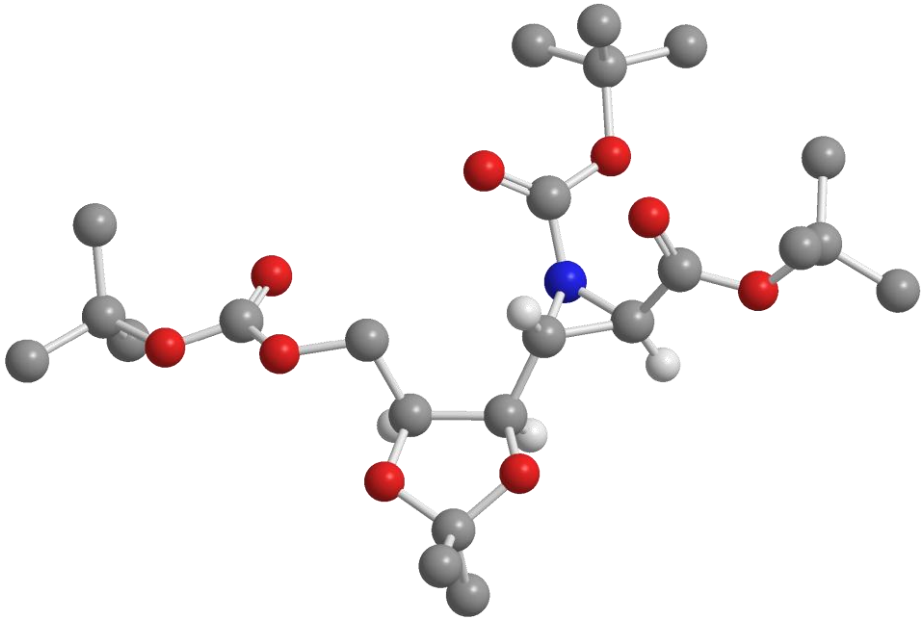
X-ray crystal structure determination for 252

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 **252** [$C_{24}H_{46}NO_8Si$]: M = 504.72, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 10.9749(3) Å, b = 12.2377(4) Å, c = 22.4965(6) Å, V = 3021.44(14) Å^3, Z = 4, μ = 1.028 mm^{-1}, colourless block, crystal dimensions = 0.10 × 0.13 × 0.29 mm^3. A total of 47561 unique reflections were measured for 4 < θ < 76 and 47380 reflections were used in the refinement. The final parameters were wR_2 = 0.139 and R_1 = 0.054 [I>0.0σ(I)], with Flack enantiopole = −0.010(13).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (2*S*,3*R*,1'*R*,2'*S*)-260

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 260

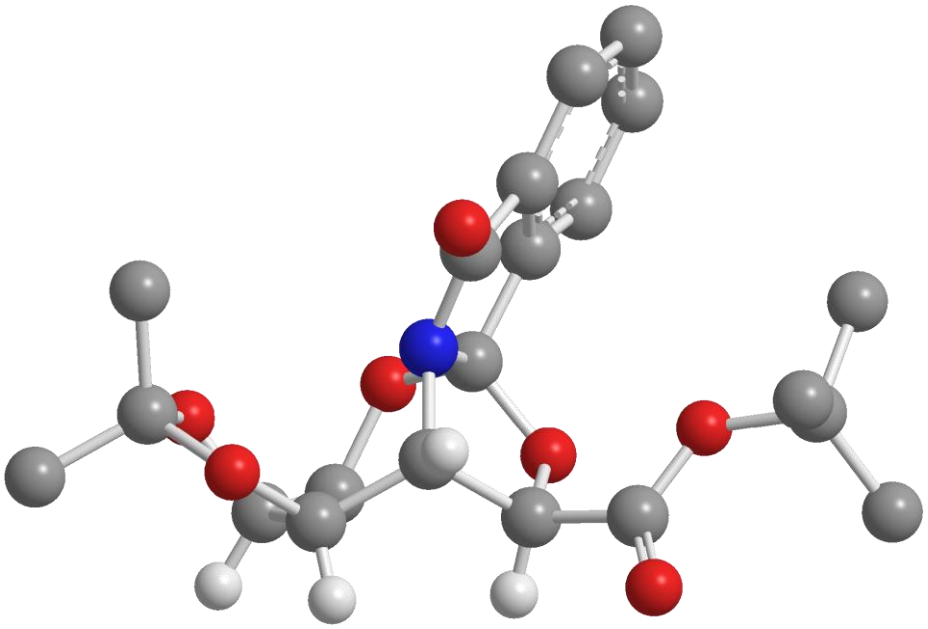
Data were collected using an Oxford Diffraction SuperNova diffractometer with graphite monochromated Cu-Kα radiation using standard procedures at 150 K. The structure was solved by direct methods (SIR92); all non-hydrogen atoms were refined with anisotropic thermal parameters. Hydrogen atoms were added at idealised positions. The structure was refined using CRYSTALS.[1]

X-ray crystal structure data for **260** [$C_{23}H_{39}NO_9$]: M = 947.13, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 10.43746(14) Å, b = 12.00285(15) Å, c = 41.7847(5) Å, V = 5234.76(12) Å^3, Z = 8, μ = 0.764 mm^{-1}, colourless plate, crystal dimensions = 0.11 × 0.17 × 0.21 mm^3. A total of 27625 unique reflections were measured for 4 < θ < 76 and 27552 reflections were used in the refinement. The final parameters were wR_2 = 0.098 and R_1 = 0.044 [I>0.0σ(I)], with Flack enantiopole = 0.04(7).[2]

X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (3*S*,4*R*,13*R*)-264

(selected H atoms are omitted for clarity)



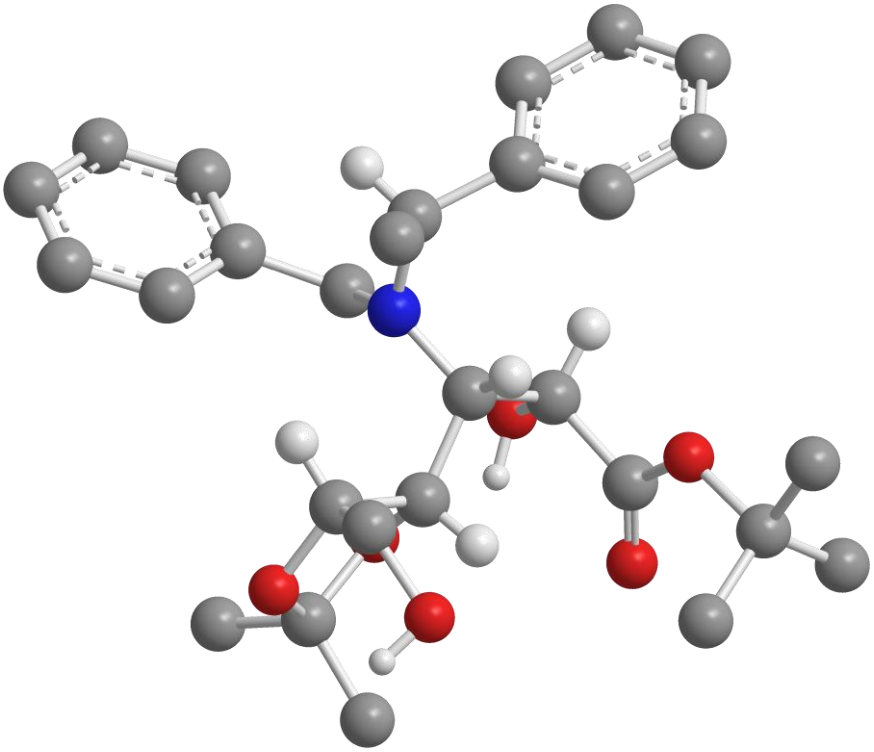
X-ray crystal structure determination for 264

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 **264** [$C_{21}H_{25}NO_7$]: M = 403.43, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 10.19767(12) Å, b = 11.88352(13) Å, c = 17.3140(3) Å, V = 2098.19(5) Å^3, Z = 4, μ = 0.802 mm^{-1}, colourless plate, crystal dimensions = 0.05 × 0.17 × 0.19 mm^3. A total of 17178 unique reflections were measured for 5 < θ < 27 and 14437 reflections were used in the refinement. The final parameters were wR_2 = 0.072 and R_1 = 0.031 [I>−3.0σ(I)], with Flack enantiopole = 0.03(7).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (2*S*,3*R*,4*S*,5*S*,α*S*)-265

(selected H atoms are omitted for clarity)



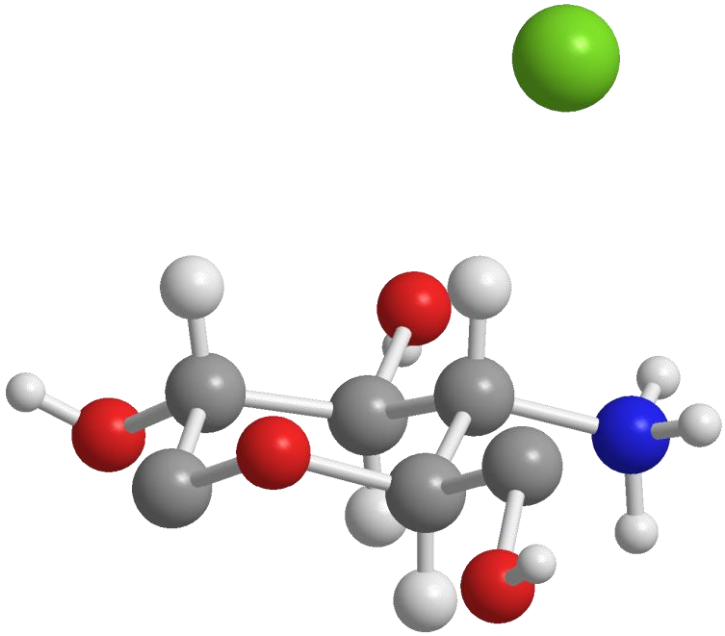
X-ray crystal structure determination for 265

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-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 **265** [$C_{28}H_{39}NO_6$]: M = 485.62, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 8.0958(1) Å, b = 15.5197(3) Å, c = 21.6546(3) Å, V = 2720.78(7) Å^3, Z = 4, μ = 0.082 mm^{-1}, colourless block, crystal dimensions = 0.21 × 0.21 × 0.25 mm^3. A total of 3499 unique reflections were measured for 5 < θ < 27 and 2603 reflections were used in the refinement. The final parameters were wR_2 = 0.081 and R_1 = 0.037 [I>−3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (*S*,*S*,*S*,*S*)-272·HCl

(selected H atoms are omitted for clarity)



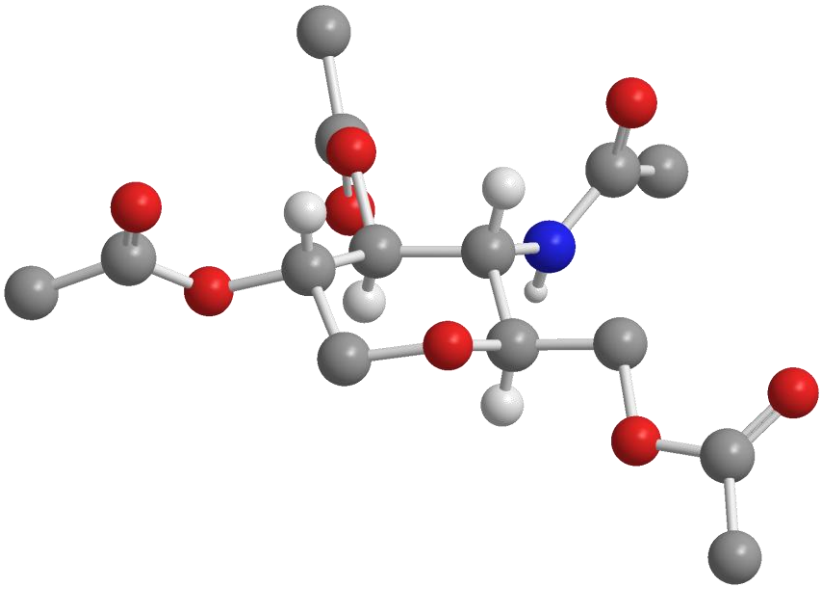
X-ray crystal structure determination for 272·HCl

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-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 **272**·HCl [$C_6H_{14}ClNO_4$]: M = 199.63, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 6.5462(2) Å, b = 8.6135(3) Å, c = 15.1907(5) Å, V = 856.54(5) Å^3, Z = 4, μ = 0.423 mm^{-1}, colourless block, crystal dimensions = 0.19 × 0.24 × 0.27 mm^3. A total of 1927 unique reflections were measured for 5 < θ < 27 and 1679 reflections were used in the refinement. The final parameters were wR_2 = 0.055 and R_1 = 0.024 [I>−3.0σ(I)], with Flack enantiopole = −0.02(6).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (2*S*,3*R*,3*S*,5*S*)-273

(selected H atoms are omitted for clarity)



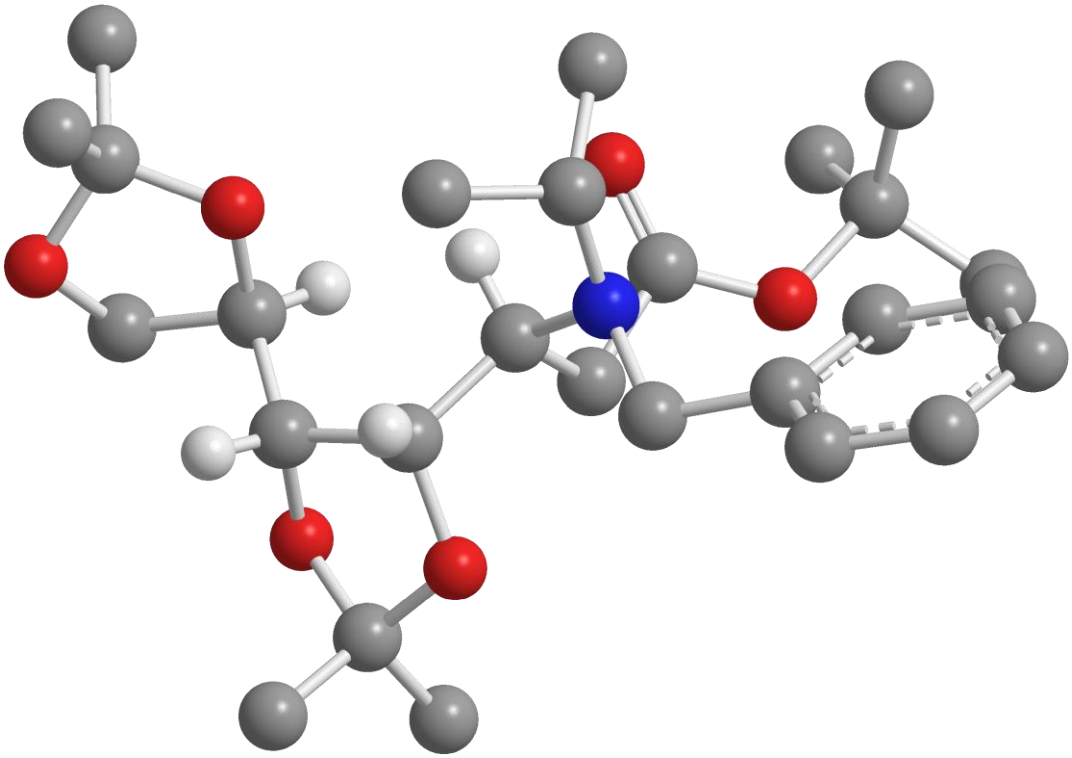
X-ray crystal structure determination for 273

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 **273** [$C_{14}H_{21}NO_8$]: M = 331.32, monoclinic, space group $P\ 2_1$, a = 5.09924(11) Å, b = 8.14026(19) Å, c = 20.2137(4) Å, β = 91.852(2)°, V = 838.62(3) Å^3, Z = 2, μ = 0.925 mm^{-1}, colourless plate, crystal dimensions = 0.06 × 0.21 × 0.24 mm^3. A total of 7222 unique reflections were measured for 4 < θ < 77 and 7222 reflections were used in the refinement. The final parameters were wR_2 = 0.095 and R_1 = 0.037 [I>−3.0σ(I)], with Flack enantiopole = 0.07(11).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (3*S*,4*S*,5*S*,6*R*)-323

(selected H atoms omitted for clarity)



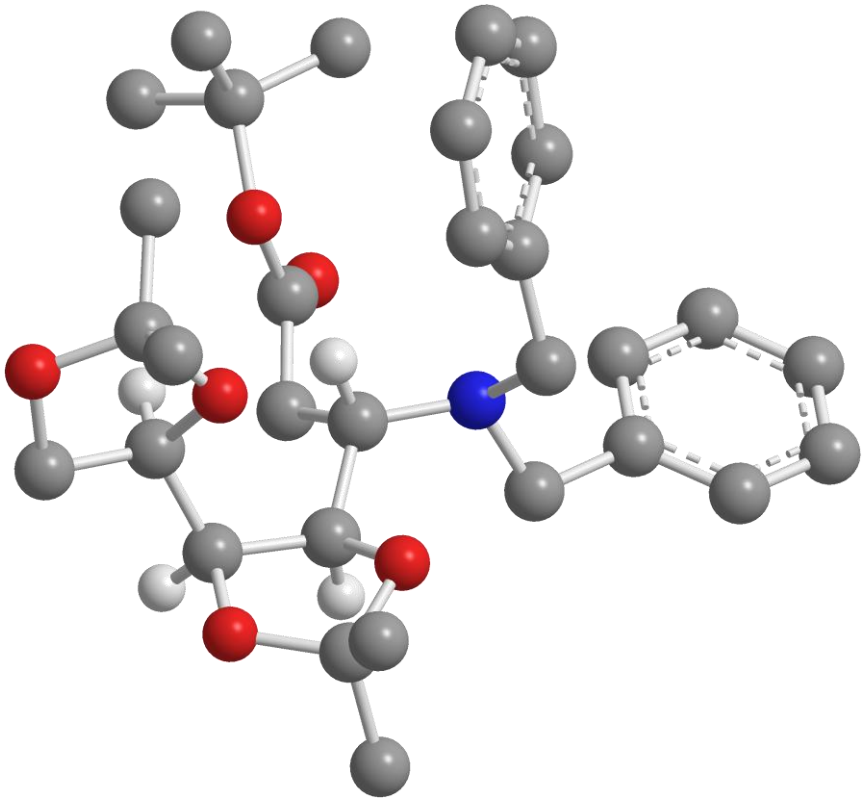
X-Ray crystal structure determination for 323

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-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 **323** [$C_{27}H_{43}NO_6$]: M = 477.64, orthorhombic, space group $P\,2_1\,2_1\,2_1$, a = 9.7606(2) Å, b = 15.6726(3) Å, c = 18.5546(4) Å, V = 2838.37(10) Å^3, Z = 4, μ = 0.078 mm^{-1}, colourless block, crystal dimensions = 0.17 × 0.18 × 0.20 mm^3. A total of 3611 unique reflections were measured for 5 < θ < 27 and 2975 reflections were used in the refinement. The final parameters were wR_2 = 0.168 and R_1 = 0.068 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (3*S*,4*R*,5*R*,6*R*)-337

(selected H atoms omitted for clarity)



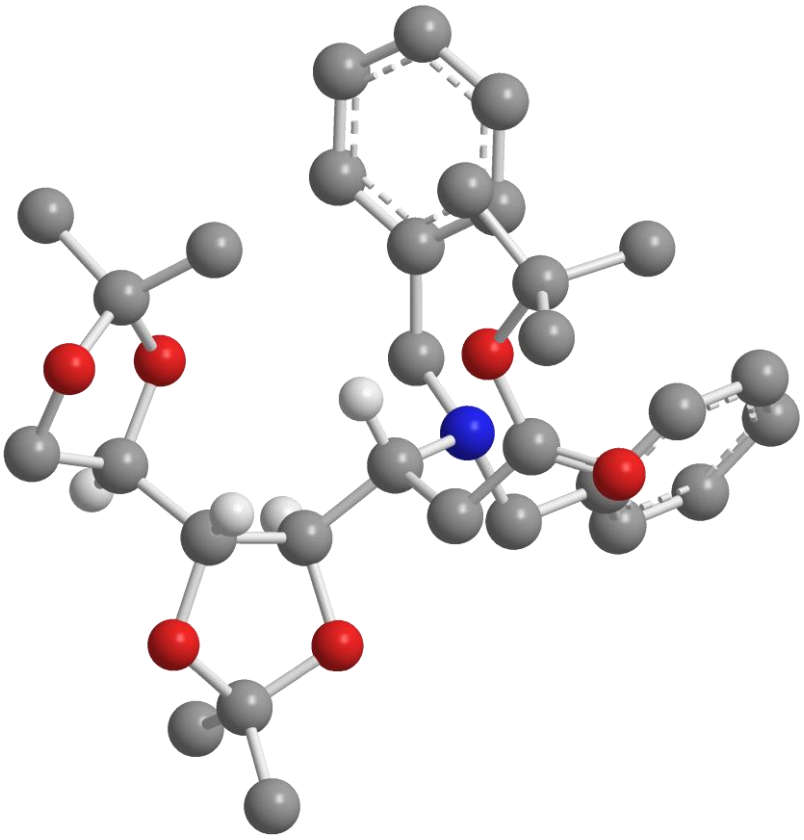
X-Ray crystal structure determination for 337

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-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 **337** [$C_{20.67}H_{28.67}N_{0.67}O_4$]: M = 525.69, orthorhombic, space group $P\,2_1\,2_1\,2_1$, a = 12.3732(3) Å, b = 12.6788(3) Å, c = 19.2260(5) Å, V = 3016.12(13) Å^3, Z = 6, μ = 0.079 mm^{-1}, colourless plate, crystal dimensions = 0.06 × 0.06 × 0.22 mm^3. A total of 3812 unique reflections were measured for 5 < θ < 27 and 3811 reflections were used in the refinement. The final parameters were wR_2 = 0.096 and R_1 = 0.070 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (3*R*,4*R*,5*S*,6*R*)-348

(selected H atoms omitted for clarity)



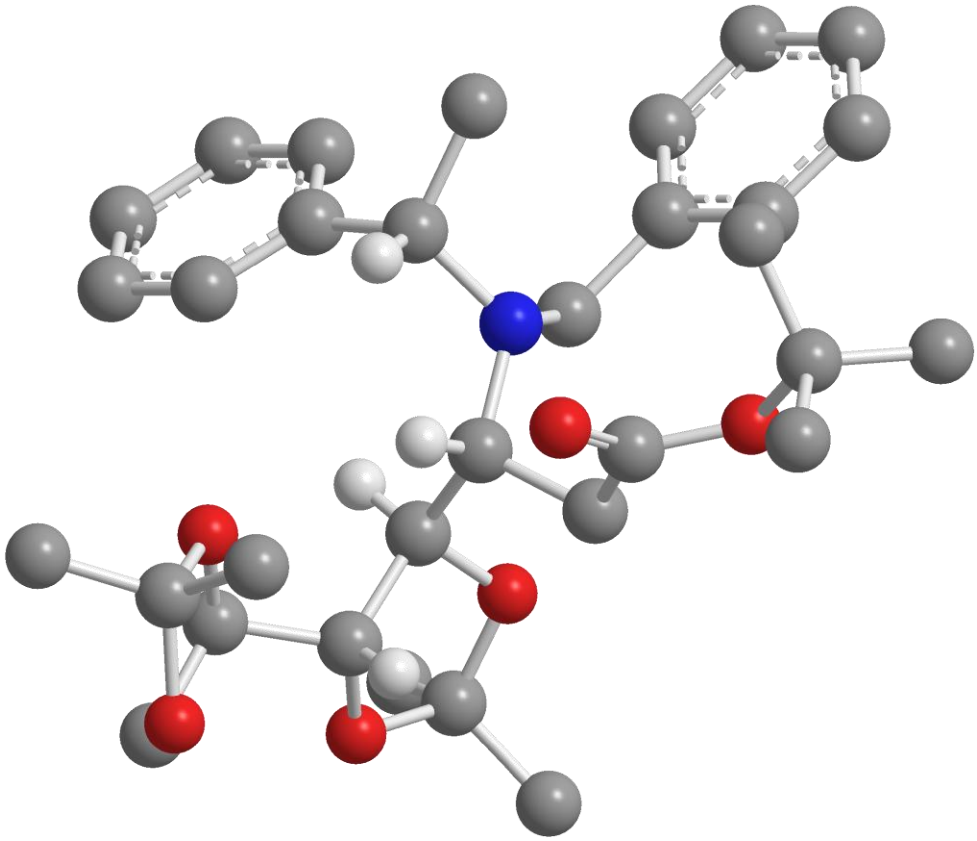
X-Ray crystal structure determination for 348

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-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 **348** [$C_{31}H_{43}NO_6$]: M = 525.69, monoclinic, space group $P\ 2_1$, a = 11.0632(3) Å, b = 10.3990(3) Å, c = 13.3019(3) Å, V = 1469.33(7) Å^3, Z = 2, μ = 0.081 mm^{-1}, colourless plate, crystal dimensions = 0.06 × 0.14 × 0.23 mm^3. A total of 3525 unique reflections were measured for 5 < θ < 27 and 2882 reflections were used in the refinement. The final parameters were wR_2 = 0.071 and R_1 = 0.032 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (3*R*,4*R*,5*S*,6*R*,α*S*)-350

(selected H atoms omitted for clarity)



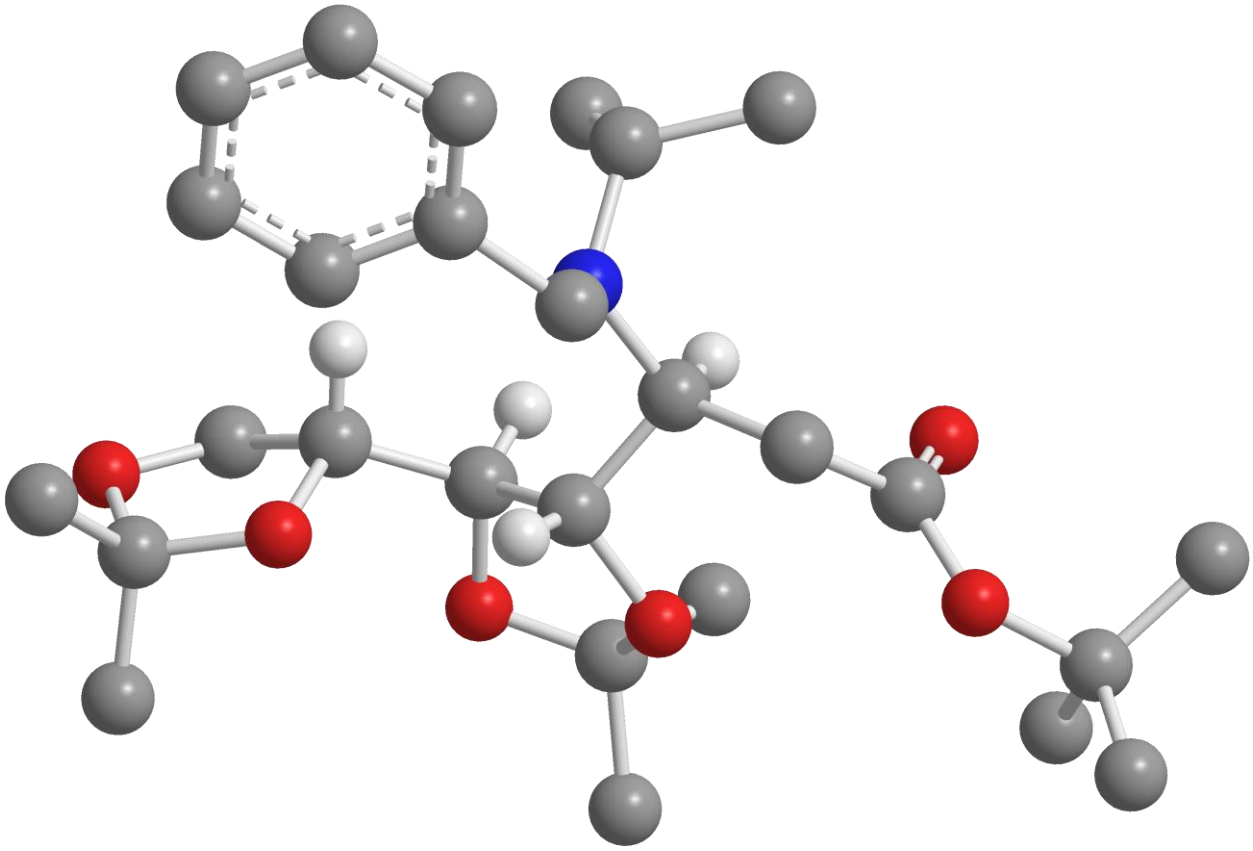
X-Ray crystal structure determination for 350

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-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 **350** [$C_{32}H_{45}NO_6$]: M = 539.71, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 8.26410(10) Å, b = 11.1934(2) Å, c = 33.1596(6) Å, V = 3067.38(9) Å^3, Z = 4, μ = 0.080 mm^{-1}, colourless plate, crystal dimensions = 0.11 × 0.14 × 0.23 mm^3. A total of 3896 unique reflections were measured for 5 < θ < 27 and 3895 reflections were used in the refinement. The final parameters were wR_2 = 0.090 and R_1 = 0.084 [I>–3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (3*S*,4*S*,5*R*,6*R*)-358

(selected H atoms omitted for clarity)



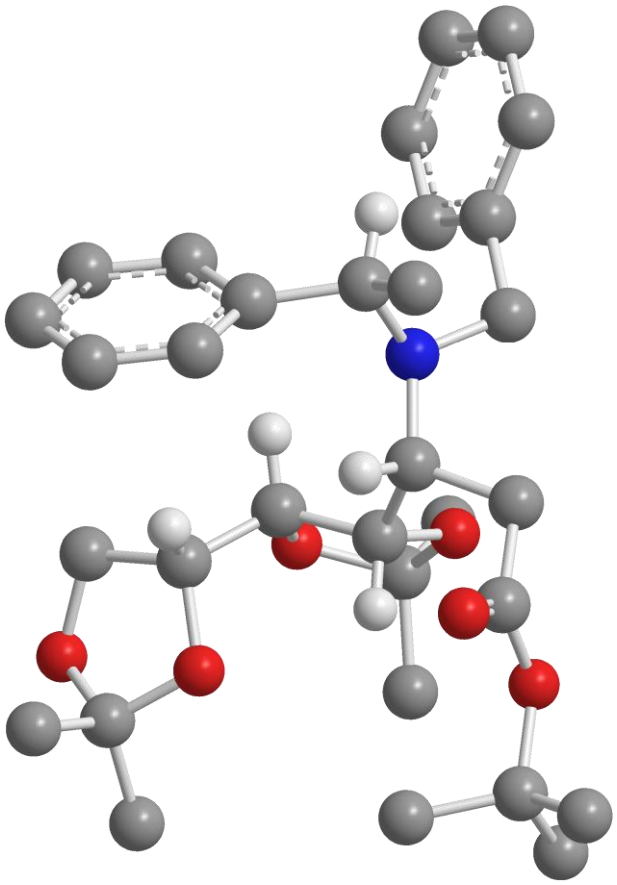
X-Ray crystal structure determination for 358

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-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 **358** [$C_{27}H_{43}NO_6$]: M = 477.64, monoclinic, space group $P\ 2_1$, a = 9.8168(5) Å, b = 11.5390(6) Å, c = 12.6474(6) Å, β = 102.880(3)°, V = 1396.60(12) Å^3, Z = 2, μ = 0.079 mm^{-1}, colourless block, crystal dimensions = 0.17 × 0.21 × 0.22 mm^3. A total of 3242 unique reflections were measured for 5 < θ < 27 and 2524 reflections were used in the refinement. The final parameters were wR_2 = 0.191 and R_1 = 0.179 [I>3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (3*R*,4*S*,5*R*,6*R*,α*R*)-363

(selected H atoms omitted for clarity)



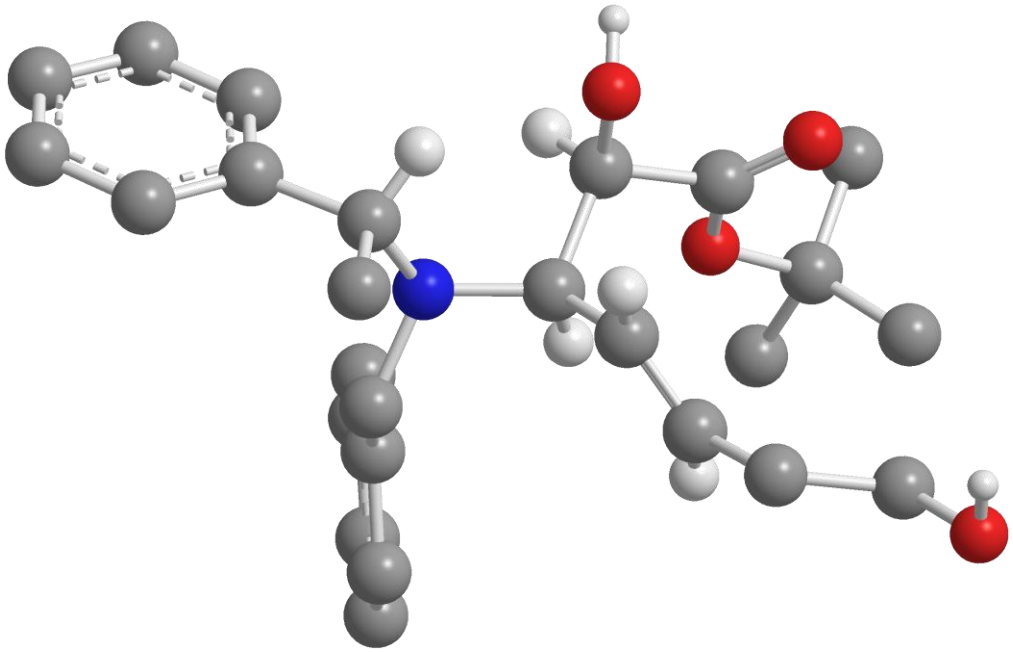
X-Ray crystal structure determination for 363

Data were collected using an Enraf-Nonius κ-CCD diffractometer with graphite monochromated Mo-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 **363** [$C_{32}H_{45}NO_6$]: M = 1079.42, triclinic, space group P 1, a = 10.5560(2) Å, b = 11.0954(2) Å, c = 14.3512(3) Å, α = 69.9777(10)º, β = 78.4438(10)º, γ = 89.5996(10)º, V = 1543.78(5) Å^3, Z = 2, μ = 0.079 mm^{-1}, colourless block, crystal dimensions = 0.22 × 0.25 × 0.32 mm^3. A total of 6983 unique reflections were measured for 5 < θ < 27 and 4753 reflections were used in the refinement. The final parameters were wR_2 = 0.099 and R_1 = 0.098 [I>3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (2*R*,3*R*,α*R*,*E*)-506

(selected H atoms are omitted for clarity)



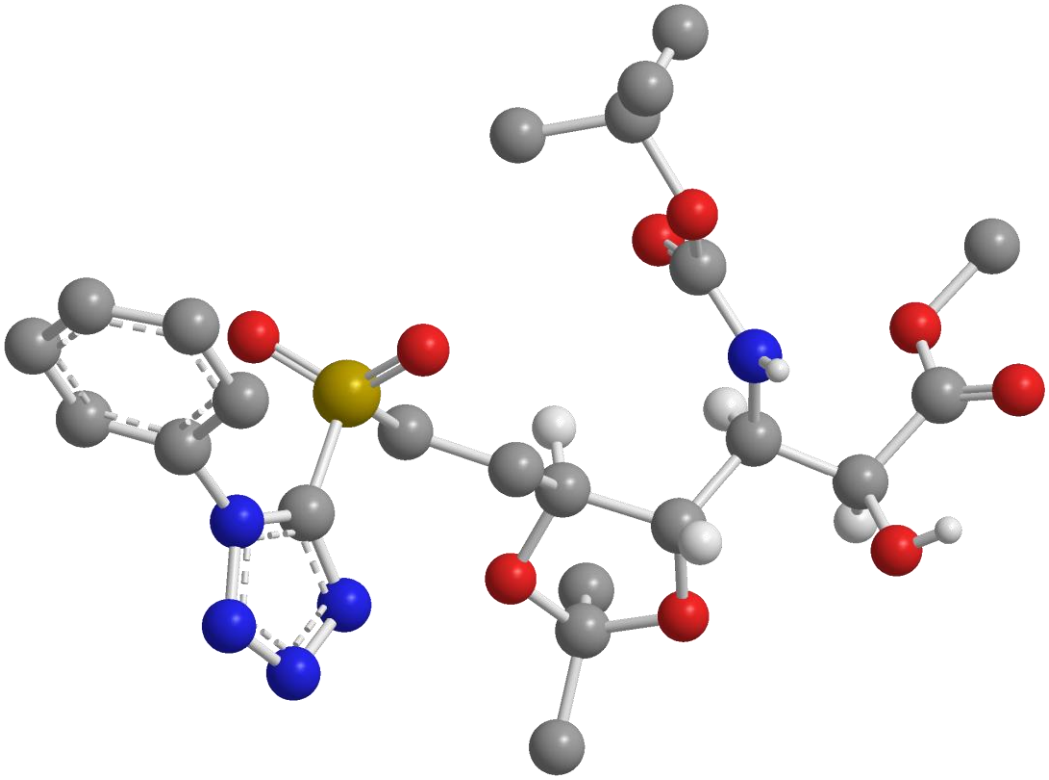
X-ray crystal structure determination for 506

Data were collected using a Nonius κ-CCD diffractometer with graphite monochromated Mo-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 **506** [$C_{26}H_{35}NO_4$]: M = 425.57, monoclinic, space group $P\ 2_1$, a = 10.3911(3) Å, b = 9.1043(2) Å, c = 13.9722(4) Å, β = 109.5339(11)°, V = 1245.74(6) Å^3, Z = 2, μ = 0.076mm^{-1}, colourless block, crystal dimensions = 0.17 × 0.21 × 0.38 mm^3. A total of 2996 unique reflections were measured for 5 < θ < 27 and 2370 reflections were used in the refinement. The final parameters were wR_2 = 0.087 and R_1 = 0.042 [I>−3.0σ(I)]. X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (*S*,*S*,*S*,*S*)-535

(selected H atoms are omitted for clarity)



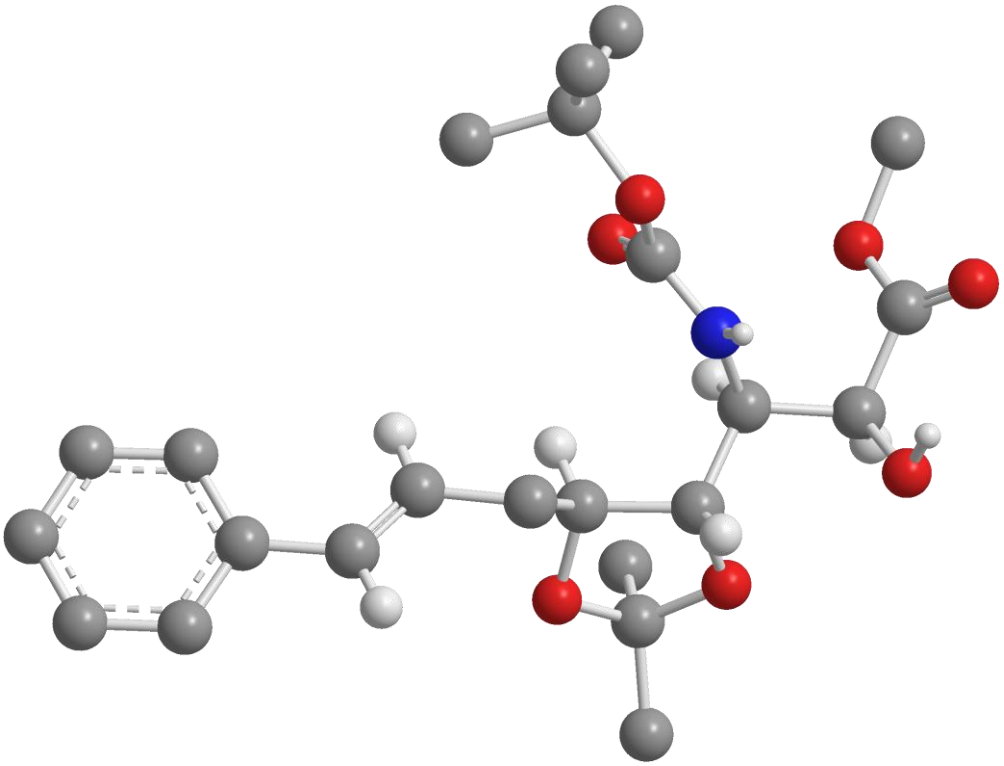
X-ray crystal structure determination for 535

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 **535** [$C_{23}H_{33}N_5O_9S$]: M = 555.61, monoclinic, space group $P\ 2_1$, a = 9.9357(5) Å, b = 5.3382(5) Å, c = 25.560(3) Å, β = 90.009(7)°, V = 1355.67(19) Å^3, Z = 2, μ = 1.573 mm^{-1}, colourless plate, crystal dimensions = 0.03 × 0.05 × 0.12 mm^3. A total of 6908 unique reflections were measured for 3 < θ < 77 and 6879 reflections were used in the refinement. The final parameters were wR_2 = 0.243 and R_1 = 0.100 [I>0.0σ(I)], with Flack enantiopole = 0.17(5).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (*S*,*S*,*S*,*S*,*E*)-536

(selected H atoms are omitted for clarity)



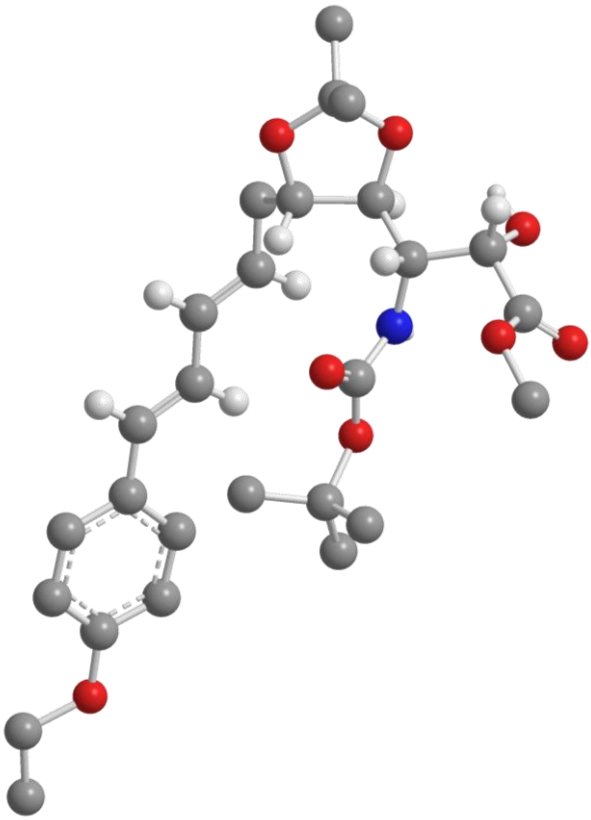
X-ray crystal structure determination for 536

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 **536** [$C_{23}H_{33}NO_7$]: M = 435.52, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 5.49231(8) Å, b = 16.4313(3) Å, c = 25.7470(4) Å, V = 2323.57(6) Å^3, Z = 4, μ = 0.756 mm^{-1}, colourless block, crystal dimensions = 0.05 × 0.10 × 0.27 mm^3. A total of 11091 unique reflections were measured for $3 < \theta < 77$ and 10112 reflections were used in the refinement. The final parameters were wR_2 = 0.078 and R_1 = 0.033 [$I>-3.0\sigma(I)$], with Flack enantiopole = −0.08(9).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

X-Ray crystal structure data for (*S*,*S*,*S*,*S*,*E*,*E*)-540

(selected H atoms are omitted for clarity)



X-ray crystal structure determination for 540

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 **540** [$C_{27}H_{39}NO_8$]: M = 505.61, orthorhombic, space group $P\ 2_1\ 2_1\ 2_1$, a = 5.3465(3) Å, b = 20.9082(13) Å, c = 25.0180(15) Å, V = 2796.7(3) Å^3, Z = 4, μ = 0.723 mm^{-1}, colourless block, crystal dimensions = 0.07 × 0.09 × 0.10 mm^3. A total of 5836 unique reflections were measured for 4 < θ < 78 and 5364 reflections were used in the refinement. The final parameters were wR_2 = 0.259 and R_1 = 0.123 [I>−3.0σ(I)], with Flack enantiopole = 0.11(6).[2] X-ray crystal structure determination was performed by Dr J. E. Thomson and Mr J. A. Lee, Chemistry Research Laboratory, University of Oxford, U.K.

[1] Betteridge, P. W.; Carruthers, J. R.; Cooper, R. I.; Prout, C. K.; Watkin, D. J. *J. Appl. Crystallogr.* **2003**, *36*, 1487.
[2] Flack, H. D.; Bernadinelli, G. *J. Appl. Cryst.* **2000**, *33*, 1143.